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Curran, István T. Horváth  
(Eds.)*

**Handbook of Fluorous  
Chemistry**

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*John A. Gladysz, Dennis P. Curran, István T. Horváth (Eds.)*

## **Handbook of Fluorous Chemistry**



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## Contents

**Preface**    *xxi*

**Contributors**    *xxiii*

<b>1</b>	<b>Fluorous Chemistry: Scope and Definition</b>	<b>1</b>
	<i>István T. Horváth, Dennis P. Curran, and J. A. Gladysz</i>	
1.1	The Birth of a Term	1
1.2	The Definition of Fluorous Today	2
1.3	Other Definitions within the Fluorous Repertoire	3
1.4	Present Scope of Fluorous Chemistry	4
	References	4
<b>2</b>	<b>A Personal View of the History of Fluorous Chemistry</b>	<b>5</b>
	<i>István T. Horváth</i>	
	References	10
<b>3</b>	<b>Fluorous Solvents and Related Media</b>	<b>11</b>
	<i>J. A. Gladysz and Charlotte Emnet</i>	
3.1	Introductory Remarks	11
3.2	Commercial Fluorous Solvents	11
3.3	Related Solvents and Media	13
3.3.1	Amphiphilic or Hybrid Solvents	13
3.3.2	Fluorous Ionic Liquids	13
3.3.3	“Faux Fluorous” Solvents	13
3.3.4	Fluorous Greases	14
3.3.5	Bonded Fluorous Phases	14
3.4	Polarities of Fluorous Solvents	14
3.5	Solubilities of Solutes in Fluorous Solvents	15
3.5.1	General Aspects	15
3.5.2	Gas Solubilities	17
3.6	Fluorous/Non-fluorous Solvent Miscibilities	18
3.7	Special Reactivity Phenomena in Fluorous Solvents	21
	References	22

<b>4</b>	<b>Strategies for the Recovery of Fluorous Catalysts and Reagents: Design and Evaluation</b>	<b>24</b>
	<i>J. A. Gladysz and Rosenildo Corrêa da Costa</i>	
4.1	Introduction; Basic Recycling Concepts	24
4.2	Fluorous/Non-Fluorous Liquid/Liquid Biphasic Catalysis	25
4.3	Fluorous Catalysis in Amphiphilic or Hybrid Solvents	25
4.4	Fluorous Catalysis Without Non-Fluorous Solvents	25
4.5	Fluorous Catalysis Without Fluorous Solvents	28
4.5.1	Thermomorphic Catalysts	28
4.5.2	Other Approaches	34
4.6	Fluorous Catalysis Without Solvents	34
4.7	Recovery of Fluorous Catalysts using Supports	35
4.8	Criteria for Recoverability	37
4.8.1	Yield as a Function of Cycle	37
4.8.2	TOF as a Function of Cycle	37
4.8.3	Catalyst Inventory	38
4.9	Slanting Data: How to Make a Non-recoverable Catalyst Appear Recoverable	38
4.10	Prospects	39
	References	40
<b>5</b>	<b>Ponytails: Structural and Electronic Considerations</b>	<b>41</b>
	<i>J. A. Gladysz</i>	
5.1	Introduction	41
5.2	Structural Aspects of Ponytails	41
5.3	NMR Characterization of Ponytails	43
5.4	Electronic Effects: Introduction	43
5.5	Electronic Effects: IR Data	45
5.6	Electronic Effects: Gas Phase Ionization Data	46
5.7	Electronic Effects: Calorimetry	48
5.8	Electronic Effects: Solution Equilibria	49
5.9	Electronic Effects: Computational Data	50
5.10	Electronic Effects: Reactivity	52
5.11	Electronic Effects: Additional Probes	53
5.12	Electronic Effects: Conclusions	53
	References	54
<b>6</b>	<b>Partition Coefficients Involving Fluorous Solvents</b>	<b>56</b>
	<i>J. A. Gladysz, Charlotte Emnet, and József Rábai</i>	
6.1	Introduction	56
6.2	Literature Data	56
6.3	Trends with Respect to Functional Groups	91
6.3.1	Non-Aromatic Hydrocarbons	91
6.3.2	Non-Aromatic Monofunctional Compounds	91
6.3.3	Simple Monoarenes	92

6.3.4	Triarylphosphines	93
6.3.5	Pyridines	93
6.3.6	Metal Complexes	94
6.4	General Trends and Special Situations	95
6.5	Quantitative Analysis and Prediction of Partition Coefficients	97
6.6	Future Directions	98
6.7	Sample Experimental Determinations	98
	References	99
<b>7</b>	<b>Separations with Fluorous Silica Gel and Related Materials</b>	<b>101</b>
	<i>Dennis P. Curran</i>	
7.1	Introduction	101
7.1.1	Fluorous Silica Gel	101
7.1.2	Types and Sources of Fluorous Silica Gel Materials and Products	102
7.2	Fluorous Solid Phase Extraction (FSPE)	103
7.2.1	Fluorous Solid Phase Extraction and its Relationship to Chromatography and Liquid/Liquid Extraction	104
7.2.2	Examples of Fluorous Solid Phase Extractions	105
7.2.3	Reverse Fluorous Synthesis with Solid Phase Extractions	109
7.3	Fluorous Flash Chromatography	110
7.4	Fluorous HPLC	111
7.4.1	Structure/Retention Trends in Fluorous Chromatography	111
7.4.2	Uses of Fluorous HPLC	114
7.4.2.1	Analysis and Purification of Organofluorine Compounds	114
7.4.2.2	Method Development for Preparative Fluorous Chromatographies and SPEs	115
7.4.2.3	Demixing in Fluorous Mixture Synthesis	115
7.4.2.4	Derivatization for Chemical Analysis	118
7.5	Separation of Fluorous Compounds on Non-Fluorous Media	118
7.6	Biphasic Reactions with Fluorous Silica Gel	123
7.7	Conclusion	125
	Acknowledgements	126
	References	126
<b>8</b>	<b>Light Fluorous Chemistry – A User's Guide</b>	<b>128</b>
	<i>Dennis P. Curran</i>	
8.1	Introduction	128
8.2	Sources of Light Fluorous Compounds and Products	132
8.3	Light Fluorous Synthesis with Fluorous Silica Gel Separations	133
8.3.1	Organic Precursors and Organic Products	133
8.3.2	Fluorous Precursors and Fluorous Products	136
8.3.3	Fluorous Precursors and Organic Products	137
8.3.4	Organic Precursors and Fluorous Products	140
8.3.5	Combinations of Solid Phase and Fluorous Methods	140
8.4	Fluorous Mixture Synthesis	142

8.4.1	Coding of Enantiomers – Fluorous Quasiracemic Synthesis	144
8.4.2	Coding of Diastereomers	146
8.4.3	Coding of Analogs	147
8.5	Fluorous Triphasic Reactions	150
8.5.1	Triphasic Detagging Reactions	150
8.5.2	Phase-Vanishing Reactions	151
8.6	Conclusion	153
	Acknowledgements	153
	References	154
<b>9</b>	<b>Getting Started in Synthesis: A Tabular Guide to Selected Monofunctional Fluorous Compounds</b>	<b>156</b>
	<i>József Rábai</i>	
9.1	Introduction	156
	Acknowledgements	160
	References	170
<b>10</b>	<b>Highlights of Applications in Synthesis and Catalysis</b>	<b>175</b>
<b>10.1</b>	<b>Synthetic Applications of Fluorous Reagents</b>	<b>175</b>
	<i>Sivaraman Dandapani</i>	
10.1.1	Introduction	175
10.1.2	Fluorous Phosphines	175
10.1.3	Fluorous Tin Reagents	176
10.1.4	Fluorous Hypervalent Iodine Reagents	177
10.1.5	Fluorous Diaryl Diselenides	178
10.1.6	Fluorous Carbodiimide	179
10.1.7	Conclusions	180
	References	181
<b>10.2</b>	<b>Radical Carbonylations Using Fluorous Tin Reagents: Convenient Workup and Facile Recycle of the Reagents</b>	<b>182</b>
	<i>Ilhyong Ryu</i>	
10.2.1	Introduction	182
10.2.2	Radical Carbonylations Using Fluorous Tin Hydrides	182
10.2.3	Radical Carbonylations Using Fluorous Allyltin Reagents	186
10.2.4	Conclusion	189
	Acknowledgements	189
	References	189
<b>10.3</b>	<b>Approaches to the Fluorous Mitsunobu Reaction</b>	<b>190</b>
	<i>Roman Dembinski</i>	
10.3.1	Introduction	190
10.3.2	Fluorous Azodicarboxylate and Fluorous Phosphine	191
10.3.2.1	Preparation of Fluorous Azodicarboxylate	191
10.3.2.2	Reactions with Fluorous Azodicarboxylate and Fluorous Phosphine	192
10.3.3	Synthesis and Separation of Fluorophilic Compounds	194



10.3.3.1	Esters	195
10.3.3.2	Ethers	200
10.3.4	Conclusion	200
	Acknowledgements	201
	References	201
<b>10.4</b>	<b>Recyclable Oxidation Reagents</b>	<b>202</b>
	<i>David Crich and Yekui Zou</i>	
10.4.1	Introduction	202
10.4.2	Organoselenium Based Oxidations	203
10.4.3	Organosulfur-Based Oxidations	210
10.4.4	Fluorous Ketone-Mediated Oxidations	214
10.4.5	Fluorous Sensitizers for Singlet Oxygenation	217
	Acknowledgments	220
	References	220
<b>10.5</b>	<b>Fluorous Protecting Groups and Tags</b>	<b>222</b>
	<i>Wei Zhang</i>	
10.5.1	Introduction	222
10.5.2	“Heavy” Fluorous Protecting Groups	226
10.5.3	“Light” Fluorous Protecting Groups	227
10.5.4	Other Fluorous Tags	231
10.5.5	Fluorous Protecting Groups in Mixture Synthesis	232
10.5.6	Fluorous Protecting Groups in Peptide and Oligosaccharide Synthesis	233
10.5.7	Conclusion	235
	References	235
<b>10.6</b>	<b>Fluorous Scavengers</b>	<b>236</b>
	<i>Craig W. Lindsley and William H. Leister</i>	
10.6.1	Introduction	236
10.6.2	Heavy Fluorous Scavenging	238
10.6.3	“Light” Fluorous Scavenging	241
10.6.4	Summary	244
	Acknowledgement	246
	References	246
<b>10.7</b>	<b>Synthesis of Perfluoroalkylated Phosphines</b>	<b>247</b>
	<i>Eric G. Hope and Alison M. Stuart</i>	
10.7.1	Introduction	247
10.7.2	Monodentate Phosphines	247
10.7.2.1	Trialkylphosphines	247
10.7.2.2	Triarylphosphines	248
10.7.3	Bidentate Phosphines	253
10.7.3.1	Perfluoroalkylated Analogs of 1,2-Bis(diphenylphosphino)ethane	253
10.7.3.2	Chiral Phosphines	253
10.7.4	Outlook	254
	References	255

<b>10.8</b>	<b>Metal Catalyzed Carbon–Carbon Bond Forming Reactions in Fluorous Biphasic Systems</b>	<b>257</b>
	<i>Siegfried Schneider, Carl Christoph Tzschucke, and Willi Bannwarth</i>	
10.8.1	Introduction	257
10.8.2	C–C Couplings with Perfluoro-Tagged Palladium Complexes	258
10.8.2.1	Negishi Reaction	258
10.8.2.2	Heck Reaction	258
10.8.2.3	Stille Couplings	260
10.8.2.4	Suzuki Couplings	262
10.8.2.5	Sonogashira Coupling	264
10.8.2.6	Allylic Substitutions	265
10.8.2.7	Cyclodimerization	265
10.8.3	Fluorous BINOL-Titanium Catalyzed Diethylzinc Additions to Aromatic Aldehydes	265
10.8.4	Perfluoro-Tagged Rhodium Catalysts	268
10.8.5	Miscellaneous	269
10.8.5.1	Kharash Addition	269
10.8.5.2	Friedel-Crafts Acylation	269
	References	270
<b>10.9</b>	<b>Hydroformylation and Hydrogenation Catalyzed by Perfluoroalkylated Phosphine/Metal Complexes</b>	<b>272</b>
	<i>Eric G. Hope and Alison M. Stuart</i>	
10.9.1	Introduction	272
10.9.2	Hydroformylation	272
10.9.2.1	Alternative Systems	273
10.9.2.1.1	Aqueous Biphasic	273
10.9.2.1.2	Ionic Liquids	273
10.9.2.1.3	Supported Catalysts	274
10.9.2.1.4	Supercritical Carbon Dioxide	275
10.9.2.2	Fluorous Systems	275
10.9.3	Hydrogenation	277
10.9.3.1	Alternative Systems	277
10.9.3.1.1	Aqueous Biphasic	277
10.9.3.1.2	Ionic Liquids	277
10.9.3.1.3	Supercritical Carbon Dioxide	278
10.9.3.2	Fluorous Systems	278
10.9.4	Outlook	279
	References	279
<b>10.10</b>	<b>Hydroformylation Catalyzed by Rhodium/Fluorinated Triarylphosphite Complexes in Fluorous Biphase Media</b>	<b>281</b>
	<i>Eric Monflier, André Mortreux, and Yves Castanet</i>	
10.10.1	Introduction	281
10.10.2	Synthesis	282
10.10.3	Hydroformylation Under Fluorous Biphasic Conditions	283

10.10.3.1	Activity and Selectivity of Catalysts	283
10.10.3.1.1	Phosphites Without Spacer Groups	283
10.10.3.1.2	Phosphites With Spacer Groups	284
10.10.3.1.3	Fluorous Analog of BINAPHOS	285
10.10.3.2	Mechanistic Aspect	286
10.10.3.3	Stability of the Catalyst and Reuse	286
10.10.4	Conclusion	288
	References	288
<b>10.11</b>	<b>Fluorous Nitrogen Ligands for Oxidation Reactions</b>	<b>290</b>
	<i>Gianluca Pozzi and Silvio Quici</i>	
10.11.1	Introduction	290
10.11.2	Oxidation of Alkenes	290
10.11.3	Oxidation of Alcohols	294
10.11.4	Oxidation of Organic Sulfides	294
10.11.5	Dye-Sensitized Photooxidation Reactions	296
10.11.6	Outlook	297
	References	297
<b>10.12</b>	<b>Synthesis of Fluorous Nitrogen Ligands and Their Metal Complexes as Precatalysts for Applications in Alkane, Alkene, and Alcohol Oxidation, and Atom Transfer Radical Reactions</b>	<b>298</b>
	<i>Jean-Marc Vincent, Dominique Lastécouères, María Contel, Mariano Laguna, and Richard H. Fish</i>	
10.12.1	Introduction	298
10.12.2	Fluorous Nitrogen Ligand Synthesis	299
10.12.2.1	Synthesis of Fluorous Soluble Metal Complexes as Precatalysts	301
10.12.3	Applications	302
10.12.3.1	Alkane and Alkene FBC Oxidation Chemistry	302
10.12.3.2	Alcohol Oxidation Chemistry	302
10.12.3.3	Atom Transfer Radical Reactions	303
10.12.3.3.1	Additions	303
10.12.3.3.2	Polymerizations	304
10.12.4	Conclusion	304
	References	305
<b>10.13</b>	<b>Enantioselective Catalysis: Biphasic Conditions</b>	<b>306</b>
	<i>Denis Sinou</i>	
10.13.1	Introduction	306
10.13.2	Reduction of Unsaturated Substrates	306
10.13.3	Carbon–Carbon Bond Formation	308
10.13.4	Oxidation	312
10.13.5	Other Reactions	313
10.13.6	Conclusion	314
	References	315

<b>10.14</b>	<b>Enantioselective Catalysis in Non-biphasic Conditions</b>	<b>316</b>
	<i>Seiji Takeuchi and Yutaka Nakamura</i>	
10.14.1	Introduction	316
10.14.2	Reactions in Organic Solvents or Amphiphilic Solvents	316
10.14.3	Reactions in Supercritical Carbon Dioxide	320
	References	322
<b>10.15</b>	<b>Combining Lipase-Catalyzed Kinetic Resolutions of Racemic Alcohols with Fluorous Phase Labeling</b>	<b>323</b>
	<i>Fritz Theil, Helmut Sonnenschein, Benno Hungerhoff, and Sauda M. Swaleh</i>	
10.15.1	Introduction	323
10.15.2	Results and Discussion	324
10.15.3	Conclusion	331
	References	332
<b>10.16</b>	<b>Enantiomeric Partitioning Using Fluorous Biphasic Methodology in Lipase-mediated (Trans)Esterifications</b>	<b>333</b>
	<i>Petr Beier and David O'Hagan</i>	
10.16.1	Introduction	333
10.16.2	Results and Discussion	334
10.16.2.1	The Efficiency and Stability of Lipase in Perfluorocarbon Media	334
10.16.2.2	Transesterification Reactions with Perfluoroalkylated Substrates	335
10.16.2.3	Partitioning of the Products Between the Liquid Phases	336
10.16.2.4	Enantiomeric Partitioning After Lipase-Mediated Reactions	338
10.16.3	Conclusion	340
	References	340
<b>10.17</b>	<b>Selective and Clean Reactions in Fluorinated Alcohols</b>	<b>341</b>
	<i>Jean-Pierre Bégué, Danièle Bonnet-Delpon, and Benoit Crousse</i>	
10.17.1	Introduction	341
10.17.2	Activation of Hydrogen Peroxide	341
10.17.2.1	Selective Oxidation of Sulfides	342
10.17.2.2	Oxidation of Thiols to Disulfides	343
10.17.3	Epoxidation	344
10.17.3.1	With Aqueous Hydrogen Peroxide	344
10.17.3.2	With Urea–Hydrogen Peroxide (UHP): H <sub>2</sub> O <sub>2</sub> 100%	344
10.17.3.3	Activation of Dioxirane: Epoxidation Reactions with Oxone® as Oxidant	345
10.17.3.4	With Oxygen	346
10.17.4	Conclusion	348
	Acknowledgements	348
	References	348
<b>10.18</b>	<b>Liquid/Solid Catalyst-Recycling Method without Fluorous Solvents</b>	<b>350</b>
	<i>Kazuaki Ishihara and Hisashi Yamamoto</i>	
10.18.1	Introduction	350
10.18.2	Fluorous Catalysis without Fluorous Solvents	350

10.18.3	Outlook	358
	References	358
<b>10.19</b>	<b>Microwave-Assisted Fluorous Chemistry</b>	<b>359</b>
	<i>Kristofer Olofsson and Mats Larhed</i>	
10.19.1	Introduction	359
10.19.2	Introducing Fluorous Groups in Microwave-Assisted Organometallic Chemistry	360
10.19.3	Fluorous Reaction Systems in Microwave Chemistry	361
10.19.4	Outlook	364
	Acknowledgment	364
	References	365
<b>11</b>	<b>Preparations</b>	<b>366</b>
11.1	( <i>R</i> )-6,6'-Diperfluorobutyl-1,1'-binaphthyl-2,2'-diol. The Copper-mediated Perfluorobutylation of Dibromobinaphthol	366
	<i>Kin Shing Chan and Yuan Tian</i>	
	References	367
11.2	( <i>R</i> )- and ( <i>S</i> )-4,4',6,6'-Tetraperfluorooctyl-1,1'-binaphthyl-2,2'-diol. The Copper-mediated Perfluorooctylation of Tetrabromobinaphthol and Resolution	367
	<i>Kin Shing Chan and Yuan Tian</i>	
	References	370
11.3	4-Aminobenzoic Acid. The Staudinger Reduction with a Fluorous Phosphine Reagent	370
	<i>Craig W. Lindsley and Zhijian Zhao</i>	
	References	371
11.4	1,2-Diethyl-6a,10-dimethoxy-1,6a,11b,11c-tetrahydro-2H-benzo[kl]xanthen-4-one. $\beta,\beta$ -Phenolic Coupling Reactions to Access Unnatural Carpanone Analogs with a Fluorous Diacetoxy Iodobenzene (F-DAIB) Reagent	371
	<i>Craig W. Lindsley and Zhijian Zhao</i>	
	References	372
11.5	4-Nitro-1,1'-biphenyl. Suzuki Coupling in Liquid/Liquid FBS	372
	<i>C. Christoph Tzschucke, Siegfried Schneider, and Willi Bannwarth</i>	
	References	373
11.6	1-(4-Nitrophenyl)-2-phenylacetylene. Sonogashira Coupling in Liquid/Liquid FBS	374
	<i>C. Christoph Tzschucke, Siegfried Schneider, and Willi Bannwarth</i>	
	References	375
11.7	4-Nitro-1,1'-biphenyl. Suzuki Coupling with a Catalyst on FRPSG without a Perfluorinated Solvent	375
	<i>C. Christoph Tzschucke, Siegfried Schneider, and Willi Bannwarth</i>	
	References	376
11.8	1-(4-Nitrophenyl)-2-phenylacetylene. Sonogashira Coupling with a Catalyst on FRPSG without a Perfluorinated Solvent	377
	<i>C. Christoph Tzschucke, Siegfried Schneider, and Willi Bannwarth</i>	
	Reference	378

- 11.9 Tris(4-perfluorohexylphenyl)phosphine. Synthesis of Perfluoroalkyl Aryl Phosphines by Copper-mediated Cross Coupling 378  
*Weiping Chen and Jianliang Xiao*  
References 379
- 11.10 Tris[4-(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)phenyl]phosphine. Synthesis of Fluoroalkyl Arylphosphines by the Heck Reaction 380  
*Weiping Chen and Jianliang Xiao*  
References 382
- 11.11 3,5-bis(Perfluorodecyl)phenylboronic Acid. An Easily Recyclable Direct Amide Condensation Catalyst 382  
*Kazuaki Ishihara and Hisashi Yamamoto*  
References 386
- 11.12 Fluorous-tagged Tetrafluorophenylbis(triflyl)methane. An Organic Solvent-swallowable and Strong Brønsted Acid Catalyst 386  
*Kazuaki Ishihara and Hisashi Yamamoto*  
References 389
- 11.13 Tetrakis[ $\mu$ -3,5-bis(perfluorooctyl)benzoato-*O,O'*] Dirhodium. Application as a Recyclable Catalyst for a Carbenoid Cyclopropanation Reaction 390  
*Gerhard Maas and Andreas Endres*  
References 392
- 11.14 1,4,7-Tris-*N*-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecyl)-1,4,7-triazacyclononane [*R<sub>f</sub>*-TACN]. A Fluorous Soluble Nitrogen Ligand via Alkylation with a Fluoroponytail, C<sub>8</sub>F<sub>17</sub>(CH<sub>2</sub>)<sub>3</sub>I 393  
*Jean-Marc Vincent and Richard H. Fish*  
Reference 394
- 11.15 Mn<sup>2+</sup>/Co<sup>2+</sup>/Cu<sup>2+</sup>/Cu<sup>+</sup> Complexes of Fluoroponytailed *R<sub>f</sub>*-Tris-*N*-1,4,7-triazacyclononane and *R<sub>f</sub>*-Carboxylate, C<sub>8</sub>F<sub>17</sub>(CH<sub>2</sub>)<sub>2</sub>COOH. Precatalysts for FBC Alkane, Alkene, and Alcohol Oxidation Chemistry 395  
*Jean-Marc Vincent, Maria Contel, Mariano Laguna, and Richard H. Fish*  
References 397
- 11.16 6,6,7,7,8,8,9,9,10,10,11,11,12,12,13,13,13-Heptadecafluoro-2-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecyl)tridecanoic Acid (Bis-*R<sub>f</sub>*-carboxylate), [C<sub>8</sub>F<sub>17</sub>(CH<sub>2</sub>)<sub>3</sub>]<sub>2</sub>CHCOOH. A Fluorous Soluble Carboxylic Acid Ligand for Metal Complexes 397  
*Jean-Marc Vincent and Richard H. Fish*  
References 399
- 11.17 1*H*,1*H*,2*H*,2*H*-Heptadecafluorodecyl Nicotinate (1) and Bis(1*H*,1*H*,2*H*,2*H*-heptadecafluorodecyl)pyridine-3,5-dicarboxylate (2). Esterification of Nicotinic Acid with a Fluoroalcohol 400  
*Takahiro Nishimura and Sakae Uemura*  
References 401
- 11.18 Pyridine-3-carbaldehyde Bis(1*H*,1*H*,2*H*,2*H*-heptadecafluorodecyl) Acetal. Acetalization of Pyridine-3-carbaldehyde with a Fluoroalcohol 401  
*Takahiro Nishimura and Sakae Uemura*  
References 402

- 11.19 2,2,2-Trifluoroethyl 2*H*,2*H*,3*H*,3*H*-perfluoroundecanoate. A Highly Fluorinated Acyl Donor Useful for the Lipase Catalyzed Labeling of Racemic Alcohols [1] 403  
*Fritz Theil, Helmut Sonnenschein, Benno Hungerhoff, and Sauda M. Swaleh*  
References and Notes 405
- 11.20 (*R*)- and (*S*)-1-Phenylethanol. Kinetic Resolution of the Racemic Alcohol by Lipase Catalyzed Enantiomer-Selective Fluorous Phase Labeling 405  
*Fritz Theil, Helmut Sonnenschein, Benno Hungerhoff, and Sauda M. Swaleh*  
References and Notes 407
- 11.21 (*R*)- and (*S*)-1-Naphthalen-2-yl-ethanol. Kinetic Resolution of the Racemic Alcohol by Lipase Catalyzed Enantiomer-Selective Fluorous Phase Delabeling of a Corresponding Highly Fluorinated Ester 407  
*Fritz Theil, Helmut Sonnenschein, Benno Hungerhoff, and Sauda M. Swaleh*  
References 409
- 11.22 Tris[4-(1*H*,1*H*-pentadecafluorooctyloxy)phenyl]phosphane 410  
*Denis Sinou and David Maillard*  
References 412
- 11.23 Bis(1*H*,1*H*,2*H*,2*H*-perfluorooctyl) Tin Oxide and 1,3-Dichloro-tetra(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)distannoxane. Synthesis and Applications of Fluorous Distannoxanes 412  
*Junzo Otera*  
References 414
- 11.24 Gb3 Oligosaccharide Derivative. Fluorous Synthesis of an Oligosaccharide 415  
*Tsuyoshi Miura and Toshiyuki Inazu*  
References 416
- 11.25 Thyrotropin-Releasing Hormone [1] (TRH). Peptide Synthesis on a Fluorous Support 416  
*Mamoru Mizuno, Kohtaro Goto, Tsuyoshi Miura, and Toshiyuki Inazu*  
References 418
- 11.26 Perfluorooctylpropyl Alcohol. Radical Addition of Perfluorooctyl Iodide to Triallyl Borate, Followed by Reductive Dehalogenation and Aqueous Deprotection 419  
*József Rábai, István Kövesi, and Ana-Maria Bonto*  
References 420
- 11.27 Perfluorooctylpropyl Amine. Use of Perfluorooctylpropyl Iodide for a Gabriel Synthesis of a Fluorophilic Amine 421  
*József Rábai, Abudurexiti Abulikemu, and Dénes Szabó*  
References 423
- 11.28 Cyclohexyl Acetate. The Acylation Reaction with a Fluorous Lanthanide Catalyst in Supercritical Carbon Dioxide with or without a Fluorous Solvent 423  
*Koichi Mikami, Hiroshi Matsuzawa, Joji Nishikido, and Mayumi Kamishima*  
References 425

- 11.29 *p*-Methoxyacetophenone. The Friedel-Crafts Acylation with a Fluorous Lanthanide Catalyst 426  
*Koichi Mikami, Hiroshi Matsuzawa, and Joji Nishikido*  
References 427
- 11.30 Tris(4-tridecafluorohexylphenyl)phosphine. Versatile Ligand Synthesized via Copper Catalyzed Cross Coupling with a Perfluoroalkyl Iodide, Lithiation and Condensation Reactions 428  
*Dave J. Adams, Eric G. Hope, Alison M. Stuart, and Andrew J. West*  
References 430
- 11.31 (*R*)-6,6'-Bis(tridecafluoro-*n*-hexyl)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl ((*R*)-RF-BINAP). A Multi-Step Sequence to a Chiral Perfluoroalkylated Bidentate Phosphine Ligand 431  
*Dave J. Adams, Eric G. Hope, Alison M. Stuart, and Andrew J. West*  
References 435
- 11.32 4-Fluorobenzyl 4-(4-Nitrophenyl)butyrate. The Mitsunobu Reaction with a Fluorous Phosphine and a Fluorous Dead Reagent 436  
*Dennis P. Curran and Sivaraman Dandapani*  
References 437
- 11.33 (*R*)-6,6'-Bis[tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)silyl]-1,1'-binaphthalene-2,2'-diol and (*R*)-6,6'-Bis[tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)silyl]-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene 437  
*Seiji Takeuchi and Yutaka Nakamura*  
References 440
- 11.34 5 $\alpha$ -Cholestan-3 $\alpha$ -ol. Inversion of Configuration via the Mitsunobu Reaction with a Fluorous Gallic Acid 441  
*Roman Dembinski and Marcin W. Markowicz*  
References 443
- 11.35 1,3-Bis(heptadecafluorooctyl)-5-chlorobenzene. Synthesis of Perfluoroalkylarenes from Aryl Bromides 443  
*Gianluca Pozzi, Marco Cavazzini, and Ian Shepperson*  
Reference 444
- 11.36 3-*tert*-Butyl-5-heptadecafluorooctyl-2-hydroxybenzaldehyde. Synthesis of Perfluoroalkylarenes from Aryl Bromides 445  
*Gianluca Pozzi, Marco Cavazzini, and Ian Shepperson*  
References 446
- 11.37 2-Phenyl-4-[[[tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)silyl]methyl]-1,3,2-dioxaborolane. The Immobilization of Boronic Acids with a Fluorous Diol 447  
*Feng-Ling Qíng*  
References 449
- 11.38 Ytterbium(III) Tris(trifluoromethylsulfonyl)methide. Preparation of a Highly Active Lanthanide Catalyst 449  
*Anthony G. M. Barrett, D. Christopher Braddock, and Jérôme J.-P. Peyralans*  
References 451



- 11.39 Bis(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)cyclopenta-1,3-diene. Preparation from Cyclopenta-1,3-diene, 1,1,1,2,2,3,3,4,4,5,5,6,6-Tridecafluoro-8-iodooctane and 3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctyl Triflate 452  
*Tomáš Bříza, Jaroslav Kvičala, and Oldřich Paleta*  
References 454
- 11.40 5,5,6,6,7,7,8,8,9,9,10,10,10-Tridecafluorodec-1-yne. Preparation from Ethynyldimethylphenylsilane and 3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctyl Triflate 454  
*Jaroslav Kvičala, Tomáš Bříza, and Oldřich Paleta*  
References 456
- 11.41 *N,N'*-Bis(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)carbodiimide 457  
*Claudio Palomo, Jesús M. Aizpurua, and Iraida Loinaz*  
References 459
- 11.42 *tert*-Butoxycarbonyl- $\alpha$ -aminoisobutyryl- $\alpha$ -aminoisobutyric Acid Benzyl Ester (Boc-Aib-Aib-OBn). Peptide Synthesis with a Fluorous Carbodiimide Reagent 459  
*Claudio Palomo, Jesús M. Aizpurua, and Iraida Loinaz*  
References 461
- 11.43 *N*-Methyl-*N*-[1-(20-oxopregna-3,5-dien-3-yl)vinyl]acetamide. Regioselective Heck Coupling Reactions with a Fluorous Tagged Bidentate Ligand to Make 2-Acylamino-1,3-butadienes 461  
*Karl S. A. Vallin*  
References 463
- 11.44 10-Iodo-9*H*,9*H*,10*H*,11*H*,11*H*-perfluorononadecane. Free Radical Chain Reactions of Fluorous Primary Alkyl Iodides 464  
*Marc Wende and J. A. Gladysz*  
References 465
- 11.45 Tris(1,1,1,5,5,5-hexafluoroacetylacetonate)chromium(III). Crystallization of A Highly Fluorinated Compound from a CO<sub>2</sub>-Expanded Liquid Solvent 466  
*Philip G. Jessop, Christopher D. Ablan, Charles A. Eckert, and Charles L. Liotta*  
References 468
- 11.46 *trans*-1,2-Dibromocyclohexane. The Phase Vanishing Bromination with FC-72 as a Screen Phase 468  
*Ilhyong Ryu, Hiroshi Matsubara, Hiroyuki Nakamura, and Dennis P. Curran*  
References 470
- 11.47 1-Hydroxymethyladamantane. Radical Hydroxymethylation with a Fluorous Tin Hydride 470  
*Ilhyong Ryu, Hiroshi Matsubara, and Dennis P. Curran*  
References 471
- 11.48 5,5-Bis(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)-2-(4-formylphenyl)-1,3-dioxane. Selective Acetal Formation with Fluorous 1,3-Diol Reagents and its Use in Multistep Synthesis 471  
*Roger W. Read and Chutian Zhang*  
References 473

11.49	1-(4-Methoxyphenoxy)-3-(4-pyridin-2-yl-piperazin-1-yl)-propan-2-ol. The Amination Reaction Using a Fluorous Isatoic Anhydride Scavenger to Remove Excess Amine 473 <i>Wei Zhang and Christine Hiu-Tung Chen</i> References 474
11.50	Borane-(1 <i>H</i> ,1 <i>H</i> ,2 <i>H</i> ,2 <i>H</i> -Perfluorodecyl) Methyl Sulfide Adduct. Preparation of a Borane-Fluorous Dialkyl Sulfide and its Application to the Hydroboration of $\beta$ -Pinene 475 <i>David Crich, Mitesh Patel, and Santhosh Neelamkavil</i> References 477
<b>12</b>	<b>Applications of Fluorous Compounds in Materials Chemistry 478</b>
<b>12.1</b>	<b>Basic Principles and Recent Advances in Fluorinated Self-Assemblies and Colloidal Systems 478</b> <i>Marie Pierre Krafft</i>
12.1.1	Introduction 478
12.1.2	Basic Physicochemical Properties 479
12.1.2.1	Fluorocarbons 479
12.1.2.2	Fluorinated Surfactants 481
12.1.2.3	Semifluorinated Alkanes: a Class of Special Amphiphiles 482
12.1.3	Self-Assembly Behavior of <i>F</i> -Amphiphiles 482
12.1.3.1	Vesicles 482
12.1.3.2	Tubules and Fibers 484
12.1.4	Bi-dimensional Films 485
12.1.4.1	Langmuir and Gibbs Monolayers 485
12.1.4.2	Self-Assembled Monolayers 485
12.1.5	Emulsions and Microemulsions Containing a Fluorocarbon or a Fluorinated Surfactant 486
12.1.5.1	Fluorocarbon Emulsions and Microemulsions 486
12.1.5.2	Water-in-CO <sub>2</sub> Microemulsions 486
12.1.5.3	Fluorocarbon Microbubbles 487
12.1.6	Fluorocarbon Polymers 487
12.1.7	Conclusions and Perspectives 488 References 488
<b>12.2</b>	<b>Fluorous Nanoparticles 491</b> <i>Marcial Moreno-Mañas and Roser Pleixats</i>
12.2.1	Introduction 491
12.2.2	Metal Nanoparticles 492
12.2.3	Nanoparticles of Metal Oxides, Halides, and Chalcogenides 501 Acknowledgements 504 References 505
<b>12.3</b>	<b>Self-Assembly of Hybrid Fluorous Materials 507</b> <i>Pierangelo Metrangolo, Tullio Pilati, and Giuseppe Resnati</i>

12.3.1	Introduction	507
12.3.2	Neutral Two-Component PFC-HC Materials	508
12.3.3	Anionic Three-Component PFC-HC-IS Materials	512
12.3.4	Polymeric PFC-HC Comb-shaped Complexes	516
12.3.5	Conclusion	518
	References	518
<b>13</b>	<b>Fluorous Materials for Biomedical Uses</b>	<b>521</b>
	<i>Jean G. Riess</i>	
13.1	Introduction	521
13.2	Specific Properties of Highly Fluorinated Materials That Are the Basis for Their Uses in Medicine and Biology	523
13.2.1	Perfluoroalkyl Chains: Bulkier, Stiffer, Hydrophobic and Lipophobic	523
13.2.2	Perfluorocarbons: Inert Liquids with Gas-like Behavior	525
13.2.3	Fluorinated Amphiphiles: a Predilection for Self-Assembly	526
13.2.4	Fluorocarbon–Hydrocarbon Diblocks: Fluorophilic/Lipophilic Amphiphiles	529
13.3	Contrast Agents for Diagnostic Imaging	530
13.3.1	Gaseous Fluorocarbon-Loaded Microbubbles as Sound Reflectors for Ultrasound Imaging	530
13.3.1.1	Needs and Challenges	530
13.3.1.2	Principles of <i>In Vivo</i> Microbubble Stabilization: a Key Role for Perfluorochemicals	530
13.3.1.3	Bubble-Specific Imaging – Harmonics and Pulse Inversion Techniques	533
13.3.1.4	Controlled Bubble Destruction: Monitoring Tissue Perfusion	533
13.3.1.5	The Products	535
13.3.1.6	Medical Imaging Applications	536
13.3.2	Targeted Fluorinated Colloids for Molecular Imaging – Molecular Markers for Specific Pathologies	539
13.3.2.1	“Passive” Targeting of Microbubbles	540
13.3.2.2	Active Site-Directed Targeting of Microbubbles	540
13.3.2.3	Targeted Fluorocarbon Emulsions for Diagnosis by Ultrasound or Magnetic Resonance Imaging	541
13.3.3	Further Uses of Fluorocarbons in Diagnosis	542
13.4	<i>In Vivo</i> Oxygen Delivery: Fluorocarbon-in-Water Emulsions	543
13.4.1	Objectives and Challenges	543
13.4.2	Selecting a Fluorocarbon with Lipophilic Character: Perfluorooctyl Bromide	544
13.4.3	Stabilizing Fluorocarbon Emulsions: Counteracting Molecular Diffusion	546
13.4.4	Fluorocarbon Emulsion Physiology and Clinical Trials	547
13.4.5	Further Research on Fluorocarbon Emulsions for Oxygen Delivery	548
13.5	Fluorocarbons as Therapeutic Aids and Tissue-Sustaining Devices	551
13.5.1	Pulmonary Applications – an Anti-Inflammatory Effect?	551

13.5.2	Cardiovascular Uses: Thrombolysis	552
13.5.3	Topical Applications: Fluorocarbon Gels	552
13.5.4	Ophthalmologic Applications	553
13.5.5	Organ and Tissue Preservation, Cell Cultures	553
13.6	Delivery of Bioactive Agents	554
13.6.1	The Parenteral Route	554
13.6.1.1	Microbubbles and Ultrasound	554
13.6.1.2	Targeted Fluorocarbon Emulsions	555
13.6.1.3	Fluorinated Vesicles and Other Self-Assembled Fluoro-Colloids	556
13.6.2	The Pulmonary Route – Dispersions of Particles within a Fluorous Phase	556
13.7	Highly Fluorinated Materials as Research Tools, Processing Aids, etc.	558
13.7.1	Research Tools	558
13.7.2	Fluorocarbons and Fluorinated Colloids as Processing Aids	559
13.8	Summary and Perspectives	560
	Acknowledgements	561
	References	561
<b>14</b>	<b>Fun and Games with Fluorous Chemistry</b>	<b>574</b>
	<i>József Rábai</i>	
14.1	Introduction: Where Does the Fun Come From?	574
14.2	Synthesis of Dyes for Fluorous and Organic Phases	575
14.2.1	How to Make the “Blue Dye”: The Taming of Aromatic Perfluoroalkylations	575
14.2.2	Preparation of a Fluorophilic “Gold Dye”: $(\text{Au}_m)(\text{HS}(\text{CH}_2)_3\text{R}_{\text{f8}})_n$	577
14.2.3	Preparation of an Organophilic “Gold Dye” $(\text{Au}_m)(\text{HS}(\text{CH}_2)_{11}\text{CH}_3)_n$	578
14.3	Fluorous Phase Systems for the Games	578
14.4	Name of the Games	580
14.4.1	Make Them Blue!	580
14.4.2	Purple Empire.	581
14.4.3	Which Phase to Winter?	581
14.4.4	Up and Down	583
14.5	Epilogue	584
	Acknowledgements	584
	References	584
	<b>Index</b>	<b>586</b>

## Preface

It is approximately ten years since the modern era of fluororous chemistry began. A historical perspective on the development of this field is provided in Chapter 2. During this period, over 500 publications on fluororous chemistry have appeared. Although there has been a steady stream of review articles and other compendia, in our view it was time for a Monograph or Handbook. This idea found resonance among many others in the fluororous community, who either contributed chapters or offered valuable counsel.

Our goal was to create a Handbook that would supply both the necessary entry-level information for beginners and advanced reference material for experienced practitioners. With respect to the former objective, Chapters 1 through 8 constitute a cohesive pedagogical introduction to the fundamentals of fluororous chemistry. In Chapter 10, a number of reviews that highlight specific synthetic applications are provided. The companion Chapters 12 and 13 similarly treat selected materials and biomedical applications of fluororous chemistry. While it was not possible to comprehensively cover all of the diverse synthetic and materials applications that have appeared, references to most of the fluororous synthesis literature up to mid-2003 can be found in this Handbook.

Chapter 9 provides lead references to the “fluororous pool”, or simple monofunctional compounds that are the starting points for most synthetic sequences. About 50 experimental procedures, in many cases representing optimized versions of those in the literature, have been collected in Chapter 11. Chapter 14 details several experimental “divertissements” that showcase some of the unusual properties of fluororous molecules. These are particularly suitable for lecture demonstrations, helping to attract new students to the field, or piquing the interest of the lay person.

We wish to express our sincere thanks to the many authors who have written chapters or subchapters for their hard work, engagement, and patience. We would also like to acknowledge here the granting agencies that supported the preparation of our sections (JAG, DFG; GL 300-3/1; DPC, NIH).

Fluororous chemistry continues to be a dynamic and evolving discipline. Indeed, the many intrinsic challenges associated with synthesis and catalysis – yield, selectivity, reactivity, overall cost, recoverability, etc. – are never-ending. One long-term mandate of fluororous chemists is to build a new world or “parallel universe” encompassing fluororous versions of all basic organic molecules, building blocks, reagents, homogeneous catalysts, macromolecules, supramolecular assemblies, etc. The following chapters illustrate that substantial progress has been made. However in constructing this parallel universe, the many fluororous

pioneers have in fact created an expanded universe, with a diverse palette of unusual phenomena and exploitable properties that have no counterparts in old-world chemistry.

Future generations of researchers will put their mark on this discipline. If this Handbook can help to catalyze these efforts, we and the other authors will feel that this undertaking has been successful. Regardless, the call to all readers is to “take a dive into the fluoruous pool”; given the high oxygen solubility, no special breathing apparatus is required, and the high density makes it difficult to sink. As is evident in the following chapters, there are a lot of good things swimming around.

New York, Spring 2004

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Left to right: John A. Gladysz, István T. Horváth, Dennis P. Curran

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## 1

**Fluorous Chemistry: Scope and Definition***István T. Horváth, Dennis P. Curran, and J. A. Gladysz***1.1****The Birth of a Term**

The title of this Handbook features a word, fluororous, which was not in the chemists vocabulary ten years ago. It was introduced in a classic 1994 paper by Horváth and Rábai, who envisioned a term that could be used analogously to “aqueous” or “aqueous media” [1]. Although there were earlier studies of reactions in “fluorous media” (defined below) [2], the general concept remained unarticulated, almost like parallel worlds unaware of each other.

Why not simply refer to fluororous solvents as non-aqueous? Importantly, fluororous solvents do not mix with most common organic solvents at room temperature. Bilayers or liquid/liquid biphasic systems form, with the more dense fluororous solvent on the bottom. Given this orthogonality, a special term is clearly justified. The word “oleophobic” can be found in the older patent literature [3], and fluororous media can be defined as simultaneously oleophobic and hydrophobic. However, this expression is cumbersome and lacks pizzazz or showroom appeal. Would you be attracted to a symposium with the title “Recent Advances in the Chemistry of Oleophobic and Hydrophobic Molecules”?

Importantly, fluororous and organic solvents usually mix at elevated temperatures. This allows the facile switching of reactions between heterogeneous and homogeneous conditions. Temperature-dependent miscibility represents one of many types of thermomorphic behavior. The adjective thermomorphic is applied in such broad contexts that a precise definition becomes problematic, but a physical property that is temperature dependent is always involved.

The 1994 paper also introduced the concept of a “ponytail”. These are most commonly fluoroalkyl moieties of the formula  $(\text{CH}_2)_m(\text{CF}_2)_{n-1}\text{CF}_3$ , often abbreviated  $(\text{CH}_2)_m\text{R}_{\text{fm}}$ . Depending on the quantity and length of the perfluoroalkyl segment, they can render molecules partially, preferentially, or even exclusively soluble in the fluororous liquid phase. This reflects a simple “like dissolves like” effect. Common organic molecules preferentially partition into organic phases ( $>95\% < 5\%$ ).

Accordingly, catalysts featuring sufficient ponytails were combined with reactants in fluororous/organic solvent mixtures. As shown in Figure 1-1, homogeneous catalysis was achieved at the high-temperature, one-phase limit. The products and catalyst were then cleanly separated at the low-temperature, two-phase limit. This was termed fluororous biphasic catalysis, and specific details are given in the historical perspective in Chapter 2.

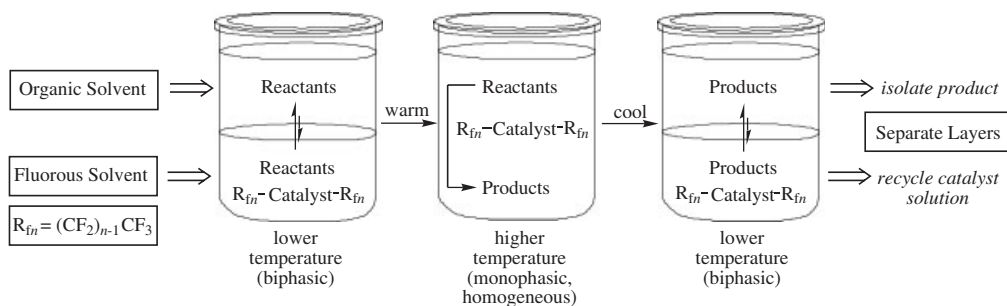


Fig. 1-1. First reaction/recovery sequence applied to a fluororous catalyst

This broad concept was expanded almost immediately to the separation of products and (spent) reagents, and to the use of ponytails of varying fluorine content to label or tag libraries of compounds. New separation techniques of fluororous solid-phase extraction and fluororous chromatography sprouted to disentangle tagged molecules from non-tagged molecules and from each other. The field now extends from fluororous nanoparticles on the materials side to fluororous peptides and enzymatic reactions on the biological side. It has evolved so far beyond its original incarnation that a review and reassessment of its working vocabulary is needed, as is provided in the following two sections.

## 1.2

### The Definition of Fluorous Today

As noted above, it was initially envisioned that fluororous would be used analogously to aqueous or aqueous media. However usage dictates definitions, and early researchers soon expanded the term to include fluoroalkyl-labeled species, and this sense dominates in current practice. Accordingly, we propose the following definition of the adjective *fluorous* [4]: “*of, relating to, or having the characteristics of highly fluorinated saturated organic materials, molecules or molecular fragments.*” Or, more simply (but less precisely), “highly fluorinated” or “rich in fluorines” and based on  $sp^3$ -hybridized carbon.

This liberal definition subsumes the original definition as well as newer uses involving such diverse subjects as organic synthesis with fluororous tags, fluororous chromatography, fluororous materials, various types of analytical measurements, and societal and sociological extensions such as “fluorous chemists” and “the fluororous community”. Astute readers will recognize that it also renames existing fields – for example, fluorocarbon surfactants are now fluororous surfactants. In the same vein, fluorocarbon blood substitutes are now fluororous blood substitutes, and Teflon becomes a fluororous polymer. The term fluororous is already creeping into the vocabulary of researchers in many of these established areas. Whether or not it is broadly accepted in these allied circles, the liberal definition does recognize that both the established and new fields build in different ways on the same unique properties of polyfluorinated molecules or fragments.

All that glitters is not gold, and everything with fluorines is not fluororous. But where should the line be drawn between fluororous and non-fluorous molecules or groups? We have

heard researchers call a single fluorine atom in a molecule a “fluorous substituent”. This is way over the line. “Fluorine” is a perfectly clear noun, and it obfuscates to replace it with a vague adjective (fluorous) modifying a vague noun (substituent). So 5-fluorouracil (5-FU) is not a fluorous molecule even though the unique properties of fluorine are in play. Perfluorohexane obviously is a fluorous molecule. In between is a vast continuum where properties and to some extent individual researchers will dictate what is or is not fluorous. Said another way, we don’t know exactly how to define a fluorous molecule or group, but we know one when we see one, as will you after you have read this book!

### 1.3

#### Other Definitions within the Fluorous Repertoire

Within the above framework, we offer the following definitions for corollary concepts that are important to this Handbook [4]:

1. “a *fluorous medium* is any phase of a perfluoroalkane, perfluorodialkylether, perfluorotrialkylamine, or similar non-polar species, **or** any similarly-composed micro-environment within a non-fluorous medium that shares key physical properties with these species.”

Fluorous media can include greases and coated phases, and are treated further in Chapter 3. It is worth emphasizing that perfluoroarenes, such as hexafluorobenzene, are not fluorous under the above definitions. They are significantly more polar than perfluoroalkanes, and preferentially partition into organic media.

*Fluorophilic* molecules, materials or fragments show an affinity for fluorous media under a given set of conditions, while *fluorophobic* ones do not. *Fluorophilicity* may be used interchangeably with *fluorous phase affinity* and is quantified by a fluorous/organic liquid/liquid partition coefficient, as described in Chapter 6.

2. “a *fluorous separation technique* is any method that separates fluorous or fluorous-labeled molecules from other types of molecules, or from each other, based primarily on the structure of the fluorous domain of the molecule(s).”

As detailed in Chapter 7, fluorous separation techniques are often (but not always) based on the interactions between a fluorous medium and a fluorous portion of a molecule, and include liquid–liquid extraction with organic and fluorous solvents, and solid–liquid extraction and chromatography with fluorous solid phases. Fluorous separation techniques can also involve interactions of fluorous molecules with each other (for example, precipitation).

3. “a *fluorous label* or *tag* is a portion or domain of a molecule that is rich in  $sp^3$  carbon–fluorine bonds and exerts primary control over the separability characteristics of the molecule in fluorous separation techniques.”

A ponytail contains at least six fully fluorinated  $sp^3$  carbons, stemming from the goal in much early fluorous research of compounds with very high fluorous/organic partition coefficients. Both tags and ponytails are (phase) labels. Many authors use label and tag and ponytail almost interchangeably. Others view a ponytail as being permanently affixed to a molecule (for example, as part of the carbon skeleton), and a tag as being removable (for example, as part of a protecting group).



It is sometimes convenient to speak of “light fluororous” and “heavy fluororous” substances. Almost always, the former contain only a single tag or ponytail, which, as detailed further in Chapter 8, should contain no more than 21 fluorine atoms. We suggest that the latter be reserved for cases where two or more ponytails emerge from a shared atom or molecular fragment.

4. “a *fluorous reaction component* is any participant in a reaction (catalyst, pre-catalyst, reagent, reactant/educt, product, scavenger, etc.) to which a *fluorous label* has been deliberately affixed.”

The labeling can be permanent (ponytail) or temporary (tag). This terminology also encompasses “fluorous reaction intermediates”.

5. “a *fluorous reaction* involves at least one *fluorous reaction component*, which afterwards can be separated from the non-fluorous or other fluororous components of the reaction mixture by a *fluorous separation technique*.”
6. “*fluorous chemistry* is the study of the structure, composition, properties and reactions of fluororous molecules, molecular fragments, materials and media.”

We believe that standardization of the field to the definitions provided above will greatly help its continued advancement. On the other hand, there are other practices that have not yet converged to a common standard, and perhaps never will. Partition coefficients provide one example. These are sometimes expressed as logarithmic values, and at other times as ratios normalized to 100 (for example, 98.3:1.7), and also as ratios with the less populated phase set to 1 (for example, 57.8:1). Symbols for ponytails and tags are another example. Some authors in this Handbook utilize “ $R_{fn}$ ” for  $(CF_2)_{n-1}CF_3$  or  $(CF_2)_nF$ , and others eschew abbreviations altogether. However, it should be noted that IUPAC has authorized the prefix F- for perfluoro, enabling “F-alkyl” to denote “perfluoroalkyl” (F-surfactant = perfluorosurfactant, etc.).

## 1.4

### Present Scope of Fluorous Chemistry

The definitions associated with fluororous chemistry in the preceding sections are so broad (as they should be) that further introductory classifications would be of little use. Rather, readers are directed to Chapters 3–8 for structured treatments of various aspects and protocols. Although Figure 1-1 is pedagogically appealing as a point of introduction, it now represents just one of countless ways to conduct fluororous reactions, and one of several main strategies for the recovery of fluororous catalysts or reagents. Since recovery can present diverse challenges, a portfolio of methodologies is normally desirable, and these variations and extensions are detailed in Chapter 4.

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- 4 These definitions are adapted from an earlier treatment: GLADYSZ, J. A.; CURRAN, D. P. *Tetrahedron* **2002**, 58, 3823.

## 2

## A Personal View of the History of Fluorous Chemistry

István T. Horváth

The fluorous story probably began with the synthesis of the first few drops of a liquid perfluoroalkane. The high density and many other unique properties were immediately apparent upon isolation [1]. The systematic development of the chemistry of perfluorocarbons actually began with the US Atomic Energy Program at Columbia University and other universities in the fall of 1941. The observation of separate liquid/liquid phases must have been the reason for the statement by Groose and Cady that “the liquid saturated fluorocarbons are substantially *insoluble* in water, alcohols, and hydrocarbons” [2]. Although the temperature dependent phase separation of perfluorinated alkanes – even from hydrocarbons – had already been established by Hildebrand in 1949 [3], the tremendous potential of the liquid/liquid phase separation was only recognized 50 years later [4].

The original fluorous biphasic concept was developed *on paper* at Exxon Corporate Research Laboratories during the search for a novel approach for the selective oxidation of methane to methanol utilizing supported [5] (or stationary [6]) liquid phase catalysis, an attractive immobilization technique for transition metal complexes developed in the late 1980s. Perfluorotributyl amine was selected as the supported or stationary liquid phase due to its intriguing properties including the high solubility of methane and, in particular, of oxygen [7], the low miscibility with methanol at ambient conditions, and a remarkable stability under air even at higher temperatures. Thus, the use of a two-phase system, consisting of a perfluorotributyl amine phase containing the oxidation catalyst and a product phase being methanol itself, was proposed. To avoid the oxidation of the catalyst and to achieve high solubility in the perfluorotributyl amine phase, perfluoroalkyl chains were to be attached to the ligand core of the catalyst (Figure 2-1). The idea of using perfluoroalkylated ligands was also in line with the successful application of electron deficient perhalogenated iron porphyrins for isobutane oxidation by Ellis and Lyons in the late 1980s [8]. However, it was later clearly established that these iron porphyrins are not stable in oxidative environments [9]. Although the fluorous approach has not resulted in a new methane oxidation catalyst, it led to the development of a much broader concept.

In terms of the personal dynamics of the fluorous story, important contributions were made by Dr. Andrew Kaldor, Director of Resource Chemistry Laboratory at Exxon Corporate Research Laboratories, who continually emphasized the necessity for thinking “outside the

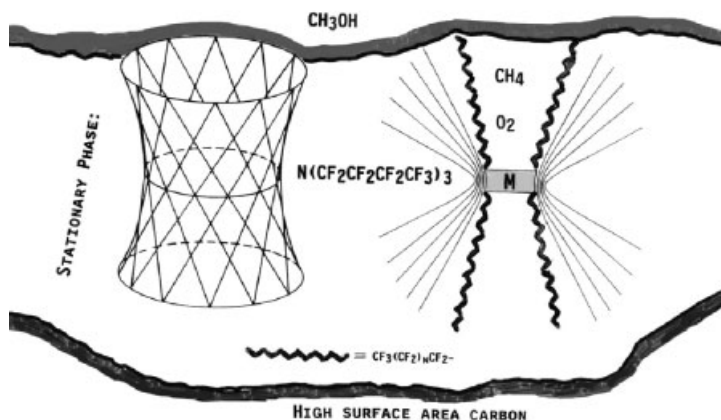
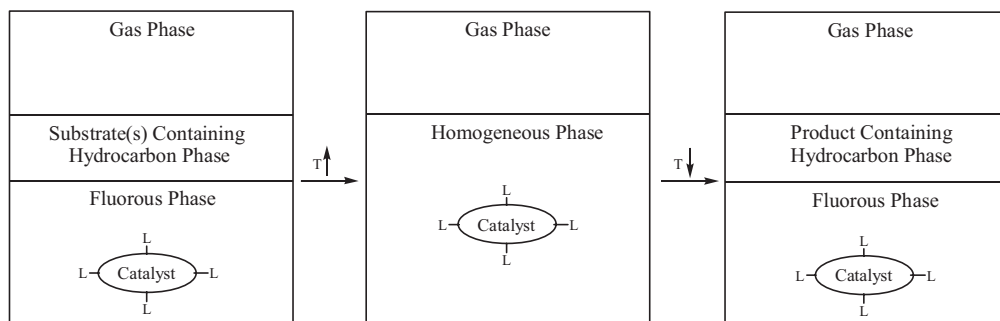


Fig. 2-1. The original drawing of the stationary liquid phase catalyst for methane oxidation to methanol showing the fluorous ponytails

box". He had asked his research staff to develop new concepts for methane conversion and to present them at a meeting. At the same time, I had asked Dr. József Rábai, an organic chemist and a visiting scientist at Exxon (from Eötvös University, Budapest, Hungary) to help me in various projects and indeed he was instrumental in transferring the idea from the drawing-board to actual experiments.

When the limited miscibility of perfluoroalkanes, perfluorodialkyl ethers, and perfluorotrialkyl amines with common organic solvents such as toluene, THF, and acetone was recognized, a general concept, the *fluorous biphasic concept* [4], was born which led to the development of *fluorous biphasic chemistry* [10]. The term *fluorous* was introduced, as the analog to the term *aqueous*, to emphasize the fact that a chemical transformation is primarily controlled by a reagent or a catalyst designed to dissolve preferentially in the fluorine phase. The *fluorous phase* was originally defined as the perfluoroalkane, perfluorodialkyl ether, or perfluorotrialkyl amine rich phase of a biphasic system. Thus, a *fluorous biphasic system* consisted of a fluorine phase containing a preferentially fluorine soluble reagent or catalyst, and a second product phase, which may be any organic or nonorganic solvent with limited solubility in the fluorine phase. Reagents and catalysts can be made fluorine soluble by attaching fluorocarbon moieties to ligands in appropriate size and number. The most effective fluorocarbon moieties are linear or branched perfluoroalkyl chains with high carbon number that may contain other heteroatoms (the "fluorous ponytails"). It was also recognized at the early stages of the development [4], that the possibility of dipole–dipole interactions render *perfluoroaryl*-containing [11] reagents and catalysts more soluble in common organic solvents and therefore less useful as part of fluorine biphasic systems.

Because of the well-known electron-withdrawing properties of the fluorine atom, the attachment of fluorine ponytails could change the electronic properties significantly and consequently the reactivity of fluorine reagents and catalysts. Therefore, the insertion of insulating groups before the fluorine ponytail may be necessary to decrease the strong electron-withdrawing effects [12]. It should be noted that tails "consisting of perfluoroalkyl and



L = Fluorous Solubilizing Groups

**Fig. 2-2.** The temperature-dependent fluorous-liquid/liquid biphasic concept

insulating methylene groups” were first introduced by Husted and Ahlbrecht of the 3M Company around 1953 [13].

Convincing evidence that such systems can be constructed was disclosed more than 40 years ago [14]. Researchers at the 3M Company faced the challenging question of how to develop dye pigments that can be employed for coloring perfluoroalkanes and Teflon, because ordinary oil or water soluble dyes were not compatible with perfluorinated materials, e.g., they form separate phases. Perfluoroalkylation of a Cu-phthalocyanine yielded a blue dye, which was soluble in perfluorotributyl amine and could be used to prepare a Teflon compatible ink.

It was recognized from the beginning that a fluorous biphasic catalyst system could become a one-phase system by increasing the temperature, which was originally demonstrated for fluorous biphasic hydroformylation [4, 12]. Thus, a fluorous catalyst could combine the advantages of one-phase catalysis with biphasic product separation by running the reaction at higher temperatures and separating the products at lower temperatures (Figure 2-2). The application of hydrocarbon soluble phosphine-modified rhodium catalysts for the hydroformylation of higher olefins such as decene-1 is limited by catalyst degradation during distillation of the aldehyde from the catalysts. While the use of water-soluble catalysts could provide easy separation for heavy aldehydes, the low solubility of the higher olefins in water could limit the application of aqueous catalysts. In contrast, a fluorous soluble phosphine-modified rhodium catalyst appeared very attractive for the hydroformylation of high molecular weight olefins, as their solubility is high in fluorous media and the catalyst could be separated from the product aldehydes. The facile separation of high molecular weight aldehydes was first demonstrated for the hydroformylation of decene-1 in the presence of the fluorous soluble  $\text{P}[\text{CH}_2\text{CH}_2(\text{CF}_2)_5\text{CF}_3]_3$ -modified rhodium catalyst. It was also shown that the solution structure of  $\text{HRh}(\text{CO})\{\text{P}[\text{CH}_2\text{CH}_2(\text{CF}_2)_5\text{CF}_3]_3\}_3$ , the key rhodium species in solution, in  $\text{C}_6\text{F}_{11}\text{CF}_3$  is similar to  $\text{HRh}(\text{CO})(\text{PPh}_3)_3$  in toluene and  $\text{HRh}(\text{CO})\{\text{P}(m\text{-C}_6\text{H}_4\text{SO}_3\text{Na})_3\}_3$  in water. The fluorous biphasic catalyst recovery was tested in a semicontinuous hydroformylation of decene-1 with the  $\text{Rh}/\text{P}[\text{CH}_2\text{CH}_2(\text{CF}_2)_5\text{CF}_3]_3$  catalyst. During nine consecutive reactions/separations a total turnover of more than 35 000 was achieved with a loss of 1.18 ppm of Rh/mol of undecanals. The  $\text{Rh}/\text{P}[\text{CH}_2\text{CH}_2(\text{CF}_2)_5\text{CF}_3]_3$  catalyst

was also used for the continuous hydroformylation of ethylene. The long-term (60 days) stability of the  $\text{Rh}/\text{P}[\text{CH}_2\text{CH}_2(\text{CF}_2)_5\text{CF}_3]_3$  catalyst was better than that of the  $\text{Rh}/\text{PPh}_3$  catalyst. Thus, the  $\text{Rh}/\text{P}[\text{CH}_2\text{CH}_2(\text{CF}_2)_5\text{CF}_3]_3$  catalyst was the first catalyst system that could be used for the hydroformylation of both low and high molecular weight olefins and provides facile catalyst separation for both low and high molecular weight aldehydes [12].

Another key player in fluorine chemistry has been Prof. John A. Gladysz, University of Erlangen, Germany. He was a consultant to Exxon and became familiar with the development of fluorine chemistry from the beginning. In fact, that is why I suggested that *Science* should ask him to write a short article [15] along with the first publication of the fluorine biphasic concept [4]. We have also collaborated for a number of years, work which was co-supported by Exxon and NSF. Our joint research program led to the synthesis of a fluorine analog of Wilkinson's catalyst,  $\text{ClRh}[\text{P}[\text{CH}_2\text{CH}_2(\text{CF}_2)_5\text{CF}_3]_3]_3$ , which was used as a catalyst for hydrogenation [16], hydroboration [17], and hydrosilylation [18] reactions.

As frequently happens in science, when a new direction is emerging in a given field, one consequence is that the same discovery is made independently in different laboratories practically at the same time. The application of perfluorinated polyalkyl ether soluble transition metal complexes in catalytic oligomerization of ethylene, oxidation of cyclohexene, and polymerization and telomerization of butadiene was described in the Ph.D. thesis of Vogt in 1991 [19]. Despite the potential springboard that these preliminary observations offered, no patents were filed and the first paper was only published in 1999 [20]. In addition, the thesis could not be accessed by any literature search methods (except through a personal pilgrimage to the library of the RWTH in Aachen). Cornils, one of the leading authorities on biphasic organometallic catalysis, has observed that "German theses which do not lead to publications do not become internationally known" [21]. After the first public disclosure of the fluorine biphasic concept at the NATO Advanced Research Workshop on Aqueous Organometallic Chemistry and Catalysis in Debrecen, Hungary in the fall of 1993, Cornils published a synopsis of the meeting including the fluorine biphasic concept with no mention of Vogt's thesis, indicating that it was unknown even to an established expert [22].

A liquid fluorocarbon as a solvent was first used in the separation of uranium isotopes in 1940 [23]. Although the remarkable chemical inertness, thermal stability, and non-flammability of fluorine solvents make them particularly attractive reaction media, they were used sparingly in the following half century. One of the first examples of the use of fluorine solvents in chemical reactions was the photodegradation of fluorine extracts of PCB-contaminated solid- or liquid-phase wastes [24]. The first systematic application of perfluoroalkanes and perfluorotrialkyl amines as inert media for organic reactions was published by Zhu of the 3M Company in 1993 [25].

Perfluoro-*cis*-2,3-dialkyloxaziridines are to my knowledge the first fluorine reagents, although their capability for reagent separation was not recognized at the time [26]. Interestingly, in this paper it is stated that good results could be obtained despite the fact that the reactions became two-phase systems. Perfluoro-*cis*-2,3-dialkyloxaziridines can be prepared from commercially available perfluorotrialkyl amines and can be used for mild and selective hydroxylation of unactivated tertiary C–H bonds in alkanes, as well as for oxidation of alkenes, alcohols, ethers, sulfides, and silanes. The application of the first fluorine tin reagent was reported by Prof. Dennis Curran in 1996, which exhibited similar reactivity to that of

the parent organic reagents but offered the facile separation of the product from the spent reagent [27].

Because of the extremely apolar nature of the fluorous media, the application of fluorous reagents is limited to apolar substrates; e.g., reactions of polar substrates in a fluorous biphasic mode could be too slow for practical applications. Curran recognized this limitation and developed a new protocol for the use of fluorous reagents [28]. The reaction of a polar substrate and a fluorous reagent is performed in a single liquid phase using a common solvent for both. Benzotrifluoride (BTF,  $C_6H_5CF_3$ ) has been found to have the suitable properties for several fluorous reagents. After the reaction is completed all liquids are removed in vacuum and the residue is treated with an organic-fluorous two-phase system to dissolve the product in the organic phase and the spent fluorous reagent in the fluorous phase. For reactions producing water-soluble side products a three-phase liquid system consisting of an organic solvent, water, and a fluorous solvent is used to separate simultaneously the organic products, the water soluble side products, and the spent fluorous reagent. Curran has in addition extended the application of the fluorous biphasic concept for multistep organic synthesis [28], which also provided a new approach to liquid-phase combinatorial synthesis [29]. Finally, the separation of fluorous compounds from each other and from non-fluorous components of various reaction systems was developed by Curran using fluorous silica gel as the sorbent [30]. It is important to note that Curran has been the major force in the introduction of fluorous chemistry to organic chemists – and they have been listening!

Finally, Wende and Gladysz [31] and Yamamoto et al. [32] have independently demonstrated that the temperature-dependent solubility of *solid* fluorous catalysts in liquid substrates or in conventional solvents containing the substrates could eliminate the need for fluorous solvents (Figure 2-3), an important new direction for commercial applications of fluorous chemistry.

As reflected by the contents of this handbook, *fluorous chemistry* has grown into a well-established area and provides a complementary approach to the chemistries performed in water, ionic liquids, super critical carbon dioxide, and in their various combinations. Since each chemical reaction could have its own *perfectly* designed environment, the possibility

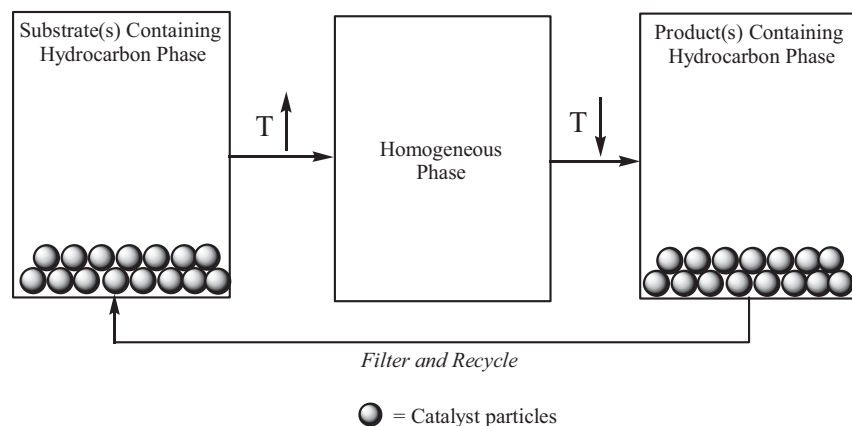


Fig. 2-3. The temperature-dependent fluorous-solid/liquid biphasic concept

of selecting from biphasic systems ranging from fluorous to aqueous systems provides a powerful portfolio for molecular designers. My association with this field, as outlined above, has been the personally most rewarding aspect of my career and I take particular enjoyment in watching the ongoing collective history that the many contributors to this handbook are helping to write.

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### 3

## Fluorous Solvents and Related Media

*J. A. Gladysz and Charlotte Emnet*

### 3.1

#### Introductory Remarks

Most applications of fluorous chemistry involve a partnership of fluorous and non-fluorous solvents. The success of these applications is often critically dependent upon the exact physical properties of both solvents. For this reason, general compendia of solvent data represent useful desk references. There are several excellent choices, and the most recent also provide some data on fluorous solvents [1]. Some general physical attributes of perfluorinated molecules are summarized in Chapter 13.2, which also contains much information on biocompatibility and medical applications.

### 3.2

#### Commercial Fluorous Solvents

As summarized in Table 3-1, numerous fluorous solvents are commercially available. Perfluorinated alkanes [2] are the most common, followed by perfluorinated dialkyl ethers and polyethers and then perfluorinated trialkyl amines. Importantly, the lone pairs in such ethers and amines are extremely low in energy. There is no residual basicity, or any other basis for appreciable intermolecular interactions. All major vendors now sell fluorous solvents. Oakwood Products, ABCR, Fluorochem, Lancaster, ACROS, and Apollo offer the largest selections.

The densities of the fluorous solvents in Table 3-1 are much greater than those of common organic solvents, including  $\text{CCl}_4$  ( $1.589 \text{ g mL}^{-1}$ ). A wide selection of boiling points is available. The *n*-perfluoroalkanes are always slightly more volatile than the corresponding *n*-alkanes, and the boiling points correlate linearly [3]. Technical solvent grades often have distinct CAS numbers and trade names, as well as lower melting points. Some of these solvents are used in the electronics industry, for example in the manufacture of printed circuits.

The most common solvent for fluorous chemistry is perfluorohexane or FC-72 (entry 1, Table 3-1). However, like “hexanes”, FC-72 is a mixture of isomers, and minor amounts of other fluorous molecules can be present [4]. For preparative chemistry this is of no consequence [4]. However, for physical measurements or mechanistic studies,  $\text{CF}_3\text{C}_6\text{F}_{11}$



Tab. 3-1. Representative commercially available fluorous solvents

Entry	Solvent	Formula	bp (°C)	mp (°C)	Density (g/mL)	Common name (trade name family)	CAS #	2003 Vendors <sup>a</sup>
1	perfluorohexane <sup>b,c</sup>	C <sub>6</sub> F <sub>14</sub>	57.1	-90	1.669	FC-72 (Fluorinert)	[355-42-0]	<i>a-e,g,h,m</i>
2	perfluoroheptane <sup>b,d</sup>	C <sub>7</sub> F <sub>16</sub>	82.4	-78	1.745	-	[335-57-9]	<i>a-d,g,h,m</i>
3	perfluorooctane(s) <sup>b,e</sup>	C <sub>8</sub> F <sub>18</sub>	103-104	-25	1.766	-	[307-34-6]	<i>a-e,g,m</i>
4	perfluoromethylcyclohexane	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub>	76.1	-37	1.787	PFCM	[355-02-2]	<i>a-e,g-i,m</i>
5	perfluoro-1,2-dimethylcyclohexane	C <sub>8</sub> F <sub>16</sub>	101.5	-56	1.867	PP3 (Flutec(R))	[306-98-9]	<i>a-d,g,m</i>
6	perfluoro-1,3-dimethylcyclohexane	C <sub>8</sub> F <sub>16</sub>	101-102	-55	1.828	-	[335-27-3]	<i>a-e,g,h,m</i>
7	perfluoro-1,3,5-trimethylcyclohexane	C <sub>9</sub> F <sub>18</sub>	125-128	-68	1.888	-	[374-76-5]	<i>a-d,m</i>
8	perfluorodecalin	C <sub>10</sub> F <sub>18</sub>	142	-10	1.908	-	[306-94-5]	<i>a-c,e,g-i,m</i>
9	1-bromoperfluorooctane	C <sub>8</sub> F <sub>17</sub> Br	142	6	1.930	-	[423-55-2]	<i>a-e,g,h</i>
10	perfluoro-2-butyltetrahydrofuran	C <sub>8</sub> F <sub>16</sub> O	99-107	-88	1.77	FC-75 (Fluorinert)	[335-36-4]	<i>a-e,h,m</i>
11	perfluoropolyether <sup>f</sup>	MW ≈ 340	57	-	1.65	HT55 (Galden)	-	<i>l</i>
12	perfluoropolyether <sup>f</sup>	MW ≈ 410	70	-	1.68	HT70 (Galden(R))	[69991-67-9]	<i>c,l,m</i>
13	perfluoropolyether <sup>f</sup>	MW ≈ 460	90	-	1.69	HT90 (Galden(R))	-	<i>c,l,m</i>
14	perfluoropolyether <sup>f</sup>	MW ≈ 580	110	-	1.72	HT110 (Galden(R))	-	<i>c,l,m</i>
15	perfluorotributylamine <sup>b,g</sup>	C <sub>12</sub> F <sub>27</sub> N	178	-	1.883	FC-43 (Fluorinert)	[311-89-7]	<i>a-e,g,h,k,m</i>
16	perfluorotripentylamine <sup>b,h</sup>	C <sub>15</sub> F <sub>33</sub> N	212-218	-	1.93	FC-70 (Fluorinert)	[338-84-1]	<i>a-e,k,m</i>
17	perfluorohexylamine	C <sub>18</sub> F <sub>39</sub> N	250-260	33	1.90	FC-71 (Fluorinert(R))	[432-08-6]	<i>a-c,m</i>

<sup>a</sup> Codes for vendors are as follows: *a* = Oakwood Products (<http://www.oakwoodchemical.com>); *b* = ABCR (<http://www.abcr.de>); *c* = Fluorochem ([http://www.fluorochem.co.uk/index2\\_ns.asp](http://www.fluorochem.co.uk/index2_ns.asp)); *d* = Lancaster (<http://www.lancastersynthesis.com>); *e* = Acros Organics (<http://www.acros.be>); *f* = 3M (<http://www.3m.com>); *g* = Aldrich (<http://www.sigmaaldrich.com/Brands/Aldrich.html>); *h* = Fluka ([http://www.sigmaaldrich.com/Brands/Fluka\\_Riedel\\_Home.html](http://www.sigmaaldrich.com/Brands/Fluka_Riedel_Home.html)); *i* = Merck (<http://pb.merck.de/servlet/PB/menu/1001723/index.html>); *j* = Oxychem (<http://www.oxychem.com>); *k* = Sigma (<http://www.sigmaaldrich.com/Brands/Sigma.html>); *l* = Solvay Solexis (<http://www.solvaysolexis.com>); *m* = Apollo Scientific Ltd. (<http://www.apolloscientific.co.uk>). <sup>b</sup> Several fluorous solvents are available in technical grades that have distinct CAS numbers and/or common names: <sup>c</sup> [86508-42-1], FC-72 [Fluorinert(R)], PP1 [Flutec(R)], *a, c, f, m*. <sup>d</sup> [86508-42-1], FC-72 [Fluorinert(R)], *a, c, f, m*. <sup>e</sup> [86508-42-1], [52623-00-4], [52923-00-4], FC-77 [Fluorinert(R)], *a, c, e, f, h, k, m*. <sup>f</sup> General formula CF<sub>3</sub>[(OCF<sub>2</sub>)<sub>2</sub>]<sub>*m*</sub>(OCF<sub>2</sub>)<sub>*n*</sub>, [OCF<sub>3</sub>], <sup>g</sup> [86508-42-1], FC-43 [Fluorinert(R)], *a, c, f, m*. <sup>h</sup> [86508-42-1], FC-70 [Fluorinert(R)], *f, m*.

[perfluoro(methylcyclohexane) or PFMC], a more expensive but homogeneous solvent, is often favored (entry 4). This ensures a higher level of reproducibility.

Most commercial perfluoropolyethers (e.g., entries 11–14) [5] contain multiple stereocenters, and are therefore mixtures of diastereomers. Perfluorodecalin is sometimes described as a mixture of *cis/trans* diastereomers, a potential that also exists for the polymethylated cyclohexanes in entries 5–7, and at other times is implied to be the more stable *trans* isomer. Substituted perfluorodecalins as well as higher homologs with additional fused rings are similarly available (not listed).

Brominated organic solvents are seldom employed in organic synthesis, but 1-bromoperfluorooctane (entry 9, Table 3-1) is commonly applied in fluororous chemistry. The availability of this compound derives in part from its use in artificial blood (e.g., *Oxygent*<sup>TM</sup>, a product of the Alliance Pharmaceutical Company) [6]. There are also ongoing efforts to develop and bring new fluororous solvents to the market.

### 3.3

#### Related Solvents and Media

##### 3.3.1

##### Amphiphilic or Hybrid Solvents

Some solvents are able to dissolve appreciable quantities of both fluororous and non-fluororous solutes, and can hence be termed “hybrid”, “universal” or “amphiphilic”. The most familiar example is  $\text{CF}_3\text{C}_6\text{H}_5$ , which is known by a variety of names such as (trifluoromethyl)-benzene,  $\alpha,\alpha,\alpha$ -trifluorotoluene, and benzotrifluoride (BTF) [7]. This solvent, which has convenient melting and boiling points of  $-29$  and  $102^\circ\text{C}$ , is not fluororous according to the definition given in Chapter 1. Another example is the ether  $\text{CF}_3(\text{CF}_2)_5\text{CH}_2\text{CH}_2\text{OCH}(\text{CH}_3)\text{CH}_2\text{CH}(\text{CH}_3)_2$  (F-626) [8], mp/bp  $< -78/214^\circ\text{C}$ , which contains a fluororous segment. Such solvents or additives offer unique possibilities for certain types of processes and/or workups, as detailed in Chapter 4.

##### 3.3.2

##### Fluororous Ionic Liquids

The fluororous ionic liquids shown in Figure 3-1 have recently been reported [9]. Solvents **1a–d** act as surfactants in conventional ionic liquids, facilitating their emulsification with fluoroalkanes. Solvent **2** exhibits a polarity comparable to those of acetone and diethyl ether, is highly miscible with apolar solvents such as alkenes, and resembles fluororous solvents in its phase behavior with organic solvents [9c].

##### 3.3.3

##### “Faux Fluororous” Solvents

Certain solvents are often mistakenly assumed to be fluororous, but are not. Of these, the most important are perfluoroarenes such as hexafluorobenzene. The arene  $\pi$  cloud and  $\text{sp}^2$  carbon–fluorine bonds lead to significant intermolecular bond dipole, induced dipole,

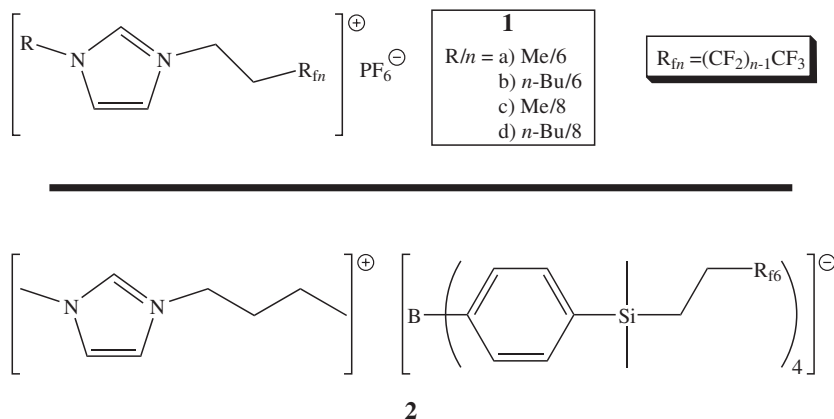


Fig. 3-1. Fluorous ionic liquids [9]

and quadrupolar interactions with non-fluorous molecules [10, 11]. However, such solvents can exhibit amphiphilic properties. Quantitative polarity data are provided in the following section.

#### 3.3.4

##### Fluorous Greases

Another possible medium for recycling fluorinated materials is a low-melting fluorinated solid or grease. There is an extensive technical literature of high-performance lubricants containing only fluorine, oxygen, and saturated carbon. These have long-term operating ranges of >300 °C under extreme conditions, and are extensively applied in the aerospace, automotive, semiconductor, and paper/textile industries. For interested researchers, the Krytox<sup>®</sup> family of products from DuPont constitutes a good starting point [12].

#### 3.3.5

##### Bonded Fluorous Phases

Chapter 7 will detail the use of fluorinated silica gel for preparative and analytical separations. However, solid supports that carry bonded fluorinated moieties represent attractive and fluorinated-solvent-free media for recycling. Several recently published protocols are further described in Chapters 10.8.2.4, and 10.8.2.5 [13, 14].

#### 3.4

##### Polarities of Fluorous Solvents

Perfluorinated solvents exhibit extremely low polarities. There are many ways to quantify polarity, ranging from familiar parameters such as dielectric constant and dipole moment to kinetic, equilibrium, and solvatochromic measurements. As analyzed elsewhere [3, 15],

one of the best scales involves the shift of the absorption maximum of a perfluoroheptyl-substituted dye. This models the ability of a solvent to solvate or complex a solute or transition state particularly well. The dye was optimized to be soluble in both fluorocarbons and very polar solvents such as DMSO. Over 100 solvents were assayed [15], and some of the resulting “Spectral Polarity Index” or  $P_S$  values are given in Table 3-2.

The data in Table 3-2 confirm that perfluoroalkanes are much less polar than the corresponding alkanes (first five entries in each column;  $P_S$  0.00–0.99 vs. 2.56–4.07). They also show that perfluorinated trialkylamines exhibit similar polarities, but those of fluorinated arenes are higher. Nonetheless, hexafluorobenzene remains less polar than benzene ( $P_S$  4.53 vs. 6.95). Interestingly, highly fluorinated alcohols such as  $\text{CF}_3\text{CF}_2\text{CF}_2\text{CH}_2\text{OH}$  and  $(\text{CF}_3)_2\text{CHOH}$  exhibit  $P_S$  values higher than those of similar non-fluorinated alcohols (9.76 and 11.08 vs. 7.62 and 7.85). This has been attributed to strong hydrogen bonding [16]. Applications of the latter solvent are highlighted in Chapter 10.17

### 3.5

#### Solubilities of Solutes in Fluorous Solvents

##### 3.5.1

##### General Aspects

It is important to distinguish between the *absolute* solubility of a solute, which is defined by a  $K_{sp}$  value (solubility constant) or similar parameter, and the *relative* solubility, which reflects the equilibrium distribution of the solute between two solvents and is defined by a partition coefficient. Absolute solubilities are treated in this section, and relative solubilities in Chapter 6. Theoretical approaches to predicting both types of solubilities are also discussed in Chapter 6 [17].

Solubilities in fluorous solvents are largely determined by two parameters: solute polarity and size. The first is an extension of the familiar “like dissolves like” paradigm. The second is uniquely important to perfluorinated solvents, which because of low intermolecular forces have large cavities (free volumes) that can accommodate small molecules. There is an extensive literature involving gas solubilities in fluorocarbons. Importantly, the data correlate with the isothermal compressibility of the solvent [18], supporting the cavity-based solubility model.

Unfortunately, quantitative solubility data for the types of solutes that would be of greatest interest to fluorous chemists, such as representative monofunctional fluorous and non-fluorous molecules, are scarce. There is some literature on solubilities of small non-fluorous molecules [19]. For example, a solution of perfluoroheptane that is saturated with octane contains 11.2 mol% octane at 27.5 °C, 31.8 mol% octane at 60.0 °C, and 45.1 mol% octane at 65.8 °C [19e]. This nicely documents the strong temperature dependences of solubilities in fluorous phases. The smaller hydrocarbon heptane is approximately twice as soluble as octane (21.4 mol%, 27.3 °C), in accord with the above generalization. Chloroform is similar (22.4 mol%, 24.6 °C). The solubilities of several fluorous arylphosphines in  $\text{CF}_3\text{C}_6\text{F}_{11}$  have been measured [20], and there is a growing body of computational data [17].

It should be emphasized that some fluorous compounds are poorly soluble in fluorous solvents at room temperature. This is most often observed with, but not limited to,

Tab. 3-2. Solvent spectral polarity index ( $P_S$ ) for fluorinated and non-fluorinated solvents [15]

Solvent	Formula	$P_S$	Solvent	Formula	$P_S$
perfluoromethylcyclohexane (PFMC)	$\text{CF}_3\text{C}_6\text{F}_{11}$	0.46	methylcyclohexane	$\text{CH}_3\text{C}_6\text{H}_{11}$	3.34
perfluoro-1,3-dimethylcyclohexane	$\text{C}_8\text{F}_{16}$	0.58	1,3-dimethylcyclohexane	$\text{C}_8\text{H}_{16}$	3.31
perfluorohexane	$\text{C}_6\text{F}_{14}$	0.00	<i>n</i> -hexane	$\text{C}_6\text{H}_{14}$	2.56
perfluorooctane	$\text{C}_8\text{F}_{18}$	0.55	<i>n</i> -octane	$\text{C}_8\text{H}_{18}$	2.86
perfluorodecalin	$\text{C}_{10}\text{F}_{18}$	0.99	decalin	$\text{C}_{10}\text{H}_{18}$	4.07
perfluorotributylamine	$(\text{C}_4\text{F}_9)_3\text{N}$	0.68	tri- <i>n</i> -butylamine	$(\text{C}_4\text{H}_9)_3\text{N}$	3.93
hexafluorobenzene	$\text{C}_6\text{F}_6$	4.53	benzene	$\text{C}_6\text{H}_6$	6.95
$\alpha,\alpha,\alpha$ -trifluorotoluene (BTF)	$\text{CF}_3\text{C}_6\text{H}_5$	7.03	toluene	$\text{CH}_3\text{C}_6\text{H}_5$	6.58
2,2,2-trifluoroethyl trifluoroacetate	$\text{CF}_3\text{CO}_2\text{CH}_2\text{CF}_3$	7.74	ethyl acetate	$\text{CH}_3\text{CO}_2\text{CH}_2\text{CH}_3$	6.96
1 <i>H</i> ,1 <i>H</i> -perfluoro-1-butanol	$\text{CF}_3(\text{CF}_2)_2\text{CH}_2\text{OH}$	9.76	1-butanol	$\text{CH}_3(\text{CH}_2)_3\text{CH}_2\text{OH}$	7.62
1,1,1,3,3,3-hexafluoroisopropanol	$(\text{CF}_3)_2\text{CHOH}$	11.08	2-propanol	$(\text{CH}_3)_2\text{CHOH}$	7.85

molecules with longer  $R_{fn}$  segments ( $n > 8$ ). Such species are even less soluble in organic solvents. Representative examples include the fluorous sulfoxides  $O=S(CH_2)_mR_{f8}$  ( $m = 2, 3$ ) [21], and certain fluorous palladacycles [22]. Also, solubilities in all solvents dramatically decrease in the series of fluorous phosphines  $P[(CH_2)_2R_{f6}]_3$ ,  $P[(CH_2)_2R_{f8}]_3$ , and  $P[(CH_2)_2R_{f10}]_3$  [23, 24].

One way to conceptualize this phenomenon is to view the ponytails as short pieces of teflon, which does not dissolve in any common fluorous or non-fluorous solvent. As the ponytails become longer, many physical properties of the molecule approach those of teflon. However, just as the miscibilities of fluorous liquid phases and organic liquid phases are highly temperature dependent, so are the solubilities of fluorous solids in fluorous or non-fluorous liquid phases highly temperature dependent [24]. Hence, much higher solubilities can be achieved at elevated temperatures. This phenomenon can be used to conduct homogeneous reactions at elevated temperatures, with catalyst or reagent recovery by solid/liquid phase separation at lower temperatures [24–26].

### 3.5.2

#### Gas Solubilities

Some specific data on gas solubilities are provided in Table 3-3. Literature values are normally compiled as mole fractions, a unit not commonly employed by preparative chemists or kineticists. These constitute the origin of the widespread statement that “gases are much more soluble in fluorocarbons than other solvents”. This generalization is indeed appropriate with reference to water, where a strong hydrogen bonding network must be disrupted, but is much less so for organic solvents [27].

As shown in Table 3-3, the solubilities of  $O_2$  in the fluorous solvent  $CF_3C_6F_{11}$  and the organic solvent THF differ by a factor of five when expressed as mol fractions (0.00456

**Tab. 3-3.** Comparison of solubility data for  $O_2$  and  $H_2$  in  $CF_3C_6F_{11}$  and THF (25 °C, 1 atm)

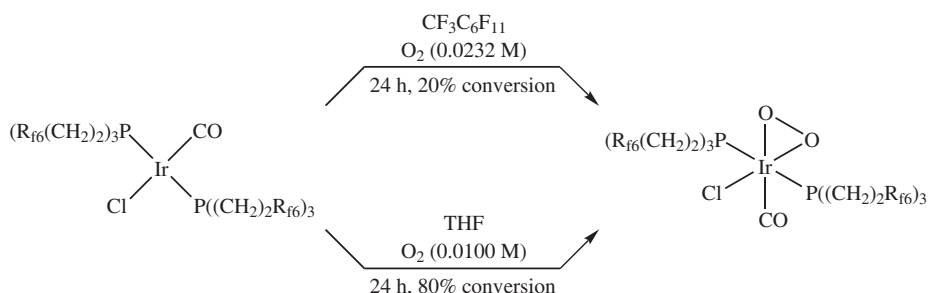
<b>Solubility [solvent property]</b>	<b><math>CF_3C_6F_{11}</math></b>	<b>THF</b>	<b>Difference</b>
$O_2$ (mol fraction)	0.00456 <sup>a</sup>	0.000816 <sup>a</sup>	factor of ~5
$O_2$ (mol ratio)	0.00453	0.000815	factor of ~5
[mol wt (g/mol)]	[350.05]	[72.11]	[factor of ~5]
$O_2$ (mol/kg)	0.0129	0.0112	~equal
[density (g/mL)]	[1.787]	[0.889]	[factor of ~2]
$O_2$ solubility (mol/L)	0.0232	0.0100	factor of ~2
$H_2$ (mol fraction)	0.0012 <sup>b</sup>	0.000274 <sup>c</sup>	factor of ~4.5
$H_2$ (mol ratio)	0.00119	0.000274	factor of ~4.5
$H_2$ (mol/kg)	0.0034	0.0038	~equal
$H_2$ (mol/L)	0.0061	0.0034	factor of ~2

<sup>a</sup> *IUPAC Solubility Data Series*, Battino, R., Ed.; Pergamon: New York, 1981, Volume 7, pp. 301 and 320. <sup>b</sup> Patrick, C. R. In *Preparation, Properties, and Industrial Applications of Organofluorine Compounds*, Banks, R. E., Ed.; Ellis Horwood: New York, 1982, p. 333. <sup>c</sup> *IUPAC Solubility Data Series*, Young, C. L., Ed.; Pergamon: New York, 1981, Volume 5/6, p. 219.

vs. 0.000816). Since the mole fractions are so small, the mol ratios are essentially identical (0.00453 vs. 0.000815). When the denominators of the mol ratios are replaced by the molecular weights of the solvents, molal concentrations can be calculated (mol gas/kg solvent). Importantly, the molecular weights of fluorocarbons tend to be higher than those of organic solvents, and those of  $\text{CF}_3\text{C}_6\text{F}_{11}$  and THF differ by a factor of ca. five. Substitution gives  $(0.00453 \text{ mol O}_2)/(350.05 \text{ g CF}_3\text{C}_6\text{F}_{11})$  and  $(0.000815 \text{ mol O}_2)/(72.11 \text{ g THF})$ , or nearly equal molal concentrations (Table 3-3).

The densities of fluorocarbons are also higher than those of common organic solvents, and  $\text{CF}_3\text{C}_6\text{F}_{11}$  is twice as dense as THF. This translates the preceding concentrations into  $(0.00453 \text{ mol O}_2)/(195.9 \text{ mL CF}_3\text{C}_6\text{F}_{11})$  and  $(0.000815 \text{ mol O}_2)/(81.1 \text{ mL THF})$ , resulting in molarities that differ by a factor of slightly more than 2 (Table 3-3). The solubility of  $\text{H}_2$  in  $\text{CF}_3\text{C}_6\text{F}_{11}$  and THF is slightly lower (0.0012 vs. 0.000274 as mol fractions). However, the relationships between molal and molar concentrations turn out to be nearly the same as with  $\text{O}_2$  (Table 3-3).

Understandably, fluorous solvents are often proposed as good media for reactions of gases. However, the above data clearly show that relative to organic solvents, any solubility-based rate accelerations must by necessity be modest. Furthermore, the addition of oxygen to the square planar iridium complex in Scheme 3-1 is much slower in  $\text{CF}_3\text{C}_6\text{F}_{11}$  than THF, despite a 2.3-fold higher oxygen concentration in the former [28]. The transition state of the rate determining step is thought to be more polar than the reactants – a very common situation in chemical reactions. This creates a rate-constant-based disadvantage for the fluorous solvent that more than counteracts the solubility-based advantage. The analogous addition of  $\text{H}_2$  to iridium is also slower in  $\text{CF}_3\text{C}_6\text{F}_{11}$  than THF.



**Scheme 3-1.** Slower reaction of oxygen in a fluorous solvent, despite a higher concentration [28]

### 3.6

#### Fluorous/Non-fluorous Solvent Miscibilities

Although fluorous chemistry can be conducted under heterogeneous liquid/liquid biphasic conditions, homogeneous monophasic conditions as in Figure 1-1 will normally give faster reactions. Towards this end, it is important to know the temperatures at which various fluorous and non-fluorous solvents become miscible. Literature data and some qualitative observations of the authors' coworkers are summarized in Table 3-4 [19c, 29, 30].

Tab. 3-4. Fluorous solvent miscibility data<sup>a</sup>

<b>Solvent system</b>	<b>Two phases at (°C)</b>	<b>One phase at (°C)</b>	<b>Reference</b>
CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> /CCl <sub>4</sub>	RT	≥26.7 <sup>b</sup>	19c
CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> /CHCl <sub>3</sub>	RT	≥50.1 <sup>b</sup>	19c
CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> /C <sub>6</sub> H <sub>6</sub>	RT	≥84.9 <sup>b</sup>	19c
CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> /CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	RT	≥88.6 <sup>b</sup>	19c
CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> /ClC <sub>6</sub> H <sub>5</sub>	RT	≥126.7 <sup>b</sup>	19c
C <sub>8</sub> F <sub>17</sub> Br/CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	RT	50–60 <sup>c</sup>	30a
C <sub>10</sub> F <sub>18</sub> <sup>d</sup> /CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	RT	64 <sup>c</sup>	30a
CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> /hexane/CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub> <sup>e</sup>	RT	36.5 <sup>c</sup>	29
CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> /hexane	0	RT <sup>c</sup>	30b
CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> /pentane	–16	RT <sup>c</sup>	30b
CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> /ether	0	RT <sup>c</sup>	30b

<sup>a</sup> All data for a 1:1 volume ratio unless otherwise stated. <sup>b</sup> Consolute temperature. <sup>c</sup> Experimental observation; not a consolute temperature.

<sup>d</sup> Perfluorodecalin. <sup>e</sup> Volume ratio 3:3:1.

With binary solvent systems, it is common to determine a “consolute” or “upper critical solution” temperature, above which phase separation cannot occur, whatever the composition [31]. As would be intuitively expected, consolute temperatures are usually found for ca. 50:50 (mol/mol) mixtures. Representative consolute temperatures are given in Table 3-4. However, as is evident from the full phase diagrams, solvents can become miscible in other proportions at much lower temperatures. For example, the phase diagram for toluene and the fluorous ionic liquid **2** [9c] is given in Figure 3-2. This system has a consolute temperature of 62 °C, but one-phase conditions can often be achieved at 55 °C or lower.

Importantly, consolute temperatures can be strongly affected by solutes or dissolved species, including impurities. It is well known that homogeneous mixtures of aqueous and certain organic solvents can often be induced to “salt out” or phase separate by adding a suitable material. Thus, researchers quickly learn that Table 3-4 provides at best a rough guide to a property that is a function of many parameters. Lighter organic solvents such as pentane and ether are the most likely to give one phase reaction conditions at room temperature.

The mixing of two liquid phases is of course entropically favorable. From an enthalpic standpoint, intermolecular attractive interactions will always be greater within the pure non-fluorous phase (which has a much greater polarity) than the pure fluorous phase (which has a much lower polarity). Upon mixing, the stronger intermolecular interactions in the former will be markedly diluted, and the intermolecular interactions felt by the fluorous molecules will only slightly increase. Hence, no enthalpic gain is to be expected. The Hildebrand-Scatchard Theory, alternatively termed Regular Solution Theory, provides a quantitative framework for this qualitative picture [32]. In principle, the consolute temperature can be related to the Hildebrand solubility parameters of the two liquids.

One aspect of this situation deserves emphasis: despite the “like dissolves like” paradigm, it is misleading to view fluorous solvents as capable of highly attractive or repulsive intermolecular interactions. Rather, they facilitate what might be viewed as a “molecular



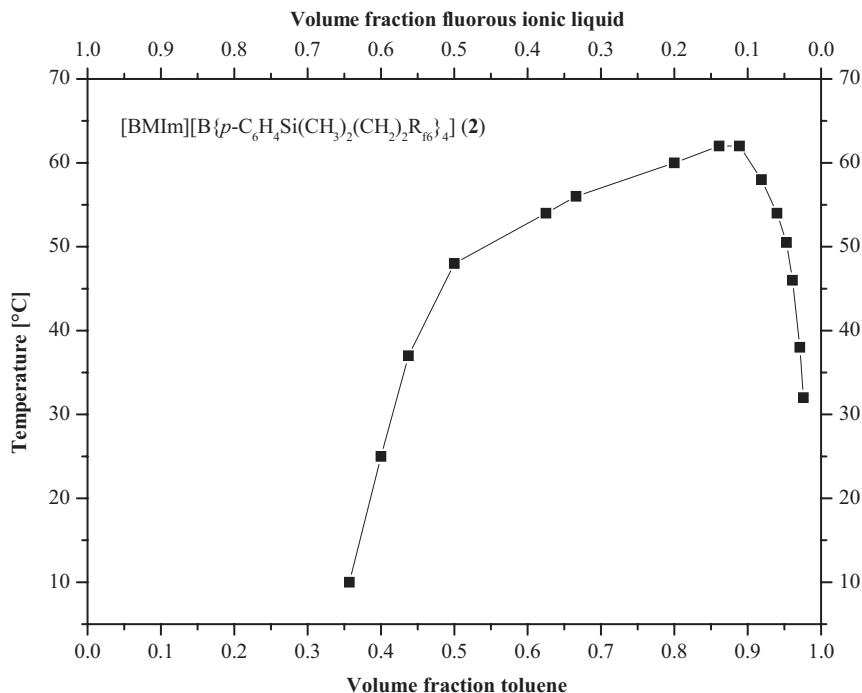


Fig. 3-2. Temperatures at which toluene and the fluorinated ionic liquid **2** (Fig. 3.1) become miscible

xenophobia” – the separation of non-fluorous molecules capable of stronger intermolecular interactions from fluorous molecules capable of only feeble ones.

Molecules from both phases of a liquid/liquid biphasic system are commonly found in each phase. This is termed solvent leaching. One familiar example is ether/water, where drying agents are needed to render the ether layer anhydrous after separating the aqueous layer. Also, the phase diagram in Figure 3-2 does not extend across the entire  $x$ -axis because small amounts of the fluorinated ionic liquid **2** remain completely dissolved in the non-fluorous toluene solvent at room temperature ( $\leq 2\%$  by volume), and a rather sizeable amount of toluene remains dissolved in **2** (ca. 35% by volume at 10 °C).

In the specific case of toluene/ $\text{CF}_3\text{C}_6\text{F}_{11}$  at 25 °C (50:50 v/v), the authors' coworkers have measured ratios of 98.4:1.6 (molar), 94.2:5.8 (mass), and 97.1:2.9 (volume) in the upper organic layer, and 3.8:96.2, 1.0:99.0, and 2.0:98.0 in the lower fluorous layer [33]. Thus, some leaching of the fluorous solvent into the non-fluorous solvent occurs under the conditions of Figure 1-1. Solvent leaching represents an intrinsic disadvantage of liquid/liquid biphasic recovery protocols. Although engineering solutions exist, this provides an impetus for alternative fluorous recovery protocols as described in Chapter 4.

Interestingly, it has recently been shown that  $\text{CO}_2$  pressure can function as a “miscibility switch” for fluorous and organic solvents [34]. This may, for certain applications, have advantages over temperature, such as with thermally labile substrates or catalysts. The compatibility of  $\text{CO}_2$  with both fluorinated solutes and organic solvents is well known, and its

**Tab. 3-5.** CO<sub>2</sub> Pressures at which 1:1 volumes of perfluoro-hexane and various organic solvents mix at 25 °C [34]

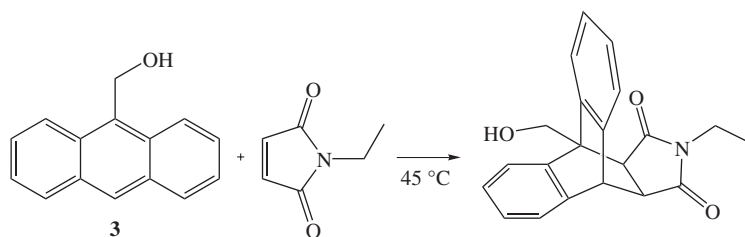
<i>Organic solvent</i>	<i>Miscibility pressure (bar)</i>
ethyl acetate	16.3
THF	18.8
chloroform	19.4
acetone	21.9
cyclohexane	26.3
propionic acid	27.5
acetic acid	27.5
toluene	32.5
decane	36.3
acetonitrile	40.0
DMF	44.4
nitromethane	44.4
ethanol	44.4
methanol	45.6
decahydronaphthalene	53.8

role is thought to be essentially that of a cosolvent. The pressures necessary to mix 1:1 volumes of perfluorohexane and various organic solvents are summarized in Table 3-5. Strongly associating solvents, such as ethanol and methanol, have some of the highest miscibility pressures. Acetic and propionic acid, which form dimers in solution, have lower miscibility pressures. Additional trends have been rationalized by the investigators, and other fluorous solvents gave similar data.

### 3.7 Special Reactivity Phenomena in Fluorous Solvents

As shown in Scheme 3-1, the low polarities of fluorous solvents can lead to lower reactivities. To balance the picture, it would seem appropriate to close this chapter with a counterexample that illustrates some of the physical principles discussed above [35]. Diels-Alder reactions have negative volumes of activation. Rates are often dramatically accelerated in aqueous relative to organic media, partly due to hydrophobic interactions. Analogous fluorophobic interactions might provide similar driving forces, and an impressive effect has been found for the cycloaddition of 9-methoxyanthracene (**3**) in Scheme 3-2. Rate constants were determined in several non-fluorous solvents, as well as C<sub>6</sub>F<sub>14</sub> and FC-75 to which a small amount of isooctane had been added (2% v/v) to solubilize the educts.

As summarized in Scheme 3-2, cycloadditions in C<sub>6</sub>F<sub>14</sub> and FC-75 are 50–42 times faster than in acetonitrile, and 6–7 times faster than in the most favorable organic solvents (CF<sub>3</sub>CH<sub>2</sub>OH, *n*-hexane). Cycloadditions are still faster in water, but this can be attributed to additional hydrogen-bond stabilization of the transition state. Importantly, **3** (the more fluorophobic educt) exhibits the lowest solubilities in C<sub>6</sub>F<sub>14</sub>, FC-75, and water. It can be computed that roughly 25% of the surface area of **3** is removed from the solvent in the



Solvent	$k_{rel}$ (45 °C) <sup>a</sup>	Saturation solubility, [3] (mM) <sup>b</sup>
C <sub>6</sub> F <sub>14</sub>	49.5	<0.005
FC-75	42.2	<0.005
<i>n</i> -C <sub>6</sub> H <sub>14</sub>	7.2	1.24 ± 0.1
( <i>n</i> -C <sub>4</sub> H <sub>9</sub> ) <sub>2</sub> O	2.3	20.9 ± 0.5
C <sub>6</sub> F <sub>6</sub>	1.4	11.22 ± 0.4
CH <sub>3</sub> CN	1.0	29.5 ± 0.7
CH <sub>3</sub> OH	3.1	29.9 ± 1.3
CF <sub>3</sub> CH <sub>2</sub> OH	7.8	18.1 ± 1.9
H <sub>2</sub> O	206	0.027 ± 0.005

<sup>a</sup> Ratios of second order rate constants. <sup>b</sup> 25 °C

**Scheme 3-2.** Acceleration of a cycloaddition in fluorous solvents [35]

transition state. Hence, the chemical potential of the transition state is raised to a lesser extent in fluorous and aqueous media. Faster rates result, and there is a parabolic dependence of the logarithm of the rate constant on the Hildebrand solubility parameter.

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## 4

## Strategies for the Recovery of Fluorous Catalysts and Reagents: Design and Evaluation

*J. A. Gladysz and Rosenildo Corrêa da Costa*

## 4.1

### Introduction; Basic Recycling Concepts

This chapter summarizes various approaches to recovering and recycling fluorous catalysts and reagents. A “process chemistry” standpoint is emphasized, as opposed to a “discovery chemistry” standpoint, where the rapid screening of a library of fluorous catalysts might be a goal. In addition, methods by which catalyst recovery can be quantified are analyzed. For exploratory work on recyclable catalysts and reagents to be meaningful, some type of recovery data are essential. Too frequently, only product yields are provided, which can be very misleading as exemplified below.

Chemists often only loosely distinguish between a catalyst precursor and the active catalyst. The former is introduced at the beginning of a reaction, and one or more steps are often needed to enter the catalytic cycle. This is particularly true for transition metal-based catalysts, for which initial ligand dissociation would be typical. Some catalyst precursors exhibit induction periods. This generally reflects some fundamental and irreversible change that must occur before entering the cycle. Regardless, *it is always the catalyst rest state that is being recycled*. Only in certain cases, such as for some simple Brønsted or Lewis acid/base catalysts, will this be identical with the catalyst precursor.

Thus, any property being exploited for catalyst recovery must *be associated with the rest state*. This can make for a “moving target”. Just like an equilibrium mixture of keto/enol tautomers, catalysts may have a distribution of rest states. Furthermore, the rest state present after the limiting reactant has been consumed, such as in a batch reactor, may be different from the rest state present in a continuous reactor. Thus, the partition coefficient, solubility, or other key property of the catalyst precursor may be substantially different from that of the species being recovered. Accordingly, rational design can carry an investigator only so far, and intuition and luck play intrinsic roles.

The situation is analogous but experimentally simpler for recoverable reagents. Here, the properties of the spent reagent or coproduct are critical to recycling. In most cases, these can be measured directly. Since a spent reagent or coproduct would be recovered analogously to a catalyst, most of the examples in the following sections involve catalysts.

## 4.2

### Fluorous/Non-Fluorous Liquid/Liquid Biphase Catalysis

This protocol, introduced in Chapter 1 and Figure 1-1 [1], is represented in slightly expanded form in Figure 4-1, sequence A. The non-fluorous solvent is nearly always an organic solvent. Reaction can be conducted at the high-temperature one-phase limit (sequence A-I), or if sufficiently rapid, at the lower temperature two-phase limit (sequence A-II). In the early days of fluorous chemistry, it was not uncommon for researchers to design for the former, only to find that reactions were rapid below the mixing temperature of the solvents [2].

Fluorous/non-fluorous liquid/liquid biphase catalysis has also been used in an inverse sense. In this case a non-fluorous catalyst is employed to effect conversions of molecules with high fluorous phase affinities [3]. The catalyst is then recovered from the upper organic layer, and the products from the lower fluorous layer. In either variant, the use of CO<sub>2</sub> pressure as a non-thermal “miscibility switch” (Chapter 3.6 and Table 3-5) [4] is certain to see use in the future. In all cases, some knowledge of the partition coefficients is necessary to optimize product isolation and catalyst recovery.

## 4.3

### Fluorous Catalysis in Amphiphilic or Hybrid Solvents

As described in Chapter 3, there are a few amphiphilic solvents that can dissolve appreciable quantities of both fluorous and organic solutes. In these cases, reactions can be run under homogeneous, one-solvent conditions as shown in Figure 4-1, sequence B. However, additional manipulations are required to effect catalyst/product separation. One approach is to remove the amphiphilic solvent and add an organic or fluorous solvent to extract the product or catalyst (sequences B-1 and B-2). In many cases, the direct addition of an organic and a fluorous solvent to the reaction mixture will give a biphasic system that can be worked up as in sequence A.

The fluorous tin hydride  $\text{HSn}[(\text{CH}_2)_2\text{R}_{\text{f}6}]_3$  has been used to showcase these protocols [5]. Reactions with adamantyl bromide in  $\text{CF}_3\text{C}_6\text{H}_5$  give adamantane and the tin bromide  $\text{BrSn}[(\text{CH}_2)_2\text{R}_{\text{f}6}]_3$ , which is easily recovered and recycled. A catalytic variant that uses  $\text{NaCNBH}_3$  and the cosolvent *t*-BuOH has been developed. Not all of the  $\text{NaCNBH}_3$  dissolves, but the reaction mixture becomes homogeneous and a triphasic aqueous/ $\text{CH}_2\text{Cl}_2$ / $\text{CF}_3\text{C}_6\text{F}_{11}$  workup efficiently separates the inorganic products, adamantane, and fluorous tin hydride catalyst.

## 4.4

### Fluorous Catalysis Without Non-Fluorous Solvents

There is intense current interest in reducing and/or eliminating the need for reaction solvents. In this context, several variations on sequence A of Figure 4-1 deserve emphasizing. As shown in sequence C, the non-fluorous solvent can be omitted in the case of liquid

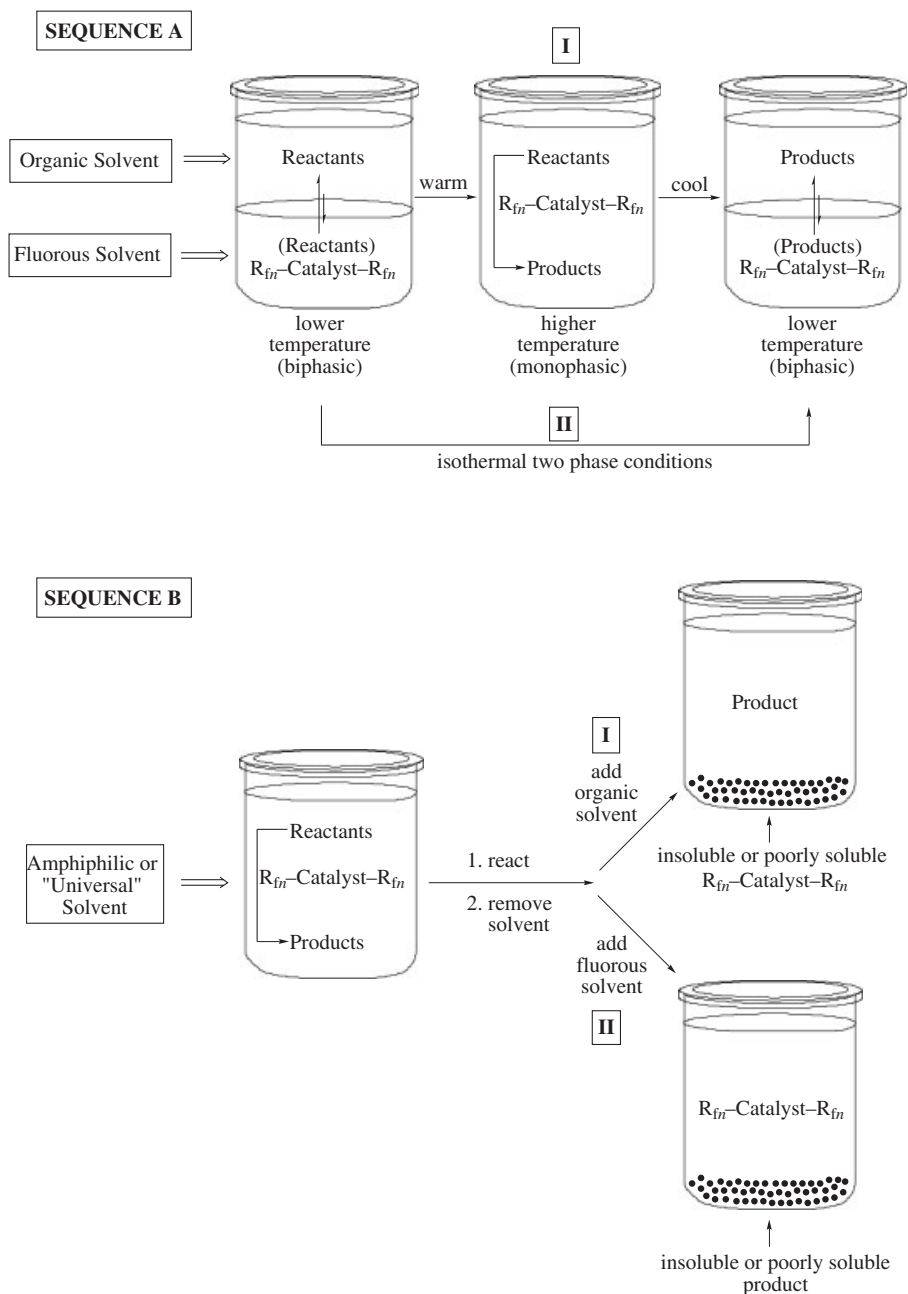


Fig. 4-1. Strategies for the recovery of fluorous catalysts  $R_{fn}$ -catalyst- $R_{fn}$

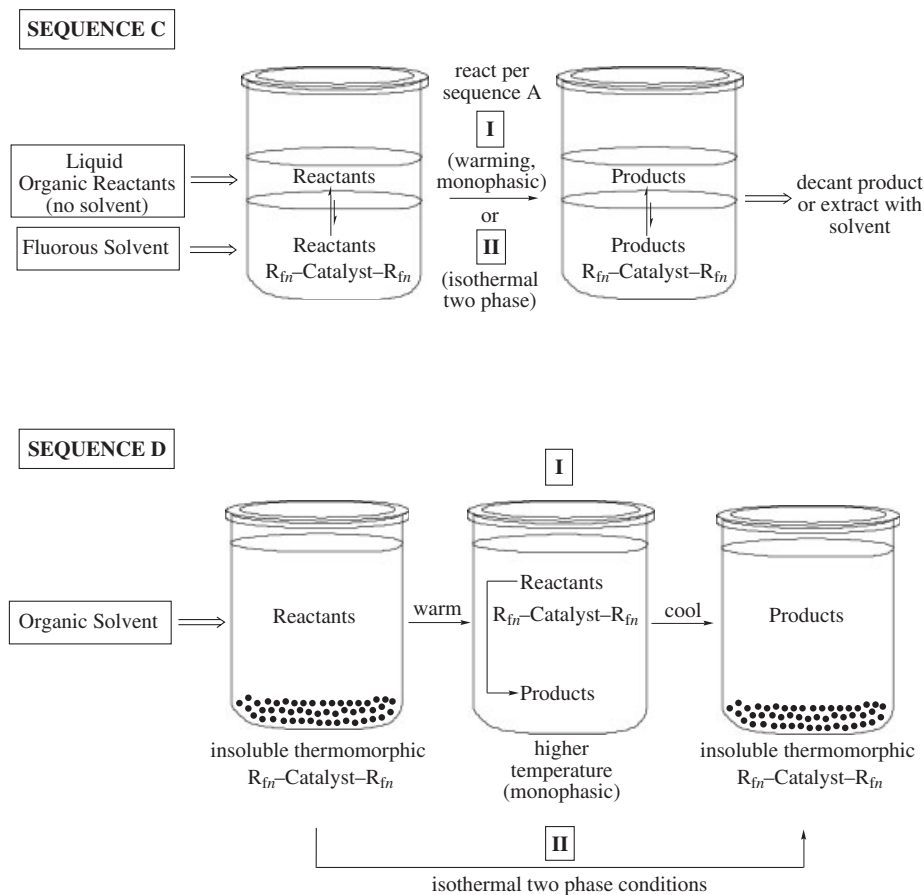


Fig. 4-1 (continued)

reactants and products. The product is simply decanted or removed by syringe. Traces of product that adhere to or remain dissolved in the fluororous phase can be carried through subsequent cycles. In cases where an exact yield for each cycle is required, an organic solvent can be added to extract the residual product.

Photographs of a specific example, an alkene hydroboration catalyzed by the fluororous rhodium complex  $\text{ClRh}\{\text{P}[(\text{CH}_2)_2\text{R}_{f6}]_3\}_3$  [**1**;  $\text{R}_{f6} = (\text{CF}_2)_5\text{CF}_3$ ] and conducted under two-phase conditions, are shown in Figure 4-2 [2]. This catalyst system exhibits an induction period on the first cycle, but not on subsequent cycles [6]. ICP-AES (inductively coupled plasma atomic emission spectrometry) measurements indicate rhodium losses of 0.4% per cycle, or (under the conditions employed) 4.5 rhodium atoms per million product molecules. For the still more fluorophilic catalyst with  $\text{R}_{f8}$  ponytails, rhodium losses decrease to 0.2% per cycle or 2.2 rhodium atoms per million product molecules.



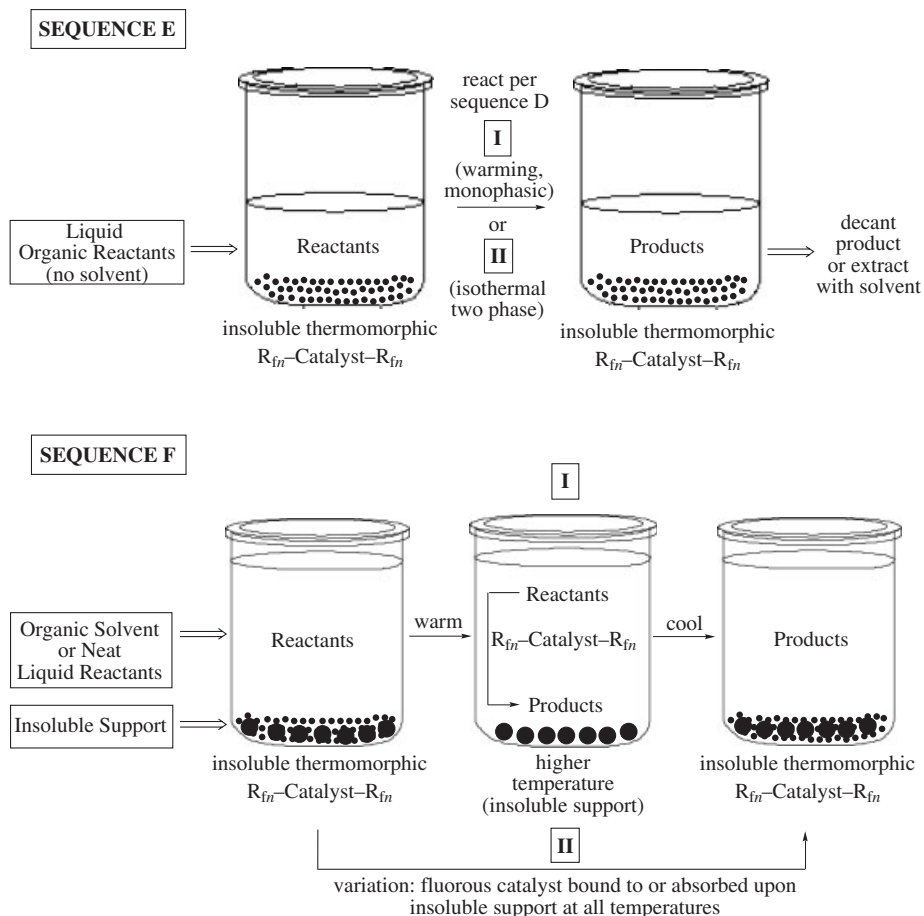


Fig. 4-1 (continued)

## 4.5

### Fluorous Catalysis Without Fluorous Solvents

#### 4.5.1

##### Thermomorphic Catalysts

An obvious counterpart to sequence C in Figure 4-1 is to eliminate the fluorous solvent, which is commonly much more expensive than the non-fluorous solvent. Many fluorous compounds with  $R_{f8}$  and  $R_{f10}$  ponytails are low melting solids or waxes with little or no solubilities in non-fluorous solvents at room temperature. Accordingly, it was proposed that the same factors that give rise to highly temperature dependent fluorous/organic liquid/liquid phase miscibilities might also give rise to highly temperature dependent fluorous/organic solid/liquid phase miscibilities [7]. A catalyst or reagent with a highly temperature-dependent property, such as solubility, is said to be *thermomorphic*. However, above the

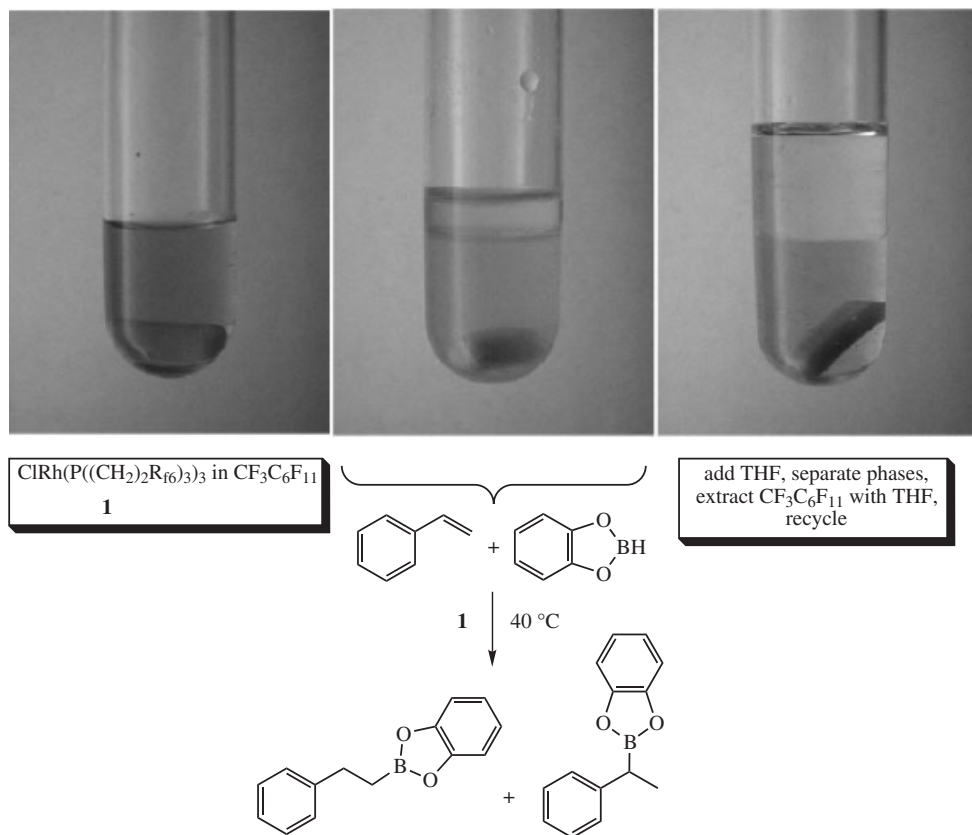
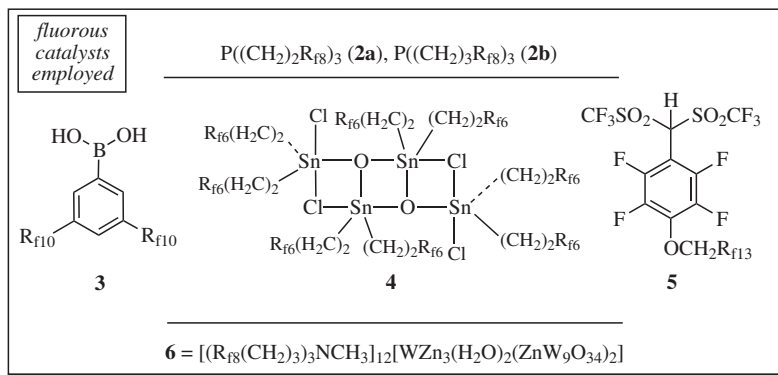


Fig. 4-2. A rhodium-catalyzed hydroboration conducted according to sequence C-II of Figure 4-1 [2]

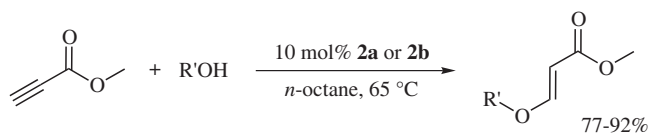
melting point of the catalyst or reagent, the issue again becomes one of liquid/liquid miscibility.

These considerations led to the development of the one-liquid-phase protocol in sequence D-I of Figure 4-1 [7]. Here a fluorous catalyst is simply suspended in an organic solvent containing the reactants. The system is warmed, dissolving the fluorous catalyst to achieve one-phase reaction conditions. Subsequent cooling precipitates the catalyst, and catalyst/product separation is achieved by a simple solid/liquid phase separation. Analogously to sequence A of Figure 4-1, there is also the possibility that reaction can proceed rapidly at the low temperature biphasic limit (sequence D-II), where only traces of the catalyst might be dissolved.

Since this newer protocol is only treated in one other chapter (10.18), the current literature is briefly reviewed here. One of the first applications involved phosphine-catalyzed conjugate additions of the type shown in Scheme 4-1A [7]. Good evidence was available that the dominant catalyst rest state for such additions was the starting phosphine. The fluorous phosphines  $\text{P}[(\text{CH}_2)_2\text{R}_{\text{f8}}]_3$  (**2a**) and  $\text{P}[(\text{CH}_2)_3\text{R}_{\text{f8}}]_3$  (**2b**) were utilized, and solubilities as a function of temperature in the reaction solvent *n*-octane are shown in Figure 4-3. Note that

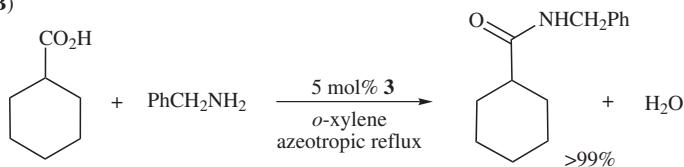


(A)



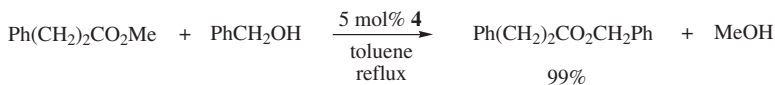
precipitated catalysts recovered by liquid/solid phase separation;  
ca. 90% recovery/cycle depending upon conditions

(B)



precipitated catalyst recovered by liquid/solid phase separation;  
88% recovery/cycle (10 cycles)

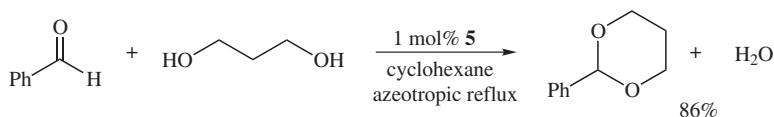
(C)



precipitated catalyst recovered by fluorous solvent extraction;  
100% recovery

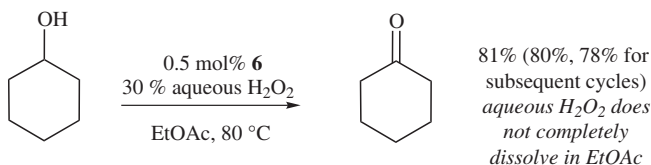
**Scheme 4-1.** Examples of sequence D in Figure 4-1; recovery of fluorous catalysts via liquid/solid phase separations [7–11]

(D)



precipitated catalyst recovered by liquid/solid phase separation;  
96% recovery

(E)



precipitated catalyst recovered by filtration;  
no leaching by <sup>19</sup>F NMR

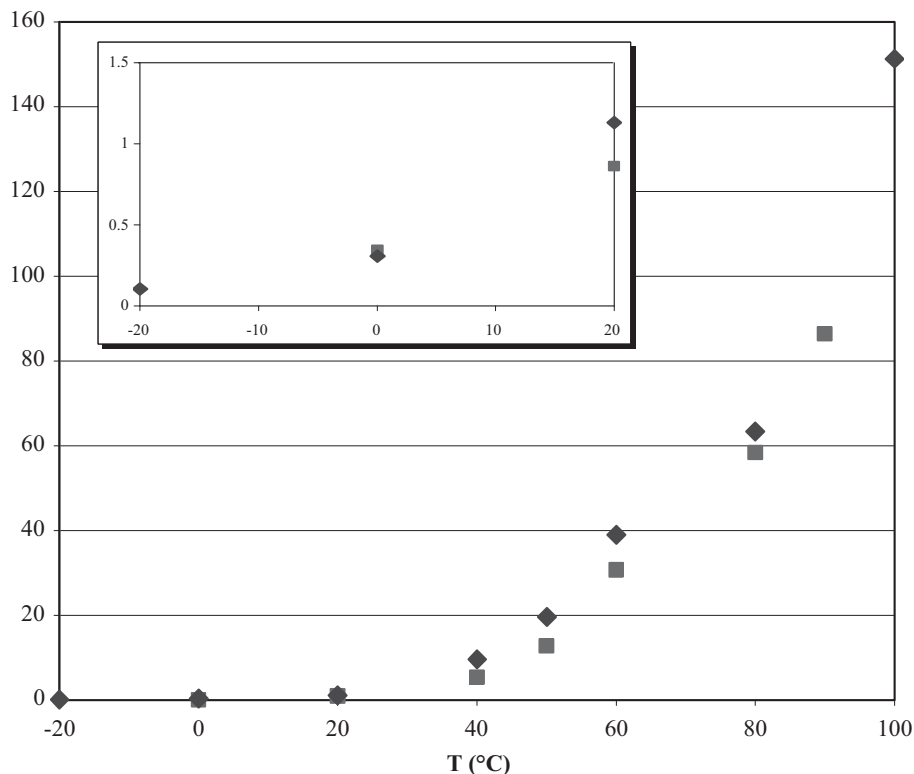
Scheme 4-1 (continued)

solubilities are very low at  $-20^\circ\text{C}$ , approximately tenth millimolar, and increase more than 600-fold on warming to  $80^\circ\text{C}$ .

Photographs of a typical cycle are given in panels A–C of Figure 4-4. After reaction under homogeneous conditions at  $65^\circ\text{C}$  (panel B), catalyst/product separation was effected by syringe at  $-30^\circ\text{C}$ . From the solubility data in Figure 4-3, less than 0.33% of the catalysts **2a,b** should leach under the workup conditions. Some catalyst discoloration is evident (panel C). The rates decrease by ca. 10%/cycle, and recovery data are presented in Section 4-7 below.

The solubilities of **2a,b** increase less dramatically with temperature in the more polar solvents toluene, chlorobenzene, and dioxane. Nonetheless, concentrations identical to those used in Scheme 4-1A and Figure 4-4 can be achieved at  $65^\circ\text{C}$ . The critical point for this recovery protocol is not a high solubility at the high-temperature limit, but a miniscule solubility at the low-temperature limit. When solubility does prove to be limiting, an obvious fix is to employ a more active catalyst. For example, **2b** is much more active than **2a** due to electronic effects, which are treated in Chapter 5.

Similar protocols have been applied to other classes of catalytic reactions, and representative examples are shown in Scheme 4-1B–E. Examples B–D involve simple transformations of organic carbonyl compounds, and fluorous Brønsted (**3**, **5**) or Lewis (**4**) acids that could logically represent catalyst rest states [8–10]. Example E involves the novel polyoxometalate salt  $\{[\text{Rf}_8(\text{CH}_2)_3]_3\text{NCH}_3\}_{12}[\text{WZn}_3(\text{H}_2\text{O})_2(\text{ZnW}_9\text{O}_{34})_2]$  (**6**), which features twelve fluorous ammonium cations [11]. The salt is insoluble in ethyl acetate (and toluene) at room temperature, but dissolves at  $80^\circ\text{C}$  to give an effective catalyst system for the oxidation of al-



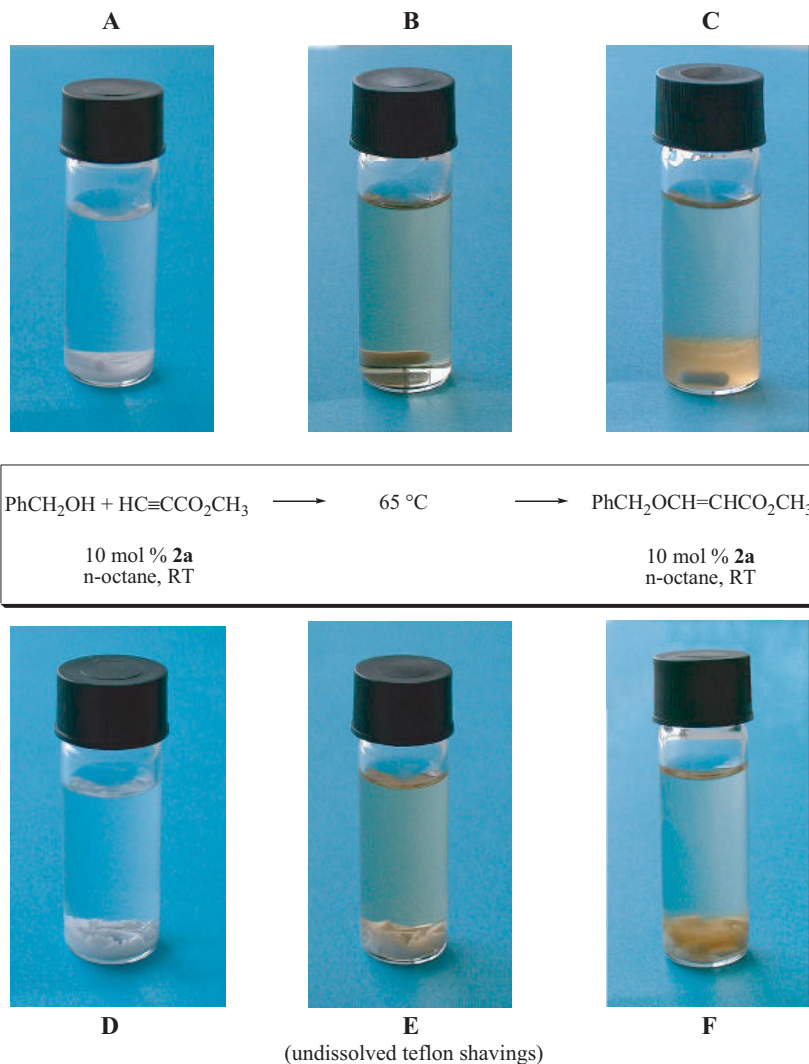
**Fig. 4-3.** Solubilities of fluorinated phosphines in *n*-octane as a function of temperature. ♦  $P[(CH_2)_2R_{f8}]_3$  (**2a**); ■  $P[(CH_2)_3R_{f8}]_3$  (**2b**) [7]

kenes and alcohols by 30% aqueous  $H_2O_2$ . Cooling precipitates the catalyst, which is reused. No ponytails are detected by  $^{19}F$  NMR (nuclear magnetic resonance) in the product phase.

The fluorinated stannyl hydride  $HSn[(CH_2)_2R_{f10}]_3$  has also been used as a catalyst in a radical chain addition and recovered via a solid/liquid phase separation [12]. This process used the amphiphilic solvent  $CF_3C_6H_5$  and a stoichiometric amount of  $NaCNBH_3$ , as described for a similar reaction in Section 4.3. Microwave heating was also employed. This is probably the earliest example of fluorinated catalyst removal from a reaction mixture via precipitation.

In one case in Scheme 4-1, a fluorinated solvent was used to extract the precipitated catalyst, and any residual dissolved species (reaction C). This leads to the question of how such catalysts might be efficiently recovered from smaller-scale reactions when loadings are modest and/or only a few milligrams of catalyst are involved. One solution is to use supports. This is treated in Section 4.7, together with additional fluorinated catalysts that are probably thermomorphic but have only been applied in the presence of supports.

The absolute solubilities of fluorinated molecules can be tailored by varying the length of the  $R_{fn}$  segments [13]. As these become longer, the poor solubility characteristics of Teflon are increasingly imparted. Hence, this protocol promises to have broad applicability. In the case of fluorinated reagents, the solubility of the spent reagent or coproduct is the critical factor



**Fig. 4-4.** Photographs of reactions that illustrate sequence D-I of Figure 4-1 (A, B, C) and sequence F-I of Figure 4-1 (D, E, F) utilizing Teflon shavings. Top row: A, room temperature; B, 65 °C; C, room temperature. Bottom row (identical, but with added Teflon shavings): D, room temperature; E, 65 °C; F, room temperature [7]

for recovery. The catalytic sequence is best suited for reactions normally conducted at elevated temperatures, and insoluble byproducts such as inorganic salts potentially complicate workup.

Several types of polymer-bound catalysts with temperature dependent solubilities have been developed. However, fluorous compounds are the first broad class of nonmacromolecular catalysts for which this strategy appears to be generally applicable.

## 4.5.2

**Other Approaches**

Fluorous compounds have recently been shown to have greatly enhanced solubilities in hydrocarbons when pressurized with 20–70 bar (atm) of CO<sub>2</sub> gas [14a], as exemplified by the procedure in Chapter 11.45. This phenomenon is conceptually related to the superior solubilities of fluorinated solutes in liquid and supercritical CO<sub>2</sub>. Some compounds that are absolutely insoluble (for example, deeply colored species) dissolve readily. One example is the dirhodium tetracarboxylate Rh<sub>2</sub>(O<sub>2</sub>CR<sub>f9</sub>)<sub>4</sub>·(MeOH)<sub>2</sub>. At least 64 mg can dissolve in 5 mL of cyclohexane under 43–59 bar. In the absence of gas expansion of the solvent volume, which is considerable, the solution would be 0.0055 M. When the pressure is released, quantitative precipitation occurs.

This procedure constitutes a non-thermal solubility “switch”, and could obviously be applied to a catalyst recovery protocol analogous to that in sequence D of Figure 4-1. It would be possible to conduct reactions at room temperature, and thermally labile educt, products, or catalysts could be employed. Progress towards these ends has been reported at conferences, and it is only a matter of time before a successful demonstration appears in the literature [14b].

As this book was going to press, the fluorous nickel acac complex Ni[R<sub>f6</sub>C(O)CHC(O)R<sub>f6</sub>]<sub>2</sub> was reported to catalyze the condensation of β-diketones with ethyl cyanoformate [15]. This complex is soluble in dichloromethane, and could be used under homogeneous conditions at room temperature and 1 mol% loadings. It could be recovered by a solid phase extraction using fluorous silica gel and dichloromethane as the eluent. This technique, which is often implemented on a column, is detailed in Chapter 7. Within the hierarchy of Figure 4-1, this protocol most closely resembles sequence B, since the fluorous catalyst must have reasonable solubility in an organic or amphiphilic medium. However, the recovery method is unique.

## 4.6

**Fluorous Catalysis Without Solvents**

One holy grail in chemistry is to eliminate solvents altogether. In principle, solvent-free protocols should be possible with fluorous catalysts as illustrated in sequence E of Figure 4-1. The organic reactants and product must be liquids, analogous to sequence C. The fluorous catalyst must be essentially insoluble at the low temperature limit, analogous to sequence D. Either higher temperature one-phase conditions, or lower-temperature two-phase conditions, can in theory be employed.

This protocol has so far been applied (in the absence of supports as described in the following section) to a single reaction, the phosphine catalyzed addition in Scheme 4-1A. The results were excellent, surpassing those obtained with sequence D-I [7]. However, since an exact yield for each cycle was sought, the product was extracted from the catalyst residue with *n*-octane. In principle, the residual product could have equally well been carried through the next cycle. Such material would ultimately be recaptured in the final cycle (if not earlier).

## 4.7

## Recovery of Fluorous Catalysts using Supports

An ongoing goal in catalysis research is to minimize the amount of catalyst required. How might very small quantities of fluorous catalysts be efficiently recovered from sequences D and E of Figure 4-1? One approach is to use a solid support to increase the mass, as shown schematically in sequence F-I of Figure 4-1. At one extreme, the support could be inert, with only a mechanical function. At another level, the support might provide physical adhesion – for example, for a waxy or gum-like catalyst. At yet another level, the support might provide attractive interactions that would enhance recovery. As noted in Chapter 3, attractive interactions between saturated fluorocarbons are small, but could nonetheless be brought into play.

This support-based approach was first tested with the phosphine catalyzed reaction in Scheme 4-1A, using Teflon shavings [7]. A picture of the reaction sequence is shown in panels D–F of Figure 4-4. Importantly, the catalyst residues became more firm and compact, suggestive of physical adhesion. The total phosphorus recovery was 97.4%, as assayed by  $^{31}\text{P}$  NMR. This corresponded to an 85.2% recovery of **2a**, and 12.2% of other species, some of which may represent alternative rest states. The total ponytail recovery was 97.9%, as assayed by  $^{19}\text{F}$  NMR. Examination of the product fraction showed 2.3% ponytail leaching (100.2% mass balance). In the absence of Teflon shavings, this increased to 7.1%.

Supports were next applied to Suzuki and Sonogashira coupling reactions with the palladium fluorous phosphine catalyst precursors **7a,b** and **8** depicted in Scheme 4-2A [16]. Complexes **7a,b** and **8**, which are soluble in ether/ $\text{C}_6\text{F}_6$  and  $\text{CHCl}_3/\text{C}_6\text{F}_6$  mixtures, were first absorbed onto the fluorous silica gel supports **9** or **10**. Owing to the presence of both fluorous and non-fluorous domains, such supports are probably capable of stronger attractive interactions with many fluorous molecules than Teflon. Reactions were conducted at 80–100 °C in dimethoxyethane with 0.001–2 mol% palladium. The mixtures were cooled to 0 °C and the support was removed and further extracted. Palladium leaching was as little as 1.9–1.6% per cycle. Additional details are provided in Chapters 10.8.2.4 and 10.8.2.5, and experimental procedures are detailed in Chapters 11.7 and 11.8. It is not yet known whether the active catalyst desorbs from the support and reacts in solution (sequence F-I of Figure 4-1), or remains bound (sequence F-II). The latter is conceptually similar to the biphasic reaction conditions in sequences A-II, C-II, and D-II. However, the former scenario has recently been demonstrated for a fluorous rhodium catalyst under  $\text{CO}_2$  pressure [14b].

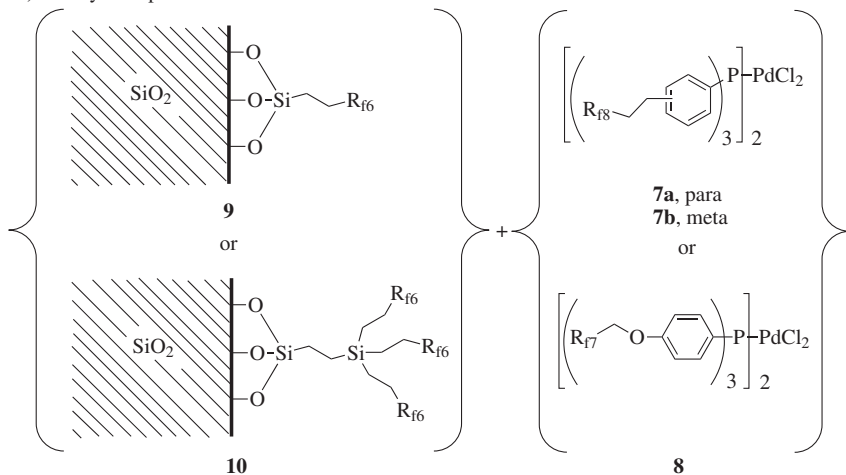
As shown in Scheme 4-2B, the fluorous dirhodium tetracarboxylate **11** has been absorbed from a hot toluene solution onto fluorous silica gel [17]. ICP-AES analysis of the supernatant and washings (room temperature) showed only 14% of the original rhodium charge in unbound form. This system catalyzes the silylation of alcohols by trialkylsilanes. The authors suggested that the catalyst remains embedded in the fluorous silica gel, and termed the procedure “bonded fluorous phase catalysis”. Importantly, the best results were obtained under solvent-free conditions. The rhodium loss was 2.5–2.6% per cycle, and the activity loss about 10%, as determined by turnover frequency (TOF) measurements. A homolog of **11** with  $\text{R}_{\text{f}13}$  groups was also prepared and studied.

Similar protocols have also been applied to stoichiometric syntheses of fluorous molecules. As depicted in Scheme 4-3, the fluorous benzylic alcohol **12** was absorbed onto

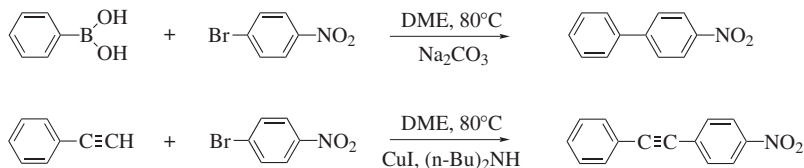


**A**

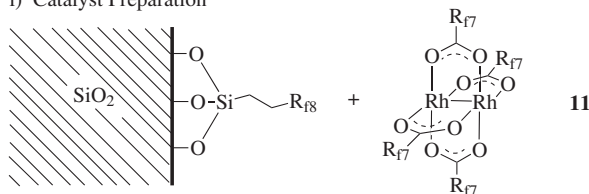
## i) Catalyst Preparations



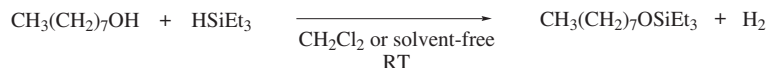
## ii) Reactions Investigated (0.001-2 mol% Pd)

**B**

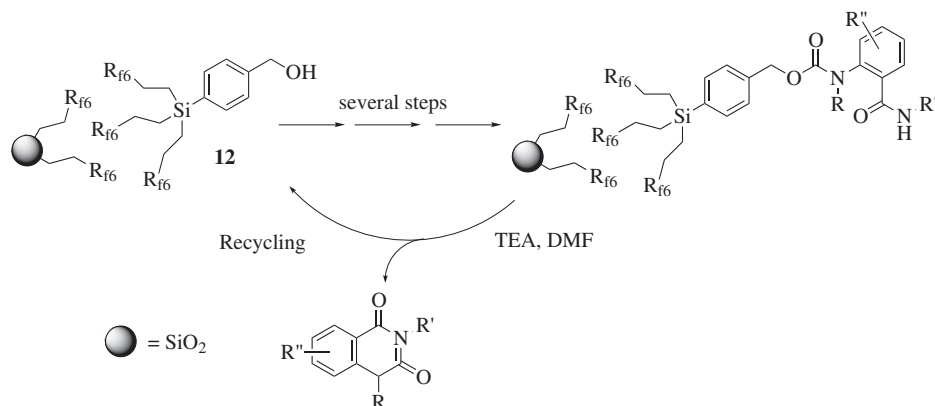
## i) Catalyst Preparation



## ii) Reaction Investigated (0.01 - 1 mol% Rh)

**Scheme 4-2.** Recovery of fluorous catalysts using fluorous silica gel [16, 17]

fluorous silica gel, and used as a protecting group for parallel syntheses of quinazoline-2,4-diones [18]. The detached protecting group remained absorbed and could be recycled. The overall procedure was termed “fluorous solid-phase organic synthesis” (FSPOS). Although control experiments clearly established the importance of the fluorous interactions, the data do not seem to exclude the reactions from occurring in solution. However, this point is only



**Scheme 4-3.** Recovery of fluorosilica gel catalysts using fluorosilica gel [18]

of importance with respect to the classification of this successful methodology. As practiced, the individual steps conceptually resemble fluorosilica gel solid phase extractions, and this subject is treated in Chapter 7.

## 4.8

### Criteria for Recoverability

The quantitative evaluation of recycling efficiency is critically important for all recyclable catalysts. Unfortunately, there is much substandard work in the literature. The following sections illustrate some of the more common pitfalls, as well as tips that can help with fluorosilica gel catalysts.

#### 4.8.1

##### Yield as a Function of Cycle

Almost without exception, papers describing recyclable catalysts report these values, and/or equivalent turnover numbers (TON). However, product yield as a function of cycle is a poor criterion for recoverability. The time selected for the cycles is often arbitrary. Suppose each cycle is allowed to run overnight (16 h). Consider a case where the reaction is in fact complete after 0.5 h. Also, assume that half the catalyst is lost in the first recycling operation. Product formation in cycle 2 would then be complete after 1.0 h (given reasonable rate law assumptions, no higher-order catalyst effects, etc.). Suppose that half the catalyst is lost in each succeeding cycle. No major yield deterioration would be noted until cycle 7, despite the recurring losses! However, if reaction rates or turnover frequencies (TOF) are assayed, the loss of activity becomes glaringly apparent in the second cycle.

#### 4.8.2

##### TOF as a Function of Cycle

As mentioned in the preceding example, this is a telling measurement but is absent in the majority of papers involving catalyst recycling. Rate data or conversion vs. time plots which

are constant or nearly so as a function of cycle represent good evidence for efficient catalyst recovery. With systems that give induction periods, comparisons between the second and third (and subsequent) cycles are more meaningful than between the first and second cycles. In any event, a high retention of activity requires a high level of catalyst recovery. A high maintenance of yield levels is a necessary but not sufficient criterion for retention of activity.

#### 4.8.3

##### Catalyst Inventory

In the next level of analysis, the challenge is to “inventory” the fate of the initial catalyst charge. Key quantities include the amounts of: (1) catalyst rest state recovered; (2) catalyst precursor recovered; (3) decomposed catalyst recovered; (4) catalyst rest state leached; (5) catalyst precursor leached; (6) decomposed catalyst leached.

These measurements can be experimentally demanding, as very small quantities are often involved. Also, the spectroscopic properties of the catalyst rest state may not match those of the well-characterized catalyst precursor. Furthermore, consider atomic absorption/emission spectroscopies, which are frequently used to quantify total metal recovery and leaching. Such techniques do not distinguish between quantities such as leached catalyst rest states and leached decomposed catalysts. Subsequent catalyst optimization depends very much upon which of these two pathways dominates: the former requires a more fluorophilic catalyst, and the latter a more stable catalyst.

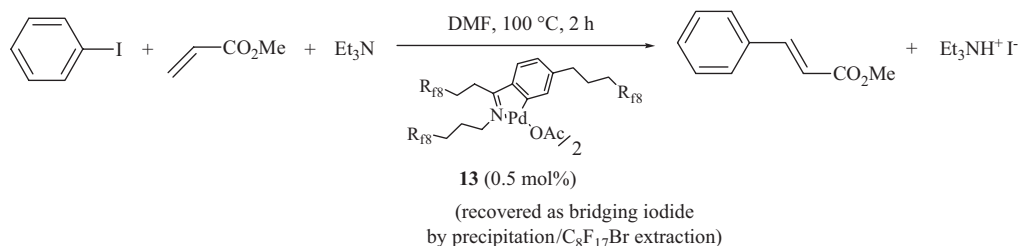
With some metal-based fluorous catalyst precursors, a fluorous ligand must dissociate before the system can enter the catalytic cycle. In a good number of these cases, this sacrificial ligand has no further role, but might leach to some degree and be detected in certain analyses, further complicating interpretation. With regard to such questions,  $^{19}\text{F}$  NMR can very easily be used to measure “total ponytail” leaching or recovery, as described for experiments associated with Scheme 4-1A above. All ponytails that terminate in an  $\text{R}_n$  group with  $n \geq 4$  give identical chemical shifts for the terminal  $\text{CF}_3$  group (Chapter 5.3). The  $^{19}\text{F}$  nucleus is easy to detect at low concentrations, and the signal can be integrated against an internal standard [7b].

#### 4.9

##### Slanting Data: How to Make a Non-recoverable Catalyst Appear Recoverable

An example from the authors’ laboratory records shows how easy it is to obtain an incorrect picture of catalyst recoverability from yield data. The fluorous palladacycle **13** in Scheme 4-4 was evaluated as a catalyst in the Heck reaction, with recovery by sequence D in Figure 4-1, or variations thereof [19]. Screening experiments were conducted at somewhat high catalyst loadings for a Heck reaction (0.5 mol%). Good yields were maintained over eight cycles, an impressive number, and in two separate runs as summarized in Scheme 4-4. Fortunately, there was not a rush to publish this data immediately.

The exceptionally talented graduate student involved was well aware of the pitfalls outlined above. Experiments were next conducted at lower loadings, and yields deteriorated over just 2–3 cycles. Rate measurements confirmed the loss of activity, and showed induction periods for every cycle (not just the first). Additional experiments showed that the palladacycle **13** simply acted as a slow steady state-source of palladium nanoparticles (unfortunately,



Cycle	Trial 1			Trial 2		
	Conversion (%)	yield (%)	TON	Conversion (%)	yield (%)	TON
1	95	86	193	99	91	204
2	95	85	191	97	89	200
3	96	98	221	98	85	191
4	94	83	187	92	78	175
5	91	75	169	90	72	162
6	90	75	167	95	86	194
7	77	50	113	86	70	158
8	60	56	126	89	75	169

**Scheme 4-4.** A non-recyclable catalyst made to appear recyclable

non-fluorous), which were the active catalysts. Only the remaining palladacycle was recycled, and when it was exhausted, activity ceased.

In conclusion, many projects involving recoverable catalysts have an “all or nothing” success aspect. A grant renewal or Dissertation may hang in the balance, and there may in some cases be a tendency not to probe the catalytic system or data such as in Scheme 4-4 too deeply. A higher catalyst loading for a reaction that is feasible at much lower catalyst loadings can be a danger sign [20]. Thus, experienced researchers maintain a skeptical eye, and one that is also appropriately focused upon claims in fluorous catalysis.

## 4.10

### Prospects

Consider in retrospect the various recycling protocols in Figure 4-1. Excellent catalyst recoveries have been obtained with sequence A, which utilizes a fluorous solvent, for commodity chemical processes [21]. However, from solvent cost considerations alone, large scale commercial applications are not likely to be developed. Nonetheless, smaller scale applications of fluorous/non-fluorous liquid/liquid biphasic catalysis have a bright future, as exemplified in other Chapters in this Handbook.

Sequences D–F of Figure 4-1, which do not rely on fluorous solvents, are poised for rapid growth. Furthermore, the variants in Figure 4-2 and Schemes 4-2 and 4-3 emphasize that homogeneous conditions are by no means essential for fluorous chemistry. The key point is that the reaction should be rapid, high-yielding, and convenient to execute, and not whether

one- or two-phase conditions apply. Finally, the use of fluorous greases or low-melting fluorous solids or polymers, which were briefly mentioned in Chapter 3, appear to present highly attractive non-liquid phases for the reversible entrainment and release of catalysts.

Process development has been an extremely active theme during the first decade of fluorous chemistry. This chapter has systematized the diverse strategies that have been applied to the recovery of fluorous catalysts and reagents, and helped to standardize the methods by which they are evaluated. The upcoming decade is certain see the continued refinement of the protocols outlined above, such as the use of CO<sub>2</sub> pressure as a miscibility and solubility switch [4, 14], as well as the development of new approaches.

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## 5

## Ponytails: Structural and Electronic Considerations

*J. A. Gladysz*

## 5.1

### Introduction

The loose distinction between ponytails, fluorous tags, and fluorous labels was discussed in Chapter 1. All of these can be viewed as tuning elements. Their primary function is to control the fluorous phase affinity of the parent molecule. In some cases a very high fluorous phase affinity is sought, and in others only a moderate one. Partition coefficients help guide ponytail design, and are presented in Chapter 6. The key variables are the length and number of the perfluoroalkyl or  $R_{fn}$  segments [ $R_{fn} = (CF_2)_{n-1}CF_3$ ].

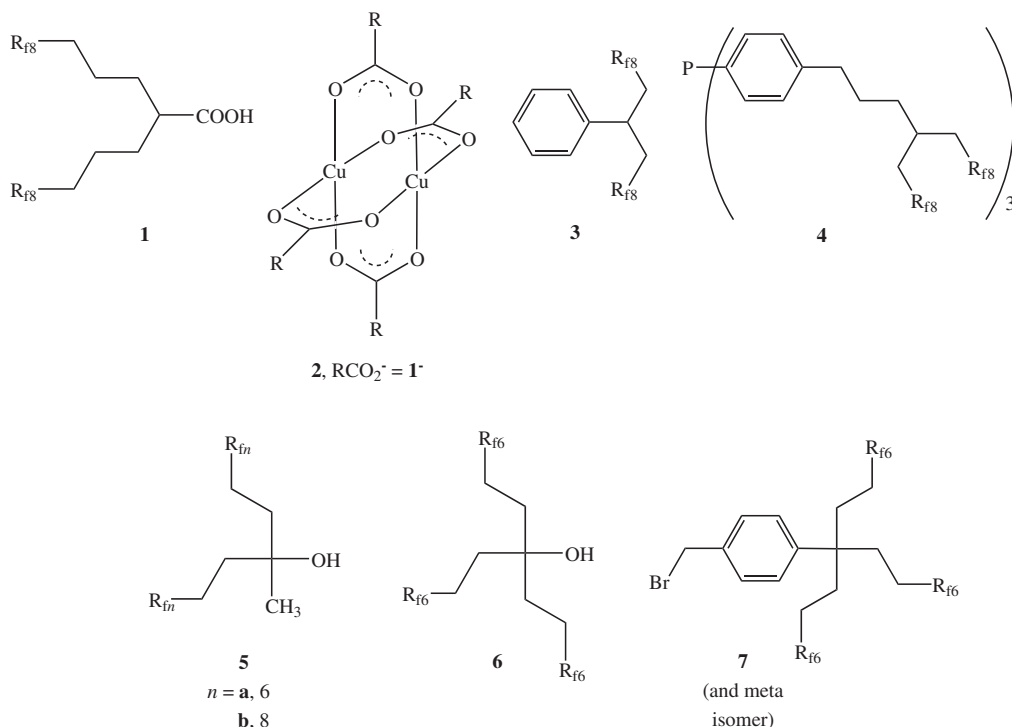
Ponytails are permanently affixed. Therefore, they can serve a secondary function of modulating the electronic properties of the fluorous catalyst or reagent, which often acts as a Lewis base or acid. Consider a ponytail of the formula  $(CH_2)_m R_{fn}$ . By adjusting the number of methylene groups or spacers,  $(CH_2)_m$ , the Lewis basicity or acidity of the active site can be tuned. High  $m$  values will give properties similar to those of non-fluorous analogs, whereas low  $m$  values will give reduced Lewis basicities or enhanced Lewis acidities. Phenyl rings or heteroatoms can also be used, alone or in combination with methylene groups, to insulate the active site from the perfluoroalkyl groups. The tuning of these electronic effects represents a major theme of this chapter.

However, other tuning functions of ponytails are certain to become of increasing importance. For example, how are solubilities, melting points, and other physical properties affected by the ponytail structure? Are there motifs that promote biodegradability? Such issues are of both fundamental and practical interest, and extend into materials applications of fluorous compounds (liquid crystals, gelators, etc.).

## 5.2

### Structural Aspects of Ponytails

The overwhelming majority of ponytails in current use have the formula  $(CH_2)_m R_{fn}$ . The  $R_{fn}$  segment should consist of at least six carbons ( $R_{f6}$ ). Smaller segments (particularly trifluoromethyl groups) are sometimes called pigtails. These can, in the presence of  $R_{f6}$  or longer segments, have appreciable effects upon fluorophilicities. Examples are provided in Chapter 6. In principle, heteroatoms such as oxygen can be incorporated *within* the  $R_{fn}$  seg-



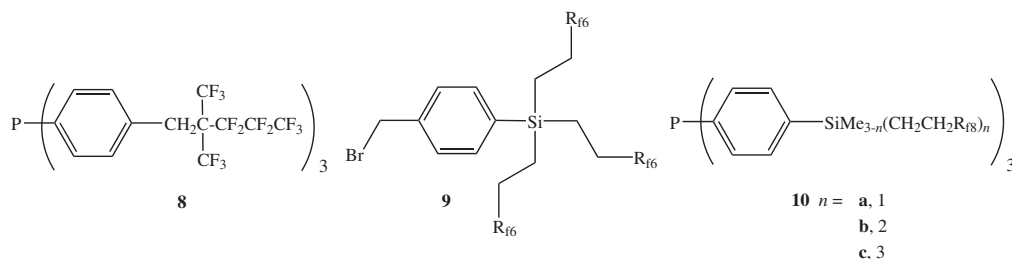
**Fig. 5-1.** Representative compounds in which perfluoroalkyl groups cap branched aliphatic segments

ment. Although only a few such systems are known [1], this represents an attractive direction for future research.

Assemblies in which branching occurs in the aliphatic segment have been reported [2–4]. Some examples are collected in Figure 5-1 (1–7). A group of the formula  $(\text{CH}_2)_l\text{CH}[(\text{CH}_2)_m\text{R}_{\text{fn}}]_2$  (see 1–4) is “doubly branched” and is sometimes termed a “split ponytail”. However, it is probably better viewed as consisting of two ponytails. A “triply branched” group of the formula  $(\text{CH}_2)_l\text{C}[(\text{CH}_2)_m\text{R}_{\text{fn}}]_3$  (see 6–7) would normally be viewed as consisting of three ponytails. There is not yet enough data to know whether such systems have any special or superior properties, but there are interesting possibilities. More work needs to be done on general synthetic routes to such compounds.

Ponytails in which branching occurs in the perfluoroalkyl segment would similarly be of interest. Such systems are extremely rare, but the triarylphosphine **8** in Figure 5-2 constitutes one example [5]. The  $\text{C}(\text{CF}_3)_2\text{CF}_2\text{CF}_2\text{CF}_3$  unit is conveniently generated via the addition of  $\text{CsF}$  to the alkene  $(\text{CF}_3)_2\text{C}=\text{CFCF}_2\text{CF}_3$ , which gives a carbanion that reacts with benzyl bromides. Heteroatoms can also serve as branch points, such as silicon in the benzyl protecting group **9** [6] or the phosphines **10b,c** [7]. Most workers would regard the silicon substituent in **9** and **10c** as having three ponytails, but the branched  $\text{C}_6\text{F}_{13}$  moiety in **8** as one.

The “spacer” consists of the entire sequence of atoms between the  $\text{R}_{\text{fn}}$  moiety and the chemically active site of the reagent or catalyst. Therefore, this includes the arene rings in **8**



**Fig. 5-2.** Representative compounds in which perfluoroalkyl groups cap other types of branched segments

and **10**, as well as the additional methylene groups in benzyl bromides **7** and **9**. Spacers may contain heteroatoms such as oxygen and nitrogen, or the silicon atoms in **9** and **10**. Ponytails that contain alternating spacer/fluorous/spacer/fluorous segments, involving moieties such as  $-\text{C}(\text{CF}_3)_2\text{OCH}_2\text{R}_{f7}$  and  $-\text{C}(\text{CF}_3)_2\text{O}(\text{CH}_2)_3\text{R}_{f8}$ , are beginning to appear (raccoon tails?) [8]. Other directions for the design of novel pony tails, as well as classification systems, have been proposed [8].

If ponytails have an “Achilles’ heel”, it is a tendency for HF elimination across  $\text{CH}_2\text{CF}_2$  junctions [9]. Thus, strong bases are avoided in certain series of compounds. Alternatively, the spacer or perfluoroalkyl segment can be modified so that HF elimination is impossible, as exemplified by **8**.

### 5.3

#### NMR Characterization of Ponytails

When the characterization of fluorous molecules is reported in the literature, it is not uncommon to find NMR data for the non-fluorous portion, but no NMR data for the fluorous portion. Typically there are a multitude of  $^{13}\text{C}$  and  $^{19}\text{F}$  signals that are not, individually at least, very informative. Table 5-1 summarizes assignments that were carefully made for the fluorous phosphine  $\text{P}[p\text{-C}_6\text{H}_4\text{SiMe}_2(\text{CH}_2)_2\text{R}_{f6}]_3$ , a lower homolog of **10a** in Figure 5-2 [7a], and the fluorous tertiary amine  $\text{N}[(\text{CH}_2)_3\text{R}_{f8}]_3$  [10]. Extensive series of 2D NMR experiments were necessary.

In both cases, all  $^{19}\text{F}$  NMR signals except for those for the two carbons at the end of the ponytail ( $\text{CF}_2\text{CF}_3$ ) and the one at the beginning ( $\text{CH}_2\text{CF}_2$ ) are clustered in a narrow 1–2 ppm range. The corresponding  $^{13}\text{C}$  NMR signals are spread over a 1 ppm range. When such data are critical for a structure proof,  $^{13}\text{C}$  NMR spectra that are simultaneously  $^1\text{H}$ - and  $^{19}\text{F}$ -decoupled (i.e.,  $^{13}\text{C}\{^1\text{H}, ^{19}\text{F}\}$  spectra) can be especially informative [10]. Such experiments require an appropriately configured triple-resonance probe.

### 5.4

#### Electronic Effects: Introduction

From the standpoint of fluorous catalyst and reagent design, it is important to know how to insulate the reactive center from the electron withdrawing perfluoroalkyl groups. With



**Tab. 5-1.** Representative  $^{19}\text{F}$  and  $^{13}\text{C}$  NMR data for  $(\text{CH}_2)_m\text{R}_{fn}$  groups [7a, 10]

A. $\text{P}(p\text{-C}_6\text{H}_4\text{Si}(\text{CH}_3)_2(\text{CH}_2)_2\text{R}_{f6})_3$		$(\text{C}_6\text{D}_6, 25^\circ\text{C})$	
	$^{19}\text{F}$ ( $\delta$ )	$^{13}\text{C}$ ( $\delta$ )	$J_{x,y}$ (Hz)
$\text{H}_2\text{C}$	—	5.62	$^1J_{\text{C,H}} = 121$
$\text{CH}_2$	—	26.6 (t)	$^2J_{\text{C,F}} = 23.5$ , $^1J_{\text{C,H}} = 125$
$\alpha$ $\text{F}_2\text{C}$	−115.8 (qm)	119.3 (tt)	$^1J_{\text{C,F}} = -254$ , $^2J_{\text{C,F}} = 30.5$ , $^3J_{\text{H,F}} = 17.5$ , $^4J_{\text{F}\alpha,\text{F}\gamma} = 15$
$\beta$ $\text{CF}_2$	−123.3 (m)	112.3 (tquin)	$^1J_{\text{C,F}} = -268$ , $^2J_{\text{C,F}} = 32.0$ , $^4J_{\text{F,F}}$ not resolved
$\gamma$ $\text{F}_2\text{C}$	−122.2 (m)	112.1 (tquin)	$^1J_{\text{C,F}} = -271$ , $^2J_{\text{C,F}} = 38.8$ , $^4J_{\text{F}\gamma,\text{F}\epsilon} = 14$
$\delta$ $\text{CF}_2$	−123.2 (m)	111.3 (tquin)	$^1J_{\text{C,F}} = -272$ , $^2J_{\text{C,F}} = 31.7$ , $^4J_{\text{F,F}}$ not resolved
$\epsilon$ $\text{F}_2\text{C}$	−126.5 (m)	109.4 (tm)	$^1J_{\text{C,F}} = -260$ , $^2J_{\text{C,F}}$ not resolved, $^4J_{\text{F}\epsilon,\text{F}\gamma} = 14$
$\zeta$ $\text{CF}_3$	−81.4 (tt)	118.1 (qt)	$^1J_{\text{C,F}} = -287$ , $^2J_{\text{C,F}} = 33.3$ , $^3J_{\text{F}\zeta,\text{F}\epsilon} = 2.2$ , $^4J_{\text{F}\zeta,\text{F}\delta} = 9.8$

$^4J_{\text{F,F}} > ^3J_{\text{F,F}}$  in accord with much precedent; the  $\text{R}_{f8}$  homolog **10a** gives (1) additional  $^{19}\text{F}$  signals that are not resolved from the  $\gamma\text{-CF}_2$  signal (−122.2 (m)) (2) additional  $^{13}\text{C}\{^{19}\text{F}\}$  signals at  $\delta$  111.8 and 111.7

**B.**  $\text{N}((\text{CH}_2)_3\text{R}_{f8})_3$  acetone- $\text{d}_6$ 

	$^{19}\text{F}$ ( $\delta$ )	$^{13}\text{C}$ ( $\delta$ )
$\text{N}$		
$\text{CH}_2$	—	53.5
$\text{H}_2\text{C}$	—	19.0
$\text{CH}_2$	—	29.4
$\text{F}_2\text{C}$	−113.9	120.3
$\text{CF}_2$	−123.5	112.2
$\text{F}_2\text{C}$	−121.2	112.3
$\text{CF}_2$	−122.5	111.8
$\text{F}_2\text{C}$	−122.5	111.9
$\text{CF}_2$	−122.3	111.3
$\text{F}_2\text{C}$	−125.8	109.5
$\text{CF}_3$	−80.8	118.1

ponytails of the formula  $(\text{CH}_2)_m\text{R}_{fn}$ , this becomes a question of the number of methylene groups. There are many sensitive probes of electronic effects, and as described in the following sections, a surprisingly large number of methylene groups are required.

There is a parallel question of the length of an  $\text{R}_{fn}$  segment needed to exert a maximum electron withdrawing effect. Computational studies with  $\text{P}[(\text{CH}_2)_2\text{CF}_3]_3$  and

$P[(CH_2)_2CF_2CF_3]_3$  indicate only a very slight increase in the vertical ionization potential (VIP) associated with the phosphorus lone pair (9.38 vs. 9.39 eV), and a similarly slight difference in the proton affinity (PA; 207.2 vs 207.8 kcal mol<sup>-1</sup>) [11]. Hence, electronic saturation in such systems is probably achieved with only two perfluorinated carbons. Accordingly, the Hammett  $\sigma$  constants associated with  $CF_3$ ,  $CF_2CF_3$ , and  $CF_2CF_2CF_2CF_3$  groups are all very close ( $\sigma_p$  0.53–0.54, 0.52, 0.52;  $\sigma_m$  0.43–0.46, 0.47–0.50, 0.47–0.52) [12].

However, it is important to pick appropriate model compounds for such comparisons. For example, ionizations become thermodynamically *more* favorable in the series  $P(CF_3)_3/P(CF_2CF_3)_3$  (VIP 11.67, 11.37 eV) and  $P(CH_2CF_3)_3/P(CH_2CF_2CF_3)_3/P(CH_2CF_2CF_2CF_3)_3$  (VIP 10.07, 10.02, 10.01 eV). This is presumably due to lone pair/ $F^-$  or  $R_{fn}^-$  hyperconjugation effects, as discussed elsewhere [11].

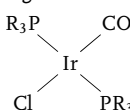
## 5.5

### Electronic Effects: IR Data

The fluorous trialkylphosphines  $P[(CH_2)_mR_{f8}]_3$  ( $m = 2-5$ , 12–15) have been converted into the iridium carbonyl complexes shown in Table 5-2 (Ir-12 through Ir-15) [13]. An adduct of tri(*n*-octyl)phosphine,  $P[(CH_2)_7CH_3]_3$ , which lacks fluorine atoms, was prepared for reference (Ir-16). IR spectra were measured under identical conditions. As the number of methylene groups ( $m$ ) increases from two to five, the  $\nu_{CO}$  values decrease from 1973.9 to 1946.1 cm<sup>-1</sup> (Table 5-2). This indicates progressively more backbonding, consistent with phosphine ligands that are more Lewis basic and less Lewis acidic. However, the values never reach the limit of the non-fluorinated phosphine complex Ir-16 (1942.3 cm<sup>-1</sup>), or converge to an alternative limit.

These data show that the electron withdrawing effect of the perfluoroalkyl groups is still felt through five methylene groups, as well as the intervening phosphorus–iridium and

Tab. 5-2. IR data for fluorous-phosphine-analogs of Vaska's complex [13, 14]



Complex	R	IR $\nu_{CO}$ (cm <sup>-1</sup> )	Medium
Ir-11	$(CH_2)_2R_{f6}$	1973.6	$C_6H_5CF_3$
Ir-12	$(CH_2)_2R_{f8}$	1973.9	$C_6H_5CF_3$
Ir-13	$(CH_2)_3R_{f8}$	1956.7	$C_6H_5CF_3$
Ir-14	$(CH_2)_4R_{f8}$	1949.2	$C_6H_5CF_3$
Ir-15	$(CH_2)_5R_{f8}$	1946.1	$C_6H_5CF_3$
Ir-16	$(CH_2)_7CH_3$	1942.3	$C_6H_5CF_3$
Ir-17	<i>p</i> - $C_6H_4(CH_2)_3R_{f8}$	1958	Nujol
Ir-18	$C_6H_5$	1952	Nujol

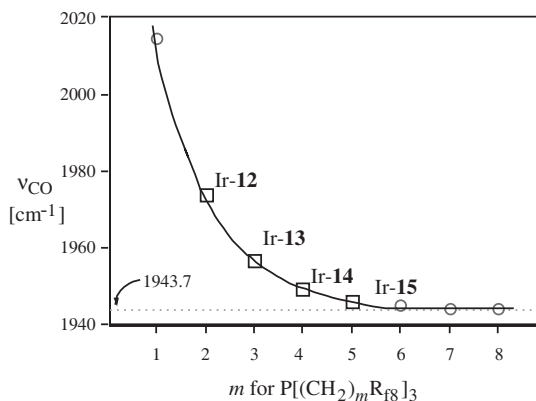


Fig. 5-3. Graphical analysis of limiting IR  $\nu_{\text{CO}}$  values for the series Ir-12–Ir-15 [13]

iridium–carbonyl bonds. Graphical analyses, such as in Figure 5-3, suggest that seven to eight methylene groups are required for essentially complete insulation (limiting value  $1943.7 \text{ cm}^{-1}$ ) [13]. Importantly, the IR (infrared) data reflect the combined effect of six ponytails, affording more resolution than experiments involving compounds with one ponytail. Note also that Ir-11 and Ir-12, which are identical except in the lengths of the  $\text{R}_{\text{fn}}$  segments, give virtually the same IR  $\nu_{\text{CO}}$  value.

A triphenylphosphine complex is included in Table 5-2 (Ir-18; Vaska's complex), together with a fluorous analog with a  $(\text{CH}_2)_3\text{R}_{\text{f8}}$  substituent in the *para* position of each ring (Ir-17) [14]. The latter features seven carbon atoms between the phosphorus and the  $\text{R}_{\text{f8}}$  segment. Nonetheless, the IR  $\nu_{\text{CO}}$  value is noticeably higher ( $1958$  vs.  $1952 \text{ cm}^{-1}$ ), indicating incomplete insulation. Similar trends have been observed for related rhodium complexes of fluorous triarylphosphines [15, 16].

## 5.6

### Electronic Effects: Gas Phase Ionization Data

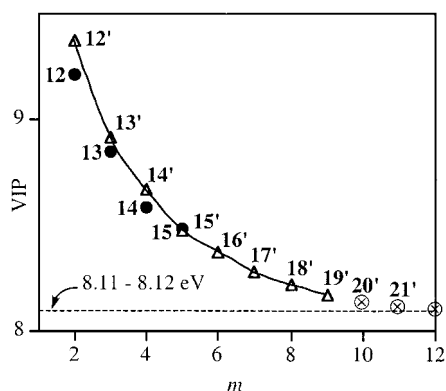
The photoelectron spectra of the fluorous phosphines 12–15 have been measured, and the VIP values associated with the phosphorus lone pairs are summarized in Table 5-3 [11]. These exhibit a monotonic decrease from 9.22 to 8.49 eV, indicating progressively more facile ionizations. As indicated by the IR data, the effect of the perfluoroalkyl group is clearly decreasing, but the asymptotic limit is by no means at hand. A graph, which includes computational data described below, is provided in Figure 5-4.

Experimental VIP values of other phosphines are given in Table 5-4, together with computational data described below. That of 14 (8.59 eV) is close to  $\text{P}(\text{CH}_3)_3$  (8.58 eV), whereas 15 (8.49 eV) is less readily ionized than  $\text{P}(\text{CH}_2\text{CH}_3)_3$  (8.34–8.28 eV) and  $\text{P}((\text{CH}_2)_3\text{CH}_3)_3$  (8.14–8.00 eV). Both 12 and 13 (9.22 and 8.85 eV) are much less readily ionized than any simple trialkylphosphine, with the former between  $\text{PH}(\text{CH}_3)_2$  and  $\text{PH}_2\text{CH}_3$  (9.08 and 9.70 eV). Hence, 12 and 13 are particularly feeble electron donors.

**Tab. 5-3.** Experimental and calculated VIP values (eV) and calculated PA values for fluorous phosphines  $P[(CH_2)_m R_{f8}]_3$  and related amines<sup>a</sup> [10, 11]

	VIP ( <i>expt</i> )	VIP ( <i>calc</i> )	PA ( <i>calc</i> )
$P[(CH_2)_2 R_{f8}]_3$ ( <b>12</b> )	9.22		
$P[(CH_2)_3 R_{f8}]_3$ ( <b>13</b> )	8.85		
$P[(CH_2)_4 R_{f8}]_3$ ( <b>14</b> )	8.59		
$P[(CH_2)_5 R_{f8}]_3$ ( <b>15</b> )	8.49		
$P[(CH_2)_2 CF_3]_3$ ( <b>12'</b> )		9.38	207.2
$P[(CH_2)_3 CF_3]_3$ ( <b>13'</b> )		8.92	217.5
$P[(CH_2)_4 CF_3]_3$ ( <b>14'</b> )		8.67	222.2
$P[(CH_2)_5 CF_3]_3$ ( <b>15'</b> )		8.48	226.5
$P[(CH_2)_6 CF_3]_3$ ( <b>16'</b> )		8.38	229.0
$P[(CH_2)_7 CF_3]_3$ ( <b>17'</b> )		8.28	231.2
$P[(CH_2)_8 CF_3]_3$ ( <b>18'</b> )		8.22	
$P[(CH_2)_9 CF_3]_3$ ( <b>19'</b> )		8.17	
$NH_2CH_2CF_2CF_3$ ( <b>26</b> )			201.4
$NH_2(CH_2)_2CF_2CF_3$ ( <b>27</b> )			207.7
$NH_2(CH_2)_3CF_2CF_3$ ( <b>28</b> )			212.1
$NH_2(CH_2)_4CF_2CF_3$ ( <b>29</b> )			214.1
$NH_2(CH_2)_5CF_2CF_3$ ( <b>30</b> )			215.8
$NH(CH_3)(CH_2)_3CF_2CF_3$ ( <b>31</b> )			219.5
$N(CH_3)_2(CH_2)_3CF_2CF_3$ ( <b>32</b> )			223.8
$NH[(CH_2)_3CF_2CF_3]_2$ ( <b>33</b> )			218.4
$N(CH_3)[(CH_2)_3CF_2CF_3]_2$ ( <b>34</b> )			222.6
$N[(CH_2)_3CF_2CF_3]_2$ ( <b>35</b> )			221.6

<sup>a</sup>alternative formatting:  $CF_3 = R_{f1}$ ;  $CF_2CF_3 = R_{f2}$ .



**Fig. 5-4.** Relationship between VIP (eV) and  $m$  for  $P[(CH_2)_m R_{f8}]_3$  (**12**–**15**, ●) and  $P[(CH_2)_m CF_3]_3$  (**12'**–**19'**, △) as well as extrapolated values for **20'**–**21'** (⊗) [11]

**Tab. 5-4.** Calculated and observed vertical ionization potentials (VIP, eV) for reference non-fluorous phosphines [11]

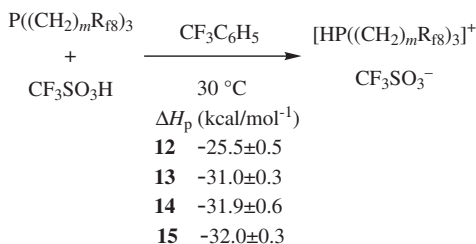
	VIP (calc)	VIP (expt)
P(CH <sub>3</sub> ) <sub>3</sub>	8.57	8.58
PH <sub>3</sub>	10.56	10.85
PH(CH <sub>3</sub> ) <sub>2</sub>	9.04	9.08
PH <sub>2</sub> CH <sub>3</sub>	9.69	9.70
P[C(CH <sub>3</sub> ) <sub>3</sub> ] <sub>3</sub>	7.51	7.70, 7.72
P(CH <sub>2</sub> CH <sub>3</sub> ) <sub>3</sub>	8.27	8.28, 8.34
P[(CH <sub>2</sub> ) <sub>2</sub> CH <sub>3</sub> ] <sub>3</sub>	8.16	
P[(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub> ] <sub>3</sub>	8.08	8.00, 8.14
P[(CH <sub>2</sub> ) <sub>4</sub> CH <sub>3</sub> ] <sub>3</sub>	8.04	
P[(CH <sub>2</sub> ) <sub>5</sub> CH <sub>3</sub> ] <sub>3</sub>	8.03	
P[(CH <sub>2</sub> ) <sub>6</sub> CH <sub>3</sub> ] <sub>3</sub>	8.01	
P[(CH <sub>2</sub> ) <sub>7</sub> CH <sub>3</sub> ] <sub>3</sub>	8.00	
P[(CH <sub>2</sub> ) <sub>8</sub> CH <sub>3</sub> ] <sub>3</sub>	7.98	
P[(CH <sub>2</sub> ) <sub>9</sub> CH <sub>3</sub> ] <sub>3</sub>	7.98	

## 5.7

### Electronic Effects: Calorimetry

The enthalpies of reaction of many amines and phosphines with triflic acid (CF<sub>3</sub>SO<sub>3</sub>H) have been measured in dichloromethane [17]. The values correlate well with Brønsted basicities in water. The fluorous phosphines **12–15** were similarly studied, but for solubility reasons trifluoromethylbenzene (CF<sub>3</sub>C<sub>6</sub>H<sub>5</sub>) was employed. The resulting enthalpies of protonation are summarized in Scheme 5-1 [11]. The reactions become more exothermic with increasing numbers of methylene groups, in accord with the VIP values.

Experiments with other phosphines show a close correlation between values in CF<sub>3</sub>C<sub>6</sub>H<sub>5</sub> and CH<sub>2</sub>Cl<sub>2</sub> [11]. On this basis (and neglecting standard deviations), the enthalpy of protonation of **12** [−25.5(0.5) kcal mol<sup>−1</sup>] is between that of P(CH<sub>3</sub>)(C<sub>6</sub>H<sub>5</sub>)<sub>2</sub> and P(CH<sub>3</sub>)<sub>2</sub>(C<sub>6</sub>H<sub>5</sub>) [−24.7(0) and −28.4(2) kcal mol<sup>−1</sup>]. The enthalpies of protonation of **14** and **15** [−31.9(6) and −32.0(3) kcal mol<sup>−1</sup>] are between those of P(CH<sub>3</sub>)<sub>3</sub> and P(CH<sub>2</sub>CH<sub>3</sub>)<sub>3</sub> [−31.6(2) and

**Scheme 5-1.** Enthalpies of protonation of fluorous phosphines [11]

$-33.7(3)$  kcal mol $^{-1}$ ]. The  $pK_a$  ( $BH^+$ ,  $H_2O$ ) values of **12**–**15** can also be extrapolated from calibration graphs (5.05, 8.08, 8.57, 8.63). That of **15** is close to  $P(CH_2CH_3)_3$  (8.69). In all comparisons, the two methylene groups in **12** again provide a distinctly inferior level of insulation [18].

## 5.8

### Electronic Effects: Solution Equilibria

Substituent effects upon the  $pK_a$  values of carboxylic acids have played an immense role in the history of physical organic chemistry. Surprisingly, extensive series of measurements involving fluorous carboxylic acids  $R_{fn}(CH_2)_mCO_2H$  have not yet been made [19]. Phosphine substitution reactions involving rhodium complexes could be used to show that **13** has a higher Lewis basicity than **12**, paralleling other data above [11]. However, better equilibrium data could be obtained with proton transfer reactions of analogous fluorous tertiary amines,  $N[(CH_2)_mR_{f8}]_3$  ( $m = 3$ – $5$ , **23**–**25**) [20]. The results, obtained from NMR chemical shift measurements in  $CDCl_3$ , are summarized in Table 5-5.

Competitions between  $N(CH_2CH_3)_3$  and **23**–**25** show progressively increasing protonation of the fluorous amine, consistent with a diminishing inductive influence of the per-fluoroalkyl group. Nonetheless, there remains a  $\Delta pK_a(CDCl_3)$  of 1.5–1.9 between the con-

**Tab. 5-5.** Relative basicities of amines in  $CDCl_3$  at 32 °C [20]

$$\begin{array}{c}
 N[R']_3 + N[R'']_3 + CF_3CO_2H \\
 \downarrow \text{1:1:1 ratio} \\
 +HN[R']_3 \quad CF_3CO_2^- + N[R'']_3 \xrightleftharpoons{K_{eq}} +HN[R'']_3 \quad CF_3CO_2^- + N[R']_3
 \end{array}$$

$N[R']_3/N[R'']_3$	$+HN[R']_3/+HN[R'']_3$	$K_{eq}$	$\Delta pK_a$
$N(CH_2CH_3)_3/N((CH_2)_3R_{f8})_3$ ( <b>23</b> )	100:0	—	—
$N(CH_2CH_3)_3/N((CH_2)_4R_{f8})_3$ ( <b>24</b> )	>95:<5	>361	>2.6
$N(CH_2CH_3)_3/N((CH_2)_5R_{f8})_3$ ( <b>25</b> )	85–90:10–15	32–81	1.5–1.9
$N((CH_2)_{11}CH_3)_3/N((CH_2)_3R_{f8})_3$ ( <b>23</b> )	>95:<5	>361	>2.6
$N((CH_2)_{11}CH_3)_3/N((CH_2)_4R_{f8})_3$ ( <b>24</b> )	85–90:10–15	32–81	1.5–1.9
$N((CH_2)_{11}CH_3)_3/N((CH_2)_5R_{f8})_3$ ( <b>25</b> )	70–75:30–25	9.0–16	0.9–1.2
$N((CH_2)_3R_{f8})_3/N((CH_2)_4R_{f8})_3$ ( <b>23</b> )      ( <b>24</b> )	40:60	0.44	0.3
$N((CH_2)_3R_{f8})_3/N((CH_2)_5R_{f8})_3$ ( <b>23</b> )      ( <b>25</b> )	<5:>95	<0.0028	>2.6
$N((CH_2)_4R_{f8})_3/N((CH_2)_5R_{f8})_3$ ( <b>24</b> )      ( <b>25</b> )	10–15:85–90	0.012–0.031	1.9–1.5

jugate acids of  $\text{N}(\text{CH}_2\text{CH}_3)_3$  and **25**, which has five methylene groups. The fluorous amines compete slightly more effectively with the *n*-dodecyl amine  $\text{N}[(\text{CH}_2)_{11}\text{CH}_3]_3$ , which is a better reference base due to the similar number of carbons. Still, a  $\Delta\text{p}K_a(\text{CDCl}_3)$  of 0.9–1.2 remains for **25**.

Pairs of fluorous amines were also compared. Competitions between **23** and **24**, **23** and **25**, and **24** and **25** (Table 5-5) show the expected order for Brønsted basicity. However, an asymptotic limit is clearly not at hand. Counter-intuitively, a greater difference is found between **24** and **25** as compared with **23** and **24**. Note that for measurements made in solution, there is always the possibility that some fluorous substances (but not others) might aggregate, giving structures with enhanced thermodynamic stabilities (micelles, gels, etc.). Such non-ideal behavior could lead to non-linear responses to certain probes, non-classical means for transmitting inductive effects, etc. One way to minimize interpretive problems is to conduct measurements over a range of concentrations, and extrapolate to infinite dilution.

## 5.9

### Electronic Effects: Computational Data

The above data clearly indicate that more than five methylene groups are required to insulate the heteroatom in tertiary phosphines or amines of the formula  $\text{E}[(\text{CH}_2)_m\text{R}_{f8}]_3$  from the electron withdrawing perfluoroalkyl groups. The author's coworkers viewed it as more productive to probe the asymptotic limit via DFT theory than to engage in additional synthesis [11, 21]. Calculations with non-fluorinated reference phosphines were first required. Key results are summarized in Table 5-4, and are in good agreement with experimental data where available. Interestingly, the *VIP* values of trialkyl phosphines  $\text{P}[(\text{CH}_2)_m\text{CH}_3]_3$  show small changes even for  $m = 7$ –9, when effective saturation is reached ( $<0.01$  eV or  $<0.23$  kcal mol<sup>-1</sup> difference, nonyl vs. decyl).

The fluorous phosphines were modeled with the trifluoromethyl ( $\text{R}_{f1}$ ) analogs  $\text{P}[(\text{CH}_2)_m\text{CF}_3]_3$  (**12'**–**15'**). As summarized in Table 5-3, the calculated *VIP* values agree very well with those of **12**–**15**, and are depicted on the same graph in Figure 5-4. A good linear relationship ( $R = 0.98$ ; plotted elsewhere) [11] allows the values computed for the higher model compounds **16'**–**19'** to be confidently extrapolated to those of the unknown fluorous phosphines **16**–**19** (predicted, eV: **16**, 8.35; **17**, 8.27; **18**, 8.21; **19**, 8.17).

The *VIP* values for **17'**, **18'**, and **19'** show differences of 0.06 and 0.05 eV. These are larger than those between  $\text{P}[(\text{CH}_2)_6\text{CH}_3]_3$ ,  $\text{P}[(\text{CH}_2)_7\text{CH}_3]_3$ , and  $\text{P}[(\text{CH}_2)_8\text{CH}_3]_3$ , which have the same number of non-fluorinated carbon atoms (0.02 and 0.01 eV; Table 5-4). This indicates a residual inductive effect of the fluorinated segment. The graphical analysis in Figure 5-4 suggests that an effective limit is almost reached with  $m = 10$  (8.14 eV), with further incremental decreases for  $m = 11$  and 12 to a limit of ca. 8.12–8.11 eV. However, the non-fluorinated phosphines in Table 5-4 converge to a still lower limit (7.98 eV). That in Figure 5-4 is between the computed *VIP* values of  $\text{P}[(\text{CH}_2)_2\text{CH}_3]_3$  and  $\text{P}[(\text{CH}_2)_3\text{CH}_3]_3$  (8.16 and 8.08 eV).

The apparent difference in limiting *VIP* values crystallizes the question as to what constitutes the best reference molecules for fluorous phosphines  $\text{P}(\text{CH}_2)_m\text{R}_{f8}$  in which the perfluoroalkyl group is “completely” insulated from phosphorus. This issue can be framed in a different, but perhaps simpler, context: are the electronic properties of a fluorous aryl system



$$\Delta H = 7.1 \text{ kcal/mol } (m = 1)$$

$$1.7 \text{ kcal/mol } (m = 2)$$

$$0.9 \text{ kcal/mol } (m = 3)$$

$$0.0 \text{ kcal/mol } (m = 4)$$

$$-0.5 \text{ kcal/mol } (m = 5)$$

$$-0.5 \text{ kcal/mol } (m = 6)$$

$$-0.6 \text{ kcal/mol } (m = 7)$$



$$\Delta H = 7.4 \text{ kcal/mol } (m = 1)$$

$$2.0 \text{ kcal/mol } (m = 2)$$

$$1.2 \text{ kcal/mol } (m = 3)$$

$$0.3 \text{ kcal/mol } (m = 4)$$

$$-0.2 \text{ kcal/mol } (m = 5)$$

$$-0.3 \text{ kcal/mol } (m = 6)$$

$$-0.5 \text{ kcal/mol } (m = 7)$$

**Scheme 5-2.** Homodesmotic exchange reactions, and computed enthalpies [11]

$p\text{-XC}_6\text{H}_4(\text{CH}_2)_m\text{R}_{\text{fn}}$  with a long methylene spacer segment best compared with those of the phenyl analog  $\text{XC}_6\text{H}_5$ ,  $p$ -tolyl analog  $p\text{-XC}_6\text{H}_4\text{CH}_3$ , or some other  $p\text{-XC}_6\text{H}_4\text{R}$  species?

It is possible to sidestep this problem with an alternative probe, homodesmotic exchange reactions [22]. Two series are given in Scheme 5-2. The left side of each equation features a molecule with  $\text{CH}_3$  and  $\text{CF}_3$  endgroups that are separated by  $m$  methylene groups. The right side of each equation features a molecule with phosphorus-atom and  $\text{CF}_3$  endgroups that are separated by  $m$  methylene groups. The other molecules in the equilibria remain constant. The enthalpies approach a limiting value as  $m$  becomes large enough to block out endgroup–endgroup interactions.

With both  $\text{P}(\text{CH}_2\text{CH}_3)_3$  [Eq. (1)] and  $\text{P}[(\text{CH}_2)_2\text{CH}_3]_3$  [Eq. (2)], the computed enthalpies indicate that seven methylene groups effectively screen the phosphorus atom from the  $\text{CF}_3$  moiety. Continuing to eight methylene groups would make a difference of at most  $0.1 \text{ kcal mol}^{-1}$  ( $0.0043 \text{ eV}$ ), a quantity that has a small effect upon equilibrium constants at room temperature. The limiting enthalpies are close to zero, and would be expected to become even closer to zero as the  $n$ -alkyl group of the phosphine utilized is lengthened.

DFT calculations have also been reported for fluorous amines with  $(\text{CH}_2)_m\text{CF}_2\text{CF}_3$  substituents ( $m = 1\text{--}5$ ) [10]. The  $PA$  values given in Table 5-3 for the primary amines **26–30** show the expected monotonic trend, but as with the analogous tertiary phosphines, an asymptotic limit is clearly not at hand. The  $\Delta PA$  values for amines that differ by one meth-



ylene group are one-half to one-third of those of the corresponding tertiary phosphines, which feature three ponytails per heteroatom (e.g., for  $m = 4$  and 5: 1.7 kcal mol<sup>-1</sup> for **29** and **30** vs. 4.3 kcal mol<sup>-1</sup> for **14'** and **15'**). Interestingly, the PA value of the fluororous tertiary amine N[(CH<sub>2</sub>)<sub>3</sub>CF<sub>2</sub>CF<sub>3</sub>]<sub>3</sub> (**35**, 221.6 kcal mol<sup>-1</sup>) indicates a higher gas phase basicity than the corresponding primary amine **28** (212.1 kcal mol<sup>-1</sup>). In other words, a (CH<sub>2</sub>)<sub>3</sub>CF<sub>2</sub>CF<sub>3</sub> substituent can stabilize a positively charged ammonium salt more than a proton in the gas phase. However, the basicity is lower than that of the fluororous dimethyl amine N(CH<sub>3</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>3</sub>CF<sub>2</sub>CF<sub>3</sub> (**32**, PA 223.8 kcal mol<sup>-1</sup>).

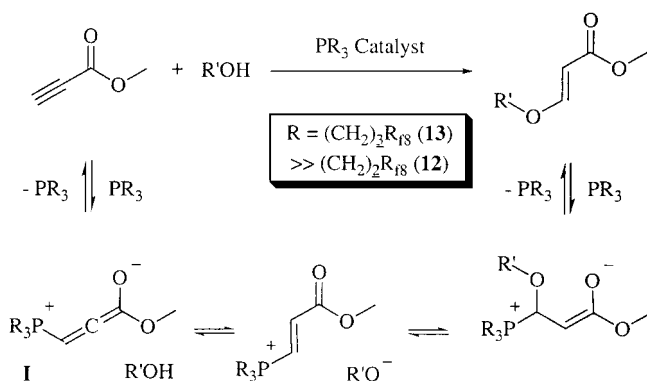
Computational studies of fluororous triarylphosphines have also been reported [15]. Consistent with the IR data in Table 5-2, the phosphorus lone pair energies calculated with *p*-(CH<sub>2</sub>)<sub>2</sub>R<sub>f6</sub> groups are much lower than those with *p*-(CH<sub>2</sub>)<sub>5</sub>CH<sub>3</sub> groups (-9.2 vs. -8.7 eV).

## 5.10

### Electronic Effects: Reactivity

Effects of ponytails upon reactivity are frequently observed. One example especially relevant to the above data is the phosphine-catalyzed addition in Scheme 5-3 [23]. The first step is a nucleophilic attack of the phosphine on the alkyne linkage of methyl propiolate to give the zwitterion **I**. Under standard conditions (*n*-octane, 65 °C), the fluororous phosphine **12**, with two insulating methylene groups, required 1.5 h for complete reaction. The phosphine **13**, which with three methylene groups should be more nucleophilic, required less than 15 min. In the same vein, phosphines **12**–**15** become progressively more air sensitive [14, 24]. Whereas **15** requires rigorous inert atmosphere conditions, **12** survives for several hours as a solid in air.

The primary fluororous iodides I(CH<sub>2</sub>)<sub>*m*</sub>R<sub>f8</sub> and similar electrophiles become progressively more reactive in S<sub>N</sub>2 reactions as *m* is increased from one to two to three [9b, 13, 24]. The fluororous tin allyls H<sub>2</sub>C=CHCH<sub>2</sub>Sn[(CH<sub>2</sub>)<sub>*m*</sub>R<sub>f6</sub>]<sub>3</sub> afford much cleaner free radical and platinum-catalyzed allylations when *m* is increased from two to three [25]. However, in cases where the fluororous catalyst or reagent functions as a Lewis or Brønsted acid, longer methylene segments decrease reactivity. The same trend is expected for the rates of certain



**Scheme 5-3.** Phosphine catalyzed addition of alcohols to methyl propiolate [23]

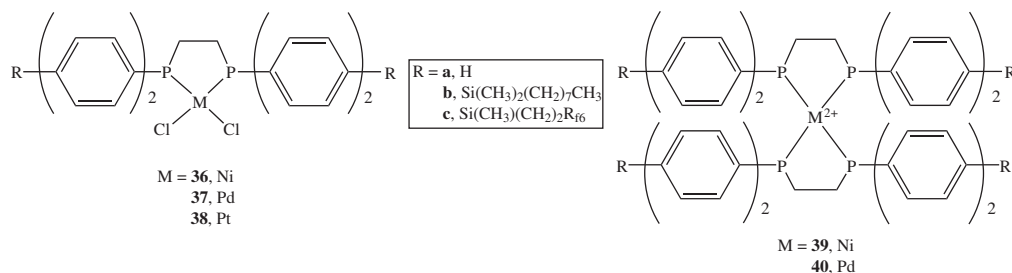


Fig. 5-5. Complexes analyzed by XPS [27]

hydrogen-atom-transfer reactions of fluorous tin hydrides [26]. In any event, such rate effects pervade fluorous chemistry. Many reflect the difficulty in fully insulating active sites from the electron-withdrawing perfluoroalkyl segments.

### 5.11

#### Electronic Effects: Additional Probes

One recent study featured several probes that are complementary to those described above, and systems in which arene rings help to insulate the perfluoroalkyl groups from the active site [27]. The fluorous and non-fluorous dppe nickel, palladium, and platinum complexes shown in Figure 5-5 were synthesized. The XPS (X-ray photoelectron spectroscopy) spectra were measured, and both the phosphorus [P(2p)] and metal [e.g., Pd(3d<sub>5/2</sub>), Pd(3d<sub>3/2</sub>)] binding energies were very similar. Those of the non-fluorous and fluorous silicon-substituted palladium complexes **37b,c** and **40b,c** which contain the same number of carbon atoms, differed by only 0.0–0.2 eV. This indicates that a *p*-C<sub>6</sub>H<sub>4</sub>Si(CH<sub>3</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub> moiety provides a very high degree of insulation.

Cyclic voltammograms of the cationic complexes **39** and **40** showed only irreversible reductions, precluding quantitative comparisons [27]. However, in principle electrochemical *E*<sup>o</sup> values represent excellent probes for the electronic effects of ponytails. NMR spectra of the platinum complexes **38a,c** exhibited essentially identical <sup>195</sup>Pt chemical shifts (–4573, –4570 ppm) and <sup>1</sup>J<sub>PtP</sub> values (3612, 3604 Hz). Analogous compounds with non-chelating triarylphosphine ligands behaved similarly.

### 5.12

#### Electronic Effects: Conclusions

The above data show that it is very challenging to “completely” insulate a reactive site from a perfluoroalkyl group in a fluorous molecule. With ponytails of the formula (CH<sub>2</sub>)<sub>*m*</sub>R<sub>fn</sub>, there are still readily detectable effects upon lengthening the spacer from four to five methylene groups. The magnitudes are such that solution equilibria can be significantly affected. The computational data in Scheme 5-2 indicate that the asymptotic limit is reached with seven to eight methylene groups, in accord with estimates from the IR data in Table 5-2.

The gas phase ionization potentials in Figure 5-4 suggest a somewhat higher limit. However, it is well known that gas-phase processes in which charge is created are subject to tre-

mendous substituent effects, in which polarizability and size play roles. This is evidenced by the stabilizing effect of a  $(\text{CH}_2)_3\text{CF}_2\text{CF}_3$  group relative to a proton upon the basicities of the fluorous amines in Table 5-3. In solution, this substituent-based stabilization is to a significant extent replaced by solvent-based stabilization, dampening certain effects of the ponytail relative to others.

Computational studies have virtually infinite resolution. Thus, a line must be drawn somewhere, i.e., when the calculated difference would no longer have reactivity implications. Even in monofunctional fluorinated compounds of the formula  $\text{X}(\text{CH}_2)_m\text{CH}_3$  ( $m = 4, 5, 11$ ;  $\text{X} = \text{F}, \text{CF}_3$ , and non-fluorinated groups), there is a clear influence of  $\text{X}$  upon properties such as atomic charge polarizations, carbon 1s orbital energies, and atomic dipole vectors over the entire carbon chain [28].

Many practicing fluorous chemists roughly calibrate themselves with respect to one or more of the experimental probes summarized above, and fine-tune the ponytails in their systems somewhat intuitively. The bottom line is that the fluorous catalyst or reagent should be convenient and practical, i.e., “reactive enough”, and a small residual electronic effect is for many applications of no significant consequence.

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## 6

## Partition Coefficients Involving Fluorous Solvents

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## 6.1

### Introduction

Partition coefficients quantify the equilibrium distribution of a solute between two immiscible phases, which are most often but not necessarily liquids. They see extensive use throughout chemistry, and their thermodynamic nuances have been analyzed in detail [1].

In order to rationally extract non-fluorous products from reactions involving fluorous solvents, partition coefficients for fluorous/non-fluorous liquid/liquid biphasic systems are necessary. The design and optimization of fluorous catalysts and reagents require analogous data. Such partition coefficients constitute a direct measure of fluorophilicity, a term that is used interchangeably with fluorous phase affinity.

By 1999, only a few partition coefficients involving fluorous and organic phases had been measured [2, 3]. Now there is a wealth of data, to which sophisticated analysis and parameterization methods have been applied [4–6]. The primary aim of this chapter is to summarize the literature reports, and qualitatively interpret the principal trends. Representative procedures for the determination of partition coefficients are also given.

## 6.2

### Literature Data

Some investigators prefer to express partition coefficients as ratios that have been normalized to 100 (e.g., 98.3:1.7), others as ratios with either the less populated phase or the non-fluorous phase set to 1 (e.g., 57.8:1), and still others as logarithmic values. The abbreviation *P* indicates a concentration ratio with the non-fluorous phase in the denominator. The natural logarithm of the CF<sub>3</sub>C<sub>6</sub>F<sub>11</sub>/toluene concentration ratio,  $\ln\{[c(\text{CF}_3\text{C}_6\text{F}_{11})]/[c(\text{toluene})]\}$ , has been given the abbreviation *f*, for fluorophilicity [4].

All partition coefficients measured in the authors' laboratories can be found in Table 6-1. Most of these involve the solvent system CF<sub>3</sub>C<sub>6</sub>F<sub>11</sub>/toluene. Many data from other research groups are also included. However, there are undoubtedly inadvertent omissions, for which the authors express their regrets. Since the entries are sorted by functional group, the placement of difunctional molecules is arbitrary. At the end of some sections, cross refer-


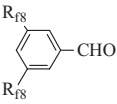
Tab. 6-1. Fluorous/organic liquid/liquid partition coefficients<sup>a</sup>

Entry	Solute <sup>b</sup>	Solvent system	Partitioning fluorous: organic ( <i>P</i> )	Method	Ref.
<b>I</b>	<b>Alkanes</b>				
I-1	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>8</sub> CH <sub>3</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	<b>5.4:94.6</b> ( <i>P</i> = 0.057)	GLC	1
I-2	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>9</sub> CH <sub>3</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	<b>4.2:95.8</b> ( <i>P</i> = 0.044)	GLC	1
I-3	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>10</sub> CH <sub>3</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	<b>3.4:96.6</b> ( <i>P</i> = 0.035)	GLC	1, 2
I-4	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>11</sub> CH <sub>3</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	<b>2.4:97.6</b> ( <i>P</i> = 0.025)	GLC	1
I-5	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>12</sub> CH <sub>3</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	<b>1.9:98.1</b> ( <i>P</i> = 0.019)	GLC	1
I-6	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>14</sub> CH <sub>3</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	<b>1.1:98.9</b> ( <i>P</i> = 0.011)	GLC	1
<b>II</b>	<b>Alkenes</b>				
II-1	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>7</sub> CH=CH <sub>2</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	<b>4.8:95.2</b> ( <i>P</i> = 0.050)	GLC	3
II-2	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>8</sub> CH=CH <sub>2</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	<b>3.7:96.3</b> ( <i>P</i> = 0.038)	GLC	3
II-3	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>9</sub> CH=CH <sub>2</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	<b>2.5:97.5</b> ( <i>P</i> = 0.026)	GLC	2
II-4	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>10</sub> CH=CH <sub>2</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	<b>1.9:98.1</b> ( <i>P</i> = 0.019)	GLC	3
II-5	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>11</sub> CH=CH <sub>2</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	<b>1.6:98.4</b> ( <i>P</i> = 0.016)	GLC	3
II-6	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>13</sub> CH=CH <sub>2</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	<b>0.9:99.1</b> ( <i>P</i> = 0.009)	GLC	3
II-7 <sup>c</sup>	R <sub>f8</sub> CH=CH <sub>2</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	93.5:6.5 ( <b><i>P</i> = 14.4</b> ) <sup>d</sup>	GLC	4a
II-8 <sup>c</sup>	<i>E</i> -R <sub>f6</sub> CH=CHC <sub>6</sub> H <sub>13</sub>	C <sub>10</sub> F <sub>18</sub> <sup>e</sup> :C <sub>16</sub> H <sub>34</sub>	63.4:36.6 ( <b><i>P</i> = 1.73</b> )	GLC	5
II-9 <sup>c</sup>		(C <sub>4</sub> F <sub>9</sub> CH=) <sub>2</sub> :C <sub>16</sub> H <sub>34</sub>	72.5:27.5 ( <b><i>P</i> = 2.63</b> )	GLC	5
II-10 <sup>c</sup>		C <sub>8</sub> F <sub>17</sub> Br:C <sub>16</sub> H <sub>34</sub>	74.9:25.1 ( <b><i>P</i> = 2.98</b> )	GLC	5
II-11 <sup>c</sup>	<i>Z</i> -R <sub>f6</sub> CH=CHC <sub>6</sub> H <sub>13</sub>	C <sub>10</sub> F <sub>18</sub> <sup>e</sup> :C <sub>16</sub> H <sub>34</sub>	62.1:37.9 ( <b><i>P</i> = 1.64</b> )	GLC	5
II-12 <sup>c</sup>		(C <sub>4</sub> F <sub>9</sub> CH=) <sub>2</sub> :C <sub>16</sub> H <sub>34</sub>	67.5:32.5 ( <b><i>P</i> = 2.08</b> )	GLC	5
II-13 <sup>c</sup>		C <sub>8</sub> F <sub>17</sub> Br:C <sub>16</sub> H <sub>34</sub>	72.6:27.4 ( <b><i>P</i> = 2.65</b> )	GLC	5
II-14 <sup>c</sup>	<i>E</i> -R <sub>f6</sub> CH=CHC <sub>8</sub> H <sub>17</sub>	C <sub>10</sub> F <sub>18</sub> <sup>e</sup> :C <sub>16</sub> H <sub>34</sub>	42:58 ( <b><i>P</i> = 0.72</b> )	GLC	5
II-15 <sup>c</sup>		(C <sub>4</sub> F <sub>9</sub> CH=) <sub>2</sub> :C <sub>16</sub> H <sub>34</sub>	49:51 ( <b><i>P</i> = 0.95</b> )	GLC	5
II-16 <sup>c</sup>		C <sub>8</sub> F <sub>17</sub> Br:C <sub>16</sub> H <sub>34</sub>	53.1:46.9 ( <b><i>P</i> = 1.13</b> )	GLC	5

Tab. 6-1. (continued)

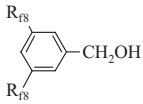
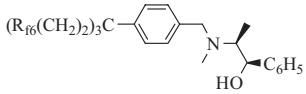
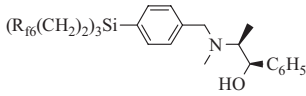
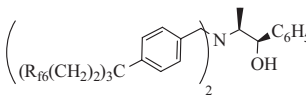
Entry	Solute <sup>b</sup>	Solvent system	Partitioning fluorous: organic ( <i>P</i> )	Method	Ref.
II-17 <sup>c</sup>	<i>Z</i> -R <sub>f6</sub> CH=CHC <sub>8</sub> H <sub>17</sub>	C <sub>10</sub> F <sub>18</sub> <sup>e</sup> :C <sub>16</sub> H <sub>34</sub>	50.0:50.0 ( <i>P</i> = 1.00)	GLC	5
II-18 <sup>c</sup>		(C <sub>4</sub> F <sub>9</sub> CH=) <sub>2</sub> :C <sub>16</sub> H <sub>34</sub>	53.1:46.9 ( <i>P</i> = 1.13)	GLC	5
II-19 <sup>c</sup>		C <sub>8</sub> F <sub>17</sub> Br:C <sub>16</sub> H <sub>34</sub>	60.0:40.0 ( <i>P</i> = 1.50)	GLC	5
II-20 <sup>c</sup>	<i>E</i> -R <sub>f6</sub> CH=CHC <sub>10</sub> H <sub>21</sub>	C <sub>10</sub> F <sub>18</sub> <sup>e</sup> :C <sub>16</sub> H <sub>34</sub>	20:80 ( <i>P</i> = 0.25)	GLC	5
II-21 <sup>c</sup>		(C <sub>4</sub> F <sub>9</sub> CH=) <sub>2</sub> :C <sub>16</sub> H <sub>34</sub>	43:57 ( <i>P</i> = 0.74)	GLC	5
II-22 <sup>c</sup>		C <sub>8</sub> F <sub>17</sub> Br:C <sub>16</sub> H <sub>34</sub>	44:56 ( <i>P</i> = 0.80)	GLC	5
II-23 <sup>c</sup>	<i>Z</i> -R <sub>f6</sub> CH=CHC <sub>10</sub> H <sub>21</sub>	C <sub>10</sub> F <sub>18</sub> <sup>e</sup> :C <sub>16</sub> H <sub>34</sub>	28:72 ( <i>P</i> = 0.38)	GLC	5
II-24 <sup>c</sup>		(C <sub>4</sub> F <sub>9</sub> CH=) <sub>2</sub> :C <sub>16</sub> H <sub>34</sub>	40:60 ( <i>P</i> = 0.68)	GLC	5
II-25 <sup>c</sup>		C <sub>8</sub> F <sub>17</sub> Br:C <sub>16</sub> H <sub>34</sub>	47:53 ( <i>P</i> = 0.88)	GLC	5
II-26 <sup>c</sup>	<i>E</i> -R <sub>f8</sub> CH=CHC <sub>6</sub> H <sub>13</sub>	C <sub>10</sub> F <sub>18</sub> <sup>e</sup> :C <sub>16</sub> H <sub>34</sub>	79.8:20.2 ( <i>P</i> = 3.95)	GLC	5
II-27 <sup>c</sup>		(C <sub>4</sub> F <sub>9</sub> CH=) <sub>2</sub> :C <sub>16</sub> H <sub>34</sub>	86.0:14.0 ( <i>P</i> = 6.13)	GLC	5
II-28 <sup>c</sup>		C <sub>8</sub> F <sub>17</sub> Br:C <sub>16</sub> H <sub>34</sub>	86.4:13.6 ( <i>P</i> = 6.38)	GLC	5
II-29 <sup>c</sup>	<i>Z</i> -R <sub>f8</sub> CH=CHC <sub>6</sub> H <sub>13</sub>	C <sub>10</sub> F <sub>18</sub> <sup>e</sup> :C <sub>16</sub> H <sub>34</sub>	77.2:22.8 ( <i>P</i> = 3.38)	GLC	5
II-30 <sup>c</sup>		(C <sub>4</sub> F <sub>9</sub> CH=) <sub>2</sub> :C <sub>16</sub> H <sub>34</sub>	82.0:18.0 ( <i>P</i> = 4.55)	GLC	5
II-31 <sup>c</sup>		C <sub>8</sub> F <sub>17</sub> Br:C <sub>16</sub> H <sub>34</sub>	83.6:16.4 ( <i>P</i> = 5.11)	GLC	5
II-32 <sup>c</sup>	<i>E</i> -R <sub>f8</sub> CH=CHC <sub>8</sub> H <sub>17</sub>	C <sub>10</sub> F <sub>18</sub> <sup>e</sup> :C <sub>16</sub> H <sub>34</sub>	72.5:27.5 ( <i>P</i> = 2.63)	GLC	5
II-33 <sup>c</sup>		(C <sub>4</sub> F <sub>9</sub> CH=) <sub>2</sub> :C <sub>16</sub> H <sub>34</sub>	76.7:23.3 ( <i>P</i> = 3.30)	GLC	5
II-34 <sup>c</sup>		C <sub>8</sub> F <sub>17</sub> Br:C <sub>16</sub> H <sub>34</sub>	79.2:20.8 ( <i>P</i> = 3.81)	GLC	5
II-35 <sup>c</sup>	<i>Z</i> -R <sub>f8</sub> CH=CHC <sub>8</sub> H <sub>17</sub>	C <sub>10</sub> F <sub>18</sub> <sup>e</sup> :C <sub>16</sub> H <sub>34</sub>	71.5:28.5 ( <i>P</i> = 2.51)	GLC	5
II-36 <sup>c</sup>		(C <sub>4</sub> F <sub>9</sub> CH=) <sub>2</sub> :C <sub>16</sub> H <sub>34</sub>	76.0:24.0 ( <i>P</i> = 3.17)	GLC	5
II-37 <sup>c</sup>		C <sub>8</sub> F <sub>17</sub> Br:C <sub>16</sub> H <sub>34</sub>	78.6:21.4 ( <i>P</i> = 3.67)	GLC	5
II-38 <sup>c</sup>	<i>E</i> -R <sub>f8</sub> CH=CHC <sub>10</sub> H <sub>21</sub>	C <sub>10</sub> F <sub>18</sub> <sup>e</sup> :C <sub>16</sub> H <sub>34</sub>	54.8:45.2 ( <i>P</i> = 1.21)	GLC	5
II-39 <sup>c</sup>		(C <sub>4</sub> F <sub>9</sub> CH=) <sub>2</sub> :C <sub>16</sub> H <sub>34</sub>	63.1:36.9 ( <i>P</i> = 1.71)	GLC	5

Tab. 6-1. (continued)

Entry	Solute <sup>b</sup>	Solvent system	Partitioning fluorous: organic (P)	Method	Ref.
II-40 <sup>c</sup>		C <sub>8</sub> F <sub>17</sub> Br:C <sub>16</sub> H <sub>34</sub>	70.8:29.2 (P = 2.43)	GLC	5
II-41 <sup>c</sup>	Z-R <sub>f8</sub> CH=CHC <sub>10</sub> H <sub>21</sub>	C <sub>10</sub> F <sub>18</sub> <sup>e</sup> :C <sub>16</sub> H <sub>34</sub>	54.1:45.9 (P = 1.18)	GLC	5
II-42 <sup>c</sup>		(C <sub>4</sub> F <sub>9</sub> CH=) <sub>2</sub> :C <sub>16</sub> H <sub>34</sub>	56.7:43.3 (P = 1.31)	GLC	5
II-43 <sup>c</sup>		C <sub>8</sub> F <sub>17</sub> Br:C <sub>16</sub> H <sub>34</sub>	65.5:34.5 (P = 1.90)	GLC	5
II-44 <sup>c</sup>	c-C <sub>5</sub> H <sub>4</sub> [(CH <sub>2</sub> ) <sub>2</sub> R <sub>f4</sub> ] <sub>2</sub> <sup>f</sup>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	55:45 (P = 1.2)	GLC	6
II-45 <sup>c</sup>	c-C <sub>5</sub> H <sub>4</sub> [(CH <sub>2</sub> ) <sub>2</sub> R <sub>f6</sub> ] <sub>2</sub> <sup>f</sup>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	83:17 (P = 4.9)	GLC	6
II-46 <sup>c</sup>	c-C <sub>5</sub> H <sub>4</sub> [(CH <sub>2</sub> ) <sub>2</sub> R <sub>f8</sub> ] <sub>2</sub> <sup>f</sup>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	90:10 (P = 8.8)	GLC	6
II-47 <sup>c</sup>	c-C <sub>5</sub> H <sub>4</sub> [(CH <sub>2</sub> ) <sub>2</sub> R <sub>f4</sub> ][(CH <sub>2</sub> ) <sub>2</sub> R <sub>f6</sub> ] <sup>f</sup>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	75:25 (P = 3.0)	GLC	6
II-48 <sup>c</sup>	c-C <sub>5</sub> H <sub>4</sub> [(CH <sub>2</sub> ) <sub>2</sub> R <sub>f4</sub> ][(CH <sub>2</sub> ) <sub>2</sub> R <sub>f8</sub> ] <sup>f</sup>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	82:18 (P = 4.6)	GLC	6
II-49 <sup>c</sup>	c-C <sub>5</sub> H <sub>4</sub> [(CH <sub>2</sub> ) <sub>2</sub> R <sub>f6</sub> ][(CH <sub>2</sub> ) <sub>2</sub> R <sub>f8</sub> ] <sup>f</sup>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	86:14 (P = 6.4)	GLC	6
	for further compounds see XII and XIII				
III	<b>Ketones and Aldehydes</b>				
III-1	cyclohexanone	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	2.2:97.8 (P = 0.022)	GLC	2
III-2	2-cyclohexen-1-one	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	1.7:98.3 (P = 0.017)	GLC	2
III-3	R <sub>f8</sub> (CH <sub>2</sub> ) <sub>3</sub> -  -C(O)(CH <sub>2</sub> ) <sub>2</sub> R <sub>f8</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	84.6:15.4 (P = 5.49)	GLC	7
III-4 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	98.6:1.4 (P = 73.0) <sup>d</sup>	GLC	4a
IV	<b>Alcohols</b>				
IV-1	cyclohexanol	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	1.6:98.4 (P = 0.016)	GLC	2
IV-2 <sup>c</sup>	CF <sub>3</sub> CH <sub>2</sub> OH	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	14.5:85.5 (P = 0.170) <sup>d</sup>	GLC	8
IV-3 <sup>c</sup>	(CF <sub>3</sub> ) <sub>2</sub> CHOH	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	26.7:73.3 (P = 0.364) <sup>d</sup>	GLC	8
IV-4 <sup>c</sup>	R <sub>f6</sub> (CH <sub>2</sub> ) <sub>2</sub> OH	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	52:48 (P = 1.1) <sup>d</sup>	GLC	8
IV-5 <sup>c</sup>	R <sub>f6</sub> (CH <sub>2</sub> ) <sub>3</sub> OH	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	44:56 (P = 0.79) <sup>d</sup>	GLC	8



Tab. 6-1. (continued)

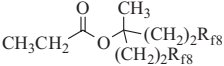
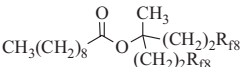
Entry	Solute <sup>b</sup>	Solvent system	Partitioning fluorous: organic ( <i>P</i> )	Method	Ref.
IV-6 <sup>c</sup>	R <sub>f8</sub> (CH <sub>2</sub> ) <sub>2</sub> OH	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	73.5:26.5 ( <i>P</i> = 2.77) <sup>d</sup>	GLC	8
IV-7 <sup>c</sup>	R <sub>f8</sub> (CH <sub>2</sub> ) <sub>3</sub> OH	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	64:36 ( <i>P</i> = 1.8) <sup>d</sup>	GLC	8
IV-8 <sup>c</sup>	R <sub>f10</sub> (CH <sub>2</sub> ) <sub>3</sub> OH	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	80.5:19.5 ( <i>P</i> = 4.14) <sup>d</sup>	GLC	8
IV-9 <sup>g</sup>	[R <sub>f6</sub> (CH <sub>2</sub> ) <sub>2</sub> ] <sub>3</sub> COH	C <sub>6</sub> F <sub>14</sub> :THF	90.9:9.1 ( <i>P</i> = 10.0)	–	9
IV-10 <sup>h</sup>		C <sub>6</sub> F <sub>14</sub> :THF	95.8:4.2 ( <i>P</i> = 23.0)	–	9
IV-11 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	97.4:2.6 ( <i>P</i> = 38.1) <sup>d</sup>	GLC	4a
IV-12 <sup>g</sup>	[R <sub>f6</sub> (CH <sub>2</sub> ) <sub>2</sub> ] <sub>2</sub> C(OCH <sub>3</sub> )CH(OH)C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> F <sub>14</sub> :THF	19:81 ( <i>P</i> = 0.24)	–	9
IV-13 <sup>g</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> CN	88:12 ( <i>P</i> = 7.3)	gravimet	10
IV-14 <sup>g</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	59:41 ( <i>P</i> = 1.4)	gravimet	10
IV-15 <sup>g</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>2</sub> Cl <sub>2</sub>	38:62 ( <i>P</i> = 0.61)	gravimet	10
IV-16 <sup>g</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> CN	82:18 ( <i>P</i> = 4.6)	gravimet	10
IV-17 <sup>g</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	48:52 ( <i>P</i> = 0.92)	gravimet	10
IV-18 <sup>g</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>2</sub> Cl <sub>2</sub>	25:75 ( <i>P</i> = 0.33)	gravimet	10
IV-19 <sup>g</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> CN	97:3 ( <i>P</i> = 32)	gravimet	10
IV-20 <sup>g</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	97:3 ( <i>P</i> = 32)	gravimet	10
IV-21 <sup>g</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>2</sub> Cl <sub>2</sub>	94:6 ( <i>P</i> = 16)	gravimet	10

for further compounds see VII

Tab. 6-1. (continued)

Entry	Solute <sup>b</sup>	Solvent system	Partitioning fluorous: organic (P)	Method	Ref.
<b>V Aliphatic Ethers</b>					
V-1 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	98.3:1.7 (P = 56.8) <sup>d</sup>	GLC	11
V-2 <sup>i</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> CN	88:12 (P = 7.3)	gravimet	12
V-3 <sup>i</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> OH	79:21 (P = 3.8)	gravimet	12
V-4 <sup>i</sup>		C <sub>6</sub> F <sub>14</sub> :C <sub>2</sub> H <sub>5</sub> OH	78:22 (P = 3.6)	gravimet	12
V-5 <sup>i</sup>		C <sub>6</sub> F <sub>14</sub> :C <sub>6</sub> H <sub>6</sub>	62:38 (P = 1.6)	gravimet	12
V-6 <sup>i</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>2</sub> Cl <sub>2</sub>	57:43 (P = 1.3)	gravimet	12
V-7 <sup>i</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> COCH <sub>3</sub>	52:48 (P = 1.1)	gravimet	12
V-8 <sup>i</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	46:54 (P = 0.85)	gravimet	12
V-9 <sup>i</sup>		C <sub>6</sub> F <sub>14</sub> :CHCl <sub>3</sub>	46:54 (P = 0.85)	gravimet	12
for further compounds see IV, VII and VIII					
<b>VI Carboxylic Acids and Derivatives</b>					
VI-1 <sup>c</sup>	R <sub>f7</sub> C(O)OC <sub>6</sub> H <sub>5</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	62:38 (P = 1.6) <sup>d</sup>	GLC	4a
VI-2 <sup>c</sup>	R <sub>f7</sub> C(O)OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	89.5:10.5 (P = 8.50) <sup>d</sup>	GLC	4a
VI-3 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	95.9:4.1 (P = 23.3) <sup>d</sup>	GLC	4a
VI-4 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	40:60 (P = 0.68) <sup>d</sup>	GLC	4a
VI-5 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	52:48 (P = 1.1) <sup>d</sup>	GLC	4a
VI-6 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	50:50 (P = 0.99) <sup>d</sup>	GLC	4a
VI-7 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	98.8:1.2 (P = 85.6) <sup>d</sup>	GLC	4a

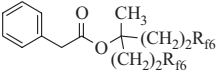
**Tab. 6-1. (continued)**

Entry	Solute <sup>b</sup>	Solvent system	Partitioning fluorous: organic (P)	Method	Ref.
VI-8 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :c-C <sub>6</sub> H <sub>12</sub>	89.0:11.0 (P = 8.10)	gravimet	13
VI-9 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :c-C <sub>6</sub> H <sub>12</sub>	90.5:9.5 (P = 9.58)	gravimet	13
VI-10 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	88.6:11.4 (P = 7.75)	gravimet	13
VI-11 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	86.6:13.4 (P = 6.46)	gravimet	13
VI-12 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>2</sub> Cl <sub>2</sub>	90.1:9.9 (P = 9.08)	gravimet	13
VI-13 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>2</sub> Cl <sub>2</sub>	93.8:6.2 (P = 15.4)	gravimet	13
VI-14 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :CHCl <sub>3</sub>	75.4:24.6 (P = 3.06)	gravimet	13
VI-15 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CHCl <sub>3</sub>	85.6:14.4 (P = 5.93)	gravimet	13
VI-16 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	72.1:27.9 (P = 2.59)	gravimet	13
VI-17 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	76.5:23.5 (P = 3.25)	gravimet	13
VI-18 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :THF	73.0:27.0 (P = 2.70)	gravimet	13
VI-19 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :THF	84.0:16.0 (P = 5.26)	gravimet	13
VI-20 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> COCH <sub>3</sub>	76.9:23.1 (P = 3.33)	gravimet	13
VI-21 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> COCH <sub>3</sub>	86.3:13.7 (P = 6.28)	gravimet	13
VI-22 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> CN	86.5:13.5 (P = 6.42)	gravimet	13
VI-23 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> CN	94.4:5.6 (P = 16.9)	gravimet	13
VI-24 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :C <sub>2</sub> H <sub>5</sub> OH	80.7:19.3 (P = 4.19)	gravimet	13
VI-25 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :C <sub>2</sub> H <sub>5</sub> OH	94.1:5.9 (P = 16.0)	gravimet	13
VI-26 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> OH	82.7:17.3 (P = 4.78)	gravimet	13
VI-27 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> OH	91.5:8.5 (P = 10.8)	gravimet	13
VI-28 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :c-C <sub>6</sub> H <sub>12</sub>	87.0:13.0 (P = 6.72)	gravimet	13
VI-29 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :c-C <sub>6</sub> H <sub>12</sub>	92.5:7.5 (P = 12.4)	gravimet	13

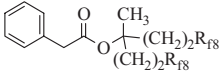
Tab. 6-1. (continued)

Entry	Solute <sup>b</sup>	Solvent system	Partitioning fluorous: organic ( <i>P</i> )	Method	Ref.
VI-30 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	84.1:15.9 ( <i>P</i> = 5.28)	gravimet	13
VI-31 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	94.5:5.5 ( <i>P</i> = 17.2)	gravimet	13
VI-32 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>2</sub> Cl <sub>2</sub>	81.9:18.1 ( <i>P</i> = 4.53)	gravimet	13
VI-33 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>2</sub> Cl <sub>2</sub>	93.2:6.8 ( <i>P</i> = 13.6)	gravimet	13
VI-34 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :CHCl <sub>3</sub>	72.5:27.5 ( <i>P</i> = 2.63)	gravimet	13
VI-35 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CHCl <sub>3</sub>	85.2:14.8 ( <i>P</i> = 5.74)	gravimet	13
VI-36 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	73.3:26.7 ( <i>P</i> = 2.74)	gravimet	13
VI-37 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	90.8:9.2 ( <i>P</i> = 9.86)	gravimet	13
VI-38 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :THF	63.0:37.0 ( <i>P</i> = 1.70)	gravimet	13
VI-39 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :THF	82.7:17.3 ( <i>P</i> = 4.79)	gravimet	13
VI-40 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> COCH <sub>3</sub>	74.5:25.5 ( <i>P</i> = 2.92)	gravimet	13
VI-41 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> COCH <sub>3</sub>	84.7:15.3 ( <i>P</i> = 5.55)	gravimet	13
VI-42 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> CN	91.8:8.2 ( <i>P</i> = 11.2)	gravimet	13
VI-43 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> CN	96.8:3.2 ( <i>P</i> = 29.9)	gravimet	13
VI-44 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :C <sub>2</sub> H <sub>5</sub> OH	85.7:14.3 ( <i>P</i> = 5.98)	gravimet	13
VI-45 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :C <sub>2</sub> H <sub>5</sub> OH	91.7:8.3 ( <i>P</i> = 11.0)	gravimet	13
VI-46 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> OH	89.9:10.1 ( <i>P</i> = 8.89)	gravimet	13
VI-47 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> OH	96.5:3.5 ( <i>P</i> = 27.3)	gravimet	13
VI-48 <sup>c</sup>	$\text{CH}_3(\text{CH}_2)_{16}\overset{\text{O}}{\overset{\parallel}{\text{C}}}\text{O}\overset{\text{CH}_3}{\underset{(\text{CH}_2)_2\text{R}_{18}}{\text{C}}}$	C <sub>6</sub> F <sub>14</sub> : <i>c</i> -C <sub>6</sub> H <sub>12</sub>	48:52 ( <i>P</i> = 0.91)	gravimet	13
VI-49 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> : <i>c</i> -C <sub>6</sub> H <sub>12</sub>	74.1:25.9 ( <i>P</i> = 2.86)	gravimet	13
VI-50 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	53.1:46.9 ( <i>P</i> = 1.13)	gravimet	13
VI-51 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	79.3:20.7 ( <i>P</i> = 3.84)	gravimet	13

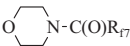
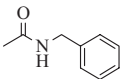
Tab. 6-1. (continued)

Entry	Solute <sup>b</sup>	Solvent system	Partitioning fluorous: organic ( <i>P</i> )	Method	Ref.
VI-52 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>2</sub> Cl <sub>2</sub>	55.0:45.0 ( <i>P</i> = 1.22)	gravimet	13
VI-53 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>2</sub> Cl <sub>2</sub>	82.4:17.6 ( <i>P</i> = 4.68)	gravimet	13
VI-54 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :CHCl <sub>3</sub>	35:65 ( <i>P</i> = 0.53)	gravimet	13
VI-55 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CHCl <sub>3</sub>	62.1:37.9 ( <i>P</i> = 1.64)	gravimet	13
VI-56 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	51.5:48.5 ( <i>P</i> = 1.06)	gravimet	13
VI-57 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	67.5:32.5 ( <i>P</i> = 2.08)	gravimet	13
VI-58 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :THF	33:67 ( <i>P</i> = 0.50)	gravimet	13
VI-59 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :THF	51.0:49.0 ( <i>P</i> = 1.04)	gravimet	13
VI-60 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> COCH <sub>3</sub>	63.9:36.1 ( <i>P</i> = 1.77)	gravimet	13
VI-61 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> COCH <sub>3</sub>	72.9:27.1 ( <i>P</i> = 2.69)	gravimet	13
VI-62 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> CN	93.5:6.5 ( <i>P</i> = 14.3)	gravimet	13
VI-63 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> CN	94.3:5.7 ( <i>P</i> = 16.4)	gravimet	13
VI-64 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :C <sub>2</sub> H <sub>5</sub> OH	89.3:10.7 ( <i>P</i> = 8.35)	gravimet	13
VI-65 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :C <sub>2</sub> H <sub>5</sub> OH	91.8:8.2 ( <i>P</i> = 11.2)	gravimet	13
VI-66 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> OH	95.1:4.9 ( <i>P</i> = 19.5)	gravimet	13
VI-67 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> OH	97.1:2.9 ( <i>P</i> = 33.7)	gravimet	13
VI-68 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> : <i>c</i> -C <sub>6</sub> H <sub>12</sub>	89.2:10.8 ( <i>P</i> = 8.26)	gravimet	13
VI-69 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> : <i>c</i> -C <sub>6</sub> H <sub>12</sub>	84.3:15.7 ( <i>P</i> = 5.37)	gravimet	13
VI-70 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	64.0:36.0 ( <i>P</i> = 1.78)	gravimet	13
VI-71 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	74.2:25.8 ( <i>P</i> = 2.87)	gravimet	13
VI-72 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>2</sub> Cl <sub>2</sub>	38:62 ( <i>P</i> = 0.61)	gravimet	13
VI-73 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>2</sub> Cl <sub>2</sub>	66.2:33.8 ( <i>P</i> = 1.96)	gravimet	13

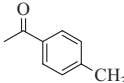
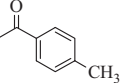
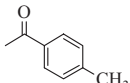
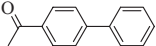
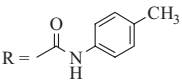
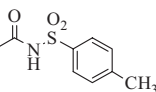
Tab. 6-1. (continued)

Entry	Solute <sup>b</sup>	Solvent system	Partitioning fluorous: organic ( <i>P</i> )	Method	Ref.
VI-74 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :CHCl <sub>3</sub>	41:59 ( <i>P</i> = 0.69)	gravimet	13
VI-75 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CHCl <sub>3</sub>	46:54 ( <i>P</i> = 0.86)	gravimet	13
VI-76 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	22:78 ( <i>P</i> = 0.29)	gravimet	13
VI-77 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	37:63 ( <i>P</i> = 0.58)	gravimet	13
VI-78 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :THF	27:73 ( <i>P</i> = 0.37)	gravimet	13
VI-79 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :THF	35:65 ( <i>P</i> = 0.55)	gravimet	13
VI-80 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> COCH <sub>3</sub>	20:80 ( <i>P</i> = 0.25)	gravimet	13
VI-81 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> COCH <sub>3</sub>	36:64 ( <i>P</i> = 0.57)	gravimet	13
VI-82 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> CN	77.4:22.6 ( <i>P</i> = 3.42)	gravimet	13
VI-83 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> CN	82.8:17.2 ( <i>P</i> = 4.81)	gravimet	13
VI-84 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :C <sub>2</sub> H <sub>5</sub> OH	76.7:23.3 ( <i>P</i> = 3.29)	gravimet	13
VI-85 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :C <sub>2</sub> H <sub>5</sub> OH	81.7:18.3 ( <i>P</i> = 4.46)	gravimet	13
VI-86 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> OH	82.3:17.7 ( <i>P</i> = 4.65)	gravimet	13
VI-87 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> OH	91.7:8.3 ( <i>P</i> = 11.1)	gravimet	13
VI-88 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> : <i>c</i> -C <sub>6</sub> H <sub>12</sub>	93.6:6.4 ( <i>P</i> = 14.62)	gravimet	13
VI-89 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> : <i>c</i> -C <sub>6</sub> H <sub>12</sub>	93.3:6.7 ( <i>P</i> = 13.92)	gravimet	13
VI-90 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	84.6:15.4 ( <i>P</i> = 5.49)	gravimet	13
VI-91 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	90.5:9.5 ( <i>P</i> = 9.53)	gravimet	13
VI-92 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>2</sub> Cl <sub>2</sub>	80.0:20.0 ( <i>P</i> = 4.00)	gravimet	13
VI-93 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>2</sub> Cl <sub>2</sub>	86.1:13.9 ( <i>P</i> = 6.21)	gravimet	13
VI-94 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :CHCl <sub>3</sub>	71.8:28.2 ( <i>P</i> = 2.55)	gravimet	13
VI-95 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CHCl <sub>3</sub>	73.0:27.0 ( <i>P</i> = 2.70)	gravimet	13

Tab. 6-1. (continued)

Entry	Solute <sup>b</sup>	Solvent system	Partitioning fluorous: organic ( <i>P</i> )	Method	Ref.
VI-96 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	56.9:43.1 ( <i>P</i> = 1.32)	gravimet	13
VI-97 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	67.1:32.9 ( <i>P</i> = 2.04)	gravimet	13
VI-98 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :THF	56.5:43.5 ( <i>P</i> = 1.30)	gravimet	13
VI-99 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :THF	75.1:24.9 ( <i>P</i> = 3.02)	gravimet	13
VI-100 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> COCH <sub>3</sub>	60.0:40.0 ( <i>P</i> = 1.50)	gravimet	13
VI-101 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> COCH <sub>3</sub>	71.1:28.9 ( <i>P</i> = 2.46)	gravimet	13
VI-102 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> CN	90.0:10.0 ( <i>P</i> = 9.00)	gravimet	13
VI-103 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> CN	94.2:5.8 ( <i>P</i> = 16.2)	gravimet	13
VI-104 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :C <sub>2</sub> H <sub>5</sub> OH	88.5:11.5 ( <i>P</i> = 7.69)	gravimet	13
VI-105 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :C <sub>2</sub> H <sub>5</sub> OH	91.1:8.9 ( <i>P</i> = 10.24)	gravimet	13
VI-106 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> OH	92.1:7.9 ( <i>P</i> = 11.7)	gravimet	13
VI-107 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> OH	95.4:4.6 ( <i>P</i> = 20.7)	gravimet	13
VI-108 <sup>c</sup>	R <sub>F7</sub> C(O)NH(CH <sub>3</sub> )	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	55:45 ( <i>P</i> = 1.2) <sup>d</sup>	GLC	4a
VI-109 <sup>c</sup>	R <sub>F7</sub> C(O)N(CH <sub>3</sub> ) <sub>2</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	58:42 ( <i>P</i> = 1.4) <sup>d</sup>	GLC	4a
VI-110 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	35:65 ( <i>P</i> = 0.54) <sup>d</sup>	GLC	4a
VI-111 <sup>c</sup>	[R <sub>F8</sub> (CH <sub>2</sub> ) <sub>3</sub> ] <sub>2</sub> C(CO <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	85.1:14.9 ( <i>P</i> = 5.70) <sup>d</sup>	gravimet	14
VI-112 <sup>c</sup>	[R <sub>F8</sub> (CH <sub>2</sub> ) <sub>3</sub> ] <sub>2</sub> CH(CO <sub>2</sub> H)	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	97.1:2.9 ( <i>P</i> = 33.1) <sup>d</sup>	gravimet	14
	[(R <sub>F6</sub> (CH <sub>2</sub> ) <sub>2</sub> ) <sub>3</sub> Si(CH <sub>2</sub> ) <sub>3</sub> ]NRR'				
VI-113 <sup>i</sup>	R = H, R' = 	C <sub>6</sub> F <sub>14</sub> :CHCl <sub>3</sub>	21:79 ( <i>P</i> = 0.27)	gravimet or HPLC	15
VI-114 <sup>i</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> CN	50.0:50.0 ( <i>P</i> = 1.00)	gravimet or HPLC	15
VI-115 <sup>i</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> OH	21:79 ( <i>P</i> = 0.27)	gravimet or HPLC	15

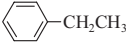
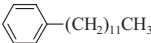




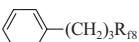
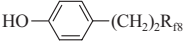
Tab. 6-1. (continued)

Entry	Solute <sup>b</sup>	Solvent system	Partitioning fluorous: organic ( <i>P</i> )	Method	Ref.
VI-116 <sup>i</sup>	R = H, R' = 	C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> CN	55:45 ( <i>P</i> = 1.2)	gravimet or HPLC	15
VI-117 <sup>i</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> OH	57:43 ( <i>P</i> = 1.3)	gravimet or HPLC	15
VI-118 <sup>i</sup>	R = CH <sub>3</sub> , R' = 	C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> CN	64:36 ( <i>P</i> = 1.8)	gravimet or HPLC	15
VI-119 <sup>i</sup>	$[(R_f6(CH_2)_2)_3Si(CH_2)_3]_2NR$	C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> OH	73:27 ( <i>P</i> = 2.7)	gravimet or HPLC	15
VI-120 <sup>i</sup>	R = 	C <sub>6</sub> F <sub>14</sub> :CHCl <sub>3</sub>	96:4 ( <i>P</i> = 26)	gravimet or HPLC	15
VI-121 <sup>i</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> CN	>99.0:<1.0 ( <i>P</i> > 100)	gravimet or HPLC	15
VI-122 <sup>i</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> OH	>99.0:<1.0 ( <i>P</i> > 100)	gravimet or HPLC	15
VI-123 <sup>i</sup>		C <sub>6</sub> F <sub>14</sub> :THF	90:10 ( <i>P</i> = 9.0)	gravimet or HPLC	15
VI-124 <sup>i</sup>	R = 	C <sub>6</sub> F <sub>14</sub> :CHCl <sub>3</sub>	86:14 ( <i>P</i> = 6)	gravimet or HPLC	15
VI-125 <sup>i</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> OH	>99.0:<1.0 ( <i>P</i> > 100)	gravimet or HPLC	15
VI-126 <sup>i</sup>	R = 	C <sub>6</sub> F <sub>14</sub> :CHCl <sub>3</sub>	96:4 ( <i>P</i> = 27)	gravimet or HPLC	15
VI-127 <sup>i</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> CN	>98:<2 ( <i>P</i> > 50)	gravimet or HPLC	15
VI-128 <sup>i</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> OH	>99.0:<1.0 ( <i>P</i> > 100)	gravimet or HPLC	15
VI-129 <sup>i</sup>		C <sub>6</sub> F <sub>14</sub> :THF	92:8 ( <i>P</i> = 11)	gravimet or HPLC	15
VI-130 <sup>i</sup>	R = 	C <sub>6</sub> F <sub>14</sub> :CHCl <sub>3</sub>	97:3 ( <i>P</i> = 37)	gravimet or HPLC	15
VI-131 <sup>i</sup>		C <sub>6</sub> F <sub>14</sub> :THF	94:6 ( <i>P</i> = 16)	gravimet or HPLC	15

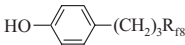
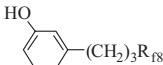
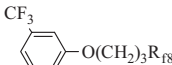
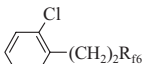
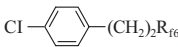
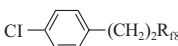
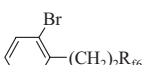
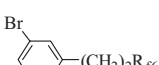
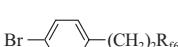
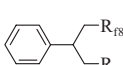
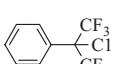
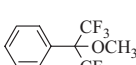
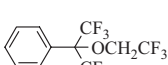
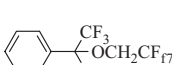
for further compounds see XIV, XV,  
XVII, and Table 6-2



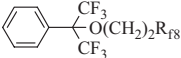
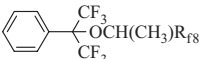
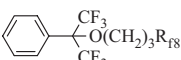

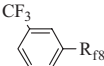
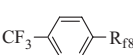
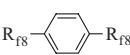
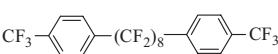
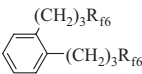
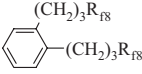
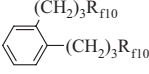
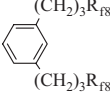

Tab. 6-1. (continued)

Entry	Solute <sup>b</sup>	Solvent system	Partitioning fluorous: organic ( <i>P</i> )	Method	Ref.
VII	Arenes, Aryl Halides, Phenols				
VII-1 <sup>c</sup>	C <sub>6</sub> H <sub>6</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	6:94 ( <i>P</i> = 0.063) <sup>d</sup>	GLC	4a
VII-2	C <sub>6</sub> HF <sub>5</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	22.4:77.6 ( <i>P</i> = 0.289)	GLC	1
VII-3	C <sub>6</sub> F <sub>6</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	28.0:72.0 ( <i>P</i> = 0.389)	GLC	1
VII-4		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	1.2:98.8 ( <i>P</i> = 0.012)	GLC	1
VII-5		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	0.9:99.1 ( <i>P</i> = 0.009)	GLC	1
VII-6 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	12.4:87.6 ( <i>P</i> = 0.142) <sup>d</sup>	GLC	4a
VII-7 <sup>i</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> CN	12:88 ( <i>P</i> = 0.13)	GLC	12
VII-8 <sup>i</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> OH	17:83 ( <i>P</i> = 0.21)	GLC	12
VII-9 <sup>i</sup>		C <sub>6</sub> F <sub>14</sub> :C <sub>2</sub> H <sub>5</sub> OH	15:85 ( <i>P</i> = 0.18)	GLC	12
VII-10 <sup>i</sup>		C <sub>6</sub> F <sub>14</sub> :C <sub>6</sub> H <sub>6</sub>	15:85 ( <i>P</i> = 0.18)	GLC	12
VII-11 <sup>i</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>2</sub> Cl <sub>2</sub>	14:86 ( <i>P</i> = 0.16)	GLC	12
VII-12 <sup>i</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> COCH <sub>3</sub>	7:93 ( <i>P</i> = 0.08)	GLC	12
VII-13 <sup>i</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	12:88 ( <i>P</i> = 0.13)	GLC	12
VII-14 <sup>i</sup>		C <sub>6</sub> F <sub>14</sub> :CHCl <sub>3</sub>	14:86 ( <i>P</i> = 0.16)	GLC	12
VII-15 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	63:37 ( <i>P</i> = 1.7) <sup>d</sup>	GLC	4a
VII-16 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	77.5:22.5 ( <i>P</i> = 3.46) <sup>d</sup>	GLC	4a
VII-17 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	85.4:14.6 ( <i>P</i> = 5.87) <sup>d</sup>	GLC	4a
VII-18		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	49.5:50.5 ( <i>P</i> = 0.980)	GLC	1
VII-19		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	20:80 ( <i>P</i> = 0.25)	<sup>1</sup> H and <sup>19</sup> F NMR	16

Tab. 6-1. (continued)

Entry	Solute <sup>b</sup>	Solvent system	Partitioning fluorous: organic (P)	Method	Ref.
VII-20		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	12:88 (P = 0.14)	<sup>1</sup> H and <sup>19</sup> F NMR	16
VII-21		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	14:86 (P = 0.16)	<sup>1</sup> H and <sup>19</sup> F NMR	16
VII-22 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	55:45 (P = 1.2) <sup>d</sup>	GLC	11
VII-23 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	35:65 (P = 0.53) <sup>d</sup>	GLC	4a
VII-24 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	26.5:73.5 (P = 0.360) <sup>d</sup>	GLC	4a
VII-25 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	41:59 (P = 0.69) <sup>d</sup>	GLC	4a
VII-26 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	25.9:74.1 (P = 0.350) <sup>d</sup>	GLC	4a
VII-27 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	19.2:80.8 (P = 0.237) <sup>d</sup>	GLC	4a
VII-28 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	18.4:81.6 (P = 0.225) <sup>d</sup>	GLC	4a
VII-29 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	97.9:2.1 (P = 46.6)	GLC	17
VII-30 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	11.5:88.5 (P = 0.130) <sup>d</sup>	GLC	11
VII-31 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	13.8:86.2 (P = 0.160) <sup>d</sup>	GLC	11
VII-32 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	35:65 (P = 0.54) <sup>d</sup>	GLC	11
VII-33 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	87.0:13.0 (P = 6.69) <sup>d</sup>	GLC	11

Tab. 6-1. (continued)

Entry	Solute <sup>b</sup>	Solvent system	Partitioning fluorous: organic ( <i>P</i> )	Method	Ref.
VII-34 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	81.2:18.8 ( <i>P</i> = 4.31) <sup>d</sup>	GLC	11
VII-35 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	80.0:20.0 ( <i>P</i> = 4.01) <sup>d</sup>	GLC	11
VII-36 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	76.1:23.9 ( <i>P</i> = 3.19) <sup>d</sup>	GLC	11
VII-37 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	81.8:18.2 ( <i>P</i> = 4.48) <sup>d</sup>	GLC	4a
VII-38 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	91.5:8.5 ( <i>P</i> = 10.7) <sup>d</sup>	GLC	4a
VII-39 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	89.4:10.6 ( <i>P</i> = 8.41) <sup>d</sup>	GLC	4a
VII-40 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	99.3:0.7 ( <i>P</i> = 145) <sup>d</sup>	GLC	4a
VII-41 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	36:64 ( <i>P</i> = 0.57) <sup>d</sup>	GLC	4a
VII-42		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	73.7:26.3 ( <i>P</i> = 2.80)	GLC	1
VII-43		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	91.2:8.8 ( <i>P</i> = 10.4)	GLC	1
VII-44		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	97.4:2.6 ( <i>P</i> = 37.5)	GLC	1
VII-45		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	90.7:9.3 ( <i>P</i> = 9.75)	GLC	1
VII-46		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	91.1:8.9 ( <i>P</i> = 10.2)	GLC	1

Tab. 6-1. (continued)

Entry	Solute <sup>b</sup>	Solvent system	Partitioning fluorous: organic ( <i>P</i> )	Method	Ref.
VII-47		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	70:30 ( <i>P</i> = 2.3)	<sup>1</sup> H and <sup>19</sup> F NMR	16
VII-48		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	72:28 ( <i>P</i> = 2.6)	<sup>1</sup> H and <sup>19</sup> F NMR	16
VII-49		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	69.5:30.5 ( <i>P</i> = 2.28)	GLC	18
VII-50		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> OH	97.0:3.0 ( <i>P</i> = 32.3)	GLC	18
VII-51		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	74.7:25.3 ( <i>P</i> = 2.95)	GLC	18
VII-52		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> OH	98.6:1.4 ( <i>P</i> = 70.4)	GLC	18
VII-53		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	73.9:26.1 ( <i>P</i> = 2.83)	GLC	18
VII-54		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> OH	98.0:2.0 ( <i>P</i> = 49.0)	GLC	18
VII-55 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	29:71 ( <i>P</i> = 0.41) <sup>d</sup>	GLC	11
VII-56 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	76.7:23.3 ( <i>P</i> = 3.29) <sup>d</sup>	GLC	11
VII-57 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	99.1:0.9 ( <i>P</i> = 107) <sup>d</sup>	GLC	11

Tab. 6-1. (continued)

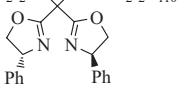


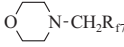
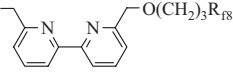
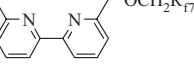
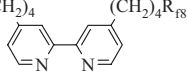
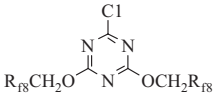
Entry	Solute <sup>b</sup>	Solvent system	Partitioning fluorous: organic ( <i>P</i> )	Method	Ref.
VII-58 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	4:96 ( <i>P</i> = 0.044) <sup>d</sup>	GLC	19
VII-59 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	98.0:2.0 ( <i>P</i> = 49.9) <sup>d</sup>	GLC	11
VII-60 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	98.3:1.7 ( <i>P</i> = 58.6) <sup>d</sup>	GLC	4a
VII-61		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	>99.7:<0.3 ( <i>P</i> > 332)	GLC	1
VII-62		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	98.0:2.0 ( <i>P</i> = 49.0)	GLC	18
VII-63		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> OH	>99.7:<0.3 ( <i>P</i> > 332)	GLC	18
VII-64 <sup>g</sup>	<i>n</i> = 6	C <sub>6</sub> F <sub>14</sub> :CHCl <sub>3</sub>	95:5 ( <i>P</i> = 19)	gravimet	20
VII-65 <sup>g</sup>	<i>n</i> = 6	C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	98:2 ( <i>P</i> = 49)	gravimet	20
VII-66 <sup>g</sup>	<i>n</i> = 8	C <sub>6</sub> F <sub>14</sub> :CH <sub>2</sub> Cl <sub>2</sub>	99:1 ( <i>P</i> = 99)	gravimet	20
VII-67 <sup>g</sup>	<i>n</i> = 8	C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	99:1 ( <i>P</i> = 99)	gravimet	20

for further compounds see III, IV, VI,  
VIII, X, XI, XIII, XIV, XV, XVI and XVII


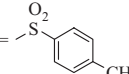
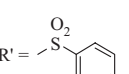
Tab. 6-1. (continued)

Entry	Solute <sup>b</sup>	Solvent system	Partitioning fluorous: organic ( <i>P</i> )	Method	Ref.
VIII	Nitrogen Heterocycles				
VIII-1 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	63:37 ( <i>P</i> = 1.7) <sup>d</sup>	GLC	4a
VIII-2 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	71:29 ( <i>P</i> = 2.4) <sup>d</sup>	GLC	4a
VIII-3 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	69:31 ( <i>P</i> = 2.2) <sup>d</sup>	GLC	4a
VIII-4		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	93.8:6.2 ( <i>P</i> = 15.1)	GLC	21
VIII-5		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	90.4:9.6 ( <i>P</i> = 9.42)	GLC	21
VIII-6		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	93.9:6.1 ( <i>P</i> = 15.4)	GLC	21
VIII-7		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	>99.7:<0.3 ( <i>P</i> > 332)	GLC	21
VIII-8		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	93.6:6.4 ( <i>P</i> = 14.6)	GLC	21
VIII-9		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	79.3:20.7 ( <i>P</i> = 3.83)	GLC	21
VIII-10 <sup>c</sup>		C <sub>8</sub> F <sub>18</sub> :CH <sub>2</sub> Cl <sub>2</sub>	82:18 ( <i>P</i> = 4.7)	gravimet	22
VIII-11 <sup>c</sup>		C <sub>8</sub> F <sub>18</sub> :CH <sub>3</sub> CN	94.6:5.4 ( <i>P</i> = 17.5)	gravimet	22
VIII-12 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>2</sub> Cl <sub>2</sub>	14:86 ( <i>P</i> = 0.16)	—	23
VIII-13 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	20:80 ( <i>P</i> = 0.25)	—	23

Tab. 6-1. (continued)

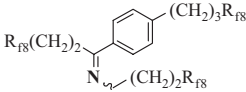
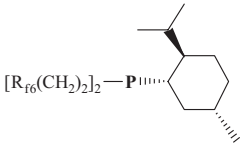
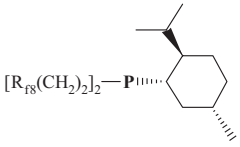
Entry	Solute <sup>b</sup>	Solvent system	Partitioning fluorous: organic ( <i>P</i> )	Method	Ref.
VIII-14 <sup>c</sup>	$R_{f10}(CH_2)_2$ 	$C_6F_{14}:CH_2Cl_2$	30:70 ( <i>P</i> = 0.42)	–	23
VIII-15 <sup>c</sup>		$C_6F_{14}:CH_3C_6H_5$	40:60 ( <i>P</i> = 0.67)	–	23
VIII-16 <sup>c</sup>		$CF_3C_6F_{11}:CH_3C_6H_5$	71:29 ( <i>P</i> = 2.4) <sup>d</sup>	GLC	24
VIII-17 <sup>c</sup>		$CF_3C_6F_{11}:CH_3C_6H_5$	55:45 ( <i>P</i> = 1.2) <sup>d</sup>	GLC	24
VIII-18 <sup>i</sup>	$R_{f8}(CH_2)_3O$ 	$n-C_8F_{18}:CH_2Cl_2$	20:80 ( <i>P</i> = 0.25)	gravimet	25a
VIII-19 <sup>i</sup>	$R_{f7}CH_2O$ 	$n-C_8F_{18}:CH_2Cl_2$	51.9:48.1 ( <i>P</i> = 1.08)	gravimet	25a
VIII-20 <sup>i</sup>	$R_{f8}(CH_2)_4$ 	$n-C_8F_{18}:CH_2Cl_2$	40:60 ( <i>P</i> = 0.67)	gravimet	25a
VIII-21 <sup>c</sup>		$CF_3C_6F_{11}:CH_3C_6H_5$	95.7:4.3 ( <i>P</i> = 22.0)	gravimet	25b
VIII-22 <sup>c</sup>		$CF_3C_6F_{11}:CH_2Cl_2$	95.2:4.8 ( <i>P</i> = 20.0)	gravimet	25b
VIII-23 <sup>c</sup>		$CF_3C_6F_{11}:THF$	83.6:16.4 ( <i>P</i> = 5.10)	gravimet	25b
	for further compounds see XIV				
IX	<b>Aliphatic Halides</b>				
IX-1 <sup>c</sup>	$R_{f6}I$	$CF_3C_6F_{11}:CH_3C_6H_5$	78.8:21.2 ( <i>P</i> = 3.71) <sup>d</sup>	GLC	4a
IX-2 <sup>c</sup>	$R_{f8}I$	$CF_3C_6F_{11}:CH_3C_6H_5$	88.5:11.5 ( <i>P</i> = 7.69) <sup>d</sup>	GLC	4a, 24
IX-3 <sup>c</sup>	$R_{f10}I$	$CF_3C_6F_{11}:CH_3C_6H_5$	94.5:5.5 ( <i>P</i> = 17.1) <sup>d</sup>	GLC	4a
IX-4	$R_{f8}(CH_2)_3I$	$CF_3C_6F_{11}:CH_3C_6H_5$	50.7:49.3 ( <i>P</i> = 1.03)	GLC	1
	for further compounds see VII				
X	<b>Amines, Imines and related Compounds</b>				
X-1	$R_{f8}(CH_2)_3NH_2$	$CF_3C_6F_{11}:CH_3C_6H_5$	70.0:30.0 ( <i>P</i> = 2.33)	GLC	4b, 26
X-2	$R_{f8}(CH_2)_4NH_2$	$CF_3C_6F_{11}:CH_3C_6H_5$	63.2:36.8 ( <i>P</i> = 1.72)	GLC	26

Tab. 6-1. (continued)

Entry	Solute <sup>b</sup>	Solvent system	Partitioning fluorous: organic ( <i>P</i> )	Method	Ref.
X-3	R <sub>f8</sub> (CH <sub>2</sub> ) <sub>5</sub> NH <sub>2</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	56.9:43.1 ( <i>P</i> = 1.32)	GLC	26
X-4 <sup>c</sup>	R <sub>f7</sub> CH <sub>2</sub> NH(CH <sub>3</sub> )	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	74.5:25.5 ( <i>P</i> = 2.92) <sup>d</sup>	GLC	4a
X-5 <sup>c</sup>	R <sub>f7</sub> 	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	30:70 ( <i>P</i> = 0.42) <sup>d</sup>	GLC	24
X-6 <sup>c</sup>	R <sub>f8</sub> (CH <sub>2</sub> ) <sub>3</sub> NH(CH <sub>3</sub> )	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	71:29 ( <i>P</i> = 2.4) <sup>d</sup>	GLC	4b
X-7	[R <sub>f8</sub> (CH <sub>2</sub> ) <sub>3</sub> ] <sub>2</sub> NH	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	96.5:3.5 ( <i>P</i> = 27.6)	GLC	4b, 26
X-8	[R <sub>f8</sub> (CH <sub>2</sub> ) <sub>4</sub> ] <sub>2</sub> NH	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	95.1:4.9 ( <i>P</i> = 19.4)	GLC	26
X-9	[R <sub>f8</sub> (CH <sub>2</sub> ) <sub>5</sub> ] <sub>2</sub> NH	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	93.0:7.0 ( <i>P</i> = 13.3)	GLC	26
X-10 <sup>c</sup>	R <sub>f7</sub> CH <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	82.2:17.8 ( <i>P</i> = 4.62) <sup>d</sup>	GLC	24
X-11 <sup>c</sup>	R <sub>f8</sub> (CH <sub>2</sub> ) <sub>3</sub> N(CH <sub>3</sub> ) <sub>2</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	79.8:20.2 ( <i>P</i> = 3.94) <sup>d</sup>	GLC	4b
X-12 <sup>c</sup>	[R <sub>f8</sub> (CH <sub>2</sub> ) <sub>3</sub> ] <sub>2</sub> N(CH <sub>3</sub> )	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	97.4:2.6 ( <i>P</i> = 37.7) <sup>d</sup>	GLC	4b
X-13	[R <sub>f8</sub> (CH <sub>2</sub> ) <sub>3</sub> ] <sub>3</sub> N	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	>99.7:<0.3 ( <i>P</i> > 332)	GLC	4b, 26
X-14	[R <sub>f8</sub> (CH <sub>2</sub> ) <sub>4</sub> ] <sub>3</sub> N	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	>99.7:<0.3 ( <i>P</i> > 332)	GLC	26
X-15	[R <sub>f8</sub> (CH <sub>2</sub> ) <sub>5</sub> ] <sub>3</sub> N [(R <sub>f6</sub> (CH <sub>2</sub> ) <sub>2</sub> ) <sub>3</sub> Si(CH <sub>2</sub> ) <sub>3</sub> ]NRR'	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	99.5:0.5 ( <i>P</i> = 199)	GLC	26
X-16 <sup>j</sup>	R = H, R' = 	C <sub>6</sub> F <sub>14</sub> :CHCl <sub>3</sub>	42:58 ( <i>P</i> = 0.71)	gravimet or HPLC	15
X-17 <sup>j</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> CN	27:73 ( <i>P</i> = 0.37)	gravimet or HPLC	15
X-18 <sup>j</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> OH	67:33 ( <i>P</i> = 2.0)	gravimet or HPLC	15
X-19 <sup>j</sup>		C <sub>6</sub> F <sub>14</sub> :THF	5:95 ( <i>P</i> = 0.05)	gravimet or HPLC	15
X-20 <sup>j</sup>	R = CH <sub>3</sub> , R' = 	C <sub>6</sub> F <sub>14</sub> :CHCl <sub>3</sub>	17:83 ( <i>P</i> = 0.20)	gravimet or HPLC	15
X-21 <sup>j</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> CN	44:56 ( <i>P</i> = 0.77)	gravimet or HPLC	15



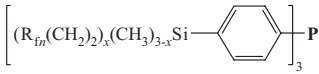
Tab. 6-1. (continued)

Entry	Solute <sup>b</sup>	Solvent system	Partitioning fluorous: organic ( <i>P</i> )	Method	Ref.
X-22 <sup>i</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> OH	87:13 ( <i>P</i> = 6.5)	gravimet or HPLC	15
X-23 <sup>i</sup>		C <sub>6</sub> F <sub>14</sub> :THF	9:91 ( <i>P</i> = 0.10)	gravimet or HPLC	15
X-24	 for further compounds see IV	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	98.7:1.3 ( <i>P</i> = 75.9)	GLC	7, 27
<b>XI</b>	<b>Phosphorus Compounds</b>				
XI-1 <sup>k</sup>	[R <sub>f6</sub> (CH <sub>2</sub> ) <sub>2</sub> ] <sub>3</sub> P	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	98.8:1.2 ( <i>P</i> = 82.3)	GLC	28
XI-2 <sup>k</sup>	[R <sub>f8</sub> (CH <sub>2</sub> ) <sub>2</sub> ] <sub>3</sub> P	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	>99.7:<0.3 ( <i>P</i> > 332)	GLC	28
XI-3 <sup>k</sup>	[R <sub>f10</sub> (CH <sub>2</sub> ) <sub>2</sub> ] <sub>3</sub> P	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	>99.7:<0.3 ( <i>P</i> > 332)	GLC	28
XI-4 <sup>k</sup>	[R <sub>f8</sub> (CH <sub>2</sub> ) <sub>3</sub> ] <sub>3</sub> P	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	98.8:1.2 ( <i>P</i> = 82.3)	GLC	28
XI-5 <sup>k</sup>	[R <sub>f8</sub> (CH <sub>2</sub> ) <sub>4</sub> ] <sub>3</sub> P	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	98.9:1.1 ( <i>P</i> = 89.9)	GLC	28
XI-6 <sup>k</sup>	[R <sub>f8</sub> (CH <sub>2</sub> ) <sub>5</sub> ] <sub>3</sub> P	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	98.9:1.1 ( <i>P</i> = 89.9)	GLC	29
XI-7 <sup>k</sup>	[R <sub>f6</sub> (CH <sub>2</sub> ) <sub>2</sub> ] <sub>3</sub> P=O	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	>99.7:<0.3 ( <i>P</i> > 332)	GLC	28
XI-8 <sup>k</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	78.4:21.6 ( <i>P</i> = 3.63)	GLC	30
XI-9 <sup>k</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	93.7:6.3 ( <i>P</i> = 14.9)	GLC	30
XI-10 <sup>j</sup>	(C <sub>6</sub> H <sub>5</sub> ) <sub>3</sub> P	C <sub>6</sub> F <sub>14</sub> :C <sub>5</sub> H <sub>12</sub>	<0.5:>99.5 ( <i>P</i> < 0.005)	–	31
XI-11	(4-R <sub>f6</sub> C <sub>6</sub> H <sub>4</sub> ) <sub>3</sub> P	1,3-(CF <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> F <sub>10</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	81:19 ( <i>P</i> = 4.4)	gravimet	32
XI-12		1,3-(CF <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> F <sub>10</sub> :THF	69:31 ( <i>P</i> = 2.2)	gravimet	32
XI-13	[4-R <sub>f6</sub> (CH <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>4</sub> ] <sub>3</sub> P	1,3-(CF <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> F <sub>10</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	47:53 ( <i>P</i> = 0.9)	gravimet	32

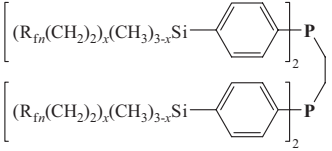
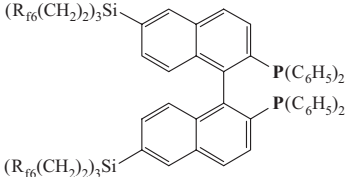
Tab. 6-1. (continued)

Entry	Solute <sup>b</sup>	Solvent system	Partitioning fluorous: organic ( <i>P</i> )	Method	Ref.
XI-14		1,3-(CF <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> F <sub>10</sub> :THF	17:83 ( <i>P</i> = 0.2)	gravimet	32
XI-15 <sup>g</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> OH	96.8:3.2 ( <i>P</i> = 30.03)	HPLC	33
XI-16 <sup>g</sup>		C <sub>6</sub> F <sub>14</sub> :THF	7:93 ( <i>P</i> = 0.08)	HPLC	33
XI-17 <sup>g</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	43:57 ( <i>P</i> = 0.75)	HPLC	33
XI-18 <sup>k</sup>	[4-R <sub>f6</sub> (CH <sub>2</sub> ) <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ] <sub>3</sub> P	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	19.5:80.5 ( <i>P</i> = 0.242)	GLC	34
XI-19 <sup>k</sup>	[4-R <sub>f8</sub> (CH <sub>2</sub> ) <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ] <sub>3</sub> P	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	66.6:33.4 ( <i>P</i> = 1.99)	GLC	34
XI-20 <sup>c</sup>	[4-R <sub>f8</sub> (CH <sub>2</sub> ) <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ] <sub>3</sub> P→BH <sub>3</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	37.3:62.7 ( <i>P</i> = 0.595)	<sup>31</sup> P NMR	17
XI-21 <sup>c</sup>	[4-(R <sub>f8</sub> CH <sub>2</sub> ) <sub>2</sub> CH(CH <sub>2</sub> ) <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ] <sub>3</sub> P→BH <sub>3</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	96.6:3.4 ( <i>P</i> = 28.4)	<sup>19</sup> F NMR	17
XI-22 <sup>g</sup>	[4-R <sub>f6</sub> (CH <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>4</sub> ] <sub>2</sub> PC <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> OH	65.0:35.0 ( <i>P</i> = 1.86)	HPLC	33
XI-23 <sup>g</sup>		C <sub>6</sub> F <sub>14</sub> :THF	5:95 ( <i>P</i> = 0.05)	HPLC	33
XI-24 <sup>g</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	5:95 ( <i>P</i> = 0.05)	HPLC	33
XI-25 <sup>g</sup>	4-R <sub>f6</sub> (CH <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>4</sub> P(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub>	C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> OH	11:89 ( <i>P</i> = 0.12)	HPLC	33
XI-26 <sup>g</sup>		C <sub>6</sub> F <sub>14</sub> :THF	2:98 ( <i>P</i> = 0.02)	HPLC	33
XI-27 <sup>g</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	5:95 ( <i>P</i> = 0.05)	HPLC	33
XI-28 <sup>g</sup>	[4-R <sub>f3</sub> (CF <sub>3</sub> ) <sub>2</sub> CCH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> ] <sub>3</sub> P	C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> OH	94.9:5.1 ( <i>P</i> = 18.48)	HPLC	33
XI-29 <sup>g</sup>		C <sub>6</sub> F <sub>14</sub> :THF	34:66 ( <i>P</i> = 0.51)	HPLC	33
XI-30 <sup>g</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	87.2:12.8 ( <i>P</i> = 6.84)	HPLC	33
XI-31 <sup>g</sup>	[4-R <sub>f3</sub> (CF <sub>3</sub> ) <sub>2</sub> CCH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> ] <sub>2</sub> PC <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> OH	77.0:23.0 ( <i>P</i> = 3.34)	HPLC	33
XI-32 <sup>g</sup>		C <sub>6</sub> F <sub>14</sub> :THF	51.2:48.8 ( <i>P</i> = 1.05)	HPLC	33
XI-33 <sup>g</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	15:85 ( <i>P</i> = 0.18)	HPLC	33
XI-34 <sup>g</sup>	4-R <sub>f3</sub> (CF <sub>3</sub> ) <sub>2</sub> CCH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> P(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub>	C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> OH	8:92 ( <i>P</i> = 0.09)	HPLC	33
XI-35 <sup>g</sup>		C <sub>6</sub> F <sub>14</sub> :THF	1:99 ( <i>P</i> = 0.01)	HPLC	33
XI-36 <sup>g</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	11:89 ( <i>P</i> = 0.12)	HPLC	33

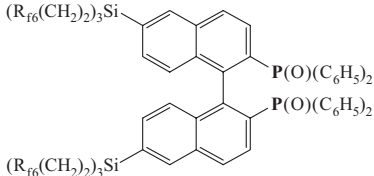
Tab. 6-1. (continued)

Entry	Solute <sup>b</sup>	Solvent system	Partitioning fluorous: organic ( <i>P</i> )	Method	Ref.
XI-37 <sup>j</sup>	$[4-(\text{CH}_3)_3\text{SiC}_6\text{H}_4]_3\text{P}$	$\text{C}_6\text{F}_{14}:\text{C}_5\text{H}_{12}$	<4:>96 ( $P < 0.044$ )	–	31
XI-38 <sup>l</sup>		$\text{C}_6\text{F}_{14}:n\text{-C}_6\text{H}_{14}$	<1:>99 ( $P < 0.01$ )	–	31
	$\left[ (\text{R}_{\text{fin}}(\text{CH}_2)_2)_x(\text{CH}_3)_{3-x}\text{Si}-\text{C}_6\text{H}_4 \right]_3\text{P}$ 				
XI-39 <sup>m</sup>	$x = 1, n = 6$	$\text{CF}_3\text{C}_6\text{F}_{11}:\text{CH}_3\text{C}_6\text{H}_5$	21:79 ( $P = 0.26$ )	ICP-AAS <sup>n</sup>	35, 36
XI-40 <sup>m</sup>		$\text{CF}_3\text{C}_6\text{F}_{11}:n\text{-C}_8\text{H}_{18}$	52:48 ( $P = 1.1$ )	ICP-AAS <sup>n</sup>	36
XI-41 <sup>m</sup>		$\text{CF}_3\text{C}_6\text{F}_{11}:n\text{-C}_5\text{H}_{12}$	60:40 ( $P = 1.5$ )	ICP-AAS <sup>n</sup>	36
XI-42 <sup>m</sup>	$x = 1, n = 8$	$\text{CF}_3\text{C}_6\text{F}_{11}:\text{CH}_3\text{C}_6\text{H}_5$	69:31 ( $P = 2.2$ )	ICP-AAS <sup>n</sup>	35, 36
XI-43 <sup>m</sup>		$\text{CF}_3\text{C}_6\text{F}_{11}:n\text{-C}_8\text{H}_{18}$	82:18 ( $P = 4.6$ )	ICP-AAS <sup>n</sup>	36
XI-44 <sup>m</sup>		$\text{CF}_3\text{C}_6\text{F}_{11}:n\text{-C}_5\text{H}_{12}$	69:31 ( $P = 2.2$ )	ICP-AAS <sup>n</sup>	36
XI-45 <sup>j</sup>		$\text{C}_6\text{F}_{14}:\text{C}_5\text{H}_{12}$	12:88 ( $P = 0.14$ )	–	31
XI-46 <sup>l</sup>		$\text{C}_6\text{F}_{14}:n\text{-C}_6\text{H}_{14}$	43.5:56.5 ( $P = 0.770$ )	–	31
XI-47 <sup>m</sup>	$x = 2, n = 6$	$\text{CF}_3\text{C}_6\text{F}_{11}:\text{CH}_3\text{C}_6\text{H}_5$	89:11 ( $P = 7.8$ )	ICP-AAS <sup>n</sup>	36
XI-48 <sup>m</sup>		$\text{CF}_3\text{C}_6\text{F}_{11}:n\text{-C}_8\text{H}_{18}$	94:6 ( $P = 17$ )	ICP-AAS <sup>n</sup>	36
XI-49 <sup>m</sup>		$\text{CF}_3\text{C}_6\text{F}_{11}:n\text{-C}_5\text{H}_{12}$	85:15 ( $P = 5.7$ )	ICP-AAS <sup>n</sup>	36
XI-50 <sup>m</sup>	$x = 2, n = 8$	$\text{CF}_3\text{C}_6\text{F}_{11}:\text{CH}_3\text{C}_6\text{H}_5$	89:11 ( $P = 7.8$ )	ICP-AAS <sup>n</sup>	36
XI-51 <sup>m</sup>		$\text{CF}_3\text{C}_6\text{F}_{11}:n\text{-C}_8\text{H}_{18}$	97:3 ( $P = 28$ )	ICP-AAS <sup>n</sup>	36
XI-52 <sup>m</sup>		$\text{CF}_3\text{C}_6\text{F}_{11}:n\text{-C}_5\text{H}_{12}$	90:10 ( $P = 9.2$ )	ICP-AAS <sup>n</sup>	36
XI-53 <sup>m</sup>	$x = 3, n = 6$	$\text{CF}_3\text{C}_6\text{F}_{11}:\text{CH}_3\text{C}_6\text{H}_5$	81:19 ( $P = 4.3$ )	ICP-AAS <sup>n</sup>	36
XI-54 <sup>m</sup>		$\text{CF}_3\text{C}_6\text{F}_{11}:n\text{-C}_8\text{H}_{18}$	90:10 ( $P = 9.4$ )	ICP-AAS <sup>n</sup>	36
XI-55 <sup>m</sup>		$\text{CF}_3\text{C}_6\text{F}_{11}:n\text{-C}_5\text{H}_{12}$	94:6 ( $P = 15$ )	ICP-AAS <sup>n</sup>	36
XI-56 <sup>m</sup>	$x = 3, n = 8$	$\text{CF}_3\text{C}_6\text{F}_{11}:\text{CH}_3\text{C}_6\text{H}_5$	68:32 ( $P = 2.1$ )	ICP-AAS <sup>n</sup>	36
XI-57 <sup>m</sup>		$\text{CF}_3\text{C}_6\text{F}_{11}:n\text{-C}_8\text{H}_{18}$	92:8 ( $P = 12$ )	ICP-AAS <sup>n</sup>	36

Tab. 6-1. (continued)

Entry	Solute <sup>b</sup>	Solvent system	Partitioning fluorous: organic (P)	Method	Ref.
XI-58 <sup>m</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> : <i>n</i> -C <sub>5</sub> H <sub>12</sub>	95:5 (P = 20)	ICP-AAS <sup>n</sup>	36
XI-59 <sup>m</sup>	<i>x</i> = 0	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	0:100 (P = 0.0)	gravimet	37
XI-60 <sup>m</sup>	<i>x</i> = 1, <i>n</i> = 6	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	29:71 (P = 0.4)	gravimet	37
XI-61 <sup>m</sup>	<i>x</i> = 2, <i>n</i> = 6	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	92:8 (P = 12)	gravimet	37
XI-62 <sup>m</sup>	<i>x</i> = 3, <i>n</i> = 6	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	>98:<2 (P > 50)	gravimet	37
XI-63 <sup>c</sup>	(4-R <sub>f7</sub> CH <sub>2</sub> OC <sub>6</sub> H <sub>4</sub> ) <sub>2</sub> PC <sub>6</sub> H <sub>5</sub>	Galden D-100:C <sub>2</sub> H <sub>5</sub> OH	62:38 (P = 1.6)	gravimet or ICP-AES <sup>o</sup>	38
XI-64 <sup>c</sup>	(4-R <sub>f7</sub> CH <sub>2</sub> OC <sub>6</sub> H <sub>4</sub> ) <sub>3</sub> P	Galden D-100:C <sub>2</sub> H <sub>5</sub> OH	96.1:3.9 (P = 24.6)	gravimet or ICP-AES <sup>o</sup>	38
XI-65 <sup>c</sup>		Galden D-100:THF	38:62 (P = 0.6)	gravimet or ICP-AES <sup>o</sup>	38
XI-66 <sup>c</sup>		Galden D-100:CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	91.2:8.8 (P = 10.4)	gravimet or ICP-AES <sup>o</sup>	38
XI-67 <sup>c</sup>		Galden D-100:CH <sub>3</sub> CN	52:48 (P = 1.1)	gravimet or ICP-AES <sup>o</sup>	38
XI-68 <sup>c</sup>		Galden D-100:CH <sub>3</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	41:59 (P = 0.7)	gravimet or ICP-AES <sup>o</sup>	38
XI-69 <sup>c</sup>	(3-R <sub>f7</sub> CH <sub>2</sub> OC <sub>6</sub> H <sub>4</sub> ) <sub>3</sub> P	Galden D-100:C <sub>2</sub> H <sub>5</sub> OH	89:11 (P = 8.0)	gravimet or ICP-AES <sup>o</sup>	38
XI-70 <sup>c</sup>	(2-R <sub>f7</sub> CH <sub>2</sub> OC <sub>6</sub> H <sub>4</sub> ) <sub>3</sub> P	Galden D-100:C <sub>2</sub> H <sub>5</sub> OH	89:11 (P = 7.7)	gravimet or ICP-AES <sup>o</sup>	38
XI-71 <sup>c</sup>	[4-R <sub>f8</sub> (CH <sub>2</sub> ) <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> ] <sub>3</sub> P	Galden D-100:C <sub>2</sub> H <sub>5</sub> OH	94.9:5.1 (P = 18.6)	gravimet or ICP-AES <sup>o</sup>	38
XI-72 <sup>8</sup>		C <sub>6</sub> F <sub>14</sub> :C <sub>6</sub> H <sub>6</sub>	74:26 (P = 2.9)	HPLC	20
XI-73 <sup>8</sup>		C <sub>6</sub> F <sub>14</sub> :C <sub>6</sub> H <sub>6</sub>	79:21 (P = 3.8)	gravimet	20
XI-74 <sup>8</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> CN	98:2 (P = 49)	HPLC	20
XI-75 <sup>8</sup>		C <sub>6</sub> F <sub>14</sub> :DMF	98:2 (P = 49)	HPLC	20

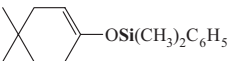

Tab. 6-1. (continued)

Entry	Solute <sup>b</sup>	Solvent system	Partitioning fluorous: organic ( <i>P</i> )	Method	Ref.
XI-76 <sup>g</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>2</sub> Cl <sub>2</sub>	76:24 ( <i>P</i> = 3.2)	gravimet	20
XI-77 <sup>g</sup>		C <sub>6</sub> F <sub>14</sub> :C <sub>6</sub> H <sub>6</sub>	90:10 ( <i>P</i> = 9.0)	gravimet	20
XI-78 <sup>g</sup>	[2-R <sub>f8</sub> (CH <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>4</sub> O] <sub>3</sub> P	C <sub>8</sub> F <sub>17</sub> H:C <sub>8</sub> H <sub>17</sub> CH=CH <sub>2</sub>	95:5 ( <i>P</i> = 19)	GLC	39
XI-79 <sup>g</sup>	[4-R <sub>f8</sub> (CH <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>4</sub> O] <sub>3</sub> P	C <sub>8</sub> F <sub>17</sub> H:C <sub>8</sub> H <sub>17</sub> CH=CH <sub>2</sub>	95:5 ( <i>P</i> = 19)	GLC	39
XI-80 <sup>g</sup>	[2,4-(R <sub>f8</sub> (CH <sub>2</sub> ) <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> O] <sub>3</sub> P	C <sub>8</sub> F <sub>17</sub> H:C <sub>8</sub> H <sub>17</sub> CH=CH <sub>2</sub>	99:1 ( <i>P</i> = 99)	GLC	39
XI-81	[3,5-(R <sub>f8</sub> (CH <sub>2</sub> ) <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> O] <sub>3</sub> P	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	92:8 ( <i>P</i> = 12)	<sup>1</sup> H and <sup>19</sup> F NMR	16
XII	<b>Tin Compounds</b>				
XII-1 <sup>g</sup>	[CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> ] <sub>3</sub> SnH	C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> CN	<0.7:>99.3 ( <i>P</i> < 0.007)	gravimet	40
XII-2 <sup>g</sup>		C <sub>6</sub> F <sub>14</sub> :C <sub>6</sub> H <sub>6</sub>	<0.3:>99.7 ( <i>P</i> < 0.003)	gravimet	40
XII-3 <sup>g</sup>	[R <sub>f4</sub> (CH <sub>2</sub> ) <sub>2</sub> ] <sub>3</sub> SnH	C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> CN	85:15 ( <i>P</i> = 5.8)	gravimet	40
XII-4 <sup>g</sup>		C <sub>6</sub> F <sub>14</sub> :C <sub>6</sub> H <sub>6</sub>	91.3:8.7 ( <i>P</i> = 10.5)	gravimet	40
XII-5 <sup>i</sup>	[R <sub>f6</sub> (CH <sub>2</sub> ) <sub>2</sub> ] <sub>3</sub> SnH	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :C <sub>6</sub> H <sub>6</sub>	97.8:2.2 ( <i>P</i> = 44.5)	gravimet	41
XII-6 <sup>j</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> OH	97.0:3.0 ( <i>P</i> = 32.3)	gravimet	41
XII-7 <sup>i</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>2</sub> Cl <sub>2</sub>	95.3:4.7 ( <i>P</i> = 20.3)	gravimet	41
XII-8 <sup>j</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	89.6:10.4 ( <i>P</i> = 8.62)	gravimet	41
XII-9 <sup>j</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CHCl <sub>3</sub>	85.9:14.1 ( <i>P</i> = 6.09)	gravimet	41
XII-10 <sup>g</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> CN	99.4:0.6 ( <i>P</i> = 160)	gravimet	40
XII-11 <sup>g</sup>		C <sub>6</sub> F <sub>14</sub> :C <sub>6</sub> H <sub>6</sub>	98:2 ( <i>P</i> = 45)	gravimet	40
XII-12 <sup>g</sup>	[R <sub>f4</sub> (CH <sub>2</sub> ) <sub>3</sub> ] <sub>3</sub> SnH	C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> CN	70:30 ( <i>P</i> = 2.3)	gravimet	40
XII-13 <sup>g</sup>		C <sub>6</sub> F <sub>14</sub> :C <sub>6</sub> H <sub>6</sub>	55:45 ( <i>P</i> = 1.2)	gravimet	40

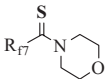
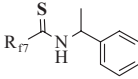
Tab. 6-1. (continued)

Entry	Solute <sup>b</sup>	Solvent system	Partitioning fluorous: organic ( <i>P</i> )	Method	Ref.
XII-14 <sup>g</sup>	$[\text{R}_{\text{f}6}(\text{CH}_2)_3]_3\text{SnH}$	$\text{C}_6\text{F}_{14}:\text{CH}_3\text{CN}$	86:14 ( <i>P</i> = 6.4)	gravimet	40
XII-15 <sup>g</sup>		$\text{C}_6\text{F}_{14}:\text{C}_6\text{H}_6$	90.9:9.1 ( <i>P</i> = 10.0)	gravimet	40
XII-16 <sup>g</sup>	$[\text{R}_{\text{f}6}(\text{CH}_2)_2]_3\text{Sn}(\text{CH}_3)_2\text{H}$	$\text{C}_6\text{F}_{14}:\text{CH}_3\text{CN}$	71:29 ( <i>P</i> = 2.4)	GLC	40
XII-17 <sup>g</sup>		$\text{C}_6\text{F}_{14}:\text{C}_6\text{H}_6$	41:59 ( <i>P</i> = 0.7)	GLC	40
XII-18 <sup>g</sup>	$[\text{R}_{\text{f}8}(\text{CH}_2)_2]_3\text{Sn}(\text{CH}_3)_2\text{H}$	$\text{C}_6\text{F}_{14}:\text{CH}_3\text{CN}$	93:7 ( <i>P</i> = 14)	GLC	40
XII-19 <sup>g</sup>		$\text{C}_6\text{F}_{14}:\text{C}_6\text{H}_6$	71:29 ( <i>P</i> = 2.5)	GLC	40
XII-20 <sup>g</sup>	$[\text{R}_{\text{f}10}(\text{CH}_2)_2]_3\text{Sn}(\text{CH}_3)_2\text{H}$	$\text{C}_6\text{F}_{14}:\text{CH}_3\text{CN}$	98:2 ( <i>P</i> = 48)	GLC	40
XII-21 <sup>g</sup>		$\text{C}_6\text{F}_{14}:\text{C}_6\text{H}_6$	82:18 ( <i>P</i> = 4.7)	GLC	40
XII-22 <sup>i</sup>	$[\text{R}_{\text{f}4}(\text{CH}_2)_2]_3\text{SnCH}_2\text{CH}=\text{CH}_2$	$\text{C}_6\text{F}_{14}:\text{CH}_3\text{CN}$	86:14 ( <i>P</i> = 6)	gravimet	42
XII-23 <sup>i</sup>		$\text{C}_6\text{F}_{14}:\text{C}_6\text{H}_6$	90:10 ( <i>P</i> = 9)	gravimet	42
XII-24 <sup>i</sup>	$[\text{R}_{\text{f}6}(\text{CH}_2)_2]_3\text{SnCH}_2\text{CH}=\text{CH}_2$	$\text{C}_6\text{F}_{14}:\text{CH}_3\text{CN}$	99:1 ( <i>P</i> = 96)	gravimet	42
XII-25 <sup>i</sup>		$\text{C}_6\text{F}_{14}:\text{C}_6\text{H}_6$	98:2 ( <i>P</i> = 48)	gravimet	42
XII-26 <sup>i</sup>	$[\text{R}_{\text{f}4}(\text{CH}_2)_3]_3\text{SnCH}_2\text{CH}=\text{CH}_2$	$\text{C}_6\text{F}_{14}:\text{CH}_3\text{CN}$	93:7 ( <i>P</i> = 14)	gravimet	42
XII-27 <sup>i</sup>		$\text{C}_6\text{F}_{14}:\text{C}_6\text{H}_6$	80:20 ( <i>P</i> = 4)	gravimet	42
XII-28 <sup>i</sup>	$[\text{R}_{\text{f}6}(\text{CH}_2)_3]_3\text{SnCH}_2\text{CH}=\text{CH}_2$	$\text{C}_6\text{F}_{14}:\text{CH}_3\text{CN}$	98:2 ( <i>P</i> = 47)	gravimet	42
XII-29 <sup>i</sup>		$\text{C}_6\text{F}_{14}:\text{C}_6\text{H}_6$	96:4 ( <i>P</i> = 25)	gravimet	42
XII-30 <sup>i</sup>	$[\text{R}_{\text{f}6}(\text{CH}_2)_2]_2\text{SnO}$	$\text{C}_6\text{F}_{14}:\text{CH}_2\text{Cl}_2$	63.0:37.0 ( <i>P</i> = 1.70)	–	43
XII-31 <sup>i</sup>		$\text{C}_6\text{F}_{14}:\text{CH}_3\text{CN}$	22:78 ( <i>P</i> = 0.28)	–	43
XII-32 <sup>i</sup>		$\text{C}_6\text{F}_{14}:\text{CH}_3\text{C}_6\text{H}_5$	65.5:34.5 ( <i>P</i> = 1.90)	–	43
XII-33 <sup>i</sup>	$[\text{Cl}(\text{R}_{\text{f}6}(\text{CH}_2)_2)_2\text{Sn}]_2\text{O}$	$\text{C}_6\text{F}_{14}:\text{CH}_3\text{C}_6\text{H}_5$	99:1 ( <i>P</i> = 99)	–	44
XII-34 <sup>i</sup>		$\text{C}_6\text{F}_{14}:\text{CH}_2\text{Cl}_2$	99:1 ( <i>P</i> = 99)	–	44
XII-35 <sup>i</sup>		$\text{C}_6\text{F}_{14}:\text{CH}_3\text{OH}$	98:2 ( <i>P</i> = 49)	–	44

Tab. 6-1. (continued)

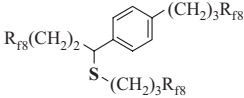
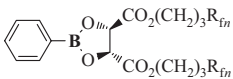
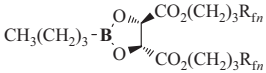
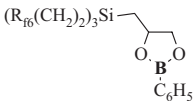
Entry	Solute <sup>b</sup>	Solvent system	Partitioning fluorous: organic ( <i>P</i> )	Method	Ref.
XIII	<b>Silicon Compounds</b>				
XIII-1	$\text{HSi}(\text{CH}_3)_2\text{C}_6\text{H}_5$	$\text{CF}_3\text{C}_6\text{F}_{11}:\text{CH}_3\text{C}_6\text{H}_5$	<b>3.6:96.4</b> ( <i>P</i> = 0.037)	GLC	45a
XIII-2 <sup>m</sup>	$\text{R}_{\text{f}6}(\text{CH}_2)_2\text{Si}(\text{CH}_3)_2\text{Cl}$	$\text{C}_6\text{F}_{14}:\text{CH}_3\text{C}_6\text{H}_5$	66:34 ( <i>P</i> = 1.9)	ICP-AAS <sup>n</sup>	46
XIII-3 <sup>m</sup>	$\text{R}_{\text{f}8}(\text{CH}_2)_2\text{Si}(\text{CH}_3)_2\text{Cl}$	$\text{C}_6\text{F}_{14}:\text{CH}_3\text{C}_6\text{H}_5$	83:17 ( <i>P</i> = 4.8)	gravimet	46
XIII-4 <sup>m</sup>	$\text{R}_{\text{f}10}(\text{CH}_2)_2\text{Si}(\text{CH}_3)_2\text{Cl}$	$\text{C}_6\text{F}_{14}:\text{CH}_3\text{C}_6\text{H}_5$	95:5 ( <i>P</i> = 18)	gravimet	46
XIII-5 <sup>m</sup>	$\text{R}_{\text{f}6}(\text{CH}_2)_2\text{Si}(\text{CH}_3)\text{Cl}_2$	$\text{C}_6\text{F}_{14}:\text{CH}_3\text{C}_6\text{H}_5$	74:26 ( <i>P</i> = 2.8)	ICP-AAS <sup>n</sup>	46
XIII-6 <sup>m</sup>	$\text{R}_{\text{f}6}(\text{CH}_2)_2\text{SiCl}_3$	$\text{C}_6\text{F}_{14}:\text{CH}_3\text{C}_6\text{H}_5$	83:17 ( <i>P</i> = 4.8)	ICP-AAS <sup>n</sup>	46
XIII-7		$\text{CF}_3\text{C}_6\text{F}_{11}:\text{CH}_3\text{C}_6\text{H}_5$	<b>0.6:99.4</b> ( <i>P</i> = 0.006)	GLC	45a
XIII-8		$\text{CF}_3\text{C}_6\text{F}_{11}:\text{CH}_3\text{C}_6\text{H}_5$	<b>0.8:99.2</b> ( <i>P</i> = 0.008)	GLC	45b
XIII-9 <sup>P</sup>	$\text{ROSi}[\text{CH}(\text{CH}_3)_2]_2(\text{CH}_2)_2\text{R}'$ <i>R</i> = 2-(2-naphthyl)ethyl; <i>R'</i> = <i>R</i> <sub>f8</sub>	$\text{C}_6\text{F}_{14}:\text{CH}_3\text{OH}$	48:52 ( <i>P</i> = 0.92)	HPLC	47
XIII-10 <sup>P</sup>		$\text{C}_6\text{F}_{14}:\text{C}_2\text{H}_5\text{OH}$	48:52 ( <i>P</i> = 0.91)	HPLC	47
XIII-11 <sup>P</sup>		$\text{C}_6\text{F}_{14}:\text{CH}_3\text{CN}$	43:57 ( <i>P</i> = 0.74)	HPLC	47
XIII-12 <sup>P</sup>		$\text{C}_6\text{F}_{14}:\text{DMF}$	28:72 ( <i>P</i> = 0.38)	HPLC	47
XIII-13 <sup>P</sup>		$\text{C}_6\text{F}_{14}:\text{CH}_2\text{Cl}_2$	12:88 ( <i>P</i> = 0.14)	HPLC	47
XIII-14 <sup>P</sup>		$\text{C}_6\text{F}_{14}:\text{THF}$	3:97 ( <i>P</i> = 0.035)	HPLC	47
XIII-15 <sup>P</sup>	<i>R</i> = 2-(2-naphthyl)ethyl; <i>R'</i> = <i>R</i> <sub>f10</sub>	$\text{C}_6\text{F}_{14}:\text{CH}_3\text{OH}$	73:27 ( <i>P</i> = 2.7)	HPLC	47
XIII-16 <sup>P</sup>	<i>R</i> = 2-(2-naphthyl)ethyl; <i>R'</i> = <i>R</i> <sub>f6</sub>	$\text{C}_6\text{F}_{14}:\text{CH}_3\text{OH}$	28:72 ( <i>P</i> = 0.39)	HPLC	47
XIII-17 <sup>P</sup>	<i>R</i> = 2-(2-naphthyl)ethyl; <i>R'</i> = <i>R</i> <sub>f4</sub>	$\text{C}_6\text{F}_{14}:\text{CH}_3\text{OH}$	11:89 ( <i>P</i> = 0.12)	HPLC	47
XIII-18 <sup>P</sup>	<i>R</i> = (S)-(-)-1-(2-naphthyl)ethyl; <i>R'</i> = <i>R</i> <sub>f8</sub>	$\text{C}_6\text{F}_{14}:\text{CH}_3\text{OH}$	60:40 ( <i>P</i> = 1.5)	HPLC	47
XIII-19 <sup>P</sup>	<i>R</i> = $\text{C}_6\text{H}_5\text{CH}=\text{CHCH}_2$ ; <i>R'</i> = <i>R</i> <sub>f8</sub>	$\text{C}_6\text{F}_{14}:\text{CH}_3\text{OH}$	57:43 ( <i>P</i> = 1.3)	HPLC	47
XIII-20 <sup>P</sup>	<i>R</i> = $\text{C}_6\text{H}_5(\text{CH}_2)_6$ ; <i>R'</i> = <i>R</i> <sub>f8</sub>	$\text{C}_6\text{F}_{14}:\text{CH}_3\text{OH}$	42:58 ( <i>P</i> = 0.72)	HPLC	47

Tab. 6-1. (continued)

Entry	Solute <sup>b</sup>	Solvent system	Partitioning fluorous: organic ( <i>P</i> )	Method	Ref.
XIII-21 <sup>P</sup>	R = CH <sub>3</sub> (CH <sub>2</sub> ) <sub>11</sub> ; R' = R <sub>f8</sub>	C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> OH	89:11 ( <i>P</i> = 8.2)	gravimet	47
XIII-22 <sup>P</sup>	R = cholestanyl; R' = R <sub>f8</sub>	C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> OH	83:17 ( <i>P</i> = 5.0)	HPLC	47
XIII-23 <sup>P</sup>	R = 2-adamantylethyl; R' = R <sub>f8</sub>	C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> OH	85:15 ( <i>P</i> = 5.7)	gravimet	47
XIII-24 <sup>P</sup>	R = 2-adamantylethyl; R' = R <sub>f6</sub>	C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> OH	66:34 ( <i>P</i> = 1.9)	gravimet	47
XIII-25 <sup>P</sup>	R = mappicine; R' = R <sub>f8</sub>	C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> OH	10:90 ( <i>P</i> = 0.11)	HPLC	47
XIII-26 <sup>m</sup>	R <sub>f6</sub> (CH <sub>2</sub> ) <sub>2</sub> Si(OCH <sub>3</sub> ) <sub>3</sub>	C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	52:48 ( <i>P</i> = 1.1)	gravimet	46
	for further compounds see IV, VI, VII, X, XI, XV and XVI				
XIV	<b>Sulfur Compounds</b>				
XIV-1 <sup>c</sup>	HS(CH <sub>2</sub> ) <sub>2</sub> C(O)OCH <sub>2</sub> CH <sub>3</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	0.5:99.5 ( <i>P</i> = 0.0054) <sup>d</sup>	GLC	24
XIV-2 <sup>c</sup>	R <sub>f8</sub> (CH <sub>2</sub> ) <sub>3</sub> SH	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	56:44 ( <i>P</i> = 1.3) <sup>d</sup>	GLC	4a
XIV-3 <sup>c</sup>	R <sub>f6</sub> S(CH <sub>2</sub> ) <sub>2</sub> C(O)OCH <sub>2</sub> CH <sub>3</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	34:66 ( <i>P</i> = 0.51) <sup>d</sup>	GLC	4a
XIV-4 <sup>c</sup>	R <sub>f8</sub> S(CH <sub>2</sub> ) <sub>2</sub> C(O)OCH <sub>2</sub> CH <sub>3</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	50:50 ( <i>P</i> = 1.0) <sup>d</sup>	GLC	24
XIV-5 <sup>c</sup>	CF <sub>3</sub> SC <sub>6</sub> H <sub>5</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	8:92 ( <i>P</i> = 0.086) <sup>d</sup>	GLC	4a
XIV-6 <sup>c</sup>	CF <sub>3</sub> S(3-C <sub>6</sub> H <sub>4</sub> CF <sub>3</sub> )	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	17.1:82.9 ( <i>P</i> = 0.206) <sup>d</sup>	GLC	4a
XIV-7 <sup>c</sup>	R <sub>f8</sub> SC <sub>6</sub> H <sub>5</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	64:36 ( <i>P</i> = 1.8) <sup>d</sup>	GLC	4a
XIV-8 <sup>c</sup>	R <sub>f7</sub> C(O)SCH <sub>3</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	76.1:23.9 ( <i>P</i> = 3.19) <sup>d</sup>	GLC	24
XIV-9 <sup>c</sup>	R <sub>f7</sub> C(S)OCH <sub>3</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	74.6:25.4 ( <i>P</i> = 2.94) <sup>d</sup>	GLC	24
XIV-10 <sup>c</sup>	R <sub>f7</sub> C(S)N(CH <sub>3</sub> ) <sub>2</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	34:66 ( <i>P</i> = 0.52) <sup>d</sup>	GLC	24
XIV-11 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	17.4:82.6 ( <i>P</i> = 0.210) <sup>d</sup>	GLC	24
XIV-12 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	13.7:86.3 ( <i>P</i> = 0.159) <sup>d</sup>	GLC	24
XIV-13	[R <sub>f8</sub> (CH <sub>2</sub> ) <sub>2</sub> ] <sub>2</sub> S	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	98.7:1.3 ( <i>P</i> = 75.9)	GLC	48



Tab. 6-1. (continued)

Entry	Solute <sup>b</sup>	Solvent system	Partitioning fluorous: organic ( <i>P</i> )	Method	Ref.
XIV-14	$[\text{R}_{18}(\text{CH}_2)_3]_2\text{S}$	$\text{CF}_3\text{C}_6\text{F}_{11}:\text{CH}_3\text{C}_6\text{H}_5$	96.6:3.4 ( <i>P</i> = 28.4)	GLC	48
XIV-15		$\text{CF}_3\text{C}_6\text{F}_{11}:\text{CH}_3\text{C}_6\text{H}_5$	99.5:0.5 ( <i>P</i> = 199)	GLC	7
	for further compounds see VI and X				
XV	<b>Boron Compounds</b>				
					
XV-1 <sup>c</sup>	<i>n</i> = 6	$\text{CF}_3\text{C}_6\text{F}_{11}:\text{CH}_3\text{C}_6\text{H}_5$	11.6:88.4 ( <i>P</i> = 0.131) <sup>d</sup>	GLC	19
XV-2 <sup>c</sup>	<i>n</i> = 8	$\text{CF}_3\text{C}_6\text{F}_{11}:\text{CH}_3\text{C}_6\text{H}_5$	24.4:75.6 ( <i>P</i> = 0.323) <sup>d</sup>	GLC	19
XV-3 <sup>c</sup>	<i>n</i> = 10	$\text{CF}_3\text{C}_6\text{F}_{11}:\text{CH}_3\text{C}_6\text{H}_5$	39:61 ( <i>P</i> = 0.63) <sup>d</sup>	GLC	19
					
XV-4 <sup>c</sup>	<i>n</i> = 6	$\text{CF}_3\text{C}_6\text{F}_{11}:\text{CH}_3\text{C}_6\text{H}_5$	21.6:78.4 ( <i>P</i> = 0.275) <sup>d</sup>	GLC	19
XV-5 <sup>c</sup>	<i>n</i> = 8	$\text{CF}_3\text{C}_6\text{F}_{11}:\text{CH}_3\text{C}_6\text{H}_5$	46:54 ( <i>P</i> = 0.86) <sup>d</sup>	GLC	19
XV-6 <sup>c</sup>	<i>n</i> = 10	$\text{CF}_3\text{C}_6\text{F}_{11}:\text{CH}_3\text{C}_6\text{H}_5$	76.1:23.9 ( <i>P</i> = 3.19) <sup>d</sup>	GLC	19
XV-7 <sup>l</sup>		$\text{FC-77}:\text{CH}_3\text{CN}$	93.0:7.0 ( <i>P</i> = 13.3)	–	49
XV-8 <sup>l</sup>		$\text{FC-77}:\text{CH}_2\text{Cl}_2$	88.3:11.7 ( <i>P</i> = 7.53)	–	49
XV-9 <sup>l</sup>		$\text{FC-77}:\text{CHCl}_3$	84.4:15.6 ( <i>P</i> = 5.43)	–	49
XV-10 <sup>l</sup>		$\text{FC-77}:\text{C}_6\text{H}_{14}$	86.7:13.3 ( <i>P</i> = 6.50)	–	49
XV-11 <sup>l</sup>		$\text{FC-77}:\text{CH}_3\text{CO}_2\text{C}_2\text{H}_5$	47:53 ( <i>P</i> = 0.88)	–	49
XV-12 <sup>l</sup>		$\text{FC-77}:\text{CH}_3\text{COCH}_3$	73.2:26.8 ( <i>P</i> = 2.73)	–	49

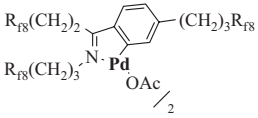
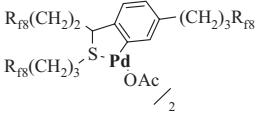
Tab. 6-1. (continued)

Entry	Solute <sup>b</sup>	Solvent system	Partitioning fluorous: organic (P)	Method	Ref.
XV-13 <sup>l</sup>		FC-77:CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	88.5:11.5 (P = 7.69)	–	49
XV-14 <sup>l</sup>		FC-77:THF	74.4:25.6 (P = 2.91)	–	49
for further compounds see XI and XVI					
XVI	<b>Transition Metal Compounds</b>				
XVI-1 <sup>l</sup>	Rh <sub>2</sub> (O <sub>2</sub> CR <sub>f7</sub> ) <sub>4</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :Et <sub>2</sub> O	83:17 (P = 4.9)	gravimet	50
XVI-2 <sup>l</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>2</sub> Cl <sub>2</sub>	94.9:5.1 (P = 18.7)	gravimet	50
XVI-3 <sup>l</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :C <sub>6</sub> H <sub>14</sub>	96.7:3.3 (P = 29.4)	gravimet	50
XVI-4 <sup>l</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	95.0:5.0 (P = 18.9)	gravimet	50
XVI-5 <sup>l</sup>	Rh <sub>2</sub> (O <sub>2</sub> CCH <sub>2</sub> R <sub>f6</sub> ) <sub>4</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :Et <sub>2</sub> O	38:62 (P = 0.6)	gravimet	50
XVI-6 <sup>l</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>2</sub> Cl <sub>2</sub>	89:11 (P = 8.5)	gravimet	50
XVI-7 <sup>l</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :C <sub>6</sub> H <sub>14</sub>	96.6:3.4 (P = 28.7)	gravimet	50
XVI-8 <sup>l</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	96.3:3.7 (P = 25.7)	gravimet	50
XVI-9 <sup>k</sup>	[(R <sub>f6</sub> (CH <sub>2</sub> ) <sub>2</sub> ) <sub>3</sub> P] <sub>3</sub> RhCl	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	99.86:0.14 (P = 713)	ICP-AES <sup>o</sup>	51
XVI-10 <sup>k</sup>	[(R <sub>f8</sub> (CH <sub>2</sub> ) <sub>2</sub> ) <sub>3</sub> P] <sub>3</sub> RhCl	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	99.88:0.12 (P = 832)	ICP-AES <sup>o</sup>	51
XVI-11 <sup>k</sup>	[(R <sub>f6</sub> (CH <sub>2</sub> ) <sub>2</sub> ) <sub>3</sub> P] <sub>3</sub> Rh(H)(CO)	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	99.5:0.5 (P = 190) <sup>d</sup>	GLC	4a, 52a
	(Ar <sub>3</sub> P) <sub>3</sub> RhCl				
XVI-12 <sup>m</sup>	Ar = 4-C <sub>6</sub> H <sub>4</sub> Si(CH <sub>3</sub> ) <sub>2</sub> (CH <sub>2</sub> ) <sub>2</sub> R <sub>f6</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :n-C <sub>8</sub> H <sub>18</sub>	99.7:0.3 (P = 293)	ICP-AAS <sup>n</sup>	35
XVI-13 <sup>c</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :n-C <sub>8</sub> H <sub>18</sub>	98.7:1.3 (P = 76)	ICP-AAS <sup>n</sup>	35
XVI-14 <sup>m</sup>	Ar = 4-C <sub>6</sub> H <sub>4</sub> Si(CH <sub>3</sub> ) <sub>2</sub> (CH <sub>2</sub> ) <sub>2</sub> R <sub>f8</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :n-C <sub>8</sub> H <sub>18</sub>	99.9:0.1 (P = 887)	ICP-AAS <sup>n</sup>	35
XVI-15 <sup>i</sup>	[R <sub>f10</sub> (CH <sub>2</sub> ) <sub>2</sub> C <sub>5</sub> H <sub>4</sub> ] <sub>3</sub> Rh(CO) <sub>2</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	44:56 (P = 0.8)	ICP-AES <sup>o</sup>	52a
XVI-16 <sup>i</sup>	[R <sub>f10</sub> (CH <sub>2</sub> ) <sub>2</sub> C <sub>5</sub> H <sub>4</sub> ] <sub>3</sub> Rh(CO)[P((CH <sub>2</sub> ) <sub>2</sub> R <sub>f6</sub> ) <sub>3</sub> ]	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	96.7:3.3 (P = 29)	ICP-AES <sup>o</sup>	52a
	[Rh(COD)(Ar <sub>2</sub> P(CH <sub>2</sub> ) <sub>n</sub> PAr <sub>2</sub> )] <sup>+</sup> X <sup>–</sup>				
XVI-17 <sup>m</sup>	Ar = C <sub>6</sub> H <sub>5</sub> X <sup>–</sup> = [B(3,5-C <sub>6</sub> H <sub>3</sub> (R <sub>f6</sub> ) <sub>2</sub> ) <sub>4</sub> ] <sup>–</sup> ; n = 4	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :THF	<1:>99 (P < 0.01)	ICP-AAS <sup>n</sup>	53
XVI-18 <sup>m</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	41:59 (P = 0.7)	ICP-AAS <sup>n</sup>	53

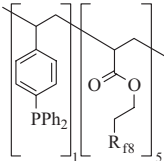
Tab. 6-1. (continued)

Entry	Solute <sup>b</sup>	Solvent system	Partitioning fluorous: organic ( <i>P</i> )	Method	Ref.
XVI-19 <sup>m</sup>	Ar = 4-C <sub>6</sub> H <sub>4</sub> [Si(CH <sub>3</sub> ) <sub>2</sub> (CH <sub>2</sub> ) <sub>2</sub> R <sub>f6</sub> ] X <sup>-</sup> = [B(3,5-C <sub>6</sub> H <sub>3</sub> (R <sub>f6</sub> ) <sub>2</sub> ) <sub>4</sub> ] <sup>-</sup> ; n = 2	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :THF	68:32 ( <i>P</i> = 2.1)	ICP-AAS <sup>n</sup>	53
XVI-20 <sup>m</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	97.1:2.9 ( <i>P</i> = 34)	ICP-AAS <sup>n</sup>	53
XVI-21 <sup>m</sup>	Ar = 4-C <sub>6</sub> H <sub>4</sub> [Si(CH <sub>3</sub> )((CH <sub>2</sub> ) <sub>2</sub> R <sub>f6</sub> ) <sub>2</sub> ] X <sup>-</sup> = BF <sub>4</sub> <sup>-</sup> ; n = 2	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :THF	89:11 ( <i>P</i> = 8.1)	ICP-AAS <sup>n</sup>	53
XVI-22 <sup>m</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	98.4:1.6 ( <i>P</i> = 61)	ICP-AAS <sup>n</sup>	53
XVI-23 <sup>m</sup>	Ar = 4-C <sub>6</sub> H <sub>4</sub> [Si(CH <sub>3</sub> )((CH <sub>2</sub> ) <sub>2</sub> R <sub>f6</sub> ) <sub>2</sub> ] X <sup>-</sup> = [B(4-C <sub>6</sub> H <sub>4</sub> R <sub>f6</sub> ) <sub>4</sub> ] <sup>-</sup> ; n = 2	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :THF	86:14 ( <i>P</i> = 6.4)	ICP-AAS <sup>n</sup>	53
XVI-24 <sup>m</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	98.5:1.5 ( <i>P</i> = 65)	ICP-AAS <sup>n</sup>	53
XVI-25 <sup>m</sup>	Ar = 4-C <sub>6</sub> H <sub>4</sub> Si((CH <sub>2</sub> ) <sub>2</sub> R <sub>f6</sub> ) <sub>3</sub> X <sup>-</sup> = BF <sub>4</sub> <sup>-</sup> ; n = 2	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :THF	97.1:2.9 ( <i>P</i> = 34)	ICP-AAS <sup>n</sup>	53
XVI-26 <sup>m</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	98.5:1.5 ( <i>P</i> = 66)	ICP-AAS <sup>n</sup>	53
XVI-27 <sup>i</sup>	[R <sub>f10</sub> (CH <sub>2</sub> ) <sub>2</sub> C <sub>5</sub> H <sub>4</sub> ] <b>Mn</b> (CO) <sub>3</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	64:36 ( <i>P</i> = 1.8)	IR	52b
XVI-28 <sup>g</sup>	[(CH <sub>3</sub> (CH <sub>2</sub> ) <sub>7</sub> ) <sub>3</sub> P] <sub>2</sub> <b>Ir</b> (Cl)(CO)	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	<0.3: >99.7 ( <i>P</i> < 0.003)	<sup>31</sup> P NMR	54
XVI-29 <sup>g</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :THF	<0.3: >99.7 ( <i>P</i> < 0.003)	<sup>31</sup> P NMR	54
XVI-30 <sup>g</sup>	[(R <sub>f6</sub> (CH <sub>2</sub> ) <sub>2</sub> ) <sub>3</sub> P] <sub>2</sub> <b>Ir</b> (Cl)(CO)	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	>99.7: <0.3 ( <i>P</i> > 332)	<sup>31</sup> P NMR	54
XVI-31 <sup>g</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> COCH <sub>3</sub>	>99.7: <0.3 ( <i>P</i> > 332)	<sup>31</sup> P NMR	54
XVI-32 <sup>g</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>2</sub> Cl <sub>2</sub>	>99.7: <0.3 ( <i>P</i> > 332)	<sup>31</sup> P NMR	54
XVI-33 <sup>g</sup>		CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :THF	>99.7: <0.3 ( <i>P</i> > 332)	<sup>31</sup> P NMR	54
XVI-34 <sup>i</sup>	[(R <sub>f6</sub> (CH <sub>2</sub> ) <sub>2</sub> ) <sub>3</sub> P] <sub>2</sub> <b>Ni</b> Cl <sub>2</sub>  NiCl <sub>2</sub> [Ar <sub>2</sub> P(CH <sub>2</sub> ) <sub>2</sub> PAr <sub>2</sub> ]	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	98.8:1.2 ( <i>P</i> = 83)	ICP-AES <sup>o</sup>	52a
XVI-35 <sup>m</sup>	Ar = 4-C <sub>6</sub> H <sub>4</sub> Si(CH <sub>3</sub> ) <sub>3</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	0:100 ( <i>P</i> = 0.0)	gravimet	55
XVI-36 <sup>m</sup>	Ar = 4-C <sub>6</sub> H <sub>4</sub> [Si(CH <sub>3</sub> ) <sub>2</sub> (CH <sub>2</sub> ) <sub>2</sub> R <sub>f6</sub> ]	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	62:38 ( <i>P</i> = 1.6)	gravimet	55
XVI-37 <sup>m</sup>	Ar = 4-C <sub>6</sub> H <sub>4</sub> [Si(CH <sub>3</sub> ) <sub>2</sub> (CH <sub>2</sub> ) <sub>2</sub> R <sub>f8</sub> ]	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	79:21 ( <i>P</i> = 3.7)	gravimet	55
XVI-38 <sup>m</sup>	Ar = 4-C <sub>6</sub> H <sub>4</sub> [Si(CH <sub>3</sub> )((CH <sub>2</sub> ) <sub>2</sub> R <sub>f6</sub> ) <sub>2</sub> ]	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	89:11 ( <i>P</i> = 8)	gravimet	55
XVI-39 <sup>m</sup>	Ar = 4-C <sub>6</sub> H <sub>4</sub> Si((CH <sub>2</sub> ) <sub>2</sub> R <sub>f6</sub> ) <sub>3</sub>	CF <sub>3</sub> C <sub>6</sub> F <sub>11</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	95.8:4.2 ( <i>P</i> = 23)	gravimet	55
XVI-40 <sup>i</sup>	Fe[C <sub>5</sub> H <sub>4</sub> (CH <sub>2</sub> ) <sub>2</sub> R <sub>f10</sub> ] <sub>2</sub>	C <sub>7</sub> F <sub>16</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	95.2:4.8 ( <i>P</i> = 20)	gravimet	52b

Tab. 6-1. (continued)

Entry	Solute <sup>b</sup>	Solvent system	Partitioning fluorous: organic (P)	Method	Ref.
XVI-41 <sup>c</sup>	$\text{Fe}[\text{C}_5\text{H}_3((\text{CH}_2)_2\text{R}_{\text{f}4})_2]_2^{\text{q}}$	$\text{CF}_3\text{C}_6\text{F}_{11}:\text{CH}_3\text{C}_6\text{H}_5$	90.9:9.1 ( $P = 10$ )	ICP-AAS <sup>n</sup>	6
XVI-42 <sup>c</sup>	$\text{Fe}[\text{C}_5\text{H}_3((\text{CH}_2)_2\text{R}_{\text{f}6})_2]_2^{\text{q}}$	$\text{CF}_3\text{C}_6\text{F}_{11}:\text{CH}_3\text{C}_6\text{H}_5$	98.6:1.4 ( $P = 72$ )	ICP-AAS <sup>n</sup>	6
XVI-43 <sup>c</sup>	$\text{Fe}[\text{C}_5\text{H}_3((\text{CH}_2)_2\text{R}_{\text{f}4})((\text{CH}_2)_2\text{R}_{\text{f}6})]_2^{\text{q}}$	$\text{CF}_3\text{C}_6\text{F}_{11}:\text{CH}_3\text{C}_6\text{H}_5$	94.4:5.6 ( $P = 17$ )	ICP-AAS <sup>n</sup>	6
XVI-44 <sup>c</sup>	$\text{Fe}[\text{C}_5\text{H}_3((\text{CH}_2)_2\text{R}_{\text{f}4})((\text{CH}_2)_2\text{R}_{\text{f}8})]_2^{\text{q}}$	$\text{CF}_3\text{C}_6\text{F}_{11}:\text{CH}_3\text{C}_6\text{H}_5$	95.7:4.3 ( $P = 22$ )	ICP-AAS <sup>n</sup>	6
XVI-45 <sup>c</sup>	$\text{Fe}[\text{C}_5\text{H}_3((\text{CH}_2)_2\text{R}_{\text{f}6})((\text{CH}_2)_2\text{R}_{\text{f}8})]_2^{\text{q}}$	$\text{CF}_3\text{C}_6\text{F}_{11}:\text{CH}_3\text{C}_6\text{H}_5$	95.7:4.3 ( $P = 22$ )	ICP-AAS <sup>n</sup>	6
XVI-46 <sup>g</sup>	$[\text{R}_{\text{f}6}(\text{CH}_2)_2\text{C}_5\text{H}_4]_2\text{ZrCl}_2$	$\text{CF}_3\text{C}_6\text{F}_{11}:\text{CH}_3\text{C}_6\text{H}_5$	95.4:4.6 ( $P = 20.7$ )	gravimet	56
XVI-47 <sup>g</sup>	$[\text{R}_{\text{f}6}(\text{CH}_2)_2\text{C}_5\text{H}_4]_2\text{Zr}(\text{CH}_3)_2$	$\text{CF}_3\text{C}_6\text{F}_{11}:\text{CH}_3\text{C}_6\text{H}_5$	87.5:12.5 ( $P = 7.00$ )	gravimet	56
XVI-48		$\text{CF}_3\text{C}_6\text{F}_{11}:\text{CH}_3\text{C}_6\text{H}_5$	95.5:4.5 ( $P = 21.2$ )	HPLC	7, 27
XVI-49		$\text{C}_8\text{F}_{17}\text{Br}:\text{DMF}$	95.9:4.1 ( $P = 23.4$ )	HPLC	7, 27
XVI-50		$\text{CF}_3\text{C}_6\text{F}_{11}:\text{CH}_3\text{C}_6\text{H}_5$	90.7:9.3 ( $P = 9.8$ )	HPLC	7
XVI-51		$\text{C}_8\text{F}_{17}\text{Br}:\text{DMF}$	91.4:8.6 ( $P = 10.6$ )	HPLC	7
XVII	<b>Supramolecular Complexes and Polymers</b>				
XVII-1 <sup>c</sup>	$[\text{R}_{\text{f}6}(\text{CH}_2)_2\text{NHCONHCH}(\text{CH}_3)_2]\cdot\text{HO}_2\text{CR}_{\text{f}6}$	$\text{C}_6\text{F}_{14}:\text{CH}_2\text{Cl}_2$	40:60 ( $P = 0.7$ )	gravimet	57
XVII-2 <sup>c</sup>	$[(\text{CF}_3\text{CH}_2\text{NH})_2\text{CO}]\cdot\text{HO}_2\text{CR}_{\text{f}6}$	$\text{C}_6\text{F}_{14}:\text{CH}_2\text{Cl}_2$	77:23 ( $P = 3.4$ )	gravimet	57
XVII-3 <sup>c</sup>	$[(\text{CF}_3\text{CH}_2\text{NH})_2\text{CO}]\cdot\text{HO}_2\text{CR}_{\text{f}17}$	$\text{C}_6\text{F}_{14}:\text{CH}_2\text{Cl}_2$	83:17 ( $P = 4.9$ )	gravimet	57
XVII-4 <sup>c</sup>	$[(\text{R}_{\text{f}4}(\text{CH}_2)_2\text{NH})_2\text{CO}]\cdot\text{HO}_2\text{CR}_{\text{f}6}$	$\text{C}_6\text{F}_{14}:\text{CH}_2\text{Cl}_2$	96:4 ( $P = 24$ )	gravimet	57
XVII-5 <sup>c</sup>	$[(\text{R}_{\text{f}6}(\text{CH}_2)_2\text{NH})_2\text{CO}]\cdot\text{HO}_2\text{CR}_{\text{f}6}$	$\text{C}_6\text{F}_{14}:\text{CH}_2\text{Cl}_2$	99:1 ( $P = 99$ )	gravimet	57
XVII-6 <sup>c</sup>		$\text{C}_6\text{F}_{14}:\text{CHCl}_3$	96:4 ( $P = 24$ )	gravimet	57

Tab. 6-1. (continued)

Entry	Solute <sup>b</sup>	Solvent system	Partitioning fluorous: organic (P)	Method	Ref.
XVII-7 <sup>c</sup>		C <sub>6</sub> F <sub>14</sub> :CH <sub>3</sub> CN	90:10 (P = 9.0)	gravimet	57
XVII-8 <sup>c</sup>	[(R <sub>f6</sub> (CH <sub>2</sub> ) <sub>2</sub> NH) <sub>2</sub> CO]·HO <sub>2</sub> CCH <sub>2</sub> R <sub>f6</sub>	C <sub>6</sub> F <sub>14</sub> :CH <sub>2</sub> Cl <sub>2</sub>	98:2 (P = 49)	gravimet	57
XVII-9 <sup>c</sup>	[(R <sub>f6</sub> (CH <sub>2</sub> ) <sub>2</sub> NH) <sub>2</sub> CO]·HO <sub>2</sub> C(CH <sub>2</sub> ) <sub>2</sub> R <sub>f8</sub>	C <sub>6</sub> F <sub>14</sub> :CH <sub>2</sub> Cl <sub>2</sub>	95:5 (P = 19)	gravimet	57
XVII-10		1,3-(CF <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> F <sub>10</sub> :CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	96.4:3.6 (P = 26.9)	gravimet	32
XVII-11		1,3-(CF <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> F <sub>10</sub> :THF	96.5:3.5 (P = 27.7)	gravimet	32

<sup>a</sup>All measurements obtained at 24 °C unless otherwise stated.

<sup>b</sup>R<sub>fm</sub> = (CF<sub>2</sub>)<sub>n-1</sub>CF<sub>3</sub>. <sup>c</sup>25 °C. <sup>d</sup>Calculated from ln P. <sup>e</sup>Perfluorodecalin.

<sup>f</sup>Mixture of isomers. <sup>g</sup>Ambient temperature implied. <sup>h</sup>–45 °C. <sup>i</sup>20 °C.

<sup>j</sup>T not given. <sup>k</sup>27 °C. <sup>l</sup>10 °C. <sup>m</sup>0 °C. <sup>n</sup>Inductively coupled plasma –

atomic absorption spectrometry. <sup>o</sup>Inductively coupled plasma – atomic

emission spectrometry. <sup>p</sup>23 °C. <sup>q</sup>Mixture of regioisomers.

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ences to other sections are given. The abbreviation  $R_{fn}[(CF_2)_{n-1}CF_3]$  is used throughout, except for trifluoromethyl groups (formally  $R_{f1}$ ).

The partition coefficients are listed *both* as ratios normalized to 100, *and* as *P* values. As some rounding is necessary, the value originally reported in the literature is indicated in **bold type**. When a *P* value has been calculated from an  $\ln P$  or *f* value, this is indicated by a footnote. All data from the authors' groups are believed to be correctly represented with respect to the number of significant digits.

GLC (gas-liquid chromatography), HPLC (high-performance liquid chromatography), and ICP-AAS/AES measurements are generally the most reliable. Gravimetric determinations where only a very small amount of the solute is present in one phase are subject to greater errors. Importantly, ICP methods give the total amount of a given *element* in a given phase. Hence, the decomposition of a solute to a species with a different partition coefficient (e.g., by oxidation), even to a small extent, can introduce error. Since GLC and HPLC assay a *molecular* characteristic, they are not subject to this problem.

Partition coefficients are temperature dependent, as illustrated by entries IV-9/IV-10 and XVI-12/XVI-13 of Table 6-1. The fluororous phase affinity of a fluororous solute is enhanced at lower temperature. However, most of the values in Table 6-1 were determined between 20 and 27 °C, as specified in the footnotes, and should not vary substantially within this range. In the most rigorous work, partition coefficients are determined over a range of concentrations and extrapolated to infinite dilution [1]. However, the concentrations used in the authors' experiments are close to those encountered in "real-life" fluororous/organic liquid/liquid biphasic separations, and the values for various classes of molecules are believed to have excellent cross-comparability.

### 6.3

#### Trends with Respect to Functional Groups

##### 6.3.1

##### Non-Aromatic Hydrocarbons

Entries I-1 to I-6 in Table 6-1 give partition coefficients ( $\text{CF}_3\text{C}_6\text{F}_{11}$ /toluene) for *n*-alkanes (decane through hexadecane), and entries II-1 to II-6 give data for the corresponding terminal alkenes. The alkanes, although very non-polar, show high affinities for the toluene phase. These increase monotonically with alkane size (5.4:94.6 for decane to 1.1:98.9 for hexadecane). This is in accord with the general trends for absolute solubilities in fluorous solvents, as discussed in Chapter 3.5. Non-fluorous solutes are thought to occupy cavities, and smaller guests are always better accommodated.

The *n*-alkenes have slightly higher toluene phase affinities, consistent with their slightly greater polarities. A comparable monotonic size trend is found (4.8:95.2 for 1-decene to 0.9:99.1 for 1-hexadecene). When the side-chain of 1-decene is perfluorinated to give  $\text{R}_{f8}\text{CH}=\text{CH}_2$ , the partition coefficient nearly reverses, to 93.5:6.5 (entry II-7). A variety of hemifluorinated disubstituted alkenes,  $\text{R}_m\text{CH}=\text{CH}(\text{CH}_2)_m\text{CH}_3$ , have been analyzed (entries II-8 to II-43). As would be expected, they exhibit intermediate fluorophilicities.

##### 6.3.2

##### Non-Aromatic Monofunctional Compounds

Entries III-1 and III-2 give partition coefficients ( $\text{CF}_3\text{C}_6\text{F}_{11}$ /toluene) for the ketones cyclohexanone and 2-cyclohexen-1-one – species more polar than alkanes and alkenes but somewhat “smaller” than specific examples discussed above. Their toluene phase affinities are also high (2.2:97.8 and 1.7:98.3). The toluene phase affinity of cyclohexanol (entry IV-1, 1.6:98.4) is higher than that of cyclohexanone, and the corresponding dimethylphenyl silyl ether is higher still (entry XIII-8, 0.8:99.2).

Section IV of Table 6-1 contains several simple fluorous alcohols. The short-chain species in entries IV-2 and IV-3 show poor fluorophilicities [7]. As the perfluoroalkyl segment lengthens in the series  $\text{R}_{f6}(\text{CH}_2)_3\text{OH}$ ,  $\text{R}_{f8}(\text{CH}_2)_3\text{OH}$ , and  $\text{R}_{f10}(\text{CH}_2)_3\text{OH}$  (entries IV-5, IV-7, IV-8), the fluorous phase affinities increase from 44:56 to 64:36 to 80.5:19.5 ( $\text{CF}_3\text{C}_6\text{F}_{11}$ /toluene). As would be expected, when a methylene group is removed from the first two compounds, the fluorophilicities also increase (52:48 and 73.5:26.5; entries IV-4 and IV-6). Similar trends are found with all other functional groups in Table 6-1.

The thiol  $\text{R}_{f8}(\text{CH}_2)_3\text{SH}$  (entry XIV-2), iodide  $\text{R}_{f8}(\text{CH}_2)_3\text{I}$  (entry IX-4), and primary amine  $\text{R}_{f8}(\text{CH}_2)_3\text{NH}_2$  (entry X-1) exhibit  $\text{CF}_3\text{C}_6\text{F}_{11}$ /toluene partition coefficients (56:44, 50.7:49.3, and 70.0:30.0) roughly comparable to that of the corresponding alcohol (64:36). Thus, more than one  $\text{R}_{f8}$ -containing ponytail is clearly needed to achieve higher fluorophilicities with simple monofunctional organic compounds.

The effect of the number of ponytails is clearly seen in amines of the formula  $[\text{R}_{f8}(\text{CH}_2)_3]_x\text{NH}_{3-x}$  (entries X-1, X-7, and X-13). As *x* increases from one to three, the fluorous phase affinities increase monotonically from 70.0:30.0 to 96.5:3.5 to the point where no GLC-detectable concentration in toluene remains ( $>99.7:<0.3$ ). Thus,  $[\text{R}_{f8}(\text{CH}_2)_3]_3\text{N}$  repre-



sents a highly immobilized fluoruous base. When the number of the methylene groups in each ponytail is increased to five, a small amount of the amine can again be detected in the toluene phase (99.5:0.5; entry X-15).

Similar trends are observed with fluoruous trialkylphosphines. Here, the lengths of the  $R_{fn}$  as well as the  $(CH_2)_m$  segments have been varied (entries XI-1 to XI-6), and very high fluoruous phase affinities can be achieved  $\{>99.7:<0.3$  for  $[R_{f8}(CH_2)_2]_3P$  and  $[R_{f10}(CH_2)_2]_3P$ . Where comparisons are possible, fluorophilicities are slightly lower than for analogous amines. Counter-intuitively from a polarity standpoint, oxidation to a phosphine oxide slightly *increases* the fluoruous phase affinity (entry XI-7 vs. XI-1).

As shown in Section XII of Table 6-1, appropriately designed trialkyltin hydrides can also be highly fluorophilic. Although the solvent systems used are slightly different, partition coefficients for the compounds  $[R_{fn}(CH_2)_2]_3SnH$  are comparable to those of the corresponding phosphines (entries XII-5 and XII-11 for  $n = 6$ ;  $n = 10$  is still more fluorophilic but due to solubility limitations an accurate value could not be determined) [8]. Another triply-branched system is the tertiary alcohol  $[(R_{f6}(CH_2)_2)_3COH]$ . The  $C_6F_{14}$ /THF partition coefficient is 90.9:9.1 at ambient temperature or 95.8:4.2 at  $-45^\circ C$  (entries IV-9 and IV-10).

Thioethers, which can only accommodate two ponytails around the central heteroatom, possess fluoruous phase affinities slightly lower than those of comparable amines and phosphines. For example, the  $CF_3C_6F_{11}$ /toluene partition coefficients for  $[R_{f8}(CH_2)_2]_2S$  and  $[R_{f8}(CH_2)_3]_2S$  are 98.7:1.3 and 96.6:3.4 (entries XIV-13 and XIV-14).

### 6.3.3

#### Simple Monoarenes

Data for simple arenes are collected in Section VII of Table 6-1, and the  $CF_3C_6F_{11}$ /toluene partition coefficients can be analyzed as follows. Both pentafluorobenzene and hexafluorobenzene preferentially partition into toluene (22.4:77.6 and 28.0:72.0; entries VII-2 and VII-3), consistent with their non-fluorous nature as described in Chapter 3.2.2. Benzene exhibits an even greater toluene phase affinity (6:94; entry VII-1). However, the introduction of a single ponytail of formula  $R_{f8}(CH_2)_3$  evens the playing field, and a partition coefficient of 49.5:50.5 is obtained (entry VII-18). This value is similar to those obtained when an  $R_{f8}(CH_2)_3$  moiety is capped with an iodide or thiol. The compound  $R_{f8}C_6H_5$  (entry VII-16), which lacks methylene spacers, is more fluorophilic still (77.5:22.5), but the electronic properties of the arene ring are strongly perturbed.

As shown in entries VII-43, VII-45, and VII-46, benzenes with two ponytails of formula  $R_{f8}(CH_2)_3$  exhibit appreciable fluorophilicities, with partition coefficients of 91.2:8.8 to 90.7:9.3. The substitution pattern has little influence. As seen with other compounds above, when the perfluoroalkyl segment of the ponytail is shortened, the fluoruous phase affinity decreases [73.7:26.3 for  $R_{f6}(CH_2)_3$ ; entry VII-42], and when it is lengthened the fluoruous phase affinity increases [97.4:2.6 for  $R_{f10}(CH_2)_3$ ; entry VII-44]. Importantly, benzenes with three ponytails of formula  $R_{f8}(CH_2)_3$  partition (within detection limits) completely into  $CF_3C_6F_{11}$ , at least when arrayed in a 1,3,5-pattern (entry VII-61).

Entries VII-49 through to VII-54, as well as VII-62 and VII-63, feature monoiodide derivatives of some of the preceding fluoruous benzenes. In all cases, the fluorophilicities decrease. Only for entry VII-62, a triply ponytailed compound, is a highly biased  $CF_3C_6F_{11}$ /

toluene partition coefficient maintained (98.0:2.0). When the more polar non-fluorous solvent methanol is employed, relative fluorine phase affinities increase. Regardless, it is clear that with monofunctional benzenes, at least three ponytails of the formula  $R_{f8}(CH_2)_3$  are required for high degrees of fluorine phase immobilization. Entries III-4, IV-11, and VI-7 – a benzaldehyde, benzyl alcohol, and methyl benzoate – show that two ponytails of formula  $R_{f8}$  (i.e., without spacers) are essentially as effective ( $CF_3C_6F_{11}$ /toluene partition coefficients 98.6:1.4, 97.4:2.6 and 98.8:1.2).

#### 6.3.4

##### Triarylphosphines

These points are further illustrated by some of the *para*-substituted fluorine triarylphosphines in Section XI of Table 6-1. With one ponytail of the formula  $R_{f6}(CH_2)_3$  per ring, the  $CF_3C_6F_{11}$ /toluene partition coefficient is 19.5:80.5 (entry XI-18). When the per-fluoroalkyl segment is lengthened, giving  $R_{f8}(CH_2)_3$ , the fluorophilicity increases (66.6:33.4; entry XI-19). When the methylene segment is shortened, giving  $R_{f6}(CH_2)_2$ , the fluorophilicity should also increase. Accordingly, the  $C_6F_{14}$ /toluene partition coefficient is 43:57 (entry XI-17). When toluene is replaced by the much more polar solvent methanol, the fluorine phase affinity becomes much higher (96.8:3.2, entry XI-15).

Entries XI-30 and XI-28 provide analogous data for a phosphine with a single methylene spacer and a branched  $R_{f6}$  moiety. In  $C_6F_{14}$ /toluene, the fluorine phase affinity is lower (87.2:12.8), but in  $C_6F_{14}$ /methanol, slightly higher (94.9:5.1). When the phenyl groups bear only *p*- $R_{f6}$  substituents (no methylene spacers), the partition coefficient in 1,3- $(CF_3)_2C_6F_{10}$ /toluene is 81:19 (entry XI-11).

It has proved problematic to attach additional ponytails directly onto the aryl moieties of fluorine triarylphosphines. Thus, there are no readily available compounds of the formula  $\{[R_{fn}(CH_2)_m]_x C_6H_{5-x}\}_3P$  ( $m > 0$ ) with truly high fluorine phase affinities. However, a clever way around this dilemma has been developed [9]. Namely, silicon-based ponytails of the formula  $[R_{fn}(CH_2)_2]_x Si(CH_3)_{3-x}$  have been used as anchors for as many as three  $R_{f6}$  or  $R_{f8}$  groups per ring [10]. As summarized in entries XI-47 through to XI-58, this gives triarylphosphines with much higher fluorine phase affinities (up to 95:5 for  $x = 3$  and  $n = 8$  in  $CF_3C_6F_{11}/n-C_5H_{12}$ ). When the exact values are carefully analyzed, some non-monotonic trends are obvious, and this point is treated further below.

Note that the analogous dppe derivative in entry XI-62, which contains two fluorine arenes on each phosphorus atom, gives a  $CF_3C_6F_{11}$ /toluene partition coefficient of  $>98:<2$ . The related BINAP derivative in entries XI-72 through to XI-75 features only a single fluorine arene on each phosphorus atom, and the  $C_6F_{14}/C_6H_6$  partition coefficient is only 74:26 (HPLC).

#### 6.3.5

##### Pyridines

The  $R_{f8}$ -monosubstituted pyridines in entries VIII-1 through to VIII-3, which are *ortho*, *meta*, and *para* isomers, give  $CF_3C_6F_{11}$ /toluene partition coefficients in the narrow range of

63:37 to 71:29. The  $R_{f8}(\text{CH}_2)_3$ -disubstituted pyridine in entry VIII-5 is rigorously comparable to the benzenoid analog in entry VII-45 (N/CH exchange), and gives an essentially identical partition coefficient (90.4:9.6 vs. 90.7:9.3). Hence, the polar pyridine nitrogen has little influence. Entry VIII-7 shows that three ponytails of the formula  $R_{f8}(\text{CH}_2)_2$  provide essentially complete fluororous phase immobilization ( $>99.7:<0.3$ ). The hydrogenation of the pyridine in entry VIII-5 to the piperidine in entry VIII-8 slightly increases fluorophilicity (90.4:9.6 vs. 93.6:6.4). This secondary amine can in turn be compared to  $\text{HN}[(\text{CH}_2)_5R_{f8}]_2$  (entry X-9) which has one less  $\text{CH}_n$  group and a very similar fluororous phase affinity (93.0:7.0).

### 6.3.6

#### Metal Complexes

Section XVI of Table 6-1 features a variety of metal complexes, the majority of which have been engineered to have high fluorophilicities. As illustrated by entries XVI-40 through to XVI-45, a ferrocene appears slightly more difficult to immobilize than a benzene ring. Two ponytails of the formula  $R_{f10}(\text{CH}_2)_2$  or four ponytails of the formula  $R_{f4}(\text{CH}_2)_2$  suffice for  $\text{CF}_3\text{C}_6\text{F}_{11}$ /toluene partition coefficients of  $>91:<9$ . The fluororous zirconocenes ( $\eta^5$ - $\text{C}_5\text{H}_4(\text{CH}_2)_2R_{f6})_2\text{ZrX}_2$  exhibit  $\text{CF}_3\text{C}_6\text{F}_{11}$ /toluene partition coefficients of 95.4:4.6 ( $\text{X} = \text{Cl}$ , entry XVI-46) and 87.5:12.5 ( $\text{X} = \text{CH}_3$ , entry XVI-47).

Compounds that are catalyst precursors are of particular interest. The neutral rhodium complexes in entries XVI-9 and XVI-10, which feature three phosphine ligands of the formula  $\text{P}[(\text{CH}_2)_2R_{fn}]_3$ , exhibit very high fluorophilicities ( $\text{CF}_3\text{C}_6\text{F}_{11}$ /toluene partition coefficients 99.86:0.14,  $n = 6$ , and 99.88:0.12,  $n = 8$ ). Those of similar square planar iridium and nickel complexes with two such phosphine ligands are slightly lower (entries XVI-30 through to XVI-34). Salts should normally have higher polarities and poorer fluororous phase affinities. However, entries XVI-20 and XVI-24 show that when appropriate cationic fluororous rhodium complexes and fluororous anions are combined,  $\text{CF}_3\text{C}_6\text{F}_{11}$ /toluene partition coefficients of 97.1:2.9 to 98.5:1.5 can be achieved. Although partition coefficients have not yet been reported, polyoxometalate salts with fluororous tetralkylammonium cations can exhibit similar fluorophilicities [11].

Entry XVI-12 illustrates an interesting effect. The central rhodium is surrounded by three fluororous triarylphosphines that have only one ponytail per ring, and a  $\text{CF}_3\text{C}_6\text{F}_{11}/n\text{-C}_8\text{H}_{18}$  partition coefficient of 52:48 at 0 °C (entry XI-40). Nonetheless, the rhodium complex is highly fluorophilic, with a partition coefficient of 99.7:0.3 under analogous conditions. Similar phenomena, in which the “sum is greater than the parts”, have been observed with other compounds that are aggregates of fluororous building blocks. Two effects are probably at work. Firstly, the ponytails are deployed in a maximally efficient way around the periphery of the molecule. Secondly, the molar volume increases, the influence of which is discussed in Section 6.5 below.

Dirhodium tetracarboxylates  $\text{Rh}_2[\text{O}_2\text{C}(\text{CH}_2)_mR_{fn}]_4$  with very high fluororous phase affinities are also available (entries XVI-1 through to XVI-8), although for some reason  $\text{CF}_3\text{C}_6\text{F}_{11}$ /ether gives much less biased partition coefficients than  $/\text{CH}_2\text{Cl}_2$ ,  $/\text{C}_6\text{H}_{14}$ , or  $/\text{toluene}$  mixtures. The fluororous nitrogen and sulfur palladacycles in entries XVI-48 through to XVI-51 contain three ponytails of the formula  $R_{f8}(\text{CH}_2)_m$  ( $m = 2$  or  $3$ ) per arene ring. The

$\text{CF}_3\text{C}_6\text{F}_{11}$ /toluene partition coefficients (95.5:4.5 and 90.7:9.3) indicate fluorophilicities somewhat lower than those of the free non-palladated ligands (98.7:1.3 and 99.5:0.5, entries X-24 and XIV-15).

## 6.4

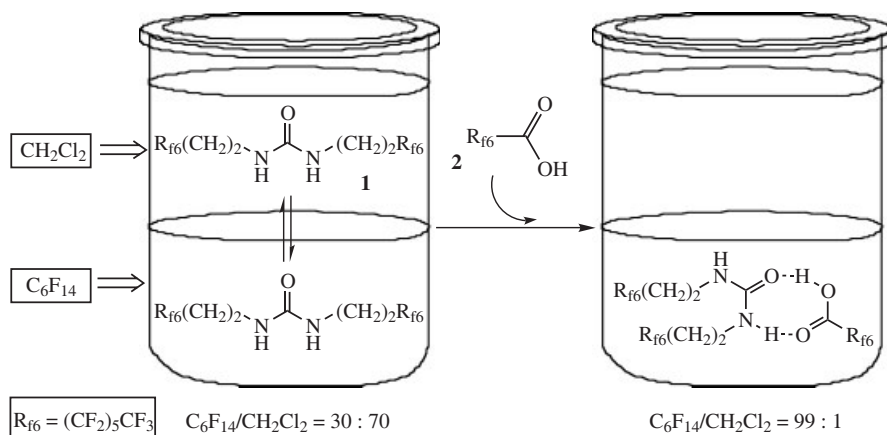
### General Trends and Special Situations

Table 6-1 shows that, with only a very few exceptions, the introduction of longer ponytails or additional ponytails leads to higher fluorous phase affinities. When additional methylene spacers are introduced, while keeping the perfluoroalkyl segments constant, fluorous phase affinities decrease. In the authors' view, compounds with  $\text{CF}_3\text{C}_6\text{F}_{11}$ /toluene partition coefficients of  $>90:<10$  have high fluorophilicities, and those with partition coefficients of  $>99:<1$  possess very high fluorophilicities. When the ratio exceeds  $>99.7:<0.3$ , the compounds can be viewed as "immobilized".

In general, simple monofunctional organic compounds, including arenes, require two ponytails of the formula  $(\text{CH}_2)_m\text{R}_{\text{f}8}$  ( $m = 2, 3$ ) for high fluorophilicities. Three such ponytails lead to very high fluorophilicities, and often essentially complete immobilization. An early rule of thumb stated that for a molecule to be preferentially soluble in a fluorous liquid phase (partition coefficient  $>50:<50$ ), 60% of the molecular weight should be fluorine-derived [12]. However, Table 6-1 contains exceptions to all of these generalizations, and selected cases are now examined in turn.

In compounds that already contain a long perfluoroalkyl segment, the introduction of a  $\text{CF}_3$  group or a "pigtail" sometimes imparts a fluorophilicity significantly greater than might be expected. For example, the  $\text{R}_{\text{f}8}$ -monosubstituted benzene in entry VII-16 can be compared with the  $\text{R}_{\text{f}8}/\text{CF}_3$ - and  $\text{R}_{\text{f}8}/\text{R}_{\text{f}8}$ -disubstituted benzenes in entries VII-37 through VII-40 and the  $\text{R}_{\text{f}8}/\text{CF}_3/\text{CF}_3$ -trisubstituted benzene in entry VII-60. Although the  $\text{CF}_3\text{C}_6\text{F}_{11}$ /toluene partition coefficients for the  $\text{R}_{\text{f}8}/\text{CF}_3$  compounds [91.5:8.5 (*meta*), 89.4:10.6 (*para*), 81.8:18.2 (*ortho*)] indicate fluorophilicities less than that of the  $\text{R}_{\text{f}8}/\text{R}_{\text{f}8}$  compound (99.3:0.7), they are in two cases distinctly greater than that of the  $\text{R}_{\text{f}8}$ -monosubstituted compound (77.5:22.5). The  $\text{R}_{\text{f}8}/\text{CF}_3/\text{CF}_3$  compound (98.3:1.7) is nearly as fluorophilic as the  $\text{R}_{\text{f}8}/\text{R}_{\text{f}8}$  compound. Thus, although trifluoromethylbenzene itself has a very poor fluorous phase affinity (entry VII-6, 12.4:87.6),  $\text{CF}_3$  groups represent legitimate design elements for enhancing fluorophilicities once a ponytail is in place. Other compounds that appear to show similar effects can be found in entries VII-33 through VII-36 and VII-55 through VII-59.

A possibly related effect, already noted in Section 6.3.6, is as follows. Some compounds that can be viewed as aggregates of fluorous building blocks give partition coefficients distinctly higher than the individual building blocks. For example, the fluorophilicity of the rhodium tris(phosphine) complex in entry XVI-12 is much greater than that of the phosphine ligand (entry XI-40). A good example involving fluorous tin complexes appeared after this chapter had been sent to the publisher [13]. Another manifestation of this phenomenon, but in a supramolecular context, is illustrated in Scheme 6-1 [14]. The fluorous *N,N'*-dialkyl urea **1** is not very fluorophilic ( $\text{C}_6\text{F}_{14}/\text{CH}_2\text{Cl}_2$  partition coefficient 30:70). However, the addition of an equivalent of the fluorous carboxylic acid **2** gives a highly fluorophilic 1:1 complex (partition coefficient 99:1). Although the partition coefficient of **2** is not known, it could well be somewhat lower due to the polar acidic functional group. In this event, two



**Scheme 6-1.** Effect of supramolecular complex formation upon a partition coefficient [14]

more polar solutes combine to give a less polar and more fluorophilic complex. Additional examples are provided in entries XVII-1 through to XVII-9 of Table 6-1.

In such compounds or complexes, three main effects are probably operating. Firstly, polar acidic and basic sites (either Brønsted or Lewis) combine to give less polar moieties. Secondly, the ponytails are directed around the outer perimeter of the molecule in an efficient manner such that solvation in non-fluorous media is impeded. One wonders whether a “Maginot line” (or perhaps more accurately, a “Maginot sphere”) of  $\text{CF}_3$ -pigtails, accompanied by a smattering of ponytails, might constitute a particularly staunch defender of the fluorous character. Thirdly, the molar volume increases, the effect of which is discussed in the following section.

The most puzzling exceptions to the generalizations regarding ponytail length and quantity and fluorous phase affinities involve silicon-substituted triarylphosphines of the formula  $\text{P}\{p\text{-C}_6\text{H}_4\text{Si}(\text{CH}_3)_{3-x}[(\text{CH}_2)_2\text{R}_{\text{fn}}]_x\}_3$  (entries XI-39 through XI-58). The partition coefficients were carefully measured in several solvent systems [9a]. The values in  $\text{CF}_3\text{C}_6\text{F}_{11}/n$ -pentane show the expected monotonic trend, with fluorophilicities increasing in the order  $x/n = 1/6 < 1/8 < 2/6 < 2/8 < 3/6 < 3/8$ . However, in  $\text{CF}_3\text{C}_6\text{F}_{11}/n$ -octane the phosphines with three ponytails show *lower* fluorous phase affinities than those with two ponytails ( $x/n = 1/6 < 1/8 < \underline{3/6} < \underline{3/8} < \underline{2/6} < \underline{2/8}$ ). The situation is similar in  $\text{CF}_3\text{C}_6\text{F}_{11}/$ toluene, but now with some of compounds with  $\text{R}_{\text{f6}}$  ponytails showing fluorous phase affinities equal to or *greater* than the homologs with  $\text{R}_{\text{f8}}$  ponytails ( $x/n = 1/6 < 1/8 < \underline{3/8} < \underline{3/6} < \underline{2/8} = \underline{2/6}$ ).

The preceding trends cannot be rationalized by any of the qualitative fluorophilicity models, but yet are real and must have an explanation. Apart from questioning the models, it should be noted that for measurements made in solution, there is always the possibility that certain fluorous solutes, but not others, might aggregate in some way. Gel formation is not uncommon, and micelles are certainly conceivable. As noted in Section 6.2, in the most rigorous studies, the concentration dependences of partition coefficients are determined.

**Tab. 6-2.** Effect of fluorous solvent on partition coefficients with toluene<sup>a,b</sup> [15]

<i>Solvent</i>	$\text{CH}_3\text{CH}_2\text{CH}(\text{CH}_3)\text{CO}_2(\text{CH}_2)_2\text{R}_{f8}$	$\text{CH}_3(\text{CH}_2)_2\text{CH}(\text{CH}_3)\text{CO}_2(\text{CH}_2)_2\text{R}_{f8}$
$(\text{CF}_3)_3\text{CC}(\text{CF}_3)_3^c$	39:61 (0.64)	32:68 (0.48)
$n\text{-C}_6\text{F}_{14}$	50:50 (0.98)	40:60 (0.68)
$\text{CF}_3\text{C}_6\text{F}_{11}$	55:45 (1.23)	49:51 (0.95)
perfluoroperhydrofluorene <sup>d</sup>	53:47 (1.13)	49:51 (0.97)
perfluorodecalin <sup>d</sup>	61:39 (1.59)	56:44 (1.28)

<sup>a</sup> Fluorous solvent:toluene (*P* value as originally determined). <sup>b</sup> 25 °C unless noted. <sup>c</sup> 40 °C. <sup>d</sup> Mixtures of *cis/trans* isomers.

The data are then extrapolated to infinite dilution, where aggregates become impossible. Perhaps some of these non-monotonic trends reflect non-ideal solution behavior.

For many compounds in Table 6-1, partition coefficients were measured with more than one non-fluorous solvent. Although there are a few curious exceptions (e.g., ether vs. toluene or hexane in entries XVI-1 through to XVI-8), the more polar the non-fluorous solvent, the greater the fraction of the fluorous solute in the fluorous phase.

In contrast, only a few compounds have been probed with more than one fluorous solvent. Naturally, it is of interest to know which ones give the most biased partition coefficients. This has been investigated with two test solutes and toluene as summarized in Table 6-2 [15]. The best results were obtained with perfluorodecalin, and all cyclic solvents tested were superior to  $n\text{-C}_6\text{F}_{14}$ . Entries of VI-8 through VI-107 of Table 6-1 also feature many parallel measurements involving  $\text{CF}_3\text{C}_6\text{F}_{11}$  and  $n\text{-C}_6\text{F}_{14}$ . In nearly all cases, the former gives the more biased partition coefficient.

## 6.5

### Quantitative Analysis and Prediction of Partition Coefficients

There have been several efforts to parameterize the above data such that fluorophilicities can be predicted [4–6]. One approach makes use of 3D QSAR descriptors and neural networks [4]. A host of parameters was considered: percent fluorine, molecular volume, molecular surface, globularity, solvent accessible surface, solvent extended surface, solvent extended volume, calculated polarizability, calculated dipole moment, calculated Hildebrand parameter, degree of chemical bond rotational freedom, and others. In the end, very good agreement between measured and predicted partition coefficients in the test group of 60 molecules was realized.

Another parameterization effort involving a test group of 90 molecules found fluorine content, dispersion, and hydrogen bond acidity factors to be most important [5a]. Polarity, hydrogen bond basicity, and size effects played much smaller roles.

The most definitive work to date involves Mobile Order and Disorder (MOD) theory [6, 16]. This has been applied to other types of liquid/liquid partition coefficients, using a five-term expression. With aprotic fluorous biphasic systems, the expression reduces to two terms. One involves the molar volumes of the fluorous and organic solvents and the solute. The other involves the corresponding cohesion parameters. Once the solvent properties have been measured, the partition coefficients are a function of only two solute variables, one of which (the molar volume) is easily calculated from group increments. The investigators use a small amount of the data in Table 6-1 to back-calculate the solute cohesion parameter and derive a second set of group increments. This allows the partition coefficients of approximately 50 additional compounds to be predicted with good accuracy.

## 6.6

### Future Directions

On the computational side, the prediction of partition coefficients is certain to attract further attention. To better interpret raw data, fluorous solutes will be increasingly scrutinized for non-ideal behavior in solution. Naturally, there will be many new entries for Table 6-1, as well as increased focus on supramolecular assemblies. However, there are some likely directions for future research that are not straightforward extensions of themes discussed above.

For example, partition coefficients for fluorous liquid/non-fluorous solid biphasic systems are of interest from several standpoints. Recently, the partitioning of small organic molecules from both fluorous and non-fluorous solvents as well as mixtures into highly cross-linked, macroporous, and insoluble organic polymers has been studied [17]. One goal is to enhance access of organic substrates to imbedded catalyst sites. Presumably due to a fluorophobic effect, fluorous/organic solvent mixtures give up to 200-fold increases in local concentrations relative to pure organic solvents. Under catalytic conditions, turnover frequencies are greatly enhanced.

## 6.7

### Sample Experimental Determinations

The following procedures illustrate recommended procedures for determining partition coefficients by GLC, HPLC, and  $^{19}\text{F}$  NMR. All correspond to entries in Table 6-1.

A [18]. A 10 mL vial was charged with 3,4-( $\text{R}_{\text{f8}}\text{CH}_2\text{CH}_2\text{CH}_2$ ) $_2\text{C}_6\text{H}_3\text{I}$  (entry VII-50; 0.0156 g, 0.0138 mmol),  $\text{CF}_3\text{C}_6\text{F}_{11}$  (2.000 mL), and MeOH (2.000 mL), fitted with a mini-inert valve, vigorously shaken (2 min), and immersed (cap-level) in a 35 °C oil bath. After 12 h, the bath was removed. After 12–24 h, a 0.500 mL aliquot of each layer was added to 0.250 mL of a standard 0.0244 M solution of eicosane in hexane. The samples were diluted with ether and GLC analysis (average of 7–8 injections) showed that 0.00325 mmol of 3,4-( $\text{R}_{\text{f8}}\text{CH}_2\text{CH}_2\text{CH}_2$ ) $_2\text{C}_6\text{H}_3\text{I}$  was in the  $\text{CF}_3\text{C}_6\text{F}_{11}$  aliquot and 0.000101 mmol in the MeOH aliquot (97.0:3.0; a 2.000/0.500 scale factor gives a total mass recovery of 0.0150 g, 97%).

B [19]. A 10 mL vial was charged with the imine palladacycle from entry XVI-48; (0.0104 g, 0.0031 mmol),  $\text{CF}_3\text{C}_6\text{F}_{11}$  (2.000 mL), and toluene (2.000 mL), fitted with a mininert valve,

and vigorously shaken (2 min). After 2 h (24 °C), a 0.250 mL aliquot of the fluorous phase and a 0.750 mL aliquot of the non-fluorous phase were removed. The solvents were evaporated and the residues dried by oil pump vacuum (1 h). Each residue was taken up in CF<sub>3</sub>C<sub>6</sub>H<sub>5</sub>/EtOH (9:1 v/v; 0.500 mL) and analyzed by HPLC (average of 5 injections, 200 × 4 mm Nucleosil 100-5 column, UV/visible detector). The relative peak intensities were (after normalization to the aliquot volumes) 95.5:4.5.

C [20]. A 5 mL flask was charged with H<sub>3</sub>B·P[*p*-C<sub>6</sub>H<sub>4</sub>(CH<sub>2</sub>)<sub>3</sub>CH(CH<sub>2</sub>R<sub>f8</sub>)<sub>2</sub>]<sub>3</sub> (entry XI-21; 0.0368 g, 0.0121 mmol) and CF<sub>3</sub>C<sub>6</sub>F<sub>11</sub> (2.00 mL). After complete dissolution, toluene (2.00 mL) was added and the mixture was vigorously shaken (20 min). The flask was kept at 25 °C for 48 h. Then aliquots (each of 0.500 mL) were taken from both phases. The CF<sub>3</sub>C<sub>6</sub>F<sub>11</sub> aliquot was evaporated to dryness. A solution of the internal standard C<sub>6</sub>F<sub>6</sub> (0.0738 g, 0.397 mmol) in CF<sub>3</sub>C<sub>6</sub>H<sub>5</sub> (12.7016 g) was prepared. Portions of this standard solution were added gravimetrically to the above aliquots (CF<sub>3</sub>C<sub>6</sub>F<sub>11</sub>: 0.6413 g solution, 0.0199 mmol C<sub>6</sub>F<sub>6</sub>; toluene: 0.0596 g solution, 0.00185 mmol C<sub>6</sub>F<sub>6</sub>). Then C<sub>6</sub>D<sub>6</sub> was added (0.05 mL each) and the samples were analyzed by <sup>19</sup>F NMR (integration of CF<sub>3</sub> signal against C<sub>6</sub>F<sub>6</sub>). The procedure was repeated, giving an average partition coefficient of 96.6:3.4 {0.00840 g of H<sub>3</sub>B·P[*p*-C<sub>6</sub>H<sub>4</sub>(CH<sub>2</sub>)<sub>3</sub>CH(CH<sub>2</sub>R<sub>f8</sub>)<sub>2</sub>]<sub>3</sub> in 0.500 mL of CF<sub>3</sub>C<sub>6</sub>F<sub>11</sub>; 0.000292 g of H<sub>3</sub>B·P[*p*-C<sub>6</sub>H<sub>4</sub>(CH<sub>2</sub>)<sub>3</sub>CH(CH<sub>2</sub>R<sub>f8</sub>)<sub>2</sub>]<sub>3</sub> in 0.500 mL of toluene}. A 2.00/0.500 scale factor gives a total mass recovery of 0.0348 g (95%).

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## 7

**Separations with Fluorous Silica Gel and Related Materials***Dennis P. Curran*

## 7.1

**Introduction**

Early work in the fluorous field relied on liquid/liquid separations to bifurcate reaction mixtures into organic and fluorous fractions [1]. However, limitations quickly arose due to the large numbers of fluorines needed to entice otherwise organic molecules to partition into a fluorous phase. The high molecular weights associated with heavy fluorous molecules are not a detraction in catalysis provided that the fluorous catalysts are efficient and can therefore be used in small quantities. In the late 1990s, the high molecular weights and attendant low organic solubilities and other unusual properties of heavy fluorous molecules posed a significant hurdle for budding chemical discovery techniques such as synthesis with fluorous reagents and protecting groups [2]. This hurdle can be surmounted by the design of appropriate heavy fluorous tags and identification of reliable reaction and separation conditions for tagged compounds [3]. Alternatively, and often more conveniently, this hurdle can be bypassed by switching from a heavy fluorous approach to a light fluorous approach that uses a solid/liquid separation in place of a liquid/liquid one. Fluorous solid phase extractions were first reported in a Note in *J. Org. Chem.* by He, Hadida and Curran in 1997 [4]. Related techniques of fluorous chromatography soon followed [5], and separations with fluorous solid phases have rapidly progressed to complement and supplement the liquid phase approaches.

## 7.1.1

**Fluorous Silica Gel**

Silica gel with a fluorocarbon bonded phase, hereafter called fluorous silica gel, is by far the most common material used for solid-based fluorous separations. The material predates the fluorous field, but for nearly two decades fluorous silica gel was like a material not matched with its natural analyte – like an ice hockey player asked to play soccer. Early reviews provide much useful information on the features of fluorous silica in separation of organic molecules without fluorines or with only a stray fluorine or two (that is, not enough fluorines to be fluorous) [6]. However, just as an ice hockey player's natural game is ice hockey, fluorous silica gel's natural game is separating fluorous molecules from non-fluorous molecules and from each other.

Outside its natural element, fluorous silica gel is a cousin of standard reverse phase silica gels such as C<sub>18</sub>; however, it is much less retentive for organic molecules so very high water contents must be used in elution solvents when non-fluorous molecules are being separated. Polarity is a factor in separations of organic compounds on fluorous silica, but it is not the sole factor since there are many examples of reversed order of elution of non-fluorous molecules on regular reverse phase and fluorous silica. Molecular size may also be important, with larger molecules tending to be retained less well on fluorous silica. In addition to the reviews cited above and company “product notes”, recent papers by Monde *et al.* of the NEOS Company (makers of Fluofix<sup>®</sup>) highlight attractive features of fluorous silica separations including the separation of geometrical isomers of various sorts [7].

It quickly became apparent after 1997 that the unique feature of fluorous silica is its ability to separate fluorous molecules from non-fluorous molecules and from each other due to the selective retention of the fluorous molecules. A 2001 review highlights early work [8], but applications have advanced quickly and this chapter provides an overview of work from 1997 through to early 2003. Additional examples of fluorous silica separations can be found in Chapter 8 on “Light Fluorous Chemistry”.

### 7.1.2

#### Types and Sources of Fluorous Silica Gel Materials and Products

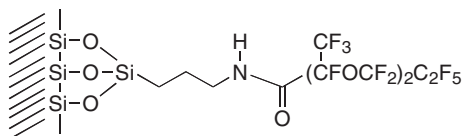
Fluorous silica gel has been prepared in ways that are generally analogous to standard reverse phase silica gels by bonding silanes to prepared silica. Most products have the general structure silica–O–Si(Me)<sub>2</sub>(CH<sub>2</sub>)<sub>n</sub>R<sub>f</sub> where *n* is 2 or 3 and R<sub>f</sub> is C<sub>6</sub>F<sub>13</sub> or C<sub>8</sub>F<sub>17</sub>; these materials are prepared from silylating reagents of the general structure XSi(Me)<sub>2</sub>(CH<sub>2</sub>)<sub>n</sub>R<sub>f</sub>. A few materials are prepared from reagents X<sub>3</sub>Si(CH<sub>2</sub>)<sub>n</sub>R<sub>f</sub> that lack methyl groups and these materials are interlinked at silicon by condensation to each other and to the support. Also, products can be made with and without endcapping, though without seems more common. Methods of preparation and even sometimes content of these materials can be trade secrets. Fortunately, all sources of fluorous silicas provide the structure of the R<sub>f</sub> group, an important factor that can dictate choice since longer R<sub>f</sub> chains retain fluorous compounds more strongly. This is typically an advantage, especially in solid phase extraction applications. Names for fluorous silica gel can be ambiguous with terms such as an “octyl bonded phase” meaning “CH<sub>2</sub>CH<sub>2</sub>C<sub>6</sub>F<sub>13</sub>” (1*H*,1*H*,2*H*,2*H*-perfluorooctyl, or perfluorohexylethyl) to some and “C<sub>8</sub>F<sub>17</sub>” (perfluorooctyl) to others. We avoid terms like “octyl” here entirely because it is unclear whether they include the spacer.

Silica gel sold under the name FluoroFlash<sup>™</sup> by Fluorous Technologies, Inc. bears a perfluorooctylethyl bonded phase: Si(CH<sub>2</sub>CH<sub>2</sub>C<sub>8</sub>F<sub>17</sub>) [9]. This is available as TLC plates and loose for flash chromatography. It is also packed in assorted cartridges for SPE (solid phase extraction) and in Biotage [10] cartridges and Samplets<sup>™</sup> for use with popular flash chromatography instruments. At this writing, the only other provider of loose fluorous silica gel appears to be Silicycle [11], whose less fluorous “Tridecafluoro-2” [Si(CH<sub>2</sub>CH<sub>2</sub>C<sub>6</sub>F<sub>13</sub>)] bonded phase is not as attractive as FluoroFlash<sup>™</sup> for SPE and flash chromatographic applications since higher water content is needed to retain fluorous materials.

In addition to these commercial grade silica gels, there are several more or less similar materials described in the literature. All of our early work was conducted on so-called “homemade” fluorous silica gel prepared by a standard procedure from silica and

The diagram shows a silane monolayer on a surface. On the left, a series of diagonal lines represents the substrate surface. Three silicon (Si) atoms are bonded to this surface, each connected to an oxygen (O) atom. These oxygen atoms are part of a chain: Si-O-Si-O-Si-O-Si. The third silicon atom in this chain is bonded to three hexafluoropropyl groups, each represented as C<sub>6</sub>F<sub>13</sub>. The groups are oriented upwards, downwards, and to the right.

1



2

In short, there are now a range of excellent commercially available products that can be used for applications from SPE through flash chromatography to HPLC. While the existing materials have been optimized well for performance by their manufacturers, there is still much room for research on new fluorosilica materials with capabilities different from currently marketed products.

### Fluorous Solid Phase Extraction (FSPE)

First described by Curran and coworkers in 1997 [4], fluorous solid phase extraction has quickly become the most common separation technique that is used in conjunction with light fluorous molecules.

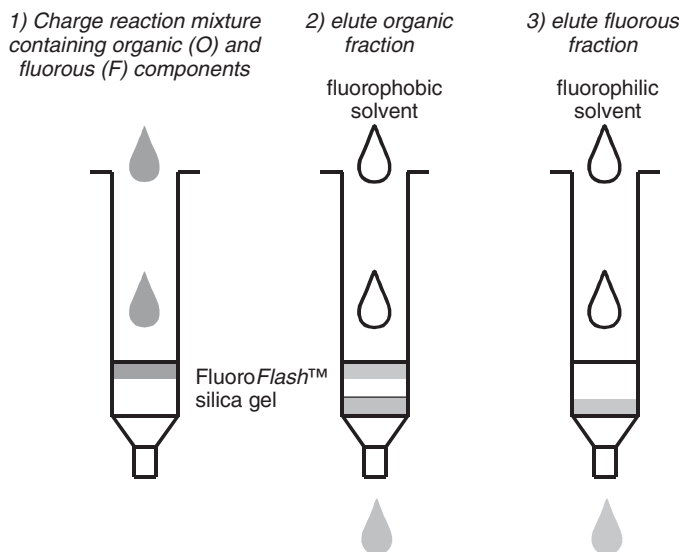


Fig. 7-1. Diagram of a solid phase extraction with fluorous silica gel

#### 7.2.1

#### Fluorous Solid Phase Extraction and its Relationship to Chromatography and Liquid/Liquid Extraction

Long a popular technique in chemical analysis [18], solid phase extraction is increasingly used in chemical synthesis due to its relative simplicity and separation power [19]. Solid phase extraction (SPE) has a resolution capability in between that of liquid/liquid extraction and chromatography, and it is productive to build analogies between SPE and both of these techniques.

Figure 7-1 shows a diagram of an idealized fluorous solid phase extraction. A mixture of a fluorous and an organic compound is loaded onto fluorous silica gel and eluted in a first-pass with a “fluorophobic” solvent. The fluorous material adsorbs onto the column while the organic material elutes with or near the solvent front. A second-pass elution with a “fluorophilic” solvent now elutes the fluorous compound with or near the solvent front. During each pass, only a single fraction is collected so this simple process resembles a filtration more than a chromatography. Unlike SPE techniques of chemical analysis where the target product or fraction is usually in the second-pass of the SPE, the fluorous SPE techniques of chemical synthesis may produce the target product in the first-pass, the second-pass or even both passes (for example, when a fluorous catalyst is being separated from an organic product and both are targeted for recovery).

Like fluorous SPEs, the uses of polar/non-polar SPEs and ion exchange SPEs are also increasing [19]. Each type of commonly used SPE process has an analogy in liquid/liquid extractions. Ion exchange processes are the solid/liquid equivalents of acid/base extractions while polar/non-polar SPEs on regular or (more typically) reverse phase silica gel are analogs of hexane/acetonitrile, hexane/methanol and related extractions. Fluorous SPEs are of

course the analogs of fluoruous/organic liquid/liquid extractions. The SPE process resembles a liquid/liquid extraction in that one of the compounds is extracted out of the initial liquid phase (the fluorophobic solvent) and onto the solid phase (the fluoruous silica), and in that the purified product fractions from the separation are in two volatile liquid phases from which the products are recovered by evaporation. Conveniently for parallel synthesis, SPE fractions can typically be analyzed directly by LC or LC-MS (liquid chromatography mass spectrometry).

The relationship between SPE and chromatography is analogous to the relationship between evaporation and distillation. A mixture of two compounds of widely differing boiling points can easily be separated by evaporating one away from the other. As the respective boiling points of the mixture components approach each other, distillations must be conducted with increasing care. Likewise, the ideal SPE is a “chromatography” wherein one component or sub-set of components has an  $R_f$  (retention factor) of 1 while the others have an  $R_f$  of zero. As the  $R_f$  values of the respective components approach each other, the separation must be done with increasing care and the SPE mutates to a chromatography. Asking when does an SPE become a chromatography is something like asking when does an evaporation become a distillation; there is a healthy grey zone where either term might be appropriate. SPEs feature high loading levels (sometimes 10% or more) and generally only two fractions – organic and fluoruous – are collected. The transition to a chromatography entails decreased loading (or, more accurately, the use of more support) with attendant increased resolution, and collection of multiple fractions.

### 7.2.2

#### Examples of Fluorous Solid Phase Extractions

Figure 7-2 summarizes the first fluoruous solid phase extraction (FSPE), which involved the use of a fluoruous tin reagent [4, 20]. SPE was used to bifurcate the crude reaction mixtures resulting from the thermal allylation of aryl aldehydes **3** with fluoruous allyl stannane **4**. A first-pass elution with acetonitrile provided the pure allylation product **5** while a second-pass with hexane provided a fluoruous tin fraction. Tin reagents **4** are best classed as heavy fluoruous reagents because their byproducts can also be removed by liquid/liquid extraction. In a series of seven allylation experiments, both liquid/liquid and SPE separations were con-

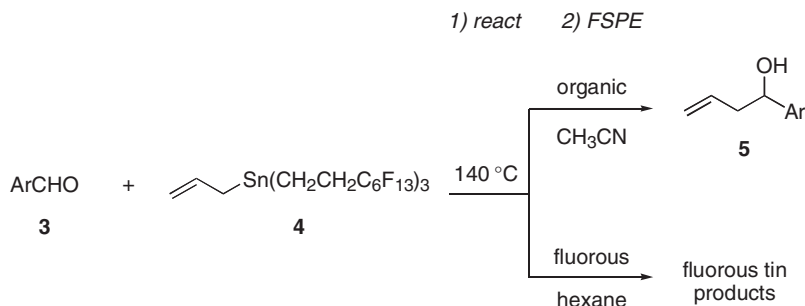


Fig. 7-2. SPE separations of heavy fluoruous tin reagents and byproducts

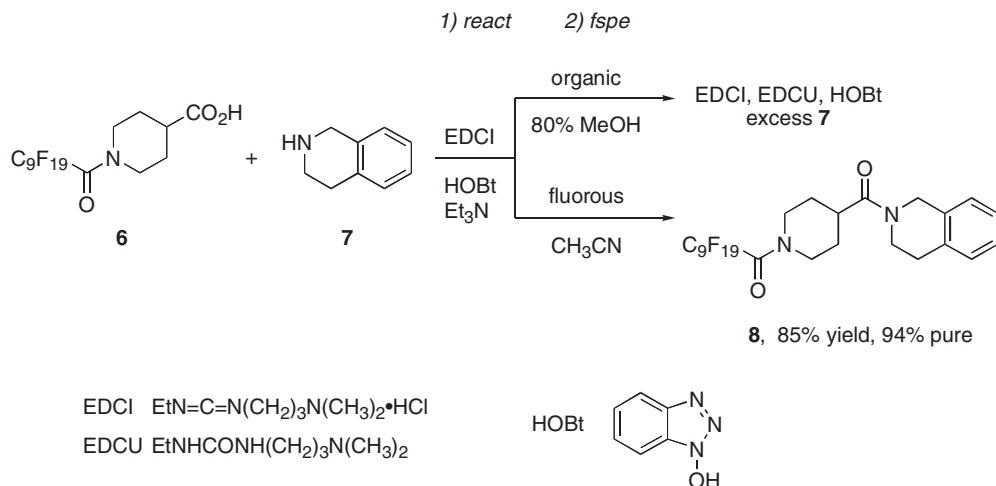


Fig. 7-3. SPE enables light fluorous synthesis

ducted and the results (yields and purities) were comparable. Related SPE separations were conducted in reactions involving homologous tin reagents with propylene spacers [20].

Subsequent to this initial work, the uses of fluorous SPE quickly shifted to light fluorous chemistry. This is understandable given that the SPE in effect enables light fluorous chemistry. However, the potential advantages of SPE have been largely overlooked in heavy fluorous chemistry, where liquid/liquid separations provide a viable option. In addition to its simplicity, the SPE procedure is attractive because no fluorous solvent is needed for either reaction or separation and because the fluorous silica is robust and reusable. Finally, SPEs of heavy fluorous compounds are attractive relative to light ones because water-free fluorophobic solvents can often be used to obtain the organic fraction.

The concept of using fluorous SPE to enable light fluorous synthesis was introduced in a pair of complementary papers in 1999 and 2000 [5, 21]. In the first [5], fluoroacyl-tagged amino acids like **6** were coupled under standard conditions with excess amines such as **7** in a reaction promoted by EDCI and HOBt (Figure 7-3). Loading of the crude mixture onto fluorous silica and first-pass elution with 80% methanol/water provided an organic fraction of excess and spent organic reagents and reactants. Second-pass elution with acetonitrile provided the pure fluorous-tagged amide **8** and related products in excellent yields and purities. Because of their relatively low fluorine content, compounds like **8** have little or no solubility in FC-72, so using liquid/liquid separation techniques for reactions such as these is pointless.

In the second paper [21], fluorous phosphines were prepared and tested as ligands and reagents. Among the six phosphines, three linear **9a–c** and three branched **10a–c**, shown in Figure 7-4, only those with three fluorous phenyl rings showed partition coefficients ( $K_p$ ) sufficiently high for use in liquid/liquid extractions. Even these high partition coefficients were limited to highly fluorophobic solvents such as methanol. In contrast, HPLC experiments showed that all of these phosphines were well retained on fluorous silica gel com-

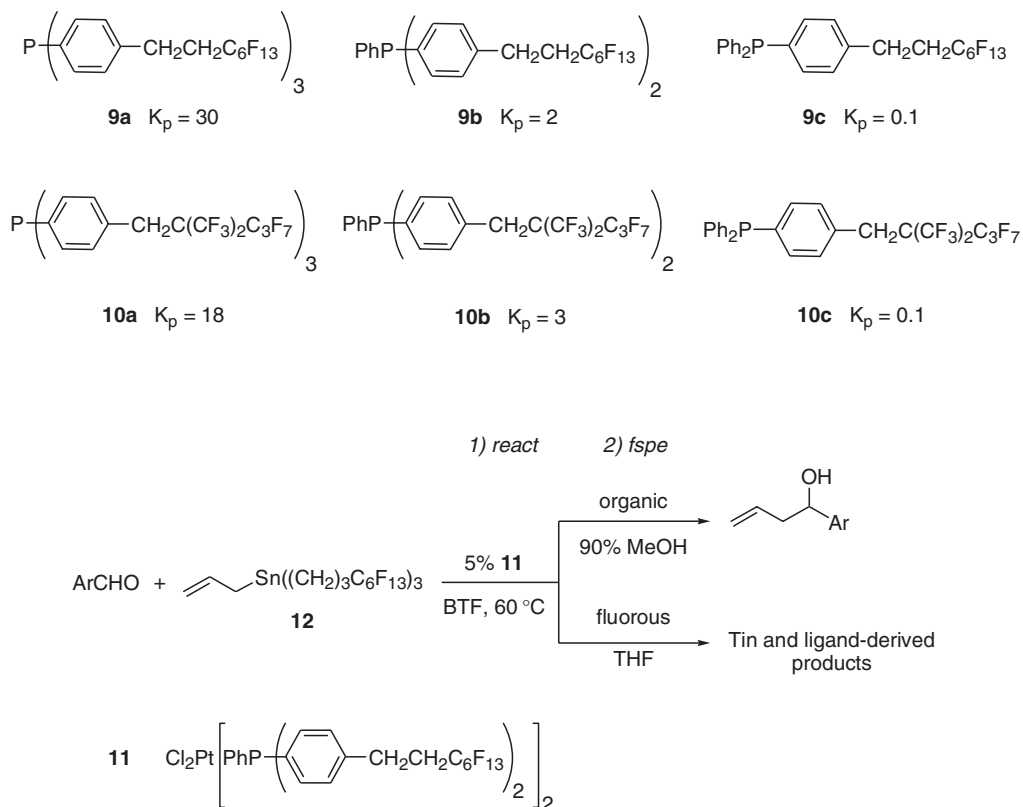


Fig. 7-4. Light fluoruous phosphines with FC-72/MeOH partition coefficients ( $K_p$ )

pared with typical organic compounds. As an example of how these phosphines can be used as ligands, platinum complex **11** was prepared and used to promote allylation of aldehydes with fluoruous stannane **12**. SPE with 90% methanol/water provided a pure product fraction free from fluoruous ligand-derived products and also free from tin products. In this application, the catalyst was apparently not stable to the reaction conditions since the fluoruous fraction was not pure catalyst but a complex mixture of products. Nonetheless, the simple isolation of pure alcohols is valuable. This work “rescued” a large number of light fluoruous phosphines and other reagents that had been made by others and discarded as reaction partners because they were found to exhibit partition coefficients too low for liquid/liquid extractions; such reagents can now routinely be separated by SPE instead.

Figure 7-5 summarizes representative recent uses of fluoruous SPE techniques, including one example each from the classes of fluoruous reagents (the Mitsunobu reaction [22]), fluoruous scavengers [23], and fluoruous protecting groups [24]. In the reagent application, the target product is in the organic fraction, while the fluoruous fraction contains spent reagents that can be recovered for reuse. In the scavenger application, the target product is again in the organic fraction, but this time the fluoruous fraction is a mixture of scavenged product



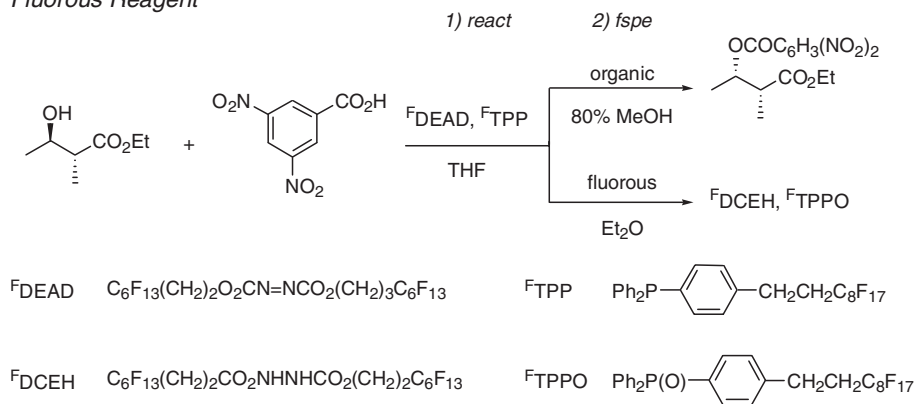
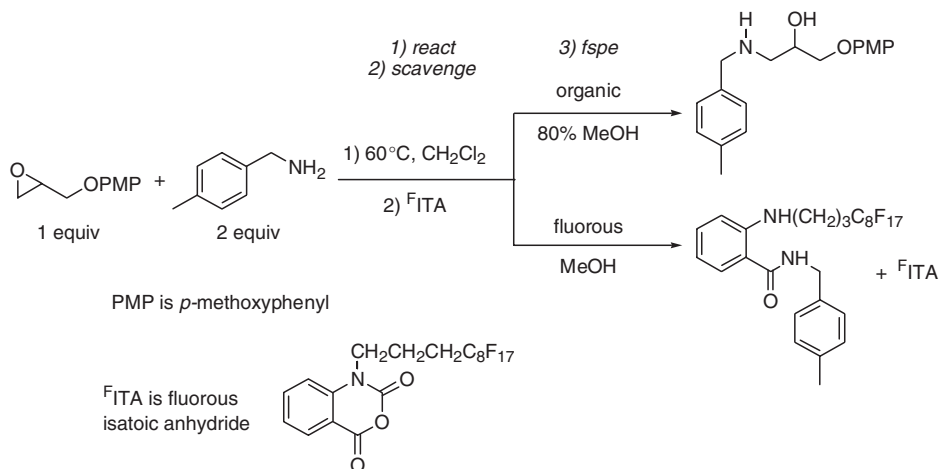
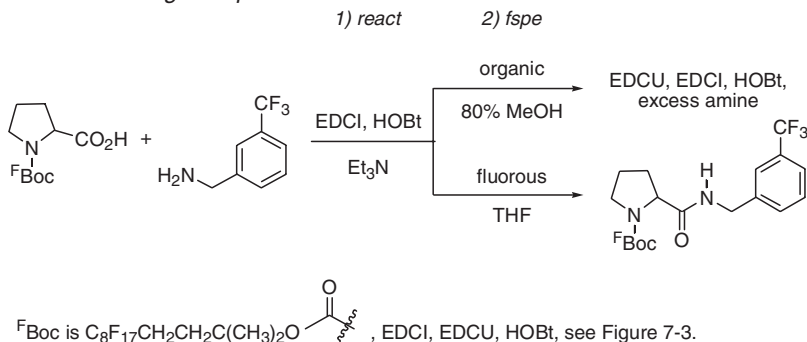
*Fluorous Reagent**Fluorous Scavenger**Fluorous Protecting Group*

Fig. 7-5. Examples of light fluorous reactions with SPE separations

and unreacted scavenger and is generally discarded. In the protecting group application, it is the organic fraction with the excess and spent reagents that is generally discarded (or occasionally, recovered) and the fluorous fraction now contains the target product. Additional examples of uses of fluorous SPE in the context of light fluorous synthesis are highlighted in Chapter 8.

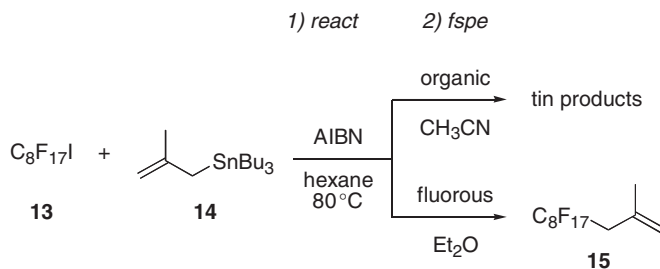
In addition to the primary literature cited herein, practical aspects of conducting fluorous solid phase reactions including solvent choices and loading levels can be found in a recent review [8], in several of the Procedures in Chapter 11 of this Handbook, and in an information sheet provided by Fluorous Technologies, Inc. [25]. Fluorous TLC plates are useful for selecting conditions for solid phase extractions. By spotting authentic or model light fluorous products in aqueous methanol or acetonitrile of varying water content (typical 0–25%), one can quickly identify the minimum water content that still holds the fluorous product at or near the baseline. Even with water contents of 25% and above, most organic compounds have  $R_f$  values well above 0.5 and often not far from 1. Even better is to use fluorous HPLC columns as predictors of successful SPEs; this is covered in Section 7.4.2.2 below.

### 7.2.3

#### Reverse Fluorous Synthesis with Solid Phase Extractions

A general theme in most fluorous reactions to date is that the final target products are not fluorous, even when fluorous protecting groups or tags are used, these are only in place at intermediate stages and are removed at the end. The synthesis of highly fluorinated molecules is itself a specialized field of significant importance [26], and such molecules lend themselves to the logical reversal of standard fluorous synthesis. In other words, the precursors and target products are themselves fluorous, so organic (or inorganic) reagents, catalysts, scavengers, etc. are used to allow easy separation of the target products from the other remaining or spent reaction components.

A powerful separation tool in the “reverse fluorous synthesis” approach is solid phase extraction. This was introduced by Ryu, Curran and coworkers in 2000 with allylation of perfluoroalkyl iodides, as summarized in Figure 7-6 [27, 28]. In a reversal of reaction of organic precursors with a fluorous allyl tin reagent (see Figure 7-3), perfluoroalkyl iodides such as **13**



AIBN is azo-*bis*-isobutyronitrile

**Fig. 7-6.** Reverse fluorous synthesis: the use of organic reagents to make fluorous target products with SPE separation

were reacted with the standard organic tin reagents such as alkyl tributyltin **14**. First-pass solid phase extraction with acetonitrile provided an organic fraction containing the tin reagent and byproducts, while second-pass elution with ether provided the fluorous target product **15**. For heavy fluorous compounds with suitable partition coefficients, fluorous/organic liquid/liquid extraction provides a viable alternative to SPE in reverse fluorous synthesis [28].

In the past, traditional organic separations have been routinely applied for the synthesis of fluorous molecules. Looking forward, reverse fluorous synthesis provides a powerful synthesis and separation strategy that is naturally suited to fluorous target molecules and will be widely applicable.

### 7.3

#### Fluorous Flash Chromatography

Bridging the large gulf between fluorous SPE and fluorous HPLC are intermediate chromatographic methods. These have only recently been exploited, and generally this has been at the SPE end of the continuum where speed is an important feature, hence the term “fluorous flash chromatography”. Compared with SPE, loading levels in fluorous flash chromatography are lower but resolution is higher. Typically, several fractions are collected and analyzed.

Perhaps the first fluorous flash chromatography resulted from a collaboration of our group and Leitner's in 1998 [29]. For a time in the late 1990s, the best synthesis of fluorous aryl bromide **18** – a key intermediate for making phosphines and other fluorous reagents – involved the copper catalyzed coupling of Grignard reagent **16** and iodide **17**. This gave target product **18** contaminated with dimer **19**. Having similar boiling points and polarities, these two compounds were not easy to separate by distillation or silica gel chromatography. However separation on homemade fluorous silica gel was straightforward because of the large differences in fluorine content. Loading of a mixture followed by elution with acetonitrile provided initial fractions containing pure **18**, while subsequent elution with THF provided fractions with the dimer **19**. Recovery was generally close to quantitative in this process, which is on the borderline between an SPE and a flash chromatography.

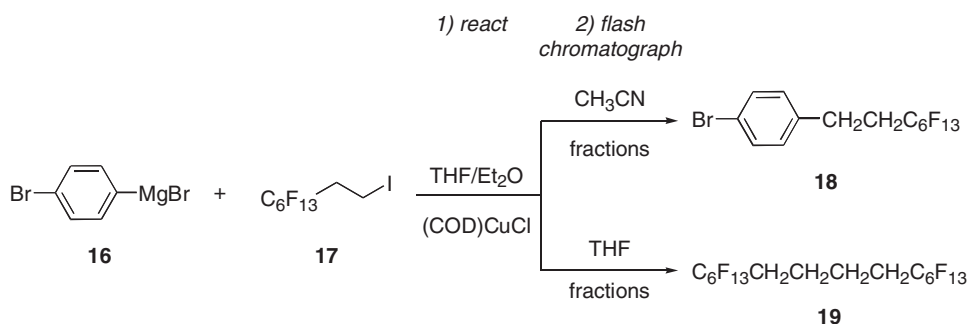


Fig. 7-7. The first fluorous flash chromatography

Until very recently, the use of fluorous flash chromatographic methods has been limited by the lack of suitable commercial silica products. However, the FluoroFlash™ line of products, including SPE and Biotage cartridges and loose silica, now fills this need and flash chromatographic methods can be considered on the one hand for separations that have been conducted by SPE (if higher resolution is needed) or on the other hand for separations that have been done by HPLC (if higher loading levels or speed are needed). As an early illustration of the potential, fluorous quasiracemate derivatives of amino acids have recently been preparatively demixed by fluorous flash chromatography [30].

## 7.4

### Fluorous HPLC

Fluorous HPLC is the separation of fluorous compounds over silica gel with a fluorocarbon bonded phase (fluorous silica gel) in a high pressure/performance liquid chromatography mode. As mentioned in Section 7.1.2, an assortment of fluorous HPLC columns is now available in sizes from analytical to semi-preparative. These columns predate the fluorous field, and early uses were primarily for chemical analysis of organic or biological molecules [6, 7]. Among the organic molecules separated were lightly fluorinated ones, and fluorous columns were generally superior at separating these molecules compared with standard reverse phase columns. For example, a Fluofix® column separates all ten fluorinated benzenes from each other, except for 1,2-difluorobenzene and 1,3-difluorobenzene, which coeluted [7]. Other fluorous HPLC columns probably behave similarly.

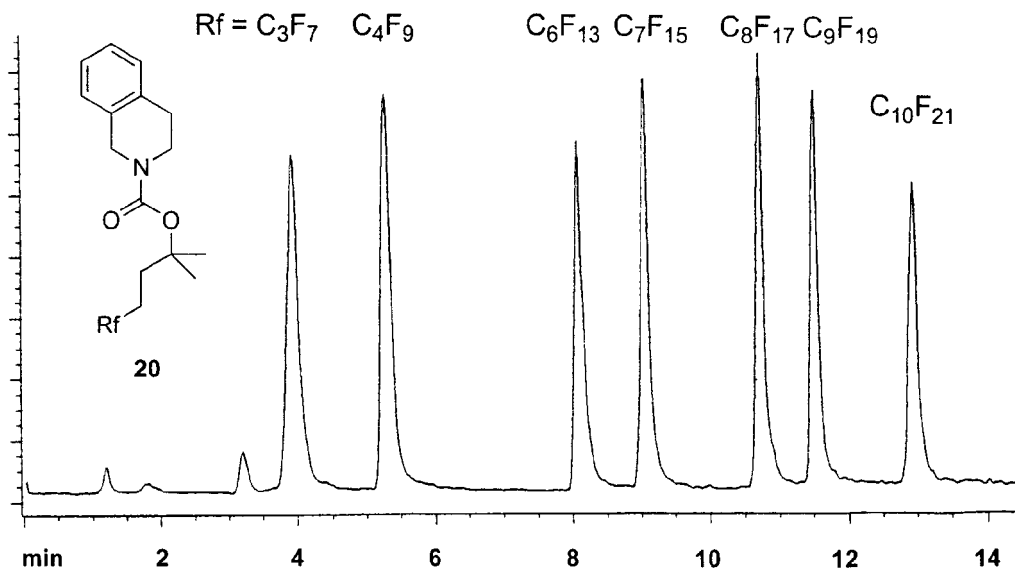
#### 7.4.1

##### Structure/Retention Trends in Fluorous Chromatography

A utilitarian if simplistic analysis of structure/retention trends in fluorous HPLC considers the fluorous and organic parts of a molecule separately. The fluorous part of the molecule exerts the “primary” effect, with separation by fluorine content being the signature of fluorous HPLC, while the organic part of the molecule exerts a significant but “secondary” effect. The primary organofluorine effect arises because the partitioning of isolated CF<sub>2</sub> groups from solvents such as MeOH or acetonitrile into fluorous silica gel is considerably more favorable than the same partitioning into reverse phase silica gel and is likewise higher than the partitioning of CH<sub>2</sub> groups to either fluorous or reverse phase silica gel [6, 7]. In short, fluorine content rules.

The facile separation of a homologous set of fluorous-tagged amides **20** over fluorous silica gel is shown in Figure 7-8. The solvent gradient starts at 80% MeOH/water and increases linearly to 100% MeOH over the 8 min. The compounds emerge in order of tag size from C<sub>3</sub>F<sub>7</sub> to C<sub>10</sub>F<sub>21</sub>. The analog bearing the C<sub>5</sub>F<sub>9</sub> tag is absent from this mixture, and its absence is readily spotted by the large gap between the C<sub>4</sub>F<sub>9</sub> and C<sub>6</sub>F<sub>13</sub> analogs.

Of special importance in this separation experiment is the behavior of molecules like the standard Boc analog of **20** (not shown) that do not bear any fluorines; these molecules emerge at or near the solvent front. Indeed in our experience, essentially all non-fluorinated organic molecules elute at or within 1 min of the solvent front with both 80% MeOH/water and 80% acetonitrile/water. This big difference in retention between fluorous and non-



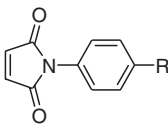
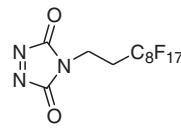
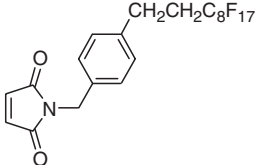
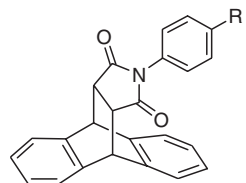
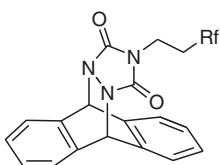
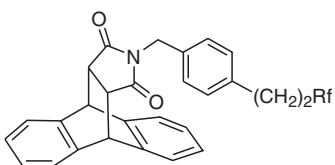
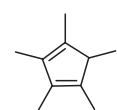
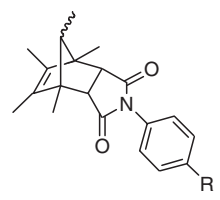
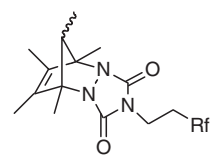
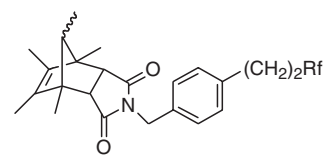
a) FluoroFlash<sup>TM</sup> hplc column, 80/20, MeOH/water to 100% MeOH over 8 min, then 100% MeOH

**Fig. 7-8.** Separation of homologs by fluorine content (FluoroFlash<sup>TM</sup> HPLC column, 80/20 MeOH/water to 100% MeOH over 8 min, then 100% MeOH)

fluorous molecules is the basis for the fluorous/organic solid phase extractions described above. Indeed, to chromatograph non-fluorous organic molecules on fluorous silica gel requires water contents of 50% or more due to the low affinity of the compounds for the support [6, 7].

The organic part of a fluorous molecule can exert significant secondary effects on its retention, and the early work on chromatography of organic and lightly fluorinated molecules provides guidelines on what types of secondary effects to expect [6, 7]. Polarity is clearly important, with salts and highly polar functional groups decreasing retention times and lipophilic groups (especially compact ones) increasing retention times. However, the retention orders of a series of compounds on fluorous and reverse phase silica gel are not always identical so the simple notion that the behavior of organic molecules or molecular fragments on fluorous silica can be predicted from reverse phase behavior is not always appropriate. Other factors that may be important are molecular size and shape (smaller being retained better) as well as the presence of specific groups such as H-bond donors or acceptors.

Figure 7-9 shows retention times on a FluoroFlash<sup>TM</sup> analytical column for a series of fluorous Diels-Alder adducts bearing C<sub>6</sub>F<sub>13</sub> or C<sub>8</sub>F<sub>17</sub> tags along with related non-fluorous controls [31]. Conditions are isocratic (80% MeOH/water) to maximize the separations. As expected, the controls from the non-fluorous *N*-phenylmaleimide emerge very close to the solvent front, while fluorous maleimide adducts with the C<sub>6</sub>F<sub>13</sub> tags generally emerge before other adducts with the C<sub>8</sub>F<sub>17</sub> tags. However, there is also a significant secondary separation and the first of the C<sub>8</sub>F<sub>17</sub> adducts (fluorous triazoline dione adduct with anthracene)

<div style="text-align: center;"> <div style="transform: rotate(-45deg); display: inline-block;">dienophile</div> <div style="display: inline-block;">diene</div> </div>	fluorous and non-fluorous <i>N</i> -phenylmaleimides	fluorous triazolinedione	fluorous <i>N</i> -benzyl maleimide
	 R = H, R = C <sub>6</sub> F <sub>13</sub>	 C <sub>8</sub> F <sub>17</sub>	 CH <sub>2</sub> CH <sub>2</sub> C <sub>8</sub> F <sub>17</sub>
anthracene	 R = H 1.8 R = C <sub>6</sub> F <sub>13</sub> 8.5	 R <sub>f</sub> = C <sub>8</sub> F <sub>17</sub> 14.8	 R <sub>f</sub> = C <sub>8</sub> F <sub>17</sub> 26.0
pentamethyl- cyclopentadiene	  R = H 2.1, syn + anti R = C <sub>6</sub> F <sub>13</sub> 13.4, syn 14.3, anti	 R <sub>f</sub> = C <sub>8</sub> F <sub>17</sub> syn, 31.2 anti, 33.3	 R <sub>f</sub> = C <sub>8</sub> F <sub>17</sub> syn, 65.0 anti, 70.7

a) separation on a FluoroFlash<sup>TM</sup> HPLC column, 15 x 150 mm, isocratic, 80% MeOH/H<sub>2</sub>O, solvent front is at about 1.7 min

**Fig. 7-9.** Retention times (min) of selected fluorous and non-fluorous Diels-Alder adducts, (separation on a FluoroFlash<sup>TM</sup> HPLC column, 15 × 150 mm isocratic, 80% MeOH/H<sub>2</sub>O, solvent front is at about 1.7 min)

emerges at 14.8 min, which is very close to the last of the C<sub>6</sub>F<sub>13</sub> adducts (fluorous maleimide adduct with pentamethyl cyclopentadiene) at 14.3 min. This raises a caution flag for fluorous mixture synthesis applications, where secondary effects could cause crossing of tagged molecules and complicate separation and analysis (see Section 7.4.2.3, below). Within the tag families, the adducts from pentamethyl cyclopentadiene are particularly well retained. This effect of compact lipophilic groups has already been observed with *t*-butyl and trimethylsilyl groups [32, 33]. Likewise, adducts of the more polar triazoline dione emerge before adducts of the *N*-benzylmaleimides with the same dienes. Finally, the power of the fluorous compounds to separate stereoisomers is also evident: in all three pairs of fluorous adducts

with pentamethyl cyclopentadiene, the *syn* adduct (methyl group on the same side as dienophile) elutes well before its *anti* isomer. These isomers could be separated in preparative fluorous HPLC experiments, but could not be separated over regular or reverse phase silica gel.

#### 7.4.2

##### Uses of Fluorous HPLC

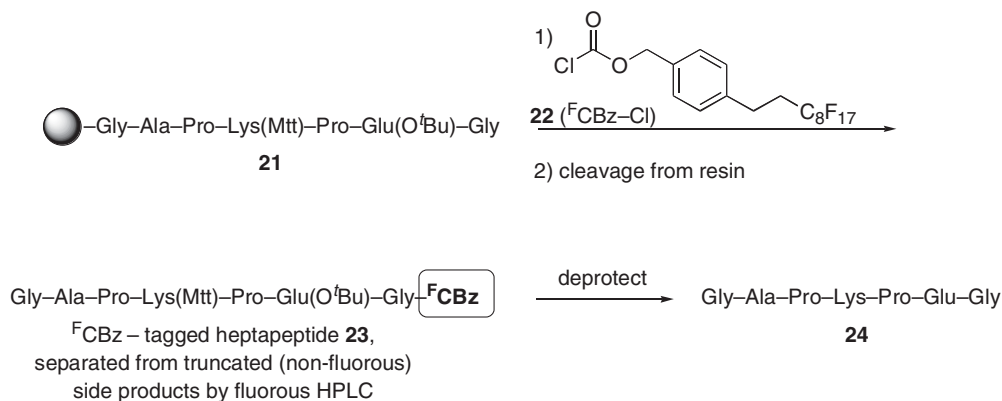
The potential utility of fluorous HPLC columns in fluorous chemistry runs the gamut of applications from the separation of molecules by differing fluorine content, through the separation of molecules with the same fluorine content by structure of the organic fragment, to separation of diastereomers bearing identical organic and fluorous components. In short, if you are making or working with fluorous molecules, you need a fluorous HPLC column. Here we present representative highlights of examples showing how and when to use fluorous HPLC.

##### 7.4.2.1 Analysis and Purification of Organofluorine Compounds

The strength of fluorous HPLC columns in analyzing and purifying fluorinated compounds of all sorts is still not widely appreciated. For molecules bearing from one to a handful of fluorines (that is, fluorinated but not fluorous), fluorous columns should routinely be evaluated alongside regular and reverse phase silica gel columns. While the primary (fluorine content) effect is at its minimum for these lightly fluorinated compounds, the unique features of the fluorous materials can still make fluorous HPLC the method of choice [6, 7]. Fluorous HPLC should be considered for typical fluorination reactions where separation of unfluorinated and lightly fluorinated products is desired, or for separation of stereoisomers of organofluorine compounds.

In the fluorous area, the unique features of fluorous columns are useful for both the purification and analysis of fluorous molecules, and we routinely analyze and sometimes purify our fluorous reagents and intermediates by fluorous HPLC. In the light fluorous area, solvents such as methanol or acetonitrile with 0–20% water are typical. As molecules move towards the heavy end, more powerfully eluting solvents are needed, and we typically begin to introduce THF at a suitable rate. Fluorous columns are readily used in both LC-MS and LC-NMR experiments, and each provides an extremely powerful tool for identification and analysis.

The recent peptide synthesis work of van Boom and coworkers nicely shows the power of fluorous HPLC when coupled with solid phase peptide synthesis (Figure 7-10) [34]. They synthesized protected heptapeptide **21** on a resin by using the standard Fmoc protection approach with HATU for coupling and Ac<sub>2</sub>O for endcapping. Exposure of the resin to HATU in each coupling was deliberately limited to 5 min to enhance the amount of truncated, endcapped products. The final sequence **21** was then tagged with <sup>19</sup>F Cbz reagent **22**, then the products were removed from the resin and purified by fluorous HPLC (Fluophase column, MeOH/water gradient with a trace of TFA). The retention provided by the fluorous tag on the target product allowed isolation of pure protected heptamer **23** even though non-optimized coupling conditions were used since the truncated, endcapped products do not bear fluorous tags. Final deprotection gave the target heptapeptide **24**.



**Fig. 7-10.** Purification of a heptapeptide by on-resin fluorous tagging, cleavage, and fluorous HPLC

#### 7.4.2.2 Method Development for Preparative Fluorous Chromatographies and SPEs

Fluorous TLC plates provide simple tools to identify solvent systems and methods for preparative fluorous chromatographies and SPEs, but the quantitative information provided by fluorous HPLC columns is often appreciated. For example, we often inject samples onto a  $4.6 \times 150$  mm FluoroFlash™ HPLC column with a linear gradient of 80% MeOH water to 100% MeOH over 30 min (a similar gradient with MeCN can also be used). Organic compounds elute at or near the solvent front under these conditions. Fluorous compounds with retention times of 20 min or more are highly suitable for simple SPE separations with high loading levels using 80% MeOH/water in the first-pass followed by 100% MeOH or THF in the second-pass. As retention times increase, the water content in the first-pass solvent can be decreased. Retention times of 15–20 min are still suitable for SPE, but lower loading levels are recommended, more careful loading is needed to prevent breakthrough, and higher water content in the first-pass solvent may be beneficial. Compounds with retention times of 10 min or more are well suited for simple flash chromatographic separations from organic compounds at or near the solvent front. Using different columns and conditions will doubtless change these absolute values, but it is nonetheless not difficult to build a small yet powerful knowledge base of HPLC data as references points for SPEs and chromatographies. For example, Lindsley's group at Merck in West Point recommends a fast analysis of fluorous compounds on reverse phase silica gel as a basis for a “go/no go” decision on fluorous SPE, and this succeeds in many instances because of the non-polar nature of the typical fluorous tags (see below) [35].

#### 7.4.2.3 Demixing in Fluorous Mixture Synthesis

In the general strategy for solution phase mixture synthesis that we have recently introduced, compounds are tagged with different “separation tags” and then the tagged compounds are mixed [36]. As desired, the mixtures are resolved into their individual components based on the structure of the tags in a process called “demixing”. In fluorous mixtures synthesis, demixing is typically conducted by chromatography over fluorous silica gel. In a recent synthesis of 560 analogs of the natural product mappicine, 80 seven-compound mix-



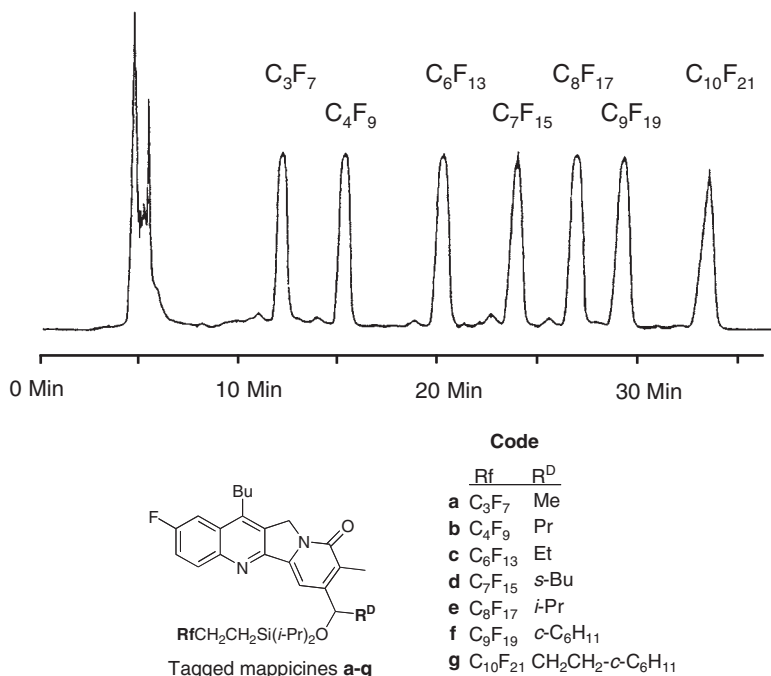
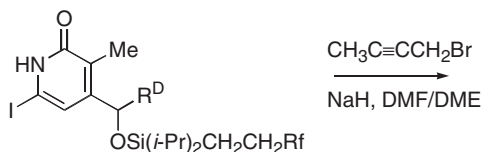


Fig. 7-11. Demixing of a mixture of seven fluorous-tagged mappicine analogs

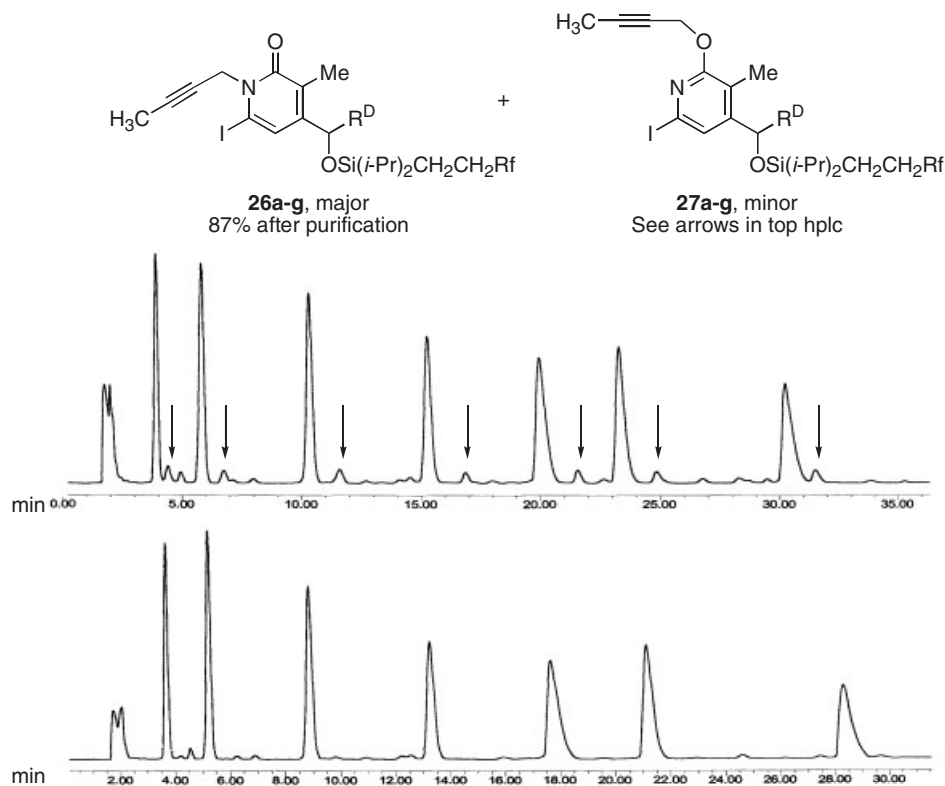
tures were prepared and demixed by serial preparative fluorous HPLC experiments. A typical chromatogram for one of these preparative experiments is shown in Figure 7-11. In each of the 80 chromatograms, the seven components were widely separated and emerged in order of tag.

Demixing is also used at intermediate stages of fluorous mixture syntheses to follow the progress of reactions, to ascertain the structures of products and to determine if any by-products are formed. In both analytical and preparative demixing experiments, the combination of the primary and secondary separation becomes important and something resembling “two chromatographies in one” results. This is best illustrated with an example. The *N*-propargylation of a seven compound mixture of pyridones **25a–g** under standard conditions provides a mixture of not seven but 14 products: seven major *N*-propargylated products **26a–g** and 7 minor *O*-propargylated products **27a–g**. The fluorous HPLC chromatogram of this mixture is shown in Figure 7-12. The primary separation is reflected in the emerging of the compounds in pairs in order by tag size. Within each pair the major (and more polar) *N*-propargyl isomer **26** emerges before the minor (and less polar) *O*-propargyl isomer **27** and the structures of all 14 components in the mixtures as well as the ratios of *N*/*O*-propargylation for each pyridone precursor are readily determined.

This is two chromatographies in one because embedded within the primary separation by tag is a secondary separation by structure of the organic compound. In other words, the experiment in Figure 7-12 is something like the sum of seven chromatographies of each of



**25a-g**, Rf/R<sup>D</sup> coding same as Figure 7-11



**Top:** The **26a-g/27a-g** crude mixture; arrows highlight the minor products **27**

**Bottom:** Pure **26a-g** mixture after silica gel flash chromatography

Both hplcs are on a FluoroFlash<sup>TM</sup> analytical column, gradient 95% MeOH/water for 15 min, then 100% MeOH

**Fig. 7-12.** Obtaining pure mixtures from impure mixtures by silica gel chromatography

the components with the different tags all piggybacked into one. If the samples are cut and combined based on tags, then a demixing is accomplished. Then if the samples are cut and combined based on *N/O*-propargylation, two pure mixtures result will from one impure mixture. Finally, if the samples are cut and not combined, both demixing and purification are accomplished.

However, the mixture can be resolved into its two underlying *N*-propargylation **26a–g** and *O*-propargylation **27a–g** sub-mixtures without the demixing that attends fluorous chromatography. Simple flash chromatography on standard silica gel results in a less polar fraction containing all seven *O*-propargylated products **27a–g** followed by a more polar fraction containing all seven *N*-propargylated compounds **26a–g**. The fluorous HPLC chromatogram of this latter mixture is also shown in Figure 7-12. This ability to purify mixtures of fluorous-tagged compounds without demixing relies on the inherent differences between fluorous silica gel and regular silica gel. On regular silica gel, the structure of the organic functionality dominates and there is a profound reordering of the elutions of the components. In this example, the reordering is so profound that the *O*-propargylation product with the longest (that is, least polar) tag still comes off far before the *N*-propargylation product with the shortest (that is, least non-polar) tag! Experiments like this clearly show that fluorous silica gel deserves its own classification and is not a standard “reverse phase” of regular silica gel [37].

#### 7.4.2.4 Derivatization for Chemical Analysis

Derivatization of chemical samples followed by SPE clean-up and HPLC analysis is common practice in analytical chemistry [18]. To date, the use of fluorous derivatizing agents coupled with SPE and/or HPLC analysis seems to have escaped the attention of the analytical community, but there is clear potential for widespread application. Take for example the fluorous triazoline dione shown in Figure 7-9. This is an excellent dienophile and could be used to derivatize mixtures containing suitable dienes for clean-up by SPE followed by HPLC analysis. The possibilities are limited only by the available derivatizing reagents.

### 7.5

#### Separation of Fluorous Compounds on Non-Fluorous Media

The unique features of separation of fluorous compounds over fluorous silica gel have generated confusion about the roles of standard media such as silica gel and reverse phase silica gel in fluorous separations. Some seem to think that these traditional media are not useful, but this is a mistaken assumption. Others seem to think that standard media can be substituted for fluorous media with no effect, and this is equally mistaken. Indeed, one of the strengths of light fluorous synthesis techniques is that regular silica, reverse phase silica and fluorous silica are all useful and in many respects complementary separation media. Here we provide guidelines on when to use and when not to use other media in place of fluorous media.

*When the target mixture to be separated contains components with the same fluorous tag, all types of separation media should be considered.* This type of separation is very common in the synthesis and purification of new fluorous reagents, reactants, catalysts, etc. For example, many procedures to prepare fluorous phosphines in the literature result in products contaminated with greater or lesser quantities of the phosphine oxides bearing the same fluorous group. While these phosphine/phosphine oxide mixtures can be separated by fluorous chromatography, their separation on standard silica gel is equally easy and is more cost efficient. Fluorous-tagged intermediates prepared on a large scale have also frequently been purified by flash chromatography on standard silica gel.

In short, when the separation targets differences in the organic domains of molecules with identical fluorous domains, regular silica gel is a material of first choice due to its low cost, while fluorous silica gel and possibly reverse phase silica gel are viable backups when performance is not satisfactory. However, even when we use regular silica gel for preparative separations, we almost always use fluorous silica gel for the analysis because it often provides superior separations of products with the same tag, especially when these are isomers. Then as we scale up syntheses of new fluorous reagents, reactants and catalysts, we almost always look to replace chromatographic separations with crystallizations or precipitations.

When the target mixture to be separated contains fluorous-tagged compounds and non-fluorous-tagged compounds, we highly recommend fluorous silica gel as the first choice separation medium. This is the case in the standard use of fluorous catalysts, reagents, reactants and scavengers in organic small molecule synthesis. This is not because regular or reverse phase silica gel cannot ever be used. Indeed in some cases they clearly can because fluorous tags are non-polar and have a tendency to behave like “lipophilic tags” that can be used in polar non-polar fractionations by SPE. Indeed, in these separations, fluorous tags  $R_f$  should be better retained than alkyl tags  $R$  of the same length since  $CF_2$  groups are more hydrophobic than  $CH_2$  groups. However, the selective retention of fluorous materials on fluorous silica gel still makes this pairing the first choice. Fluorous/non-fluorous separations will be larger on fluorous silica. This provides for more robust methods that work better across diverse members of a library and are more easily translated into other settings. Compared with an SPE with standard reverse phase silica gel, higher loading levels will be possible with fluorous silica gel and first-pass solvents will have considerably lower water content.

We have observed the superiority of fluorous silica gel in separating fluorous-tagged and non-tagged compounds many times, and this can be illustrated even by simple TLC experiments, as shown in Figure 7-13 [38]. The targeted mixture for separation comprises organic alcohol **A**, a model for an organic reaction product, and fluorous alcohol **B**, a model for a fluorous reagent or scavenger. TLC separations are shown on standard silica gel in two different solvent systems (hexane/EtOAc, 9/1 and 2/1), on reverse phase silica gel (MeOH/water 7/3), and on fluorous silica gel (MeOH/water 8/2).

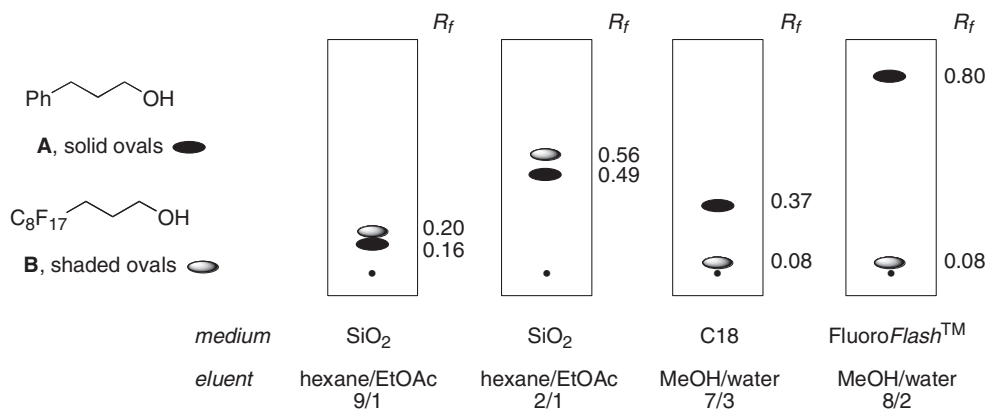


Fig. 7-13. Simple TLC experiments show the superiority of fluorous silica gel over other media

water, 70/30), and on fluorous silica gel (MeOH/water, 80/20). The solvent system for the reverse phase TLC was chosen such that the better retained fluorous alcohol had about the same retention factor ( $R_f = 0.08$ ) on both reverse phase and fluorous TLC plates.

Visual inspection shows the clear superiority of the fluorous silica gel to effect this separation. The separation on regular silica gel would require a very careful chromatography. The  $C_8F_{17}$  group of **B** is much more lipophilic than the phenyl group of **A**, yet **B** is only slightly better retained, presumably because of the strong interaction of the alcohol with the silica gel. Although obviously inferior to fluorous silica gel, the separation provided by reverse phase silica gel does not look unpromising at first glance. However, consider a library experiment where **B** is being separated from organic products of diverse structures. On both regular silica gel and reverse phase silica gel, these products could potentially span the whole range of the TLC plate from top to bottom. On the fluorous silica, all the organic products are expected to have retention factors of 0.5 or above. In a simple view, the fluorous silica gel provides a general “fluorous/organic” separation but the regular and reverse phase silica gels do not.

In summary, moving away from fluorous silica gel for a fluorous/non-fluorous separation eliminates one of the principle features of the fluorous methods – the selective retention of fluorous compounds on fluorous silica. This does not mean that fluorous/non-fluorous separation are not possible, it simply means that they may not be as robust or reliable and that it may take more time to identify suitable general conditions, especially in library synthesis. If you want to get it right the first time, then just use fluorous silica gel.

When the target mixture to be separated contains isomers or analogs bearing different fluorous tags, fluorous silica is again the first choice because of its ability to separate by fluorine content. This is the case in demixing at the end of a fluorous mixture synthesis. Again, it might be possible to use other media in some applications, but fluorous media will be superior. This point is illustrated in Figures 7-14 a and b, which show attempted demixings of the mappicine mixture FTI 7,6,2 (**28a–g**) on standard “ $C_{18}$ ” reverse phase column, on a “PFP” column [PFP is “pentafluorophenyl” in the bonded phase silica– $OSi(Me)_2CH_2CH_2C_6F_5$ ], and on a FluoroFlash™ column.

Depending on your point of view, the demixings on the  $C_{18}$  and PFP columns are partially successful, no doubt because hydrophobicity increases as  $CF_2$  groups are added to the fluorous tag. But they are clearly not optimal for at least three reasons: (1) the compounds elute

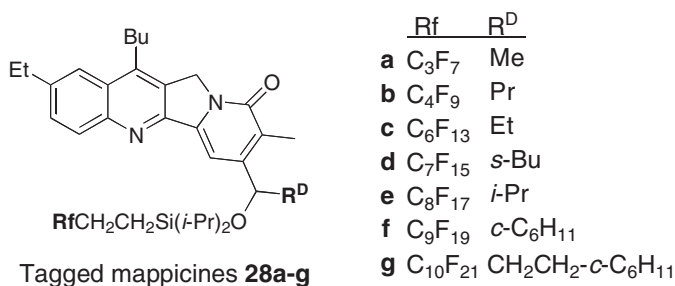
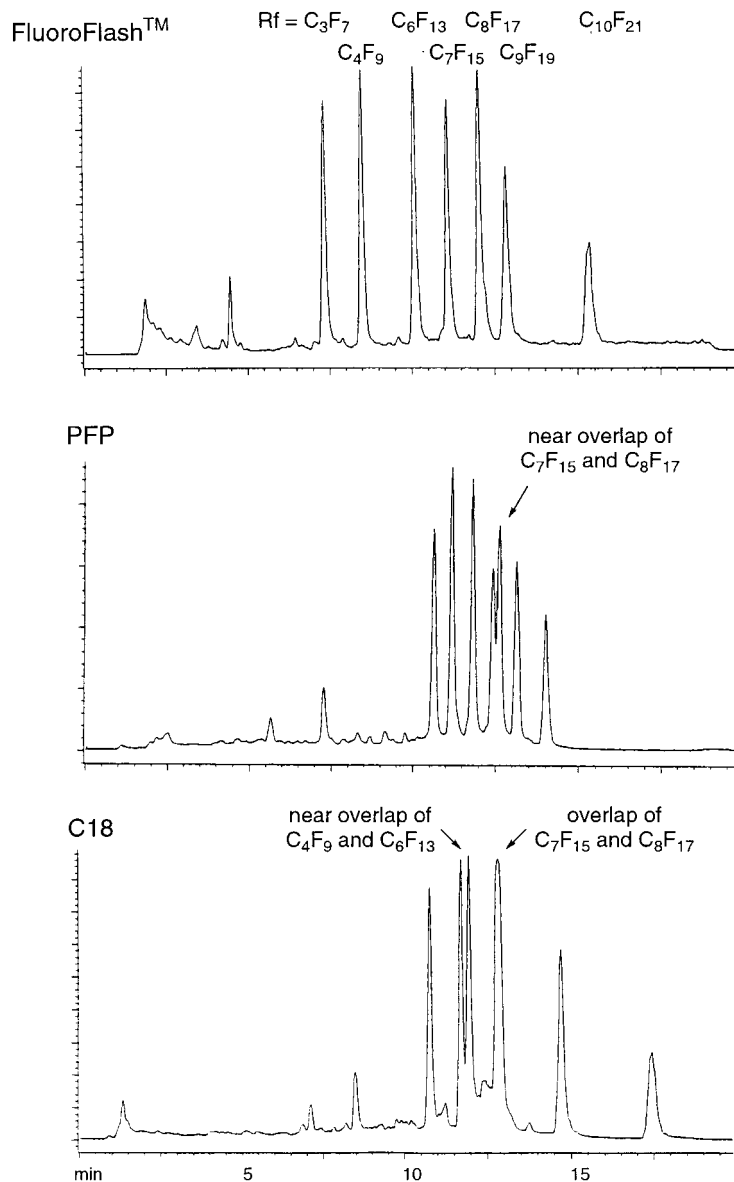


Fig. 7-14a. Structure and tag coding of mixture FTI 7,5,6 (**28a–g**)



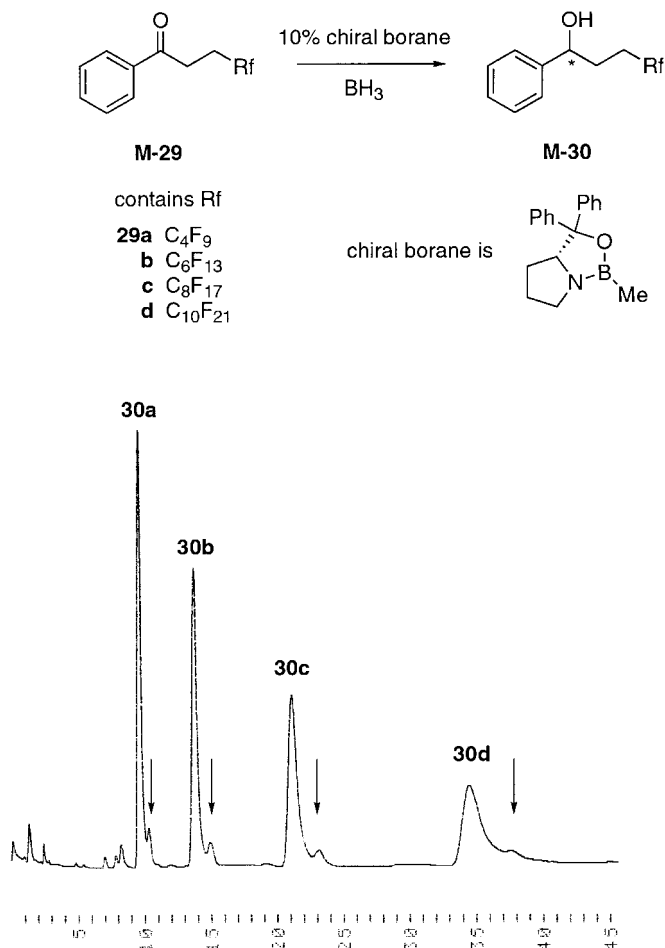
a) 80/20, MeOH/water to 100% MeOH over 8 min, then 100% MeOH

**Fig. 7-14b.** Comparison of reverse phase (C<sub>18</sub>), pentafluorophenyl (PFP) and fluorous HPLC columns in demixing of FTI 7,5,6 (**28a–g**, 80/20, MeOH/water to 100%, MeOH over 8 min, then 100% MeOH)

in a narrower range (that is, there is more chance for overlapping peaks), (2) accumulated organic (non-tagged) impurities are expected to elute at or near the solvent front on the fluorous column but may elute across the chromatogram of the other two columns (notice how some of the minor peaks are intersperse with the target peaks, especially in the  $C_{18}$  chromatogram), and (3) sacrificing the selective fluorine–fluorine interaction increases the likelihood that secondary separations will overwhelm the tag effects and peaks will overlap or even swap places. This is readily seen by comparing the compounds with the  $C_8F_{17}$  and  $C_9F_{19}$  tags, which are well resolved in the fluorous chromatogram (top), are barely resolved (could not be preparatively separated) in the PFP chromatogram (middle), and overlap in the  $C_{18}$  chromatogram (bottom). Even worse, the  $C_4F_9$  and  $C_6F_{13}$  tagged compounds nearly overlap in the  $C_{18}$  chromatogram; there is no room for a prospective analog with a  $C_5F_{11}$  tag (which was omitted only because the required precursor was not available when the synthesis was started.) These problems were induced by a deliberate mismatching of tag and side-chain substituents, and so could have been avoided. However in many mixture applications, side chain effects on chromatography cannot be predicted in advance, so the best possible tag-based separation medium, fluorous silica gel, is needed.

Recently, Matsuzawa and Mikami have recommended that  $\beta$ -cyclodextrin columns be used for demixing of fluorous-tagged compounds [39]. They propose a selective inclusion of the fluorous tags into the cyclodextrin as the basis for a separation of homologous esters of fluorous alcohols and conclude that cyclodextrin columns are superior to fluorous columns. Mikami appears to conclude that the cyclodextrin columns are superior because demixings are faster on these columns. We believe that this conclusion is premature, and that there are pitfalls to be avoided here. Mikami's model compounds are derived from the same organic unit and differ only in the fluorous tag. Compounds differing only in their fluorous tags must separate to some extent on virtually any standard column due to their differences in polarity. For example, had we tagged any single compound in Figure 7-14a with different fluorous tags and analyzed only by reverse phase HPLC, we could easily have concluded that this would be an appropriate demixing media. However the results in Figure 7-14b clearly show that fluorous silica gel is superior. The reverse phase columns in Figure 7-14b and perhaps the cyclodextrin columns in Mikami's work provide inherently faster separations because the compounds elute closer together. We view this as a disadvantage, not an advantage. Optimization of the speed of any demixing is easily done by adjusting the solvent gradient.

Nonetheless, the cyclodextrin columns are a promising lead and more work to evaluate their merits relative to regular, reverse phase and fluorous silica is warranted. As with the other materials above, cyclodextrin columns do not have to be universally superior to fluorous ones to be useful. This point is nicely illustrated by recent work from the Takeuchi group [40]. They reduced a mixture of ketones **M-29** bearing the same homologous tag with chiral and achiral reducing agents, and recorded the chromatograms of the resulting alcohol mixtures **M-30** on a  $\beta$ -cyclodextrin column. The chromatogram from the chiral reduction product is shown in Figure 7-15. Since only the tags vary, the sample can be demixed to its tag components by any type of medium, but the chiral cyclodextrin column provides a secondary separation of the enantiomers so the ee of each product can be quantified. The chromatogram also shows that tags do not affect the stereoselective reduction, since all of the products are formed in about the same ee.



a) separation on SUMICHIRAL OA-7500 cyclodextrin column;  
 acetonitrile/water, 55/45; minor enantiomers are highlighted with arrows;  
 Chromatogram provided by Prof. S. Takeuchi and Dr. Y. Nakamura  
 Niigata University of Pharmacy and Applied Life Sciences

**Fig. 7-15.** Analysis of a non-racemic fluorous alcohol mixture from chiral reduction

## 7.6

### Biphase Reactions with Fluorous Silica Gel

Recently, fluorous solid materials have been added directly to reaction mixtures in methods that parallel fluorous liquid/liquid biphase reactions and fluorous thermomorphic reactions (Chapter 4). Gladysz first added Teflon<sup>®</sup> to conjugate addition reactions of benzyl alcohol **31** to methyl propiolate **32** catalyzed by the fluorous phosphine **33** (Figure 7-16) [41]. After heating to promote reaction, cooling and decantation, the product **34** was isolated from the



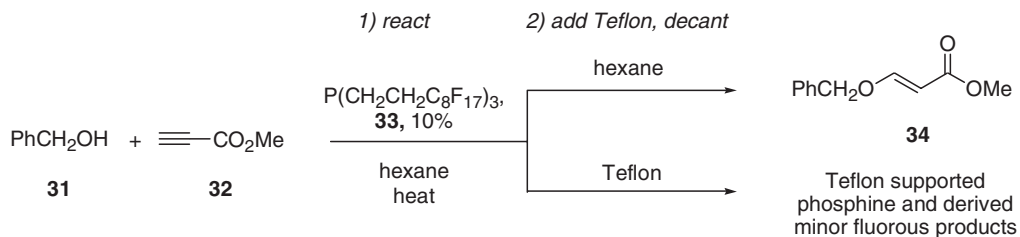


Fig. 7-16. Recovering a fluororous phosphine catalyst with the aid of Teflon

hexane phase in high yield contaminated by only 0.4% of the catalyst. Extraction of the Teflon<sup>®</sup> shavings provided about 98% recovery of the fluororous material which was mostly (89.5%) phosphine **33** along with two other species that were postulated to be unspecified educts on the reaction pathway. One of the strengths of this work is that the ability to recover the catalyst intact is clearly demonstrated. However, it is not entirely clear whether the fluororous nature of Teflon<sup>®</sup> is essential for the removal of the catalyst in this reaction. This phosphine has a low solubility in hexane at room temperature or below, and can also be conveniently used in thermomorphing reactions without any added support.

More recently, the groups working with Bannwarth and Tsang have reported similar techniques with fluororous silica gel [13, 14]. Bannwarth and coworkers have conducted bi-phasic Heck and Suzuki reactions with catalyst **35** deposited on fluororous silica gel [13] (Figure 7-17). After heating, cooling and filtration, the product is isolated from the liquid phase and the fluororous solid phase is used directly in additional cycles. In one experiment, only about 2% of the originally introduced Pd was found in the organic product. However, the recovered catalyst on the silica gel was not analyzed, and the catalyst itself is heavily fluororous and is highly insoluble in organic solvents. So the experiments still leave unclear whether the fluororous silica gel functions as a passive support (in other words, non-fluorous materials or no materials at all could also be used) or an active support (the catalyst does not just precipitate but actively partitions onto the support). Unfortunately, the possibility that some

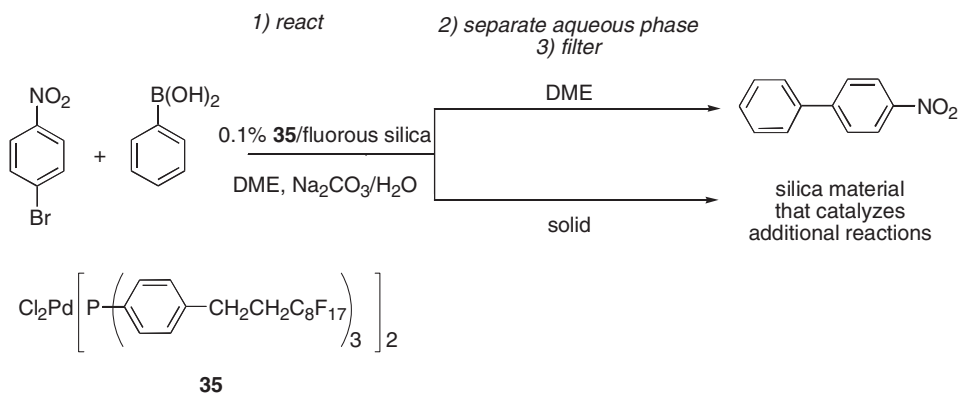


Fig. 7-17. Suzuki reaction with a silica-supported fluororous palladium catalyst

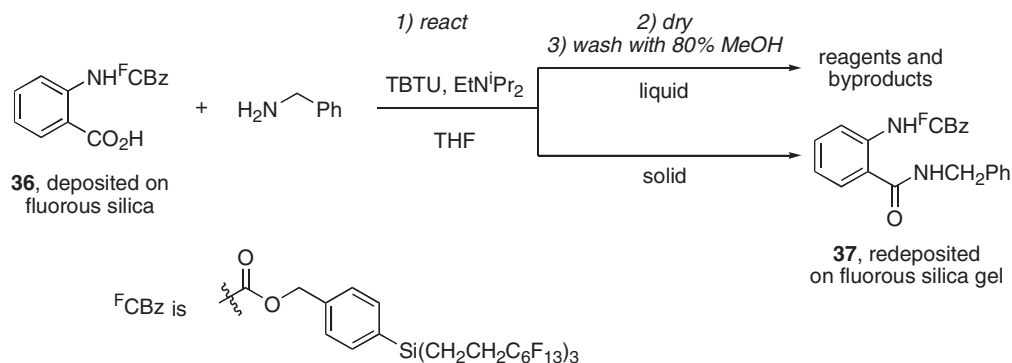


Fig. 7-18. Extraction, reaction and redeposition on a silica-supported fluororous intermediate

active palladium species simply leaches from the support and catalyzes successive reactions must also be considered, since this has been shown to occur with solid-supported palladium catalysts [42]. Going forward, it will be important to sort out these possibilities with appropriate experiments. However the convenience of having a support to hold the catalyst, especially on a small scale, is already evident.

In a somewhat different approach, Bannwarth and coworkers also reported the synthesis of quinazoline diones by using a heavy fluororous Cbz tag and supporting intermediates on silica (Figure 7-18) [43]. For example, supported intermediate **36** is treated with a primary amine, TBTU and Hunig's base in THF. Since THF is an excellent solvent for fluororous compounds, the tagged intermediates and products will partition predominately into the THF phase during the reaction. Then the solvent is removed to redeposit the residual materials, and the non-fluororous compounds are washed away with 8/1 methanol/water to give a pure supported product **37** ready for the next reaction.

This process very closely resembles the fluororous solid phase extractions described above. Indeed, one of the standard SPE procedures is to add fluororous silica gel to a reaction mixture and then to evaporate the solvent to deposit the residue on the silica. This material is then washed with MeOH/H<sub>2</sub>O in the first-pass of the SPE. The difference here is that the second-pass of the SPE is omitted. Instead, the solid-supported fluororous material is simply added to the next reaction, where the reaction solvent for the next step extracts it off. The convenience of having a free-flowing powder of a supported product is clear, and the use of the heavy fluororous tags as opposed to light ones no doubt helps to minimize the amount of fluororous silica that is needed to support the intermediates.

## 7.7

### Conclusion

Originally called silica gel with a fluorocarbon bonded phase, fluororous silica gel predates the fluororous field. However for almost two decades, it was like a separation medium without its natural analyte. While it found and still finds important niche roles in analysis of non-fluorinated or lightly fluorinated organic or biological molecules, its natural calling is in the

analytical and preparative separation of fluorous compounds either from non-fluorous compounds or from each other. From modest beginnings in a simple solid phase extraction of a heavy fluorous tin derivative, fluorous silica gel has emerged to facilitate whole new branches of fluorous chemistry, including all light fluorous synthesis techniques and fluorous mixture synthesis. In turn, the increased use of fluorous silica gel in its natural element is generating a better understanding of its properties, and this has engendered new applications in analytical and preparative separations. As awareness of the power and properties of fluorous silica gel continues to increase, so will its use both in and beyond the fluorous field.

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- 10 Biotage is on the web at [www.dyax.com/biotage.asp](http://www.dyax.com/biotage.asp).
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## 8

**Light Fluorous Chemistry – A User's Guide***Dennis P. Curran***8.1****Introduction**

After a brief induction period, the field of heavy fluorous chemistry prospered rapidly following Horváth and Rábai's 1994 paper introducing "fluorous biphasic catalysis" [1]. The original focus on catalysis was soon complemented by fluorous protecting groups, reagents, scavengers and so on as the broader potential of fluorous chemistry began to be recognized (see the reviews in Chapter 9). Underpinning all this work was the need for high or at least moderate partition coefficients into fluorous solvents for the fluorous component of any reaction. Indeed, much of the early work in the field focused on making ligands, especially phosphines, of differing fluorine content to answer the central question: how many fluorines are needed to make a molecule fluorous? An early guideline advanced independently by both Horváth and our group is still handy – molecules require about 60% fluorine by molecular weight to be useful in liquid/liquid separations. Recently, more sophisticated and correspondingly more useful treatments of solubility have emerged [2].

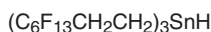
Researchers apparently underestimated the number of fluorines needed to make a molecule fluorous, since many of the early molecules that were made did not exhibit high partition coefficients into fluorous solvents. Increasing the fluorine content of a large organic molecule to the region of 60% requires hefty fluorous tags since fluoroalkyl groups themselves are only about 75% fluorous. In 1997, we proposed what has quickly proven to be a general solution to the problem of what to do when partition coefficients are too low for liquid/liquid extractions. We replaced the liquid/liquid extraction with a solid phase extraction (SPE) over fluorous silica gel [3]. This procedure and subsequent fluorous flash chromatography and HPLC (see Chapter 7) enabled the field of light fluorous chemistry to develop.

The names "light" and "heavy" refer qualitatively to the weight of the fluorous tags involved in the techniques [4]. Representative light and heavy fluorous molecules along with their molecular weights are shown in Figure 8-1 [5, 6]. Heavy fluorous molecules typically contain at least 39 fluorines, and often many more, adorned on one or more tags (or sometimes termed "ponytails"). At the low end, molecular weights can be over 1 000 mu, while catalysts with multiple ligands each in turn having multiple fluoroalkyl groups can weigh 3 000 mu or more. Heavy fluorous molecules must full their weight by virtue of ease of

**Heavy**

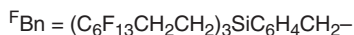
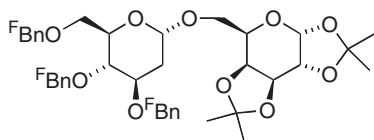
original fluororous  
Wilkinson's complex (ref 1)

MW = 3354    %F = 66



first fluororous tin hydride (ref 5)

MW = 1161    %F = 64



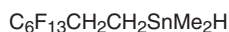
fluororous sugar (ref 6)

MW = 3838    %F = 58

**Light**

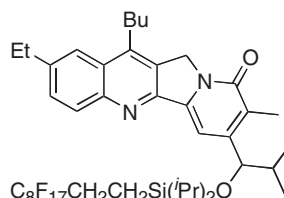
fluororous platinum catalyst (ref 15)

MW = 1483    %F = 33



fluororous tin hydride (ref 5)

MW = 497    %F = 50



fluororous mappicine (ref 47)

MW = 881    %F = 37

**Fig. 8-1.** Representative heavy and light fluororous molecules with molecular weights and fluorine contents

recovery and reuse. Many heavy fluororous applications involve catalysts, where the mass of fluororous material is not a major concern since so little is being used in the first place. Heavy fluororous molecules can be separated from reaction mixtures by both liquid/liquid and solid/liquid techniques. While liquid/liquid techniques are far more prevalent, the convenience of fluororous solid phase extractions, especially on a small scale, should not be overlooked.

Light fluororous molecules typically contain 21 fluorines or fewer, and molecular weights can range from 400 to about 900 mu (or more for catalysts containing multiple light ligands). They may exhibit little or even no solubility in fluororous solvents, so separations with fluororous solid phases are often the only practical methods. In addition to their lower molecular weights and decreased cost, light fluororous molecules typically have far better solubilities in organic solvents than their heavy siblings, so identifying suitable reaction solvents and conditions is not difficult. Often, conditions for traditional organic reactions with no fluororous reaction components can simply be hijacked and used directly.

Between light fluororous chemistry and heavy fluororous chemistry lies a continuum (bantam weight fluororous chemistry, middle weight fluororous chemistry, welter weight fluororous chemistry, etc.) exhibiting features intermediate between the two ends of the spectrum.

Within the broad confines of "separation strategy", both light and heavy fluororous synthe-

	Traditional Solution Phase	Solid Phase	Fluorous
Wide array of chemistry	✓	~	✓
Literature methods used without modification	✓		✓
High yields with molar equivalent stoichiometries	✓		✓
Easy separation of excess reagents and byproducts		✓✓	✓
Easy purification of impure products	~		✓
Routine chromatographic analysis	✓		✓
Diverse solvent selection	✓		✓
Convenient spectroscopic analysis	✓		✓
Large mixtures possible		✓	
Small mixtures possible		✓	✓
Convenient for parallel synthesis		✓	✓
mmol/g of reactants	2-3	0.1-1	1-2

**Fig. 8-2.** Qualitative comparison of traditional solution phase, solid phase and fluorous methods

sis involve molecules with separation tags [7]. The most common separation tags to date have been polymers [8], so a comparison of traditional solution phase methods and polymer-bound methods to light fluorous methods is instructive (Figure 8-2). Traditional solution phase methods are strong in reaction, analysis and identification features, but separation is a major bottleneck. In addition, mixture synthesis is not practical if individual products are targeted.

Attachment of a reagent or intermediate to a resin makes the transition from the chemistry of molecules to the chemistry of materials [9]. Separation of insoluble polymer-bound materials by filtration is exceptionally easy, and the commercially important techniques of peptide and oligonucleotide synthesis attest to the value of solid phase synthesis. Split-mix synthesis is also a powerful technique that is facilitated by the simple feature that one bead can easily be separated from another [10].

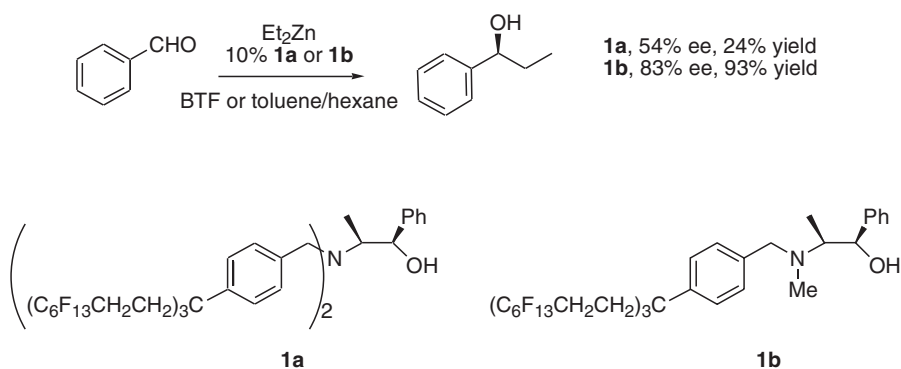
With these advantages come disadvantages. Finding suitably general reaction conditions can be time consuming, and large excesses of reagents and reactants are typically required to drive reactions to completion. Despite the excesses, reaction times can be long. Near-quantitative yields are essential since there are no general ways to purify resin-bound compounds. Swelling characteristics and backbone functionalities of polymers limit their applications. Despite major advances, analysis and identification are not nearly as straightforward

for materials as they are for molecules. Some of these limitations can be bypassed by using polymer-bound reagents (sometimes called polymer-assisted solution phase synthesis) [11], but the slow reactions, the need for large excesses and the swelling limitations remain. Despite these limitations, solid phase techniques have added major new options for many reactions and chemistries.

In contrast to solid phase methods, light fluorous methods involve molecules and not materials. Reaction chemistry typically occurs in solution, so light fluorous chemistry is best considered solution phase synthesis with separation tagging. The fluorous tag enables a simple SPE separation, not unlike the filtrations of solid phase synthesis. However reactions are often rapid and clean and large excesses of reagents are neither required nor even beneficial in many cases. The full complement of small-molecule analytical (TLC, HPLC, and in many cases even GC) and identification (NMR, MS, IR, etc.) techniques are routinely in play. Also, using fluorous-tagged molecules actually expands rather than contracts separation options since in addition to all the standard methods (distillation, crystallization/precipitation, chromatography over regular or reverse phase silica gel), separations over fluorous silica gel are viable and often uniquely powerful added options. Molecular masses of light fluorous molecules (indicated by the polymer standard of  $\text{mmol g}^{-1}$  in Figure 8-2) are typically closer to traditional non-tagged molecules than to polymers.

Heavy fluorous methods share most of the features and advantages of their lighter cousins, except for one – the ready identification of suitable reaction conditions and solvents. In our experience, finding suitable reaction solvents for heavy fluorous molecules is more analogous to solid phase synthesis than to light fluorous synthesis. The direct porting of traditional conditions is only occasionally successful and case-by-case optimization is needed. Generally, the problem is finding solvents in which both the heavy fluorous and non-fluorous reaction components are soluble, and many potential solutions, including the use of hybrid (partially fluorinated) solvents are now available [12].

Some observations by Takeuchi and coworkers nicely illustrate the qualitative differences between light and heavy fluorous molecules (Figure 8-3) [13]. Heavy fluorous amino alcohol **1a** (MW = 2436) bears 78 fluorines and exhibits excellent partition coefficients (>95/5) out of several organic solvents into FC-72. However these same properties that are so favorable



**Fig. 8-3.** Yield and selectivity differences in asymmetric ethylations with heavier and lighter fluorine ligands



in separation cause problems in reaction. Attempted asymmetric ethylation of benzaldehyde with diethyl zinc in toluene/hexane was not successful, presumably because **1a** is not soluble in toluene. Substituting the partially fluorinated benzotrifluoride ( $\text{C}_6\text{H}_5\text{CF}_3$ ) [12b] for toluene produced alcohol **2** in 24% yield and 54% ee. This result is still inferior though to the 93% yield and 83% ee obtained with the lighter (39 fluorines, MW = 1308) amino alcohol **1b**. Amino alcohol **1b** is more a “middle-weight” fluorous compound than a light one, since it can be recovered and recycled by liquid/liquid extraction. But multiple extractions are needed, and separation by solid phase extraction is more convenient.

It is not appropriate to conclude from these experiments that heavy fluorous ligand **1b** is inferior across the board to middle-weight ligand **1a** in both yield and ee. It is more likely that middle-weight amino alcohol **1a** is more similar to the standard organic amino alcohol, so standard conditions may be used. While not certain, it is possible that with further optimization of conditions, amino alcohol **1a** could provide similar yields and ee to **1a**. However time is money, and middle-weight and especially light fluorous reagents and catalysts can save both by obviating the lengthy process of optimization of reaction conditions.

## 8.2

### Sources of Light Fluorous Compounds and Products

Most light fluorous techniques involve the use of fluorous silica gel (silica gel with a fluorocarbon bonded phase), and varieties and sources of this material are covered in detail in Chapter 7. Fluorous triphasic reactions are currently the only light techniques that use fluorous solvents, and the types and sources of these solvents are covered in Chapter 4.

When possible, the examples in the following sections will feature commercial light fluorous compounds. Fluorous Technologies, Inc. currently offers by far the broadest selection of light fluorous compounds, including assorted reagents, reactants, scavengers, protecting groups, tags, ligands and catalysts [14]. Although the selection is increasing rapidly, it is still not large when compared with traditional or resin-bound reaction components, and the synthesis and study of new light fluorous reaction components is a lively research enterprise. For those so-inclined to make their own reagents, a diverse array of building blocks are available from many suppliers including Aldrich, Fluka, Ozark, Gelest, Matrix and Fluorochem, to name a few. Representative key building blocks are shown in Figure 8-4, and chemistries to incorporate these building blocks into both heavy and light fluorous molecules are featured throughout this Handbook. So the balance of this chapter will focus on the use of light fluorous molecules rather than their synthesis.

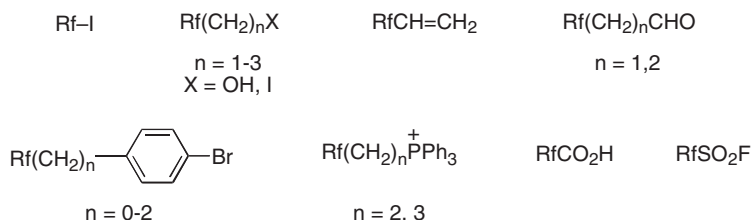


Fig. 8-4. Representative commercial or readily available fluorous building blocks

### 8.3

#### Light Fluorous Synthesis with Fluorous Silica Gel Separations

Light fluorous synthesis techniques were introduced by Curran and coworkers in a pair of papers 1999 [4] and 2000 [15]; the first paper demonstrated the principles in a fluorous protecting group setting and the second in the setting of fluorous reagents and ligands (phosphines). Today, reactions of light fluorous molecules are frequently coupled with SPE separations over fluorous silica gel, and the resulting methods have broad general applicability in the synthesis of many classes of organic molecules. Early work in the area is covered in several reviews and overviews [16]; however, the recent review of Zhang is recommended as timely overview [17].

Here we give a high level treatment and highlight by way of example the different ways that light fluorous synthesis methods are being used. The framework is that of “strategy-level separations” with separation tags, introduced first in 1996 [18] and then laid out in more detail in 1998 [5] and thereafter [19]. Reactions are organized based on the phase behavior of their precursors and products into five broad categories: (1) organic precursors and products (fluorous reagents, reactants, catalysts, scavengers are used); (2) fluorous precursors and products (fluorous tags or protecting groups are used with standard non-fluorous reagents); (3) fluorous precursors and organic products (a “phase-switch” is conducted by removing a fluorous tag); (4) organic precursors and fluorous products (a “phase switch” is conducted by adding a fluorous tag); and (5) combinations of solid-phase and fluorous methods. The division is for organizational purposes only. In practice, all of the methods can be mixed and matched not only with each other but with other strategy separation methods such as polymer-assisted solution phase synthesis.

#### 8.3.1

##### Organic Precursors and Organic Products

The separation goal of “product purification by workup” [5] dictates that traditional solution phase synthesis of small organic molecules be modified such that, ideally, the only “organic molecules” left at the end of a simple workup are the target molecules [16]. Here “organic molecules” are defined more narrowly as molecules partitioning into organic solvents. Workup level separation techniques include extraction (liquid/liquid or solid/liquid), evaporation and filtration. The traditional approach of converting small organic molecule precursors into products is popular in medicinal chemistry and natural products settings because target molecules need not be tagged in any way. Reagents, reactants, catalysts and scavengers can be inorganic or volatile molecules, but more typically bear separation tags including polymers, ionizable and other chemical tags, or fluorous tags. The relative merits of the fluorous tagging approach have been summarized in the Introduction (Section 8.1). An assortment of fluorous reaction components are now commercially available and reaction conditions are typically taken directly from related non-fluorous examples. So this is not only one of the most powerful but also surely the simplest of light fluorous techniques. If you are new to fluorous methods, then here is the place to start.

In Figures 8.5–8.7, representative examples are selected from recent work to highlight the broad potential applications of fluorous reagents, fluorous catalysts and fluorous scavengers.

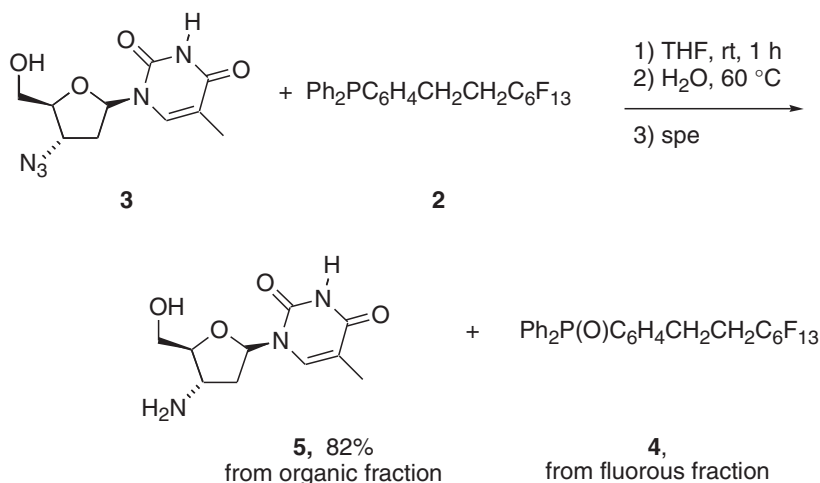
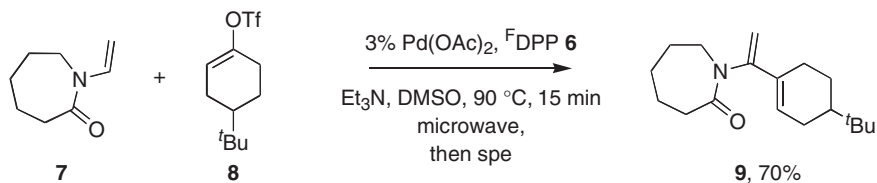


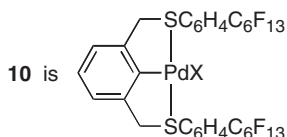
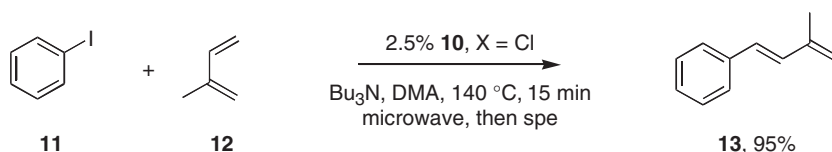
Fig. 8-5. The fluororous Staudinger reaction: representative use of a light fluororous reagent

The reagent application involves fluororous triarylphosphine **2**. Many olefination and other reactions rely on the conversion of triphenylphosphine to its derived phosphine oxide as a driving force. Separation of the phosphine oxide from target products is notoriously difficult, and careful chromatography is often the method of choice. Lindsley and coworkers at Merck [20] have introduced a simple yet general protocol for conducting parallel solution phase Staudinger reactions, and Figure 8-5 shows a representative example. Reduction of **3** with fluororous phosphine **2** in THF, followed by rapid solid phase extraction over FluoroFlash<sup>TM</sup> silica gel with 85% MeOH/water, provides amine **5** in excellent yield and purity. This reaction is typical of light fluororous synthesis techniques that use a standard organic solvent for reaction and replace a chromatography with an SPE, and it shows excellent functional group tolerance and generality [20]. Since organic compounds are not retained with 85% MeOH/water, these SPE conditions should be translatable to essentially any reaction producing phosphine oxide **4**. In head-to-head comparisons with resin-bound phosphines, fluororous phosphine **2** promoted a much faster reaction, and provided products in better yields and purities. Consumption of reactants and formation of products was readily monitored by TLC.

The pace of development of heavy fluororous catalysts has far exceeded light fluororous catalysts to date, but work with light fluororous catalysts is accelerating. Figure 8-6 shows recent examples of reactions of fluororous palladium catalysts. Heck reactions mediated by catalysts **6** and **10** can be conducted under traditional or microwave [21] conditions, and the catalyst-derived products can be removed by simple fluororous SPE [22, 23]. Fluorous dppp analog **6** shares with its non-fluorous counterpart the ability to promote the unusual  $\alpha$ -addition pathway in the addition of triflate **8** to **7** to give enamide **9**. Catalyst **10** shares with its non-fluorous counterpart high stability. After addition of iodobenzene **11** to isoprene **12** to give **13**, catalyst **10** can be recovered after the fluororous SPE, recrystallized, and reused. We project



<sup>F</sup>Dppp **6** is (C<sub>4</sub>F<sub>9</sub>CH<sub>2</sub>CH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>)<sub>2</sub>PCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>P(C<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>CH<sub>2</sub>C<sub>4</sub>F<sub>9</sub>)<sub>2</sub>



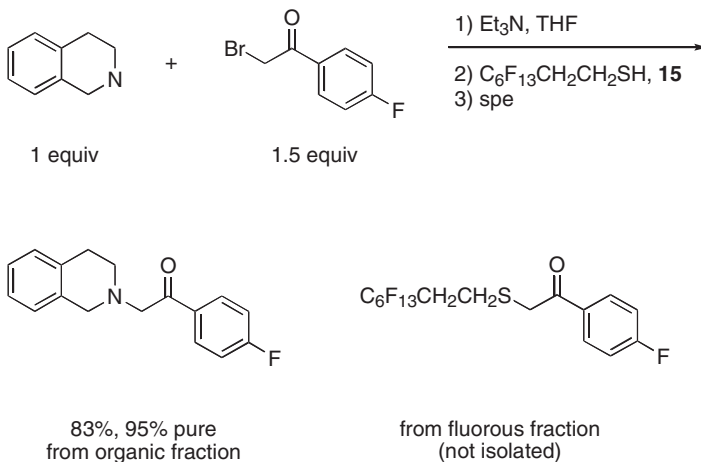
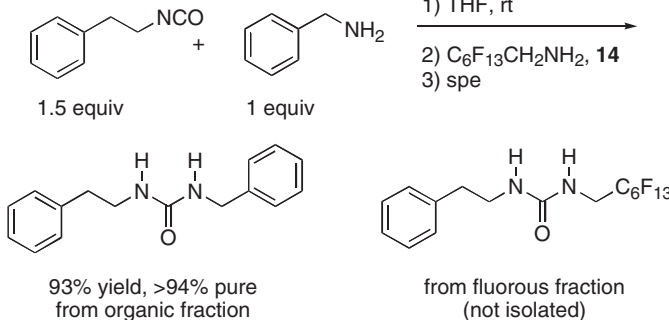
**10** can be recovered in 80-90% yield after fluororous solid phase extraction and recrystallization

Fig. 8-6. Microwave fluororous palladium reactions: representative uses of light fluororous catalysts

that the use of light fluororous catalysts coupled with SPE should be a general way to solve the problem of catalyst separation and recovery from small scales and upwards.

In parallel synthesis work, when target products will be contaminated with excess reagents or reactants or their byproducts, the technique of scavenging is often used to switch the phase preference of these undesired product components from organic to another phase for rapid separation. Although introduced at about the same time as polymer scavenging [24], fluororous scavenging is only now starting to catch on as its favorable features begin to attract attention. Early leaders in this area are Lindsley and coworkers at Merck [25] and Zhang and coworkers at FTI [26], and Figure 8-7 shows one example from each of these groups. In each case, the target reaction is conducted with one of the reagents in modest excess. Addition of the fluororous scavengers **14** and **15**, followed by rapid reaction and then fluororous SPE serves to retain the scavenged adduct and the excess scavenger while allowing the target product to pass.

The usefulness of these techniques expands proportionately as more and more fluororous reagents, catalysts, ligands and scavengers are introduced and commercialized. Additional information on currently available compounds, including phosphines, tin reagents and catalysts, and fluororous diethylazodicarboxylates (DEAD reagents), selenium and sulfur reagents, hypervalent iodine reagents, a large assortment of transition metal and lanthanide catalysts, and assorted scavengers and scavenging techniques can be found in various reviews in Chapter 10.



**Fig. 8-7.** Nucleophilic scavenging: representative uses of light fluoros scavengers

### 8.3.2

## Fluorous Precursors and Fluorous Products

Although it has since been broadened to encompass essentially all fluorous techniques, the term “fluorous synthesis” was originally introduced by analogy to solid phase synthesis to describe the conversion of fluorous-tagged precursors to fluorous-tagged products. The concepts of this type of fluorous tagging were introduced in 1997 [24], and early implementations employed heavy fluorous molecules [27]. Recently, heavy fluorous tags and liquid/liquid separations have shown excellent potential in carbohydrate and peptide synthesis [28]. However, the majority of applications in this area shifted to the light fluorous mode following its introduction in 1999 [5]. Protecting group and tag applications are covered in this Handbook in more detail by W. Zhang (see review in Chapter 10); here we briefly provide features, concepts, and two representative applications.

Fluorous tagging applications of substrates and products can loosely be classified into one

of two groups based on the secondary role of the tag (the primary role is to facilitate separation): (1) fluoros protecting groups, and (2) fluoros traceless or displaceable tags. Fluorous tagging of target products is advantageous because the majority of commercially available reagents, reactants, catalysts and scavengers are not fluoros and therefore can easily be separated from fluoros-tagged target products following reactions. For parallel synthesis, a single protecting group can make a whole library of compounds fluoros. The predictable separations enable fluoros tagging to provide a combination of speed and high purity not matched by methods with other types of tags or without tags. Finally, recovery of the residual tag at the end of a sequence of reactions is frequently possible, so there is potential to reuse the tags another day.

Figure 8-8 shows a representative application of a fluoros protecting group along with a selection of known fluoros protecting groups. In the application, a fluoros carbobenzyloxy ( $^F\text{Cbz}$ ) group is attached with reagent **16** to phenylalanine **17** by standard chemistry [29]. Then, the remaining acid of **18** is coupled with excess amounts of amines such as **19** under typical peptide coupling conditions with EDCI, HOBt and  $\text{Et}_3\text{N}$ . Following the coupling, rapid fluoros solid phase extraction provides an organic fraction containing excess and spent reagents and reactants followed by a fluoros fraction containing the target product **20**.

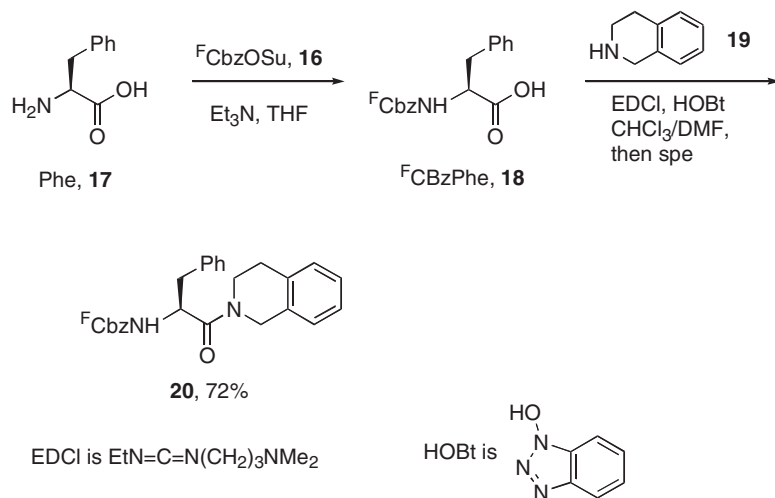
Reagent **16** is commercially available along with fluoros Boc ( $^F\text{Boc}$ ) reagent **21** for nitrogen protection [30]. For oxygen protection, commercially available silane **22** can be converted *in situ* into either a halide or triflate for subsequent silylation. So-called “FluoMar<sup>TM</sup> reagent” (named after the solid phase analog, the “Marshall resin”) can be acylated to make esters, and this group serves doubly for protection and later diversification by displacement [31]. A selection of other fluoros protecting groups that are suitable for light fluoros synthesis, including the  $^F$ alkoxydiphenylsilyl group **23** and the  $^F\text{THP}$  group **24**, can be prepared from commercial fluoros building blocks in two or three steps [32].

Figure 8-9 shows an example of a displaceable fluoros tag from the work of Zhang at Fluorous Technologies, Inc [33]. Addition of thiol **25** to dichloropyrimidine **26** provides two regioisomeric tagged scaffolds **27** and **28**. Unlike polymer tagging where separation of such regioisomers cannot be contemplated, **27** and **28** are readily separated by standard flash chromatography and are isolated in 69 and 23% yields, respectively. Moving ahead with the major isomer **27**, displacement with excess imidazole **29** followed by SPE separation provides **30**. Oxidation of the thiol to the sulfone with Oxone<sup>TM</sup>, followed by tag displacement and final SPE gives product **31** in 79% yield and 90% purity. An assortment of interesting and unusual heterocycles can be made by this powerful solution phase sequence.

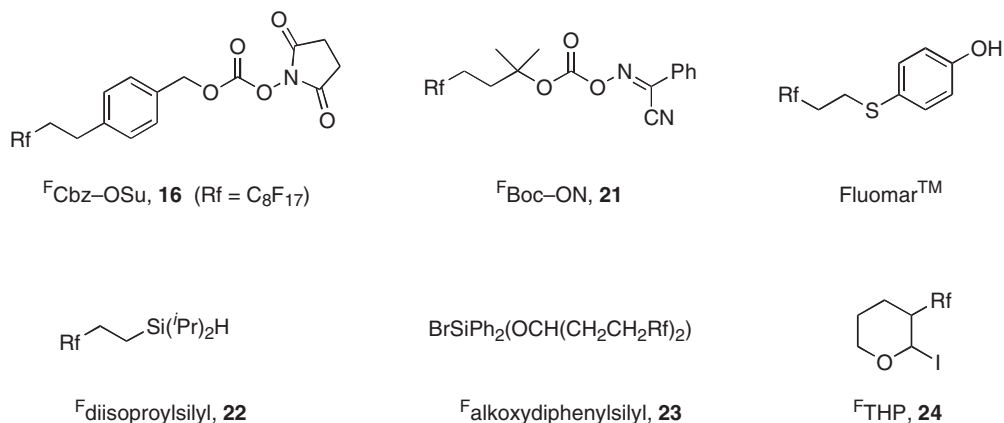
### 8.3.3

#### Fluorous Precursors and Organic Products

When target compounds bear fluoros protecting groups or tags, a late (often the final) step in the synthetic sequence is the removal of the fluoros tag. This is illustrated by the displacement reaction of **30** to give **31** in Figure 8-9. Tag removal is an example of a “phase switch”, because the phase preference of the target molecules changes from fluoros to organic. In practice, this means that the target fraction of a fluoros SPE changes from the second to the first.



## Representative Fluorous Protecting Group Reagents



**Fig. 8-8.** Introduction and use of a fluorous Cbz group and some fluorous protecting reagents

Since the residual tag in any detagging reaction will always be fluorous, its separation from detagged products by SPE is built in. Standard deprotection offers little beyond that, but well planned phase switches allow synthetic chemistry to dictate separation features. Consider the simple hydantoin synthesis in Figure 8-10 [34]. Reaction of fluorous amino ester **32** with isocyanate **33** provides adduct **34**, which can be separated from excess isocyanate and other non-fluorous byproducts by SPE. However unreacted starting material **32** would presumably not be separated from **34** by SPE since it bears the same fluorous tag. Now, “cyclative cleavage” of crude **34** occurs with tag removal and attendant phase switch to give target hydantoin **35** which is present in the first pass of the SPE [35]. The original

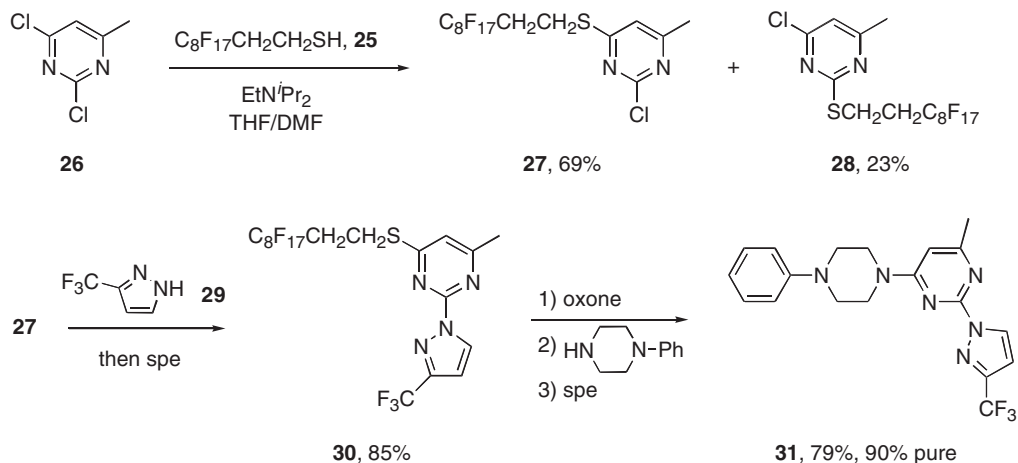


Fig. 8-9. A displaceable fluorous tag in action

precursor **32** does not react under these conditions and it is retained on the column during the first pass. In short, well planned phase switches like this can serve as separation “check points” for one or more prior steps of a synthetic sequence by allowing molecules that pass the test [that is, that have successfully reacted in the prior step(s)] to switch from fluorous to organic and preventing molecules that fail the test from switching.

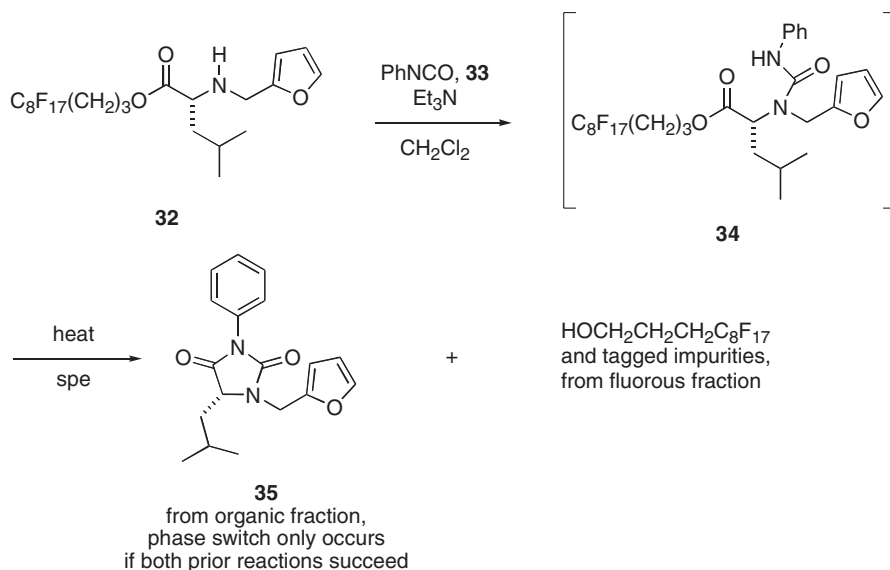


Fig. 8-10. Phase switching in a fluorous hydantoin synthesis



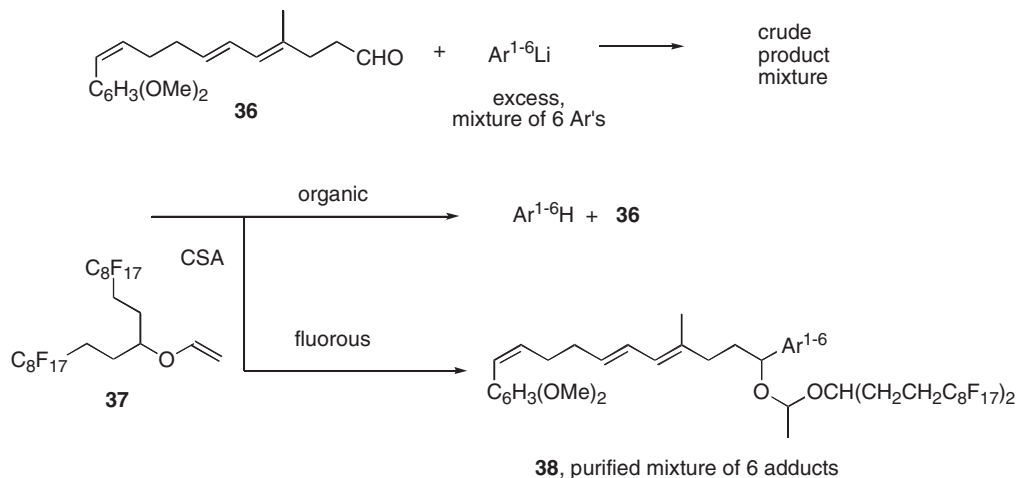


Fig. 8-11. Organic-to-fluorous phase switch for mixture purification

#### 8.3.4

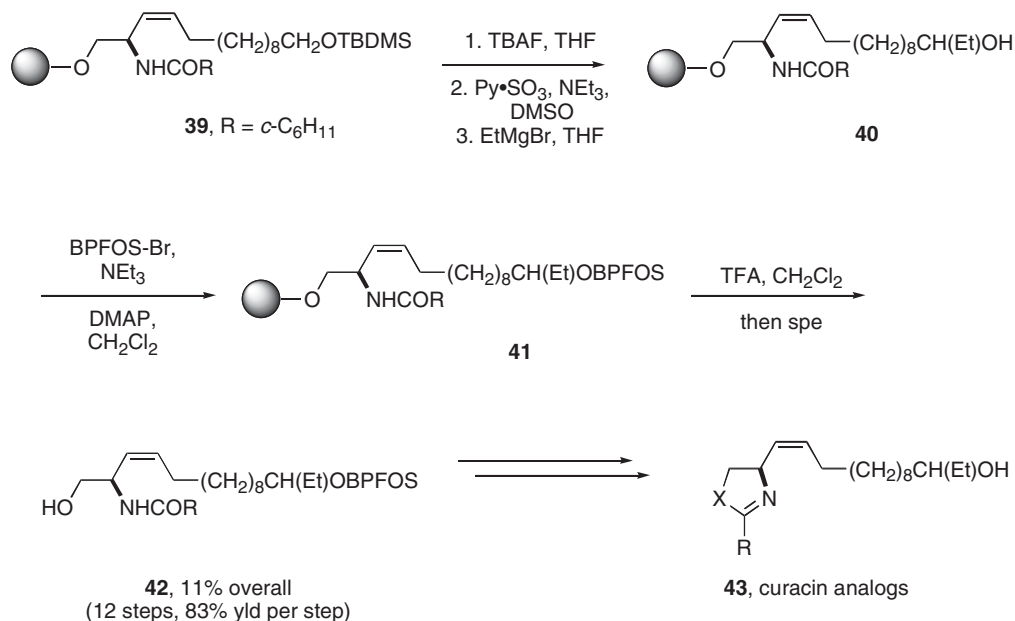
##### Organic Precursors and Fluorous Products

The phase switching of an organic precursor to a fluorous target product occurs each time a fluorous tag is introduced, and this always permits facile separation of tagged products from untagged starting materials. However the potential for separation goes beyond this in well planned applications. An innovative sequence that makes this point is shown in Figure 8-11. Wipf, Reeves and coworkers added an equimolar mixture of six aryl- and heteroaryl lithium reagents to aldehyde **36** [36]. The alcohol products of this reaction were then captured for removal from starting aldehyde **36**, protonated heteroaromatics and other byproducts by reaction with fluorous vinyl ether **37** to give purified mixture **38**. This early application is best considered as on the low end of heavy fluorous synthesis, and liquid/liquid extraction proved practical provided that water was added to help drive the fluorous products **38** out of methanol and into FC-72. Today, tag **37** or even a lighter variant could be used in combination with SPE to effect this unique type of purification of a mixture by phase-switching (or not) a subset of components based on the presence (or absence) of a target functional group (here, an alcohol).

#### 8.3.5

##### Combinations of Solid Phase and Fluorous Methods

Phase tagging methods are not mutually exclusive and can be beneficially combined, as illustrated by a number of recent studies that unite fluorous and solid phase methods. The first work in this area was probably done by Wipf and Rover, and is summarized in Figure 8-12 [37]. Resin-bound precursor **39** prepared over several steps (not shown) was deprotected and oxidized, and ethyl magnesium bromide was added. Next, the resulting resin-bound alcohols **40** were tagged with the fluorous BPFOS group to give **41**. Left untagged were by-



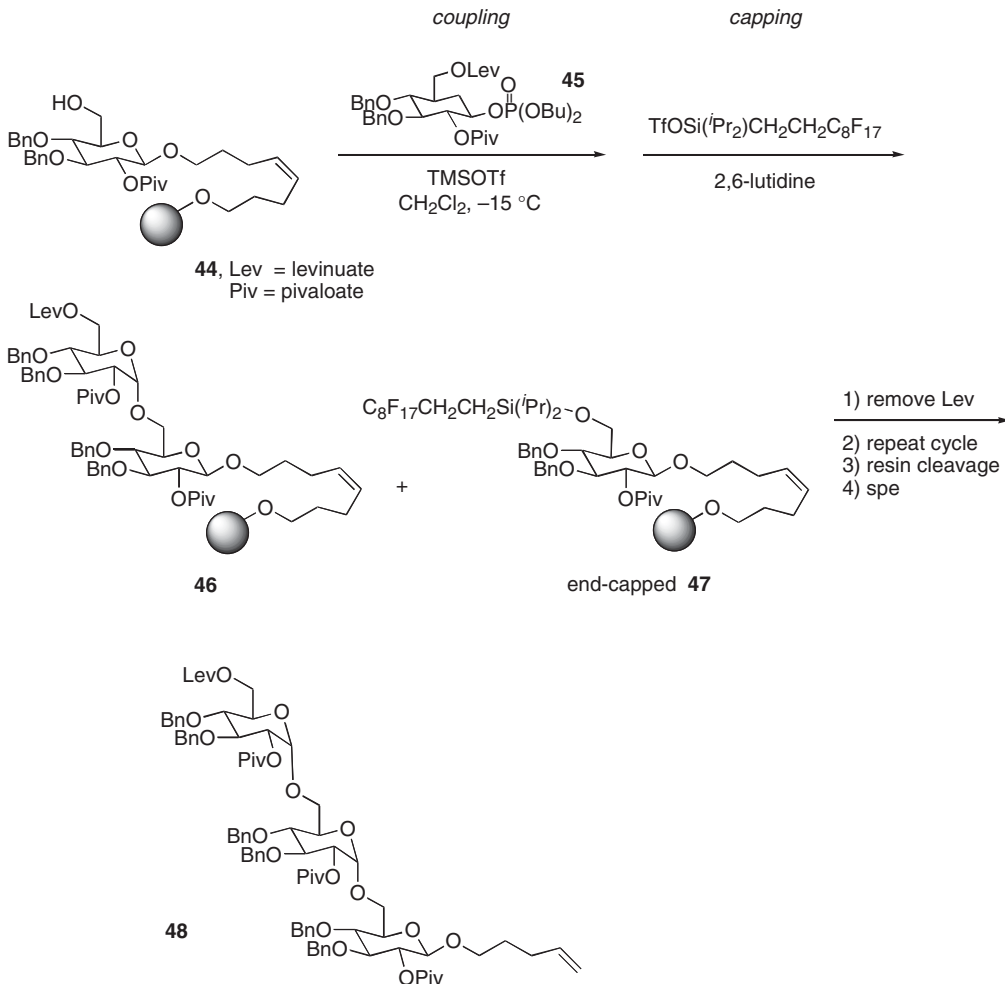
BPFOS-Br is *tert*-butyl phenyl-1*H*,1*H*,2*H*,2*H*-heptafluorodecyloxysilyl bromide,  $\text{BrSi}(\text{Ph})(^t\text{Bu})\text{CH}_2\text{CH}_2\text{C}_8\text{F}_{17}$

Fig. 8-12. The first example of a solid-to-fluorous phase switch

products resulting from the failure of the prior steps. Now, the crude product was removed from the resin and partitioned by SPE into an untagged fraction of impurities and a tagged fraction of **42**, which was isolated in 11% yield and in good purity over 11 total steps. Subsequent transformations provided the target oxazoles and thiazoles **43**, which are analogs of the natural product curacin.

The Wipf work nicely illustrates how fluorous tagging can be used in combination with solid phase synthesis to give pure products in complex, multi-step reaction sequences where quantitative yields cannot reasonably be expected. The recent elegant work of van Boom and coworkers [38], featured in Chapter 7, shows the potential for fluorous tagging in peptide synthesis and also shows that fluorous chromatography can play a powerful role in this setting.

Fluorous tags can also be used to mark undesired rather than desired products for subsequent SPE separation in a solid phase synthesis. This type of “fluorous end capping” has been deployed by Seeberger and coworkers in automated solid phase carbohydrate synthesis [39], and a representative example of a coupling/capping sequence with a fluorous silyl tri-*tert*-butoxy silane is illustrated in Figure 8-13. Resin-bound acceptor saccharide **44** is coupled with solution phase donor **45** with associated coupling reagents. After separation of the reagent-derived products from the resin by filtration, unreacted acceptor saccharide **44** is endcapped



**Fig. 8-13.** Fluorous endcapping in solid phase carbohydrate synthesis

with fluoros silyl triflate to give **47**. Deprotection of **46** prepares the resin-bound material for the next coupling cycle. After cleavage of the crude product from the resin, SPE bifurcation then gives a non-fluorous target fraction containing **48** followed by a fluoros fraction containing truncated, endcapped products. The usefulness of the method was validated by the synthesis of several di- and trisaccharides.

## 8.4

## Fluorous Mixture Synthesis

The speed and efficiency of mixture methods compel their consideration for synthesis of chemical libraries. However problems with analysis, separation and identification of mixture components can be formidable. Split-mix synthesis is a powerful technique that is typically

used to make small quantities of large numbers of compounds [8]. This solid phase technique mixes beads, not compounds, so separation is easy. As with other solid phase techniques, on-bead analysis of mixtures is limited, but the identification problem has been solved by the introduction of a number of ingenious encoding methods. Solution phase mixture synthesis without any separation tags has been used for some time to make large mixture libraries [40]. Little effort is made to analyze, separate or identify members of these libraries. Instead, various methods of deconvolution are used to interrogate mixtures and to identify features or even structures of active components.

Introduced in 2001 [41], fluorous mixture synthesis is the first and (to date) the only mixture synthesis method based on solution phase chemistry with separation tags that provides for the analysis, isolation and identification of individual pure products. Fluorous tags are used for target precursors and products. The use of individual tagged compounds as described above expedites synthesis by increasing speed and purity. Mixing tagged compounds also leverages synthesis by producing more compounds per unit effort. Fluorous mixture synthesis complements existing mixture techniques well since its strength is making larger quantities of smaller numbers of compound. (The largest fluorous mixture library reported to date is 560 members, although libraries an order of magnitude larger than this appear practical with existing technology.)

The diagram in Figure 8-14 illustrates the steps of a fluorous mixture synthesis for a simple three component mixture. Each of the initial three building blocks is coded by attachment to one of three homologous compounds, and then the tagged compounds are mixed. During the mixture synthesis phase, three-times more compounds are produced per reaction or separation compared with individual samples. The saving is proportional to the number of mixture steps – the more steps you do, the more work you save. This means that fluorous mixture synthesis is especially valuable in longer synthetic exercises, such as natural products synthesis, or in parallel synthesis exercises with late splits (the later the split and the larger the split, the more work saved). Before the final detagging step, the mixtures are “demixed” into their underlyingly pure components.

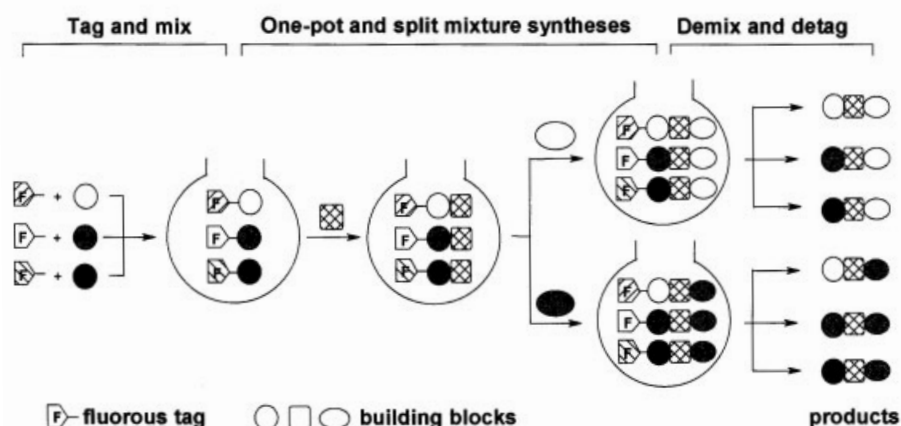


Fig. 8-14. The steps of fluorous mixture synthesis

Demixing is a separation based on the tag structure, and fluorous HPLC is used here because it separates primarily by fluorine content so components are expected to elute in order of tag size [42]. This expectation is confirmed by LC-MS or other traditional means. Finally, the individual products are detagged to give the final products. This detagging reaction should be simple and clean; simple because after the demixing there are now three times as many reactions to conduct (now the same number as a traditional parallel synthesis), and clean because the demixing is also an HPLC so highly pure final products can be generated simply by residual tag removal by evaporation or SPE.

Although preparative demixing is typically left until the end of a synthesis, analytical demixing can be done at any time and thus the mixture components can be separated, analyzed and identified on demand. For example, has a given reaction gone to completion and are there any byproducts? An LC-MS or even better LC-NMR experiment can answer such questions for each and every component of the mixture. While we give here a high level treatment, the implementation of fluorous mixture synthesis has induced us to evaluate and deploy a number of new techniques for analysis and characterization, and our papers (see below) contain more details on the practice of fluorous mixture synthesis in the laboratory. Fluorous mixture synthesis methods have been used to code enantiomers, diastereomers and analogs, and examples of each are provided.

#### 8.4.1

#### Coding of Enantiomers – Fluorous Quasiracemic Synthesis

If you are an organic chemist, you have probably done a mixture synthesis without giving it a second thought. Racemic synthesis, or synthesis with an equal mixture of two enantiomers, was standard practice for decades and is still often used. Analysis of racemates poses no problems since enantiomers exhibit identical properties in many experiments (TLC, NMR, etc.). However separation and identification problems are non-trivial; at the end of a synthesis, how do you separate the two enantiomers and how do you know which enantiomer is which? These questions cannot usually be answered at a strategic level at the beginning of a synthesis, and instead research is needed at the end (finding a suitable chiral column, crystallizing a derivative, etc.).

Today, when both enantiomers of a compound are needed, they might well be made individually by asymmetric synthesis. However this takes up to twice as many steps as racemic synthesis. The new technique of fluorous quasiracemic synthesis unites the efficiency of racemic synthesis with the selectivity of asymmetric synthesis [31, 43]. Enantiomeric (ideally, enantiopure) precursors are tagged with different fluorous tags to make quasienantiomers (“quasi” because they are not isomers), which are then mixed to make a quasiracemate. Despite differing only by one or two  $\text{CF}_2$  groups, the quasienantiomeric components of the mixture can be demixed on demand with fluorous silica gel. However this is generally not necessary during a synthesis since, like enantiomers, quasienantiomers effectively exhibit identical spectroscopic properties so product analysis is routine. Preparative demixing at the end followed by detagging provides the two enantiomeric products of known absolute configuration as coded by the tag.

Quasiracemic synthesis was introduced with syntheses of mappicine and pyridovericin highlighted in Figure 8-15. To prepare mappicine, synthesis of enantiomers *R*-**50** and *S*-**50** by asymmetric reduction of **49** was followed by tagging ( $\text{C}_6\text{F}_{13}$  to *R* and  $\text{C}_8\text{F}_{17}$  to *S*) and

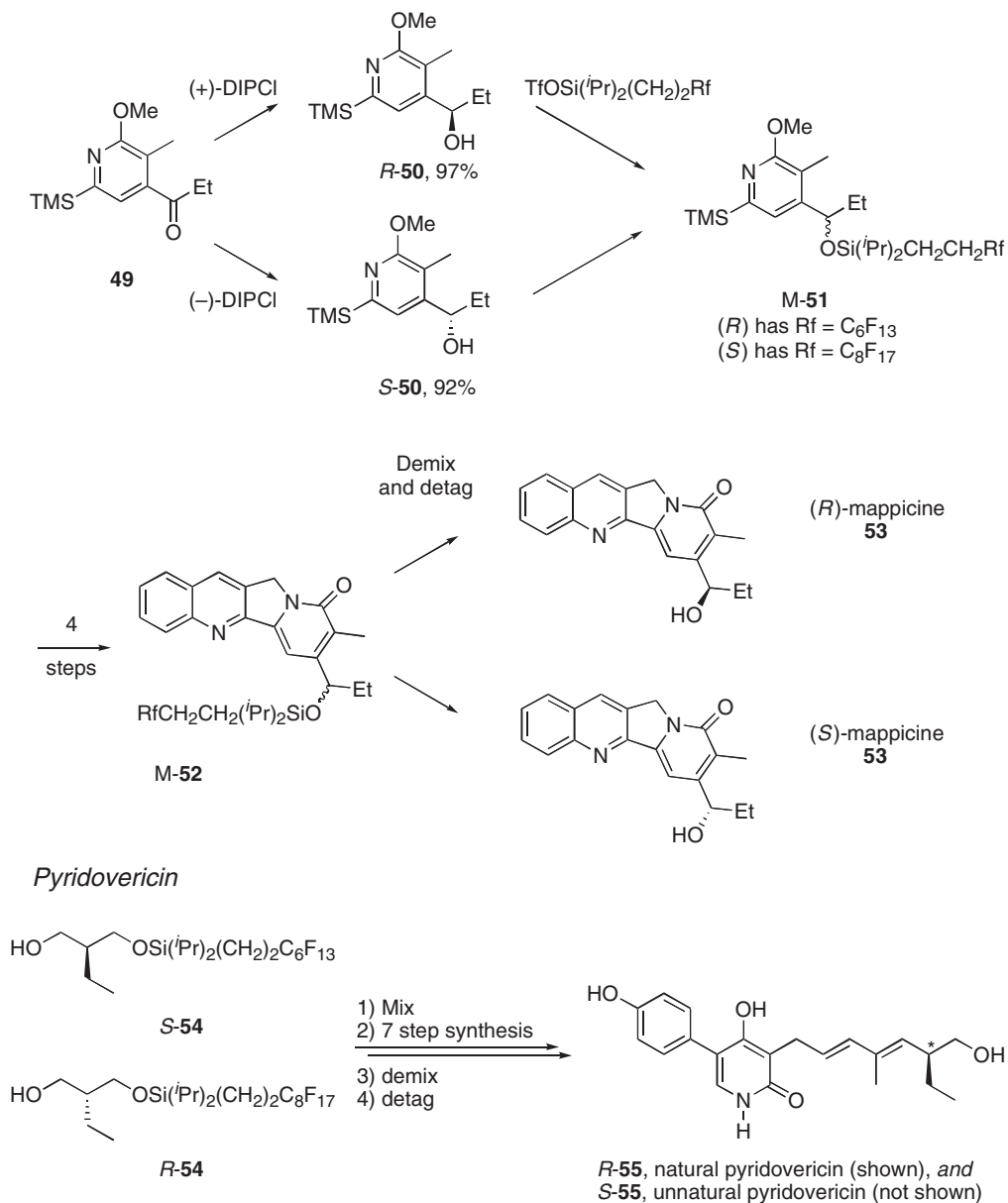


Fig. 8-15. Summaries of fluorous quasiracemic syntheses of mappicine and pyridovericin

mixing to give **M-51**. Four step quasiracemic synthesis with a cascade radical annulation as the key step then gave tagged mappicine quasiracemate **M-52**. This was demixed into its quasienantiomeric components, which were detagged to give natural *S*-mappicine **53** and its enantiomer *R*-mappicine.

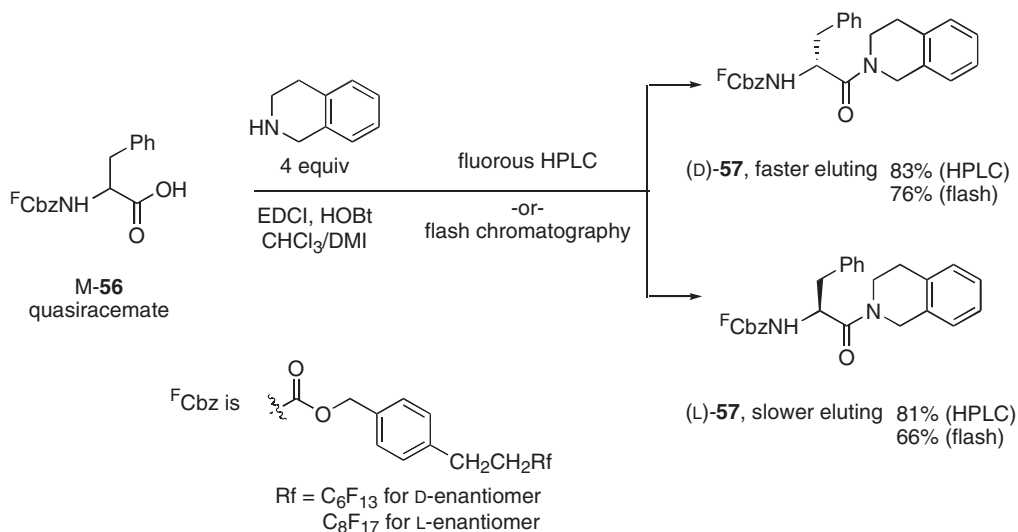


Fig. 8-16. Coupling and demixing of an amino acid quasiracemate

Pyridovericin's absolute configuration was unknown, and both enantiomers were produced over a seven-step synthesis that started by mixing quasienantiomers *R/S*-54. A completion of the synthesis, demixing and detagging gave *R*- and *S*-pyridovericin 55, and the *S*-enantiomer proved to be the natural product. A shortcoming of this synthesis was that the final products were not enantiopure due to partial epimerization during the synthesis. Traditional racemic synthesis is immune to racemization, so quasiracemic synthesis shares its susceptibility to this nasty disease with asymmetric synthesis.

Quasiracemates of most of the naturally occurring amino acids and their enantiomers have recently been produced with  $^{\text{F}}$ Cbz tags [26]. Natural L-enantiomers were given  $\text{C}_8\text{F}_{17}$  tags, while D-enantiomers got the shorter  $\text{C}_6\text{F}_{13}$  tags. Nucleophiles can be derivatized with these quasiracemates to provide both possible enantiomers (or diastereomers, if the nucleophile is chiral) in a single reaction and separation. In the example shown in Figure 8-16, coupling of tetrahydroisoquinoline with the quasiracemate of phenylalanine (Cbz-Phe) M-56 gives a crude reaction product that is subjected to rapid fluororous flash chromatography. An initial fraction containing unreacted and spent reactants is discarded. This is followed by a first fluororous fraction containing the (D)-57 and later a second fluororous fraction containing (L)-57. The fractions are well separated and there is no detectable cross-contamination. In short, two derivatives are obtained for the work of one.

#### 8.4.2

#### Coding of Diastereomers

At the next level up, fluororous tags can be used to encode diastereomers for mixture synthesis. This can of course be done in combination with enantiomers to provide a general scheme for isomeric tagging. There is an additional level of complexity here since tagged

diastereomers could have different reaction and separation properties, but so far such problems have been surmountable.

We have made all 16 possible isomers of the insect pheromone **64** by a combination of fluorous mixture synthesis (four encoding elements) and splitting (four encoding elements) [44]. All four isomers of **58a–d** were prepared with suitable fluorous *para*-methoxyphenylacetal tags. After mixing, PMP cleavage and oxidation, the quasiisomer mixture M-**59a–d** was divided in half for Kocienski-Julia olefination with either *R* or *S* sulfone **60** to give two mixtures of M-**61**. Deprotection, oxidation and a second split and pair of Julia olefinations with the same enantiomeric sulfones **60** gave **62** as four mixtures of four compounds. Deprotection, Wittig reaction and careful reduction with diimide then gave four mixtures of four compounds M-**63a–d** with each mixture containing one of the four possible sets of configurations at C7 and C11, and all four of the possible sets at C2 and C3. Demixing of each of the four mixtures followed by simple detagging and acylation provided all 16 of the pheromone isomers **64** in individual pure form at about the 20 mg scale.

More recently, we have completed a more ambitious synthesis of all 16 dihydroxy THF isomers of the natural product acetogenin murisolin **66**, starting from the tagged diastereomers **65** and using a similar “4-mix/4-split” strategy, and we have been able to confirm the structure of murisolin [45]. Workers in the acetogenin area have long recognized that stereoisomers of these compounds can have very similar spectroscopic properties [46]. Although just how similar are they? The 16 murisolin isomers **66** exhibit only six unique sets of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra at 600 MHz! Every isomer shares an identical spectrum with at least one and sometimes three other diastereoisomers. Clearly, high field NMR spectroscopy cannot provide all the answers in structure assignments of these compounds, even when all the authentic samples are on hand for comparison. Fluorous mixture synthesis is a great aid for difficult stereostructure problems such as murisolin. With all the candidate isomers on hand for a given compound, other methods such as derivatization, chromatography and optical rotation can then be assessed to differentiate similar candidate structures.

#### 8.4.3

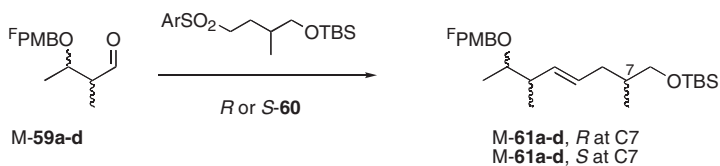
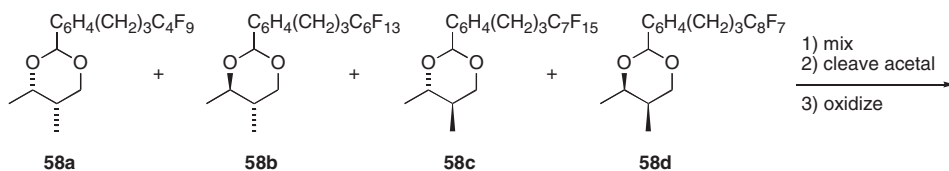
#### Coding of Analogs

Increasing the level of difficulty one more notch, a series of analogs can be coded with fluorous tags. Now the risk of the secondary separation dominating over the primary tag-based separation in fluorous HPLC increases (see Chapter 7), but the problem is far from unmanageable and can be minimized by intelligent choice of tag coding scheme. In the longest linear fluorous mixture synthesis to date, four truncated analogs of the complex natural product discodermolide have been made over eight steps [47]. Figure 8-18 illustrates the power of splitting in a 7-mix/8-split/10-split exercise to make 560 analogs of the natural product mappicine conducted by Fluorous Technologies, Inc. (FTI) [48].

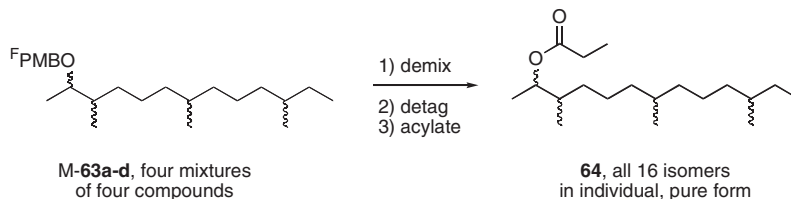
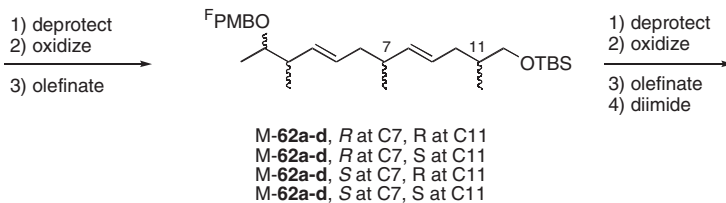
Seven alcohols **67** bearing different  $\text{R}^{\text{D}}$  substituents were coded with seven different fluorous tags and the tagged compounds **68** were mixed and taken through a four-step sequence with splitting in the last two steps. The product mixture M-**69** after iododesilylation and demethylation was divided into eight for reactions with eight different propargyl bromides. Each of these eight products M-**70** was divided into ten for reaction with ten different isonitriles. The result was 80 individual mixtures M-**71**, each of which contained one of the 80



## Pheromones



$\text{F}^{\text{PMB}}$  is  $\text{Rf}(\text{CH}_2)_3\text{OC}_6\text{H}_4\text{CH}_2$ , where  $\text{Rf}$  is  $\text{C}_4\text{F}_9$ ,  $\text{C}_6\text{F}_{13}$ ,  $\text{C}_7\text{F}_{15}$ , or  $\text{C}_8\text{F}_{17}$



## Acetogenins

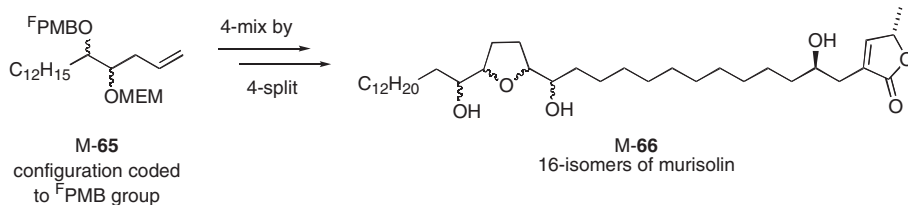


Fig. 8-17. Fluorous mixture synthesis approaches to pheromone and acetogenin isomers

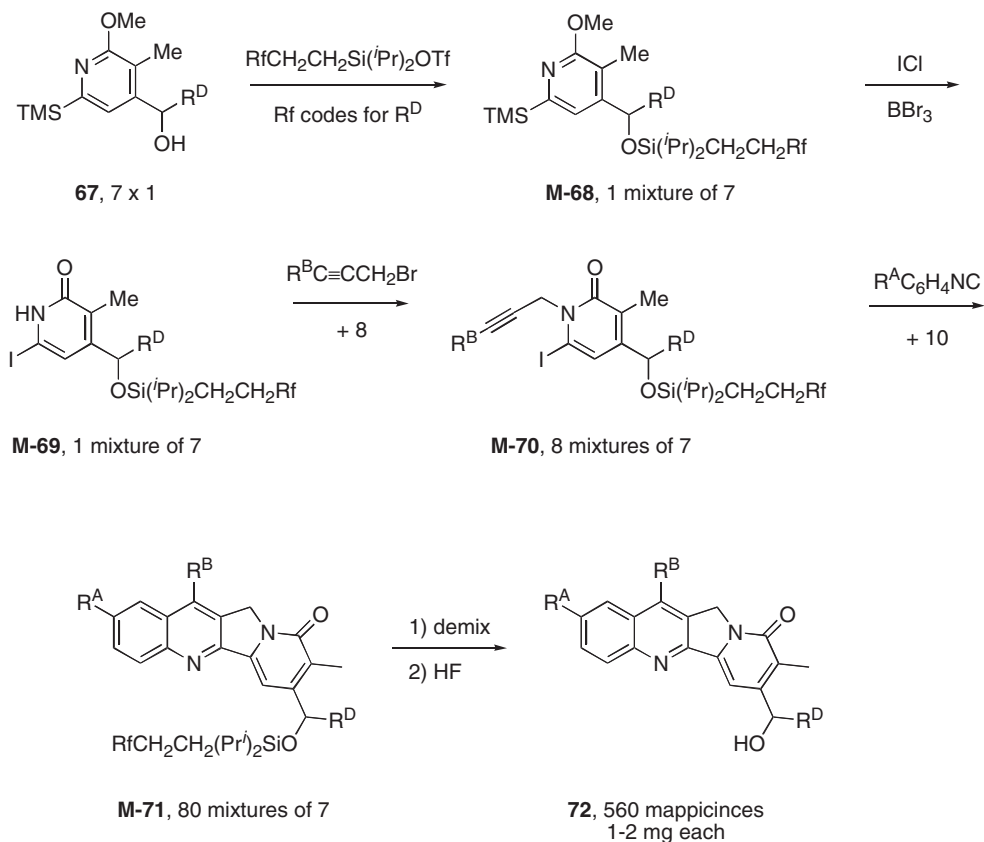


Fig. 8-18. FTI's fluororous mixture synthesis of 560 mappicine analogs

possible combinations of  $\text{R}^A$  and  $\text{R}^B$  and all seven possible combinations of  $\text{R}^D$ . Eighty demixings by serial fluororous HPLC followed by 560 detaggings with  $\text{HCl}$  and SPE through reverse phase silica gel (tag is retained, product passes) provide all 560 mappicines **72**.

This synthesis began with about 15 g of the first mixture **M-68** and produced about 1 g total weight of the 560 analogs **72**. Thus fluororous mixture synthesis is scalable. The mixture part of the synthesis required only 90 steps ( $1 + 1 + 8 + 80$ ) compared with the 630 steps ( $7 + 7 + 56 + 560$ ) needed for the equivalent parallel synthesis, for a saving of 540 steps. The efficiency is also evident in the demixings, where 560 pure compounds were obtained from only 80 HPLC separations. The exercise proved to be more than a technology validation, since several of the mappicines in this library have shown promising activity in RNase-H screens [49]. The best of these are being evaluated as potential lead compounds for the development of new AIDS chemotherapies.

While there are only a handful of papers on fluororous mixture syntheses to date, the results in these papers auger very well for future applications in natural products chemistry, drug discovery and other areas.

## 8.5

### Fluorous Triphasic Reactions

As with fluorous mixture synthesis, fluorous triphasic reactions are nascent techniques with a potentially big future; however, triphasic applications are likely to be more on the process and production end of the chemical spectrum than on the discovery end. Fluorous biphasic reactions and fluorous triphasic reactions share an analogous name and both use fluorous reaction solvents. However the similarities end there. Fluorous biphasic reactions involve a reaction first and then a separation. They rely on heavy fluorous molecules and strive for homogenous reaction media. In contrast, fluorous triphasic reactions involve a reaction and a separation simultaneously with the reaction driving the separation. Light fluorous molecules are used, and homogeneity is verboten. We summarize here two types of applications: triphasic detagging and phase-vanishing reactions.

#### 8.5.1

##### Triphasic Detagging Reactions

Fluorous triphasic reactions were introduced in 2001 in a setting of detagging of silyl ethers, and proof-of-principle experiments showed the viability of triphasic reactions as well as their ability to separate doped, non-tagged impurities from tagged compounds simultaneous with detagging [50]. The need to separate tagged from untagged compounds arises frequently in the real world during multi-step synthesis with fluorous tags (Section 8.3.2), and during kinetic resolution of racemates.

Figure 8-19 shows a recent coupling of an enzyme kinetic resolution and fluorous triphasic reaction to efficiently resolve 2-naphthyl ethanol [51]. Deacylation of racemic ester derivative *rac*-**73** occurs with high enantioselectivity to provide alcohol *R*-**74** and ester *S*-**73** [52]. These can be separated by chromatography or repeated fluorous/organic liquid/liquid extraction and the recovered ester can be cleaved. However this is a two step process (separation followed by reaction), and the separation step is solvent-intensive. The coupling of the kinetic resolution with a fluorous triphasic detagging condenses the separation and reaction steps into one and dramatically reduces solvent use.

After filtration of the enzyme preparation and evaporation, the crude mixture of *R*-**74** and *S*-**73** is added to the source side of a U-tube containing MeOH. The receiving side of the U-tube contains MeOH/MeONa, and these two phases are separated by FC-72, which behaves like a liquid membrane regulating the exchange between the two organic phases. After 2 days, the contents of the two organic phases were recovered and analyzed. Remarkably, *S*-**74** was recovered from the source side and the *R*-**74** was recovered from the receiving side, while the transesterified tag was recovered from the fluorous phase. The results show that FC-72 permits the diffusion of the tagged enantiomer *R*-**73** through the fluorous phase to the receiving side where it is detagged to *R*-**74** and then stranded. The *S*-**74** enantiomer has no tag in the first place so it remains in the source phase, while the residual tag is now quite fluorous and it heads for the FC-72.

Here a chemical reaction—transesterification—provides the energy to drive a non-equilibrium separation. At equilibrium, both organic phases must contain racemic alcohol **74**, but reaching this equilibrium is agonizingly slow because of the low solubility of the

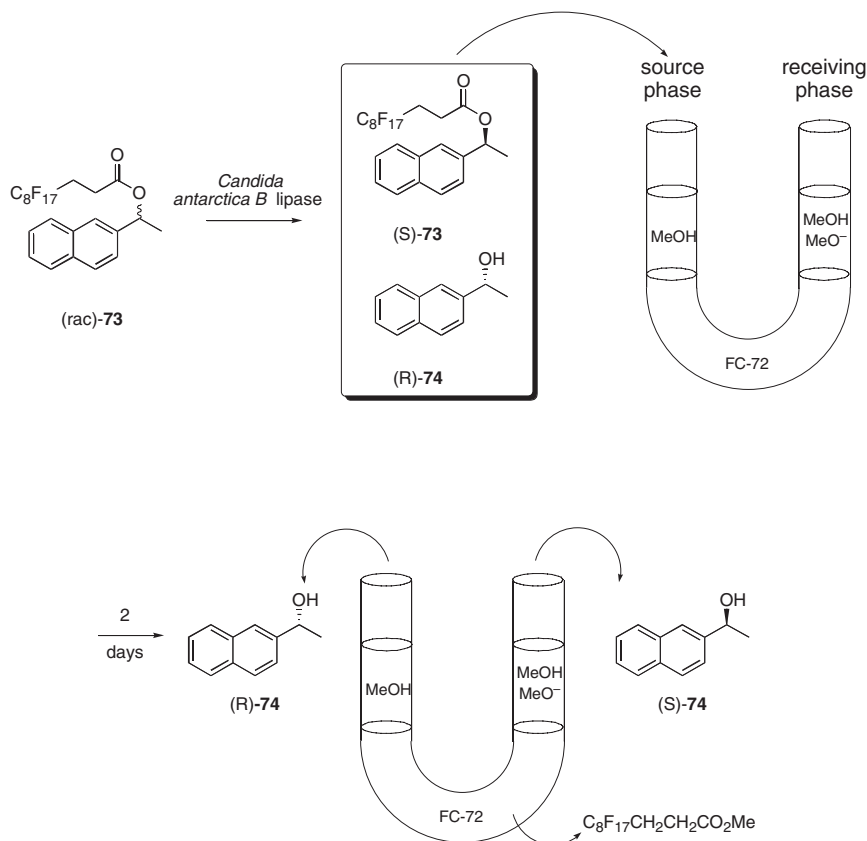


Fig. 8-19. A combined enzymatic kinetic resolution and triphasic separation

alcohol in the fluorous solvent. In short, these early results suggest that fluorous triphasic reactions have excellent potential for use in detagging, and resolutions loom as an important application.

### 8.5.2

#### Phase-Vanishing Reactions

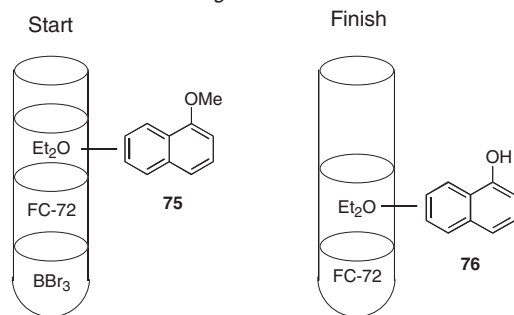
At the upper end, light fluorous chemistry merges into heavy fluorous chemistry as the number of fluorine atoms increases. At the lower end, fluorous chemistry vanishes entirely as the number of fluorine atoms decreases. The natural conclusion is that it is impossible to do fluorous chemistry without fluorinated reaction components. However this conclusion is wrong! In phase-vanishing reactions, not only does a phase vanish, but so do all the fluorinated reaction components. The only thing fluorinated is the solvent, which again serves as a barrier to regulate the passing of a non-fluorous reaction component.

An assortment of small molecules, especially halogenated or polyhalogenated ones, have

some solubility in perfluorinated solvents yet are not miscible. When such molecules can also be used as reagents or reactants in organic transformations, the requirements are met for a phase-vanishing reaction. Such reactions control addition rates chemically rather than mechanically, and should be especially convenient for exothermic reactions or any other reactions where a low-tech (or basic) yet effective regulation of addition rate is needed. In some cases, the vanishing of the reagent phase also provides a visual indication that the reaction is at or near completion.

Reagents for phase-vanishing reactions can be more or less dense than the fluorinated solvent, and an example of the former is shown in Figure 8-20. Ryu and coworkers have demethylated aryl methyl ethers **75** with  $\text{BBr}_3$  ( $d = 2.65$ ) separated from an ether phase by perfluorohexane ( $d = 1.7$ ) [53]. Gradual diffusion of the  $\text{BBr}_3$

#### Single Reaction with More Dense Reagent



#### Three Reactions with Less Dense Reagent

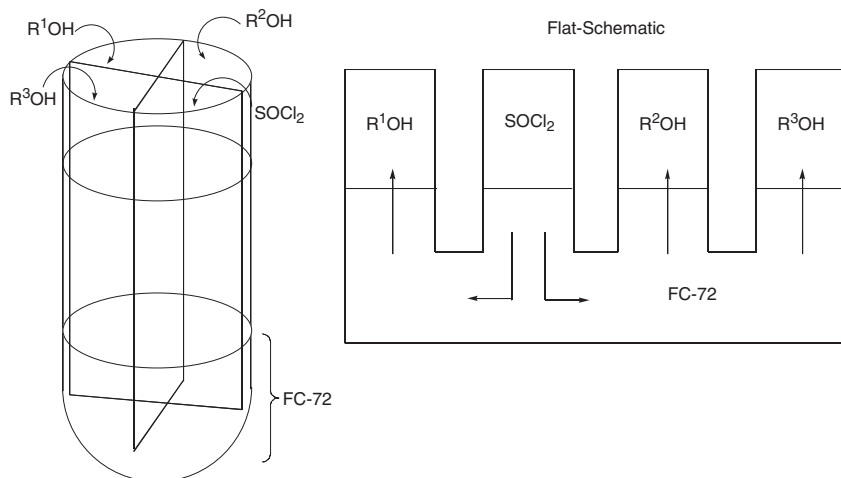


Fig. 8-20. Phase-vanishing reactions with reagents more (top) and less (bottom) dense than FC-72

through the perfluorohexane followed by demethylation forms the phenol **76** in the ether phase. When  $\text{BBr}_3$  is used stoichiometrically, its phase vanishes towards the end of the reaction, hence the name. Cooling or mechanical means to limit an addition or control the heat evolution are not used in this low-tech reaction.

With reagents less dense than the fluorosolvant, Nakamura and coworkers showed that a U-tube set up can be used with the substrate on one side, the reagent on the other, and the fluorosolvant in the middle [54]. When used stoichiometrically, the reagent phase again vanishes near the end of the reaction. Figure 8-20 illustrates this system in a simple and convenient parallel set up for simultaneous chlorination of three alcohols. The top part of a test tube was divided into four compartments by glass slits, while the bottom was left open. FC-72 was added to a level above the lower end of the slits, then toluene solutions of three different alcohols were added to three of the compartments and thionyl chloride ( $d = 1.63$ ) was added to the fourth. After 1 day, the thionyl chloride phase had vanished and the three chlorides were isolated from their corresponding compartments in 70–80% yields. Cross contamination could not be detected.

Clearly, any number of parallel reactions can be conducted in this way with suitably compartmentalized vessels. The same vessel design can also be used for parallel reactions with more dense reagents with the proviso that even one more substrate can be used since the reagent sits on the bottom and does not require its own compartment [53b].

## 8.6

### Conclusion

Now about four years old, light fluorosolvant techniques are already supplementing heavy fluorosolvant techniques in catalytic and other important applications. However more importantly, they are complementing heavy fluorosolvant techniques by opening up powerful new options. Many light fluorosolvant techniques are enabled by fluorosolvant silica gel separation methods. Uses of light fluorosolvant reagents, catalysts and scavengers have almost no learning curve and are well within the comfort zone for the majority of practicing bench chemists. For some important reactions, everything that is needed is now commercially available, and basic fluorosolvant SPE techniques are so similar to traditional methods that they can be learned easily without any difficulties. A step above this, fluorosolvant tagging techniques reward a small time investment devoted to learning with significant potential time savings and purity gains in expedited parallel synthesis. The nascent technique of fluorosolvant mixture synthesis leverages the effort of tagging by producing even more compounds, and mixture synthesis can be used to make enantiomers, diastereomers or analogs. Finally, fluorosolvant triphasic reactions are liquid-based methods that show that light fluorosolvant chemistry is not limited to silica techniques. As with mixture synthesis, the triphasic class has just been introduced and not only practical but probably also conceptual advances are still ahead.

### Acknowledgements

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## 9

## Getting Started in Synthesis: A Tabular Guide to Selected Monofunctional Fluorous Compounds

József Rábai

## 9.1

### Introduction

The first steps when beginning a fluorous project are to purchase the necessary fluorous starting materials and synthesize the target molecules. The vendors of fluorous solvents listed in Table 3-1 also provide a number of fluorous building blocks, as does Fluorous Technologies Inc. (FTI, <http://fluorous.com/index2.html>). This chapter, augmented by the references to the table of partition coefficients in Chapter 6 (Table 6-1), is intended as a guide to the synthesis of simple fluorous molecules. It is by no means comprehensive, but does provide many useful leads for researchers just beginning in this field.

Looking first backwards to Table 6-1, it is easy to visually scan various families of functional groups and locate lead references. However, if the partition coefficient has not been measured, the molecule is not included. Furthermore, superior syntheses may have been developed after the initial literature report.

Recognizing this gap, this chapter summarizes a wide range of monofunctional “heavy” fluorous compounds and selected “light” fluorous compounds in a tabular form. In most cases, abbreviated synthetic details are indicated (“ $\Rightarrow$ ” symbol), followed by the literature reference. In some cases, particularly useful reactions are indicated (“ $\bullet +$ ” symbol). More complex target molecules can then be assembled from perfluoroalkyl- and organic groups of appropriate topologies, sometimes inserting “insulator” groups between these constituents (cf. Chapters 4 and 5).

The latter strategy or modular synthesis calls for an “*F*-tool-kit” suitable for the most diverse applications. At one extreme, various target *F*-entities with linear perfluoroalkyl groups exhibit good organic solubilities under reaction conditions at higher temperatures, but quantitatively precipitate at lower temperatures (thermomorphism). At the other extreme *F*-derivatives with flexible and branched perfluoropolyether type substituents could have rather wide fluid temperature ranges (high-tech lubricants).

Syntheses involving highly fluorinated compounds will certainly provide simultaneous feelings of frustration and pleasure for those so engaged. This derives from differences in reactivity and solubility patterns from those experienced in traditional organic chemistry. The high electronegativity of fluorine atoms and perfluoroalkyl-groups strongly affect reac-

tion centers, unless appropriately positioned (cf. Chapter 5). Moreover, macroscopic properties, such as solubility, fluorophilicity, volatility, melting and boiling point, transition enthalpies, etc. are all governed by the composition and structure of the molecules. The higher their fluorous character, the more unique properties will be expressed.

The trifluoromethyl group, which can be regarded as the shortest *F*-ponytail, appears in the Beilstein database with a frequency one order of magnitude greater than all longer  $R_{fn}$  segments combined ( $R_{f1}GH^*/R_{f2-24}GH^* = 205\,000:24\,000$ ). Hence, some prototype chemistries known only for  $CF_3$ -compounds are also displayed in the Tables. In the first series of Tables, molecules without hydrogen atoms are collected. In the second, hydrogen atoms of all descriptions are allowed.

### Series I [no hydrogen included]

9.1.1 Perfluoroalkanes, perfluoroalkenes and perfluoroalkynes

9.1.2 Perfluoroalkyl halides and related compounds

9.1.3 Perfluoroethers, perfluoroalkanones and perfluoroalkanecarboxylic acid halides

9.1.4 Perfluoroalkylsulfides and disulfides, perfluoroalkanesulfonyl halides and anhydrides

9.1.5 Tris(perfluoroalkyl)amines, perfluoroazomethines, perfluoroalkanenitriles, tris(perfluoroalkyl)triazines and perfluoroalkyl isocyanates

9.1.6 Perfluoroalkylmagnesium-, zinc-, copper(I)-, lithium-, and caesium intermediates.

Tab. 9.1-1. Perfluoroalkanes, perfluoroalkenes and perfluoroalkynes

Compound [C,F]	Remarks ("⇒" for synthesis of; "•+" for reaction of; etc.)	Ref.
$C_nF_{2n+2}$ , <i>cyclo</i> - $C_nF_{2n}$ , etc.	⇒ • + Disclosure of a "Secret World": Properties of Fluorocarbons	1
Perfluoroalkanes	⇒ • + Synthesis and Chemistry of Perfluoroalkanes. A review	2
$CF_3CF_2CF=C(CF_3)_2$	• + $KF + ROCH_2Cl/PTC$ , rt. → $ROCH_2C(CF_3)_2CF_2CF_2CF_3$ (82%)	3
$CF_3(CF_2)_3CF=CF_2$	⇒ $R_{f6}CO_2Na$ /heating → $R_{f4}CF=CF_2$ + isomers, in a 73:27 ratio	4
$R_{fn}CF=CF_2$ , $n = 1, 2, 3, 5, 7$	⇒ Prepared by the pyrolysis of the salts of $R_{fn+2}CO_2H$ 's	5
$(CF_3)_2C=CF_2$	⇒ <i>cyclo</i> - $C_4F_8/25$ s at 710–730 °C/ → yield: 45%, bp = 6–9 °C	6
$R_{fn}C\equiv CR_{fm}$ , $n = 2, 4, 8$ ; $m = 4, 6, 8$	⇒ $R_{fn}C\equiv CH + R_{fm}I/220$ °C → $R_{fn}CI=CHR_{fm}$ /base-PTC → overall yield: 40–59%	7

Tab. 9.1-2. Perfluoroalkyl halides and related compounds

Compound [C,F,X]	Remarks ("⇒" for synthesis of; "• + " for reaction of; etc.)	Ref.
$R_{fn}I$ , $n = 1, 3$	⇒ $R_{fn}CO_2Na + I_2/DMF$ , reflux → yield: 70–80%	8
$R_{fn}I$ , $n = 1-12$	⇒ Ref. 9. Uses and reactions of: Ref. 10	9, 10
$(CF_3)_2CF(CF_2CF_2)_nI$	⇒ $(CF_3)_2CFI + CF_2=CF_2/175\text{ °C}$ → mix of telomers; $n = 1$ (major) > $n = 2-4$ (minor)	11
$Cl(CF_2)_nI$ , $n = 2, 4, 6$	• + $CH_2=CHR$ /acid treated Fe catalyst → $Cl(CF_2)_nCH_2CH(I)R$	12
$C_8F_{17}Br$	⇒ $C_8F_{17}H + CBr_4/300\text{ °C}$ , 24 h → yield: 40%	13
$C_8F_{17}Cl$	⇒ $C_8F_{17}H + CCl_4/350\text{ °C}$ , 24 h → yield: 31%	13
$X(CF_2)_nCl$	• + $CH_2=CHR/(NH_4)_2S_2O_8-HCO_2Na$ → $X(CF_2)_n(CH_2)_2R$ (70–80%)	14
$R_{f6}CCl_3$	⇒ $R_{f6}I + CCl_4/Zn$ , $EtCO_2H$ , $CH_2Cl_2$ , 2 h → yield: 51%	15
$R_{f9}CCl_3$	⇒ $R_{f10}I + AlCl_3/\sim 115\text{ °C}$ , 28 h → yield: 55%	16
$(CF_3)_2CFO(CF_2)_3CCl_3$	⇒ $(CF_3)_2CFO(CF_2)_4I + AlCl_3/100\text{ °C}$ , 63 h → yield: 43%	16
$CCl_3(CF_2)_4N=N(CF_2)_4CCl_3$	• + $SO_3/H_2SO_4/Hg^{2+}$ → $HO_2C(CF_2)_4N=N(CF_2)_4CO_2H$ , yield: 95%	17
$(CF_3CF_2)_2NCF_2CF_2I$	⇒ $(CF_3CF_2)_2NCF_2CF_2COF/LiI$ , 180 °C, 18 h → yield: 72%	18
$CF_3(CF_2)_7OCF_2CF_2I$	⇒ $R_{f7}COF + CF_2=CF_2/KF/I_2$ , diglyme, $-196\text{ °C}$ , 7 d → yield: 46%	19
$C_3F_7OCF(CF_3)CF_2OCFICF_3$	• + $PhI/Cu$ , bipy, DMSO → $C_3F_7OCF(CF_3)CF_2OCFPhCF_3$ (73%)	20
$(CF_3)_2CFOCF_2CF_2I$	⇒ $(CF_3)_2CFOK + CF_2=CF_2 + I_2$ or $ICl/CH_3CN$ → bp = 86–87 °C	21
$F_5SCF_2I$	⇒ $F_5SCF_2CO_2Ag + I_2$ /heating → yield: 54%	22
$F_5SCF_2CF_2I$	⇒ $S_2F_{10} + ICF_2CF_2I + CF_2=CF_2/-196\text{ to }155\text{ °C/}$ → yield: 49%	23
$F_5SCF_2CF_2Br$	⇒ $F_5SBr + CF_2=CF_2/90\text{ °C}$ , 2 d → bp = 60–62 °C	24
$F_5SCF_2CF_2Cl$	⇒ $SF_5Cl + CF_2=CF_2/(PhCO)_2O_2$ , 90 °C, 10 h → yield: 22% to $C_2F_4$	25
$(CF_3)_3GeI$	⇒ Ref. 26. Commercially available	26

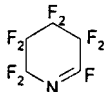
Tab. 9.1-3. Perfluoroethers, perfluoroalkanones and perfluoroalkanecarboxylic acid halides

Compound [C,F,O(X)]	Remarks ("⇒" for synthesis of; "• + " for reaction of; etc.)	Ref.
$R_fCF(CF_2)_nCF_2O$ , $n = 2, 3$	• + $AlCl_3$ , heating → $R_fCCl(CF_2)_nCCl_2O$	27
$R_{f6}OR_{f6}$	• + $AlCl_3/185\text{ °C}$ , 14 h → $R_{f5}COCl$ (63%) + $R_{f5}CCl_3$ (51%)	28
$R_fC(O)F(CF_3)_2$	⇒ $R_fCOF/CsF$ -catalyst + $CF_2=CFCF_3$ → yield: 39–75%, $R_f = (CF_3)_2CF$ ; $C_3F_7$ , $CF_3$ ; etc.	29
$C_3F_7OCF(CF_3)CF_2OCF(CF_3)COCF_3$	⇒ $C_3F_7OCF(CF_3)CF_2OCF(CF_3)COF + CF_3SnMe_3/$ 140 °C, 20 h, sealed tube → yield: 49%	30
$C_7F_{15}COCl$	⇒ $C_7F_{15}CO_2H + SOCl_2/DMF$ , heating, 4 h → yield: 90%	31
$C_3F_7O[CF(CF_3)CF_2O]_nCF(CF_3)COF$	⇒ $CF_3CFCF_2O + KF$ /diglyme → acid fluorides, $n = 1-4$	32
$C_7F_{15}COF$	⇒ $C_7F_{15}CO_2H + HCF_2CF_2N(CH_3)_2/0-25\text{ °C}$ , 2 h → yield: 75%	33

**Tab. 9.1-4.** Perfluoroalkylsulfides and disulfides, perfluoroalkanesulfonyl halides and anhydrides

Compound [C,F,S(O,X)]	Remarks ("⇒" for synthesis of; "• + " for reaction of; etc.)	Ref.
(C <sub>3</sub> F <sub>7</sub> ) <sub>2</sub> S	⇒ C <sub>3</sub> F <sub>7</sub> I + S <sub>x</sub> /300 °C, 10 h → yield: 11%, bp = 88 °C	34
(C <sub>7</sub> F <sub>15</sub> ) <sub>2</sub> S <sub>2</sub>	⇒ C <sub>7</sub> F <sub>15</sub> I + S <sub>x</sub> /255 °C, 17 h → yield: 60%, mp = 39 °C, bp = 247 °C	34
C <sub>6</sub> F <sub>13</sub> SO <sub>2</sub> Cl	• + C <sub>6</sub> H <sub>6</sub> /RuCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>3</sub> → C <sub>6</sub> H <sub>5</sub> C <sub>6</sub> F <sub>13</sub> , yield: 44%	35
C <sub>8</sub> F <sub>17</sub> SO <sub>2</sub> X, X = F, Cl	⇒ Title compounds were obtained in ~98% purity from a mixture containing branched isomers by cooling to –20 °C and filtration of the crystalline linear isomers	36
R <sub>fn</sub> SO <sub>2</sub> Cl and/or (R <sub>fn</sub> SO <sub>2</sub> ) <sub>2</sub> O	⇒ R <sub>fn</sub> SO <sub>3</sub> K + PCl <sub>5</sub> ·2ZnCl <sub>2</sub> → "high yield and purity". When PCl <sub>5</sub> reacted with perfluoroalkanesulfonic acids, yields anhydrides	37
( <i>cyclo</i> -C <sub>2</sub> F <sub>5</sub> C <sub>6</sub> F <sub>10</sub> SO <sub>2</sub> ) <sub>2</sub> O	• Used for the thermal perfluoroalkylation of dyes (e.g., pyranthrone, Cu phthalocyanine) to yield fluoruous derivatives for staining PTFE	38

**Tab. 9.1-5.** Tris(perfluoroalkyl)amines, perfluoroazomethines, perfluoroalkanenitriles, tris(perfluoroalkyl)triazines and perfluoroalkyl isocyanates

Compound [C,F,N(O)]	Remarks ("⇒" for synthesis of; "• + " for reaction of; etc.)	Ref.
(C <sub>4</sub> F <sub>9</sub> ) <sub>3</sub> N	• An inert medium for organic reactions	39
	⇒ Prepared by the defluorination of undecafluoropiperidine with steel wool at 500 °C/1 atm, yield: 40%	40
CF <sub>3</sub> CF <sub>2</sub> CF <sub>2</sub> CF <sub>2</sub> N=CFCF <sub>2</sub> CF <sub>2</sub> CF <sub>3</sub>	⇒ (C <sub>4</sub> F <sub>9</sub> ) <sub>3</sub> N + SbF <sub>5</sub> catalyst/120 °C, 4 h, (–C <sub>4</sub> F <sub>10</sub> ) → yield: 67%	41
C <sub>7</sub> F <sub>15</sub> CN	⇒ C <sub>7</sub> F <sub>15</sub> CONH <sub>2</sub> + P <sub>2</sub> O <sub>5</sub> /200 °C → yield: 84%, bp = 103–104 °C	42
2,4,6-(C <sub>7</sub> F <sub>15</sub> ) <sub>3</sub> -1,3,5-triazine	⇒ C <sub>7</sub> F <sub>15</sub> CN/aniline, 120–140 °C, 13 h → yield: 77%	43
R <sub>f3</sub> NCO	⇒ R <sub>f3</sub> N=NR <sub>f3</sub> + CO/300 °C, 800 atm, 8 h → yield: 11% + C <sub>6</sub> F <sub>14</sub>	44
R <sub>f7</sub> NCO	⇒ R <sub>f7</sub> COCl + Me <sub>3</sub> SiN <sub>3</sub> → yield: 82%	45

**Tab. 9.1-6.** Perfluoroalkylmagnesium- and perfluoroalkylzinc halides; perfluoroalkyl copper(I)-, perfluoroalkyl-lithium-, and perfluoroalkyl-caesium intermediates

<b>Compound [C,F,Mg/Zn/Cu/Li/Cs]</b>	<b>Remarks ("⇒" for synthesis of; "• + " for reaction of; etc.)</b>	<b>Ref.</b>
$R_{f8}MgBr/THF$	$\Rightarrow C_8F_{17}I + PhMgBr$ or $C_2H_5MgBr/THF$ at $-70\text{ }^{\circ}C/ \rightarrow R_{f8}MgBr \rightarrow R_{f8}C(CH_3)_2OH$ or $R_{f8}C(CF_3)_2OH$ , in 90 or 64% yields, resp.	46
$R_{fn}MgBr/ether, n = 4, 6, 8, 10$	$\Rightarrow C_nF_{2n+1}I + C_2H_5MgBr/ether$ at $-35$ to $-40\text{ }^{\circ}C/ \rightarrow R_{fn}MgBr/ether$ ; quenched by $PhCH_2CH=O$ to yield $PhCH_2CH(OH)R_{fn}$ .	47
$(CF_3)_2CF_2ZnI/THF$	• + $PhCOF/py \rightarrow PhCOCF(CF_3)_2$ , yield: $\sim 100\%$	48
$R_{fn}Cu.solvent$	$\Rightarrow R_{fn}I + 2Cu/DMSO, 110-120\text{ }^{\circ}C, 2\text{ h} \rightarrow R_{fn}Cu$ , yield $> 80\%$	49
" $C_8F_{17}Li$ " / ether ( $-78\text{ }^{\circ}C$ )	$\Rightarrow$ Generated <i>in situ</i> : $C_8F_{17}I + CH_3Li-LiBr/ether, -78\text{ }^{\circ}C$	50
$CF_3CF_2CF_2C(CF_3)_2^-Cs^+$	• + $ArCH_2Br \rightarrow ArCH_2C(CF_3)_2R_{f3}$ , 10 examples, yields: $\sim 60\%$	51
Miscellaneous <i>F</i> -organometallics	$\Rightarrow$ • + Synthesis and reactivity of <i>F</i> -organometallics. A review	52

## Series II [hydrogen included]

9.2.1 Hydroperfluoroalkanes, perfluoroalkylalkanes/cycloalkanes, perfluoroalkylalkenes and perfluoroalkylalkynes, perfluoroalkylarenes, (perfluoroalkyl)alkylarenes and related compounds

9.2.2 (Perfluoroalkyl)alkyl halides; perfluoroalkyl- and (perfluoroalkyl)alkyl aryl/benzyl halides

9.2.3 Perfluoroalkylalkanols and ethers

9.2.4 Fluorous mercaptanes, sulfides, sulfoxides, sulfonates, sulfonimides and selenides

9.2.5 Fluorous amines, anilines, pyridines; phosphines and phosphites

9.2.6 Fluorous boron-, silicon-, tin-, lithium-, zinc-, and magnesium compounds

9.2.7 Fluorous aldehydes and ketones

9.2.8 Fluorous carboxylic acids

9.2.9 Fluorous esters and carbonic acid derivatives

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**Tab. 9.2-1.** Hydroperfluoroalkanes, perfluoroalkylalkanes/cycloalkanes, perfluoroalkylalkenes and perfluoroalkylalkynes, perfluoroalkylarenes, (perfluoroalkyl)alkylarenes and related compounds

Compound [C,F,H]	Remarks ("⇒" for synthesis of; "• + " for reaction of; etc.)	Ref.
$R_{fn}CF_2H$ ( $n = 2-4$ )	⇒ $R_{fn}CF_2I + H_2$ /Raney Ni, 60 atm, 350 °C → yield: 80%	9a
$(CF_3)_3CH$	⇒ Prepared as described and its thermodynamic acidity studied	53
$F(CF_2)_8(CH_2)_8H$	⇒ $R_{f8}I + CH_2=CHC_6H_{13}$ /AIBN → $R_{f8}CH_2CH(I)C_6H_{13}$ ; + Zn/HCl in $CH_3OH$ → title product, its gel formation from alcohols studied	54
$CF_3$ -cyclo- $C_6H_{11}$	⇒ • + As a new solvent? Limits of use	55
$R_{fn}CH=CH_2$	⇒ $R_{fn}CH_2CH_2I + NaOH/C_2H_5OH$ , 30 °C, 1 h → yield: 99%	56
$R_{fn}CH=CH_2$ , $n = 4, 6, 8, 10$	⇒ $R_{fn}I + CH_2=CHSi(CH_3)_3$ → $R_{fn}CH_2CHSi(CH_3)_3$ ; + $Bu_4NF$ → overall yield: 58–86%	57
$R_{f8}CH_2CH=CH_2$	⇒ $R_{f8}I + CH_2=CHCH_2Cl$ /AIBN → title olefin + adduct	58
$(CF_3)_3CCH_2CH=CH_2$	⇒ $(CF_3)_2C=CF_2/CsF + CH_2=CHCH_2I$ /diglyme → yield: 80%	59
$CF_3(CF_2)_2C(CF_3)_2CH_2CH=CH_2$	⇒ Alkylation of perfluoro-2-methyl-2-pentylcarbanion with alkyl and allyl halides. Study the effect of solvents and $F^-$ -sources	60
$(C_2F_5)_2C(CF_3)OCH_2CH=CH_2$	⇒ $(C_2F_5)_2C(CF_3)OK + CH_2=CHCH_2Br/CH_3CN$ , reflux → bp 120 °C	61
$(CF_3)_2NCH_2CH=CH_2$ ,	⇒ $(CF_3)_2N^-Cs^+ + CH_2=CHCH_2Br$ → yield: 44%, bp = 42 °C	62
$n-C_4F_9CH=CHC_4F_9-n$	• + Remains unaffected when heated at 130 °C with $Et_2NH$ or $Br_2$ for several weeks, by <i>m</i> -chloroperbenzoic acid	63
$R_{fn}C\equiv CH$ , $n = 4, 6$	⇒ $R_{fn}I + HC\equiv CC(CH_3)_2OH$ /electrocatal. → $R_{fn}CH=CIC(CH_3)_2OH$ → $R_{fn}C\equiv CC(CH_3)_2OH$ → overall yield: 55–60%	64
$C_8F_{17}C_6H_5$ , etc.	⇒ $C_8F_{17}I + C_6H_6/K_2CO_3$ , 2% Ru-C, 30 h, 170 °C → yield: 89%	65
$R_{f8}Ph$	⇒ $PhH + R_{f8}N=NR_{f8}/CF_2ClCFCl_2$ , $h\nu$ , 2 h → yield: 70%	66
$R_{fn}R$ , ( $R = Ar, Het$ )	⇒ $2R_{fn}I + ArH/\sim 250$ °C, 15 h → $R_{fn}Ar + R_{fn}H + I_2$ , yield: 60–65%	67
	⇒ $R_{fn}I + ArH + ^tBu_2O_2$ , $\sim 150$ °C, 8 h → $R_{fn}Ar$ , yield: 40–95%	67d
$R_{f8}C_6H_4CF_3$ ; $R_{f8}C_6H_3(CF_3)_2$ ( <i>o</i> -, <i>m</i> - and <i>p</i> -; and 1,3,5-isomers)	⇒ $R_{fn}I + ArI/Cu$ , DMSO/130–135 °C, 6 h → yield: 48–84%	68
$F_5S(CF_2)_6C_6H_5$	⇒ $F_5S(CF_2)_6I + C_6H_6$ (160–165 °C/14 d) → yield: 51% by GC	69
$R_{f8}CH_2CH_2Ph$	⇒ $PhMgCl + R_{f8}CH_2CH_2I/CuBr\cdot THF$ , 18 h, r.t. → yield: 89%	70
$R_{f10}CH_2CH_2Ph$	⇒ $PhB(OH)_2 + R_{f10}CH_2CH_2I/Pd(PPh_3)_4$ , $NaHCO_3$ , $H_2O-CH_3OCH_2CH_2OCH_3$ , 5 h → yield: 89%	71

Tab. 9.2-1 (continued)

Compound [C,F,H]	Remarks ("⇒" for synthesis of; "• + " for reaction of; etc.)	Ref.
$R_{fn}Ar$	⇒ $ArBr + R_{fn}I/Cu, DMSO \rightarrow$ good yields	72
$R_{fn}CH_2CH_2Ar$ via $R_{fn}CH=CHAr$	⇒ $ArX + CH_2=CHR_{fn}/Pd-cat \rightarrow ArCH=CHR_{fn};$ + $H_2/Pd-C \rightarrow$ overall yield: 70–90%	73
$(R_{fn}CH_2CH=CH)_xAr$ , $n = 6, 8, 10$ $(R_{fn}CH_2CH_2CH_2)_xAr$ ; $x = 1-3$	⇒ $[R_{fn}CH_2CH_2PPh_3]^+I^- + Ar(CHO)_x \rightarrow$ $(R_{fn}CH_2CH=CH)_xAr; + H_2/cat \rightarrow$ overall yield: 68–90%	74

Tab. 9.2-2. (Perfluoroalkyl)alkyl halides; perfluoroalkyl- and (perfluoroalkyl)alkyl aryl/benzyl halides

Compound [C,F,H,X]	Remarks ("⇒" for synthesis of; "• + " for reaction of; etc.)	Ref.
$R_{f3}CH_2I$	⇒ $R_{f3}CH_2OTs + KI/\text{diethylene glycol}, T > 190^\circ C \rightarrow$ yield: 84%	75
$R_{fn}CH_2CH_2I$	⇒ $R_{fn}I + CH_2=CH_2/290-390^\circ C$ for $n = 4, 6, 8, 10 \rightarrow$ yield: ~95%	76, 77
$R_{f6}CH_2CH_2CH_2I$	⇒ $R_{f6}(CH_2)_3OH + KI, P_2O_5/H_3PO_4 \rightarrow$ yield: 88% (72% conversion)	56
$R_{f8}CH_2CH_2CH_2I$	⇒ $R_{f8}(CH_2)_3OH + KI, P_2O_5/H_3PO_4; P_2O_5/SiO_2 \rightarrow$ yield: 70–85%	78
$R_{f8}CH_2CH_2CH_2CH_2I$	⇒ $R_{f8}(CH_2)_4OH + KI, P_2O_5/H_3PO_4 (120^\circ C/4 h) \rightarrow$ yield: 92%	79
$F_5S(CF_2CF_2)_3CH_2CH_2I$	⇒ $CH_2=CH_2 + F_5S(CF_2CF_2)_3I/tBu_2O_2 \rightarrow$ yield: 28%	80
$1,3,5-BrC_6H_3(R_{f8})_2$	⇒ $1,3,5-Br_3C_6H_3 + 2 R_{f8}I + 4 Cu/DMF, 120^\circ C, 18 h \rightarrow$ yield: 60%	81
$1,3,5-BrC_6H_3(R_{f10})_2$	⇒ $m-(R_{f10})_2C_6H_4 + NBS/H_2SO_4-CF_3CO_2H, 50^\circ C, 8 h \rightarrow$ yield: 94%	82
$1,2,4,6-IC_6H_2[(CH_2)_3R_{f8}]_3;$ $1,2,4-, 1,2,5-; 1,3,4-$ $IC_6H_3[(CH_2)_3R_{f8}]_2$	⇒ $C_6H_3(CH_2CH_2CH_2R_{f8})_3$ or $C_6H_4(CH_2CH_2CH_2R_{f8})_2 +$ $I_2/H_5IO_6$ in $AcOH, H_2SO_4/H_2O \rightarrow$ yields of respective iodoarenes: 61–97%	83
$3,5-(R_{f8})_2C_6H_3CH_2Br$	⇒ $3,5-(R_{f8})_2C_6H_3CH_2OH + PBr_3/THF \rightarrow$ yield: 62%	84

Tab. 9.2-3. Perfluoroalkylalkanols and ethers

Compound [C,F,H,O]	Remarks ("⇒" for synthesis of; "•+" for reaction of; etc.)	Ref.
$C_3F_7OCF(CF_3)CF_2OCF(CF_3)CH_2OH$	⇒ $C_3F_7OCF(CF_3)CF_2OCF(CF_3)CO_2CH_3 + NaBH_4/\text{ether} \rightarrow (81\%)$	85
$(CF_3)_3CCH_2OH$	⇒ $(CF_3)_3CH + CH_2O/Et_3N, 100\text{ }^\circ\text{C}, 55\text{ h} \rightarrow \text{no yield data given}$	86
$R_{fn}CH_2CH_2CH_2OH, n = 6, 8, 10$	⇒ One pot synthesis from $R_{fn}I$ and triallyl borate, yield: 74–79%	87
$(C_6F_{13}CH_2CH_2)_2C(CH_2OH)_2$	⇒ Preparation of and use for acetalization	88
$(R_{f8}CH_2CH_2)_2CHOH$	⇒ $C_8F_{17}CH_2CH_2I + Mg/\text{ultrasound}; + HCO_2Et \rightarrow \text{yield: } 93\%$	89
$R_{f8}CH_2CH_2C(CH_3)_2OH$ $[R_{f6}(CH_2)_n]_2C(CH_3)OH, n = 2, 3$	⇒ $R_f(CH_2)_nMgX + Me_2CO$ or $EtOAc \rightarrow \text{yield: } 60\text{--}79\%$ ; used for the synthesis of $^F\text{Boc-transfer reagents}$	90
$R_{f6}CH_2CH_2C(CH_3)_2OH,$ $[R_{fn}(CH_2)_2]_2C(CH_3)OH, n = 6, 8$	⇒ Conveniently prepared by the reaction of appropriate Grignard reagents with acetone and ethyl acetate, respectively	91
$R_{f6}CH_2CH_2C(CH_3)_2OH$	⇒ $R_{f6}I + CH_2=CHC(CH_3)_2OH/Cu, 120\text{ }^\circ\text{C} \rightarrow R_{f6}CH_2CH(I)C(CH_3)_2OH (83\%); + Bu_3SnH \rightarrow \text{yield: } 67\%$	92
$R_{fn}CH_2CH_2C(CH_3)_2OH, n = 4, 6, 8$	⇒ $R_{fn}CH=CH_2 + (CH_3)_2CHOH/\text{acetone}, h\nu, \text{r.t.}, 3\text{ d} \rightarrow \text{yield: } 91\%$	93
$(R_{f6}CH_2CH_2)_3COH$	⇒ $C_6F_{17}CH_2CH_2I + Mg/\text{ether}; + CH_3OC(O)OCH_3 \rightarrow \text{yield: } 40\%$	94
$3,5\text{--}(C_8F_{17})_2C_6H_3CH_2OH$	⇒ $3,5\text{--}(R_{f8})_2C_6H_3CO_2CH_3 + LiAlH_4/Et_2O, 5\text{ h reflux} \rightarrow \text{yield: } 90\%$	68
$C_8F_{17}-\begin{array}{c} Si(CH_3)_3 \\   \\ CH_3 \end{array}-OH$	⇒ $CH_3COSi(CH_3)_3 + C_8F_{17}I/C_2H_5MgBr, -45\text{ }^\circ\text{C to r.t.} \rightarrow \text{yield: } 45\%, \text{mp} = 29\text{ }^\circ\text{C}$	95
$R_{f6}CH_2CH_2OCH(CH_3)CH_2CH(CH_3)_2$	⇒ • + A new fluorous/organic amphiphilic ether solvent	96
$(CF_3)_3CCH_2OCH_2C(CF_3)_3$	⇒ $(CF_3)_2C=CF_2/CsF + (ClCH_2)_2O \rightarrow \text{yield: } 71\%, \text{bp} = 156\text{--}157\text{ }^\circ\text{C}$	97
$(CF_3)_3CCH_2OCH_3$	⇒ $(CF_3)_2C=CF_2 + ClCH_2OCH_3/CsF, \text{diglyme}, 70\text{ }^\circ\text{C} \rightarrow \text{yield: } 90\%$ • + $SO_3/H_2SO_4; \text{r.t.}, 1\text{ h} \rightarrow (CF_3)_3CCH_2OH, \text{yield: } 45\%$	98
$(CF_3)_3COCH_3, (CF_3)_3COC_2H_5$	⇒ $(CF_3)_3CONa + R_2SO_4/\text{tetraglyme} \rightarrow \text{yield: } \sim 95\%$	99
$R_{fn}CH_2CH(-O-)CH_2, n = 4, 6, 8$	⇒ (a) $R_{fn}I + CH_2=CHCH_2OAc \rightarrow R_{fn}CH_2CH(I)CH_2OAc + R_{fn}CH_2CH(OAc)CH_2I;$ (b) + $KOH/\text{hexane} \rightarrow \text{yield: } 94\text{--}96\%$	100



Tab. 9.2-4. Fluorous mercaptanes, sulfides, sulfoxides, sulfonates, sulfonimides and selenides

Compound [C,F,H,S/Se(O)]	Remarks ("⇒" for synthesis of; "• + " for reaction of; etc.)	Ref.
$R_{fn}CH_2SH$ , $n = 2, 3$	⇒ $R_{fn}COX$ ( $X = H, Cl$ ) + $H_2S$ , 200 °C, 3000 atm → yield: 39–54%	101
$R_{f6}CH_2CH_2SH$	⇒ $R_{f6}(CH_2)_2I + H_2NCSNH_2$ /dioxane → yield: 94%, unlike alcohol type solvents no foul-smelling byproducts are formed in dioxane!	102
$R_{f8}CH_2CH_2CH_2SH$	• + $(C_8H_{17})_4NAuCl_4/CF_3Ph + NaBH_4/H_2O$ → $(Au_x)[HS(CH_2)_3R_{f8}]_y$ Example for an isolable and fluorous soluble gold nanocluster	103
$F_5S(CF_2)_6CH_2CH_2SH$	⇒ $F_5S(CF_2)_6(CH_2)_2I + NaH/AcSH-THF$ → $F_5S(CF_2)_6(CH_2)_2SAC$ ; + $LiAlH_4/THF$ → overall yield: 90%	104
$R_{f7}SCH_3$	⇒ $R_{f7}C(O)SCH_3/CH_3CN$ , $h\nu/(-CO)$ → yield: 81%	105
$R_{f8}CH_2CH_2SCH_3$	⇒ $R_{f8}CH_2CH_2SCoCH_3 + NaOCH_3$ ; $CH_3I$ → yield: 94%	106
$R_{fn}SCH_2CH_2OH$ ; $n = 4, 6$	⇒ $HO(CH_2)_2SH + R_{fn}I/Na_2SO_3$ , $HCO_2Na$ , $DMF-H_2O$ , r.t. → yield: 64–71%	107
$[R_{f8}(CH_2)_n]_2S$ , $n = 2, 3$	⇒ $R_{f8}(CH_2)_nI + Li_2S/THF$ → yields: 67–71%	108
$ArSR_{fn}$ , $n = 3$	⇒ $ArSH + R_{fn}I + NaOH$ , $PhCH_2NEt_3Cl$ → yield: 83%	109
$ArSR_{fn}$ , e.g.: $Ar = p-CH_3C_6H_4$ , $n = 6$	⇒ (a) $ArSH + N(C_2H_5)_3 + R_{f6}Br/DMF$ , $h\nu$ → yield: 52%; ⇒ (b) $ArSK + R_{f6}Br/DMF \sim 3$ atm → yield: 77%	110, 111
$R_{f8}(CH_2)_nS(O)(CH_2)_nR_{f8}$ , $n = 2, 3$	⇒ $[R_{f8}(CH_2)_n]_2S + CH_3CO_3H$ → yield: 80–85%	108
$R_{fn}CH_2CH_2S(O)CH_3$ , $n = 4, 6$	⇒ $(CH_3)_2S_2/NaBH_4 + R_{fn}(CH_2)_2I$ → $R_{fn}(CH_2)_2SCH_3$ ; + $H_2O_2/CH_3OH$ → overall yield: 71%	112
$R_{f7}CH_2OSO_2CF_3$	⇒ $R_{f7}CH_2OH + (CF_3SO_2)_2O/py$ , $CH_2Cl_2$ → yield: 92%	113
$R_{f7}CH_2OSO_2C_4F_9$	⇒ $R_{f7}CH_2OH + R_{f4}SO_2F/TEA$ , ether → yield: 95%	114
$R_{f8}CH_2CH_2CH_2OTs$	⇒ $R_{f8}CH_2CH_2CH_2OH + TsCl/CH_2Cl_2-aq.NaOH$ → yield: 70%	115
$(R_{fn}SO_2)_2NH$ , $n = 2, 4, 8$	⇒ Products were obtained after high-vacuum sublimation or short-path distillation from conc. $H_2SO_4$	116
$2,4-(R_{f8})_2C_6H_3SeC_4H_9$	⇒ $2,4-I_2C_6H_3NH_2 + R_{f8}I/Cu$ , $DMSO$ , 120 °C → $2,4-(R_{f8})_2C_6H_3NH_2$ ; + $NaNO_2$ , $HBr$ , $CuBr$ → $2,4-(R_{f8})_2C_6H_3Br$ ; + $C_4H_9SeLi/THF$ , –80 to –25 °C → $2,4-(R_{f8})_2C_6H_3SeC_4H_9$ , overall yield: 36%	117
$3,5-(R_{f8})_2C_6H_3SeC_4H_9$	⇒ Prepared by multiple step synthesis from $3,5-I_2C_6H_3NH_2$ and used as a catalyst in Bayer-Villiger oxidation	118

Tab. 9.2-5. Fluororous amines, anilines, pyridines; phosphines and phosphites

Compound [C,F,H,N/P(O)]	Remarks ("⇒" for synthesis of; "•+" for reaction of; etc.)	Ref.
$R_{f7}CH_2NH_2$ , $(R_{f7}CH_2)_2NH$	⇒ Precursors of tetrasubstituted ureas, thermally stable fluids, recoverable in 99% after a 63 h at 270 °C test	119
$(R_{f9}CH_2)_2NH$	⇒ $(R_{f9}CO)_2NH + LiAlH_4 \rightarrow$ no yield data reported, mp = 85–86 °C	120
$[(CF_3)_3C]_2NH$	⇒ multistep synthesis/bp = 100–101 °C/	121
$R_{f7}CH_2N(CH_3)_2$	⇒ $R_{f7}CSN(CH_3)_2 + BH_3/diglyme \rightarrow$ yield: 59%, GC purity: 99%	122
$(CF_2)_4NCH_2CF_2CF_3$	⇒ $CF_2CF_2CF_2CF=N + KF + CF_3CF_2CH_2OSO_2CF_3 \rightarrow$ yield: 71%	123
$CF_3CF_2(CF_3)NCH_3$	⇒ $CF_3CF=NCF_3 + CsF + (CH_3)_2SO_4/CH_3CN \rightarrow$ yield: 46%	124
$[(CF_3)_3CCH_2]_3N$	⇒ $(CF_3)_2C=CF_2 + CsF + (ClCH_2)_3N/diglyme \rightarrow$ yield: 32%	97
$R_{fn}CH_2CH_2NH_2$ , $n = 2, 4, 6, 8$	⇒ $R_{fn}CH_2CH_2I + NaN_3 \rightarrow R_{fn}CH_2CH_2N_3$ ; $H_2/Pt \rightarrow$	125
$NH_{3-x}[(CH_2)_mR_{f8}]_x$ , $m = 3-5$ , $x = 1, 2$ $N[(CH_2)_mR_{f8}]_3 = N(R_{fh})_3$	⇒ $R_{f8}(CH_2)_{m-1}CHO + NH(R_{fh})_2$ or $H_2NCH_2Ph/Na(AcO)_3BH \rightarrow N(R_{fh})_3$ or $NH_{2-x}(CH_2Ph)[(CH_2)_mR_{f8}]_x + H_2/Pd-C \rightarrow$ 78–91%	126
$[(R_{f6}CH_2CH_2)_3SiCH_2CH_2CH_2]_2NH$	⇒ $[(R_{f6}CH_2CH_2)_3SiCH_2CH_2CH_2]_2NCOCF_3 + LiAlH_4/ether \rightarrow$ yield: 97% • + RNCO $\rightarrow$ fluororous soluble ureas, easy to remove by extraction	127
$(R_{f8}CH_2CH_2CH_2)_2NCH_3$	⇒ $R_{f8}(CH_2)_3NH(CH_3) + R_{f8}(CH_2)_3I/THF$ , 60 °C, 24 h $\rightarrow$ yield: 84%	128
$[(R_{f8}CH_2CH_2CH_2)_3NCH_3]^+CH_3OSO_3^- = R_f^+CH_3OSO_3^-$	⇒ • + $Na_{12}[(WZnM_2(H_2O)_2)(ZnW_9O_{34})_2] \rightarrow$ fluororous soluble salts of polyoxometalates: e.g. $(R_f^+)_{12}[WZn_3(H_2O)_2](ZnW_9O_{34})_2]^{12-}$	129
2,4,6- $(R_{f8})_3C_6H_2NH_2$ , 4,2,6- $(CF_3)(R_{f8})_2C_6H_2NH_2$ , 4,2,6- $(Me_3C)(R_{f8})_2C_6H_2NH_2$ 2,6- and 3,5- $(C_8F_{17}CH_2CH_2)_2C_5H_3N$	⇒ $C_6H_5N(CH_3)_2$ , 4- $CF_3C_6H_4NH_2$ or $Me_3CC_6H_4NH_2 + R_{f8}I/Cu_2O$ , DMSO, 130 °C, 1 to 3 d $\rightarrow$ yield: 45, 65, and 27%, resp.	130
$s-[R_{f8}(CH_2)_2]_3py$ , 2,6- $[R_{f8}(CH_2)_3]_2py$	⇒ $C_8F_{17}CH_2CH_2ZnI/THF + Br_2py/Cl_2Pd(PPh_3)_3 \rightarrow$ yield: 31–85%	131
2,6- $(R_{f6})_2py$	⇒ $py(CHO)_x \rightarrow (R_{f8}CH_2CH=CH)_xpy$ ; + $H_2/Pd-C \rightarrow$ yield: 93%	
$P[(CH_2)_\gamma R_{fn}]_3$ , $\gamma = 2$ , $n = 6, 8, 10$ ; $\gamma = 3, 4$ , $n = 8$	⇒ 2,6- $Br_2py + C_6F_{13}I/Cu$ , DMSO, 125 °C $\rightarrow$ yield: 89%	132
$R_{f8}(CH_2)_mPH_2$ ; $R_{f8}(CH_2)_mP[(CH_2)_{m'}R_{f8}]_2$	⇒ $PH_3 + CH_2=CH(CH_2)_{\gamma-2}R_{fn}/AIBN$ or VAZO $\rightarrow$ yield: 63–81%	133, 134
	⇒ $LiPH_2 + R_{f8}(CH_2)_mI \rightarrow R_{f8}(CH_2)_mPH_2$ ; + $R_{f8}(CH_2)_{m'-2}CH=CH_2/AIBN$ or VAZO $\rightarrow$ good yields: $m = 2-4$ , $m/m' = 3/2, 2/3, 4/3, 3/4$	79
$(R_{f8}CH_2CH_2O)_3P$	⇒ $R_{f8}CH_2CH_2OH + PCl_3/py-ether \rightarrow$ yield: 55%	133

Tab. 9.2-6. Fluorous boron-, silicon-, tin-, lithium-, zinc-, and magnesium compounds

Compound [C,F,H,B/Si/Sn/Metal]	Remarks ("⇒" for synthesis of; "• + " for reaction of; etc.)	Ref.
$(R_{f10})_2C_6H_3B(OH)_2$	⇒ Multistep synthesis: $1,3-C_6H_4I_2 \rightarrow 1,3-C_6H_4(R_{f10})_2 \rightarrow 1,3,5-BrC_6H_3(R_{f10})_2 \rightarrow 1,3,5-(RO)_2BC_6H_3(R_{f10})_2 \rightarrow$ overall yield: 35–40%	82
$NaB[C_6H_4(SiMe_2CH_2CH_2C_6F_{13})\cdot p]_4$	⇒ $ArBr + {}^tBuLi/ether, -78\text{ }^\circ C \rightarrow ArLi/ether;$	135
$NaB[C_6H_4C_6F_{13}\cdot p]_4$	+ $BF_3\cdot O(C_2H_5)_2; \rightarrow LiB[Ar]_4/ether; + NaCl-H_2O \rightarrow$ overall yield: 70–80%	136
$NaB[C_6H_3(C_6F_{13})_2\cdot 3,5]_4$	⇒ Multistep procedure starting from $1,3-C_6H_4I_2$ and $C_6F_{13}I$	137
$(R_{f6}CH_2CH_2)_3SiH$	• + $(CH_2=CHCH_2)_2NCOCF_3/H_2PtCl_6, 80\text{ }^\circ C, 12\text{ h} \rightarrow [(R_{f6}CH_2CH_2)_3SiCH_2CH_2CH_2]_2NCOCF_3$ , yield: 33–37%	127
$R_{fn}Si(CH_3)_3, n = 1-3$	⇒ $(CH_3)_3SiCl + R_{fn}Br/PhCN; + [(C_2H_5)_2N]_3P/PhCN \rightarrow$	138
$(R_{f6}CH_2CH_2)_3SiCH_2CH=CH_2$	• + Useful perfluoroalkyl-anion transfer reagents	139
$p-(R_{f6}CH_2CH_2)_3SiC_6H_4CH_2Br$	⇒ $(R_{f6}CH_2CH_2)_3SiBr + CH_2CH=CH_2MgBr \rightarrow$ yield: 98%	140
$p-(R_{f6}CH_2CH_2)_3SiC_6H_4CH_2Br$	⇒ $[R_{f6}(CH_2)_2]_3SiBr + p-TolMgBr \rightarrow [R_{f6}(CH_2)_2]_3SiTol-p$ (84%); + $Br_2 \rightarrow$ no yield data reported	141
$(R_{f10}CH_2CH_2)_3SiC_6H_4CO_2H$	⇒ Multistep synthesis from $R_{f10}CH_2CH_2I$ and $HSiCl_3$	142
$R_{fn}(CH_2)_2Si(i-Pr)_2Br, n = 6, 8$	⇒ $R_{fn}(CH_2)_2Si({}^iPr)_2H + Br_2/FC-72 \rightarrow$ • Used up immediately	143
$(R_{fn}CH_2CH_2)_{3-x}Si(CH_3)_xBr, n = 6, 8; x = 0, 1, 2$	⇒ $R_{fn}(CH_2)_2I + Mg/ether \rightarrow R_{fn}(CH_2)_2MgI;$ + $HSi(CH_3)_{2-x}Cl_{x+1} \rightarrow (R_{fn}CH_2CH_2)_{3-x}Si(CH_3)_xH;$ + $Br_2/hexane \rightarrow$ product	144
$R_{f10}CH_2CH_2Si(CH_3)_2Cl$	⇒ $R_{f10}CH=CH_2 + HSi(CH_3)_2Cl/RhCl(PPh_3)_3 \rightarrow$ yield: 85%	145
$R_{f3}C(CF_3)_2CH_2CH_2CH_2SiMe_2Cl$	⇒ $R_{f3}C(CF_3)_2CH_2CH=CH_2 + HSiMe_2Cl/H_2PtCl_6/$ heating $\rightarrow$ 81%	146
$[R_{f8}CH_2CH_2Si(CH_3)_2]_2O$	⇒ $R_{f8}I + [CH_2=CH_2Si(CH_3)_2]_2O/AIBN \rightarrow [R_{f8}CH_2CH_2Si(CH_3)_2]_2O; + Bu_3SnH, 80\text{ }^\circ C, 2\text{ h} \rightarrow$ overall yield: 65%	147
$SiO_2(-O)_3Si(CH_2)_3NHC(O)CF(CF_3)\cdot OCF_2CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	⇒ <i>Silica</i> - $(-O)_3Si(CH_2)_3NH_2 + R_fOR_fC(O)F \rightarrow$	148
$[R_{f6}(CH_2)_3]_3SnCH_2CH=CH_2$	• + Useful fluorous allyl-transfer reagent	149
$4-RC_6H_4Sn[(CH_2)_2R_{f6}]_3$	⇒ • + $ArOSO_2CF_3/DMF-THF, PdCl_2(PPh_3)_2, LiCl \rightarrow 4-RC_6H_4Ar$	150
$(R_{f6}CH_2CH_2)_3SnR, R = Ph, Br, H$	⇒ $Cl_3SnPh + R_{f6}CH_2CH_2MgI \rightarrow (R_{f6}CH_2CH_2)_3SnPh;$ + $Br_2 \rightarrow (R_{f6}CH_2CH_2)_3SnBr; + LiAlH_4 \rightarrow$ overall yield: 65%	151
$(R_{f6}CH_2CH_2)_3SnN_3$	⇒ $(R_{f6}CH_2CH_2)_3SnBr + NaN_3, ether-H_2O, 25\text{ }^\circ C \rightarrow$ yield: 97%	152
$Sn[N(SO_2C_8F_{17})_2]_4$	• + Catalyst for Bayer-Villiger oxidation	153
$R_{fn}CH_2CH_2Li/Et_2O, n = 6, 8$	⇒ $R_{fn}(CH_2)_2I/{}^tBuLi, ether; + HSi({}^iPr)_2Cl \rightarrow R_{fn}(CH_2)_2Si({}^iPr)_2H$	143
$R_{f8}CH_2CH_2ZnI/THF$	⇒ $R_{fn}CH_2CH_2I + Zn/THF, BrCH_2CH_2Br, (CH_3)_3CCl \rightarrow$ yield: >70%	131
$R_{f6}CH_2CH_2MgI$	• Precursor for the synthesis of the first fluorous tin hydride/azide: $\{(R_{f6}CH_2CH_2)SnX, X = H, N_3\}$ applied in "Fluorous Synthesis"	151, 154

Tab. 9.2-7. Fluorous aldehydes and ketones

Compound [C,F,H,O]	Remarks ("⇒" for synthesis of; "•+" for reaction of; etc.)	Ref.
C <sub>8</sub> F <sub>17</sub> CHO	⇒ C <sub>8</sub> F <sub>17</sub> I + (CH <sub>3</sub> ) <sub>2</sub> NCHO/Al-PbBr <sub>2</sub> , r.t. → yield: 95%	155
R <sub>fn</sub> CHO, n = 1, 2, 3, 7	⇒ R <sub>fn</sub> CO <sub>2</sub> R + LiAlH <sub>4</sub> /ether, -78 °C, "inverse addition" → 70–76%	156
R <sub>fn</sub> CH <sub>2</sub> CHO	⇒ R <sub>fn</sub> I + CH <sub>2</sub> =CHOAc/AIBN, 4 h, 80 °C → R <sub>fn</sub> CH <sub>2</sub> CHIOAc; + CH <sub>2</sub> =CHCO <sub>2</sub> H/C <sub>2</sub> H <sub>2</sub> Cl <sub>4</sub> , reflux, 12 h → aldehyde yield: 85%	157
R <sub>f6</sub> CH(CH <sub>3</sub> )CHO	⇒ R <sub>f6</sub> CH=CH <sub>2</sub> + CO/H <sub>2</sub> -cat → 78% ee at 21% conversion; cat: a polymer supported (R,S)-BINAPHOS-Rh(I) complex	158
C <sub>n</sub> F <sub>2n+1</sub> (CH <sub>2</sub> ) <sub>m</sub> CHO, m = 1–4	⇒ Oxidation of C <sub>n</sub> F <sub>2n+1</sub> (CH <sub>2</sub> ) <sub>m</sub> CH <sub>2</sub> OH by (a), (b) or (c) methods: (a) Swern, (b) PyH <sup>+</sup> CrO <sub>3</sub> Cl <sup>-</sup> , (c) Dess-Martin periodinane	159, 126
3,5-(C <sub>8</sub> F <sub>17</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CHO	⇒ 3,5-(R <sub>f8</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CH <sub>2</sub> OH + PyH <sup>+</sup> CrO <sub>3</sub> Cl <sup>-</sup> /CH <sub>2</sub> Cl <sub>2</sub> → yield: 85%	68
R <sub>fn</sub> COCH <sub>3</sub> , R <sub>fn</sub> COCH <sub>2</sub> COR <sub>fm</sub>	⇒ R <sub>fn</sub> CO <sub>2</sub> H + CH <sub>3</sub> MgBr → R <sub>fn</sub> COCH <sub>3</sub> ; + R <sub>fm</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> , NaOC <sub>2</sub> H <sub>5</sub> → good overall yields: (a) n = m = 6, (b) n, m = 6, 1; n = m = 6, 7	160
R <sub>f8</sub> CH <sub>2</sub> CH <sub>2</sub> COCF <sub>3</sub>	⇒ R <sub>f8</sub> CH <sub>2</sub> CH <sub>2</sub> I + Mg/ether, CF <sub>3</sub> CO <sub>2</sub> CH <sub>3</sub> → yield: 32%	161
F[CF(CF <sub>3</sub> )CF <sub>2</sub> O] <sub>n</sub> CF(CF <sub>3</sub> )–COCH <sub>2</sub> COCH <sub>3</sub> , n = 1–4	⇒ F[CF(CF <sub>3</sub> )CF <sub>2</sub> O] <sub>n</sub> CF(CF <sub>3</sub> )CO <sub>2</sub> CH <sub>3</sub> + CH <sub>3</sub> COCH <sub>3</sub> /NaH → no yield data reported	162

Tab. 9.2-8. Fluorous carboxylic acids

Compound [C,F,H,O]	Remarks ("⇒" for synthesis of; "• + " for reaction of; etc.)	Ref.
$R_{fn}CO_2H$	⇒ $R_{fn}CF_2I + XSO_3H$ ( $X = Cl, F$ ) → $R_{fn}CF_2OSO_2X$ ; + $H_2O$ → overall yield: >70%	163
$R_{fn}CO_2H$ , $n = 2, 3, 5, 6, 7, 11$	⇒ $R_{fn+1}I(Br) + \text{Rongalite-NaHCO}_3/\text{DMF-H}_2\text{O}$ → yield: 51–86%	164
$C_nF_{2n+1}CO_2H$ , $n = 4, 6, 8$	⇒ $C_nF_{2n+1}I + Zn-Cu/CO_2, (CH_3O)_3PO, -20\text{ }^\circ\text{C}$ → yield: 91%	165
$(CF_3)_2CFOCF(CF_3)CO_2H$ (+)- and (–)-PIPA	⇒ (+)-PIPA and (–)-PIPA have been prepared from $CF_3COCF_3$ and $CF_3CFCF_2O$ precursors by a multistep synthesis	166
$C_6F_{13}CH_2CO_2H$	⇒ $R_{f6}(CH_2)_2OH + CrO_3/H_2SO_4, \text{acetone-ether}$ → yield: 98% • + $Rh_2(OAc)_4/\text{toluene}, 110\text{ }^\circ\text{C}$ (–4 AcOH) → $(R_{f6}CH_2CO_2)_4Rh_2$	167, 168
$(CF_3)_3COCH_2CO_2H$	⇒ $(CF_3)_2CCF_2O + HF$ → $(CF_3)_3COH$ ; + $ClCH_2CO_2R$ → No yield data in Chem. Abstr.	169
$R_{fn}(CH_2)_mOCH_2CO_2H$ , $n/m = 7/1, 8/2, 10/2$	⇒ $R_{fn}(CH_2)_mOH + BrCH_2CO_2H/NaH, THF, \text{r.t.}$ → yield: 70–96% • + $BH_3/THF, 0\text{ }^\circ\text{C}$ to r.t. → $R_{fn}(CH_2)_mO(CH_2)_2OH$ , yield: 79–96%	170
$R_{fn}CH_2CH_2CO_2H$ , $n = 6, 8, 10$	⇒ $R_{fn}CH_2CH_2I + Mg/\text{ether}$ → $R_{fn}CH_2CH_2MgI$ ; + $CO_2$ → No yield data in Chem. Abstr. ⇒ $R_{f6}(CH_2)_3OH + NaIO_4, \text{cat-RuCl}_3$ → yield: 64% • + $SOCl_2$ → $R_{f6}(CH_2)_2COCl$ ; + ferrocene/ $AlCl_3$ → $-(R_{f-acyl})_{1,2}Fc$	171
$(C_8F_{17}CH_2CH_2CH_2)_2CHCO_2H$	⇒ $R_{f8}(CH_2)_3I + CH_2(CO_2C_2H_5)_2 \rightarrow \rightarrow \rightarrow$ overall yield: 58%	172
$C_8F_{17}CH_2CH_2CON(CH_2CH_2CH_2-C_8F_{17})CH_2CH_2CO_2H$	⇒ Used as a protective group for oligosaccharide synthesis • Precursor for new fluorous supports for peptide synthesis	173
$3,4,5-[C_8F_{17}(CH_2)_4O]_3C_6H_2CO_2H$	⇒ Preparation and use for Mitsunobu-inversion of chiral <i>sec</i> -alcohols	174

Tab. 9.2-9. Fluororous esters and carbonic acid derivatives

Compound [C,F,H,O]	Remarks ("⇒" for synthesis of; "• + " for reaction of; etc.)	Ref.
$R_{fn}CO_2C_2H_5$ , $n = 4, 6, 8$	$\Rightarrow R_{fn}I + ClCO_2C_2H_5 + (C_2H_5O)_2CO + Zn-Cu \rightarrow$ yield: 50–70%	175
$Br(CF_2)_6CO_2C_2H_5$	$\Rightarrow Br(CF_2)_6CCl_3 + SO_3/H_2SO_4 + C_2H_5OH \rightarrow$ yield: 67%	176
$C_3F_7OCF(CF_3)CF_2OCF(CF_3)CO_2CH_3$	$\Rightarrow C_3F_7OCF(CF_3)CF_2OCF(CF_3)COF + CH_3OH/Na_2CO_3$ , MgSO <sub>4</sub> , silica gel $\rightarrow$ yield: 86%	85
$R_{f8}CH_2CH_2CH(CO_2CH_3)_2$	$\Rightarrow R_{f8}CH_2CH_2I + CH_2(CO_2CH_3)_2/NaH$ or $K_2CO_3$ in THF $\rightarrow$ high yields (~85%) with negligible elimination and dialkylation	177
$R_{f8}(CH_2)_nCO_2CH_2CF_3$ , $n = 1, 2$	$\Rightarrow R_{f8}CH_2CH_2OH \rightarrow \sim CH_2OTs \rightarrow \sim CH_2Br \rightarrow$ $\sim CH_2MgBr \rightarrow \sim CH_2CO_2H \rightarrow \sim CH_2COCl \rightarrow$ title ester, overall yield: 55%	178
$(CF_3)_3CCO_2C_2H_5$	$\Rightarrow (CF_3)_2C=CF_2/CsF + ClC(O)OC_2H_5 \rightarrow$ yield: 76%, bp = 106 °C	179
$4-R_{f8}CH_2CH_2C_6H_4CO_2CH_3$	$\Rightarrow 4-BrC_6H_4CO_2CH_3 + R_{f8}CH=CH_2/Pd-cat$ , NaOAc, DMF, 125 °C, 14 h, $\rightarrow R_{f8}CH=CH_2C_6H_4CO_2CH_3$ (72%); $+ H_2/Pd-C \rightarrow$ (88%)	180
$(CF_3)_3CCH_2CH_2CO_2CH_3$	$\Rightarrow (CF_3)_3CH + CH_2=CHCO_2CH_3/(C_2H_5)_3N \rightarrow$ yield: 30%	181
$3,5-(C_8F_{17})_2C_6H_3CO_2CH_3$	$\Rightarrow R_{f8}I + 3,5-Br_2C_6H_3CO_2CH_3 + Cu/DMSO$ , 135 °C $\rightarrow$ yield: 79%	68
$R_{f6}CH_2CH_2OCOCl$	$\Rightarrow R_{fn}CH_2CH_2OH + COCl_2/toluene$ , reflux 24 h $\rightarrow$ yield: ~95%	182
$(CF_3)_3COCOCl$	$\Rightarrow (CF_3)_3COK + COCl_2/mesitylene \rightarrow$ yield: 54%	183
$R_{f7}CH_2NCO$	$\Rightarrow R_{f7}CH_2NH_2 + COCl_2 \rightarrow$ yield: 78%, bp = 166–168 °C	42
$R_{f9}CH_2NCO$	$\Rightarrow R_{f9}CH_2NH_2 + COCl_2/dioxane \rightarrow$ mp = 46–47 °C	184
$(C_7F_{15}CH_2)_2NCOCl$	$\Rightarrow (C_7F_{15}CH_2)_2NH + excess COCl_2/autogenous$ pressure, 140 °C, 14 h $\rightarrow$ yield: 100%, mp = 22 °C, bp = 70 °C/0.1 mmHg	119
$R_{fn}CH_2CH_2N=C=NCH_2CH_2R_{fn}$ , $n = 4, 6, 8$	$\Rightarrow R_{fn}(CH_2)_2N_3 + PPh_3/THF$ , < r.t. $\rightarrow$ $R_{fn}(CH_2)_2N=PPh_3$ ; $+ CS_2 \rightarrow$ $\Rightarrow [R_{fn}(CH_2)_2NH]_2CO + Ph_3PBr_2 + N(C_2H_5)_3$ in $CH_2Cl_2/C_6F_{14} \rightarrow$	185, 186
$R_{fn}(CH_2)_mO_2CNHNNHCO_2(CH_2)_mR_{fn}$ $n/m = 3/1, 4/2, 6/2, 6/3$	• $+ NBS$ or $Br_2/py$ , $CH_2Cl_2 \rightarrow$ $R_{fn}(CH_2)_mO_2CN=NCO_2(CH_2)_mR_{fn}$ ; yield: 79–100%; used for fluororous Mitsunobu reaction	182, 187

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## 10

# Highlights of Applications in Synthesis and Catalysis

### 10.1

#### Synthetic Applications of Fluorous Reagents

*Sivaraman Dandapani*

#### 10.1.1

##### Introduction

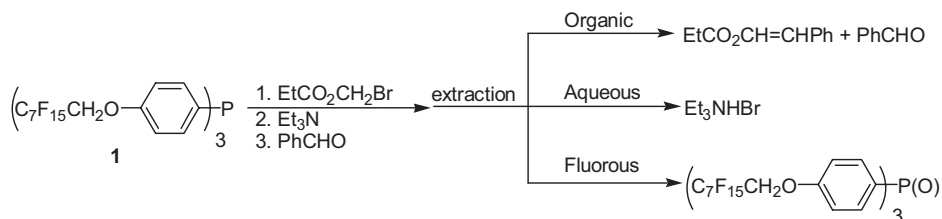
The widespread practice of combinatorial chemistry has raised new challenges for synthetic organic chemists. There is a need to synthesize a large number of compounds with high purity in a short time. In many cases separation of the desired product from the crude reaction mixture is the rate limiting process. Solid phase organic synthesis came along to rescue the separation problems. In polymer supported solid phase organic synthesis, a tedious chromatographic separation is replaced with a simple filtration. However, the time saved in separation comes with a price tag – longer reaction time due to heterogeneity of the reaction medium. Also, it is hard to use regular analytical methods for characterizing polymer bound intermediates or monitoring the progress of reactions. Use of a fluorous phase in synthetic organic chemistry has provided a pathway to carry out easy separation without sacrificing time at the reaction stage [1]. This section will focus on several families of fluorous reagents including fluorous phosphines, fluorous tin reagents, fluorous iodo arenes, fluorous selenides and fluorous carbodiimides.

#### 10.1.2

##### Fluorous Phosphines

Phosphines are popular ligands in organometallic chemistry and prevalent reagents in organic synthesis. The pioneering work of Horváth with fluorous trialkyl phosphines as ligands in hydroformylation reactions marked the beginning of Fluorous Biphasic Catalysis (FBC) [2]. Subsequently a wide assortment of phosphine ligands have been successfully employed as ligands in a number of different chemical transformations under FBC conditions. These developments have been reviewed in other chapters of this book [3] and elsewhere [4]. The utility of fluorous phosphines as reagents in organic reactions will be discussed here [5].

Sinou and coworkers have used a heavy fluorous phosphine for carrying out Wittig reactions with stabilized ylides [6]. Fluorous phosphine **1** was treated with ethyl bromoace-



**Scheme 10.1-1.** Heavy fluoros Wittig reactions

tate to form the corresponding fluoros phosphonium salt (Scheme 10.1-1). The salt was deprotonated with triethylamine to form the ylide, which was reacted with benzaldehyde to form the alkene. The crude reaction mixture was subjected to a liquid/liquid/liquid extraction with a fluoros solvent (D-100 containing mainly perfluorooctane), organic solvent (ether) and water. The desired organic product, i.e., the alkene (along with unreacted benzaldehyde), triethyl ammonium bromide and fluoros phosphine oxide partitioned into the organic, aqueous and fluoros layers respectively. Fluoros phosphine oxide recovered from the fluoros layer was reduced to fluoros phosphine **1** using trichlorosilane. Ten different Wittig reactions were carried out with this protocol and in all the cases pure alkene was isolated directly after liquid-liquid-liquid extraction.

Fluoros phosphines have also been employed in Staudinger reactions by groups working with Bannwarth [7] and Lindsley [8]. Both of these groups used fluoros solid phase extraction (FSPE) to purify the crude reaction mixture.

### 10.1.3

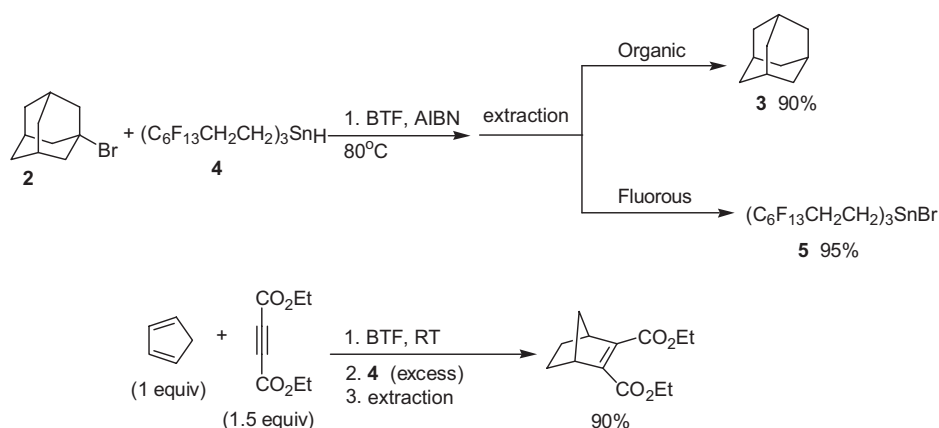
#### Fluoros Tin Reagents

Tin reagents bring about vital transformations in organic chemistry and they continue to be central to the discipline of organic synthesis [9]. Trialkyltin reagents are very popular in reductive radical chemistry in spite of the accompanying problems of separation, toxicity and disposal of tin byproducts. These problems are reduced to a significant extent with tin hydrides by employing a catalytic procedure [10]. Purification problems associated with tin hydride chemistry have been addressed by traditional strategies [11] and by the introduction of fluoros tin hydrides [12]. In addition to fluoros tin hydrides, fluoros tin azides [13], fluoros tin oxides [14], fluoros allyl tin reagents [15] and Stille reactions with fluoros aryl tin compounds [16] have also been developed (Table 10.1-1).

The reduction of adamantyl bromide by fluoros tin hydride is illustrated here in Scheme 10.1-2. Initial attempts to reduce adamantyl bromide **2** to adamantane **3** using fluoros tin hydride **4** and AIBN in typical organic solvents (such as benzene, toluene and *tert*-butyl alcohol) or a fluoros solvent (perfluoromethylcyclohexane, PFMC) or biphasic solvent mixtures proved to be disappointing. In all these cases, the reaction mixture was non-homogeneous. However, the reaction mixture became homogeneous when benzotrifluoride (BTF) was used as the solvent, and the reduction was complete in 3 h at 80 °C in this solvent. At the end of the reaction, most of the BTF was removed and the crude reaction mixture was partitioned between dichloromethane and PFMC. The layers were separated and evaporated. Pure adamantane **3** was isolated in 90% yield from the dichloromethane layer and the fluoros tin bromide **5** was isolated in 95% yield from the PFMC layer.

Tab. 10.1-1. Fluorous tin reagents

Reagent	Applications	Mode of purification employed
$(R_fCH_2CH_2)_mSnMe_{3-m}H$	Reduction of alkyl halides, radical cyclizations, Giese reactions and hydrostannylations	$R_f = C_6F_{13}$ , $m = 3$ , liq/liq extraction
$(R_fCH_2CH_2CH_2)_3SnCH_2CH=CH_2$	Thermal allylation of aldehydes, Barbier and Keck allylations	$R_f = C_{10}F_{21}$ , $m = 1$ , FSPE $R_f = C_6F_{13}$ liq/liq extraction
$(C_6F_{13}CH_2CH_2)_3SnN_3$	Synthesis of tetrazoles	$R_f = C_4F_9$ FSPE Liq/liq extraction
$(C_6F_{13}CH_2CH_2)_3SnAr$ ; Ar = aryl	Stille reactions	Liq/liq extraction
$[(C_6F_{13}CH_2CH_2)_2(Cl)Sn]_2O$	Trans-esterifications	Liq/liq extraction and FSPE



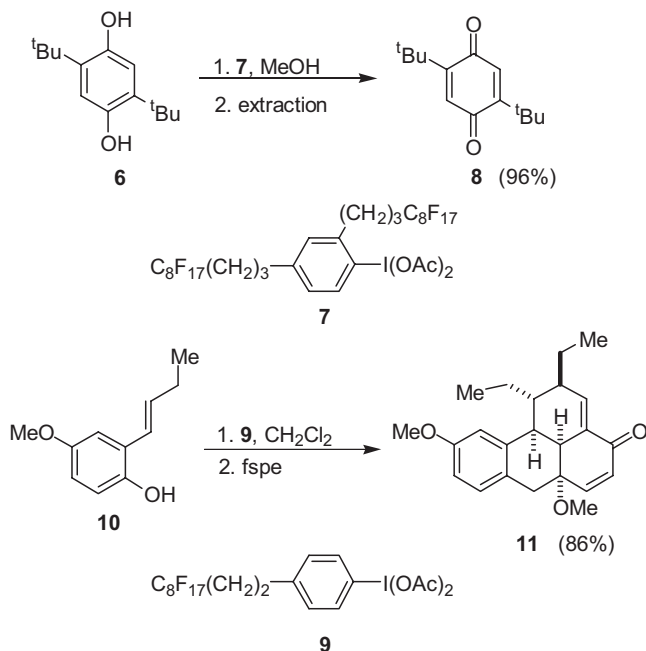
Scheme 10.1-2. Reactions of fluorous tin hydride

Fluorous tin hydride **4** also undergoes hydrostannylation reactions with alkenes and alkynes. This reaction was taken advantage of in scavenging excess dienophile (dimethyl acetylene dicarboxylate) present at the end of a Diels-Alder reaction (Scheme 10.1-2). The desired cycloadduct was obtained by evaporation of the organic phase and was free of the starting alkene.

#### 10.1.4

#### Fluorous Hypervalent Iodine Reagents

Gladysz and coworkers have developed a family of fluorous diacetoxy iodo arenes and evaluated them for oxidation of hydroquinones to quinones [17]. Oxidation of hydroquinone **6** with iodoarene **7** is illustrative of the utility of this reagent (Scheme 10.1-3). Hydroquinone **6** was dissolved in MeOH and treated with fluorous iodo arene **7**. After 3 h PFMC was added to give a biphasic system MeOH/PFMC. The phases were separated and quinone **8** was isolated in 96% yield from the MeOH layer while the reduced fluorous aryl iodide (not shown) was isolated in quantitative yield from the fluorous layer. The aryl iodide obtained from



**Scheme 10.1-3.** Oxidations using fluorous hypervalent iodine reagents

the fluorous phase was reoxidized to a diacetoxy iodo compound for reuse in hydroquinone oxidation.

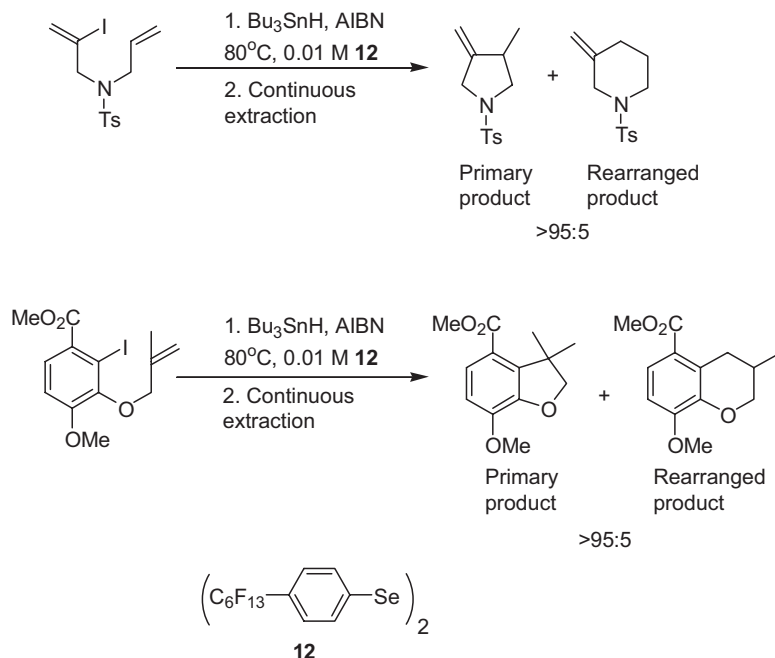
Lindsley and coworkers have used the light fluorous diacetoxy iodo arene **9** [18] to access unnatural carpanone analogs [19]. Styrene phenol **10** on reaction with iodo arene **9** gives carpanone analog **11**. FSPE was used to separate **11** from the crude reaction mixture.

#### 10.1.5

##### Fluorous Diaryl Diselenides

One of the side reactions in stannane mediated radical reduction of alkyl halides, is the rearrangement of the alkyl radical. This undesirable radical rearrangement pathway can be avoided to a considerable extent by using benzeneselenol. Primary alkyl radicals can abstract hydrogen atoms about 500 times faster from benzene selenol compared with that of a tri-alkyl stannane. Benzeneselenol can be conveniently generated *in situ* by reduction of diphenyldiselenide with stannanes. Crich and coworkers have developed a fluorous diaryl diselenide for catalyzing stannane mediated radical reactions which not only suppressed the radical rearrangements but also facilitated separation [20].

Fluorous diselenide **12** carrying two perfluoro hexyl chains showed sufficient solubility in organic solvents for applications in radical chemistry, but was not sufficiently fluorous to be extracted into the fluorous layer in a simple organic liquid/fluorous liquid biphasic extraction. Crich and coworkers solved this problem by designing a suitable continuous extractor.



**Scheme 10.1-4.** Fluorous benzene selenol catalyzed reductive cyclizations

Details of this continuous extraction procedure are described by Crich elsewhere in this book [21]. We expect FSPE to work equally well for the separation of this light fluorosulfide.

Fluorous diselenide **12** was then applied for the inhibition of stannane mediated rearrangements (Scheme 10.1-4). The initial 5-exo radical cyclization of vinyl radicals was not interrupted but the product radical did not undergo undesired homoallyl rearrangement, instead it was efficiently reduced by fluorosulfide. The crude reaction mixtures from these reactions were treated with benzoyl peroxide (to regenerate fluorosulfide) and subjected to continuous extraction which allowed ready purification of the reaction mixture and recovery of fluorosulfide **12**.

Crich and coworkers extended the utility of fluorosulfide diaryl diselenides by developing a protocol for efficient conversion of vicinal dimesylates into alkenes by a catalytic amount of fluorosulfide diaryl diselenides and sodium borohydride [22].

#### 10.1.6

#### Fluorous Carbodiimide

Fluorous ureas are sparingly soluble in organic solvents and fluorosulfide solvents. Palomo and coworkers found that the solubility of fluorosulfide ureas in fluorosulfide solvents can be dramatically increased by the addition of stoichiometric amounts of fluorosulfide alkanolic acids [23]. Fluorous urea forms a stable complex with fluorosulfide acid and the complex has a preferential solubility in fluorosulfide solvents (Scheme 10.1-5).





compounds from organics. Fluorous liquid/organic liquid extraction, which started the ball rolling, continues to remain prevalent in heavy fluorous arena. Crich's modified continuous extraction procedure allows light fluorous compounds to be extracted using a minimum amount of fluorous liquid. Separations over a fluorous solid phase (FSPE) are not only easy to conduct in parallel, but also amenable to automation. These FSPE procedures are gaining acceptance by medicinal chemists.

The full utility of the fluorous methods can be realized only with the availability of a large collection of reagents and protecting groups. It is now possible to make an educated guess about the retention behavior of new fluorous compounds based on previously studied examples [24]. This helps in designing new fluorous compounds suitable for the specific separation technique of interest. Given the considerable interest in solution phase combinatorial chemistry in and beyond medicinal chemistry, we are optimistic that more and more chemists will find fluorous chemistry attractive in the years to come.

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- 18 This compound is commercially available from Fluorous Technologies Inc. See [www.fluorous.com](http://www.fluorous.com) for details.
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- 24 D. P. CURRAN, "Separations with Fluorous Silica Gel", see Chapter 7.7.

## 10.2

### Radical Carbonylations Using Fluorous Tin Reagents: Convenient Workup and Facile Recycle of the Reagents

*Ilhyong Ryu*

#### 10.2.1

##### Introduction

Radical carbonylation is emerging as a promising method for the introduction of carbon monoxide into organic molecules [1–5]. A key step is the addition of carbon radicals to carbon monoxide to give acyl radicals [6], which can be sequenced in a number of inter- and intramolecular addition processes [2] and atom and group transfer processes [7]. The first report on efficient synthesis of aldehydes by radical carbonylation used tributyltin hydride as a hydrogen transfer reagent [8]. Shortly thereafter the radical carbonylation step was sequenced with the addition to allyltributyltin to give  $\beta,\gamma$ -unsaturated ketones [9]. The purpose of this chapter is to give an overview of radical carbonylation reactions using fluorous tin reagents, with an emphasis on the advantageous workup procedure, compared with that for conventional tin reagents, as well as on the reactivity differences between traditional and fluorous tin reagents. Since tin hydrides and allyltin reagents have been widely used as chain carriers for a number of synthetically useful radical reactions, we believe that the features contained in this chapter have a broad scope for application to many tin-mediated radical reactions [10].

#### 10.2.2

##### Radical Carbonylations Using Fluorous Tin Hydrides

The evolution of fluorous methods in the 1990s has greatly influenced the way that preparative organic chemistry is carried out [11–14], and tin mediated radical chemistry is no ex-

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- 20 (a) D. CRICH, X. HAO, M. LUCAS, *Org. Lett.* **1999**, *1*, 269. (b) D. CRICH, X. HAO, M. LUCAS, *Tetrahedron* **1999**, *55*, 14261.
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- 24 D. P. CURRAN, "Separations with Fluorous Silica Gel", see Chapter 7.7.

## 10.2

### Radical Carbonylations Using Fluorous Tin Reagents: Convenient Workup and Facile Recycle of the Reagents

Ilhyong Ryu

#### 10.2.1

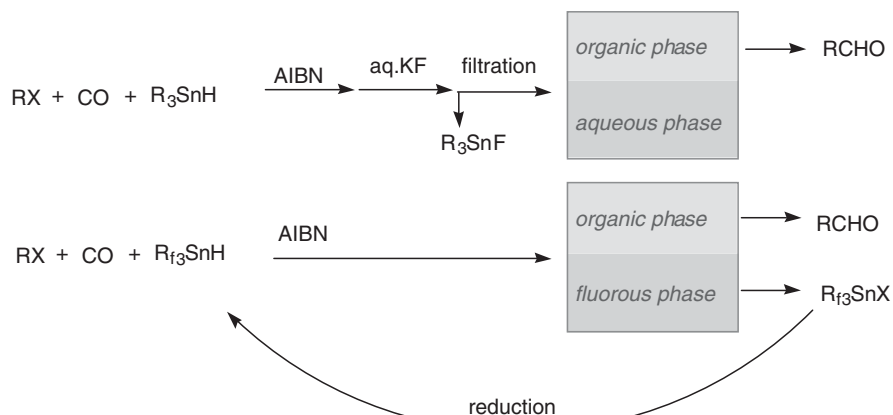
##### Introduction

Radical carbonylation is emerging as a promising method for the introduction of carbon monoxide into organic molecules [1–5]. A key step is the addition of carbon radicals to carbon monoxide to give acyl radicals [6], which can be sequenced in a number of inter- and intramolecular addition processes [2] and atom and group transfer processes [7]. The first report on efficient synthesis of aldehydes by radical carbonylation used tributyltin hydride as a hydrogen transfer reagent [8]. Shortly thereafter the radical carbonylation step was sequenced with the addition to allyltributyltin to give  $\beta,\gamma$ -unsaturated ketones [9]. The purpose of this chapter is to give an overview of radical carbonylation reactions using fluorous tin reagents, with an emphasis on the advantageous workup procedure, compared with that for conventional tin reagents, as well as on the reactivity differences between traditional and fluorous tin reagents. Since tin hydrides and allyltin reagents have been widely used as chain carriers for a number of synthetically useful radical reactions, we believe that the features contained in this chapter have a broad scope for application to many tin-mediated radical reactions [10].

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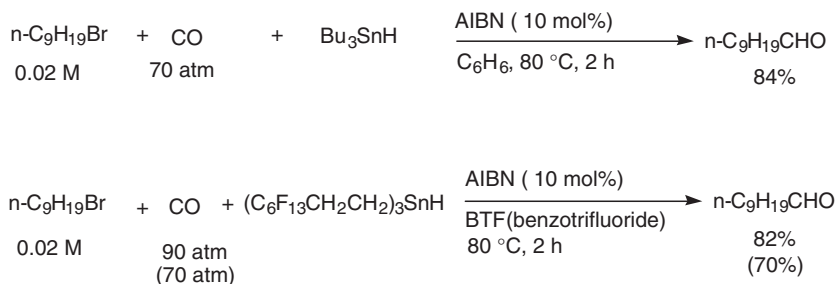


**Scheme 10.2-1.** Typical workup procedure of conventional and fluorous radical carbonylation

ception. Having the invention of fluorous tin hydride [15, 16] and allyltin [17] available for radical chain reactions from the Curran group, we jointly set out to develop “fluorous versions” of radical carbonylation reactions. Radical reactions using fluorous tin reagents have the great advantage of easy separation of products and reagents by fluorous/organic liquid/liquid extraction or fluorous/solid phase extraction, which also ensures the facile recycling of tin reagents. The first equation in Scheme 10.2-1 demonstrates a typical workup procedure to separate the tin reagent and product associated with the use of traditional tributyltin hydride. Treatment with aqueous potassium fluoride forms insoluble tributyltin fluoride, which is then filtered off. The filtrate was next partitioned into organic and aqueous layers. The second equation in Scheme 10.2-1 refers to the case of a fluorous radical reaction, which can employ organic/fluorous biphasic workup to separate the product and fluorous tin halide. The fact that tin fluoride is difficult to reduce to the parent tin hydride in the former case is a disadvantage of the traditional workup, whereas tin halides other than fluoride, whether fluorous or triorganyl, are easily reduced to the corresponding tin hydride, allowing for the recycling of tin reagents in the latter case.

To compare the relative reactivity of fluorous tin hydride with a conventional triorganyltin hydride [18], the radical formylation of nonyl bromide was examined at 70 atm of CO pressure (Scheme 10.2-2). Tributyltin hydride gave a good yield of decanal (84%), which is a reflection of a higher formylation/reduction ratio, whereas ethylene-spaced fluorous tin hydride gave an inferior result under identical conditions (70%). Fine tuning of reaction conditions by increasing CO pressure to 90 atm effectively pushed the efficiency of the fluorous tin hydride to a level comparable to that of tributyltin hydride. This difference is well understood in terms of a slightly higher ability of ethylene-spaced fluorous tin hydride to deliver hydrogen to the radical center, which is consistent with the fact that the rate constant for primary alkyl radical trapping by fluorous tin hydride is about twice that for tributyltin hydride at 20 °C [19].

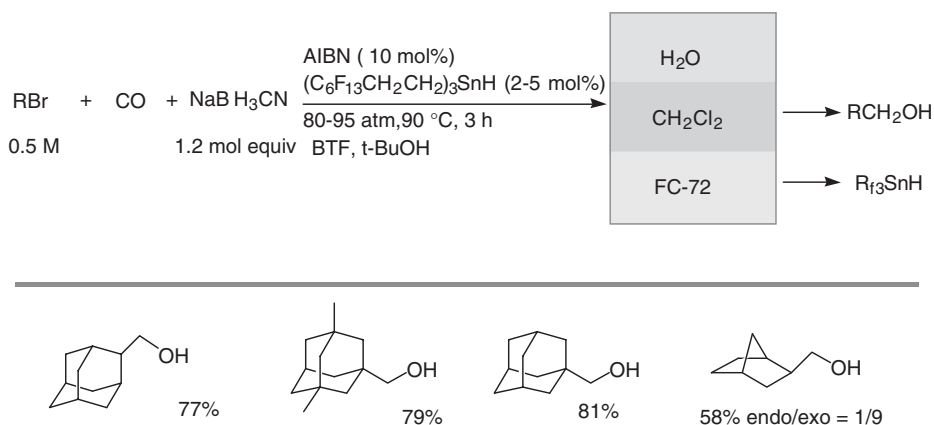
As a model study for tin hydride mediated radical carbonylation, fluorous hydroxymethylation of organic halides was examined using a catalytic quantity of a fluorous tin hy-



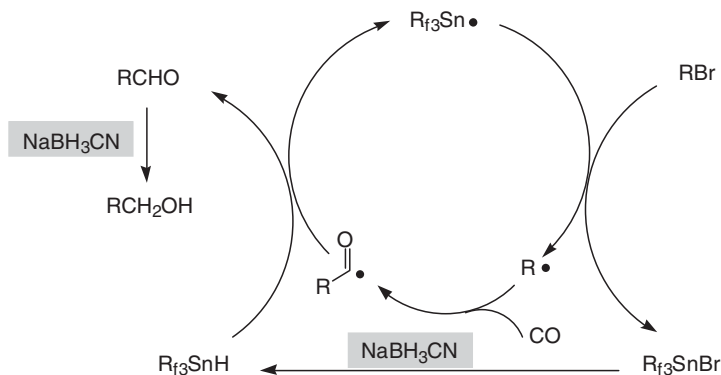
**Scheme 10.2.2.** Slightly higher reactivity of fluorous tin hydride

drude. While a similar hydroxymethylation, which is based on radical formylation and *in situ* reduction, was previously examined using a catalytic amount of triphenylgermyl hydride and an excess amount of sodium cyanoborohydride [20], the reaction conditions had not been optimized for tin hydride reagents. We found that the hydroxymethylation reaction of alkyl bromides works well when a catalytic amount of fluorous tin hydride was used together with 1.2 mol equivalent of sodium cyanoborohydride [21], and some results are shown in Scheme 10.2-3 [18]. The catalytic cycle is given in Scheme 10.2-4. The product isolation was easily carried out by a triphasic (aqueous/organic/fluorous) extractive workup and the fluorous tin hydride was recovered from the FC-72 layer by evaporation.

For the cases in Schemes 10.2-3 and 10.2-4, benzotrifluoride (BTF) is used as an amphiphilic solvent to dissolve both organic substrates and fluorous reagents in order to create a homogeneous reaction medium. Recently we have reported that F-626, 1*H*,1*H*,2*H*,2*H*-perfluorooctyl 1,3-dimethylbutyl ether [22], is a useful high boiling solvent for both fluorous and non-fluorous reactions [23]. Thus, we tested F-626 in place of BTF and found that it works equally well (Scheme 10.2-5). Judging from its partition coefficient (1/3.6 in EtOH/FC-72), F-626 is more fluorophilic than BTF (1/0.18 in EtOH/FC-72). Thus, through tripha-

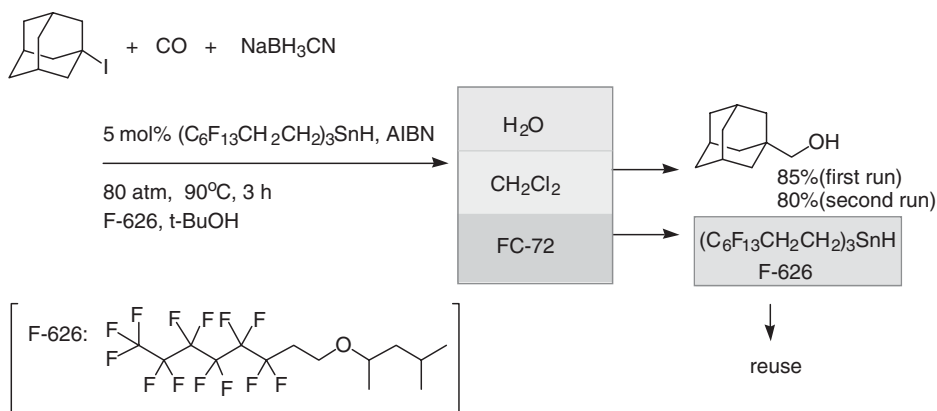


**Scheme 10.2.3.** Hydroxymethylation of RBr using a catalytic amount of fluorous tin hydride



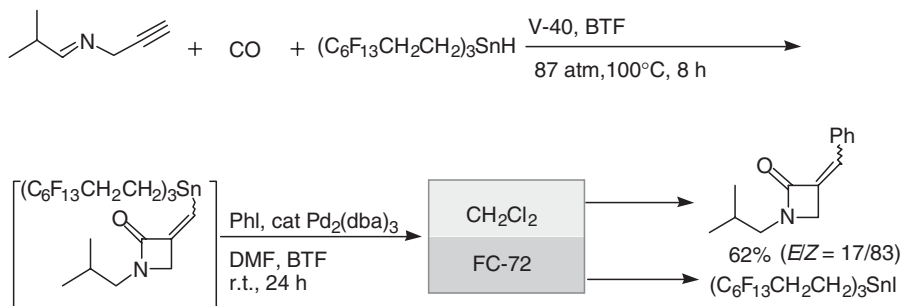
**Scheme 10.2-4.** Catalytic cycle for fluorous hydroxymethylation of RBR

sic workup, F-626 remained in the FC-72 together with the fluorous tin hydride. Evaporation of the FC-72 layer gave an F-626 solution containing fluorous tin hydride. The solution is reused conveniently for the second run experiment without adding additional F-626 solvent (Scheme 10.2-5). F-626, fluorous-tagged solvent, has a relatively high boiling point (80 °C at 9 Torr), nevertheless its facile removal by biphasic workup ensures its use without worrying about the general dilemma of how to remove a high-boiling solvent from a reaction mixture.



**Scheme 10.2-5.** Hydroxymethylation using an F-626 solution containing fluorous tin hydride

Among the stannylcarbonylation reactions [24–26], which constitute a useful variant of tin mediated radical carbonylations, the reaction with azaenynes is particularly useful for synthesizing lactams having a wide range of ring sizes [26]. The following example demonstrates the synthesis of a  $\beta$ -lactam by stannylcarbonylation of an azaenylene with a fluorous tin hydride [27]. The crude  $\alpha$ -stannylmethylene lactam was subjected to Stille coupling reaction



"without isolation"

**Scheme 10.2-6.** Consecutive stannylocarbonylation/Stille coupling sequence

with iodobenzene without isolation. After the reaction, a fluorous/organic biphasic workup allows for the separation of the  $\alpha$ -phenylmethylene lactam and fluorous tin iodide (Scheme 10.2-6).

### 10.2.3

#### Radical Carbonylations Using Fluorous Allyltin Reagents

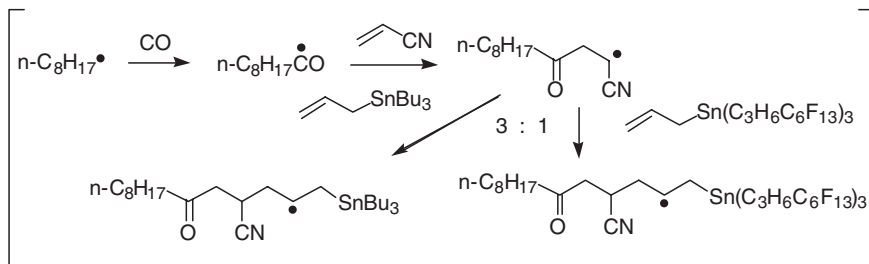
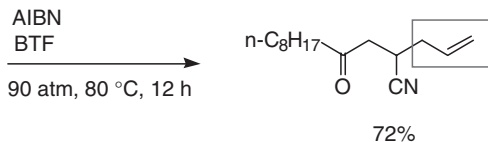
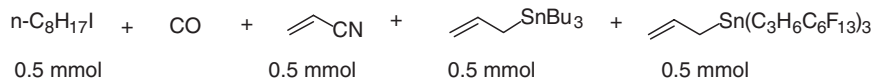
Allyltin compounds are powerful UMCT (unimolecular chain transfer) [28] players in radical chemistry. We have reported that a four-component coupling reaction consisting of alkyl halides, carbon monoxide, electron-deficient alkenes, and allyltributyltin [29] is a particularly efficient process leading to  $\beta$ -functionalized  $\delta,\epsilon$ -unsaturated ketones. To ascertain the potential of propylene-spaced fluorous allyltin [17] in such a carbonylative four-component coupling reaction, we carried out a competitive experiment using a system containing an equimolar amount of conventional allyltributyltin. This revealed that the conventional allyltributyltin is three times more reactive toward the  $\text{S}_{\text{H}}2'$  reaction than the fluorous allyltin (Scheme 10.2-7) [30].

We offset the modest reactivity of a propylene-spaced fluorous allyltin by employing a higher concentration to ensure an effective chain propagation. To separate coupling products and fluorous tin halides, fluorous/organic biphasic workup (method **A**) and fluorous solid phase extraction (FSPE) with fluorous reverse phase silica (FRPS) (method **B**) [31] were carried out, as outlined in Scheme 10.2-8. Thus, after the reaction, BTF (benzotrifluoride) was removed by vacuum evaporation and the resulting oil was partitioned into acetonitrile and FC-72 (method **A**). Evaporation of the acetonitrile layer, followed by short column chromatography on silica gel, gave the pure four-component coupling product.

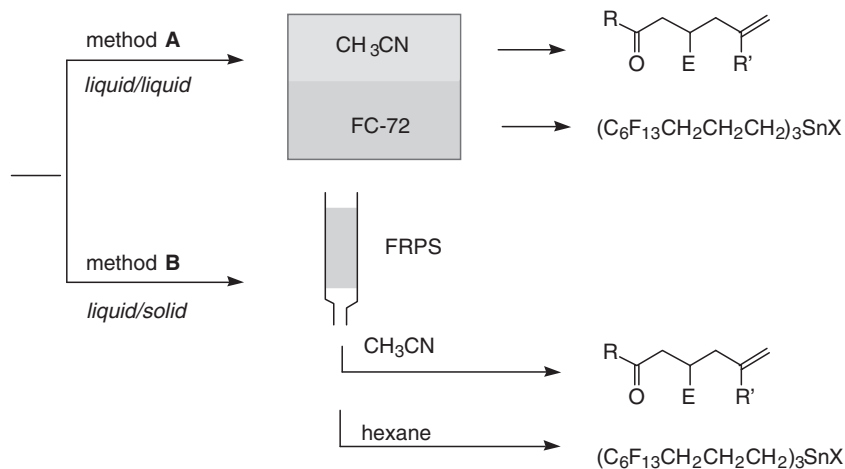
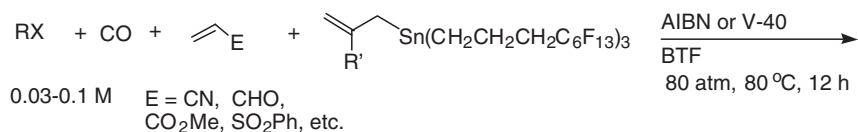
Scheme 10.2-9 lists the results of four-component coupling reactions, where alkyl halides, CO, electron-deficient alkenes and fluorous allyl- and methallyltin compounds are coupled in the given sequence [30]. The isolation of the final example was carried out using FRPS (method **B**).

An attempted four-carbon component reaction using perfluoroalkyl iodides in place of alkyl iodides was unsuccessful, and gave simply allylated perfluoroalkanes in good yields [32]. Apparently, the highly electrophilic perfluoroalkyl radicals prefer to react with electron-

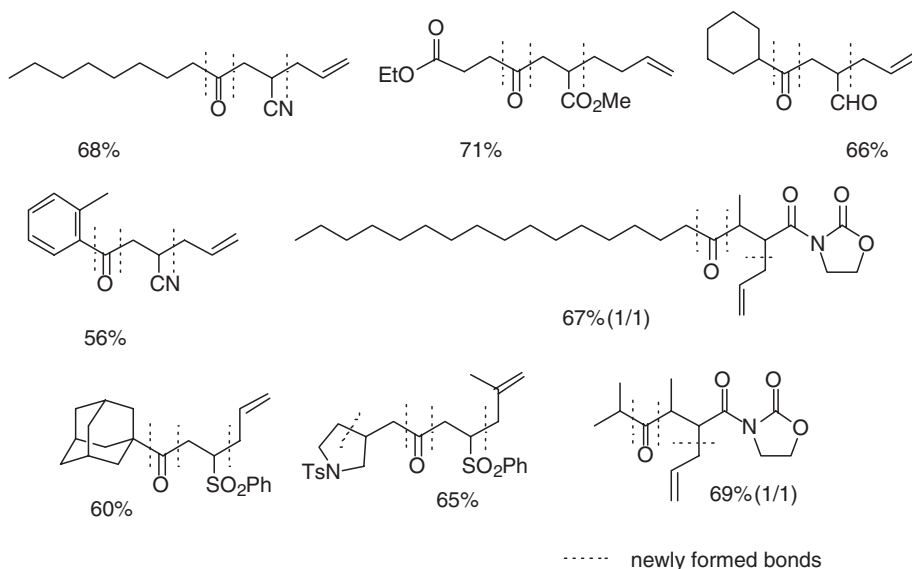




**Scheme 10.2.7.** Competitive experiments using a mixture of fluorous and conventional allyltin compounds

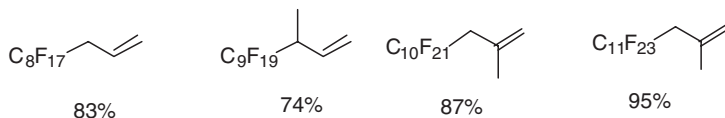
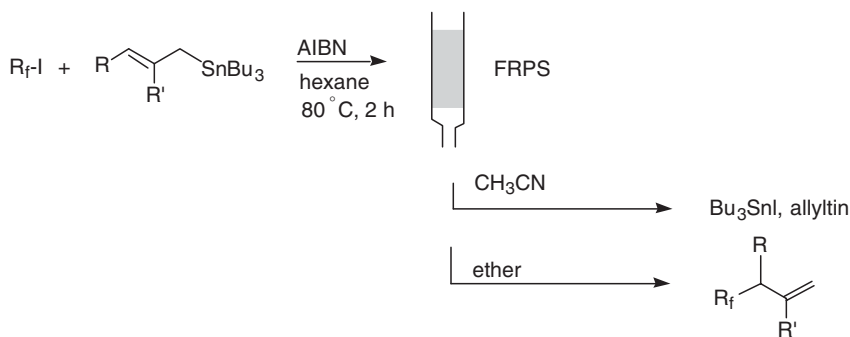


**Scheme 10.2.8.** Fluorous allyltin mediated four-component coupling reaction and two types of separation methods **A** and **B**



**Scheme 10.2-9.** Fluorous allyltin mediated four-component coupling reaction

rich allyltin rather than carbon monoxide and electron-deficient alkenes. Thus, we tested a simple synthetic procedure of perfluorinated allylic compounds starting from perfluoroalkyl iodides and allyltributyltin compounds. FRPS is conveniently used for the separation of fluorous products and organic reagents (Scheme 10.2-10). The simplified workup procedures to isolate products will allow for the easy implementation of the parallel synthesis using an



**Scheme 10.2-10.** Synthesis of perfluoroalkanes by radical addition and isolation by FRPS

automated reaction apparatus. Gladysz and coworkers reported that fluorous/organic bi-phase workup is also useful for isolating allylated perfluorooctane, which was obtained by the photolysis of perfluorooctyl iodide and allyltributyltin [33].

#### 10.2.4

### Conclusion

Fluorous tin reagents can be used successfully for radical carbonylation reactions with a slight modification to the original reaction conditions established for conventional tributyltin reagents. Catalytic hydroxymethylation of organic halides works well with a fluorous tin hydride, where the triphasic workup is conveniently used for the separation of fluorous tin hydride, inorganic salts, and products. The usefulness of fluorous allyltin and methallyltin reagents for the cascade type free-radical carbonylation was also established. Using fluorous/organic liquid/liquid extraction or fluorous-solid phase extraction (FSPE) with fluorous reverse phase silica, the tedious procedure of removing organotin reagents and/or byproducts can be circumvented. These results suggest that fluorous tin reagents have the potential to be applicable to a wide range of tin-based radical reactions.

### Acknowledgements

I wish to acknowledge Professor Dennis P. Curran for giving me the excellent opportunity to use fluorous tin reagents for radical carbonylations and for editing this manuscript. I also thank Professor Mitsuo Komatsu and all coworkers listed in the references for their collaboration on this project.

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### 10.3

#### Approaches to the Fluorous Mitsunobu Reaction

Roman Dembinski

##### 10.3.1

##### Introduction

The Mitsunobu protocol (Scheme 10.3-1) involves the reaction of an alcohol **1** and an acidic pronucleophile **2** (NuH), promoted usually by stoichiometric amounts of diethyl or diisopropyl azodicarboxylate **3** (DEAD or DIAD) and triphenylphosphine **4** (TPP) [1]. This reaction yields product **5** with formation of a C–O, C–N, C–S, C–X or C–C bond, along with dicarboalkoxyhydrazine **6** and triphenylphosphine oxide **7** (TPPO).

The Mitsunobu reaction has been widely used in organic synthesis, often for the inversion of configuration in secondary alcohols or the synthesis of aryl ethers. Synthetic advances

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### 10.3

#### Approaches to the Fluorous Mitsunobu Reaction

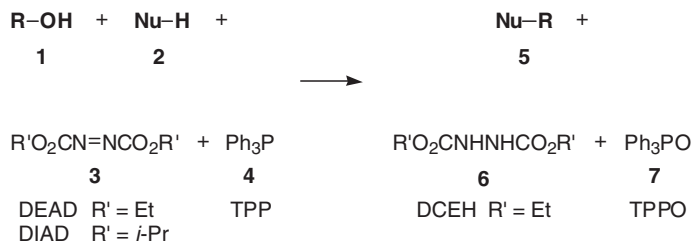
Roman Dembinski

##### 10.3.1

##### Introduction

The Mitsunobu protocol (Scheme 10.3-1) involves the reaction of an alcohol **1** and an acidic pronucleophile **2** (NuH), promoted usually by stoichiometric amounts of diethyl or diisopropyl azodicarboxylate **3** (DEAD or DIAD) and triphenylphosphine **4** (TPP) [1]. This reaction yields product **5** with formation of a C–O, C–N, C–S, C–X or C–C bond, along with dicarboalkoxyhydrazine **6** and triphenylphosphine oxide **7** (TPPO).

The Mitsunobu reaction has been widely used in organic synthesis, often for the inversion of configuration in secondary alcohols or the synthesis of aryl ethers. Synthetic advances



Scheme 10.3-1. The Mitsunobu reaction

have been summarized in various reviews [1, 2]. Recently, new coupling reagents have been introduced [2h, 3] and the mechanistic features have received additional clarification [4]. Although the lack of material conservation hindered larger scale applications, the reaction is popular in small scale and automated parallel synthesis [5] due to its stereoselectivity, compatibility with a wide range of functional groups, and mild reaction conditions. However, separation of the desired product from the spent and excess reagents consumes time and resources.

To simplify workup, the reaction can be carried out on a polymer support [6–11] or in the presence of separation-friendly Mitsunobu reagents. Polymer-bound phosphines [12–14] and azodicarboxylates [15] have been introduced, though their large excesses are inevitable. Appropriately substituted reagents can be removed by acid–base extractions [16–19] or by decomposition to volatile products [16]. Furthermore, “impurity annihilation” may simplify removal of residual reagents and byproducts [20]. These reagents allow solution-phase reactions, but they require extra reaction chemistry to effect the separation. This potentially adds time, limits the scope, and hampers recycling of the reagents. It can be assumed that laborious isolations affect the yields, which are usually reported to be in the range of 60–90%. The fluorous approach offers appealing solutions to the separation problems of the Mitsunobu reaction by simplifying the isolation protocol, and improving the yields.

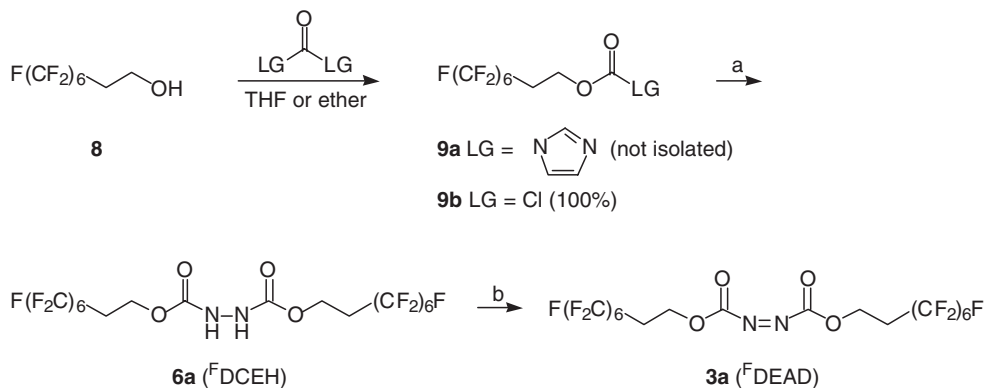
### 10.3.2

#### Fluorous Azodicarboxylate and Fluorous Phosphine

The most common approach to transforming the Mitsunobu reaction into fluorous conditions includes construction of fluorophilic participating reagents, thus allowing phase separation of fluorous byproducts from organic products. This has led to the synthesis of fluorous azodicarboxylates and the application of fluorous phosphines.

##### 10.3.2.1 Preparation of Fluorous Azodicarboxylate

The fluorous DEAD reagent has been synthesized concurrently by Dandapani and Curran [21], and Dobbs and McGregor-Johnson [22] (Scheme 10.3-2). 1H,1H,2H,2H-perfluoro-1-octanol **8** is treated with 1,1'-carbonyldiimidazole in THF, or phosgene in ether to give the fluorous imidazolide **9a** or chloroformate **9b**. Without further purification, both compounds are reacted with hydrazine hydrochloride/triethylamine in THF or hydrazine hydrate in ethanol. The fluorous hydrazine **6a** is isolated as a white solid after chromatography or



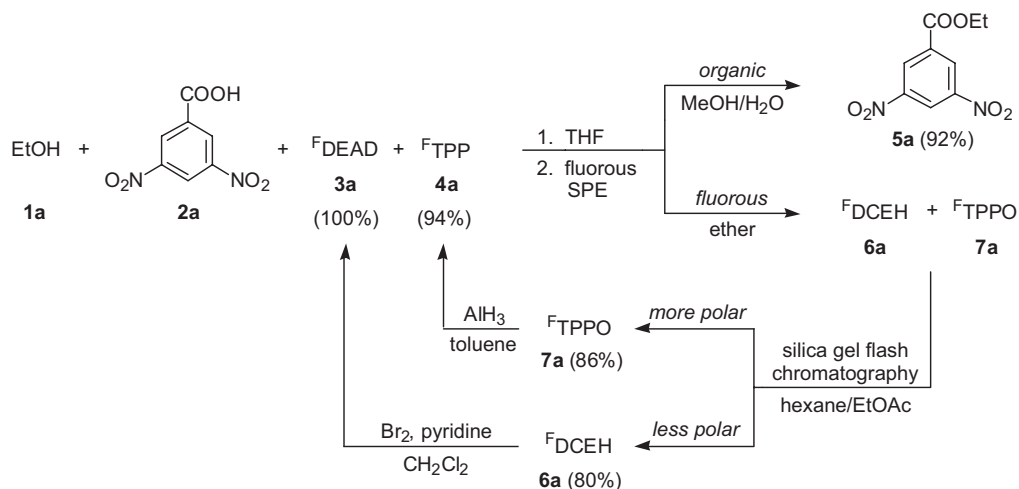
**Scheme 10.3-2.** Synthesis of fluorous DEAD **3a**. Reagents: (a) from **9a**  $\text{NH}_2\text{NH}_2\cdot\text{HCl}$ ,  $\text{Et}_3\text{N}$  (85% for two steps), from **9b**  $\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$ ,  $\text{EtOH}$  (80%). (b)  $\text{Br}_2$ , pyridine,  $\text{CH}_2\text{Cl}_2$  (100%), or *N*-bromosuccinimide, pyridine (79%)

recrystallization from methanol. Oxidation of **6a** with bromine/pyridine in dichloromethane or *N*-bromosuccinimide in pyridine is superior to treatment by other reagents such as iodosobenzene diacetate, lead tetraacetate, or manganese dioxide [22]. The fluorous azodicarboxylate **3a** (<sup>F</sup>DEAD) is obtained in 85–63% overall yield. The <sup>F</sup>DEAD reagent (molecular weight 810), a pale cream/yellow solid that can be recrystallized from ethanol, is stable as a solid at ambient temperature for several months, and in solution ( $\text{CDCl}_3$ ) for at least two weeks. Preparation of fluorous phosphines is reviewed in Chapter 10.7.

### 10.3.2.2 Reactions with Fluorous Azodicarboxylate and Fluorous Phosphine

To explore the efficiency of modified reagents, the Mitsunobu reaction has been examined with fluorous DEAD and regular phosphine [21, 22], or regular DEAD and fluorous phosphine [21]. Concurrent traditional reactions have also been conducted. The reactions take longer times but have comparable yields to those with non-fluorous Mitsunobu reagents. The protocol for isolation requires both reagents to be fluorous for facile separation by solid phase or liquid/liquid extraction. Accordingly, a fully fluorous reaction has been developed.

Dandapani and Curran have established an elegant separation of the organic product from fluorous byproducts allowing regeneration of the latter (Scheme 10.3-3) [21]. When ethanol **1a**, 3,5-dinitrobenzoic acid **2a**, <sup>F</sup>DEAD **3a**, and fluorous phosphine  $\text{PhP}[\text{C}_6\text{H}_4\text{-}p\text{-(CH}_2)_2(\text{CF}_2)_6\text{F}]_2$  **4a** (<sup>F</sup>TPP, molecular weight 954) react in the Mitsunobu reaction, the solvent is removed and the crude reaction mixture is subjected to solid phase extraction (SPE) on fluorous silica. Elution with  $\text{MeOH}/\text{H}_2\text{O}$  (8:2) gives the organic Mitsunobu adduct **5a** in 92% yield. Further elution with ether gives a mixture of the fluorous phosphine oxide **7a** and the fluorous hydrazine **6a** (<sup>F</sup>DCEH). This mixture of fluorous byproducts is readily separated on regular silica gel by eluting with hexane/ $\text{EtOAc}$  (3:2). The less polar hydrazine **6a** is eluted first and isolated in 80% yield; the more polar phosphine oxide **7a** follows in 86% yield. Both the reduction of the fluorous phosphine oxide **7a** with  $\text{AlH}_3$  to regenerate **4a**, and



**Scheme 10.3-3.** Separation and recycling of fluorous byproducts in the fluorous Mitsunobu reaction (SPE = solid phase extraction) [21]

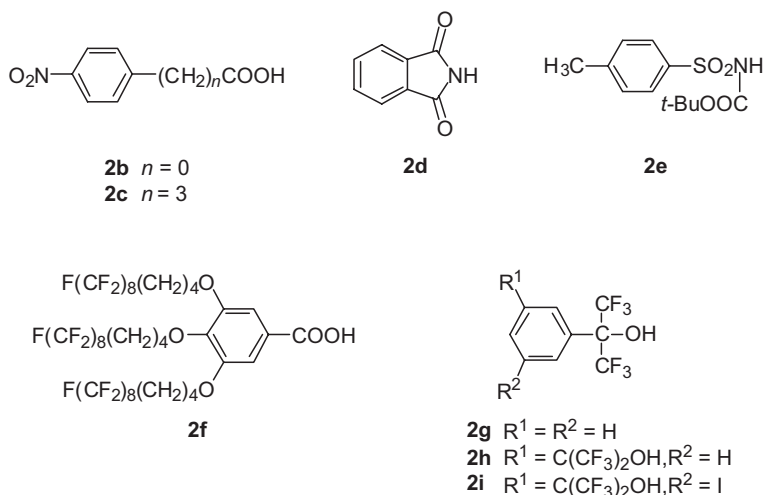
the oxidation of the fluorous hydrazine **6a** to reconstitute **3a** (also a step on the synthetic route to the <sup>F</sup>DEAD, cf. Scheme 10.3-2), are quantitative reactions. Thus, effective recycling of the fluorous reagent-based byproducts **6a** and **7a** is possible.

The order of addition of reagents may affect the course of the Mitsunobu reaction [2c]. A solution of phosphine and the alcohol can be added to the solution of azodicarboxylate and nucleophile (procedure A). Since DEAD is a strong oxidant, Michael acceptor, and dienophile, it is advantageous to avoid an excess. In the classical way, the phosphine, the alcohol, and the nucleophile are dissolved in the solvent and the azodicarboxylate is added dropwise to the solution (procedure B). Alternatively, azodicarboxylate and phosphine are reacted first to form an adduct, followed by addition of the alcohol and the nucleophile (procedure C). These three procedural variations have been investigated in reactions of simple alcohols and nucleophiles (Scheme 10.3-4) with <sup>F</sup>DEAD **3a** and <sup>F</sup>TPP **4a** (Table 10.3-1) [21].

Procedure A has been used with 3,5-dinitrobenzoic acid **2a** and 4-nitrobenzoic acid **2b**, and procedure C has been used for the 4-(4-nitrophenyl)butyric acid **2c**. For nitrogen nucleophiles, such as phthalimide **2d** and *N*-(*t*-butoxycarbonyl)-*p*-toluene sulfonamide **2e**, procedure B has been examined for both and procedure C for the latter. All of the procedures provide examples of quantitative conversions and very good yields, although for the sulfonamide **2e** procedure C is advantageous over procedure B [21].

The stereochemistry of the Mitsunobu reaction has been confirmed with the use of the lighter fluorous phosphine Ph<sub>2</sub>PC<sub>6</sub>H<sub>4</sub>-*p*-(CH<sub>2</sub>)<sub>2</sub>(CF<sub>2</sub>)<sub>8</sub>F **4b** [21]. The *anti*-3-hydroxy-2-methylbutyric acid ethyl ester yields the expected *syn* (inverted) products with nitrobenzoic acids **2a** or **2b**. Similarly, 5 $\alpha$ -cholestan-3 $\alpha$ -ol dinitrophenyl ester is obtained with inversion of configuration when 5 $\alpha$ -cholestan-3 $\beta$ -ol reacts with **2a**. Although the hydrophobicity of





**Scheme 10.3-4.** Selected reaction components (NuH) for fluorous Mitsunobu reactions summarized in Tables 10.3-1 and 10.3-2

the cholestanol ester affects the fluorous solid phase extraction, a good yield is achieved by chromatography on regular silica gel. An examination of the stereochemistry for reactions of *S*-(+)-2-octanol with benzoic acid, and *R*-(+)-1-phenylbutanol with phthalimide **2d**, in the presence of <sup>F</sup>DEAD and regular phosphine **4**, has also revealed complete inversion [22].

The fluorous phosphines have been selected based upon a correlation of fluorophilicity with HPLC retention times on a fluorous column [23, see Chapter 7]. The preferred phosphine for the fluorous Mitsunobu reaction is  $\text{Ph}_2\text{PC}_6\text{H}_4\text{-}p\text{-(CH}_2)_2(\text{CF}_2)_8\text{F}$  **4b** (molecular weight 698). Fluorous phosphines with longer chains or with three fluorous phenyl rings are also available, but the longer retentions and added molecular weight of these analogs offer no distinct advantage for SPE separations.

To explore the effect of a reduction in the fluorous content, other fluorous azodicarboxylates **3** that differ in the length of the spacer or perfluoroalkyl group [ $\text{R}' = \text{F}(\text{CF}_2)_3\text{CH}_2$ ,  $\text{F}(\text{CF}_2)_4(\text{CH}_2)_3$ ,  $\text{F}(\text{CF}_2)_6(\text{CH}_2)_3$ ] have also been synthesized by the same reaction sequence as is shown in Scheme 10.3-2 [21]. Of those tested the one with the same amount of fluorine as **3a** gives similar results. When the fluorous content is reduced, as for  $\text{R}' = \text{F}(\text{CF}_2)_4(\text{CH}_2)_3$ , the precursor hydrazine partitions between the organic and fluorous fractions during SPE. The <sup>F</sup>DEAD **3a** with 60.9% fluorine content and an ethylene spacer group has been the most extensively examined and is the most popular.

### 10.3.3

#### Synthesis and Separation of Fluorophilic Compounds

Fluorine-containing compounds have been used in the Mitsunobu reaction, either as the alcohol [24–27] or pronucleophilic component [28–31]. Fluorous esters have also been synthesized by other methods and isolated by fluorous liquid/liquid extraction [32–34, see

Chapter 10.15]. This chapter presents advances in which the combination of both the Mitsunobu reaction and fluorous separation have been applied.

### 10.3.3.1 Esters

The fluorous phase labeling is based on the introduction of a fluorous “ponytail” into the product (see Chapter 5) subsequent exploitation for separation, then followed by “detagging” to yield a final product. This concept suits the Mitsunobu reaction well, and allows for efficient separation without column chromatography.

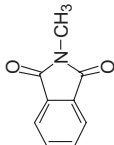
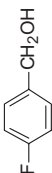
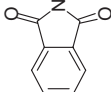
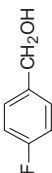
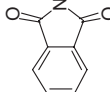
The synthesis of fluorous-tagged esters via the Mitsunobu reaction has been reported by Markowicz and Dembinski [35]. For the best fluorous partitioning, the total fluorine content of the fluorous phase-compatible molecule should equal or exceed 60%. The number of perfluoroalkyl groups is also an important factor, as appropriate shielding of the hydrocarbon domain leads to better fluorous solubility and partition. Accordingly, a tagging unit has been developed from inexpensive gallic acid. The 3,4,5-*tris*(4-perfluorooctyl-1-butoxy)benzoic acid **2f** (Scheme 10.3-4) is obtained by etherification of gallic acid methyl ester with 4-perfluorooctyl butyl iodide or bromide, and subsequent base hydrolysis [36]. The three perfluoroalkyl ponytails provide appropriate shielding, and a fluorine content of 60.9% for the ArCOO unit (Nu, molecular weight 1592), thus exceeding the requirements for good fluorous partitioning.

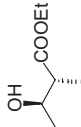
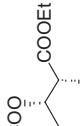
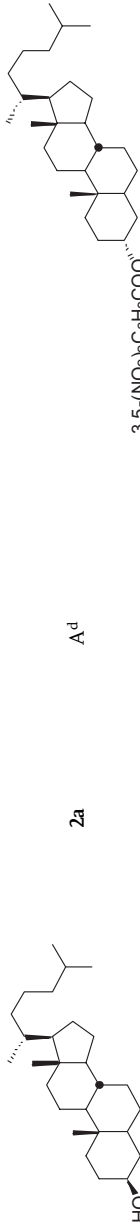
The use of fluorous tagged nucleophile **2f** in the Mitsunobu reaction offers two other advantages: (i) the fluorous esters are solids and can be easily isolated by simple crystallization, eliminating the need to use fluorous solvents; (ii) the fluorous tagged nucleophile (Nu) can be readily cleaved from the organic products by saponification with excellent yield [33, 36], thereby providing recycling opportunities.

The reactions of several representative alcohols with various functional groups and different carbon skeletons have been investigated (Table 10.3-2). All reactions are carried out with TPP **4**, in homogeneous conditions as THF provides good solubility for **2f**. Since the literature does not provide support for any advantage in using DEAD over diisopropyl azodicarboxylate (DIAD) [2, 10, 37, 38], the less expensive *i*-Pr derivative is preferred. After reaction by procedure B, separation is carried out according to the organic liquid/fluorous solid principle [39]. The THF is replaced by chloroform/methanol and the mixture is cooled to  $-10^{\circ}\text{C}$ . The highly fluorous products are immiscible with the organic phase and precipitate readily. The analytically pure esters are separated from the organic byproducts by simple filtration, avoiding a chromatographic step. Most alcohols afford complete reaction and the almost quantitative, with respect to the fluorous tagging group, isolation of esters. Such an approach eliminates the use of fluorous solvents, and complements SPE especially for the separation of fluorous esters with large organic parts, such as cholestanol [21, 40].

Hydrolysis of the fluorinated ester allows high yield isolation of the alcohol and recovery of the fluorous tag. A selected alcohol, 5 $\alpha$ -cholestan-3 $\alpha$ -ol, is isolated in 94% yield after saponification of the fluorous ester obtained from **2f** and 5 $\alpha$ -cholestan-3 $\beta$ -ol. This example also confirms the expected inversion of configuration. The tagging acid **2f** is recovered in 78% yield. Thus, the highly fluorinated carboxylic acid **2f** is a useful acyl donor for the acylation of alcohols in the Mitsunobu reaction, with a simple, chromatography- and fluorous solvent-free separation protocol and excellent yields. This example demonstrates the effectiveness of fluorous tags for liquid/solid partition and develops a new aspect of fluorous chemistry.

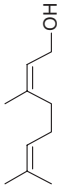



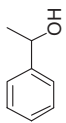
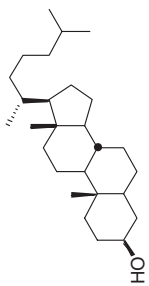
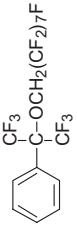
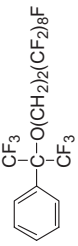
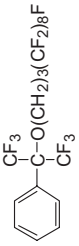
Tab. 10.3-1. Products of the Mitsunobu reaction with DEAD **3a** and TPP **4a** (or **4b**) reagents [21]

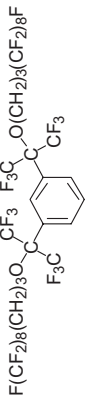
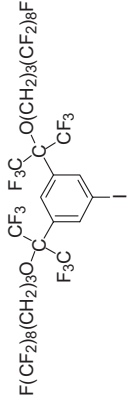
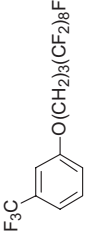
Alcohol <b>1</b>	NuH <b>2<sup>a</sup></b>	Procedure <sup>b</sup>	Product <b>5</b> (NuR)	Yield (%)
CH <sub>3</sub> OH	<b>2a</b>	A	3,5-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> COOCH <sub>3</sub>	93
	<b>2c</b>	C	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> (CH <sub>2</sub> ) <sub>3</sub> COOCH <sub>3</sub>	93
CH <sub>3</sub> CH <sub>2</sub> OH CH <sub>2</sub> =CHCH <sub>2</sub> OH	<b>2d</b>	B		91
	<b>2e</b>	C	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> SO <sub>2</sub> -N-CH <sub>3</sub> COO- <i>t</i> -Bu	90
	<b>2a</b>	A	3,5-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> COOCH <sub>2</sub> CH <sub>3</sub>	92
	<b>2c</b>	C	3,5-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> COOCH <sub>2</sub> CH=CH <sub>2</sub> 4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> (CH <sub>2</sub> ) <sub>3</sub> COOCH <sub>2</sub> CH=CH <sub>2</sub>	85 78
	<b>2d</b>	B		79
	<b>2e</b>	C	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> SO <sub>2</sub> -N-CH <sub>2</sub> CH=CH <sub>2</sub> COO- <i>t</i> -Bu	95
	<b>2a</b>	A	3,5-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> COOCH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> -4-F	75 <sup>c</sup>
	<b>2c</b>	C	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> (CH <sub>2</sub> ) <sub>3</sub> COOCH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> -4-F	88
	<b>2d</b>	B		75

2e	C	$4\text{-CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{-N-CH}_2\text{C}_6\text{H}_4\text{-4-F}$ $\text{COO-}i\text{-Bu}$	88
2a	A <sup>d</sup>		83
2b	A <sup>d</sup>		62
2a	A <sup>d</sup>		72

<sup>a</sup> For structures see Schemes 10.3.3 and 10.3.4. <sup>b</sup> Procedures: A. Addition of <sup>18</sup>F-TPP and the alcohol in ether to the <sup>18</sup>F-DEAD and NuH in ether. B. Addition of a solution of <sup>18</sup>F-DEAD in THF to a solution of NuH, <sup>18</sup>F-TPP, and the alcohol. C. <sup>18</sup>F-DEAD in THF was added to a solution of <sup>18</sup>F-TPP in THF, followed by the alcohol, and the NuH. <sup>c</sup> 91% purity. <sup>d</sup> With Ph<sub>2</sub>PC<sub>6</sub>H<sub>4</sub>-p-(CH<sub>2</sub>)<sub>2</sub>(CF<sub>2</sub>)<sub>8</sub>F **4b**.

Tab. 10.3-2. Products of the Mitsunobu reaction with azocarboxylates **3** and TPP **4** reagents isolated by fluoros separation [35, 41]

Alcohol <b>1</b>	NuH <b>2<sup>a</sup></b>	Product <b>5 (NuR)</b>	Yield (%)
	<b>2f<sup>b</sup></b>	$3,4,5\text{-[F(CF}_2)_8(\text{CH}_2)_4\text{O]}_3\text{C}_6\text{H}_5\text{COOCH}_2\text{CH}_3$	95
	<b>2f<sup>b</sup></b>	$3,4,5\text{-[F(CF}_2)_8(\text{CH}_2)_4\text{O]}_3\text{C}_6\text{H}_5\text{COO}$	83
	<b>2f<sup>b</sup></b>	$3,4,5\text{-[F(CF}_2)_8(\text{CH}_2)_4\text{O]}_3\text{C}_6\text{H}_5\text{COO}$	93
	<b>2f<sup>b</sup></b>	$3,4,5\text{-[F(CF}_2)_8(\text{CH}_2)_4\text{O]}_3\text{C}_6\text{H}_5\text{COO}$	96
	<b>2f<sup>b</sup></b>	$3,4,5\text{-[F(CF}_2)_8(\text{CH}_2)_4\text{O]}_3\text{C}_6\text{H}_5\text{COO}$	92
	<b>2f<sup>b</sup></b>	$3,4,5\text{-[F(CF}_2)_8(\text{CH}_2)_4\text{O]}_3\text{C}_6\text{H}_5\text{COO}$	94
$\text{F(CF}_2)_7\text{CH}_2\text{OH}$	<b>2g<sup>c</sup></b>		0
$\text{F(CF}_2)_8(\text{CH}_2)_2\text{OH}$	<b>2g<sup>c</sup></b>		11 <sup>d</sup>
$\text{F(CF}_2)_8(\text{CH}_2)_3\text{OH}$	<b>2g<sup>c</sup></b>		88

2h <sup>c</sup>		61
2i <sup>c</sup>		86
(CF <sub>3</sub> ) <sub>3</sub> COH <sup>c</sup>	(CF <sub>3</sub> ) <sub>3</sub> CO(CH <sub>2</sub> ) <sub>3</sub> (CF <sub>2</sub> ) <sub>8</sub> F	91
3-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> OH <sup>c</sup>		76

<sup>a</sup> For structures see Scheme 10.3-4. <sup>b</sup> Reaction conducted with DIAD in THF by procedure B. <sup>c</sup> Reaction conducted with DEAD in benzonitrile by procedure B. <sup>d</sup> Mixture of isomers: F(CF<sub>2</sub>)<sub>8</sub>CH<sub>2</sub>CH<sub>2</sub>ONu and F(CF<sub>2</sub>)<sub>8</sub>CH(ONu)CH<sub>3</sub> ~ 10:1.

### 10.3.3.2 Ethers

Substituted hexafluoropropanols are readily accessible by the reaction of aromatic hydrocarbons and hexafluoroacetone. 2-Phenyl hexafluoropropanol can be used, due to its reactivity, as a protecting group for alcohols [30]. Rábai et al. [41] have shown that the Mitsunobu reaction can be applied effectively for the synthesis of fluorous ethers from either fluorine-containing component. The reaction of the 2-aryl hexafluoropropanols **2g–i** in the presence of DEAD and TPP with aliphatic perfluoroalcohols containing different spacers has been examined (Table 10.3-2). Reaction is sensitive to the electron-withdrawing effect. The 1H,1H,2H,2H,3H,3H-perfluoro-1-undecanol can be used as the alcohol component with commendable yields, however, the conversion to an ether drops significantly for 1H,1H,2H,2H-perfluoro-1-decanol due to competing dehydration. The three methylene groups in 1H,1H,2H,2H,3H,3H-perfluoro-1-undecanol provide sufficient insulation, while no ether formation is observed with 1H,1H-perfluoro-1-octanol. The additional nucleophiles, 3-trifluoromethylphenol and perfluoro-*tert*-butanol have also been examined. These reactions are carried out by procedure B in benzotrifluoride, which provides acceptable solubility for all reaction components. After removal of the solvent, the fluorophilic ethers are efficiently separated from the reagent-driven organic byproducts by partition in the two-phase solvent system, methanol and perfluorohexanes (FC-72) or perfluoromethylcyclohexane. Thus, the Mitsunobu reaction offers a complementary method to the Williamson synthesis [37] for the preparation of highly fluorophilic ethers [41].

### 10.3.4

#### Conclusion

The fluorous Mitsunobu reaction offers convenient procedures for the synthesis and separation of organic or fluorophilic esters. When fluorous DEAD and fluorous phosphines are used, solvent evaporation followed by solid phase extraction over fluorous silica gel affords the products. An alternative workup can probably be achieved by liquid/liquid extraction. The depleted fluorous reagents can be readily recovered by the SPE column, separated by standard flash chromatography, and recycled. <sup>F</sup>DEAD and fluorous phosphines are commercially available.

The use of highly fluorinated carboxylic acids or alcohols as pronucleophiles for the acylation or etherification of alcohols also offers separation advantages (chromatography-free procedures). In addition, organic liquid/fluorous solid separation eliminates the need for fluorous solvents.

Fluorous isolation and/or reagents compliment existing methods for the chromatography-free separation of esters, amides, or ethers from byproducts in the Mitsunobu reaction. These fluorous Mitsunobu reactions and reagents will probably find applications in chemical discovery or natural product synthesis, and are particularly convenient for solution phase parallel synthesis. The ability to recover and regenerate the reagents encourages larger scale applications. It could be anticipated that the combination of existing methods of the preparation of fluorophilic and non-fluorophilic compounds via the Mitsunobu reaction, or other procedures employing fluorous separations, will lead to increased synthetic efficiency.

## Acknowledgements

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## 10.4

### Recyclable Oxidation Reagents

David Crich\* and Yekui Zou

#### 10.4.1

##### Introduction

Oxidations are some of the most widespread transformations in chemistry, both in the research laboratory and in industrial scale production: many are also notoriously wasteful and environmentally harmful when the stoichiometric generation of reduced reagents, often transition metal based, is taken into account. It is not surprising therefore that the development of catalytic and/or more environmentally benign oxidation processes has long provided a fertile ground for the imagination of the organic chemist [1]. The fluorous approach to waste management offers several advantages in the design of oxidation systems. Paramount among these are the obvious ease of separation and recyclability but, and perhaps equally important in the long run, is the issue of enhanced catalyst/reagent longevity resulting from minimization of self-oxidation. This chapter focuses on the synthesis and application of recyclable fluorous oxidation reagents, be they stoichiometric or catalytic. It does not include the use of fluorous ligands to support transition metal catalyzed reactions [2] as these are covered elsewhere in this volume. Similarly, the use of trifluoroethanol and

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hexafluoroisopropanol as solvents capable of promoting oxidation reactions with hydrogen peroxide is covered elsewhere in this handbook and not here [3].

#### 10.4.2

#### Organoselenium Based Oxidations

Selenium based reagents have long provided a paradox for organic chemists with their ability to effect mild, functional group tolerant oxidations being offset by their toxicity and, frequently, problems associated with their complete removal from organic products. Selenium dioxide, the archetypical reagent in the field, set the standard in all senses and was consequently one of the earlier oxidants to be successfully targeted for incorporation in a catalytic cycle [2, 4]. The discovery of the selenoxide *syn*-elimination [5] and the recognition of its potential in synthesis [6–8], followed rapidly by the advent of oxidation processes based on areneselenenic and areneseleninic acids ( $\text{Se}^{\text{II}}$  and  $\text{Se}^{\text{IV}}$ , respectively) [9–11], and peroxy versions of the same [12] firmly established organoselenium reagents as powerful, versatile oxidants for use in organic synthesis. These extremely useful reagents, capable of bringing about a wide variety of oxidative processes, nevertheless continue to suffer from the perceived problem of toxicity and occasionally from purification problems. The introduction of sequences employing catalytic quantities of areneseleninic acids and their anhydrides [9, 13] alleviated this problem somewhat but as catalyst loadings are often relatively high these methods still fall short of the ideal. The purification problem alluded to above arises from the disproportionation of the selenenic acid, the immediate product of the *syn*-elimination, into the diselenide and the selenenic acid (Scheme 10.4-1) thereby multiplying the number of byproducts for separation. Obviously, the problem can be minimized by working in the presence of excess oxidant, resulting in the conversion of all species into the seleninic acid, but in many instances this is not desirable. Moreover, the high polarity and insolubility of the areneseleninic acids does little to facilitate their recycling.

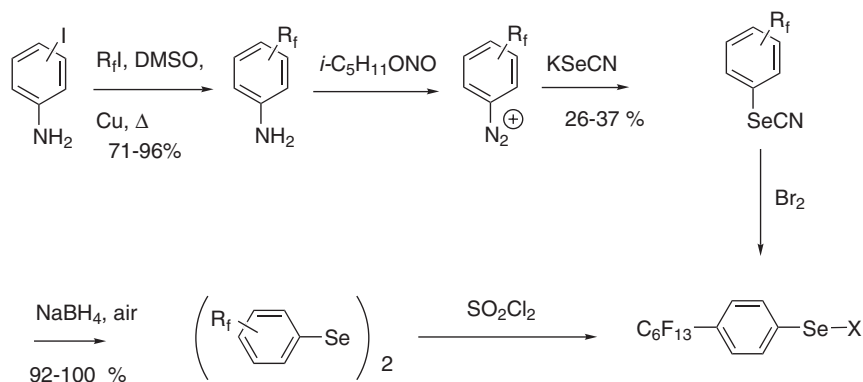


**Scheme 10.4-1.** Disproportionation of areneseleninic acid

Polymer-bound diphenylselenoxide and phenylseleninic acid are both known and have been employed in catalytic oxidations but neither have been widely employed [14–17], perhaps because they predate the 1990s explosion [18] in field of supported reagents and their use in combinatorial chemistry. More recently polymer-supported benzeneselenenyl halides, selenocyanates, and selenosulfonates have been reported and successfully applied in a number of typical transformations, including oxidative *syn*-eliminations. The issue of recyclability of these reagents is, however, rarely addressed and never quantified [19].

Several groups have responded to the challenge of presenting the chemical advantages of organoselenium based oxidants in a more environmentally acceptable format with the design and synthesis of fluorosulfonates.

Diselenides containing a single fluorosulfonate chain were prepared as illustrated in Scheme 10.4-2 [20, 21]. These compounds nicely illustrate one of the chief paradoxes in the area of so-called heavy fluorosulfonates, namely the compromise between the desire for high fluorine content to ensure preferential solubility in a fluorosulfonate phase and the high molecular



1:  $R_f = p\text{-C}_{10}\text{F}_{21}$ , MW: 1346, %F: 59, mp: 142-144 °C

2:  $R_f = p\text{-C}_8\text{F}_{17}$ , MW: 1146, %F: 56, mp: 122-124 °C

3:  $R_f = p\text{-C}_6\text{F}_{13}$ , MW: 948, %F: 52, mp: 95-97 °C

4:  $R_f = m\text{-C}_6\text{F}_{13}$ , MW: 948, %F: 52, mp: 63 °C

5: X = Cl, %F: 48

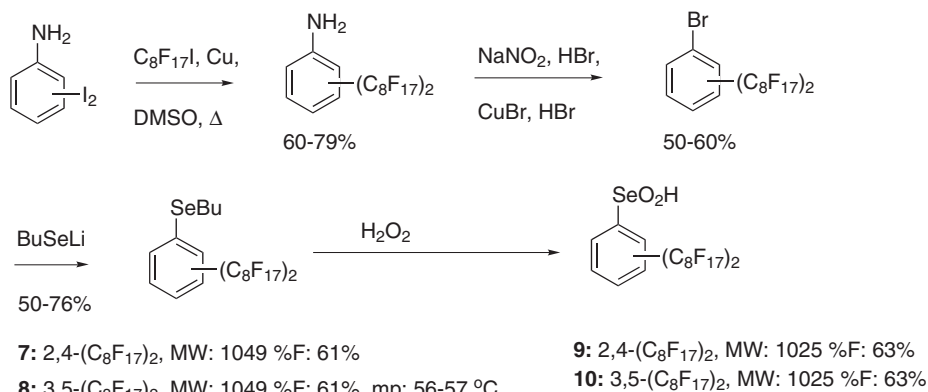
6: X = Br, %F: 44

**Scheme 10.4-2.** Synthesis of fluoroselenenyl halides

weight that is thereby imparted to the molecule. The bis(perfluorodecylphenyl) diselenide **1** was completely insoluble in all solvents assayed, fluoros and non-fluorous; whereas the perfluorooctyl analog **2**, with its lower melting point and molecular weight, was more soluble. The perfluorohexyl series **3** and **4** were, as expected, the most soluble with the less crystalline *m*-isomer [**22**] **4** having the highest solubility of the series [**23**]. Unfortunately, at only 52% fluorine by weight both **3** and **4** were below the threshold for efficient extraction into an organic phase by simple partitioning. This problem was readily overcome by use of a continuous extractor which was modified by incorporation of a cooling jacket around the extraction chamber to prevent co-solubility of the two phases in the hot apparatus [**21**]. This device proved to be very effective and enabled efficient extraction of fluoros compounds with as little as 38% fluorine in a matter of hours. The diselenide **3** was converted into the selenenyl chloride **5** quantitatively by exposure to sulfuryl chloride, whereas the corresponding selenenyl bromide **6** was obtained by treatment of the intermediate selenocyanate with bromine (Scheme 10.4-2) [**24**].

Compounds with two fluoros chains were prepared by an alternative protocol involving nucleophilic aromatic substitution of fluoros aryl bromides by lithium butylselenide (Scheme 10.4-3) [**25**, **26**]. In the case of the symmetric 3,5-disubstituted system **8** it was specifically noted that an approach similar to that of Scheme 10.4-2 for the introduction of selenium via a modified Sandmeyer reaction using selenocyanate as nucleophile did not function [**26**]. The butylselenides **7** and **8** were subsequently converted into the seleninic acids **9** and **10** *in situ* by oxidation with hydrogen peroxide. Although neither of these seleninic acids were isolated and characterized, it was reported that, in contrast to the reagents of Scheme 10.4-2, both were readily extracted into fluoros solvents under standard conditions, thereby underlining the influence of the degree of fluorine incorporation.

Trifluoromethylseleninic acid **11** has been prepared but, apparently, not applied as an oxi-

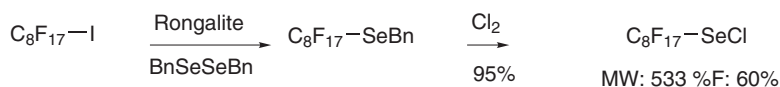


**Scheme 10.4-3.** Synthesis of fluoroseleninic acids

dant in organic systems [27, 28]. Similarly, the preparation of a series of perfluoro-arylseleninic acids **12** has been reported but, so far, without application [29]. It is doubtful whether either of these latter compounds contain sufficient fluorine to be considered “fluorous”.

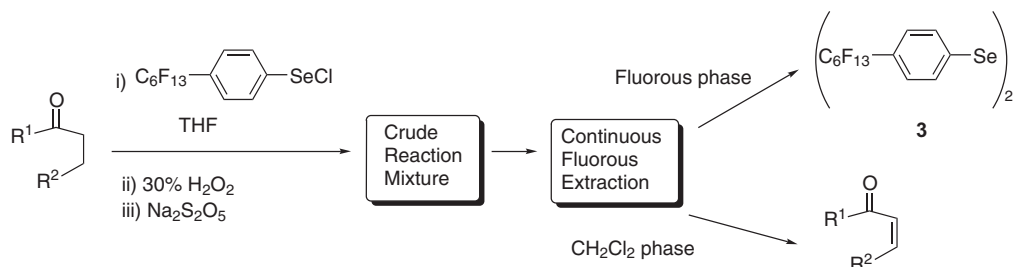


A convenient preparation of a series of perfluoroalkylselenenyl halides has recently been reported (Scheme 10.4-4) and it is possible that these compounds will find application as fluoroselenium-based oxidants in the near future [30].



**Scheme 10.4-4.** Synthesis of a perfluoroalkylselenenyl chloride

The fluoroselenenyl chloride **5** has been used in the dehydrogenation of ketones to their  $\alpha,\beta$ -unsaturated derivatives in direct analogy to the use of benzeneselenenyl chloride. This chemistry was predicated on the early work of Sharpless with benzeneselenenyl chloride itself [31] and involved stirring the ketone with **5** in THF at room temperature to give the  $\alpha$ -selenenyl ketone, doubtless via an acid catalyzed enolization, followed by addition of hydrogen peroxide, resulting in oxidative *syn*-elimination and formation of the enone (Scheme 10.4-5). After completion, sodium metabisulfite was added to the reaction mixture to reduce the selenenic and seleninic acid byproducts to the fluorous diselenide **3**, which was then recovered for reuse by continuous fluorous extraction. In each of the examples

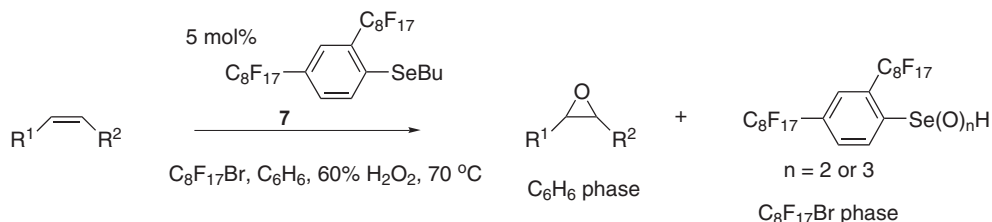


**Scheme 10.4-5.** Dehydrogenation of carbonyl compounds with a fluorous selenenyl chloride

studied the overall process was high yielding and the diselenide was recovered in very high yield (Table 10.4-1). Esters could be converted into their  $\alpha,\beta$ -unsaturated congeners by treatment of the lithium enolate with the fluorous selenenyl chloride **5** followed by the oxidative *syn*-elimination, then recovery of the diselenide **3** by metabisulfite reduction and continuous fluorous extraction (Table 10.4-1). Overall, the isolated yields of enones compare favorably with those obtained by analogous non-fluorous processes, especially when the ease and high yield recovery of the organoselenium moiety is taken into account. It should be noted that Barton and coworkers, in their dehydrogenation of ketones to enones with catalytic diphenyl

**Tab. 10.4-1.** Dehydrogenation of carbonyl compounds and recovery of the fluorous diselenide **3**

Substrate	Product (% yield)	% Yield	% Recovered <b>3</b>
		82	84
		81	92
		86	97
		90	99
		86	95





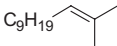
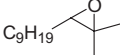
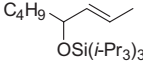
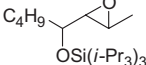
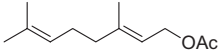
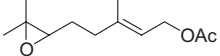
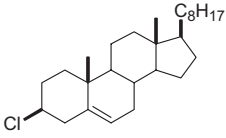
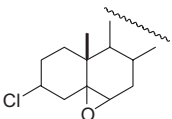

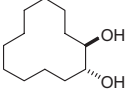


**Scheme 10.4-6.** Catalysis of epoxidation by a fluoroselenic acid

diselenide and *m*-iodoxybenzoic acid as oxidant, reported a recovery of diphenyl diselenide with yields as high as 95% following treatment with sodium dithionite [13]. However, that process required multiple extractions between aqueous and organic phases and was not as convenient as the single extraction set out in Scheme 10.4-5.

Following on from the work of Hori and Sharpless [9], and Grieco et al. [12] with catalytic benzeneseleninic acid and hydrogen peroxide, Knochel and coworkers have employed the fluoros butylselenide **7** as a precursor to an active catalyst in the epoxidation of alkenes (Scheme 10.4-6) [25]. In this system the selenide first undergoes oxidation to the selenoxide followed by *syn*-elimination to the selenenic acid. Further oxidation gives the seleninic acid **9** and, possibly, the perseleninic acid. These species, which were not characterized, catalyze the epoxidations which were conducted at 70 °C in a biphasic mixture of benzene and perfluorooctyl bromide. It was noted that the use of 60% hydrogen peroxide was critical for the success of the operation as the more dilute 30% solutions caused the formation of emulsions. After completion the fluoros phase, containing either the seleninic acid or the perseleninic acid, was separated off for reuse whereas the epoxide was obtained from the organic phase in the usual manner. Control experiments indicated that <0.1% of the catalyst was lost to the organic phase and that the recycled fluoros solution of catalyst could be employed for at least ten cycles with no loss of activity, indicating excellent catalyst stability. The examples in Table 10.4-2 show that the process is high yielding and tolerant of esters and the more robust silyl ethers. The yields are generally somewhat superior to those conducted with benzeneseleninic acid itself [12], and approach those obtained, albeit for a limited range of examples, by catalysis with 2-nitro- and 2,4-dinitrobenzeneseleninic acid [9] and other electron deficient benzeneseleninic acids [32]. In two cases (Table 10.4-2) the isolated product was the *trans*-diol resulting from opening of an intermediate epoxide and this is reminiscent of the results observed on attempted epoxidation with catalytic amounts of the polymer-supported seleninic acid and hydrogen peroxide when it was typically the major pathway [16].

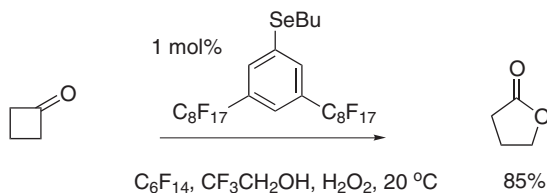
Sheldon and coworkers have employed the regioisomeric butylselenide **8** as a catalyst precursor in the hydrogen peroxide mediated oxidation of aldehydes and ketones [26]. As with the Knochel epoxidation sequence the true catalyst, the perseleninic acid, is generated *in situ* from **8** by oxidation, *syn*-elimination, and further oxidation. In a biphasic system comprised of the perfluorohexane and trifluoroethanol, cyclobutanone underwent Baeyer-Villiger oxidation to  $\gamma$ -butyrolactone with 1 mol% of **8** in excellent yield in 2 h at room temperature (Scheme 10.4-7). It was noted, however, that under these conditions the persele-

Tab. 10.4-2. Epoxidation with hydrogen peroxide catalyzed by **7**

Substrate	Product	% Yield
		92
		93
		97 (1:1 isomeric mixture)
		63
		80 (4:1 isomeric mixture)
		63
		68

nicinic acid formed on oxidation of **8** provoked the formation of emulsions. Oxidations could be conducted in a monophasic system using hexafluoroisopropanol, which satisfactorily dissolved the catalyst and hydrogen peroxide, but the optimum system was a triphasic one comprised of perfluorodecalin, 1,2-dichloroethane and 60% hydrogen peroxide (Table 10.4-3).


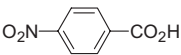
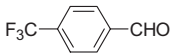
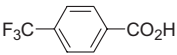
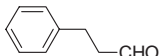
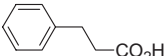


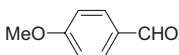
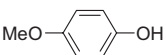
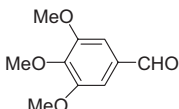
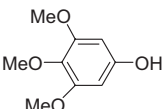
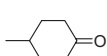
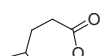
The perseleninic acid derived from **8** was found to have a partition coefficient of  $>100$



Scheme 10.4-7. Catalysis of a Baeyer-Villiger reaction by a fluorous selenium reagent



**Tab. 10.4-3.** Oxidation of carbonyl compounds with hydrogen peroxide catalyzed by 2 mol% of **8**

Substrate	Product	% Yield
		90
		90
		75
		80
		70
		75
		80

between perfluorohexanes and 1,2-dichloroethane at room temperature thereby ensuring its facile recovery. Unlike the case of the above epoxidation system of Knochel, however, there was a gradual diminution in yield with extended recycling of the catalyst solution (Table 10.4-4) and it was suggested that this might be the result of mechanical losses or catalyst decomposition.

The oxidations reported in Scheme 10.4-6 and in Table 10.4-3 closely parallel those obtained with typical electron deficient areneseleninic acids and hydrogen peroxide [33–36], and with polystyrene-bound benzeneseleninic acid and hydrogen peroxide [16], over which they nevertheless possess the obvious advantage of facile catalyst separation.

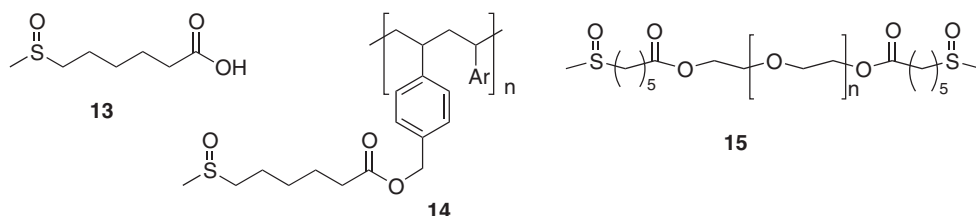
**Tab. 10.4-4.** Diminishing yields in the oxidation of *p*-nitrobenzaldehyde to *p*-nitrobenzoic acid with recycled catalyst

Cycle	% Yield
1	90
2	71
3	86
4	78
5	50

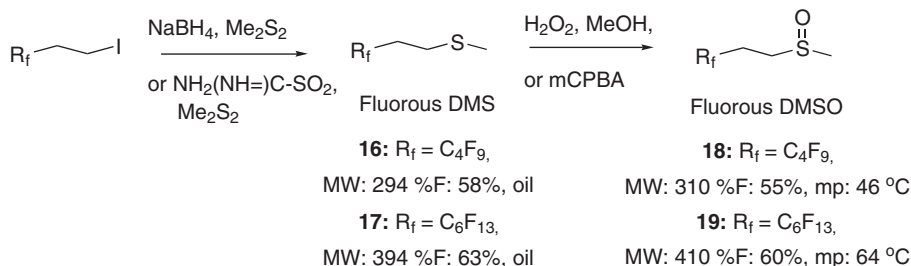
## 10.4.3

## Organosulfur-Based Oxidations

The oxidation of aldehydes and ketones based on the activated dimethyl sulfoxide and dimethyl sulfide are extremely well known and in very widespread use in organic research laboratories. The popularity of these methods stems from a combination of the mildness of the reaction conditions, the ready availability of the reagents, the exceptional functional group compatibility, and the metal-free nature of the oxidations [37–39]. Nevertheless, a considerable disadvantage of these methods, which portends against their use on an industrial scale, is the release of stoichiometric quantities of volatile, malodorous dimethyl sulfide. The problem has been addressed by the use of extractable non-volatile (**13**) and both insoluble (**14**) and soluble (**15**) polymer-supported and sulfoxides [40, 41].

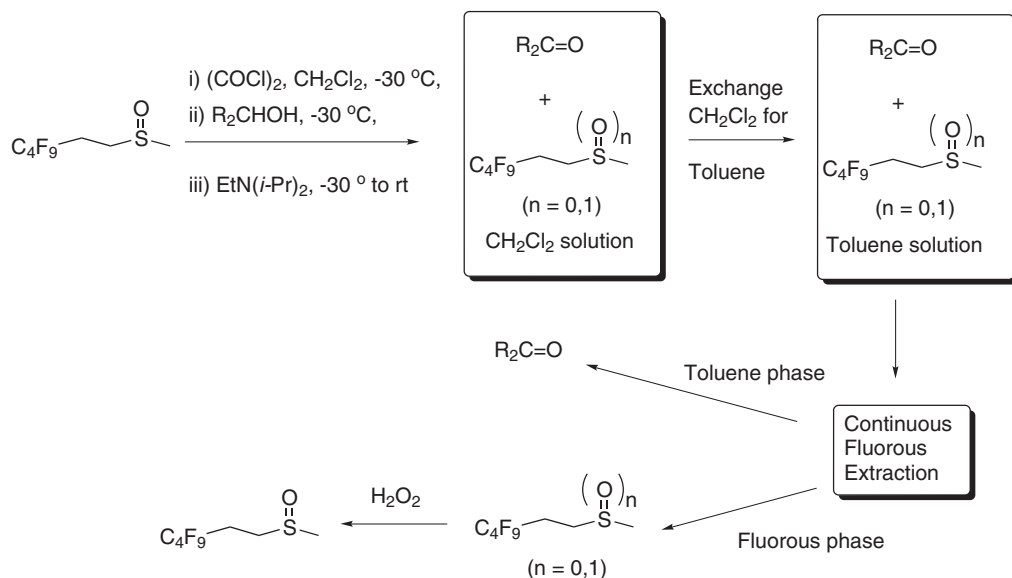


The fluororous solution to this problem uses a more readily available fluororous sulfoxide, which was prepared as outlined in Scheme 10.4-8 [42–44].



**Scheme 10.4-8.** Synthesis of fluororous sulfides and sulfoxides for oxidation reactions

Two sulfides, odor-free **16** and **17**, were prepared by the protocol of Scheme 10.4-8, and then converted into the corresponding, equally odor-free sulfoxides **18** and **19** by oxidation with hydrogen peroxide in methanol [45]. No over-oxidation to the sulfones was observed in this process, it having been previously determined that more forceful conditions are required for the exhaustive oxidation of such perfluoroalkylethyl sulfides [46]. Evidently, the ability to oxidize the sulfides to the sulfoxides with cheap, clean hydrogen peroxide without concerns of over-oxidation both in the initial preparation and in subsequent recycling reactions represents a considerable advantage of the method. The more highly fluororous sulfoxide **19** was found to be insufficiently soluble in dichloromethane at low temperatures, which prevented its use in the Swern type oxidations, but the lower homolog **18** proved ideal



**Scheme 10.4-9.** The fluorous Swern protocol

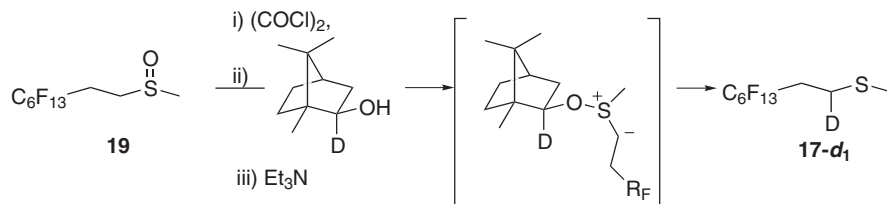
for the purpose. A number of Swern oxidations were conducted using 3 equiv of **18**. After the oxidation, the excess of **18** and the reduced sulfide byproduct **16** were recovered by a process which included aqueous washing then replacement of the dichloromethane by toluene and brief continuous extraction. The organic product was then obtained from the toluene layer in the usual manner whereas the fluorine layer afforded a mixture of **16** and **18**, which was simply reoxidized with hydrogen peroxide to afford pure recovered **18** (Scheme 10.4-9). The somewhat polar **18** did not partition efficiently between dichloromethane and perfluorohexanes but did so between the less polar toluene and perfluorohexanes, hence the switch in organic solvents prior to the fluorine extraction. As is seen from Table 10.4-5, a number of oxidations were conducted in the presence of a wide variety of functional groups, thereby demonstrating the broad generality of the method. In each case (Table 10.4-5) the sulfoxide **18** was recovered for reuse in high yield.

When deuterioisoborneol was subjected to the fluorine Swern reaction with sulfoxide **19**, and the oxidative recycling step omitted from the workup, it was possible to isolate the fluorine sulfide **17** by silica gel chromatography. A combination of <sup>1</sup>H- and <sup>2</sup>H-NMR spectroscopy revealed that deuterium had been incorporated into the *S*-methylene group of **16**, indicating that the oxidation falls into the category of true Swern oxidations and proceeds via a sulfur ylid with subsequent intramolecular hydrogen transfer (Scheme 10.4-10) [47, 48]. The strongly electron-withdrawing nature of the fluorine chain and its effect on acidity of neighboring C–H bonds accounts for the highly regioselective deprotonation, from the *S*-methylene rather than the *S*-methyl group.

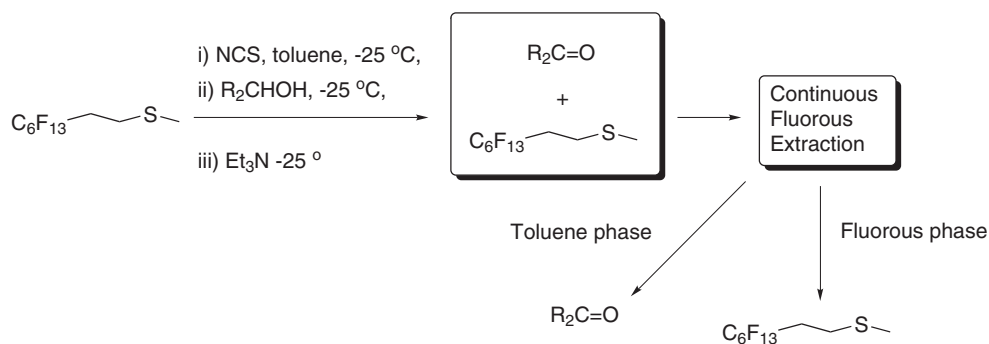
The application of fluorine sulfides in the Corey-Kim reaction [49] was also investigated [43] with the aid of the fluorine sulfide **17** (Scheme 10.4-11, Table 10.4-6). As the sulfide is

Tab. 10.4-5. Fluorous Swern oxidations with sulfoxide **18** (DAM = dianisylmethyl)

Substrate	Product	% Yield	% Recovered <b>18</b>
		92	87
		77	84
		91	88
		91	86
		90	89
		94	90
		83	86
		81	86
		81	84
		80	88
		79	85



Scheme 10.4-10. Mechanism of the fluorous Swern reaction



Scheme 10.4-11. The fluorous Corey-Kim protocol

Tab. 10.4-6. Fluorous Corey–Kim oxidations with fluorous sulfide 17

Substrate	Product	% Yield	% Recovered 17
		83	76
		86	73
		78	73
		88	72
		88	75

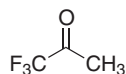
the reagent in this oxidation no oxidative step was necessary in the workup, however, it is important to note that in order to obtain high recoveries of fluorosulfide it was necessary to work with as near stoichiometric sulfide as possible. This results from the oxidation of any excess sulfide by the excess NCS thereby preventing its recovery, at least in the form of the sulfide.

Overall, fluorosulfur versions of the Swern and Corey-Kim reactions closely parallel those conducted with the more familiar dimethyl sulfoxide and dimethyl methyl sulfide in terms of practicality, yield and functional group tolerance. They offer the obvious advantage of recovery of the fluorosulfur reagents and elimination of obnoxious sulfur-based odors.

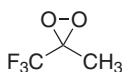
#### 10.4.4

##### Fluorosulfur Ketone-Mediated Oxidations

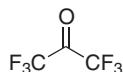
Dimethyl dioxirane is a powerful reagent, generated from acetone and Oxone, for the transformation of alkenes into epoxides and for a variety of other oxidations [50–53]. A more active version is trifluoromethyl methyl dioxirane (**21**), derived from trifluoromethylacetone (**20**), and this reagent has been widely applied in epoxidation and other oxidation sequences whether preformed or generated *in situ* [50–59]. Hexafluoroacetone (**22**) is converted into 2-hydroperoxyhexafluoro-2-propanol (**23**) with concentrated hydrogen peroxide and this reagent has also been shown to effect epoxidation of alkenes under stoichiometric and catalytic conditions [60–62]. Recycling these trifluoromethyl based dioxiranes is, however, impractical owing to a combination of their low molecular weight and high volatility with their instability [52, 53, 63, 64]. The problem of instability has been addressed by the preparation of the silica gel-supported reagent **24** [65]. This substance was reported to be an efficient catalyst for the epoxidation of alkenes with Oxone, with activity comparable to the freely diffusing analog **25**. Unlike **25** however, which was 85% decomposed after a single run, **24** was found to retain most of its activity for up to ten cycles. The difference in stability between **24** and **25** was attributed to the isolation of molecules on the support preventing decomposition



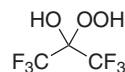
**20**: %F: 51



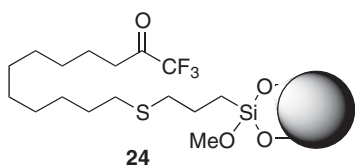
**21**: %F: 44



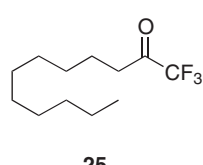
**22**: %F: 68



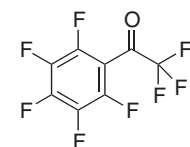
**23**: %F: 57



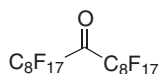
**24**



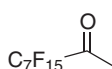
**25**



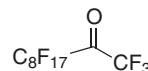
**26**: MW: 264, %F: 58



**27**: MW: 866, %F: 75, mp 110 °C



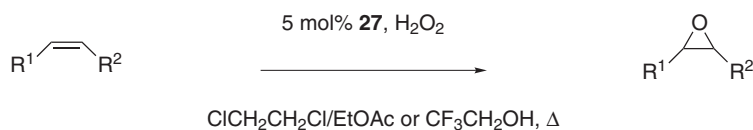
**28**: MW: 412, %F: 69, oil



**29**: MW: 516, %F: 73, mp 38 °C

via 1,2,4,5-tetroxane formation and to the suppression of Baeyer-Villiger decomposition pathways by the support. Ketone **24** was readily recycled by simple filtration but it was noted that there was an unquantified loss in each cycle owing to the partial solubility in the reaction medium [65].

Fluorous solutions to the problem have been reported. Thus, the epoxidation of cyclooctene with anhydrous hydrogen peroxide in ethyl acetate with catalytic quantities of **22**, **26** and **27** was investigated by Sheldon and coworkers. These investigators reported an initial rate with **27** some four times that with **22**, whereas oxidation with **26** proceeded at half the initial rate of that with **22** [66]. In subsequent studies, 5 mol% of perfluoroheptadecan-9-one (**27**), presumably converted into the peroxyhydrate *in situ*, was demonstrated to bring about effective epoxidation of a range of alcohols in conjunction with anhydrous hydrogen peroxide in a 10:1 mixture of 1,2-dichloroethane and ethyl acetate at reflux (Scheme 10.4-12). All but the most acid sensitive substrates were successfully epoxidized in high yield under these conditions. Success was obtained in the cases of  $\alpha$ -pinene and camphene by buffering the reaction mixture with a small amount of base (Table 10.4-7). The choice of a mixed solvent resulted from the insufficient solubility of **27** in halogenated solvents alone. The low solubility of **27** presented a considerable advantage in so far as on cooling the reaction mixtures, it crystallized from solution thereby permitting recycling by simple filtration: 80–92% of the catalyst could be recovered in this manner and this was shown to have no loss of activity in subsequent experiments. The identical transformations could be conducted with **27** and 60% hydrogen peroxide in trifluoroethanol at reflux (Scheme 10.4-12, Table 10.4-7). Ketone **27** could also be recovered by crystallization from these reaction mixtures although not as efficiently as from dichloroethane owing to its higher solubility in trifluoroethanol.






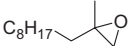
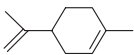
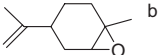

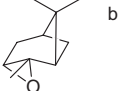

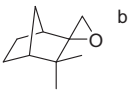


**Scheme 10.4-12.** Fluorous ketone catalysis of epoxidation with hydrogen peroxide

Crousse, Delpon, and coworkers investigated fluorous ketones **28** and **29** as catalysts for the epoxidation of dodecene and cyclooctene with Oxone as the stoichiometric oxidant in both acetonitrile/water and hexafluoroisopropanol/water mixtures, invoking the corresponding dioxiranes as the reactive intermediates [67, 68]. Ketones **28** and **29** both catalyzed epoxidation under these conditions, but unfortunately the most reactive of the pair (**28**) was found to be subject to Baeyer-Villiger oxidation and could not be recycled. A compromise was reached with the trifluoromethyl perfluoroethylketone **30**, readily prepared as shown in Scheme 10.4-13. In these compounds the ethylene spacer group attenuates the electron withdrawing effect of the second perfluoroalkyl group, thereby permitting greater reactivity in epoxidation, yet the proximity of this second perfluoroalkyl group is sufficient to prevent Baeyer-Villiger oxidation of the ketone group.

This ketone (**30**) effectively promotes epoxidation of alkenes by Oxone in hexafluoroisopropanol/water mixtures, buffered by sodium bicarbonate, at 25 °C (Scheme 10.4-14, Table 10.4-8). Two higher homologs, **31** and **32** were also prepared and investigated with **31** being

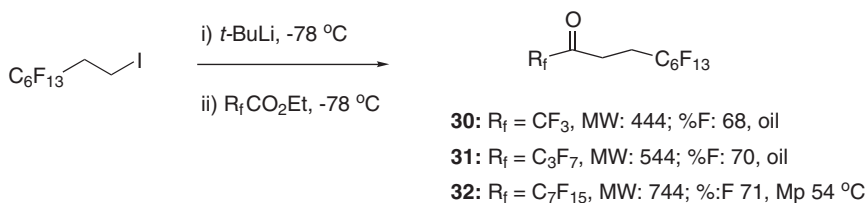
Tab. 10.4-7. Epoxidations with hydrogen peroxide catalyzed by ketone **27**

Substrate	Product	% Yield in $C_2H_4Cl_2/EtOAc$	% Yield in $CF_3CH_2OH$
		100	100
		92	89
$C_8H_{17}$ 	$C_8H_{17}$ 	96	63 <sup>a</sup>
	 <sup>b</sup>	72	
	 <sup>b</sup>	55 <sup>a</sup>	–
	 <sup>b</sup>	49 <sup>a</sup>	–

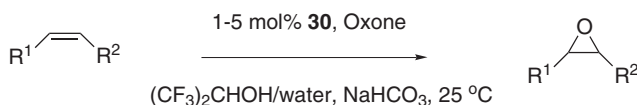
<sup>a</sup> reactions conducted in the presence of 5 mol%  $Na_2HPO_4$ <sup>b</sup> stereochemistry undefined

less active than **30** and **32** completely inactive under the standard conditions. Unfortunately, the recovery of ketone **30** from these reaction mixtures by fluorous extraction or by fluorous chromatography was not efficient (<50%), even if GC analysis of the crude reaction mixtures indicated no decomposition [67, 68].

The use of ketone **30** in hydrogen peroxide mediated epoxidations, analogous to those of Scheme 10.4-12 (Table 10.4-7) was also assayed. Thus, cyclooctene underwent 50% con-





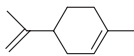
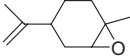
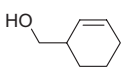
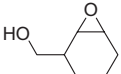
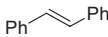
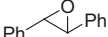
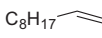
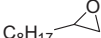
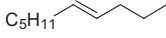
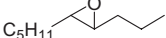
Scheme 10.4-13. Synthesis of an optimized fluorous ketone for epoxidation with Oxone



Scheme 10.4-14. Fluorous ketone catalysis of epoxidation with Oxone



Tab. 10.4-8. Epoxidations with oxone catalyzed by ketone **30** in 3:1 hexafluoroisopropanol/water

Substrate	Product	Mol% <b>30</b>	% Yield
		1	81
		1	71 (1:1 mixture)
		1	68 (1.5:1 mixture)
		5	93
		5	92
		5	96

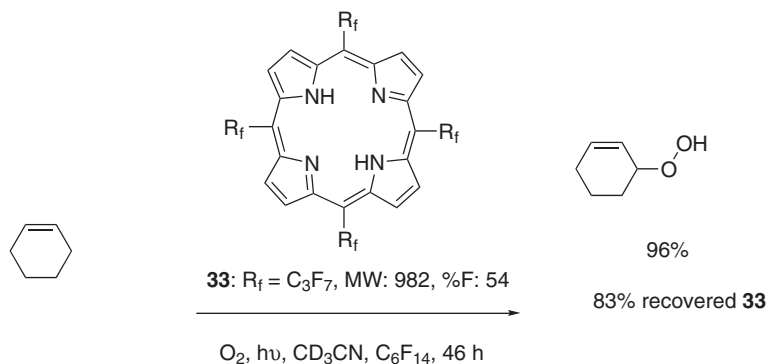
version into the epoxide in acetonitrile with 10 mol% of **30**, while 100% conversion was achieved with only 1 mol% of **30** in 1:1 hexafluoroisopropanol/acetonitrile. Unfortunately, even with 10 mol% of **30** the less reactive dodecene only furnished a 20% yield of the epoxide even in the mixed solvent, suggesting that **30** is a much less effective catalyst under the hydrogen peroxide conditions.

Overall, it is clear that the combination of **27** and hydrogen peroxide in hot dichloroethane/ethyl acetate, passing via the peroxyhydrate, is a superior system for the epoxidation of alkenes than the combination of **30** and Oxone, invoking an intermediate dioxirane. The reasons for this superiority are simple and center on the use of the less expensive oxidant, hydrogen peroxide, and the very facile, highly efficient recovery of the catalyst by simple cooling and filtration. The use of hydrogen peroxide rather than Oxone also gives **27** the edge over the silica supported ketone **24** even if the recovery conditions are very similar.

#### 10.4.5

##### Fluorous Sensitizers for Singlet Oxygenation

Porphyrins are often employed as sensitizers in the singlet oxygenation of alkenes. Yet they are far from ideal, being themselves subject to competitive degradation by the singlet oxygen they serve to generate. A solution to this problem has been provided in the form of the tetrakis(heptafluoropropyl)porphyrin **33** [69], whose synthesis was described earlier [70]. In a biphasic mixture of perfluorohexane and deuterioacetonitrile this sensitizer enables the photo-initiated singlet oxygenation of cyclohexene in excellent yield with only minimal self-degradation (Scheme 10.4-15). In a preparative scale oxygenation, 2Z-decene-4-ol, a substrate whose tetraphenylporphyrin-sensitized singlet oxygenation was reported to be both difficult



**Scheme 10.4-15.** Allylic oxygenation sensitized by a fluorous porphyrin

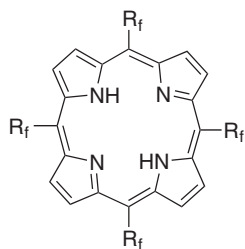
and accompanied by considerable degradation of the sensitizer, was converted into 3-hydroperoxy-1-decene-4-ol in 59% yield in a perfluorohexane/acetonitrile system; analysis of the fluorous layer revealed 57% residual sensitizer after 10 days irradiation.

A related porphyrin to **33** is the chloroperfluoropolyether modified system **34** which, interestingly, is highly soluble in  $\text{scCO}_2$  [71]. A series of porphyrins bearing fluorous chains on the pyrrole rings (**35**) has also been synthesized [72]. However, neither the solubility of these substances in fluorous solvents nor their ability to act as sensitizer have yet been described.

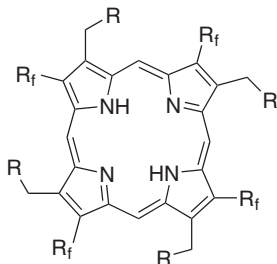
The known propensity of  $\text{C}_{60}$  to act as a powerful sensitizer for singlet oxygenation [73–75], coupled with the use of **33** in singlet oxygenations prompted the development of a  $\text{C}_{60}$  derivative (**36**) bearing a fluorous chain. This substance was found to effect singlet oxygenation of alkenes very rapidly with catalyst loadings as low as 0.05 mol%, especially when the reactions were conducted in hexafluorobenzene (Table 10.4-9) as opposed to toluene [76]. A particularly noteworthy example is that of the oxygenation of the difficult case of 2-decene-4-ol when a yield of 91% was obtained, albeit after 24 h irradiation. The use of  $\text{C}_{60}$  in this last oxygenation, or that of **36** in toluene, resulted in very much diminished yields, pointing to the importance of the combination of **36** with the employment of hexafluorobenzene as the solvent. A more highly fluorous  $\text{C}_{60}$  derivative was subsequently prepared and used to sensitize the formation of singlet oxygen in perfluorohexane [77]. Although no actual oxidations were performed with this latter reagent it was used to establish that the lifetime of singlet oxygen in perfluorohexane was 7 ms, some two orders of magnitude greater than in benzene or toluene [77, 78].

For comparison, a soluble poly(ethylene glycol)supported tetraphenylporphyrin (**37**) has been synthesized and shown to be effective in photooxygenation reactions [79]. Moreover the catalyst was readily recovered from solution by precipitation with ether and the recycled substance was reported to be as active as the virgin material: quite how **35** is protected from reaction with singlet oxygen is unclear.

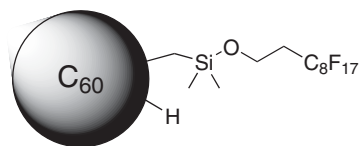
Thus, it appears that the appendage of fluorous chains to both porphyrins and  $\text{C}_{60}$  leads to superior sensitizers for the generation of singlet oxygen, resulting in both more efficient and less readily oxidized catalysts, especially when employed in perfluoroalkane or perfluoroarene solvents. A caveat arises though in light of the work of Chambers, who showed



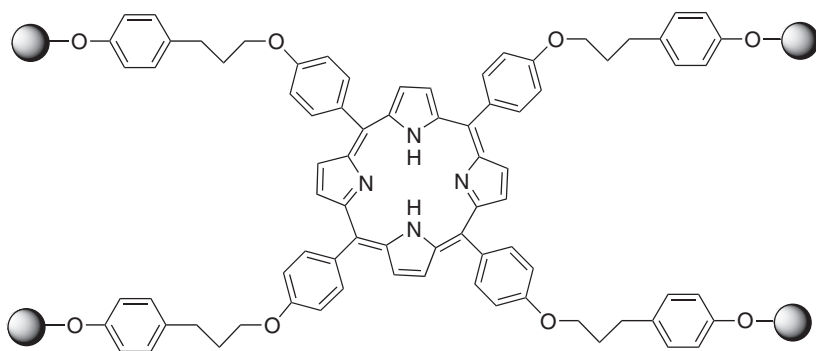
**34:**  $R_f = \text{CF}_2(\text{OC}_3\text{F}_7)_2\text{Cl}$ ,  
MW: 1976, %F: 53



**35**



**36:** MW: 1256, %F: 26



**37**

**Tab. 10.4-9.** Singlet oxygenations sensitized by **36** hexafluorobenzene

Substrate	Product	Mol% <b>36</b>	% Yield
		0.05	91
		0.5	95
		0.5	94 (87:13 mixture)
		1.5	91

that simple tetraphenylporphyrin-sensitized singlet oxygen reactions can be carried out very effectively when a catalytic quantity of the porphyrin is suspended in either perfluorohexanes or perfluorooctanes [80]. These latter reactions owe their success to the high solubility of oxygen in the fluoruous hydrocarbons and to the extended lifetime of singlet oxygen in fluoruous hydrocarbons [77, 78], and perhaps also to the insoluble nature of the sensitizer, which should limit its oxidation by singlet oxygen. This prompts the question as to the true importance of **33** and **36** in the above sequences when compared with the increased solubility of oxygen in the fluoruous media employed. It also has to be noted that in none of the above cases, with the exception of the polymer-supported system **37**, was actual catalyst recovery described leading one to wonder if the best solution might simply be the use of inexpensive tetraphenylporphyrin in a perfluorohydrocarbon as reported by Chambers [80].

### Acknowledgments

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## 10.5

### Fluorous Protecting Groups and Tags

Wei Zhang

#### 10.5.1

##### Introduction

Protecting group chemistry is an important sub-discipline of organic synthesis [1]. In traditional solution-phase synthesis, as the structure complexity increases, the control of diverse reactivity can be achieved by the introduction of protecting groups to block undesired reaction sites and allow chemical transformations to take place elsewhere within a molecule. In solid-phase synthesis, however, protecting groups usually serve as a linker to anchor substrates onto the solid support [2]. Linkers for solid-phase synthesis have bifunctional moieties; one of the functionalities is permanently bound to a solid support while the other one is temporarily attached to a starting material so that it can be cleaved to release the product from the support at the end of the synthesis. A spacer between the linker and the support is also used to give attached-substrates more mobility and better reaction kinetics. Linkers and

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## 10.5

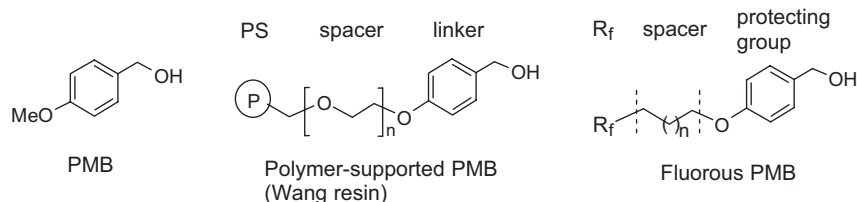
### Fluorous Protecting Groups and Tags

Wei Zhang

#### 10.5.1

##### Introduction

Protecting group chemistry is an important sub-discipline of organic synthesis [1]. In traditional solution-phase synthesis, as the structure complexity increases, the control of diverse reactivity can be achieved by the introduction of protecting groups to block undesired reaction sites and allow chemical transformations to take place elsewhere within a molecule. In solid-phase synthesis, however, protecting groups usually serve as a linker to anchor substrates onto the solid support [2]. Linkers for solid-phase synthesis have bifunctional moieties; one of the functionalities is permanently bound to a solid support while the other one is temporarily attached to a starting material so that it can be cleaved to release the product from the support at the end of the synthesis. A spacer between the linker and the support is also used to give attached-substrates more mobility and better reaction kinetics. Linkers and



**Scheme 10.5-1.** Normal, polymer-supported, and fluorous PMB protecting groups

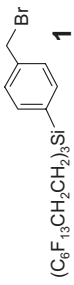
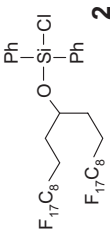
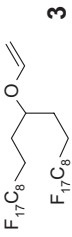
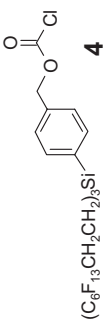
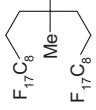
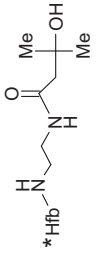
their associated techniques play a key role in the solid-phase combinatorial chemistry (Scheme 10.5-1).

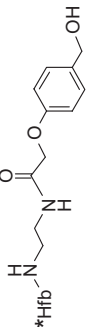
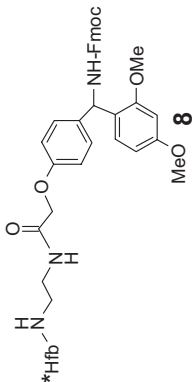
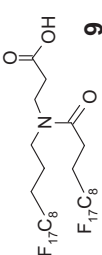
The recent development of fluorous synthesis has provided a solution-phase alternative to solid-phase synthesis [3]. Functionalized perfluoroalkyl groups (R<sub>f</sub>), instead of polymer supports (PS), are employed as the “phase tag” to facilitate the separation process. Compared with solid-phase synthesis, fluorous synthesis has some unique features: (1) good solubility of fluorous compound in many organic solvents; (2) favorable solution-phase reaction kinetics; (3) easy intermediate analysis and purification by conventional tools such as NMR, MS, and HPLC; (4) easy adaptation of literature reaction conditions; and (5) flexibility of reaction scale and scope. As an important part of fluorous synthesis, fluorous protecting groups and related tags have been developed and applied in numerous solution-phase syntheses. Similar to their polymer-supported counterparts, the fluorous protecting groups are attached to a perfluoroalkyl chain through a spacer (Scheme 10.5-1). The spacer in fluorous protecting groups is used to separate the functional group from the strong electron-withdrawing R<sub>f</sub> group to minimize its effect in the reactivity of the functional group. Each fluorous protecting group has a definite molecular weight, while polymer-supported protecting groups are usually expressed by resin loading (mmol g<sup>-1</sup>) in a certain range. With the use of fluorous protecting groups, chemists can have accurate control of stoichiometry and do not have to worry about the swelling properties associated with the resin. Scheme 10.5-1 shows the structures of a normal *p*-methoxybenzyl (PMB) group along with its polymer-supported (PS-PMB) and fluorous (F-PMB) versions.

Fluorous protecting groups can be classified into two categories based on their fluorine content and associated separation methods. The “heavy” fluorous protecting groups usually contain greater than 60% of fluorine by molecular weight. The “light” ones contain less than 40% of fluorine. Reactions involving “heavy” fluorous protecting groups usually require a certain amount of fluorous solvent for the reactions, and product purifications are conducted by liquid extraction in an organic/fluorous biphasic system or an aqueous/organic/fluorous triphasic system. With “light” fluorous protection groups, reactions can be performed without fluorous solvent and the separations are accomplished by fluorous silica gel-based solid-phase extraction (FSPE) or fluorous HPLC (FHPLC). FSPE can efficiently separate fluorous molecules from non-fluorous molecules, while FHPLC can separate a mixture of fluorous compounds based on their fluorine content (see Chapter 8). This chapter reviews the progress on fluorous protecting group chemistry. Its application in solution-phase parallel and mixture syntheses for small molecules, peptides, and oligosaccharides will be discussed.



Tab. 105-1. "Heavy" fluorous protecting groups

Protecting group	Structure	Functional group protected	Conditions for		Reference
			protection	de-protection	
F-Benzyl (F-Bn)		Alcohols	NaH, TBAI DMF, BTF	H <sub>2</sub> /Pd(OH) <sub>2</sub> FC-72	4
F-Silyl		Alcohols	NEt <sub>3</sub> , DMAP CH <sub>2</sub> CH <sub>2</sub> , rt	TBAF, THF 3 h, rt	5
F-Alkoxy ethyl		Alcohols Amines	cat. CSA Et <sub>2</sub> O, rt or THF, 65 °C	CSA Et <sub>2</sub> O, MeOH 3 h, rt	6
F-Carbobenzylloxy (F-Cbz)		Amines	DIEPA or NEt <sub>3</sub> THF	NEt <sub>3</sub> , DMF	7a
F- <i>t</i> -Butoxy		Carboxylic acids	DCC, DMAP CH <sub>2</sub> CH <sub>2</sub> , rt	TFA 15 h, rt	8
		Carboxylic acids			9

F- <i>p</i> -Methoxybenzyl (F-PMB)		Alcohols	9
F-Trialkoxybenzhydryl (F-Rink-type)		Carboxylic acids	9
F-Carbonyl (Bpf')		Alcohols	10

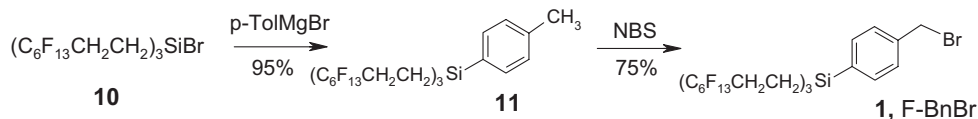
\*Hfb is a fluorous support containing six C<sub>8</sub>F<sub>17</sub> groups.

## 10.5.2

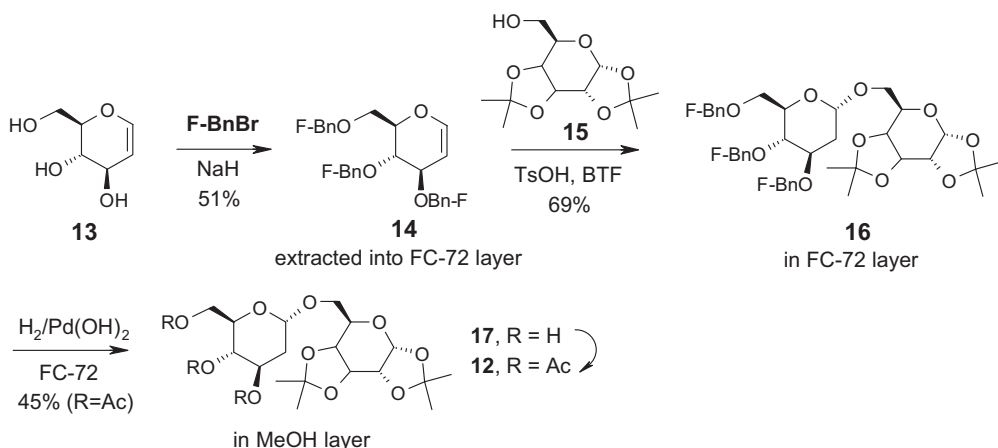
## “Heavy” Fluorous Protecting Groups

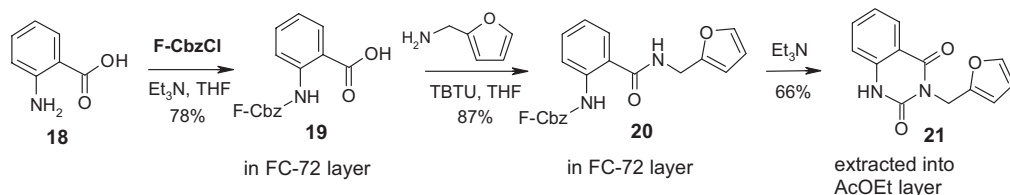
“Heavy” fluorous protecting groups usually contain two, three or even more  $R_f$  chains. “Heavy” fluorous protection agents have been reported in the literature including F-benzyl bromide [4], F-alkyloxysilylchloride [5], F-vinyl ether [6], F-carbobenzyloxy chloride (F-CbzCl) [7], F-*t*-butyl alcohol [8], F-*p*-methoxybenzyl (F-PMB or F-Wang-type) bromide [9], F-trialkoxymethyl Fmoc amine (F-Rink-type) [9], F-carboxylic acid [10]. Their structures, utilities, and general conditions for protection and deprotection are summarized in Table 10.5-1.

The Curran group reported the synthesis of fluorous benzyl bromide **1** [4]. It was prepared by the reaction of *p*-tolyl magnesium bromide with readily available tris(perfluorohexylethyl)silyl bromide **10** followed by bromination of the intermediate **11** (Scheme 10.5-2). The utility of F-BnBr as an alcohol protecting agent was demonstrated in the synthesis of disaccharide **12** (Scheme 10.5-3). The hydroxyl group of D-glucal **13** was protected with 4 equiv of F-BnBr using NaH as a base and BTF as the solvent. The crude tribenzyl glucal derivative **14** was purified by triphasic ( $H_2O/CH_2CH_2/FC-72$ ) extraction to remove organic and inorganic materials followed by flash silica gel chromatography to remove the excess benzylating agent and other impurities. The fluorous glucal **14** was then coupled with excess diacetone galactose **15** under standard reaction conditions in BTF to give pure fluorous disaccharide **16** after triphasic extraction. The fluorous compound **16** was debenzylated by catalytic hydrogenation with  $H_2$  and  $Pd(OH)_2$  in FC-72. After another triphasic extraction,



Scheme 10.5-2. Preparation of F-BnBr

Scheme 10.5-3. F-Bn in the synthesis of disaccharide **12**



**Scheme 10.5-4.** F-Cbz in the synthesis of quinazoline-2,4-dione **21**

the product **17** in the organic phase was acylated to give disaccharide **12**. The deprotected F-Bn can be recovered from the FC-72 layer as **11**.

F-alkyloxysilylchloride **2** and F-vinyl ether **3** were both developed by the Wipf group for alcohol and amine protections [5, 6]. F-CbzCl **4** was developed by Bannwarth and coworkers, who have applied it in fluorous biphasic synthesis of quinazoline-2,4-diones (Scheme 10.5-4) [7a]. Amidation of fluorous protected anthranic acid **19** followed by cyclative deprotection of **20** led to the formation of quinazoline-2,4-dione **21**. This chemistry has been modified by absorption of the fluorous chains onto the fluorous silica gel *via* strong fluorine–fluorine interactions to eliminate the use of fluorous solvents for the reaction and separations [7b].

Cobas and coworkers prepared several F-*t*-butyl alcohols bearing one or two  $R_f$  chains [8]. Only those with two  $R_f$  chains such as **5** were found to have a strong affinity for fluorous liquid extraction. The Inazu group recently reported the preparation of F-*t*-butyl alcohol **6**, which is attached to a much bigger fluorous tag Hfb that contains six  $C_8F_{17}$  chains [9]. The same fluorous support Hfb was used in the preparation of F-PMB **7** and F-trialkoxymethyl-type protecting group **8** [9]. Inazu and coworkers developed Bfp tagged-fluorous carboxylic acid **9** [10]. Application of Hfb and Bfp tagged protection agents in peptide and oligosaccharide synthesis will be discussed in Section 10.5.6.

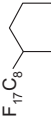
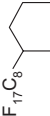
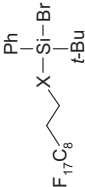



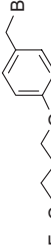
### 10.5.3

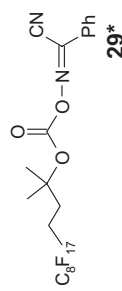
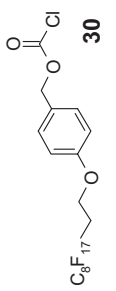
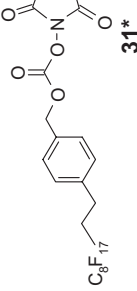
#### “Light” Fluorous Protecting Groups

The disadvantage of being costly and environmentally persistent when using “heavy” tags and fluorous solvents has been addressed by using “light” fluorous tags which not only gave “heavy” fluorous pony tails a big hair cut but also eliminated the use of a fluorous solvent at both the reaction and separation steps (see Chapter 8). Improved solubility and hence the reactivity of “light” fluorous-tagged molecules in organic solvents is a bonus. The combination of “light” fluorous tags with FSPE and FHPLC has become a trend in the development of new fluorous synthesis [11]. “Light” fluorous protecting agents listed in Table 10.5-2 include F-tetrahydropyranyl (F-THP) iodide and its sulfoxide analog [12], F-silylbromide [5], F-silane [13], F-PMB bromide [14], F-*t*-butyl alcohol [8], F-primary alcohol [15], F-BocOSu [16], F-CbzCl [17], and F-CbzOSu [18].

Wipf and coworkers reported the synthesis of two types of F-THP protection groups, **22** and **23**, both containing a single  $C_8F_{17}$  chain [12]. These two compounds were used to protect alcohols and the purification was carried out by SPE over fluorous silica gel. The Wipf group also prepared the single  $R_f$  chain silylbromide **24** [5]. The purification of protected substrates was done by liquid/liquid extraction with FC-72/ $CH_3CN$ . An alternative F-silyl

**Tab. 10.5-2.** “Light” fluoros protecting groups

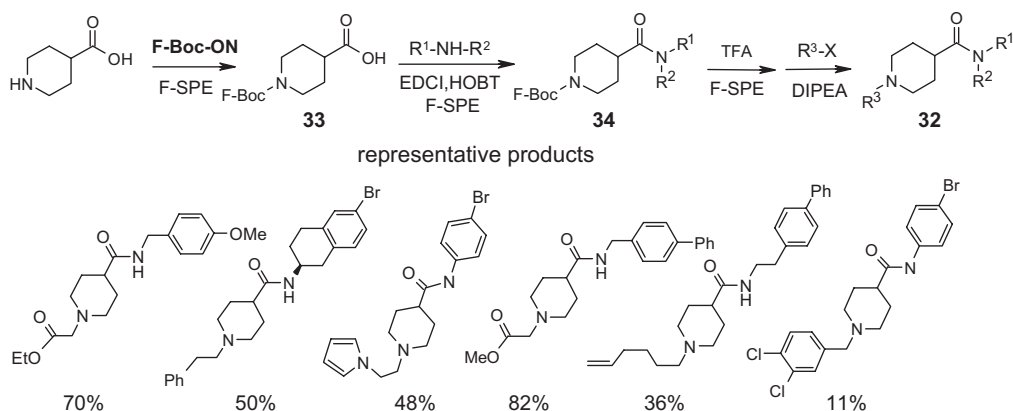
Protecting group	Structure	Functional group protected	Conditions for Protection	Deprotection	Reference
F-THP	 <p><b>22</b></p>  <p><b>23</b></p>	Alcohols	Cp <sub>2</sub> ZrCl <sub>2</sub> , AgClO <sub>4</sub> CH <sub>2</sub> Cl <sub>2</sub> , 4 Å MS	TsOH, MeOH, THF, 70 °C	12
F-Silyl	 <p><b>24</b> X = O or nothing</p>	Alcohols	NEt <sub>3</sub> , DMAP CH <sub>2</sub> CH <sub>2</sub> , rt	TBAF, THF 3 h, rt	5
F-4-Butyloxy	 <p><b>25*</b></p>	Alcohols	TfOH, 2,6-lutidine CH <sub>2</sub> Cl <sub>2</sub>	HF·Py THF	13
F-4-Butyloxy	 <p><b>26</b></p>	Carboxylic acids	DCC, DMAP CH <sub>2</sub> CH <sub>2</sub> , rt	TFA 15 h, rt	8
F-Alkoxy	 <p><b>27*</b></p>	Carboxylic acids	DIC, HOBT, DMAP, DMF	cyclative deprotection	15
F-PMB	 <p><b>28*</b></p>	Alcohols	t-BuOK, THF	DDQ	14

F-Boc	 <b>29*</b>	Amines	THF	TFA, CH <sub>2</sub> Cl <sub>2</sub>	16
F-Cbz	 <b>30</b>	Amines	DIPEA	TFA, H <sub>2</sub> O (98/2)	17
	 <b>31*</b>	Amines	NEt <sub>3</sub> , THF/H <sub>2</sub> O	H <sub>2</sub> , Pd-C MeOH	18

\* Homologs with different R<sub>f</sub> groups are also prepared.

group **25** and its homologs with a different fluorine content ( $R_f = C_3F_7$  to  $C_{10}F_{21}$ ) prepared by the Curran group has been employed in the fluorous mixture synthesis of mappicines [13] as well as quasiracemic synthesis of enantiomers of pyridovericin [19] (Section 10.5.5). PMB bromide **28** with a  $C_8F_{17}$  chain and its homologs have been applied to the mixture synthesis of truncated analogs of discodermolide [14] (Section 10.5.5). A *t*-butyl alcohol **26** with a  $C_6F_{13}$  chain prepared by the Cobas group was found to have the best reactivity compared with its analogs containing two  $C_6F_{13}$  or  $C_8F_{17}$  chains [8]. However, a protected substrate with the single  $C_6F_{13}$  chain did not have sufficient affinity for fluorous liquid extraction. The use of FSPE is expected to improve the separation efficiency dramatically.

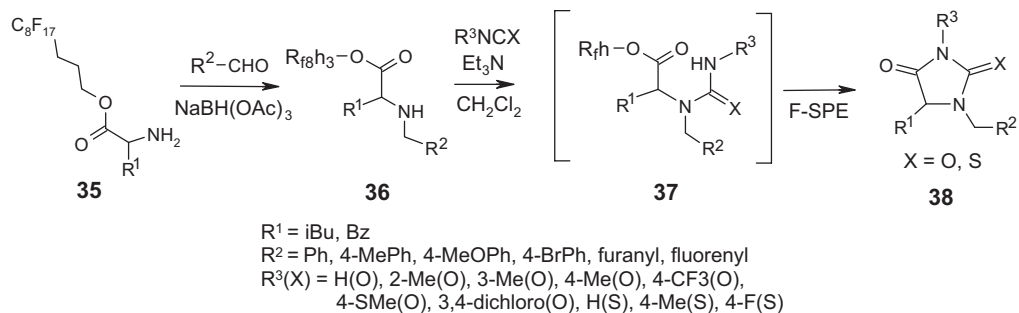
Curran and coworkers have prepared a series of F-BocON compounds containing different  $R_f$  chains [16]. The BocON **29** with a single  $C_8F_{17}$  chain was used in the parallel synthesis of isonipecotic acid derivatives **32** (Scheme 10.5-5). The amino group of the isonipecotic acid was first protected by the F-Boc. The fluorous intermediate **33** was then coupled with eight amines ( $R^1NHR^2$ ) to give **34**. After deprotection of F-Boc with TFA, the resulting compounds were further reacted with 12 electrophiles ( $R^3X$ ) to give a 96-compound library.



**Scheme 10.5-5.** Synthesis of isonipecotic acid derivatives with F-Boc

F-CbzCl **30** and F-CbzOsu **31** have been prepared by the van Boom and the Curran groups, respectively. The F-CbzCl has been employed in the purification of synthetic peptides [17] (Section 10.5.6). F-CbzOsu compounds with a  $C_6F_{13}$  or  $C_8F_{17}$  chain have been used to attach to 18 natural (L)-amino acids as well as 18 synthetic (D)-amino acids [18]. These protected amino acids could be useful building blocks for fluorous synthesis of small molecules and peptides.

Using primary fluorous alcohol **27** protected amino acids as the starting material, Zhang and Lu at FTI recently prepared a 120-member hydantoin and thiohydantoin library by parallel synthesis (Scheme 10.5-6) [15]. Two fluorous amino esters **35** ( $R^1 = i\text{-Bu}$  and  $Bz$ ) underwent reductive amination with six aldehydes. Each of the 12 intermediates **36** was further reacted with ten aryl isocyanates or aryl isothiocyanates. *In situ* cyclization of the resulting ureas or thioureas **37** displaced the fluorous tag and afforded the heterocyclic products **38**.



**Scheme 10.5-6.** Synthesis of a substituted hydantoin and thiohydantoin library

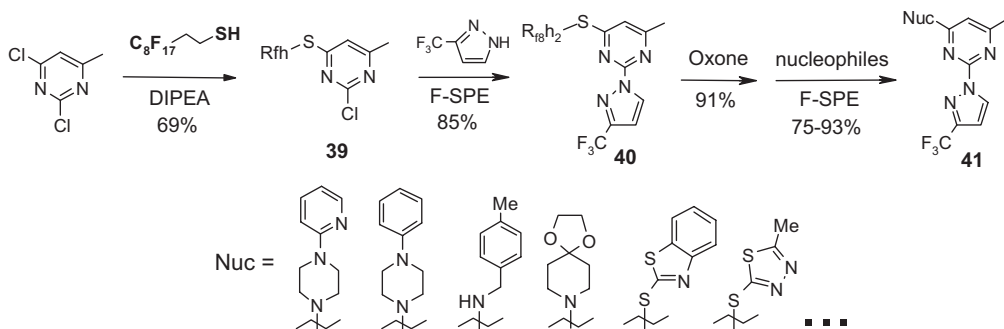
The average yield for this two-step synthesis was around 50% and purities of the final products after FSPE were between 85 and 95%. This work shows the power of fluorous tags to effect the speedy synthesis of high quality libraries in solution.

#### 10.5.4

##### Other Fluorous Tags

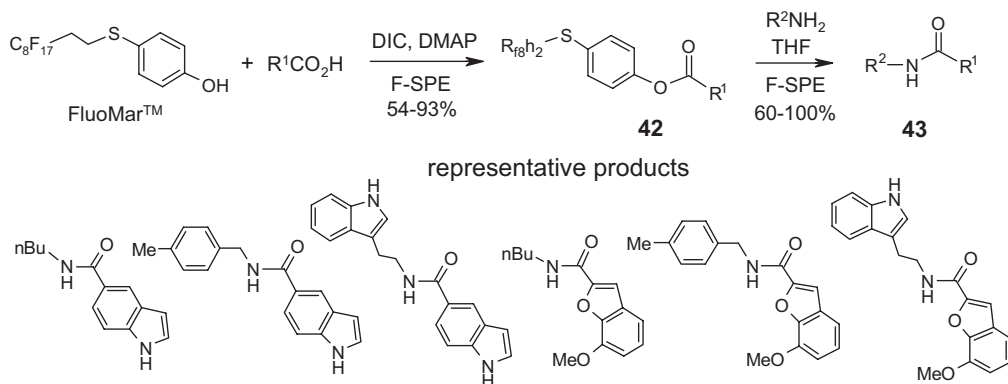
In addition to fluorous protecting groups, other fluorous moieties can also be used as “phase tags” attached to starting materials for parallel synthesis. For example, fluorous thiol was used as a nucleophile to displace the chlorine in a pyrimidine ring (Scheme 10.5-7) [20]. The tagged substrate **39** was further displaced with a 3-(trifluoromethyl)-pyrazole to give **40**. The thiol tag was then activated by oxidation to a sulfone and displaced by a set of nucleophiles to afford disubstituted pyrimidines **41**. The purities of final products after the FSPE were greater than 90%.

The Marshall resin is well-known in solid-phase synthesis. FTI recently introduced FluoMar™ as a fluorous version of the Marshall resin for solution-phase synthesis (Scheme 10.5-8) [21]. In the preparation of a demonstration library, carboxylic acids were coupled with FluoMar™ under standard conditions using diisopropylcarbodiimide (DIC) and dimethylaminopyridine (DMAP). The fluorous tag in compound **42** was then displaced with a set of amines to give amides **43**.



**Scheme 10.5-7.** Synthesis of disubstituted pyrimidines with a fluorous thiol tag





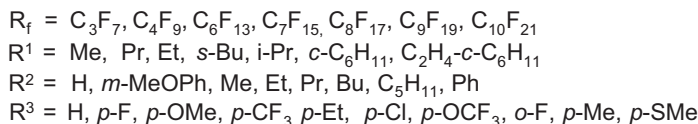
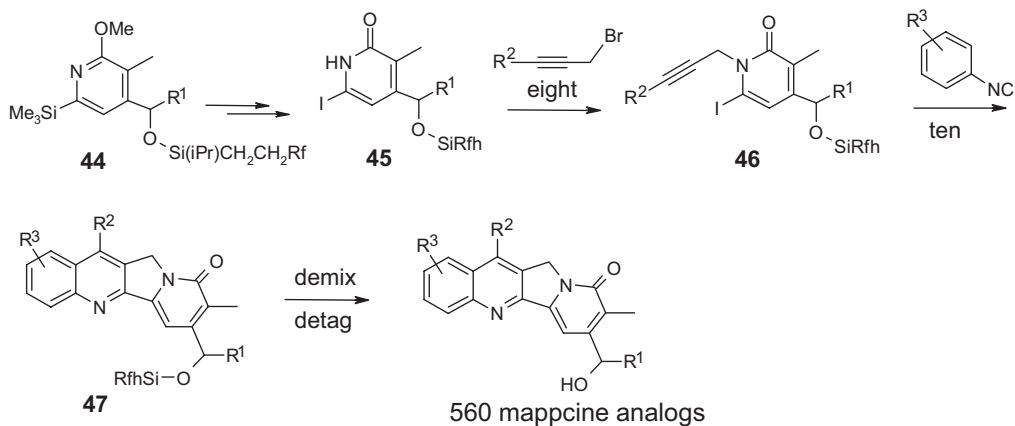
**Scheme 10.5-8.** Fluorinated tag in the parallel synthesis of amides

#### 10.5.5

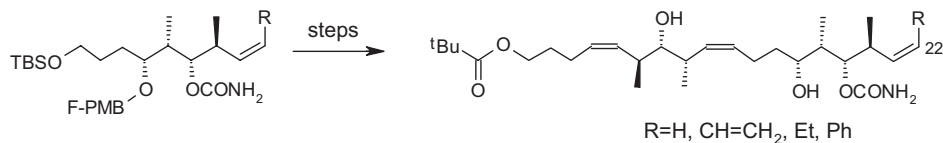
#### Fluorous Protecting Groups in Mixture Synthesis

In the fluorous mixture synthesis (see Chapter 7), a set of starting materials is individually tagged with a corresponding set of homologous fluorous protecting groups. The tagged substrates are then mixed and taken through a multi-step mixture synthesis. The tagged final products are demixed by FHPLC and deprotected to give individually pure products.

The utility of F-silyl groups has been demonstrated in the mixture synthesis of a 560-member mappicine library (Scheme 10.5-9) [13b]. Seven pyridines **44** with different  $R^1$  groups were protected with seven F-silyl groups with different  $R_f$  chains and underwent a



**Scheme 10.5-9.** F-Silyl tags in mixture synthesis of mappicine analogs

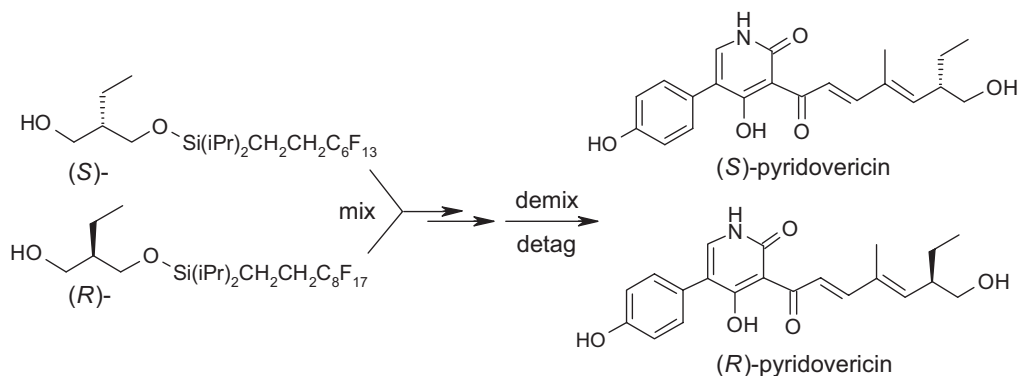


**Scheme 10.5-10.** F-PMB tag in the synthesis of (+)-discodermolide and truncated analogs

four-step mixture synthesis including reactions with eight *N*-propargylbromides and ten isonitriles to give 80 tagged product mixtures **47**. Each mixture sample of **47** was demixed by FHPCL and then detagged by HF-pyridine to give a 560-member mappicine library.

Four F-PMB bromides ( $R_f = \text{C}_4\text{F}_9, \text{C}_6\text{F}_{13}, \text{C}_8\text{F}_{17}, \text{C}_{10}\text{F}_{21}$ ) have been used to protect the hydroxyl group of four starting materials with different *R* groups (H,  $\text{CH}=\text{CH}_2$ , Et, Ph) in the synthesis of four truncated analogs of natural product (+)-discodermolide at the C22 position (Scheme 10.5-10) [14].

Different fluororous group protected enantiomers can be mixed, undergo quasiracemic synthesis, and lead to the formation of two enantiomeric products. In a synthesis of two enantiomers of pyridovericin (Scheme 10.5-11), the (*S*)- and (*R*)-tagged starting materials with two different fluororous silanes ( $R_f = \text{C}_6\text{F}_{13}$  and  $\text{C}_8\text{F}_{17}$ ). The mixture was then taken through a multi-step synthesis to give a tagged product mixture. FHPCL demixing of two quasienantiomers followed by deprotection released (*S*)- and (*R*)-enantiomers of pyridovericin [19].

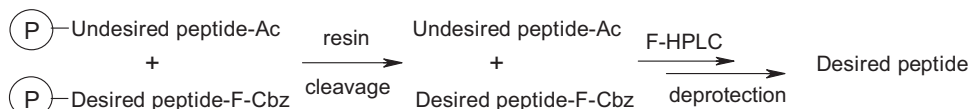


**Scheme 10.5-11.** F-Silyl tags in quasiracemic synthesis of (*S*)- and (*R*)-pyridovericins

### 10.5.6

#### Fluorous Protecting Groups in Peptide and Oligosaccharide Synthesis

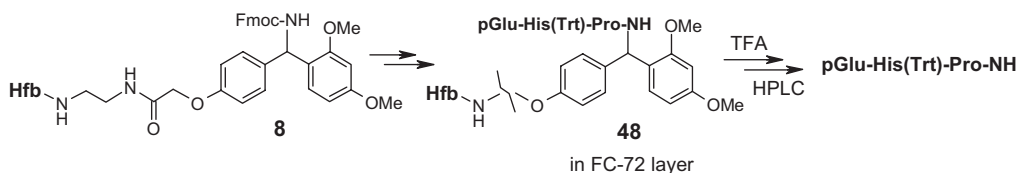
The van Boom group reported the use of fluororous protection strategy in solid-phase peptide synthesis (Scheme 10.5-12) [17]. The unreacted free amino groups at each condensation step were capped with an acetyl group. The amino group of the final product was tagged with F-Cbz. Cleavage of oligomers from the resin provided a mixture of the desired F-Cbz-tagged



**Scheme 10.5-12.** F-Cbz tagging of desired product in solid-phase peptide synthesis

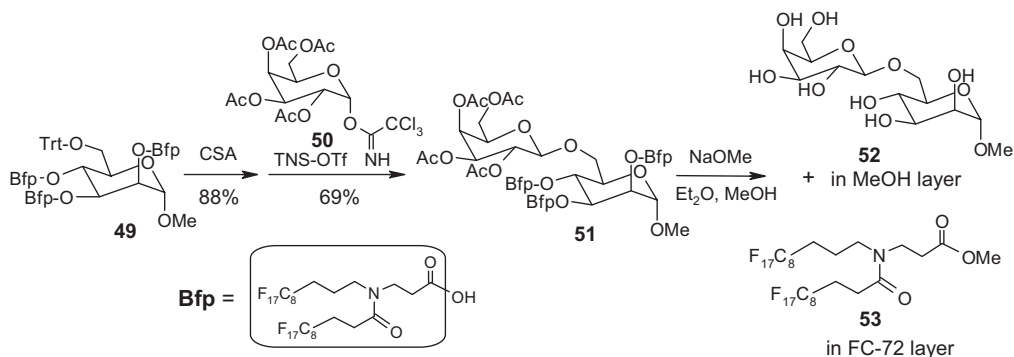
product and acetyl-capped non-fluorous truncated sequences. The F-Cbz tagged product was separated from the non-fluorous material by FHPLC and then detagged to provide the desired product. Peptides containing 7 to 20 amino acids were prepared by this method.

Inazu and coworkers employed a fluorous Rink-type protecting group with an Hfb tag as the fluorous support in a tripeptide synthesis (Scheme 10.5-13) [9]. At each coupling step, a four-fold excess of amino acid derivative was used. The excess reagent and coupling agents were removed by extraction with MeCN from the FC-72 layer. Product **48** in the FC-72 layer was deprotected and purified by HPLC to give a pure tripeptide.



**Scheme 10.5-13.** Use of fluorous tagged substrate for solution-phase peptide synthesis

Fluorous protecting groups have also been used in oligosaccharide synthesis. The Inazu group employed a fluorous propanoyl (Bfp) containing two  $C_8F_{17}$  chains to protect three hydroxyl groups of a mannose derivative (Scheme 10.5-14) [10a]. The triphenylmethyl (Trt) group of **49** was selectively removed by treatment with 10-camphorsulfonic acid (CSA). The deprotected hydroxyl group was coupled with galactose derivative **50** to give fluorous disaccharide **51**. Deprotection of both the acetyl and Bfp groups followed by FC-72/MeOH extraction gave disaccharide **52** in the MeOH layer in 93%. The protection group was re-



**Scheme 10.5-14.** Synthesis of disaccharide with Bfp protection

covered from the FC-72 layer as a methyl ester **53** in 92%. A tetrasaccharide was also prepared in the same manner.

Seeberger and coworkers reported a different approach [22]. A fluorous silyl protection group [ $\text{Si}(i\text{-Pr})_2\text{CH}_2\text{CH}_2\text{C}_6\text{F}_{13}$ ] was used to cap the hydroxyl group of the undesired sequence, while the desired oligomeric species were non-fluorous. HPLC was used for the separation of the desired oligosaccharide from the fluorous byproduct. Since the final product was the untagged species, no detagging step was needed.

#### 10.5.7

### Conclusion

The use of a protecting group in fluorous synthesis is a “one stone hits two birds” strategy. The functional group protection and the “phase tag” introduction can be accomplished by a single operation. Traditional solution-phase reaction conditions can be used for fluorous protections as well as deprotections. Liquid extraction with fluorous solvents can be used for purification of “heavy” fluorous compounds. FSPE and FHPLC can be used to separate “light” fluorous compounds without the use of fluorous solvents. Similar to the linkers used in solid-phase synthesis, the fluorous protecting groups can be used as the phase tag for solution-phase parallel and combinatorial synthesis. The current demands for higher purity, larger quantity, and more diversified molecules have shifted the drug discovery effort from solid-phase synthesis towards solution-phase synthesis. Such a change in the pharmaceutical mentality presents many opportunities to the development of fluorous protecting group and related technologies in the synthesis of small molecule, peptide and oligosaccharide libraries for lead generation and optimization programs.

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## 10.6

### Fluorous Scavengers

Craig W. Lindsley\* and William H. Leister

#### 10.6.1

##### Introduction

During the early 1990s, most research under the rubric of combinatorial chemistry employed solid-phase organic synthesis (SPOS) to generate large libraries of small molecules [1]. SPOS was an attractive strategy in that reaction work-up and purification involved only simple filtration and resin washing. Despite this key advantage, SPOS failed to deliver an increase in drug candidates and never received wide acceptance due to a number of practical issues that have been discussed at length elsewhere [2]. By the end of the decade, a complementary approach emerged under the moniker “solution-phase parallel synthesis” (SPPS) [3]. This homogeneous solution phase approach was hampered, not by conducting the reactions themselves, but by the time-consuming workup and purification procedures [4]. As more interest was focused on SPPS, researchers from both academia and industry quickly developed an arsenal of practical tools for expedient purification based on simple phase-separation methods, which have gained general acceptance by both organic and medicinal chemists.

Key to the success of this SPPS was the development of “scavenging reagents” [5]. Scavenging (quenching) reagents are highly effective tools for the rapid purification and isolation of the desired product(s) from a solution phase reaction by forming either covalent or ionic bonds with excess reactants and/or reaction byproducts. In general terms, scavenging can be

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## 10.6

### Fluorous Scavengers

Craig W. Lindsley\* and William H. Leister

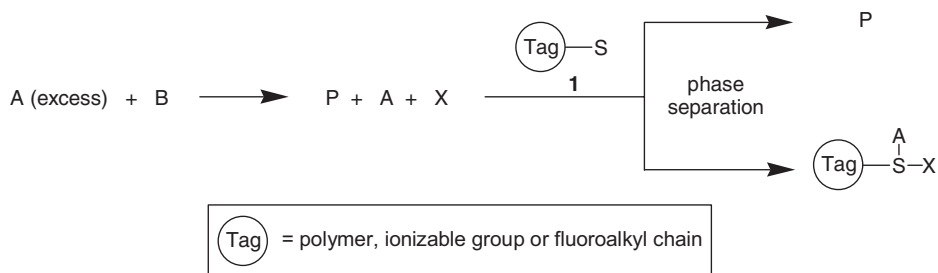
#### 10.6.1

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considered a “phase switching” technique wherein a chemoselective reaction is employed to switch the phase of one product relative to another by virtue of a “tag” attached to the scavenging reagent. There are three major classes of scavenging reagents categorized by the nature of the phase tag: solid-phase polymers, ionizable functional groups and fluoroalkyl chains. In a typical scenario, an excess of reactant **A** is combined with **B** to provide product **P** along with **A** and other reaction byproducts **X** in a homogeneous solution phase reaction. Then, **A** and **X** are chemoselectively removed from solution in a subsequent “scavenging” step with a scavenging reagent **1** linked to a phase tag. After separation of the resulting phases, the product, **P**, is obtained in high purity simply by evaporation of the solvent (Scheme 10.6-1).



**Scheme 10.6-1.** SPPS with scavenging reagents

The most commonly used tags are solid-phase polymers, and hence, a wealth of literature centers on the applications of polymer-supported scavenger reagents to transfer a captive species from the organic liquid phase to the solid phase for removal by filtration [5, 6]. Indeed, this approach has gained wide-spread acceptance due to the commercial availability of a diverse array of electrophilic and nucleophilic polymer-supported scavenging reagents [7]. However, polymer-supported scavengers do have limitations. Firstly, hindered access to pendant functionality, especially in higher-loading resins, and the biphasic, heterogeneous nature of the reaction system results in slower overall kinetics. Secondly, solvent selection and volume is dictated by the swelling requirements of the resin matrix and is critical for effective scavenging. Finally, reactions employing polymer-supported reagents are not readily scalable (for example, increasing from 0.1 mol to 10 mmol) for the resynthesis of active compounds.

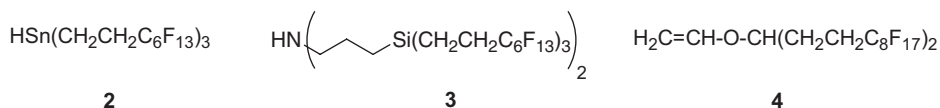
Another commonly used tagging strategy involves linking a scavenger to an ionizable functional group, such as a COOH ( $\text{p}K_{\text{a}} < 5$ ) or an  $\text{NR}_2$  ( $\text{p}K_{\text{a}} > 25$ ) [8]. In this instance, the captured species can be selectively phase transferred by either pH adjusted liquid/liquid extraction or by solid-phase extraction (SPE) on an ion-exchange cartridge leaving the desired product either in the organic liquid phase or in the SPE cartridge eluent. SPE is a very attractive method for purification as a crude reaction is simply applied to a disposable silica plug, grafted with either a sulfonic acid (SCX – strong cation exchange) or a tertiary amine (SAX – strong anion exchange), and neutral molecules are eluted off with methanol while ionizable functional groups are retained on the SPE cartridge. Unfortunately, this strategy impacts the diversity of a library by limiting the presence of ionizable groups to either neutral or orthogonally charged library members.

Concurrently, Curran and coworkers were developing new methodologies that extended the generality of the fluorous phase as a strategic alternative to the aqueous, organic liquid and solid phase [9]. Relying on the affinity that fluoroalkyl chains have for each and the phobia that they exhibit towards both organic molecules/solvents and aqueous solvents, researchers began examining fluorous tags as a means of phase switching. Initially, efforts centered on “heavy” fluorous tags (60% or more fluorine content by molecular weight, i.e., 18 or more difluoromethylene,  $\text{CF}_2$ , groups) that utilized liquid/liquid phase separation to isolate fluorous-tagged molecules from untagged organics. Typically, a three-phase liquid/liquid extraction, requiring an organic layer, aqueous layer, and a fluorous layer (a per-fluorohexane such as FC-72) delivers pure material. More recently, fluorous solid phase extraction (FSPE) employing fluorous silica gel (reverse-phase silica gel with a fluoro-carbon bonded phase) has been developed to effectively separate both “heavy” fluorous-tagged molecules as well as “light” fluorous-tagged molecules (4–10  $\text{CF}_2$  groups) from untagged organics [10]. The FSPE columns, referred to as FluoroFlash<sup>TM</sup> columns, retain the fluorous-tagged material when eluted with a fluorophobic solvent, such as 80/20 MeOH/ $\text{H}_2\text{O}$ , allowing the untagged organic molecule to rapidly elute from the column [11]. Homogeneous reaction kinetics, generality with respect to charged and neutral functional groups and a variety of efficient phase separation options, have spurred a dramatic increase in the development of fluorous scavenging reagents and protocols.

#### 10.6.2

##### Heavy Fluorous Scavenging

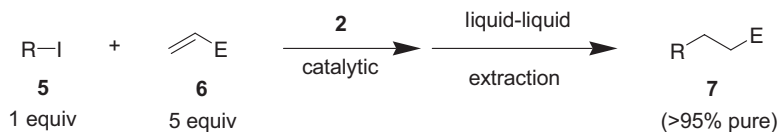
The concept of fluorous scavenging was introduced by Curran in 1996 and only a few applications of heavy fluorous scavenging have been reported to date [12]. These heavy fluorous scavengers contain two or more fluoroalkyl chains and depend on liquid/liquid extraction for purification and include a fluorous trialkyltin hydride **2** for scavenging excess alkenes, a fluorous amine **3** for scavenging isocyanates and a fluorous vinyl ether **4** that served as a “catch and release” agent to separate excess alcohols from reaction mixtures (Scheme 10.6-2) [13]. Importantly, these heavy fluorous reagents were not commercially available and had to be prepared and partitioning coefficients optimized prior to use.



**Scheme 10.6-2.** Heavy fluorous scavengers

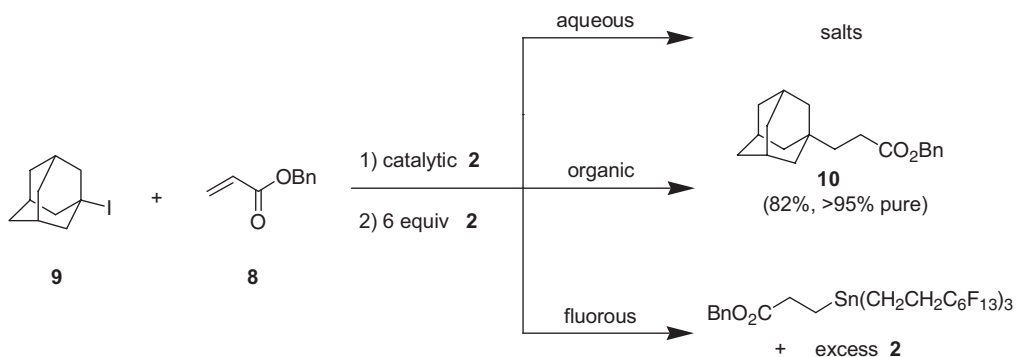
In both catalytic and stoichiometric quantities, **2** was shown to be generally useful for reductive radical and hydrostannation reactions with easy separation from the organic products by liquid/liquid extraction. In Giese reactions, catalytic **2** delivered high yields of product **7** with various alkyl halides **5** when excess alkene **6** (5.0 equiv) was used (Scheme 10.6-3). When the alkene component was volatile, the product **7** was afforded in >95% purity. However, if the excess alkene was not volatile, purity would be poor for this protocol. Since





**Scheme 10.6-3.** Generic Giese reaction with catalytic **2**

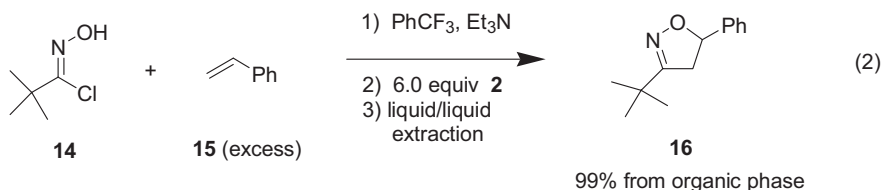
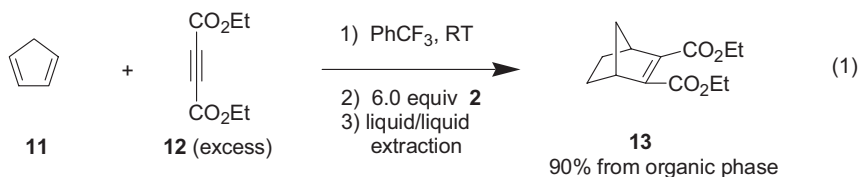
all of the fluorous products partition into the fluorous phase preferentially, hydrostannation, with excess **2**, was reasoned to be a method for removing excess alkene. This hypothesis introduced the technique of “fluorous quenching (scavenging)” whereby a residual undesired organic component at the end of a reaction can be removed by switching to the fluorous phase during workup. In the event, excess, non-volatile benzyl acrylate **8** was first treated with adamantyl iodide **9** and catalytic **2**. When the reaction was judged complete, six equivalents of **2** were added to hydrostannate the excess **8** (Scheme 10.6-4).



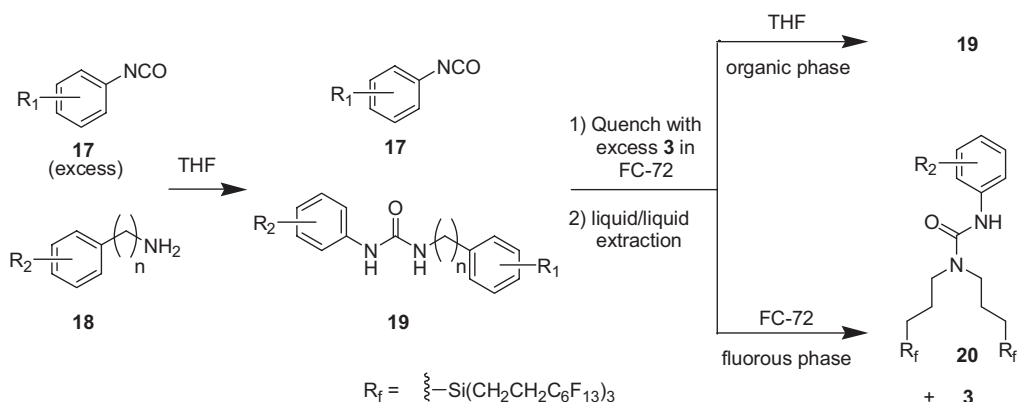
**Scheme 10.6-4.** Heavy fluorous scavenging in the Giese reaction with **2**

After three-phase (FC-72/dichloromethane/water) extractive workup, the organic phase yielded the desired adduct **10** in 82% yield and free from **8**. The application of fluorous scavenging with **2** was further extended to standard Diels-Alder [Eq. (1)] and nitrile oxide cycloadditions [Eq. (2)] with excellent results (Scheme 10.6-5) [13a].

The next heavy fluorous scavenger, amine **3**, was developed specifically with automated SPPS in mind, and proved to be effective for the general scavenging of excess isocyanates in the SPPS of aryl ureas (Scheme 10.6-6). In a generic reaction sequence, excess isocyanate **17** is treated with an amine **18** in THF to generate the aryl urea **19** along with the excess **17**. The reaction is then quenched with fluorous scavenger **3** in FC-72, followed by liquid/liquid extraction to afford pure aryl urea **13** in the organic phase and excess **3** and the scavenged urea adduct **20** in the FC-72 layer. Utilizing an HP 7686 synthesizer, this scavenging protocol could be completely automated to produce several  $3 \times 4$  and  $3 \times 3$  aryl urea libraries with HPLC purities and yields averaging >97% and 86%, respectively. For every library member produced in this fully automated procedure, the organic layer contained less than 0.5 mol% F as determined by  $^{19}\text{F}$  NMR. Several library members were found to be more



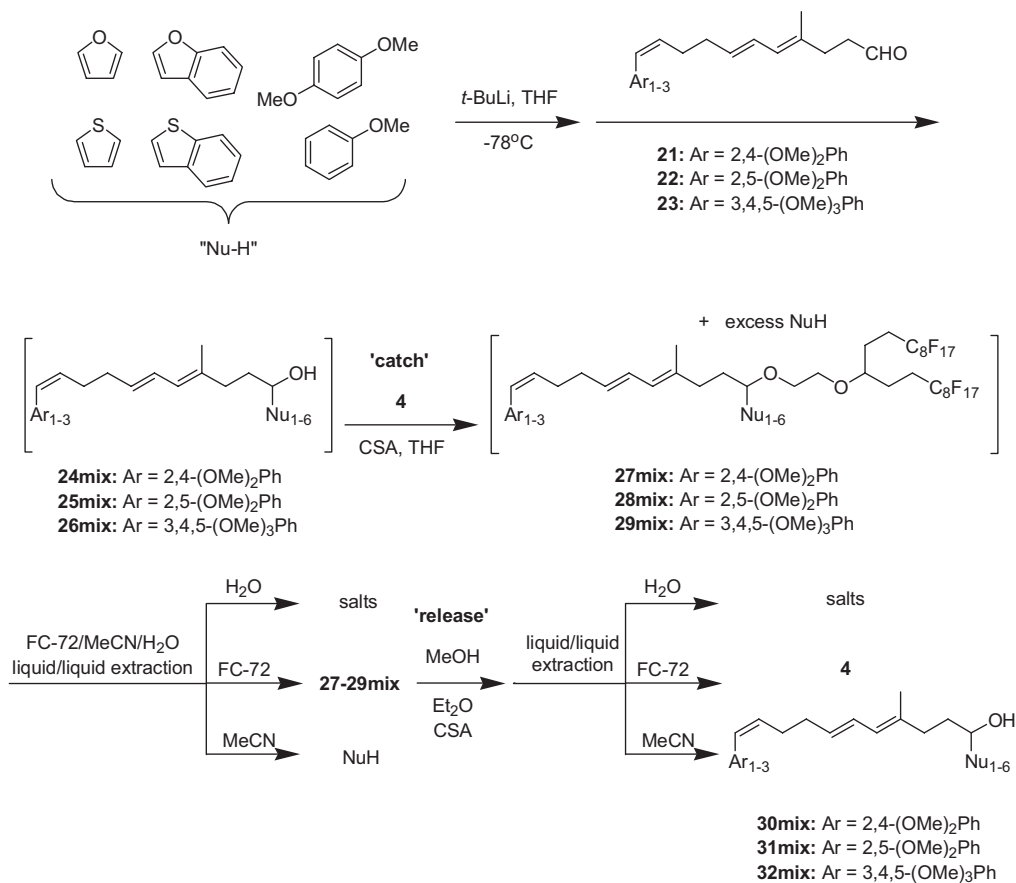
**Scheme 10.6-5.** Application of **2** to Diels-Alder and nitrile oxide cycloaddition reactions



**Scheme 10.6-6.** Heavy fluororous isocyanate scavenging with **3**

potent  $\text{Cl}^-$  secretion inhibitors in the human T84 colon cancer cell line than existing inhibitors [13b].

The next application of heavy fluororous scavenging involved a “catch and release” purification strategy for the mixture synthesis of curacin A analogs using vinyl ether **4** [13c]. In a prototypical example (Scheme 10.6-7), Wipf and coworkers prepared mixtures of up to 18 compounds by exposure of three aldehydes, **21–23**, to an excess of a 1:1:1:1:1 ratio of organolithium reagents (Nu-H) to ensure complete 1,2-addition. The resulting mixture of alcohols, **24–26mix**, was quenched (“caught”) with **4** to provide a mixture of fluororous-tagged adducts **27–29mix** contaminated with excess Nu-H. After liquid/liquid extraction with FC-72/ $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ , **27–29mix** were transferred into the FC-72 layer. The alcohols **30–32mix** were “released” from the fluororous tag by methanolysis and delivered to the organic phase in pure form by another fluororous/organic/aqueous extraction. Following this “catch and release” scavenging protocol, six mixture libraries of analogs were prepared and screened. Despite their simplified structures, this approach identified, in short order, the most potent curacin A analogs identified to date.



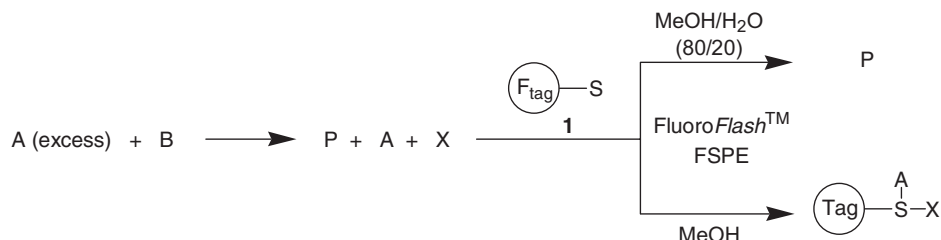
Scheme 10.6-7. "Catch and release" scavenging with 4

Two additional examples of heavy fluorous "catch and release" scavenging in conjunction with liquid/liquid extraction have been reported. In 1997, Curran and coworkers employed a fluorous silane to "catch" alkoxides, generated by the addition of Grignard reagents to carbonyl compounds, and subsequently "released" by treatment with fluoride [9]. In 1999, Curran's lab disclosed the application of a fluorous tin azide for the "catch and release" purification of functionalized tetrazoles [13d].

### 10.6.3

#### "Light" Fluorous Scavenging

The concept of "light" fluorous scavenging was simultaneously introduced in 2002 by researchers from Fluorous Technologies and Merck Research Laboratories and in less than one year multiple applications have been reported based on the paradigm illustrated in Scheme 10.6-8 [14].



**Scheme 10.6-8.** Light fluorine scavenging paradigm

As opposed to the “heavy” scavengers described earlier, these new “light” fluorine reagents contain a single fluorine chain (usually less than 19 F atoms) in the phase tag (molecular weight is significantly reduced), the liquid/liquid extraction has been replaced with a solid-phase extraction over fluorine silica gel (FSPE on *FluoroFlash*<sup>TM</sup> SPE cartridges), and both the reagents and the separation media are commercially available [11, 15]. From the beginning, the goal was to develop a “toolkit” of fluorine-tagged equivalents of known polymer-supported scavenging reagents, and thus far, a dozen light fluorine-tagged scavengers have been described (Table 10.6-1) with applications for quenching excess electrophiles (entries 1–5) and nucleophiles (entries 6–12) in SPPS [14, 16].

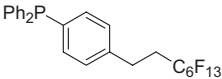
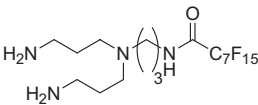
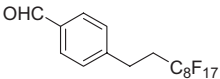
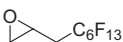
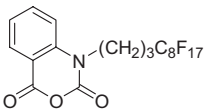
Every application of these scavengers in concert with FSPE has provided the desired products in excellent isolated yields and with purities exceeding 94%. Some representative examples of light fluorine scavengers for SPPS are illustrated in Scheme 10.6-9 [14].

All of the scavengers depicted in Table 10.6-1 provided rapid quenching as compared with their polymer-supported congeners due to homogeneous reaction kinetics. Indeed, in a critical study, fluorine thiol **42** required only 5 min to achieve >95% quenching of bromide **41** as opposed to 50 min for the analogous polymer-supported thiol **43** (Scheme 10.6-10) [14a]. Quenching rates could be further accelerated to less than 1 min for a number of fluorine scavengers by the application of microwave heating [16]. In general, a 10–20 fold decrease in reaction time was observed with light fluorine scavengers versus the analogous polymer-supported scavenger.

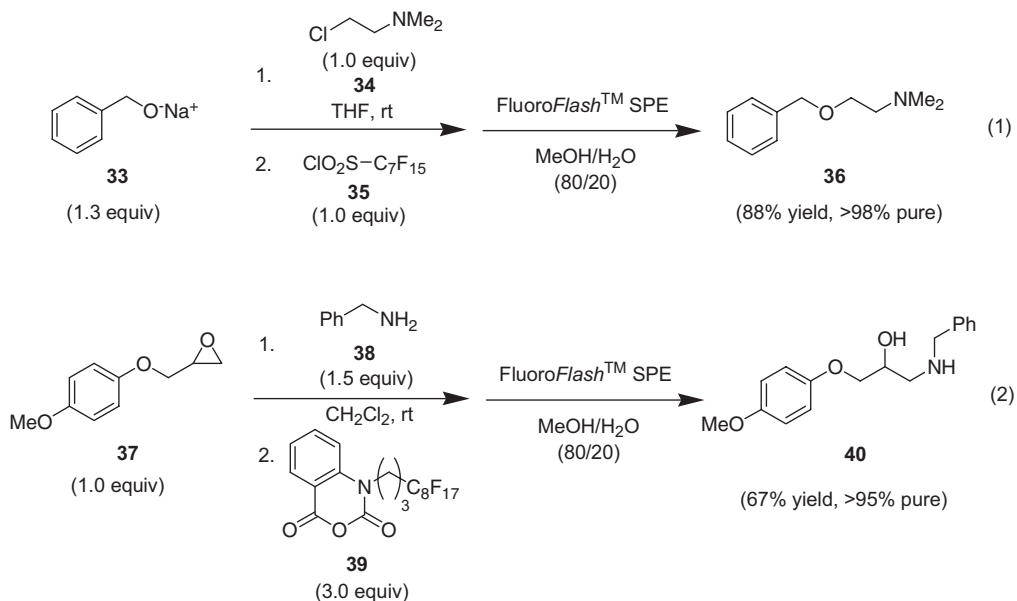
Key to the success of the light fluorine scavengers was the ease of rapid purification, in parallel, by FSPE. Significantly, both Merck and FTI have reported that the *FluoroFlash*<sup>TM</sup> SPE columns can be reused up to ten times without loss of efficiency and several sizes (2–10 g) are commercially available [14, 16]. Moreover, multi-gram separations of fluorine-tagged from untagged organics are possible employing fluorine silica gel in Biotage<sup>TM</sup> cartridges with aqueous methanol gradients on a Horizon<sup>TM</sup> High Performance FLASH chromatography unit affording excellent results [11, 16, 17].

Based on the reaction conditions and the nature of the fluorine scavenger employed, there are three major variations to the standard “light” fluorine scavenging paradigm depicted in Scheme 10.6-8 [14]. Often times, a solution-phase tertiary amine base may be employed in a fluorine scavenging reaction to either deprotonate the scavenger or to sequester acid generated during the reaction. Since the amine base will co-elute with the desired organic product resulting in contamination, the base must be removed prior to SPE. The first variation [Eq. (1), Scheme 10.6-11] to address this issue required a mildly acidic aqueous workup

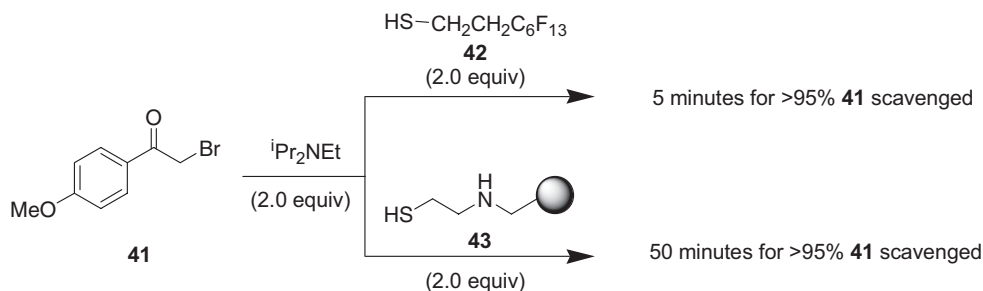
Tab. 10.6-1. Light fluoruous scavengers and applications

Entry	Fluorous scavenger	Scavenger for ...	Functional groups scavenged	Ref.
1	$\text{H}_2\text{N}-\text{CH}_2\text{C}_8\text{F}_{17}$	electrophiles	acid chlorides, isocyanates, sulfonyl chlorides	14b
2	$\text{HS}-\text{CH}_2\text{CH}_2\text{C}_6\text{F}_{13}$	electrophiles	$\alpha$ -bromocarbonyl compounds, epoxides, activated halides, michael acceptors	14a,b
3		electrophiles	activated halides	16
4		electrophiles	acid chlorides, isocyanates, sulfonyl chlorides, acidic phenols, carboxylic acids	14c
5	$\text{HO}-\text{CH}_2\text{CH}_2\text{C}_6\text{F}_{13}$	electrophiles	trialkylsilyl chlorides/triflates	16
6		nucleophiles	organometallics, reducing agents	16
7	$\text{ClO}_2\text{S}-\text{C}_7\text{F}_{15}$	nucleophiles	1°,2°-amines, alcohols, alkoxides	14b
8	$\text{HO}_3\text{S}-\text{C}_8\text{F}_{17}$	nucleophiles	1°,2°-amines, anilines	14b
9	$\text{ClOC}-\text{C}_7\text{F}_{15}$	nucleophiles	1°,2°-amines, alcohols, alkoxides	14b
10		nucleophiles	1°,2°-amines, thiols, thiophenols, organometallic reagents	14b
11	$\text{OCN}-\text{CH}_2\text{CH}_2\text{C}_8\text{F}_{17}$	nucleophiles	1°,2°-amines	14d
12		nucleophiles	1°,2°-amines	14d

prior to FSPE to reprotonate excess **42** and remove solution-phase tertiary amine base **46**. Then, standard FSPE of the organic layer provided the desired product **47** in high yield and purity [14a]. A second common variation [Eq. (2), Scheme 10.6-11] involves the replacement of the solution-phase tertiary amine base **46** with an excess of a polymer-supported tertiary amine base **48**. Under this protocol, the aqueous workup could be avoided and the FSPE step also removed the polymer-supported base affording **47** in similar yield and purity [14b]. The third variation centers on the properties of the fluoruous reagent/scavenger. During the course of a scavenging reaction, the fluoruous reagent/scavenger can be converted into a charged species such as a salt. When this occurs, the scavenger may co-elute with the organics during the FSPE step, as the salt will have reasonable solubility in aqueous methanol, leading to impure products. Therefore, when employing a polar, basic scavenger such as **52** and/or a fluoruous-tagged tertiary amine base **51** [Eq. (3), Scheme 10.6-11] a mixed sorbent



Scheme 10.6-9. Representative light fluororous scavenging



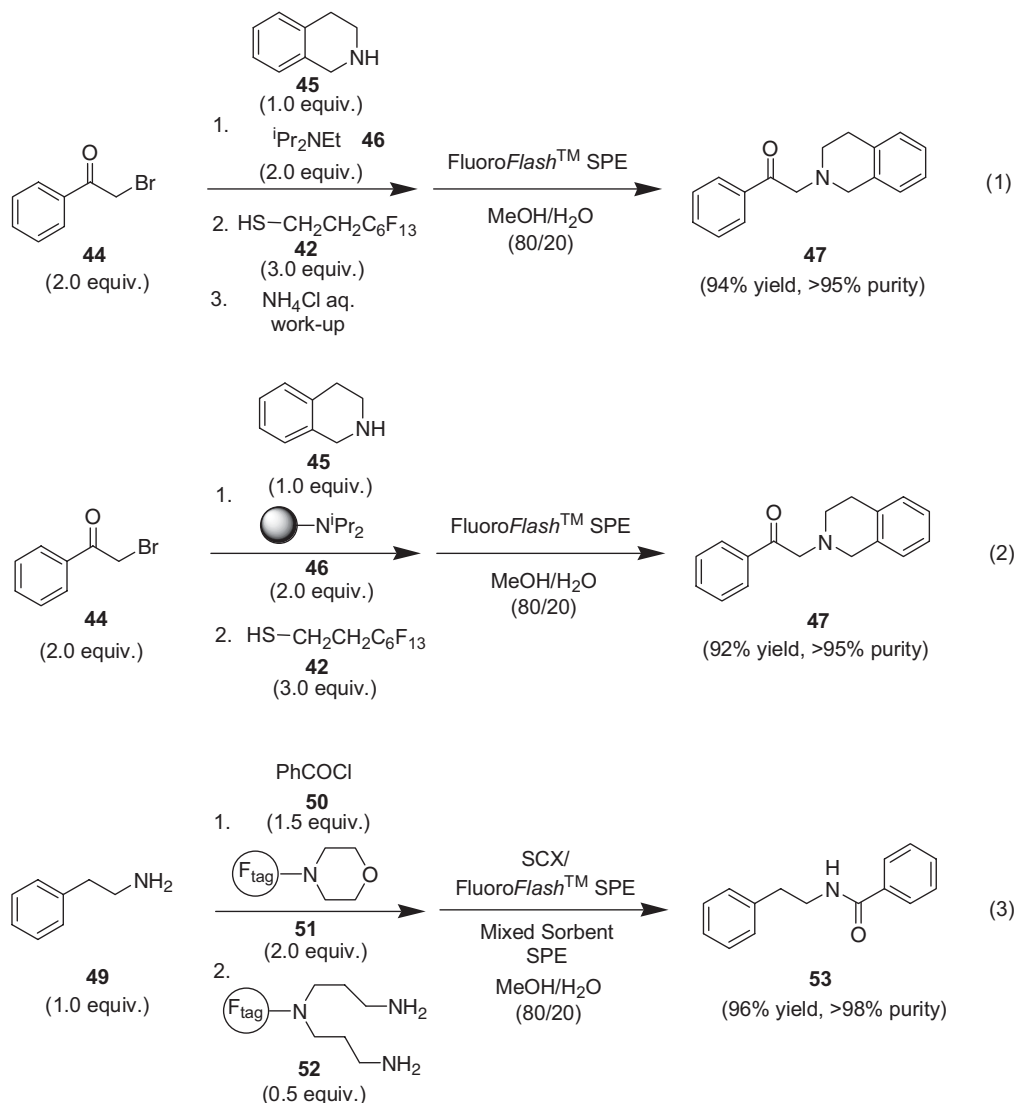
Scheme 10.6-10. Light fluororous versus polymer-supported thiol scavengers

SPE cartridge [an ion exchange column (SCX or SAX) fitted inside a FluoroFlash™ SPE cartridge] served to neutralize amine hydrochloride salts and cleanly separate fluororous-tagged from untagged organics. Under this protocol, the crude reaction could be applied directly to the mixed sorbent SPE cartridge and thereby avoid both an aqueous workup and the diminished kinetics of polymer-supported reagents [14c].

#### 10.6.4

#### Summary

The future for fluororous scavenging to impact on the way in which both organic and medicinal chemistry are conducted looks very promising. These solution-phase tools overcome the



**Scheme 10.6-11.** Variations on the light fluororous scavenging paradigm

major limitations of polymer-supported and ionic phase tags while providing economic and environmental benefits. Importantly, fluororous scavenging technology has several noteworthy advantages: (1) inexpensive and commercially available reagents and separations media; (2) homogeneous solution-phase kinetics; (3) liquid/liquid and solid-phase extraction protocols for maximum workup flexibility; and (4) both the reactions and the purification strategies are readily scalable. As additional reagents and protocols are developed, fluororous scavenging technology will no doubt occupy a prominent position in the fields of organic and solution-phase parallel synthesis.

## Acknowledgement

The authors would like to thank Professor Dennis Curran (University of Pittsburgh) and Dr. Phil Yeske (FTI) for helpful conversations.

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- 17 Commercially available from Biotage, Inc., [www.biotage.com](http://www.biotage.com).



## 10.7

## Synthesis of Perfluoroalkylated Phosphines

Eric G. Hope and Alison M. Stuart

## 10.7.1

## Introduction

Since Horváth and Rábai's seminal paper on fluorous biphasic catalysis [1] much of the subsequent work in this field has focused on the synthesis of fluorous-soluble phosphines. Phosphines are ubiquitous in homogeneous catalysis and perfluoroalkylated phosphines have already been applied successfully to a range of applications in the fluorous biphasic system, such as hydroformylation, hydrogenation, hydroboration, hydrosilylation as well as carbon–carbon bond forming reactions. Generally, the rule of thumb is that >60% fluorine is required for preferential fluorous phase solubility, but there are also reports of using the more lightly fluorinated phosphines for catalysis in supercritical carbon dioxide. Some of these applications are described in detail in other chapters (hydroformylation and hydrogenation in Chapter 10.9 and carbon–carbon bond forming reactions in Chapter 10.8) and so the aim of this chapter is to review the synthesis of perfluoroalkylated phosphines used for both fluorous biphasic catalysis and for homogeneous catalysis in supercritical carbon dioxide.

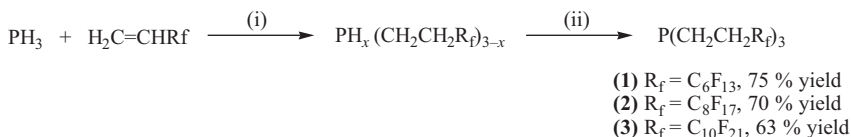
## 10.7.2

## Monodentate Phosphines

## 10.7.2.1 Trialkylphosphines

The first phosphine prepared specifically for its application in fluorous biphasic catalysis was the trialkylphosphine,  $P(\text{CH}_2\text{CH}_2\text{C}_6\text{F}_{13})_3$  (**1**) [1]. Although this ligand had been synthesized previously [2], Horváth and Rábai developed an alternative route by the radical addition of  $\text{PH}_3$  to 1*H*,1*H*,2*H*-perfluoro-1-octene. This reaction is carried out in two steps in a glass-lined autoclave in the presence of the radical initiator, azobis(isobutyronitrile) (AIBN), to give the fluorous phosphine (**1**) in 26% yield. Subsequently, this route was improved by Gladysz to give much better yields (Scheme 10.7-1) and to synthesize ligands (**2**) and (**3**) which contain the longer perfluoroalkyl chains [3]. Not surprisingly, as the length of the perfluoroalkyl group increases, the partition coefficient of the phosphine in a perfluoromethylcyclohexane/toluene biphasic system increases (Table 10.7-1), but their absolute solubilities in perfluorocarbon solvents decrease with increasing chain length.

In order to avoid using the highly toxic phosphine,  $\text{PH}_3$ , we and others have developed



**Scheme 10.7-1.** (i) AIBN, 85 °C; (ii)  $\text{H}_2\text{C}=\text{CHRf}$ , VAZO, 90 °C

**Tab. 10.7-1.** Partition coefficients (P) of trialkylphosphines in perfluoromethylcyclohexane/toluene

Ligand	log P
P(CH <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> F <sub>13</sub> ) <sub>3</sub>	1.915
P(CH <sub>2</sub> CH <sub>2</sub> C <sub>8</sub> F <sub>17</sub> ) <sub>3</sub>	>2.52
P(CH <sub>2</sub> CH <sub>2</sub> C <sub>10</sub> F <sub>21</sub> ) <sub>3</sub>	>2.52
P(CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> C <sub>8</sub> F <sub>17</sub> ) <sub>3</sub>	1.915
P(CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> C <sub>8</sub> F <sub>17</sub> ) <sub>3</sub>	1.954

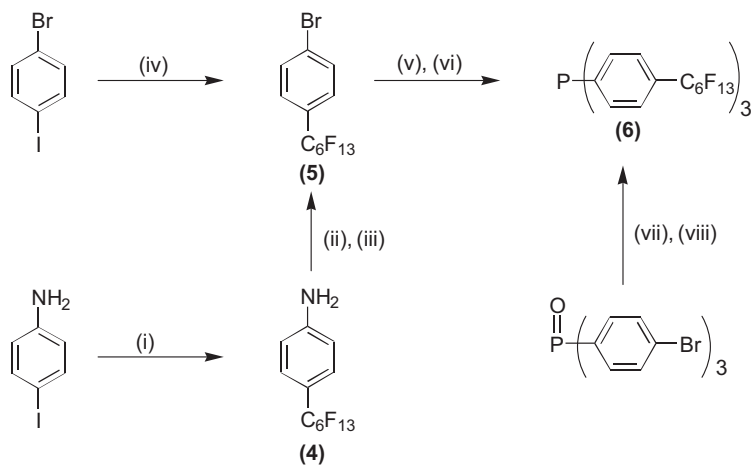
alternative routes to phosphine (1) from 1*H*,1*H*,2*H*,2*H*-perfluorohexyl iodide and phosphorus trichloride. In its original synthesis, the ligand was prepared by the reaction of F<sub>13</sub>C<sub>6</sub>CH<sub>2</sub>CH<sub>2</sub>ZnI with PCl<sub>3</sub> [2]. Knochel and coworkers have also reacted the dialkylzinc reagent, (F<sub>13</sub>C<sub>6</sub>CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>Zn, with PCl<sub>3</sub> and then BH<sub>3</sub>.SMe<sub>2</sub> to give the stable borane adduct, (F<sub>13</sub>C<sub>6</sub>CH<sub>2</sub>CH<sub>2</sub>)<sub>3</sub>P.BH<sub>3</sub> in 75% yield [4]. Alternatively, the Grignard reagent, F<sub>13</sub>C<sub>6</sub>CH<sub>2</sub>CH<sub>2</sub>MgI, can be synthesized and it has been reacted with a series of phosphorus chloride reagents (Ph<sub>2</sub>PCl, PhPCl<sub>2</sub> and PCl<sub>3</sub>) [5, 6]. Unfortunately, however, we were unable to extend the Grignard route to derivatives with longer perfluoroalkyl substituents [7].

Two trialkylphosphines with longer hydrocarbon spacer units, P(CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>C<sub>8</sub>F<sub>17</sub>)<sub>3</sub> and P(CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>C<sub>8</sub>F<sub>17</sub>)<sub>3</sub>, were synthesized by Gladysz's radical addition of PH<sub>3</sub> to CH<sub>2</sub>=CHCH<sub>2</sub>C<sub>8</sub>F<sub>17</sub> and CH<sub>2</sub>=CHCH<sub>2</sub>CH<sub>2</sub>C<sub>8</sub>F<sub>17</sub>, respectively [3], and a series of unsymmetrically substituted fluororous trialkylphosphines has also been synthesized (Scheme 10.7-2) [8]. Initially, the efficiency of the spacer units was probed by examining the variation in  $\nu_{\text{CO}}$  values for a series of *trans*-[IrCl(CO)L<sub>2</sub>] complexes [8]. Even with five methylene units the electron-withdrawing inductive effect of the fluororous ponytails was still apparent. Further experimental and computational studies on the fluororous phosphines predicted that between eight and ten methylene groups would be needed to insulate effectively a phosphorus lone pair from a perfluoroalkyl segment [9].

**Scheme 10.7-2.** (i) –45 °C, THF; (ii) H<sub>2</sub>C=CH(CH<sub>2</sub>)<sub>*n*–2</sub>C<sub>8</sub>F<sub>17</sub>, VAZO, 100 °C

### 10.7.2.2 Triarylphosphines

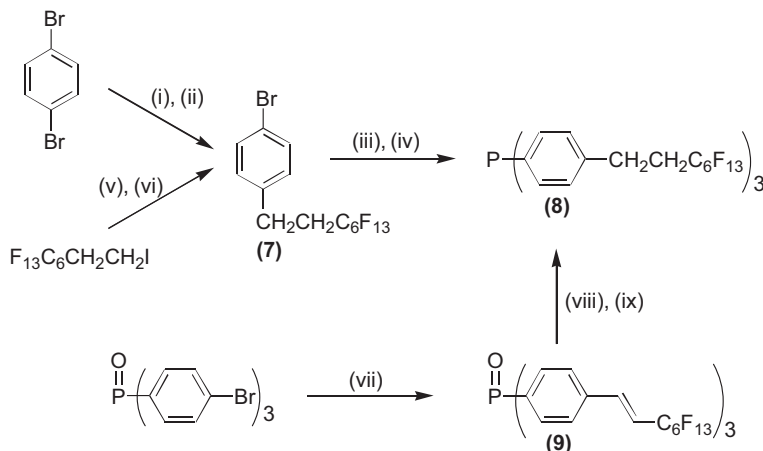
Since triphenylphosphine is probably the most widely used ligand in homogeneous catalysis, many different approaches have been developed by groups all over the world to synthesize a range of perfluoroalkylated analogs of triphenylphosphine. In 1997 there were two independent reports [5, 10] on the synthesis of the first fluororous-soluble triarylphosphine (6) and both groups used the same copper coupling methodology, developed by McLoughlin and Thrower [11], to introduce the perfluoroalkyl group directly onto the aromatic ring (Scheme 10.7-3) to form (5). Our selective copper coupling reaction between bromiodobenzene and perfluorohexyl iodide has also been used to synthesize a series of *meta*-derivatized triarylphosphines [12], but when 2-bromoperfluorohexyl benzene was lithiated with *n*-BuLi and then reacted with PCl<sub>3</sub>, the *tris*-derivatized phosphine was not formed [13]. The main product was (F<sub>13</sub>C<sub>6</sub>C<sub>6</sub>H<sub>4</sub>)<sub>2</sub>PCl, which was air- and moisture-stable due to the two *ortho*-perfluoroalkyl units protecting the phosphorus atom from attack by incoming nu-



**Scheme 10.7-3.** (i) Cu, C<sub>6</sub>F<sub>13</sub>I, DMSO, 120 °C; (ii) NaNO<sub>2</sub>, HBr; (iii) CuBr; (iv) Cu, C<sub>6</sub>F<sub>13</sub>I, 2,2'-bipyridine, DMSO, C<sub>6</sub>H<sub>5</sub>F, 70 °C; (v) *n*-BuLi, Et<sub>2</sub>O, −78 °C; (vi) PCl<sub>3</sub>, Et<sub>2</sub>O; (vii) Cu, C<sub>6</sub>F<sub>13</sub>I, DMSO, 120 °C; (viii) HSiCl<sub>3</sub>, Et<sub>3</sub>N, toluene, reflux

cleophilic reagents. More recently, Chen and Xiao [14] carried out the copper coupling reaction between *tris*(4-bromophenyl)phosphine oxide and perfluorohexyl iodide (Scheme 10.7-3) and then reduced the resulting triarylphosphine oxide to form the perfluoroalkylated triarylphosphine (6). This method has also been used to introduce the perfluorooctyl group in good yields, whereas, although the copper coupling reaction between perfluorooctyl iodide and 4-bromiodobenzene proceeds well, only poor yields of the desired phosphine are obtained in the second step because of the poor solubility of the 4-bromoperfluorooctylbenzene in ether at low temperature.

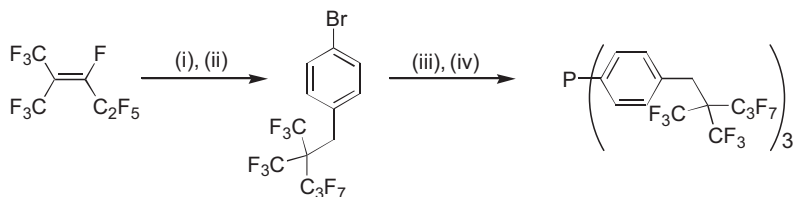
A number of different methods have been developed to synthesize fluorine-derivatized triarylphosphines containing two “CH<sub>2</sub>” spacer groups between the aromatic ring and the perfluoroalkyl group. Leitner and coworkers synthesized triarylphosphine (8) for the rhodium-catalyzed hydroformylation of 1-octene in supercritical CO<sub>2</sub> [15, 16]. The first step is a Cu<sup>I</sup> catalyzed coupling of the Grignard reagent, 4-BrC<sub>6</sub>H<sub>4</sub>MgBr, with 1*H*,1*H*,2*H*,2*H*-perfluorooctyl iodide to form the bromoaromatic (7) (Scheme 10.7-4), but significant amounts of the Wurtz coupled product, F<sub>13</sub>C<sub>6</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>C<sub>6</sub>F<sub>13</sub>, are also produced. Initially, it was impossible to purify the crude reaction mixture by either column chromatography or distillation, but fluorine reverse phase silica gel provided a straightforward separation giving poor yields of bromoaromatic (7) [17]. Curran developed a much cleaner route to (7) by the palladium-catalyzed coupling of F<sub>13</sub>C<sub>6</sub>CH<sub>2</sub>CH<sub>2</sub>ZnI with 4-bromiodobenzene and found that the use of *t*-BuLi in the lithiation step led to better yields of the triarylphosphine (8) [18]. An alternative route involved the Heck reaction to form the triarylphosphine oxide (9), which was then hydrogenated to form the (CH<sub>2</sub>)<sub>2</sub> spacer group and, finally, reduced to form the triarylphosphine (8) [19]. Similarly, a Heck reaction between 1*H*,1*H*,2*H*-perfluoroalkenes and arene diazonium salts, as well as aryl iodides, followed by a straightforward hydrogenation provided good access to perfluoroalkylated bromoaromatics such as (7) [20]. An alternative efficient route to aromatics containing a (CH<sub>2</sub>)<sub>2</sub>R<sub>f</sub> group that



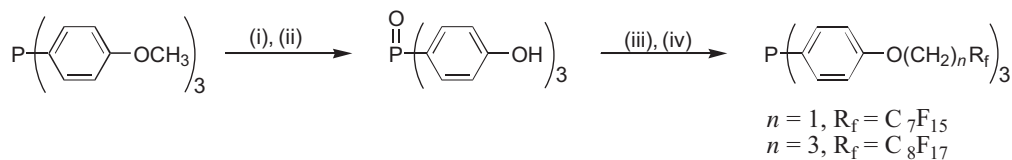
**Scheme 10.7-4.** (i) Mg, Et<sub>2</sub>O; (ii) F<sub>13</sub>C<sub>6</sub>CH<sub>2</sub>CH<sub>2</sub>I, [( $\eta^4$ -C<sub>8</sub>H<sub>12</sub>)CuCl] (10 mol %), Et<sub>2</sub>O, 0 °C to RT; (iii) *n*-BuLi, Et<sub>2</sub>O; (iv) PCl<sub>3</sub>; (v) Zn, THF, 25 °C; (vi) 4-BrC<sub>6</sub>H<sub>4</sub>I, Pd(PPh<sub>3</sub>)<sub>4</sub>, 45 °C; (vii) H<sub>2</sub>C=CHC<sub>6</sub>F<sub>13</sub>, palladacycle, NaOAc, DMF, 125 °C; (viii) 10 bar H<sub>2</sub>, 10 % Pd/C, EtOAc, RT; (ix) HSiCl<sub>3</sub>, Et<sub>3</sub>N, toluene, 120 °C

seems to have been overlooked is the palladium catalyzed Suzuki cross-coupling reaction of 1*H*,1*H*,2*H*-perfluoroalkenes with aryl boronic acids [21].

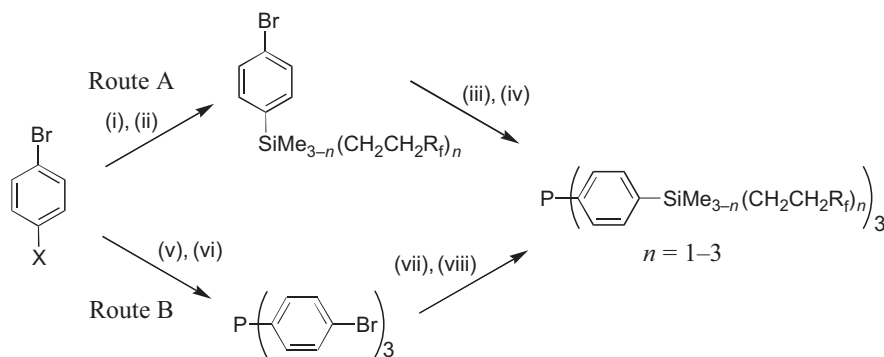
Curran and coworkers [18] synthesized the first triarylphosphine that contains a branched fluoros ponytail (Scheme 10.7-5) and more recently, Gladysz's group [22] has increased the hydrocarbon "spacer" between the aromatic ring and the fluoros ponytails to three methylene units. Here, they carried out a Wittig reaction between 4-bromobenzaldehyde and [Ph<sub>3</sub>PCH<sub>2</sub>CH<sub>2</sub>R<sub>f</sub>]<sup>+</sup>I<sup>−</sup> to give 4-BrC<sub>6</sub>H<sub>4</sub>CH=CHCH<sub>2</sub>R<sub>f</sub> in excellent yields. After hydrogenating the double bond, the bromoaromatic was subjected to the usual low temperature lithiation with *n*-BuLi and condensation with phosphorus trichloride allowed the formation of a series of perfluoroalkylated triarylphosphines [P(4-C<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>R<sub>f</sub>)<sub>3</sub>, R<sub>f</sub> = C<sub>6</sub>F<sub>13</sub>, C<sub>8</sub>F<sub>17</sub>, C<sub>10</sub>F<sub>21</sub>]. An alternative spacer unit, O(CH<sub>2</sub>)<sub>*n*</sub>R<sub>f</sub> (*n* = 1 or 3), was prepared by the O-alkylation of *para*-hydroxy-arylphosphines or -arylphosphine oxides (Scheme 10.7-6) and the extension to *ortho*- and *meta*-derivatized ligands is straightforward [23, 24]. Finally, van Koten has introduced a silyl spacer group in the *para*-position of triarylphosphines to attach between three and nine perfluoroalkyl groups, P[4-C<sub>6</sub>H<sub>4</sub>SiMe<sub>3−*n*</sub>(CH<sub>2</sub>CH<sub>2</sub>R<sub>f</sub>)<sub>*n*</sub>]<sub>3</sub> [25]. Two different methods were used to synthesize this series of fluoros triarylphosphines, but the most efficient method was route B where the expensive perfluoroalkylated silyl group was introduced in the last step (Scheme 10.7-7).



**Scheme 10.7-5.** (i) CsF, DMF, 45 °C; (ii) 4-BrC<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>Br; (iii) *t*-BuLi; (iv) PCl<sub>3</sub>



**Scheme 10.7-6.** (i)  $H_2O_2$ , acetone; (ii)  $BBr_3$ ,  $CH_2Cl_2$ ; (iii)  $F_{15}C_7CH_2OTf$  or  $F_{17}C_8(CH_2)_3I$ ,  $Cs_2CO_3$ , DMF,  $65\text{ }^\circ\text{C}$ ; (iv)  $HSiCl_3$ ,  $Et_3N$ , toluene,  $130\text{ }^\circ\text{C}$



**Scheme 10.7-7.** (i)  $X = I$ ,  $n\text{-BuLi}$ ,  $0\text{ }^\circ\text{C}$ ; (ii)  $XSiMe_{3-n}(CH_2CH_2Rf)_n$ ,  $-78\text{ }^\circ\text{C}$  to RT; (iii)  $t\text{-BuLi}$ ,  $-78\text{ }^\circ\text{C}$  then RT; (iv)  $PCl_3$ ,  $-78\text{ }^\circ\text{C}$  to RT; (v)  $X = Br$ ,  $n\text{-BuLi}$ , RT; (vi)  $PCl_3$ ,  $78\text{ }^\circ\text{C}$  to RT; (vii)  $t\text{-BuLi}$ ,  $-78\text{ }^\circ\text{C}$ ; (viii)  $XSiMe_{3-n}(CH_2CH_2Rf)_n$ ,  $-78\text{ }^\circ\text{C}$  to RT

Both the  $\nu_{CO}$  data for  $trans\text{-}[MCl(CO)L_2]$  ( $M = Rh, Ir$ ) complexes and  $^1J_{PtP}$  coupling constants of  $cis\text{-}[PtCl_2L_2]$  complexes have been used to gain an insight into the electronic effects of the perfluoroalkyl substituents on triarylphosphines (Table 10.7-2) [26]. Clearly, the additional spacer units between the aromatic ring and the perfluoroalkyl group provide much better insulation of the electronic effect than when the fluoros ponytail is attached directly to the aryl ring. The downside, however, is that these phosphines normally have lower partition coefficients between perfluorocarbon and organic solvents than  $P(4\text{-}C_6H_4C_6F_{13})_3$  (Table 10.7-3). In the series of silyl-derivatized phosphines containing three, six or nine fluoros ponytails, the triarylphosphines that contain six perfluoroalkyl groups gave the

**Tab. 10.7-2.** Selected spectroscopic data of metal complexes containing perfluoroalkylated triarylphosphines

Ligand	$\nu_{CO} (cm^{-1})$ of $trans\text{-}[IrCl(CO)L_2]$	$\nu_{CO} (cm^{-1})$ of $trans\text{-}[RhCl(CO)L_2]$	$^1J_{PtP} (Hz)$ of $cis\text{-}[PtCl_2L_2]$
$PPh_3$	1952	1965	3672
$P(4\text{-}C_6H_4CH_2CH_2CH_2C_8F_{17})_3$	1958	—	—
$P(4\text{-}C_6H_4CH_2CH_2C_6F_{13})_3$	—	1972	3679
$P(4\text{-}C_6H_4C_6F_{13})_3$	1979	1993	3631
$P(4\text{-}C_6H_4OCH_3)_3$	1961	1958	3703
$P(4\text{-}C_6H_4OCH_2C_7F_{15})_3$	1967	1977	3680

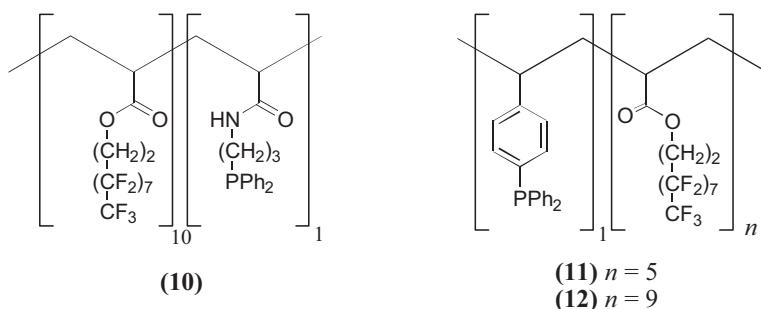
**Tab. 10.7-3.** Partition coefficients (P) of triarylphosphines in perfluoromethylcyclohexane/toluene

Ligand	log P
$P(4-C_6H_4C_6F_{13})_3$	0.865 <sup>a</sup>
$P(4-C_6H_4CH_2CH_2C_6F_{13})_3$	-0.125 <sup>b</sup>
$P(4-C_6H_4CH_2CH_2CH_2C_6F_{13})_3$	-0.615
$P(4-C_6H_4CH_2CH_2CH_2C_8F_{17})_3$	0.300
$P[4-C_6H_4SiMe_2(CH_2CH_2C_6F_{13})]_3$	-0.585
$P[4-C_6H_4SiMe(CH_2CH_2C_6F_{13})_2]_3$	0.892
$P[4-C_6H_4Si(CH_2CH_2C_6F_{13})_3]_3$	0.633

<sup>a</sup> Perfluorocarbon solvent is perfluoro-1,3-dimethylcyclohexane.<sup>b</sup> Perfluorocarbon solvent is perfluorohexane.

optimum result, but, even then, all of the triarylphosphines have lower partition coefficients than the fluororous trialkylphosphines. However, triarylphosphines are much easier to handle since they are less air sensitive and in some catalytic applications the electron-withdrawing characteristics can provide an advantage.

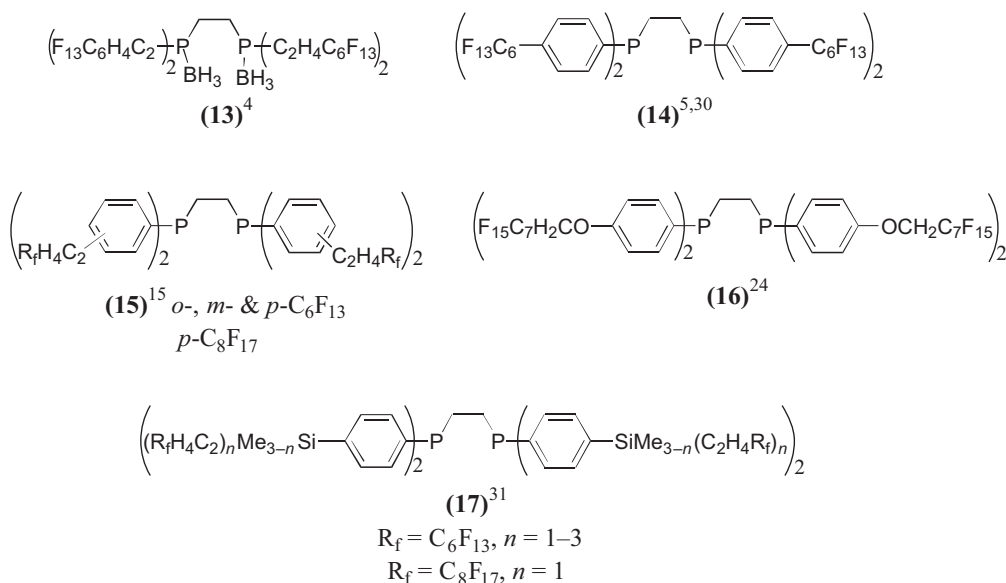
Both Bergbreiter [27] and Xiao [28] independently designed a completely different approach to anchoring arylphosphines in fluororous solvents by synthesizing fluororous-soluble polymer-supported alkylarylphosphines and triarylphosphines, respectively (Scheme 10.7-8). Both fluoroacrylate polymers were prepared by the radical copolymerization of 1*H*,1*H*,2*H*,2*H*-perfluorodecylacrylate in benzotrifluoride in the presence of AIBN and Xiao's triarylphosphine (**11**) was shown to have a better partition coefficient in perfluoro-1,3-dimethylcyclohexane than either  $P(4-C_6H_4C_6F_{13})_3$  or  $P(4-C_6H_4CH_2CH_2C_6F_{13})_3$ . Bergbreiter synthesized the direct analog of Wilkinson's catalyst with phosphine (**10**) and not only was it shown to have comparable rates of hydrogenation to the traditional homogeneous catalyst, but it was also recycled successfully seven times without loss of activity under an inert atmosphere [27]. Xiao, on the other hand, examined the application of his fluororous soluble polymer ligands in the hydroformylation of olefins and acrylates under fluororous biphasic conditions and in supercritical carbon dioxide [28, 29].

**Scheme 10.7-8**

## 10.7.3

**Bidentate Phosphines****10.7.3.1 Perfluoroalkylated Analogs of 1,2-Bis(diphenylphosphino)ethane**

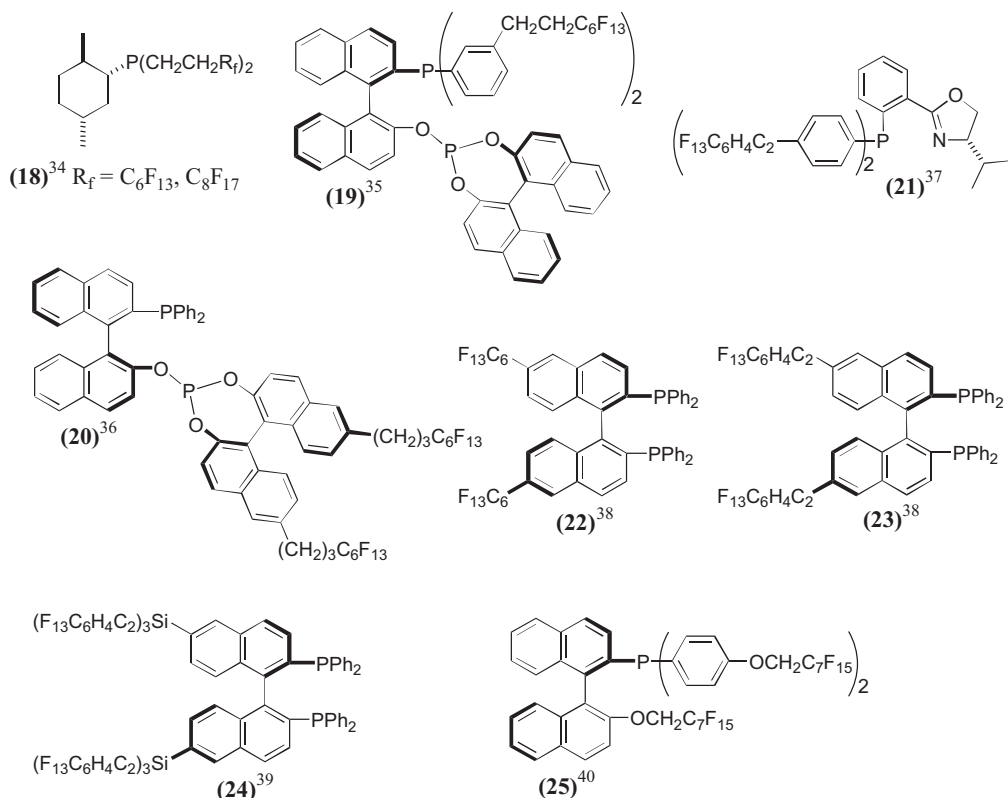
Although chelating ligands normally enhance catalyst stability, only one class of achiral perfluoroalkylated bidentate phosphines have been reported and they are all straightforward analogs of 1,2-bis(diphenylphosphino)ethane (Scheme 10.7-9). All of these ligands have been synthesized using known methodology developed in the synthesis of either the trialkyl- or triaryl-phosphines. The advantage of Deelman's diphosphines (**17**) are that more than one perfluoroalkyl group can be attached to each aromatic ring and he has demonstrated that the ligands containing either eight or twelve perfluorohexyl groups are extremely soluble in perfluoromethylcyclohexane [31]. However, only the bidentate ligands (**14**) and (**17**) have actually been investigated in fluorous biphasic catalysis [32, 33].



Scheme 10.7-9

**10.7.3.2 Chiral Phosphines**

The concept of synthesizing a chiral fluorous ligand that can be recycled is particularly attractive since most chiral ligands for asymmetric catalysis are expensive and time-consuming to prepare. A number of perfluoroalkylated chiral phosphines have now been synthesized (Scheme 10.7-10), but there are no successful reports of their effective recycle. In fact, only phosphines (**18**) and (**24**) have reasonable partition coefficients between perfluorocarbon and organic solvents and phosphine (**25**) can be extracted into the fluorous phase with multiple extractions. All of the other phosphines, (**19**)–(**23**), are only “lightly fluorinated” and have been used for catalysis in supercritical carbon dioxide.



Scheme 10.7-10

Apart from Ojima's BINAPHOS analog (20), all of the chiral ligands were synthesized using known methodology to introduce the perfluorinated chains. The enantiopure fluorous BINOL derivative (29) was used to synthesize (20) and was prepared by the palladium-catalyzed addition of perfluorohexyl iodide to (27), followed by reduction of the diiodide (28) with  $\text{LiAlH}_4$  and, finally, deprotection with TBAF to give (29) in 37% overall yield from (26) (Scheme 10.7-11).

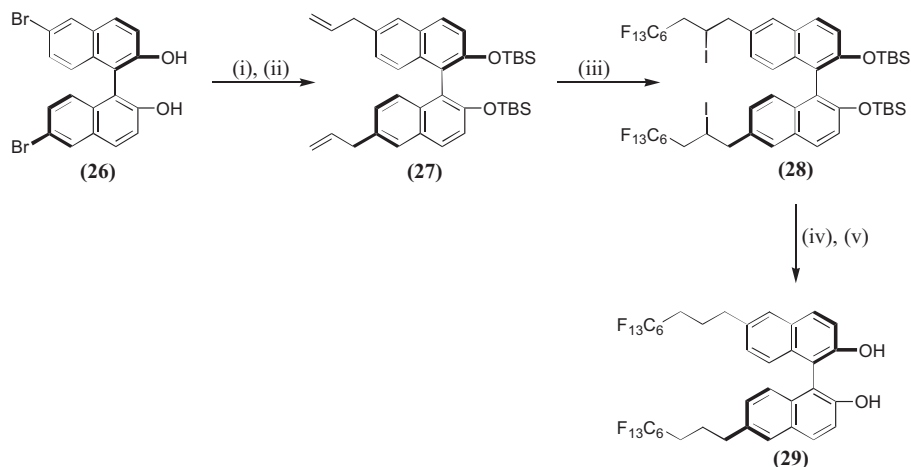
#### 10.7.4

#### Outlook

There are two main areas for development: (1) new synthetic methodologies to existing perfluoroalkylated phosphine ligands and (2) the synthesis of novel perfluoroalkylated ligands driven by their potential catalytic applications in the fluorous biphasic system, in organic solvents using the novel thermomorphic approach [41] or in supercritical  $\text{CO}_2$ .

- (1) As indicated above, a diverse range of synthetic approaches have already been exploited for phosphine synthesis and, although alternative coupling reactions are available in the





**Scheme 10.7-11.** (i) TBSCl, imidazole, DMF, RT; (ii)  $\text{Bu}_3\text{Sn}(\text{CH}_2\text{CH}=\text{CH}_2)$ ,  $\text{Pd}(\text{PPh}_3)_4$  (5 mol %), benzene,  $90^\circ\text{C}$ ; (iii)  $\text{F}_{13}\text{C}_6\text{I}$ ,  $\text{Pd}(\text{PPh}_3)_4$  (10 mol %), hexane,  $90^\circ\text{C}$ ; (iv)  $\text{LiAlH}_4$ ,  $\text{Et}_2\text{O}$ ,  $0^\circ\text{C}$  to RT; (v) TBAF, THF, RT

synthetic chemists armory, it is unlikely that these will bring significant advances. To date, Suzuki coupling reactions have found least widespread application and, perhaps, improved reaction yields may be possible using this approach.

- (2) The synthesis of novel phosphine ligands will be driven by academic and commercial expediency. At this stage, commercially-viable applications of catalysis using fluororous techniques have not been realized, and novel ligand synthesis must be directed to afford even better catalyst/product separation. There has been relatively little work on triaryl-phosphines with more than one perfluoroalkyl group per arene ring or using branched perfluoroalkyl chains and work in this area could lead to important developments. However, for fluororous solvent applications, there would be concerns over the absolute solubility of the ligand/catalyst if the total number of fluororous ponytails is increased substantially. In these cases, perhaps mixed systems incorporating both long ( $\text{C}_6\text{F}_{13}$ ) and short ( $\text{CF}_3$ ) or alkyl ( $\text{C}_6\text{H}_{13}$ ) functional groups might warrant evaluation.

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## 10.8

## Metal Catalyzed Carbon–Carbon Bond Forming Reactions in Fluorous Biphasic Systems

Siegfried Schneider, Carl Christoph Tzschucke, and Willi Bannwarth

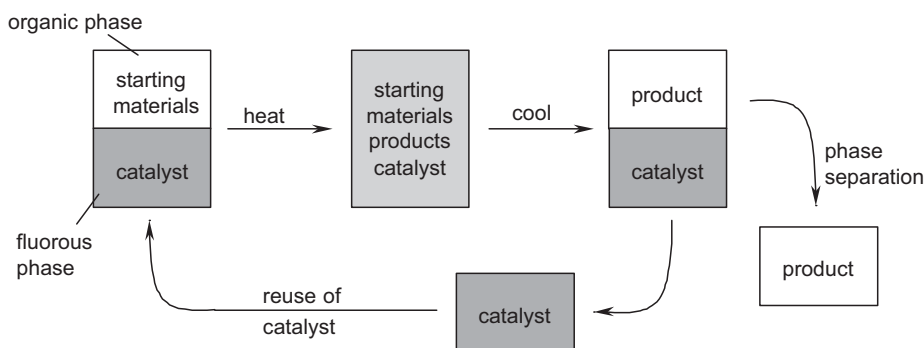
## 10.8.1

## Introduction

Metal catalyzed cross coupling reactions are one of the most prominent reaction types in synthetic organic chemistry. They are employed in various areas such as synthesis of natural products, supramolecular chemistry, material science and medicinal chemistry and have been reviewed in numerous articles and monographs [1]. Specifically, the search for new chemical entities in medicinal chemistry requires the synthesis of increasing numbers of compounds in shorter periods of time. To meet this demand, not only do parallel synthesis formats need to be employed, but also the simplification of workup procedures becomes increasingly important. In catalytic processes this can be accompanied by the recovery and reuse of the catalyst.

Recently, several concepts have been developed to simplify workup procedures and to avoid time-consuming purification steps such as column chromatography or distillation [2, 3]. They consist in essence in the use of polymer-supported catalysts [4], the use of molten salts (or ionic liquids) as reaction media [5, 6], reactions in  $\text{scCO}_2$  or water [7, 8], and the use of fluorous biphasic systems (FBS) [9–14]. In the FBS concept, perfluorinated ligands mediate the solubility of the pertinent catalyst in fluorous solvents. According to Scheme 10.8-1 the reaction is carried out in a two-phase mixture consisting of a perfluorinated and an organic solvent. Such two-phase systems often become homogeneous at elevated temperatures. Lowering the temperature after reaction leads to reformation of the two phases. The organic phase contains the product and the fluorous phase the catalyst to be reused.

In this chapter we describe the evolution of metal catalyzed carbon–carbon bond formations under FBS conditions over the past eight years. The actual synthesis of catalysts and aspects of coordination chemistry of catalysts will not be discussed.



Scheme 10.8-1

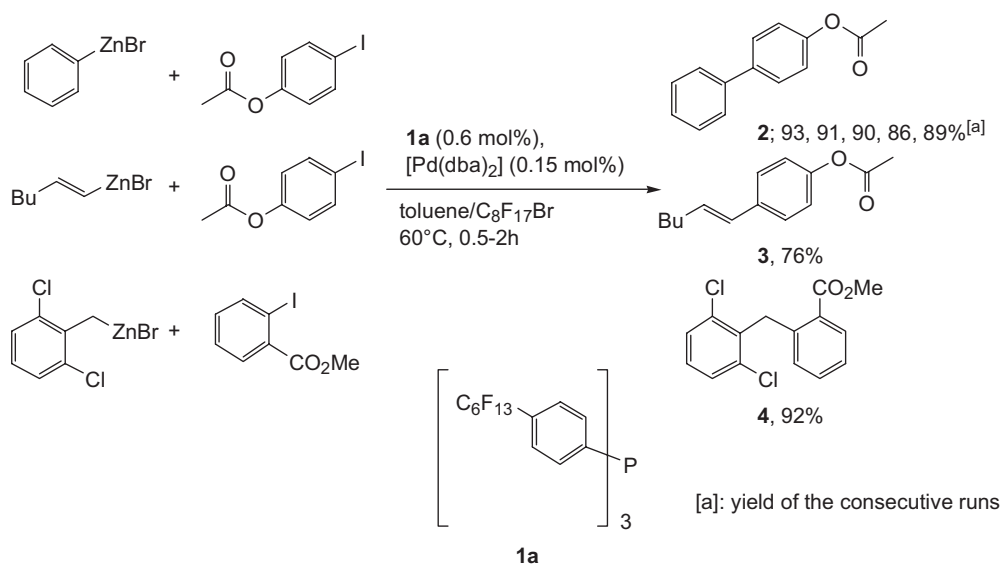
## 10.8.2

**C–C Couplings with Perfluoro-Tagged Palladium Complexes**

Palladium catalyzed cross-coupling reactions often require relatively large amounts of catalysts, which have to be removed from the reaction product. Perfluoro-labelled Pd complexes offer a solution to this problem, since the perfluoro-labelled catalysts are soluble in fluoruous solvents and can be separated from the organic product very easily by liquid/liquid extractions. There are numerous examples in the literature demonstrating the power of this methodology.

**10.8.2.1 Negishi Reaction**

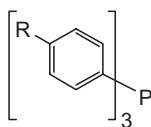
Betzemeier and Knochel performed cross-couplings of aryl iodides with arylzinc bromides in a toluene/1-bromoperfluorooctane ( $C_8F_{17}Br$ ) mixture in the presence of a Pd catalyst derived from perfluoro-tagged phosphane **1a** and  $Pd_2(dba)_3$  (Scheme 10.8-2) [15]. The reaction was carried out at 60 °C for 30 min with 0.15 mol% of catalyst yielding the desired coupling products in excellent yields (87–99%; 9 examples). By using 1.5 mol% of catalyst it was possible to reuse the catalyst up to four times yielding biphenyl-derivative **2**. This cross-coupling reaction could be extended to benzyl- and alkenyl-zinc bromides forming compound **3** (76%) and **4** (92%).



Scheme 10.8-2

**10.8.2.2 Heck Reaction**

The first Heck reaction in perfluorinated solvents was described by Moineau et al. with either  $Pd_2(dba)_3$  or  $Pd(OAc)_2$  as the palladium source and the perfluorinated phosphanes **1a–1c** as the ligands (Scheme 10.8-3) [16]. Reactions between iodobenzene and methyl acrylate were conducted with 0.5 mol% of catalyst in an acetonitrile/D-100 (mainly *n*-per-



**1a:** R = C<sub>6</sub>F<sub>13</sub>

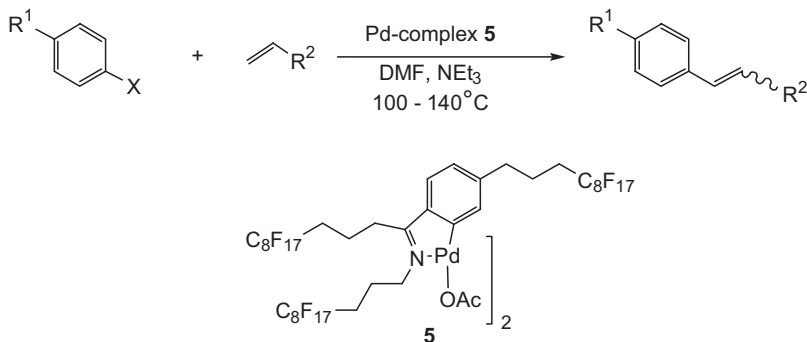
**1b:** R = OCH<sub>2</sub>C<sub>7</sub>F<sub>15</sub>

**1c:** R = O(CH<sub>2</sub>)<sub>2</sub>OCH<sub>2</sub>CF<sub>2</sub>[OCF(CF<sub>3</sub>)CF<sub>2</sub>]<sub>q</sub>(OCF<sub>2</sub>)<sub>p</sub>OCF<sub>3</sub>  
with *p* = 3.38 and *q* = 0.11

**Scheme 10.8-3**

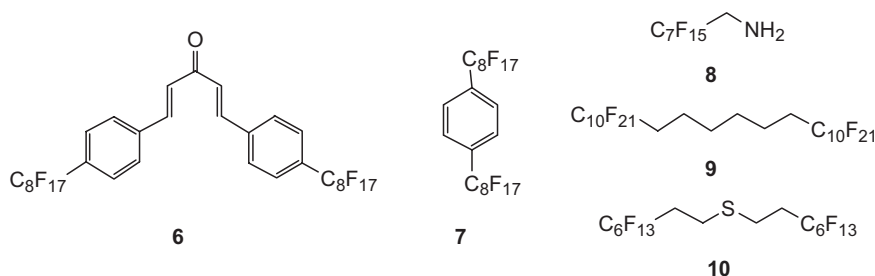
fluorooctane) mixture at 80 °C for 4 h. The expected products were formed quantitatively and good selectivity (88–93%) was observed. Recycling of the catalyst was possible, but resulted in lower conversions of the iodobenzene in the second and third runs, respectively.

Rocabay and Gladysz prepared a fluorous Schiff base, which was converted into palladacycle **5**. This represents a phosphane-free Pd catalyst which additionally shows a thermomorphic behavior (Scheme 10.8-4) [17]. Reactions were performed under homogeneous conditions (DMF, 100–140 °C) without fluorous solvents using 0.68–1.83 × 10<sup>−6</sup> mol% of the palladacycle. After workup the Heck coupling products were obtained in 49–100% yield. Recycling experiments were done with 0.02 mol% of **5** using C<sub>8</sub>F<sub>17</sub>Br as the “carrier”, which forms a biphasic mixture with DMF. After phase separation and removal of C<sub>8</sub>F<sub>17</sub>Br the catalyst was charged with fresh starting materials and DMF. The results revealed a gradual loss of conversion and yield. The authors assumed that loss of activity is either due to limited stability of the catalyst or that the catalyst is stable but the recycling is not as efficient as anticipated. Reaction rate and transmission electron microscopy indicated the presence of soluble Pd nanoparticles as the active catalyst.

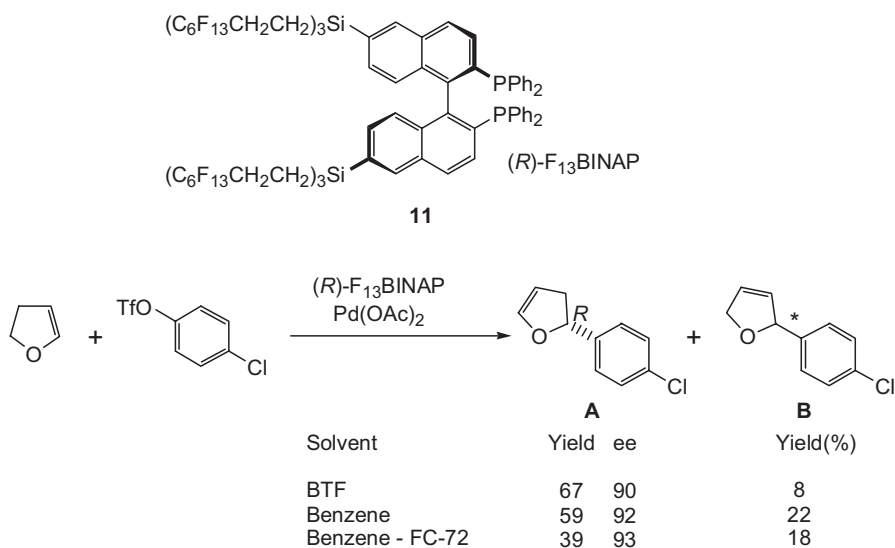


**Scheme 10.8-4**

Stabilized Pd nanoparticles of compounds featuring perfluorinated chains **6–10** were described by Moreno-Mañas et al. (Scheme 10.8-5) [18, 19]. The Pd nanoparticles were obtained by the reduction of PdCl<sub>2</sub> with methanol in the presence of **6–10**, respectively. The presence of such nanoparticles was confirmed by transmission electron microscopy. Owing to the stabilization by the perfluorinated ligand the palladium colloids are soluble in perfluorinated solvents. Pd nanoparticles stabilized by 1,5-bis[4-bis(perfluorooctyl)phenyl]-1,4-pentadien-3-one (**6**) were active in Heck and Suzuki couplings [18].



Scheme 10.8-5

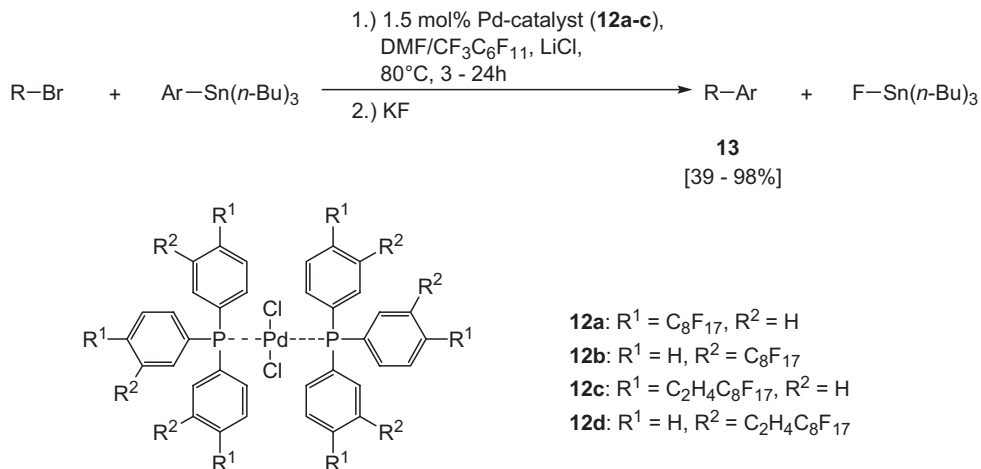


Scheme 10.8-6

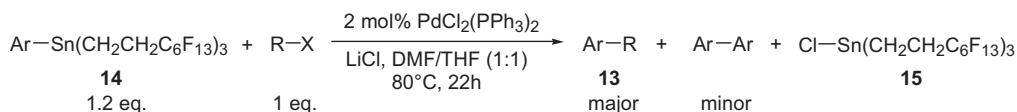
Nakamura et al. prepared a fluorous BINAP [(R)-F<sub>13</sub>BINAP] ligand and applied it to the asymmetric Heck reaction of 2,3-dihydrofuran with 4-chlorophenyl triflate (Scheme 10.8-6) [20]. Results showed that (R)-F<sub>13</sub>BINAP **11** is soluble in fluorinated solvents, but easily oxidized during the reaction. A similar enantioselectivity to that of the original reaction (91% ee) published by Hayashi was obtained in BTF (90% ee) and an even higher enantiomeric excess was achieved in a benzene/FC-72 (93% ee) solvent mixture [21]. Because of the instability of the (R)-F<sub>13</sub>BINAP towards oxygen, recovery and reuse of the ligand was not efficient.

### 10.8.2.3 Stille Couplings

Schneider and Bannwarth reported the synthesis of fluorous bis(triphenylphosphane)-palladium dichloride complexes (**12a–c**) and their application in Stille couplings (Scheme 10.8-7) [22]. The reactions were performed in DMF/perfluoromethylcyclohexane (PFMCH) (1:1) with 1 equiv of LiCl as additive at 80 °C for 3 to 24 h. From the organic phase the C–C



Scheme 10.8-7



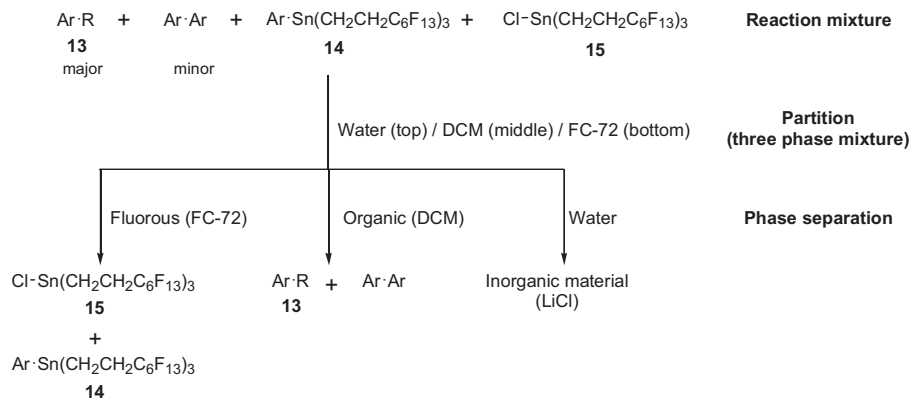
Scheme 10.8-8

coupling products (**13**) were obtained in good yields while the fluorous phase containing the catalyst was used as such for the next cycle. The catalysts could be used up to six times without significant decrease in yield.

Curran and coworkers reported the cross coupling reaction between perfluoro-tagged stannanes **14** and aryl halides under FBS conditions (Scheme 10.8-8) [23, 24]. The perfluoro-tagged tin byproduct **15** and the excess of the tin substrate **14** were removed by simple extraction.

The Stille couplings were performed in DMF/THF (1:1) with 2 mol% of  $\text{PdCl}_2(\text{PPh}_3)_2$  at  $80^\circ\text{C}$  for 22 h with LiCl as an additive. Yields of the coupling products **13** were generally high (>80%) and the recovery of the fluorous byproduct **15** was efficient (80–90%). The workup was performed as outlined in Scheme 10.8-9 by extraction in a three-phase system consisting of water, DCM and FC-72. The fluorous byproduct **15** remained in the fluorous phase and could be recycled, whereas the crude product was in the DCM phase which was further purified by preparative TLC yielding the desired cross coupling product **13**. In contrast to common Stille coupling reactions the use of LiCl as an additive was crucial, even with aryl halides as the substrates, probably because an interaction between the chloride ion and the fluorous tin reagent promotes the transmetalation step. Without LiCl low reaction rates, long reaction times and incomplete conversions were observed.

Curran, Hallberg and coworkers also performed Stille coupling reactions with fluorous tin reagents under microwave irradiation [25, 26]. It was possible to reduce the reaction time dramatically from 22 h with conventional heating to less than 6 min with microwave heat-



Scheme 10.8-9

ing. The workup was similar to that outlined before with fair to good yields (50–96%) of the coupling products.

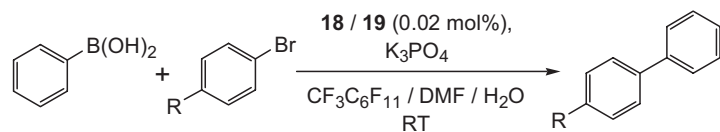
#### 10.8.2.4 Suzuki Couplings

Schneider and Bannwarth applied fluorous bis(triphenylphosphane)palladium dichloride complexes **12a–d** as catalyst precursors to Suzuki reactions [27]. The reactions took place in an H<sub>2</sub>O/DME/PFMCH tri-phasic mixture at 75 °C for 2 h with 1.5 mol% of the Pd complex. It could be demonstrated that perfluoro-tagged complexes **12a–d** are highly effective pre-catalysts for Suzuki couplings under FBS conditions with either electron-rich or electron-deficient bromoarenes and arylboronic acids. The catalysts could be recycled and reused after phase separation up to six times without significant decrease in coupling yields. It could be shown in one example that the amount of catalyst could be reduced from 1.5 mol% to 0.1 mol% still resulting in a high yield (>86%) in the first run but considerable loss of activity in repetitive cycles.

Rocaboy and Gladysz prepared perfluoro-tagged dialkylsulfides [R<sup>F</sup>(CH<sub>2</sub>)<sub>n</sub>]<sub>2</sub>S (*n* = 2 **16**; *n* = 3 **17**) which are soluble in most fluorous and organic solvents with a CF<sub>3</sub>C<sub>6</sub>F<sub>11</sub>/toluene partition coefficient of 98.7:1.3 for **16** and 96.6:3.4 for **17** at 24 °C (Scheme 10.8-10) [28]. Reaction of **16** or **17** with Na<sub>2</sub>PdCl<sub>4</sub> gave Pd complexes **18** and **19**, respectively, which are soluble in only a limited range of fluorinated solvents at room temperature. With **18** and **19** as the catalyst they were able to achieve turnover numbers (TON) of 4500–5000 in Suzuki couplings of aryl bromides and phenylboronic acid in CF<sub>3</sub>C<sub>6</sub>F<sub>11</sub>/DMF/H<sub>2</sub>O in the presence of K<sub>3</sub>PO<sub>4</sub>. Under fluorous recycling conditions decreased activities of the catalysts were observed. For this loss of activity the following reasons could be responsible:

- (1) inefficient recycling of the perfluoro-tagged catalyst;
- (2) gradual deactivation of the catalyst;
- (3) slow generation of an active non-recyclable heterogeneous catalyst from a homogeneous precursor and recycling of the remaining precursor;
- (4) generation of a heterogeneous catalyst which is not stable but efficiently recycled.

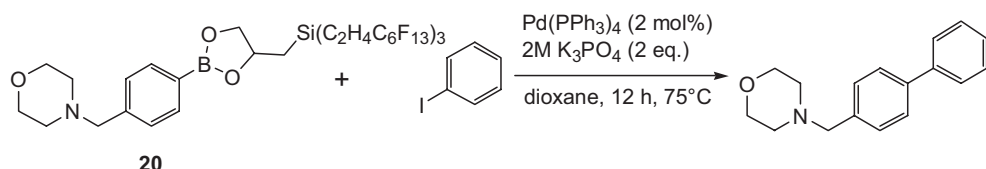




Scheme 10.8-10

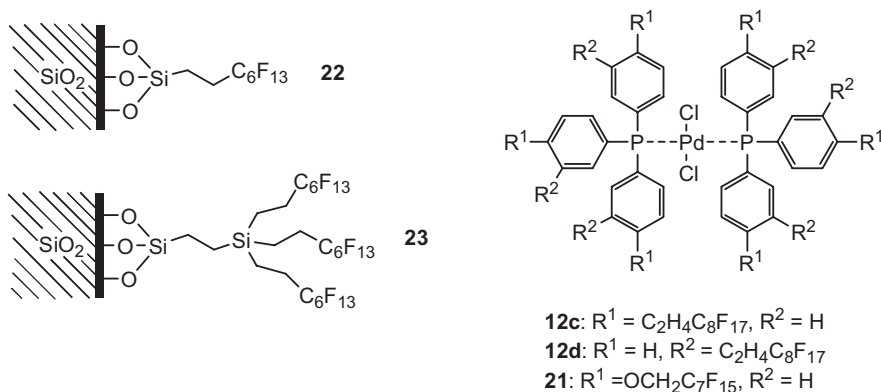
The appearance of palladium black in recycling experiments and recent reports on heterogeneous or metallic palladium species lead the authors to favor possibilities (3) and (4) [18, 19, 29, 30].

In accordance with Curran's work on Stille reactions with perfluoro-tagged organotin compounds, Chen et al. prepared a series of perfluoro-tagged boronic acid esters (**20**) and applied them to Suzuki reactions (Scheme 10.8-11) [31]. The reaction was performed with 2 mol% of  $Pd(PPh_3)_4$  in aqueous dioxane. The desired biaryl derivative was obtained by extraction and chromatographic workup in 76% yield, but no further examples were given.



Scheme 10.8-11

In examples employing perfluoro-tagged catalysts in FBC, separation of the catalyst followed by its reapplication was usually achieved by liquid/liquid extraction between a fluorous and an organic solvent. Fluorous solvents have the disadvantage of being relatively expensive and environmentally persistent. Bannwarth and coworkers have developed new protocols, which allow for the separation and recycling of perfluoro-tagged catalysts without the need of fluorous solvents [32]. They have employed Pd complexes **12c**, **12d** and **21**, immobilized by adsorption on fluorous reverse phase silica gels (FRPSG) **22** and **23**, and demonstrated the application to Suzuki couplings in organic solvents (Scheme 10.8-12). Silica with coarse grain of 100–300  $\mu m$  particle size was used with loadings of between 0.1 and 100 mg complex per g FRPSG. The coupling of *para*-nitrobromobenzene and phenylboronic acid was carried out using 10 mg Pd complex per g FRPSG with 0.1 mol% palladium. Complete conversions were obtained and recycling was possible by filtration or decantation

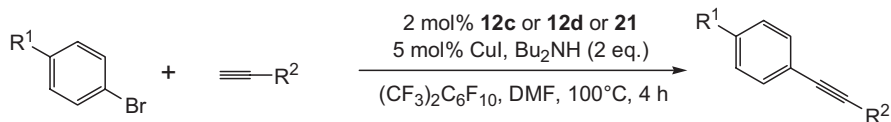


Scheme 10.8-12

without significant decrease of activity (yield over four cycles with three different immobilized complexes 98–91%). With 0.001 mol% of catalyst, a TON of 131 000 was observed. ICP-MS measurements indicated a leaching of 1.9% of catalyst when adsorbed onto FRPSG **22** and 1.6% when adsorbed onto FRPSG **23**, respectively. Suzuki couplings with catalyst **12c** on support **22** were performed with different substrates giving high yields for electron deficient aryl bromides and for aryl iodides.

#### 10.8.2.5 Sonogashira Coupling

Markert and Bannwarth employed the Pd complexes **12c**, **12d** and **21** as catalyst precursors for the coupling of bromoarenes with alkynes (Scheme 10.8-13) [33]. The reactions were carried out in a mixture of DMF and perfluorodimethylcyclohexane at 100 °C for 4 h with 2 mol% of **12c**, **12d** or **21** and 5 mol% of CuI as the co-catalyst in the presence of 2 equiv of Bu<sub>2</sub>NH.

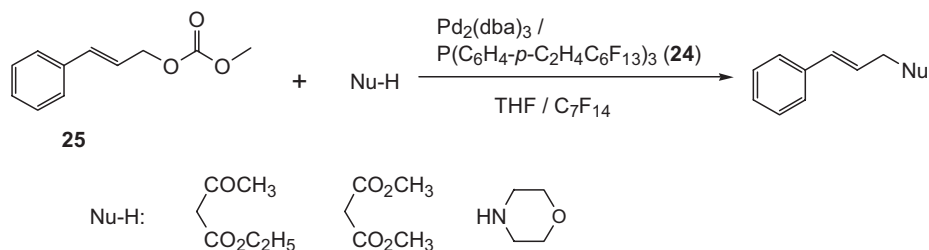


$\text{R}^1 = \text{NO}_2$ ; COMe; CO<sub>2</sub>Et, OMe

$\text{R}^2 = \text{TIPS}$ ; Ph; CMe<sub>2</sub>OH

Scheme 10.8-13

After the reaction, the phases were separated at 0 °C and the fluorous phase containing the catalyst was washed several times with DMF and was reused as such for the next run. As is known for Sonogashira couplings, electron-deficient bromoarenes proved to be good substrates, whereas the coupling of donor-substituted bromoarene resulted in lower yields. Recycling and reuse of the catalyst was possible in most cases but no influence of the product yield being dependent on the position of the perfluoro-tag in the phosphane or the nature of the spacer group was observed.



Scheme 10.8-14

Perfluoro-tagged Pd complexes **12c**, **12d** and **21** adsorbed on FRPSG **22** (2 mol%) were also used for Sonogashira couplings of phenyl acetylene and *p*-nitrobromobenzene, without the need for fluorous solvents, similar to the protocol outlined for Suzuki couplings [32]. High yields were obtained for three successive experiments. By reducing the amount of catalyst down to 0.2 mol%, conversion was still complete, but a significant drop of product yield was observed in the second run.

#### 10.8.2.6 Allylic Substitutions

Leitner and coworkers described Pd catalyzed nucleophilic substitutions of allylic substrates with different nucleophiles (Scheme 10.8-14) [34]. They used  $\text{Pd}_2(\text{dba})_3$  as the palladium source and phosphane **24** as the perfluoro-tagged ligand. Reaction between cinnamyl methyl carbonate (**25**) and various nucleophiles ( $\text{Nu-H}$ ) were performed in a  $\text{THF}/\text{C}_7\text{F}_{14}$  biphasic mixture at 25 °C or 50 °C for 15 to 80 min. A decrease in conversion was observed only after the ninth run (with a 5 mol% Pd complex). By reducing the amount of Pd complex to 1 mol%, five quantitative recyclings were possible. The standard protocol was also applied to the condensation of dimethyl malonate with allyl methyl carbonate, (2-vinyl)butyl carbonate and cyclohex-2-enyl carbonate. In each case two recyclings were performed without any decrease in conversion (100%).

#### 10.8.2.7 Cyclodimerization

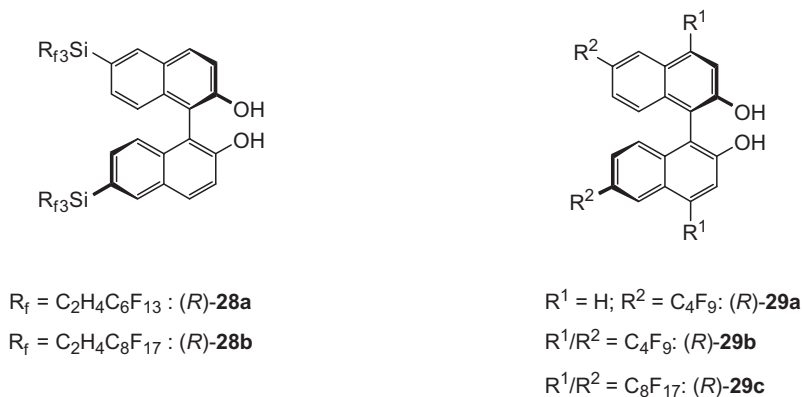
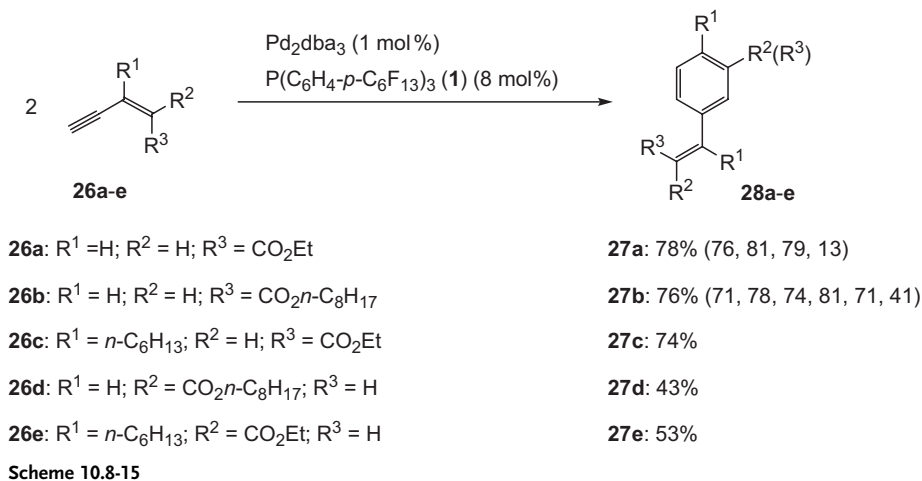
Cyclodimerizations of conjugated enynes **26a–e** in the presence of perfluoro-tagged Pd catalyst were reported by Saito et al. (Scheme 10.8-15) [35]. Reactions of enynes **26a–e** were carried out in toluene/hexane/perfluorodecaline with 1 mol% of  $\text{Pd}_2(\text{dba})_3$  as the palladium source and 8 mol% of perfluoro-tagged phosphane **1** at 65–80 °C for 1–4 h giving the desired products (**27a–e**) in moderate to good yield (43–78%).

Recovery of the perfluoro-tagged catalyst was possible up to four times. However, ICP atomic emission analysis of the fluorous phase indicated that the concentration of the palladium species decreased significantly.

### 10.8.3

#### Fluorous BINOL-Titanium Catalyzed Diethylzinc Additions to Aromatic Aldehydes

Curran and coworkers and Chan and coworkers independently described the asymmetric addition of diethylzinc to aldehydes mediated by chiral perfluoro-tagged BINOL-Ti-catalysts

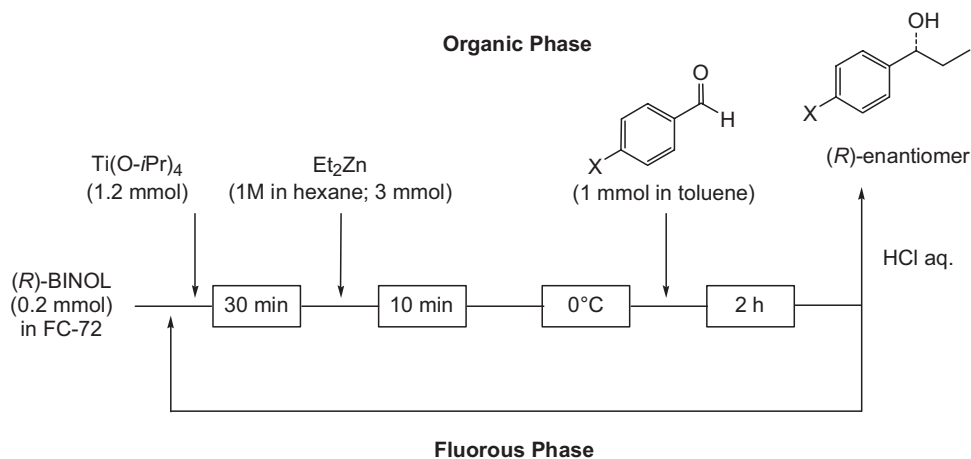


[36–39]. Whereas Curran tagged the BINOL ligands (**28a/b**) with perfluoro-silyl ponytails, Chan attached perfluororalkyl residues directly to the BINOL core (**29a–c**) (Scheme 10.8-16).

The approximate partition coefficients of the perfluoro-tagged BINOLS **28** and **29** are shown in Table 10.8-1.

**Tab. 10.8-1.** Approximate partition coefficients of the perfluoro-tagged BINOLs **28** and **29**

<i>BINOL</i>	<i>Solvent system</i>	<i>Organic-/fluorous-solvent</i>
<b>28a</b>	toluene/FC-72	2/98
<b>28b</b>	toluene/FC-72	1/99
<b>29a</b>	hexane/perfluoro-(methyldecaline)	1/2
<b>29b</b>	hexane/perfluoro-(methyldecaline)	1/15
<b>29c</b>	hexane/perfluoro-(methyldecaline)	1/53



Scheme 10.8-17

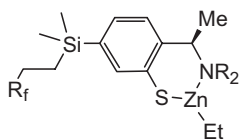
With BINOLs **28a** and **28b** reactions were performed in a biphasic solvent system according to Scheme 10.8-17.

High yields (81–97%) were obtained with enantioselectivities (78–84%) comparable to reactions in non-fluorous uniphase systems. Furthermore, it was possible to recycle and reuse the fluorous-tagged BINOLs (**28a/b**) by solid phase extraction on FRPSG giving nearly the same yield and enantioselectivity as in the first run.

Reactions with Ti complexes of **29a–c** were performed at 45 °C in a perfluoro-(methyldecalin)/hexane biphasic mixture. Lower enantioselectivities were obtained than with **28a/b**, which was possibly due to the higher reaction temperature employed. Enantioselectivity in consecutive runs strongly depended on the fluorine content of the BINOL ligand. With **29a** high yield (99%) and good enantioselectivity (ee 70%) were obtained for the diethylzinc addition to benzaldehyde in the first run, which significantly dropped in the second cycle (ee 28%), whereas with **29c** enantioselectivity was somewhat lower (ee 54–60%), but did not decrease during nine runs. The **29c**-Ti complex was also used as a catalyst for the triethyl aluminum addition to benzaldehyde, where good yields and ee values were obtained up to the sixth run (yield 82%; ee 80%) [39].

The zinc-catalysts **30–32** were introduced by van Koten and coworkers for enantioselective additions of diethylzinc to benzaldehyde under FBS conditions (Scheme 10.8-18) [40].

Reactions were performed with 2.5 mol% of **30–32** in a monophasic (hexane) or a biphasic (octane/PFMCH) system, respectively. In the monophasic system conversions (90–100%) and enantiomeric excesses (82–94%) were higher than with the untagged complex **33** (conversion 81%; ee 72%). In the biphasic system the initial enantioselectivity was high but dropped in consecutive runs [**30** (ee drop from 72% in second run to 37% in the third run); **31** (61%, third to 36%, fourth); **32** (76%, third to 43%, fourth)]. The experiments indicated that an increase in length of the perfluoroalkyl chain does not necessarily have a positive effect on the number of runs for which the catalyst can be reused.

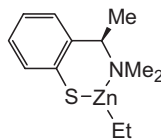


**30:** R = Me; R<sub>f</sub> = C<sub>6</sub>F<sub>13</sub>

**31:** R = Me; R<sub>f</sub> = C<sub>10</sub>F<sub>21</sub>

**32:** R = -(CH<sub>2</sub>)<sub>4</sub>-; R<sub>f</sub> = C<sub>10</sub>F<sub>21</sub>

**Scheme 10.8-18**

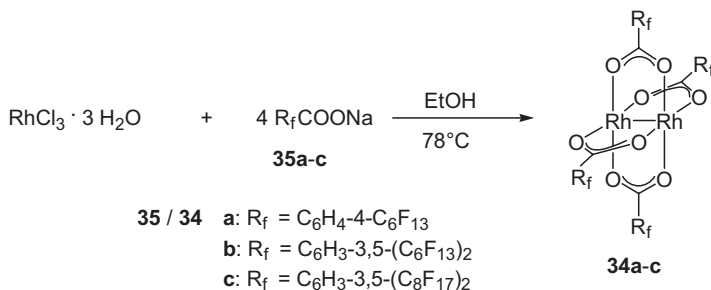


**33**

#### 10.8.4

#### Perfluoro-Tagged Rhodium Catalysts

Endres and Maas prepared dimeric rhodium(II) carboxylate complexes **34a–c** from the sodium salts **35a–c** and rhodium(III) chloride hydrate in ethanol (Scheme 10.8-19) [41, 42].

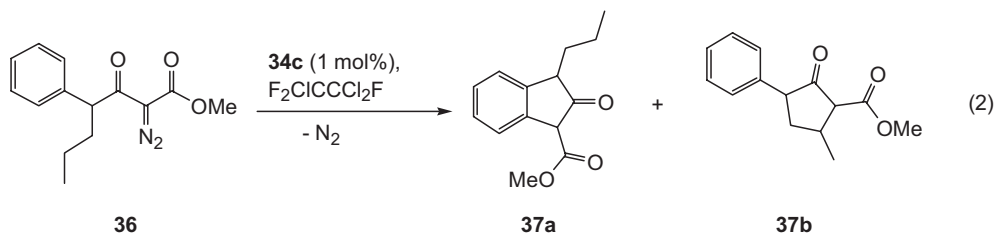
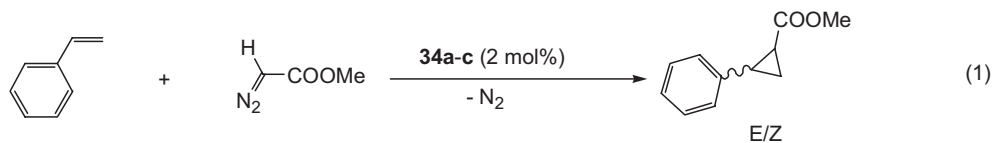


**Scheme 10.8-19**

Complexes **34a–c** were applied to cyclopropanations of styrenes with methyl diazoacetate [Eq. (1), Scheme 10.8-20]. Reactions were performed in CH<sub>2</sub>Cl<sub>2</sub> with **34a** or in the fluororous/organic hybrid solvent FC-113 (CCl<sub>2</sub>F-CClF<sub>2</sub>) with **34b–c**.

Recovery of the catalyst was achieved by extraction into PFMCH (with **34a**) or by replacement of FC-113 with PFMCH/CH<sub>2</sub>Cl<sub>2</sub> (with **34b–c**) and phase separation, respectively. Yields remained high over four cycles with **34a** (70–71%) or five cycles with **34b–c** (67–70% with **34b** and 75–76% with **34c**), respectively. Nevertheless, a total loss of 56% of **34a** (after four cycles), 51% and 38% of **34b** and **34c**, respectively, after five cycles, as shown by gravimetric determination, was observed. The authors attributed this to a partial destruction of the complex.

Intramolecular carbenoid C–H insertions of  $\alpha$ -diazo- $\beta$ -keto ester **36** [Eq. (2); Scheme 10.8-20] were catalyzed by **34c** with good selectivity for **37a** and good yield [67% (**37a**):3% (**37b**)] [42]. By extraction with PFMCH/CH<sub>2</sub>Cl<sub>2</sub>, 96% of the catalyst could be recycled.



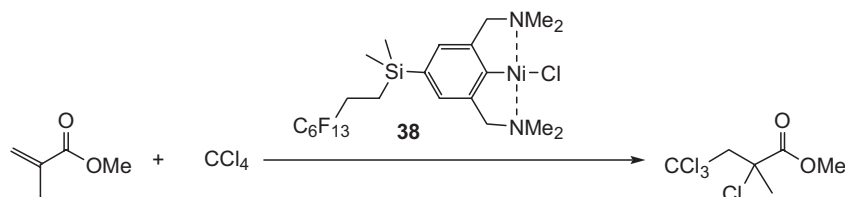
Scheme 10.8-20

## 10.8.5

## Miscellaneous

## 10.8.5.1 Kharash Addition

The addition reaction of  $\text{CCl}_4$  to methylmethacrylate in DCM was catalyzed by perfluoro-tagged nickel compound **38** as described by Kleijn et al. (Scheme 10.8-21) [43].

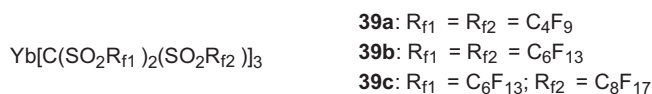


Scheme 10.8-21

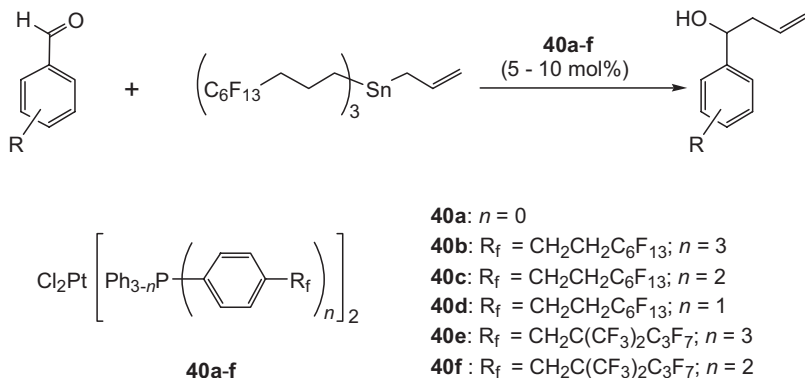
Unfortunately, **38** did not have an improved affinity for fluorous solvents which prevented its efficient recycling.

## 10.8.5.2 Friedel-Crafts Acylation

The Friedel-Crafts acylation of arenes with acetic anhydride was efficiently catalyzed by ytterbium tris(perfluoroalkanesulfonyl)methides **39a–c** (Scheme 10.8-22) [44]. It was dem-



Scheme 10.8-22



Scheme 10.8-23

onstrated that catalyst **39c** could be recovered in 96% yield by extraction of the reaction mixture with hot perfluoromethyldecaline and could be reused in a second run.

The reaction of perfluoro-tagged allyltin compounds with aldehydes catalyzed by  $\text{PtCl}_2(\text{PPh}_3)_2$  (**40a**) and  $\text{PtCl}_2[\text{PPh}_{3-n}(\text{C}_6\text{H}_4-4-\text{R}_f)_n]_2$  (**40b–f**), where  $\text{R}_f$  represents a linear or branched perfluoro alkyl chain, was described by Curran and coworkers (Scheme 10.8-23) [45, 46]. The reactions were performed using 5 to 10 mol% of catalyst **40a–f** without perfluorinated solvents. Purifications were done by solid phase extraction on FRPSG. All products were obtained in good yields (56–100%) and excellent purities (95–100%). By using catalysts **40b–c** and **40e–f** neither fluororous phosphane nor the fluororous tin compounds could be detected by NMR. Recovery and reuse of either phosphanes or Pt-complexes by solid phase extraction was not successful.

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## 10.9

### Hydroformylation and Hydrogenation Catalyzed by Perfluoroalkylated Phosphine/Metal Complexes

*Eric G. Hope and Alison M. Stuart*

#### 10.9.1

##### Introduction

Although homogeneous catalytic systems, typically discrete soluble metal complexes, offer a number of significant advantages (such as enhanced chemo-, regio- and enantio-selectivity, and/or milder reaction conditions) over comparable heterogeneous catalytic systems, many have not been and will not be industrially commercialized because of one major issue: the separation of the metal catalyst from the reaction product(s). This arises from the relative, thermal instability of many homogeneous catalysts, which are typically unstable above ca. 150 °C, linked with the easiest and most commonly employed separation procedure on an industrial scale – distillation. Consequently, there has been significant interest in the design of processes that draw upon the principle advantages of both homogeneous and heterogeneous catalysts, including supported systems, supercritical fluids and alternative solvent systems such as ionic liquids, aqueous biphasic and fluorous solvents. In this contribution, we highlight the applications of fluorous solvents and perfluoroalkylated phosphine ligands/metal catalysts in two, industrially important, processes: hydroformylation and hydrogenation. In a subsequent contribution, closely related work on hydroformylation with perfluoroalkylated phosphite ligands is discussed (see Chapter 10.10).

#### 10.9.2

##### Hydroformylation

The hydroformylation of alkenes, essentially the addition of syngas ( $\text{CO} + \text{H}_2$ ) across the double bond (Scheme 10.9-1), has been extensively investigated and was exploited commercially for the first time in the 1950s using cobalt-carbonyl catalysts [1]. Enhanced hydrogenation to give alcohols coupled with improved selectivity to the linear (*n*-) product has been accomplished by the introduction of phosphine ligands [2] and these technologies are still in use today for the hydroformylation of long-chain alkenes. In the hydroformylation of propene, where the volatile butanal product can be readily distilled directly from the reactor, more selective rhodium-triphenylphosphine catalysts operating under milder reaction con-

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#### 10.9.1

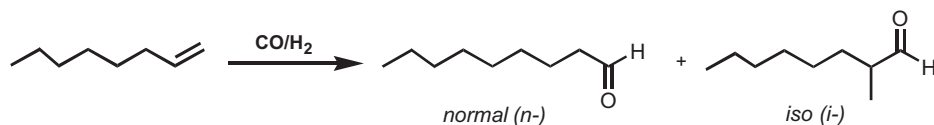
##### Introduction

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#### 10.9.2

##### Hydroformylation

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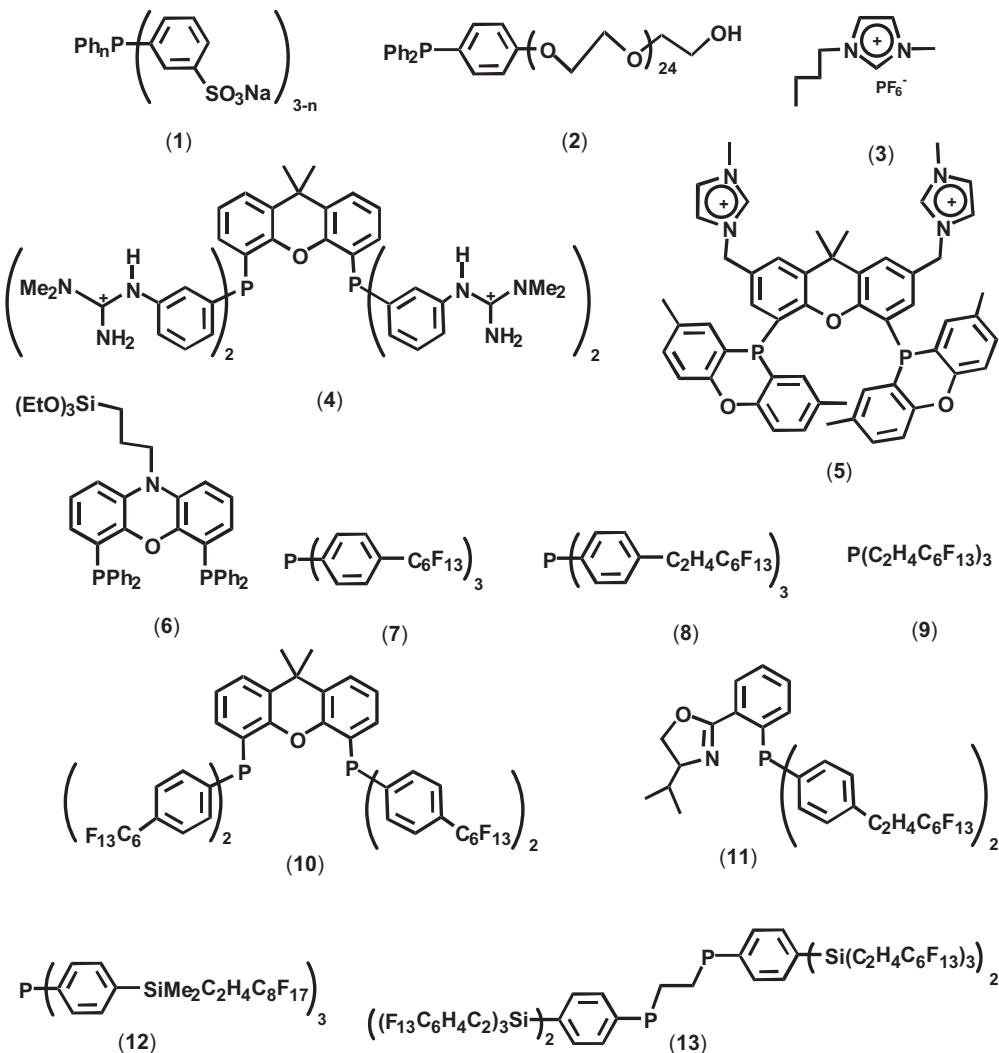
Scheme 10.9-1

ditions have replaced the cobalt-based catalysts in continuous processes operating at 3.5 million tonnes per annum [3]. However, the thermal instability of these rhodium catalysts has precluded their widespread adoption and has led to the evaluation of a number of alternative approaches including fluoros chemistry. In fact, Horváth and Rábai highlighted the potential for fluoros technologies for the hydroformylation of long chain alkenes in their original disclosure on the fluoros biphasic [4].

### 10.9.2.1 Alternative Systems

**10.9.2.1.1 Aqueous Biphasic** The relative instability of the rhodium-based catalysts has already been overcome, and the technique exploited commercially, in the Ruhrchemie-Rhône Poulenc hydroformylation of propene where the sodium salt of a sulfonated triphenylphosphine ligand (**1**) (Scheme 10.9-2) is used to solubilize the rhodium catalyst in the aqueous phase [5]. In this process, the second phase is toluene and the reaction is carried out in a batch process with rapid stirring to ensure that the two immiscible phases are intimately mixed. After reaction, the system is allowed to separate and the organic product phase is simply decanted from the aqueous catalyst phase. However, this approach has not been extended to the hydroformylation of longer chain alkenes because of their very low aqueous solubility leading to commercially prohibitive low reaction rates. A potential solution to this problem was reported five years ago in which the sulfonated triphenylphosphine ligand has been replaced with triphenyl phosphine functionalized with a single, very long, polyethylene glycol ponytail (**2**) [6]. Here, although the rhodium-phosphine catalyst is exclusively soluble in water at room temperature, on heating the ponytail undergoes a phase transition rendering the catalyst preferentially soluble in the organic phase. Consequently, the catalyst acts on the substrate under classical homogeneous conditions but, on cooling, reversal of the phase transition returns the catalyst to the aqueous phase allowing the product to be separated by a simple decantation.

**10.9.2.1.2 Ionic Liquids** Ionic liquids, such as 1-butyl-3-methylimidazolium hexafluorophosphate (**3**), are salts that are (1) liquid at room temperature, (2) have extremely low vapor pressures, (3) can be tuned to dissolve organic compounds and (4) can dissolve ionic catalysts or, in specific examples, the liquid may act as a catalyst as well as the solvent. Consequently, there has been considerable interest in their potential application as alternative solvents for organic synthesis and catalysis. In initial work on the rhodium-catalyzed hydroformylation of 1-pentene, using the sulfonated phosphine ligand (**1**) to solubilize the catalyst in the ionic liquid, conversions were disappointingly low [7]. More recently, two groups have reported highly active and regioselective rhodium-catalyzed hydroformylation of 1-octene with Xantphos-type ligands in ionic liquids, {(4) *n*:*i* 21:1 and <0.07% rhodium



Scheme 10.9-2

leaching [8]; (5) *n*:*i* 49:1 and <5 parts per billion rhodium loss [9]], where separation of the 1-nonanal product can be achieved again by a simple decantation.

**10.9.2.1.3 Supported Catalysts** Rhodium catalysts for hydroformylation supported on both insoluble (for example inorganic oxides or polymers) and soluble (for example dendrimers) materials have been reported. Work on insoluble solid supports has been dogged by loss of activity and high levels of catalyst leaching as a consequence of bonds breaking between the catalyst and support during catalysis. However, acceptable catalyst leaching (<100 parts per billion rhodium) coupled with reasonable activity and excellent regioselectivity (*n*:*i* 40:1)

has been demonstrated for a sol-gel solution incorporating a triethoxysilyl-functionalized Xantphos-type ligand (**6**) [10]. Dendrimers are large tree-like soluble molecules with a globular shape making them suitable for ultrafiltration in which the solvent and reaction product(s) pass through whilst the dendrimer is retained. Rhodium for hydroformylation can be supported on the “surface” of the dendrimer functionalized with phosphines, and such a system shows enhanced regioselectivity but loss of activity on recycling [11].

**10.9.2.1.4 Supercritical Carbon Dioxide** Most metal-containing complexes, particularly rhodium-based hydroformylation catalysts incorporating aryl-phosphine ligands, are virtually insoluble in apolar  $\text{scCO}_2$ . Solubility can be enhanced by the incorporation of the perfluoroalkyl groups characteristic of fluorine chemistry and reaction rates and regioselectivities for the hydroformylation of long chain alkenes, comparable to those observed under fluorine biphasic conditions, have been reported using derivatized rhodium catalysts [12, 13]. In two reports, significantly enhanced rates of reaction have been reported in  $\text{scCO}_2$  in comparison with those in toluene for the rhodium-catalyzed hydroformylation of acrylic esters using the perfluoroalkylated phosphine (**7**) [14], or a fluoropolymer ligand [15]. However, although there has been considerable interest in  $\text{scCO}_2$  as an environmentally friendly solvent for homogeneous catalysis [16, 17], for which removal of the solvent just requires decompression back to the gaseous phase, this does not per se overcome the principle issue for homogeneous catalysis outlined above; that is the separation of product from catalyst. In theory, since solubility in supercritical fluids is pressure dependent, with careful control of the catalyst/substrate/product system it should be feasible to accomplish the desired separation, and this has been achieved with moderate success ( $< 170$  parts per billion rhodium leaching) in the hydroformylation of 1-octene using the perfluoroalkylated triphenylphosphine (**8**) [12]. Alternative approaches to the catalyst/product separation problem have combined  $\text{scCO}_2$  with a supported catalyst [for example (**6**)] [18] and  $\text{scCO}_2$  with an ionic liquid [19], both of which are potentially very powerful systems but, in both cases the reaction rates are relatively low.

#### 10.9.2.2 Fluorous Systems

In the earliest reports of the application of perfluorocarbon solvents and perfluoroalkylated ligands/metal catalysts, Horváth and Rábai outlined the hydroformylation of 1-octene in a toluene/ $\text{CF}_3\text{C}_6\text{F}_{11}$  (PP2) two-phase system at  $100^\circ\text{C}$  under 10 atm  $\text{CO}/\text{H}_2$  (1:1) using a catalyst generated *in situ* from  $[\text{Rh}(\text{CO})_2(\text{acac})]$  and  $\text{P}(\text{C}_2\text{H}_4\text{C}_6\text{F}_{13})_3$  (**9**) (1:40), which gave an 85% conversion into aldehydes with an  $n/i$  ratio of 2.9 [4, 20]. In the following full paper [21], an in-depth analysis of hydroformylation under fluorine biphasic conditions generated a series of important conclusions. Here, the hydroformylation of 1-decene and ethylene were investigated with the same rhodium catalyst (generated *in situ*) under both batch and semi-continuous conditions at  $100^\circ\text{C}$  and 1.1 MPa  $\text{CO}/\text{H}_2$  (1:1) in a 50/50 vol% toluene/PP2 biphasic system. The long-term stability of this catalyst under these conditions is significantly greater than that for the catalyst based on triphenylphosphine, the regioselectivity is similar, but the catalytic activity is an order of magnitude lower. The reaction, as expected, is first-order in both rhodium and alkene and is inhibited by excess phosphine, whereas the regioselectivity increases with phosphine concentration such that the best  $n/i$  ratio (7.84) is obtained at a P:Rh ratio of approximately 100:1 ([ligand] =  $0.3 \text{ mol dm}^{-3}$ ). The semi-continuous experi-

ments were highly successful with total turnovers of up to 35 000 during nine cycles with only 1.18 parts per million (4.2%) loss of rhodium per mol of product(s), which arises from the low solubility of the catalyst in the organic phase.

It is well established that triarylphosphines give much better regioselectivity in rhodium-catalyzed hydroformylation reactions than trialkylphosphines [3, 22], so we have evaluated rhodium catalysts based upon (7) [23, 24]. Initial screening of the hydroformylation of 1-hexene in a toluene/1,3-(CF<sub>3</sub>)<sub>2</sub>C<sub>6</sub>F<sub>10</sub> (PP3) two-phase system at 70 °C under 20 atm CO/H<sub>2</sub> (1:1) using a catalyst generated *in situ* from [Rh(CO)<sub>2</sub>(acac)] and (7) (1:3) gave a 98% conversion into aldehydes with an *n/i* ratio of 3.8. Visual inspection of the solvent system under 20 atm syngas in high pressure sapphire NMR tubes indicated that the alkene starting materials are miscible with the fluoruous solvent at the reaction temperature whilst the more polar aldehyde products are immiscible, and this work led to an evaluation of the perfluoroalkylated rhodium hydroformylation catalyst in the absence of the second organic phase. Here, thorough investigation of the hydroformylation of 1-octene in PP2 between 70 and 90 °C under 20 atm CO/H<sub>2</sub> (1:1) using the same rhodium catalyst with metal:ligand ratios of 1:3 and 1:10 gave 95–98% conversions with *n/i* ratios of 3.0–6.3. Crucially, rhodium leaching levels, detected at the best regioselectivity (*n/i* 6.3; conditions rhodium:phosphine 1:10; 70 °C), were excellent (80 parts per billion) indicating that the omission of toluene from the solvent system has enabled the development of a process which is nearing the rigorous retention of rhodium, whilst maintaining both the high reaction rate and good regioselectivity, which are required for commercial application.

Table 10.9-1 summarizes the key catalytic data for these hydroformylation reactions under fluoruous biphasic conditions alongside data for representative examples from the alternative solvent systems outlined above. In general, the results are comparable: in some cases better regioselectivities, in others better reaction rates, in yet others better catalyst retention. In at-

**Tab. 10.9-1.** Rhodium catalyzed hydroformylation of 1-octene<sup>a</sup>

System	Ligand	Pressure (bar)	T (°C)	TOF (h <sup>-1</sup> )	Rate (mol dm <sup>-3</sup> h <sup>-1</sup> )	<i>n/i</i>	Rh loss (mg per mol product)	Ref.
Homogeneous <sup>b</sup>	PPh <sub>3</sub>	15	95	770	2.0	8.8:1	n.a.	3
Aqueous biphasic <sup>b</sup>	(1)	50	120	400	1.1	19:1	<0.005	5
Aqueous biphasic	(2)	50	100	182	0.5	n.r.	n.r.	6
Ionic liquids	(4)	30	100	50	n.r.	21:1	<0.07% <sup>c</sup>	8
Ionic liquids	(5)	46	100	318	1.2	49:1	<0.005	9
Supported catalyst	(6)	50	80	287	0.19	40:1	<0.1	10
scCO <sub>2</sub>	(8)	200	65	430	14.2	5.5:1	<0.17	12
Supported/scCO <sub>2</sub>	(6)	170	90	160	n.r.	33:1	<1.2	18
Fluoruous biphasic	(9)	10	100	837	0.1	4.5:1	0.12	21
Fluoruous biphasic	(7)	20	70	4400	8.8	6.3:1	0.08	24

<sup>a</sup> n.a. = Not applicable; n.r. = not reported. <sup>b</sup> Propene as substrate.

<sup>c</sup> Reported as a % of catalyst loading.

tempts to improve regioselectivity and catalyst retention under fluoruous biphasic conditions, we and others have been investigating perfluoroalkylated bidentate ligands based upon Xantphos, for example (**10**) [25], and BIPHEPHOS [26, 27]. Unfortunately, the introduction of perfluoroalkyl units onto biphenol has, to-date, prevented the synthesis of fluoruous BIPHEPHOS-type bisphosphite ligands whilst (**10**) with only four perfluoroalkyl groups, although it is active in the rhodium-catalyzed hydroformylation of 1-octene (*n*:*i* 23:1), is not soluble in fluoruous solvents and attempts to increase the number of perfluoroalkyl substituents has not yet been successful. These latest results appear to suggest that the future development of fluoruous chemistry in hydroformylation probably rests with simpler, monodentate, ligand systems.

### 10.9.3

#### Hydrogenation

The hydrogenation of unsaturated organic compounds represents one of the most environmentally benign processes in that it produces virtually no waste. Since heterogeneous catalysts (for example Raney nickel, palladium on carbon) are highly effective and efficient, homogeneous hydrogenation catalysts will only find application when other factors (for example, substrate incompatibility, enantioselectivity, transfer hydrogenation to avoid the need to use gaseous hydrogen) are important [28]. The classic industrial example is the rhodium-catalyzed homogeneous enantioselective hydrogenation of dehydroaminoacids in the synthesis of L-dopa [29]. In these cases, as for the homogeneous hydroformylation catalysts outlined above, product/catalyst separation is a major issue that has led to the synthesis and evaluation of homogeneous catalysts under a variety of alternative regimes.

#### 10.9.3.1 Alternative Systems

**10.9.3.1.1 Aqueous Biphasic** So far, no industrial process for hydrogenation under aqueous biphasic conditions has been commercialized. In the research laboratories, the biphasic hydrogenation of a wide variety of substrates has been investigated using mainly sulfonated ligands, for example (**1**), for solubilizing the catalyst [30, 31], leading to the biphasic hydrogenation of CO<sub>2</sub> to formic acid [32]. Enantioselective hydrogenation has also been extensively studied, but reaction rates and enantiomeric excesses have usually been lower than those obtained in conventional media [30].

**10.9.3.1.2 Ionic Liquids** Early work on the hydrogenation of 1-pentene in (**3**) used cationic rhodium(I) species, for example [Rh(nbd)(PPh<sub>3</sub>)<sub>2</sub>][PF<sub>6</sub>] that did not require functionalized ligands, offered acceptable reactivities, that were anion dependent, with low (<0.02%) rhodium leaching levels [7]. Similarly, up to 90% ee and quantitative conversions have been reported for up to five recycles of conventional ruthenium-BINAP catalysts in the asymmetric hydrogenation of tiglic acid in (**3**) followed by extraction of the 2-methylbutanoic acid product with scCO<sub>2</sub> [33]. In a recent development, [Rh(COD)(PPh<sub>3</sub>)<sub>2</sub>][BF<sub>4</sub>] has been used for the hydrogenation of water-soluble alkenes in a water:ionic liquid system that is monophasic at the reaction temperature (80 °C) but phase separates at room temperature for the facile separation of the water-soluble product and reuse of the catalyst phase [34].



**10.9.3.1.3 Supercritical Carbon Dioxide** Since permanent gases are fully miscible with supercritical fluids, hydrogenation in  $\text{scCO}_2$  is particularly attractive and work in this area has been reviewed [16, 17]. Of particular interest are enhanced reactivities in ruthenium-catalyzed hydrogenation of  $\text{CO}_2$  to formic acid in the presence of base [35, 36], and highly enantioselective hydrogenation of prochiral  $\alpha,\beta$ -unsaturated carboxylic acids [37, 38]. Catalyst/product separation remains a key issue that has been elegantly overcome in an iridium-catalyzed enantioselective (ee up to 81%) hydrogenation of imines using the perfluoroalkylated phosphine-imine ligand (**11**), where the catalyst is soluble in  $\text{scCO}_2$  in the presence of the substrate, but precipitates once all the substrate has been used up. This allows the catalyst to be recycled several times without significant loss of either activity or enantioselectivity [39].

### 10.9.3.2 Fluorous Systems

In contrast with the research into hydroformylation under FBS conditions that has been directed towards a commercially important process, publications on hydrogenation under FBS conditions have been focused upon the physical and chemical consequences of using perfluoroalkylated phosphine ligands and fluoruous solvents and the ability to recover and recycle the metal catalyst. Horváth and coworkers [40], using the analog of Wilkinson's catalyst,  $[\text{RhClL}_3]$ , where  $\text{L} = \text{P}(\text{C}_2\text{H}_4\text{C}_6\text{F}_{13})_3$  (**9**), studied the hydrogenation of a series of alkenes (2-cyclohexen-1-one, 1-dodecene, cyclododecene and 4-bromostyrene) in a toluene:PP2 biphase under 1 atm  $\text{H}_2$  at 45 °C affording the hydrogen addition products in 87–98% yields. Although the catalyst activity is significantly poorer than those for conventional homogeneous catalysts, recovery and reuse of the catalyst was illustrated by re-charging the fluoruous phase with second and third aliquots of substrate and obtaining comparable conversions, but some catalyst decomposition was also observed. It is well known that alkyl phosphines give much less effective analogs of Wilkinson's catalyst than aryl phosphines, and perfluoroalkylated aryl phosphines have been evaluated by other groups. A soluble fluoropolymer supported alkylidiphenyl phosphine is active for the hydrogenation of 1-octene and cyclohexene in a THF:perfluorooctane biphase under 2 atm  $\text{H}_2$  at 25 °C, where reuse seven times shows no loss in activity although rhodium leaching levels have not been measured [41]. Using styrene as a substrate, we have directly compared the catalytic activities of the analogs of Wilkinson's catalyst containing perfluoroalkylated phosphines, for example (**7**), with those of their protio-parents in toluene/hexane:PP3 or fluorobenzene:PP3 biphases under 1 atm  $\text{H}_2$  at 63.5 or 75 °C, respectively, where just the introduction of the fluoruous phase had a significant impact upon the rates of reaction, but <1 ppm rhodium leaching was observed [42]. In line with well-established trends, the incorporation of the electron withdrawing perfluoroalkyl groups caused a reduction in rate relative to those for the protio-parents and this effect is most pronounced for the trialkyl phosphine with the  $\text{C}_2\text{H}_4$  spacer unit, indicating that it is a poorer electronic insulator than the  $\text{C}_6\text{H}_4$  group. The most promising results were obtained for a  $\text{C}_6\text{H}_4\text{OCH}_2$  spacer group although, even with this unit, complete electronic insulation of the phosphorus atom was not possible. The most effective insulation is reported in a direct comparison of the aryl-silyl spacer ligand (**12**; TOF 870  $\text{h}^{-1}$ ) with Wilkinson's catalyst (TOF 960  $\text{h}^{-1}$ ) in the hydrogenation of 1-octene in  $\alpha,\alpha,\alpha$ -trifluorotoluene under 1 atm  $\text{H}_2$  at 80 °C [43]. In PP2 [using (**12**), 1-octene at 80 °C] the TOF drops to 177  $\text{h}^{-1}$ , but on cooling to 0 °C a biphase forms that allows separation of the

octane product and the catalyst phase to be recycled nine times with just 3 ppm (0.12%) rhodium leaching per cycle. The reactivity appears to increase during the subsequent cycles, although this can be ascribed to loss of the perfluorocarbon solvent (ca. 12% per cycle) during phase separation and the non-zero miscibility of PP2 with the product phase. The best catalyst retention (> 99.92%) has been reported following hydrogenation of 1-octyne under 1 atm H<sub>2</sub> at 40 °C with the cationic [Rh(COD)(**13**)] [BF<sub>4</sub>] in a FC-75/hexane biphasic system, where the chelating bidentate phosphine ligand (**13**) has 12 fluorinated ponytails [44].

It is rather difficult, and not particularly informative, to make a detailed comparison between these data for hydrogenation in fluorocarbon solvents and those for hydrogenation in alternative media since the studies have employed a wide range of metals, types of catalyst, pressures of hydrogen and substrates, but in most cases reactivities are poorer than those reported in conventional organic solvents. Perfluoroalkylated chiral ligands have been prepared [45, 46], but they are not preferentially soluble in fluorinated solvents and to achieve this would require considerable further modification. Therefore, although enantioselective hydrogenation in aqueous systems and in supercritical CO<sub>2</sub> has been investigated, the likely application of fluorinated chemistry in this area appears remote.

#### 10.9.4

#### Outlook

In just nine years, considerable advances have been made in the understanding of fluorinated chemistry. Research on hydroformylation under FBS conditions has turned full-circle and attention in the future must focus on improving catalyst stability with simple, readily prepared ligands and chemical engineering process design directed towards guaranteeing solvent and catalyst losses at commercially acceptable levels.

At this point in time, the question about whether fluorinated or these other alternative approaches to the heterogenization of homogeneous hydroformylation or hydrogenation catalysts can be commercialized cannot be answered. All of these processes have one or more disadvantages (expensive ligand and/or solvent, environmental compatibility, high catalyst leaching, high pressures, low rates) and for most the complicated process of the transfer of the technology from the academic laboratory to larger scales or, indeed, pilot plant has not been attempted. Until these issues and a full cost analysis for the complete process have been undertaken, commercialization of any of these alternative technologies cannot be contemplated.

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## 10.10

### Hydroformylation Catalyzed by Rhodium/Fluorinated Triarylphosphite Complexes in Fluorous Biphasic Media

*Eric Monflier, André Mortreux, and Yves Castanet*

#### 10.10.1

##### Introduction

Hydroformylation of higher olefins is an important industrial process where less selective cobalt-based catalysts have to be employed because the more reactive and selective rhodium-based catalysts cannot be separated from the long chain aldehyde products without decomposition [1]. To circumvent this problem, five major strategies have been developed: (1) anchoring of rhodium catalysts to resins, polymeric, dendrimeric or inorganic materials [2–4]; (2) immobilization of the catalyst in a thin liquid film supported on inorganic materials [5–7]; (3) the use of amphiphilic ligands which allow the extraction of the rhodium catalyst into another phase at the end of the reaction [8–9]; (4) the use of supercritical fluids as reaction media [10–15]; and (5) the use of two-phase systems where the catalyst is dissolved in a phase which contains neither the substrate nor the products. In the biphasic approach, the rhodium catalyst can be dissolved in a molten salt [16, 17], in a fluorocarbon phase [18–31] or in an aqueous phase. Owing to the low solubility of higher olefins in water, the use of aqueous media requires the presence of a mass-transfer promoter [32–34], a surface-active phosphine [35, 36] or a thermoregulated phase transfer phosphine [37].

Among these different approaches, the fluorous biphasic catalysis is a particularly elegant concept as the two phases are generally readily separated at room temperature and can become homogeneous at higher temperatures [38, 39]. Obviously, this behavior allows combination of the activity of homogeneous catalysts with the simplicity of product isolation. The hydroformylation of olefins in a fluorocarbon phase was first reported by Horváth and Rábai in 1994 [18, 19]. The rhodium catalyst was dissolved in the fluorous phase by using a trialkylphosphine  $\text{P}[\text{CH}_2\text{CH}_2(\text{CF}_2)_5\text{CF}_3]_3$  prepared by hydrophosphinylation of the corresponding fluorinated alkene. This catalyst displays satisfactory activities in a perfluoromethylcyclohexane/toluene solvent system and the normal to branched aldehyde ratio ( $l/b$ ) was comparable to that obtained in a conventional solvent with  $\text{HRh}(\text{CO})(\text{PPh}_3)_3$  ( $l/b = 2.9$ ). Since this pioneering work, the attention of research groups has been focused on the synthesis of new fluorinated ligands showing a better affinity for the fluorous phase and a better  $l/b$  ratio. With the aim of maintaining the high selectivities and activities observed in classical organic solvents, three classes of ligands have been rapidly developed for

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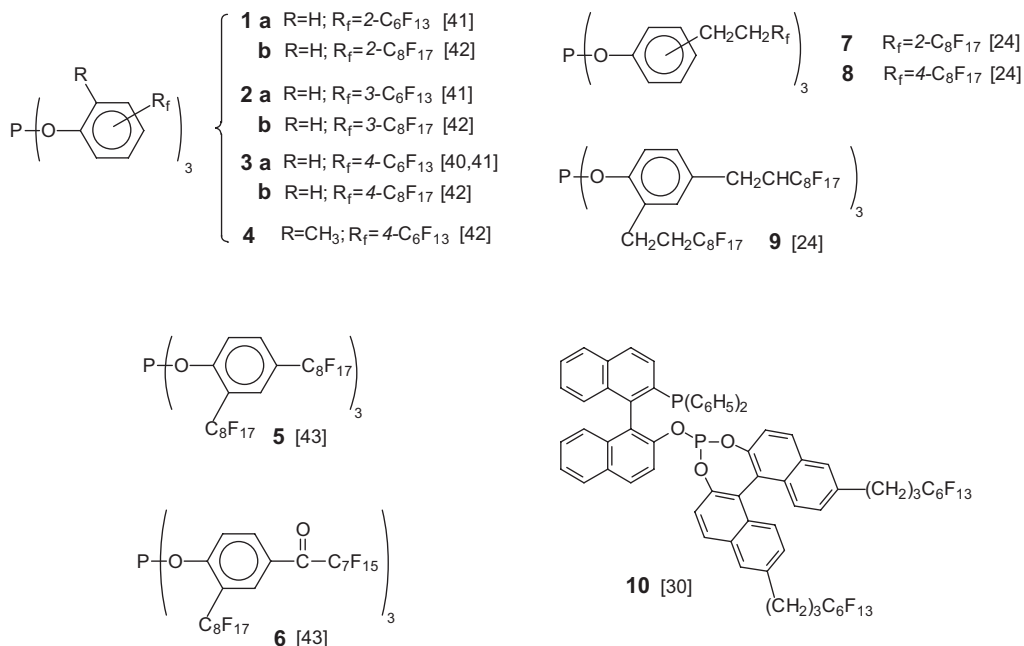
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Among these different approaches, the fluorous biphasic catalysis is a particularly elegant concept as the two phases are generally readily separated at room temperature and can become homogeneous at higher temperatures [38, 39]. Obviously, this behavior allows combination of the activity of homogeneous catalysts with the simplicity of product isolation. The hydroformylation of olefins in a fluorocarbon phase was first reported by Horváth and Rábai in 1994 [18, 19]. The rhodium catalyst was dissolved in the fluorous phase by using a trialkylphosphine  $\text{P}[\text{CH}_2\text{CH}_2(\text{CF}_2)_5\text{CF}_3]_3$  prepared by hydrophosphinylation of the corresponding fluorinated alkene. This catalyst displays satisfactory activities in a perfluoromethylcyclohexane/toluene solvent system and the normal to branched aldehyde ratio ( $l/b$ ) was comparable to that obtained in a conventional solvent with  $\text{HRh}(\text{CO})(\text{PPh}_3)_3$  ( $l/b = 2.9$ ). Since this pioneering work, the attention of research groups has been focused on the synthesis of new fluorinated ligands showing a better affinity for the fluorous phase and a better  $l/b$  ratio. With the aim of maintaining the high selectivities and activities observed in classical organic solvents, three classes of ligands have been rapidly developed for



**Scheme 10.10-1.** Fluororous phosphites used in hydroformylation under fluororous biphasic conditions

hydroformylation under fluororous biphasic conditions: triarylphosphines [13] and triarylphosphites [23, 40–43] bearing one or two perfluoroalkyl groups per aromatic ring and more recently, chiral phosphine–phosphite ligands with fluororous ponytails [30].

We will describe here, firstly, the general routes used to synthesize these new phosphites and, secondly, the behavior of catalysts generated *in situ* from these phosphites and  $\text{Rh}(\text{acac})(\text{CO})_2$ . The results obtained with fluororous ponytailed triarylphosphines will not be discussed.

#### 10.10.2

##### Synthesis

Scheme 10.10-1 summarizes the fluororous phosphites synthesized and tested in hydroformylation under fluororous biphasic conditions. The first approach developed to synthesize fluororous phosphites consists of attaching one perfluoroalkyl group directly onto the aromatic ring (phosphites **1** to **4**). These compounds were prepared in 20–66% overall yield in two steps. The first step involves a copper mediated coupling reaction between halophenol derivatives and 1-iodoperfluoroalkane [40–42], and the second step is the reaction of the corresponding phenol with phosphorus chloride. The partition coefficients ( $pK_a$ ) of the **2b** and **3b** phosphites in a 1-decene/ $\text{C}_8\text{F}_{17}\text{H}$  (50:50, v:v) mixture were determined at room temperature and were found to be 2.7/97.3 for both phosphites. The above two step synthetic sequence was also successfully used to synthesize phosphites bearing two fluororous ponytails

per ring (phosphites **5** and **6**) [43]. As expected, it was found that phosphites **5** and **6** are more fluorophilic than ligands **1–4** [ $pK_a$  of **6** = 0.9/99.1; 1-decene/ $C_8F_{17}H$  (50:50); rt].

In order to minimize the strong electron withdrawing effect of the perfluoroalkyl group, the synthesis of fluorous analogs of  $P(OPh)_3$  where aromatic rings are separated from the perfluoroalkyl groups by two methylene groups has also been performed (phosphites **7** and **8**) [23, 27]. The route developed for the synthesis of these phosphites was based on the reaction of Grignard reagents derived from monobromoanisoles with 1*H*,1*H*,2*H*,2*H*-perfluorodecanyl iodide in the presence of copper catalysts, followed by cleavage of the methoxy group by  $BBr_3$  and reaction of the corresponding phenol with  $PCl_3$ . Using this route, phosphites **7** and **8** were easily obtained with overall isolated yields of 35–45%. Owing to the presence of methylene groups, their partition coefficients [ $pK_a$  of **7** and **8** = 5/95; 1-decene/ $C_8F_{17}$  (50:50); rt] were logically lower than those found for phosphites **2b** or **3b**. The synthesis of phosphite **9** by applying the above method was more tedious (overall isolated yield of 3%). Although phosphite **9** contains insulating methylene groups, its solubility was similar to that of **5** [ $pK_a$  of **9** = 1/99; 1-decene/ $C_8F_{17}H$  (50:50); rt], suggesting that this phosphite is also a good candidate for fluorous biphasic hydroformylation reaction. Although their use in rhodium catalyzed hydroformylation has not been reported to date, it must be pointed out that Gladysz et al. have recently described a more convenient synthesis of a highly fluorocarbon-soluble phosphite of formula  $P\{OC_6H_3[(CH_2)_3C_8F_{17}]_2\}_3$  [overall isolated yield of 60% –  $pK_a$  of this phosphite = 8.92; toluene/ $CF_3C_6F_{11}$  (50:50); rt] [44].

The synthesis of fluorous analogs of BINAPHOS was initially reported by Leitner et al. [11], but the first use as a ligand in hydroformylation under fluorous biphasic conditions was described by Ojima et al. in 2001 [30]. In contrast with Leitner's approach which allows the introduction of a (1*H*,1*H*,2*H*,2*H*-perfluorohexyl) group at the *meta*-position of the diphenylphosphinyl moiety, Ojima et al. chose to substitute the peripheral naphthyl moieties with 1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluorononyl groups (overall isolated yield 30% – ligand **10**). Although the fluorine content of ligand **10** was low, the authors reported that **10** was very soluble in perfluorotoluene. However, it was found that this ligand was preferentially soluble in toluene over perfluoromethylcyclohexane, which will clearly prevent an efficient recovery of the catalyst.

### 10.10.3

#### Hydroformylation Under Fluorous Biphasic Conditions

##### 10.10.3.1 Activity and Selectivity of Catalysts

**10.10.3.1.1 Phosphites Without Spacer Groups** Phosphites **1** to **6** induce high activity in hydroformylation of terminal alkenes in comparison with the classical ligands  $PPh_3$  and  $P(OPh)_3$  (Table 10.10-1). Nevertheless, considerable differences in activity and selectivity exist according to the nature, the position and the number of substituents on the aromatic ring of the phosphite. For instance, bulky *ortho*-substituted phosphites lead to catalytic systems that are much more active than those resulting from their *meta*- or *para*-counterparts. However, these *ortho*-phosphites give lower *l/b* ratios. Indeed, the *l/b* ratios are found to be

**Tab. 10.10-1.** Hydroformylation of higher alkenes under fluororous biphasic conditions with phosphites **1** to **6**

Conditions	Substrate	Ligand	TOF <sup>a</sup> (h <sup>-1</sup> )	<i>l/b</i> ratio	Aldehyde selectivity (%)	Ref.
A	1-hexene	PPh <sub>3</sub>	900	2.7	93.1	25
B	1-hexene	P(OPh) <sub>3</sub>	1700	2.9	92	25
B	1-hexene	<b>1a</b>	4200	0.9	99.2	25
B	1-hexene	<b>2a</b>	1300	5.2	96.1	25
B	1-hexene	<b>3a</b>	2650	8.4	85.4	25
B	2-nonene	<b>3a</b>	880	–	75.1	25
C	1-octene	<b>3a</b>	15600	6.3	83.9	25
D	1-decene	<b>1b</b>	10000	2.3	71	23
D	1-decene	<b>2b</b>	6300	5.8	80	23
D	1-decene	<b>3b</b>	3500	5.3	85	23
D	1-decene	<b>4</b>	7100	2.9	80	23
D	1-decene	<b>5</b>	7900	2.4	46	23
D	1-decene	<b>6</b>	6200	2.6	39	23
D	1-octene	<b>2b</b>	6900	6.3	87	23
E	2-octene	<b>2b</b>	1400	–	75	23
E	4-octene	<b>2b</b>	800	–	76	23

Conditions:

A – A solution of [Rh(acac)(CO)<sub>2</sub>] (10.0 mmol dm<sup>-3</sup>), ligand (30 mmol dm<sup>-3</sup>), 1-hexene (8 mmol, 1 cm<sup>3</sup>), toluene (4 cm<sup>3</sup>) at 70 °C, 20 bar CO/H<sub>2</sub> (1:1) for 1 h.

B – A solution of [Rh(acac)(CO)<sub>2</sub>] (10.0 mmol dm<sup>-3</sup>), ligand (30 mmol dm<sup>-3</sup>), 1-hexene (8 mmol, 1 cm<sup>3</sup>) in a mixture of perfluoro-1,3-dimethylcyclohexane (2 cm<sup>3</sup>) and toluene (2 cm<sup>3</sup>) at 70 °C, 20 bar CO/H<sub>2</sub> (1:1) for 1 h.

C – A solution of [Rh(acac)(CO)<sub>2</sub>] (2.0 mmol dm<sup>-3</sup>), ligand (6 mmol dm<sup>-3</sup>), 1-octene (1 cm<sup>3</sup>) in perfluoro-1,3-dimethylcyclohexane (4 cm<sup>3</sup>) at 80 °C, 20 bar CO/H<sub>2</sub> (1:1) for 1 h.

D – [Rh(acac)(CO)<sub>2</sub>] (10 mg, 0.039 mmol), ligand (0.194 mmol), alkene (77.4 mmol), 1H-perfluorooctane (15 cm<sup>3</sup>), undecane (internal standard for GC analysis, 1.21 g), 80 °C, 40 bar CO/H<sub>2</sub> (1:1).

E – As conditions D except C<sub>8</sub>F<sub>17</sub>H (10 cm<sup>3</sup>), toluene (10 cm<sup>3</sup>).

<sup>a</sup>TOF = initial turn over frequency: moles of alkene converted per mole Rh per hour.

between **2** and **3**, i.e., greatly inferior to those observed with the *meta*- and *para*-phosphites (ca. 5–8) and slightly inferior or similar to those obtained with ligands PPh<sub>3</sub> or P(OPh)<sub>3</sub>.

Typically the reactivity decreases with the size of the substrate and, more unexpectedly, the *l/b* ratio and aldehyde selectivity vary in the same way. Interestingly, internal alkenes are also hydroformylated with significant activity with these catalytic systems. Another interesting feature of the process is that better reaction rates and *l/b* ratios are obtained when the reaction is carried out in the absence of an organic solvent.

**10.10.3.1.2 Phosphites With Spacer Groups** This class of phosphites showed little difference compared with phosphites **1–6** (see Table 10.10-2). Indeed, the *ortho*-substituted phos-



**Tab. 10.10-2.** Hydroformylation of higher alkenes under fluororous biphasic conditions with fluororous phosphites with spacer groups [24]

Phosphite	Substrate	Solvent	Time <sup>a</sup> (min)	TOF <sup>b</sup> (h <sup>-1</sup> )	<i>l/b</i>	Aldehyde selectivity (%)
7	1-decene	C <sub>8</sub> F <sub>17</sub> H	15	10000	2.0	85
8	1-decene	C <sub>8</sub> F <sub>17</sub> H	30	3900	3.5	95
9	1-decene	C <sub>8</sub> F <sub>17</sub> H	12	11000	2.0	85
8	1-decene	C <sub>8</sub> F <sub>17</sub> H/Tol.	60	3500	3.0	98
8	1-decene	PFMC	60	3800	3.0	98
8	1-decene	PFMD	90	2500	3.3	95
8	1-decene	PFPP	90	2300	3.6	95
8	1-octene	C <sub>8</sub> F <sub>17</sub> H/Tol.	60	3600	3.0	95
8	1-dodecene	C <sub>8</sub> F <sub>17</sub> H/Tol.	60	2600	3.0	94
8	2-decene	C <sub>8</sub> F <sub>17</sub> H/Tol.	90	1200	–	82
8	4-decene	C <sub>8</sub> F <sub>17</sub> H/Tol.	150	440	–	77
8	cyclohexene	C <sub>8</sub> F <sub>17</sub> H/Tol.	–	45	–	100

Conditions: [Rh(acac)(CO)<sub>2</sub>] (10 mg, 0.039 mmol), phosphite (0.194 mmol), alkene (77.4 mmol), solvent (15 cm<sup>3</sup>: pure fluororous solvent or 10 cm<sup>3</sup> C<sub>8</sub>F<sub>17</sub>H and 10 cm<sup>3</sup> toluene), undecane (1.21 g), 80 °C, 40 bar CO/H<sub>2</sub> (1:1).

<sup>a</sup>Time required to reach 100% conversion. <sup>b</sup>TOF = initial turn over frequency: moles of alkene converted per mole Rh per hour.

phites **7** and **9** differ from the *para*-substituted **8** by much higher activities (TOF > 10 000 versus 3900 h<sup>-1</sup>, respectively), a lower *l/b* ratio (2 versus 3.5) and a lower aldehyde selectivity. The main difference lies in the fact that the *l/b* ratio with the *para*-substituted phosphite **8** is much lower than that obtained with phosphites **2** or **3** and close to that obtained with P(OPh)<sub>3</sub>.

Experiments performed with different fluororous solvents proved that the nature of the fluororous phase has practically no effect on the *l/b* ratio or on the aldehyde selectivity. On the other hand, this factor greatly influences the activity since the TOF dropped from 3900 h<sup>-1</sup> when using 1H-perfluorooctane to 3800, 2500 and 2300 h<sup>-1</sup> with perfluoromethylcyclohexane (PFMC), perfluoromethyldecane (PFMD) and perfluoroperhydrophenanthrene (PFPP), respectively. These observations are explained by the fact that at the reaction temperature (80 °C), PFMD and PFPP are not totally miscible with 1-decene, in contrast to the 1-decene–C<sub>8</sub>F<sub>17</sub>H and 1-decene–PFMC combinations [24].

Other heavy terminal olefins behave similarly to 1-decene (Table 10.10-2) giving, for example, with phosphite **8**, an *l/b* ratio of about 3.0 and an aldehyde selectivity of 95%. However, the activity drops markedly on going from 1-decene to 1-dodecene, presumably again due to its partial solubility with the fluororous solvent C<sub>8</sub>F<sub>17</sub>H.

**10.10.3.1.3 Fluororous Analog of BINAPHOS** The asymmetric hydroformylation of styrene catalyzed by the (*S,R*)-**10**/Rh complex was briefly investigated in various fluororous solvents with or without toluene. The nature of the solvent has no significant effect on the catalytic

activity of the catalyst. While the regioselectivity was slightly higher than that observed in an organic solvent (*l/b* ratio: 6/94 versus 12/88), the enantioselectivity was lower (87 versus 94%) and an apparent racemization was observed in the course of the reaction [30].

### 10.10.3.2 Mechanistic Aspect

The results obtained with *ortho*-substituted phosphites differ from those of *meta*- or *para*-counterparts through a remarkably higher initial rate under the same conditions. At the same time, they lead to a more modest *l/b* ratio and aldehyde selectivity. This difference is probably related to the fact that with the former bulky phosphites, only one phosphite coordinates to the Rh center to give the active species  $\text{HRhLf}(\text{CO})_3$  (Lf = fluorous phosphite) [45]. In contrast with the latter phosphites that are less sterically demanding, two phosphites are bonded to rhodium [ $\text{HRhLf}_2(\text{CO})_2$ ] as in the classical triphenyl phosphine modified catalyst. Complex  $\text{HRhLf}(\text{CO})_3$  is more prone to CO dissociation than  $\text{HRhLf}_2(\text{CO})_2$ , resulting in a much higher reaction rate. Owing to the large space available with the  $\text{HRhLf}(\text{CO})_3$  system in comparison with  $\text{HRhLf}_2(\text{CO})_2$ , the reactions giving the branched aldehyde as well as the  $\beta$ -H elimination proceed with relative ease, resulting in modest linearity and aldehyde selectivity.

An other important finding is the high *l/b* ratio observed with *meta*- and *para*-phosphites 2 and 3. Electron withdrawing groups attached to the aryl rings of these phosphites afford less basic ligands. Consequently, the electron density on complex  $\text{HRhLf}_2(\text{CO})_2$  decreases, which promotes the olefin insertion on its terminal carbon, giving a linear alkylrhodium intermediate leading to the linear aldehyde. On the other hand, a decrease in the electronic density on the metal also favors the CO dissociation and hence the formation of low coordinated alkylrhodium species, which induce easier  $\beta$ -H elimination and thus olefin isomerization [46].

In the case of phosphites 5 and 6, the combination of the steric and electron withdrawing effects significantly promotes the  $\beta$ -H elimination, leading to a very low aldehyde selectivity.

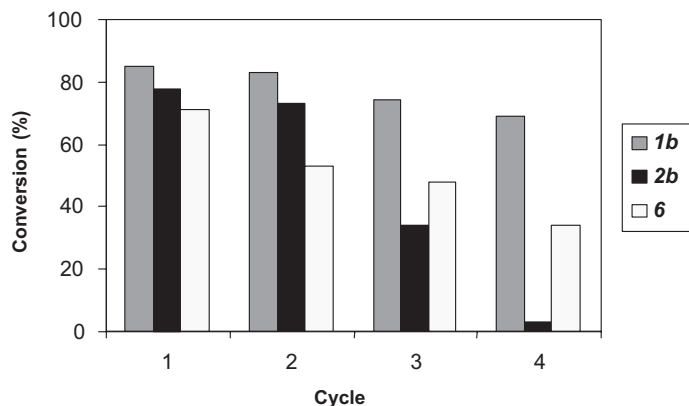
### 10.10.3.3 Stability of the Catalyst and Reuse

Investigations on the recovery and reuse of the catalytic system have been made with phosphites 1b, 2b and 6 on the one hand and with phosphites 7, 8 and 9 on the other.

Figure 10.10-1 shows the evolution of the conversion for four reaction cycles with phosphites 1b, 2b and 6. With each phosphite, the activity decreased after each reuse but whereas the decrease was moderate in the case of *ortho*-substituted phosphites 1b and 6, in the case of 2b, the activity fell dramatically after the second cycle and practically no activity was observed during the fourth run. Concomitantly, the *l/b* ratio and the aldehyde selectivity decreased after the first run with phosphite 2b whilst they remained practically unchanged with 1b and 6.

In the case of phosphites with spacer groups (Figure 10.10-2), the activity was maintained or even slightly increased (with phosphite 8) during the three first cycles. On the other hand, the conversion dramatically dropped during the course of the fourth cycle with *ortho*-substituted phosphite 7.

The decrease in activity is more significant than could be expected according to the high partition coefficient of the phosphates, and the variations of the *l/b* ratio observed during the recovery experiments have been interpreted by considering that the phosphites are not stable

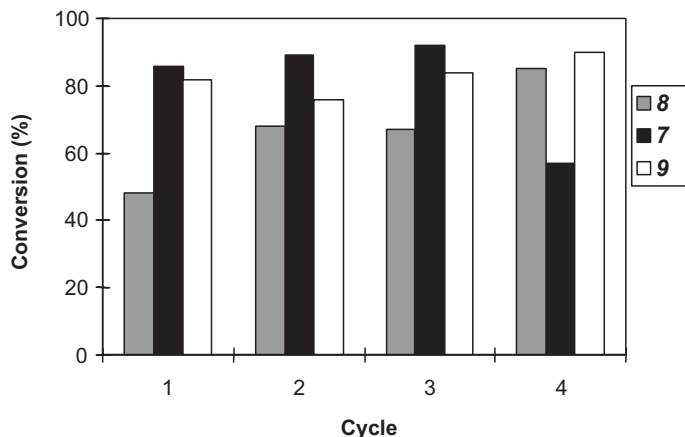


**Fig. 10.10-1.** Conversion of 1-decene during recycling experiments with phosphites **1b**, **2b** and **6** (reaction conditions D, Table 10.10-1); reaction time 5 min with **1b**, 10 min with **2b** and **6**

in the reaction medium. Various methods of decomposition could be envisaged for the fluorous phosphites. The main modes include hydrolysis by water produced by aldehyde condensation, nucleophilic attack on the aldehyde and oxidative cyclization with aldehydes [47, 48].

Aldol condensation of aldehydes could give traces of water that could react with phosphate, but no evidence of formation of the expected aldol products was found by GC-MS [25].

To estimate the extent of the other modes of decomposition, the stability of various fluorous phosphites has been studied under hydroformylation reaction conditions. A sample of each phosphite was heated in a mixture of 1-decene/ $C_8F_{17}H$  (1/1, v/v) or in a mixture of 1-



**Fig. 10.10-2.** Conversion of 1-decene during recycling experiments with phosphites **7**, **8** and **9** (reaction conditions of Table 10.10-2 in pure  $C_8F_{17}H$ ); reaction time 10 min

decene/undecanal/C<sub>8</sub>F<sub>17</sub>H (1/1/1, v/v/v). <sup>31</sup>P NMR analyses of the fluorous phase after 1 h showed that in the absence of aldehyde, all phosphites remained unchanged. In contrast, in the presence of undecanal, a large portion of the *para*- and *meta*-substituted phosphites **2b** and **8** were converted into oxidation products (30% and 50% of the decomposition, respectively) whereas bulky *ortho*-substituted phosphites **1b**, **7** and **9** appeared more stable (3%, 20% and 20% of the decomposition, respectively) [24].

The decrease in the ligand concentration due to the attack of the phosphites by aldehydes explains the change in *l/b* ratios and the aldehyde selectivity observed with some phosphites. Nevertheless, owing to the good stability in particular of phosphites **1b** and **6**, other parameters can be taken into account to explain the decrease in activity observed with these ligands [23, 24].

#### 10.10.4

#### Conclusion

Although the rhodium complexes associated with phosphites can catalyze the hydroformylation of higher olefins in a fluorocarbon/hydrocarbon biphasic medium, the stability and recovery studies indicates undoubtedly that “simple” fluorinated analogs of P(OPh)<sub>3</sub> are not stable in hydroformylation conditions. If the objective is to provide an industrial process for hydroformylation of higher olefins, the development of more fluorosoluble phosphites. The development of more fluorous-soluble and stable phosphites should be envisaged.

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## 10.11

**Fluorous Nitrogen Ligands for Oxidation Reactions***Gianluca Pozzi and Silvio Quici*

## 10.11.1

**Introduction**

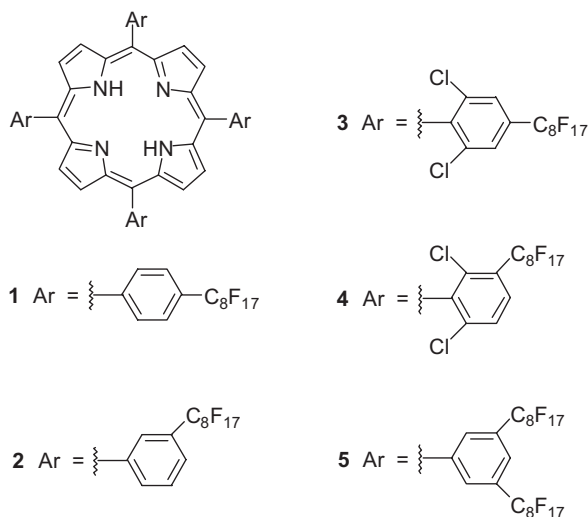
Selective oxidation reactions catalyzed by transition-metal complexes of organic ligands under homogeneous conditions have been the subject of intense investigations throughout the last three decades [1]. A wealth of theoretical and experimental data is now available and some impressive results have been achieved, as in the case of titanium-mediated asymmetric epoxidation of allylic alcohols [2]. Nevertheless, two major issues still prevent the widespread application of most of these homogeneous catalytic systems: (a) considerable synthetic efforts are often required for the preparation of suitable organic ligands and (b) the corresponding catalytically active complexes suffer from limited stability in the oxidative environment. Immobilization onto organic polymers or inorganic supports represents the most obvious and explored strategy for increasing the lifetime of homogeneous oxidation catalysts and possibly recycling them after completion of the reaction [3]. In addition, water-soluble organometallic oxidation catalysts have been tested under aqueous/organic biphasic conditions [4, 5], and evidence for some positive effects related to the use of alternative reaction media such as ionic liquids [6], supercritical CO<sub>2</sub> or CO<sub>2</sub>-expanded solvents [7] has recently been presented.

Fluorous biphasic (FB) techniques are particularly suited to oxidation reactions, where the substrates are converted into products of greater polarity and these are then very easily expelled from the fluorous phase [8]. This fact, together with the thermal and chemical inertness of perfluorocarbons and the possible improvement of the catalyst stability due to its confinement in the fluorous phase, made catalytic oxidation reactions one of the first and most appealing targets for fluorous chemistry [9]. In this short chapter, complementary to the contribution by J.-M. Vincent et al. (see Chapter 10.12), attempts at using the FB approach in the case of oxidation reactions catalyzed by metal complexes of bi- and polydentate nitrogen ligands will be highlighted, with emphasis on the epoxidation of alkenes, the aerobic oxidation of alcohols to carbonyl compounds and the oxidation of organic sulfides to sulfoxides and/or sulfones. Unfortunately, a direct, fair comparison of the results obtained with those reported using related homogeneous catalysts immobilized onto solids or dissolved in alternative reaction media is seriously hampered by the very different conditions employed (nature of substrates and oxidants, molar ratio of the oxidant/substrate/catalyst, temperature and so forth). Therefore, in this limited space the pros and cons of the different approaches will not be discussed.

## 10.11.2

**Oxidation of Alkenes**

Metal complexes of fluorous tetraarylporphyrins **1–5** (Scheme 10.11-1) have been used as catalysts in the epoxidation of alkenes under FB [9] or more traditional conditions



**Scheme 10.11-1.** Fluorous tetraarylporphyrins

[10], depending on their affinity for perfluorocarbons. Free base porphyrins **1–5** were readily metalated with transition metal cations under standard conditions normally employed for their non-fluorous counterparts. In particular, porphyrins **1–4** were metalated with  $\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$  in boiling DMF to give their respective  $\text{Mn}^{\text{III}}$  complexes **Mn-1–Mn-4** [10], whereas the perfluorocarbon-soluble porphyrin **5** was similarly converted into the  $\text{Co}^{\text{II}}$  complex **Co-5** by treatment with  $\text{Co}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$  [9].

Complexes **Mn-1–Mn-4** (% F < 60%) were investigated under aqueous/organic biphasic conditions by using NaOCl or 30%  $\text{H}_2\text{O}_2$  as oxygen donors [10]. Cyclooctene and 1-dodecene were used as models of reactive and poorly reactive alkenes, respectively, whereas the robust complex  $\{\text{Mn}^{\text{III}}\text{-(5,10,15,20-tetrakis-(2,6-dichlorophenyl)porphyrin)}\}$ chloride (**Mn-6**) was used as a reference catalyst (Table 10.11-1). Computational studies taking into account electronic effects, indicated that the introduction of  $\text{R}_f$  substituents on the *meso*-phenyl rings should improve the ligand stability under oxidizing conditions [11]. The experimental results did not confirm this hypothesis: **Mn-1–Mn-4** underwent extensive decomposition and only poor yields in epoxide were obtained. Apparently, factors not considered in computational studies, such as solvation effects and the steric protection provided by the bulky chlorine atoms in the 2,6-positions of the *meso*-aryl rings, prevailed in determining the catalytic activity. Nevertheless, the introduction of  $\text{R}_f$  substituents coupled with steric protection had a definite positive effect on the course of the epoxidation of terminal alkenes catalyzed by **Mn-4**, which gave consistently higher epoxide yields than the reference catalyst **Mn-6**. This effect was particularly marked in reactions carried out in  $\text{CH}_2\text{Cl}_2$  as the solvent and using aqueous NaOCl as the oxygen donor [10].

The perfluorocarbon-soluble complex **Co-5** (% F = 65%) proved to be an efficient catalyst for the FB epoxidation of alkenes with molecular oxygen and 2-methylpropanal as the reducing agent (Table 10.11-2) [9]. Reactions were carried out at room temperature under  $\text{O}_2$

Tab. 10.11-1. Catalytic epoxidation of alkenes by aqueous NaOCl at pH = 10<sup>a</sup>

Catalyst	Substrate	Time (h)	Yield (%)	Selectivity <sup>b</sup> (%)
Mn-6	cyclooctene <sup>c</sup>	3	80	88
Mn-1	cyclooctene <sup>c</sup>	1	8	95
Mn-2	cyclooctene <sup>c</sup>	1	5	95
Mn-3	cyclooctene <sup>c</sup>	3	35	67
Mn-4	cyclooctene <sup>c</sup>	3	90	92
Mn-6	1-dodecene	4	33	69
Mn-6	1-decene	3	54	80
Mn-6	hexadec-1-ene	3	18	45
Mn-4	1-dodecene	3	67	96
Mn-4	1-decene	3	65	86
Mn-4	hexadec-1-ene	3	63	70
Mn-4	2-methylundec-1-ene	3	41	41
Mn-4	1-methylcyclohexene	4	15	23
Mn-4	norbornene	4	60	60

<sup>a</sup> Reaction conditions:  $T = 0\text{ }^{\circ}\text{C}$ ; solvent =  $\text{CH}_2\text{Cl}_2$ ; molar ratio alkene/oxidant/catalyst = 1/2/0.001. <sup>b</sup> Selectivity = (moles of epoxide)/(moles of substrate converted). <sup>c</sup> Solvent =  $\text{AcOEt}$ .

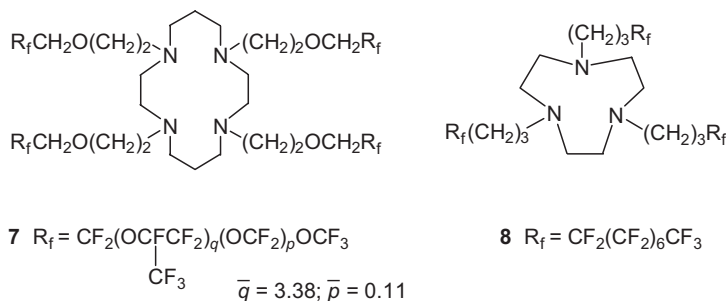
at atmospheric pressure, by adding a solution of the catalyst in perfluorohexane to a solution of the substrate in  $\text{CH}_3\text{CN}$  containing an excess of 2-methylpropanal and vigorously stirring the resulting biphasic mixture. The epoxide yields varied from 95% for cyclic substrates to 52% for terminal alkenes, and the fluoruous phase containing the catalyst could be easily separated and reused at least three times in the case of the oxidation of cyclooctene. Rather interestingly, the FB approach allowed the use of a much higher substrate/catalyst ratio (1000/1) than that reported for the oxidation of (other) alkenes with  $\text{O}_2$ /aldehyde catalyzed by cobalt complexes of standard tetraarylporphyrins (20/1) [12]. Moreover, epoxide yields were higher than those obtained in reactions catalyzed by Mn-4 under optimized aqueous/organic conditions, except for 1-dodecene (entry 2, Table 10.11-2, versus entry 10, Table 10.11-1).

Tab. 10.11-2. FB catalytic epoxidation of alkenes with  $\text{O}_2$ /2-methylpropanal catalyzed by Co-5<sup>a</sup>

Substrate	Time (h)	Yield (%)	Selectivity <sup>b</sup> (%)
Cyclooctene	3	95	88
1-Dodecene <sup>c</sup>	14	52	87
2-Methylundec-1-ene	5	72	90
1-Methylcyclohexene	4	95	95
Norbornene	5	90	95

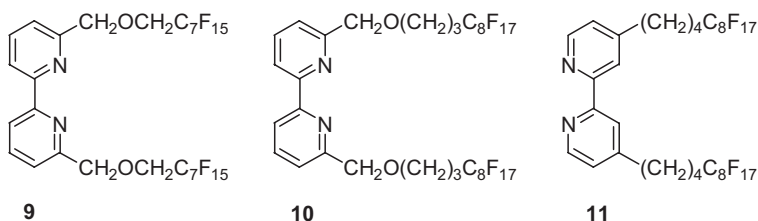
<sup>a</sup> In  $\text{CH}_3\text{CN}$ /perfluorooctane 1/1 v/v. Reaction conditions:  $T = 25\text{ }^{\circ}\text{C}$ ; molar ratio alkene/aldehyde/catalyst = 1/2/0.001. <sup>b</sup> Selectivity = (moles of epoxide)/(moles of substrate converted). <sup>c</sup> Using 3-methylbutanal instead of 2-methylpropanal.





**Scheme 10.11-2.** Fluorous polyazamacrocycles

Tetraazamacrocycle **7** (Scheme 10.11-2) was developed as an alternative to the synthetically demanding porphyrin ligands [13]. At the same time, the triazamacrocycle **8** (Scheme 10.11-2) bearing three  $R_f$  substituents was independently introduced by Fish and coworkers [14]. Metal complexes of these ligands provided new FB catalysts for the oxidative functionalization of hydrocarbons in the presence of *t*-BuOOH and  $\text{O}_2$ . In particular, oxidation of cyclohexene afforded mixtures of 2-cyclohexen-1-one and 2-cyclohexen-1-ol.



**Scheme 10.11-3.** Fluorous bipyridines

Perfluoroalkylated bipyridines **9–11** (Scheme 10.11-3) are readily soluble in some organic solvents, for instance  $\text{CH}_2\text{Cl}_2$ , and were tested in the ruthenium-catalyzed epoxidation of *trans*-stilbene with  $\text{NaIO}_4$  under aqueous/organic biphasic conditions [15], as previously described for 2,2'-bipyridine [16]. In the presence of this ligand, oxidative cleavage of the carbon–carbon double bond strongly affected epoxidation yields at room temperature. The use of fluorous bipyridines **9–11** reduced the incidence of the side reaction and *trans*-stilbene epoxide was obtained in good yields (70–87%) [15]. Since the fluorous affinity of the ruthenium catalysts generated *in situ* from **9–11** was found to be higher than that of the free ligands, *trans*-stilbene epoxidation was also studied in an aqueous/organic/fluorous triphasic system at  $0^\circ\text{C}$ . Higher epoxide yields (92–96%) were obtained and the fluorous phase could be reused without addition of  $\text{RuCl}_3$  for at least three further runs before the epoxide yields decreased significantly.

## 10.11.3

**Oxidation of Alcohols**

Primary and benzylic alcohols were oxidized smoothly to the corresponding aldehydes by  $O_2$  in the presence of catalytic amounts of 2,2,6,6-tetramethylpiperidine-1-oxyl radical (TEMPO, 3.5%) and a  $Cu^I$  complex (2%) generated *in situ* from  $CuBr \cdot Me_2S$  and bipyridine **11** [17]. Reactions were carried out at 90 °C in a biphasic  $C_8F_{17}Br/C_6H_5Cl$  system affording analytically pure aldehydes in 73–96% isolated yield. The recyclability of the catalyst was demonstrated by the case of the oxidation of 4-nitrobenzyl alcohol to give 4-nitrobenzaldehyde: the fluororous phase was reused eight times with a slight decrease in aldehyde yield (from 93% to 86%) and no apparent decrease in reaction rate. Secondary alcohols also underwent oxidation to the corresponding ketones under fluororous biphasic conditions [17, 18]. Reaction rates and yields were comparable to those observed with primary alcohols in the case of benzylic, allylic and cyclic substrates, but in general secondary alcohols were less easily oxidized and higher amounts of TEMPO (up to 10%) were required in order to achieve fast reactions. Sterically hindered secondary alcohols were particularly difficult to oxidize and incomplete conversions were observed even using 10% TEMPO. This allowed the selective oxidation of the less sterically hindered isomer in *cis-trans* mixtures of 2-, 3- and 4-substituted cyclohexanols and the easy separation of the unreacted isomer by column chromatography [18].

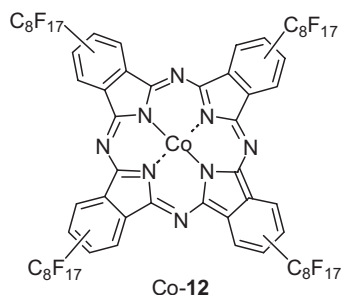
## 10.11.4

**Oxidation of Organic Sulfides**

The first example of FB oxidation of sulfides dates back to 1995: dibenzothiophene and diphenylsulfide gave the corresponding sulfones in low yields (1.4% and 10%, respectively) upon treatment with  $O_2$  at 100 °C in the presence of a not fully characterized perfluoro-carbon-soluble iron-phthalocyanine [19].

Following this earlier report,  $Co^{II}$ -tetraarylporphyrin **Co-5** and  $Co^{II}$ -phthalocyanine **Co-12** (Scheme 10.11-4) were tested as catalysts for the FB oxidation of methyl phenyl sulfide and *para*-substituted aryl methyl sulfides with  $O_2$  and a sacrificial aldehyde (Table 10.11-3) [20].

Turnover numbers comparable to those obtained in similar FB oxidations catalyzed by nickel complexes of fluorinated 1,3-diketones were observed [21]. Sulfoxides were usually obtained in good yields (50–100%) and selectivities (>90%) together with variable amounts



**Scheme 10.11-4.** Cobalt(II) complex of a fluororous phthalocyanine

**Tab. 10.11-3.** Catalytic oxidation of aryl methyl sulfides with O<sub>2</sub>/2,2-dimethylpropanal under FB conditions<sup>a</sup>

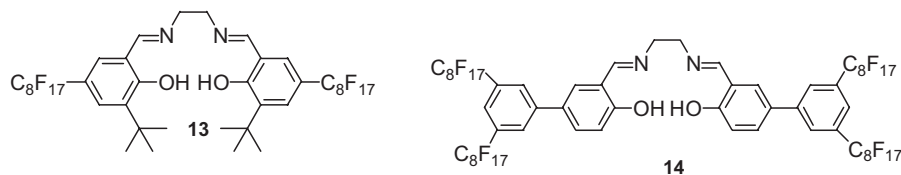
Catalyst	Substrate	Conversion (%)	Selectivity	
			Sulfoxide (%)	Sulfone (%)
Co-5	PhSCH <sub>3</sub>	82	90	10
Co-5	<i>p</i> -CH <sub>3</sub> OPhSCH <sub>3</sub>	100	–	100
Co-5	<i>p</i> -CH <sub>3</sub> PhSCH <sub>3</sub>	100	94	6
Co-5	<i>p</i> -ClPhSCH <sub>3</sub>	67	100	–
Co-5	<i>p</i> -FPhSCH <sub>3</sub>	100	95	5
Co-5	<i>p</i> -NO <sub>2</sub> PhSCH <sub>3</sub>	100	10	–
Co-12	PhSCH <sub>3</sub>	68	100	–
Co-12	<i>p</i> -CH <sub>3</sub> OPhSCH <sub>3</sub>	59	100	–
Co-12	<i>p</i> -CH <sub>3</sub> PhSCH <sub>3</sub>	40	100	–
Co-12	<i>p</i> -ClPhSCH <sub>3</sub>	58	100	–
Co-12	<i>p</i> -FPhSCH <sub>3</sub>	49	100	–
Co-12	<i>p</i> -NO <sub>2</sub> PhSCH <sub>3</sub>	100	15	85

<sup>a</sup> In CH<sub>2</sub>Cl<sub>2</sub>/perfluorooctane 1/1 v/v. Reaction conditions: *T* = 20 °C; *t* = 4 h; molar ratio sulfide/aldehyde/catalyst = 1/1/0.001.

of sulfones. The latter were the major products both in the oxidation of *p*-nitrophenyl methyl sulfide and *p*-methoxyphenyl methyl sulfide catalyzed by Co-5. The absence of any definite relationship between the electronic properties of the *para*-substituents and selectivity ruled out the hypothesis of a heterolytic reaction mechanism involving the formation of high-valent oxometal species. Moreover, the addition of a free-radical scavenger was found to inhibit the oxidation process, thus suggesting that acyl and peroxyacyl radicals generated by the action of the cobalt complexes on the sacrificial aldehyde were the true oxidizing agents. As a consequence of the peculiar reaction environment, both Co-5 and Co-12 were progressively bleached and the effectiveness of their recycling was limited.

Formation of high-valent oxometal species from (salen)metal complexes and iodosylbenzene (PhIO) and the mechanism of the oxygen transfer from these species to alkyl aryl sulfides have been investigated in detail [22]. Fluorous salen ligands **13** and **14** (Scheme 10.11-5) were synthesized and the corresponding (salen)manganese(III) complexes Mn-**13** and Mn-**14** were evaluated in the oxidation of alkyl aryl sulfides with PhIO under homogeneous and FB conditions, respectively [23].

Both complexes were able to catalyze the oxidation of *p*-substituted methyl phenyl sulfides at a substrate/catalyst molar ratio = 100, with good sulfoxide selectivities (≥90%). It should

**Scheme 10.11-5.** Achiral fluorous salen ligands

**Tab. 10.11-4.** Catalytic oxidation of aryl methyl sulfides with PhIO catalyzed by achiral (salen)manganese(III) complexes<sup>a</sup>

Catalyst	Substrate	Conversion (%)	Selectivity	
			Sulfoxide (%)	Sulfone (%)
Mn-13 <sup>b</sup>	PhSCH <sub>3</sub>	70	91	9
Mn-13 <sup>b</sup>	<i>p</i> -BrPhSCH <sub>3</sub>	59	91	9
Mn-13 <sup>b</sup>	<i>p</i> -NO <sub>2</sub> PhSCH <sub>3</sub>	64	88	12
Mn-14 <sup>c</sup>	PhSCH <sub>3</sub>	95	95	5
Mn-14 <sup>c</sup>	<i>p</i> -BrPhSCH <sub>3</sub>	87	96	4
Mn-14 <sup>c</sup>	<i>p</i> -NO <sub>2</sub> PhSCH <sub>3</sub>	100	95	5

<sup>a</sup> Reaction conditions: *T* = 25 °C; *t* = 5 h; molar ratio sulfide/oxidant/catalyst = 1/1/0.01. <sup>b</sup> Homogeneous conditions (CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>CN 1/1 v/v). <sup>c</sup> FB conditions (CH<sub>3</sub>CN/perfluorooctane 1/1 v/v).

be noted that FB reactions catalyzed by Mn-14 consistently afforded higher sulfoxide yields than homogeneous reactions catalyzed by Mn-13 (Table 10.11-4). Moreover, three consecutive recyclings of the fluorous layer were performed with no appreciable loss of catalytic activity and selectivity.

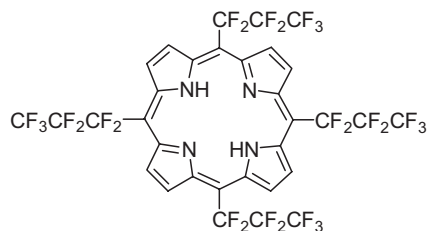
#### 10.11.5

##### Dye-Sensitized Photooxidation Reactions

Oxidation of unsaturated compounds with singlet oxygen (<sup>1</sup>O<sub>2</sub>) has been extensively studied because of its considerable synthetic interest [24]. Dye-sensitized photooxidation of triplet oxygen is a practical method for generation of the labile <sup>1</sup>O<sub>2</sub> reagent on the laboratory scale. However, the presence of the dye and/or of its decomposition derivatives in the final reaction mixture can complicate the purification of the desired organic products. Another point to be considered is the choice of solvent, which must readily dissolve O<sub>2</sub>, ensure a relatively long lifetime to the generated <sup>1</sup>O<sub>2</sub> and be inert to this reagent. Perfluorocarbons fulfill all of these requirements and have been used as alternative media for the photooxidation of alkenes to give hydroperoxides, in the presence of tetraphenylporphyrin (TPP) dissolved in pyridine as a sensitizer [25]. The biphasic mixture was irradiated while maintaining a constant supply of O<sub>2</sub>. After completion of the reaction the two layers were separated to give an organic phase containing the hydroperoxide (plus TPP and its decomposition products) and a fluorous phase free from organic compounds.

The issues of sensitizer degradation and purification of the oxidation products were taken into account by DiMagno et al. who used the electron-deficient fluorous porphyrin **15** (Scheme 10.11-6) as a sensitizer in the photooxidation of cyclohexene and allylic alcohols in CH<sub>3</sub>CN/perfluorohexanes [26].

In a CCl<sub>4</sub> solution, porphyrin **15** showed increased chemical stability toward <sup>1</sup>O<sub>2</sub> and hydroperoxides with respect to TPP. However, physical segregation into the fluorous phase was found to be the most important factor in reducing the incidence of degradation processes. In addition, the FB approach ensured the easy separation of the hydroperoxides from



15

**Scheme 10.11-6.** 5,10,15,20-Tetrakis(heptafluoropropyl)porphyrin

15 at the end of the reaction. The fluorous layer containing the sensitizer (57–94% of the starting material depending on reaction conditions) could be reused without further treatments.

#### 10.11.6

##### Outlook

Most catalytic FB oxidation reactions reported so far are based on the use of metal complexes of perfluoroalkylated nitrogen ligands. The inherent stability and recyclability problems of such oxidation catalysts have yet to be fully solved by the FB approach (or any other immobilization technique or alternative reaction media for that matter). However, some advantages over standard homogeneous conditions, especially the ease of separation of the catalysts from reaction products, have been proved. More importantly, fundamental information on the behavior of fluorous compounds has been obtained through the design, synthesis and use of perfluoroalkylated nitrogen ligands.

Catalytic systems based on metal-free organic molecules (organocatalysts) have been actively investigated in the last few years and their use in organic synthesis is likely to increase in the future. Indeed, organocatalysts are often easier to prepare, less expensive and more stable compared with organometallic complexes performing the same catalytic function. Development of fluorous nitrogen-based organocatalysts for selective oxidative processes, including asymmetric reactions, could eliminate some drawbacks associated with the use of fluorous organometallic catalysts, including leaching of metals into the organic phase. As pointed out by Dalko and Moisan, a large array of ligands originally designed for metal-mediated catalytic reactions are among the most effective organocatalysts [27]. Some of the fluorous ligands discussed here could thus find new application in metal-free oxidation reactions. On the other hand, the basic knowledge acquired while developing those ligands will certainly be helpful for the efficient design and synthesis of new fluorous organocatalysts such as imines, iminium salts, (poly)aminoacids and  $\alpha$ -amidoketones.

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## 10.12

### Synthesis of Fluorous Nitrogen Ligands and Their Metal Complexes as Precatalysts for Applications in Alkane, Alkene, and Alcohol Oxidation, and Atom Transfer Radical Reactions

Jean-Marc Vincent, Dominique Lastécouères, María Contel, Mariano Laguna, and Richard H. Fish

#### 10.12.1

##### Introduction

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## 10.12

### Synthesis of Fluorous Nitrogen Ligands and Their Metal Complexes as Precatalysts for Applications in Alkane, Alkene, and Alcohol Oxidation, and Atom Transfer Radical Reactions

Jean-Marc Vincent, Dominique Lastécouères, María Contel, Mariano Laguna, and Richard H. Fish

#### 10.12.1

##### Introduction

Since the seminal paper in 1994 by Horváth and Rábai that introduced the fluorous biphasic catalysis concept (FBC), as first applied to rhodium(I) catalyzed hydroformylation of

alkenes [1], numerous examples of this methodology for many classical organic reactions have been demonstrated [2]. Unlike the more classical aqueous/hydrocarbon biphasic systems, water sensitive reactants can also be employed, with the solubility of organic substrates being higher in the perfluorocarbons than in water; therefore, more favorable reaction kinetics could be expected. Moreover, because of the unique thermomorph properties of the perfluorocarbon solvents, it is possible under FBC reaction conditions, by judiciously choosing the solvent system, to obtain a homogeneous monophasic solution when elevating the temperature of the reaction mixture, while reformation of the biphasic system occurs at room temperature. In 1996, we initiated an FBC program at the Lawrence Berkeley National Laboratory, with the objective of developing new catalytic systems for alkane/alkene oxidation chemistry. Thus, the FBC process appeared as a very attractive procedure for alkane and alkene functionalization reactions, not only for the ability to recycle the catalyst, but also because of the chemical inertness of the fluorocarbon solvents, and their unique characteristic of solubilizing  $O_2$  in large concentrations.

In this chapter, we will scrutinize a number of fluoroponytailed nitrogen ligand structures and discuss their synthesis for use in our FBC reactions as ligands for precatalyst, fluoroponytailed metal complexes. In other aspects of our FBC studies, we will describe the results obtained in the two main fields of application for these fluoroponytailed, ligated metal complexes as precatalysts, which encompass alkane, alkene, and alcohol oxidations, as well as atom transfer radical reactions. In addition, we will place our results in perspective relative to those of other colleagues' contributions to the FBC field, in these same areas of research.

### 10.12.2

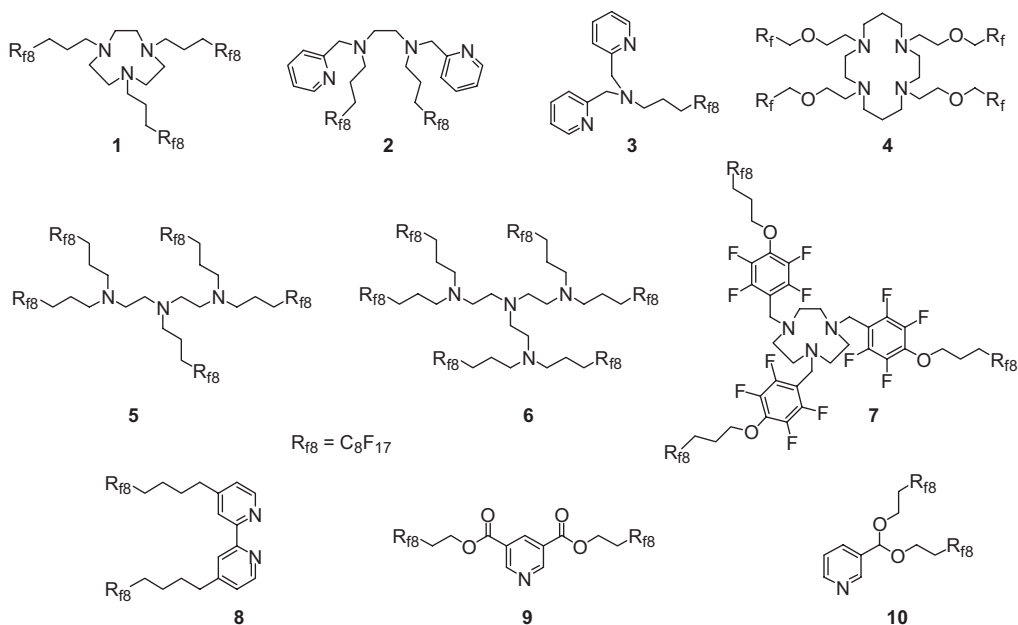
#### Fluorous Nitrogen Ligand Synthesis

Nitrogen ligands are widely used in coordination chemistry, particularly in the field of oxidation catalysis [3]. Relatively simple synthetic procedures are available for the introduction of the fluoroponytails, making the nitrogen ligands valuable targets for the development of fluorous catalysis with transition metal complexes. Representative examples of fluorous nitrogen ligands that have been prepared and, for most of them, applied to fluorous catalysis chemistry, are presented in Scheme 10.12-1.

One of the most successful synthetic strategies used to obtain fluorous nitrogen ligands was the direct alkylation of secondary amines ( $R_2NH$ ) with perfluoroalkyl iodide derivatives, such as  $R_{f8}(CH_2)_3I$  ( $R_{f8} = C_8F_{17}$ ) [4, 5]. The three methylene spacer was necessary not only to insulate the nitrogen ligating atom from the strong electron withdrawing effect of the perfluoroalkyl chain, but also to avoid a facile elimination reaction of HI, which predominantly occurs during the alkylation step when a two methylene spacer was used. Ligands **1**, **2**, and **3** were synthesized in fair to good yields (50, 60 and 40%, respectively) by reaction of the corresponding secondary amines with  $R_{f8}(CH_2)_3I$  in DMSO/ $K_2CO_3$  at 90 °C [4, 5]. Interestingly, amongst the three ligands mentioned, the 1,4,7-triazacyclononane (TACN) derivative, **1**, with a fluorine content of 64.2%, was the only ligand found that was soluble in perfluorocarbons at room temperature.

Furthermore, tosylate derivatives have also been shown to be effective alkylating agents. The fluorous peralkylated cyclam, **4**, was obtained in 60% yield by refluxing





**Scheme 10.12-1.** Examples of nitrogen ligands used in fluorous biphasic catalysis chemistry

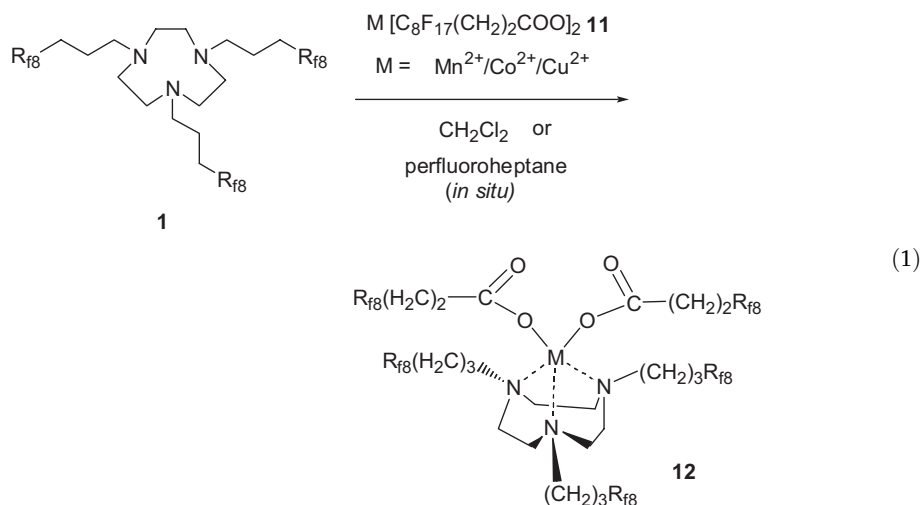
$R_fCH_2O(CH_2)_2OTs$  in  $CH_3CN/Na_2CO_3$  for 24 h [6]. The tosylate,  $R_{f8}(CH_2)_3OTs$ , was recently used in our group in Bordeaux for the preparation of the fluorous, peralkylated polyamino ligands, **5** and **6** [7]. The alkylations were conducted by refluxing a  $CH_3CN/K_2CO_3$  solution of the diethylenetriamine or tris-aminoethylamine with the tosylate (1.1 equiv per amine group) for 48 h; the ligands **5** and **6** being obtained in 65 and 55% yields, respectively. Interestingly, more recently we have shown that using  $R_{f8}(CH_2)_3I$ , instead of the corresponding tosylate, enables one to not only increase the yield of **5** from 65 to 79%, but also to isolate the ligand as a powder rather than an oil. Moreover, an aromatic nucleophilic substitution on the *N*-pentafluorophenyl TACN derivatives was used for the preparation of the fluorous TACN, **7** [5]. This reaction proceeds efficiently (yield 80%) by reacting  $R_{f8}(CH_2)_3OH$  in a 50% NaOH/trifluorotoluene mixture at 85 °C in the presence of a phase transfer agent. Rather surprisingly, this ligand with three fluoroponytails and a fluorine content of 58.6% was found not to be soluble in perfluorocarbons at room temperature.

Bipyridines are another important class of nitrogen ligands in coordination chemistry and transition metal catalysis. The fluorous bipyridine ligand, **8**, was conveniently prepared in 40% yield by reacting the dianion, obtained from 4,4'-dimethyl-2,2'-bipyridine, with  $R_{f8}(CH_2)_3I$  at low temperature (−78 °C) [8a]. Recent studies at Zaragoza/Berkeley provided full synthetic details and spectroscopic characterization of ligand **8** [8b]. The fluorous pyridine ligand, **9**, was synthesized in moderate yield (26%) by reacting the 3,5-diacylchloride pyridine with the alcohol  $R_{f8}(CH_2)_2OH$ , while the pyridine ligand, **10**, was prepared in excellent yield (94%) from pyridine-3-carbaldehyde and  $R_{f8}(CH_2)_2OH$  in the presence of trifluoromethanesulfonic acid [9].

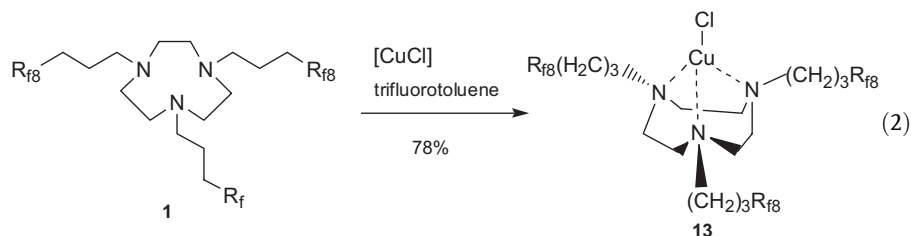
## 10.12.2.1 Synthesis of Fluorous Soluble Metal Complexes as Precatalysts

In the previous section, we established the parameters necessary to solubilize important nitrogen ligands in fluorocarbon media. In a concomitant manner, important metal complexes that are required as precatalysts for many classical catalytic reactions require special attention with regards to fluorocarbon solubility, simply because of the polar nature of these complexes. Thus, in our experience we found that, in many cases, the counter anion also needed fluoroponytails to ensure fluorocarbon solubility, even if the metal ion was coordinated to a fluorous soluble ligand such as **1** (Scheme 10.12-1). Therefore, we [4, 5] and Pozzi et al. [6] addressed this critical aspect by using fluoroponytailed carboxylate ligands as counter ions for the metal ions of interest [4, 5].

When the above mentioned fluoroponytailed metal carboxylates, such as the complexes **11** [Eq. (1)], were reacted with fluorous soluble ligand **1**, either *in situ* ( $\text{Mn}^{2+}$  and  $\text{Co}^{2+}$  complexes in perfluoroheptane) [4, 5], or via isolation and characterization ( $\text{Cu}^{2+}$  complex,  $\text{CH}_2\text{Cl}_2$ ) [8b], to provide precatalysts **12** for alkene, alkane, and alcohol FBC oxidation, the complexes formed were fully fluorocarbon soluble [Eq. (1)].



In another example, the reaction of a  $\text{Cu}^{\text{I}}$  complex,  $[\text{CuCl}]$ , with ligand  $\text{R}_{\text{f8}}$ -TACN **1**, provided a fully fluorocarbon soluble complex **13** (fully characterized) [8b], without appended fluoroponytails on the  $\text{Cu}^{\text{I}}$  metal ion [Eq. (2), isolated from trifluoromethylbenzene]. This appears to be a general phenomena with  $\text{Cu}^{\text{I}}$  complexes and fluoroponytailed ligands, and apparently is predicated on their hydrophobic properties, which engender their solubility in hydrophobic solvents, such as fluorocarbons.



## 10.12.3

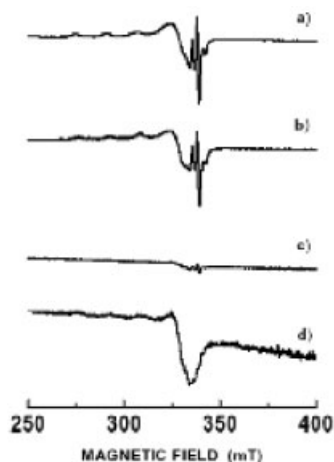
**Applications****10.12.3.1 Alkane and Alkene FBC Oxidation Chemistry**

In 1997 we demonstrated unequivocally, possibly for the first time, that this novel FBC approach for separation of the  $R_f\text{-Mn}^{2+}$  and  $\text{-Co}^{2+}$  precatalysts from the substrates was indeed viable for oxidation of alkanes and alkenes in the presence of the necessary oxidants, TBHP and  $O_2$  gas [4]; shortly after, Pozzi et al. also verified this FBC oxidation chemistry [6]. The  $R_f\text{-TACN}$  complexes **12** [Eq. (1)] were found to be particularly effective for allylic oxidation of alkenes; the  $\text{Cu}^{2+}$  analog [Eq. (1)] and the  $\text{Cu}^I$  complex **13** [Eq. (2)] gave comparable results [8b]. We also provided clear evidence that these FBC oxidation reactions occurred via classical autoxidation mechanisms [4, 5]. The limited scope of the substrates studied also showed that allylic oxidation, for example cyclohexene to cyclohexenol and cyclohexenone, was more favorable than alkane functionalization with cyclohexane as the substrate, based on thermodynamic grounds.

**10.12.3.2 Alcohol Oxidation Chemistry**

The selective oxidation of alcohols to ketones or aldehydes is a very important transformation in organic chemistry. Using the bipyridine ligand, **8** (2 mol%),  $\text{CuBr}\cdot\text{Me}_2\text{S}$  (2 mol%), and TEMPO (3.5–10 mol%) under  $O_2$  (1 atm) in biphasic perfluorooctyl bromide/chlorobenzene at  $90^\circ\text{C}$ , various primary and secondary alcohols (aromatic and aliphatic) were oxidized to the corresponding aldehydes and ketones in good to excellent yields [10, 11]. The stability of the catalyst was found to be excellent, with no observed decrease in yield and reaction rate during the oxidation of 4-nitrobenzyl alcohol to the corresponding aldehyde, after eight reaction cycles. Furthermore, the fluorous biphasic system consisting of  $\text{Pd}(\text{OAc})_2$  (5 mol%)/**10** (20 mol%), in perfluorodecalin/toluene, under  $O_2$  (1 atm) at  $80^\circ\text{C}$ , was another effective catalytic process for the oxidation of primary and secondary alcohols (aliphatic and aromatic) to aldehydes and ketones [9]. Recycling efficiency was also excellent, the yield of isolated acetophenone after five cycles still being 74%, compared with 98% for the first run.

The Zaragoza/Berkeley groups have recently studied the mechanism of the FBC oxidation of 4-nitrobenzyl alcohol to 4-nitrobenzaldehyde at  $90^\circ\text{C}$  (single phase) with the precatalyst,  $R_f\text{-TACN-R}_f\text{-Cu}^{2+}$  **12** [Eq. (2)], TEMPO, and  $O_2$ , by using EPR techniques [8b]. The EPR spectra clearly defined a  $\text{Cu}^{II}$  to  $\text{Cu}^I$  redox reaction, and the role of TEMPO and  $O_2$  in this selective conversion to aldehyde from alcohol. Precatalyst  $R_f\text{-TACN-R}_f\text{-Cu}^{2+}$  [Eq. (2)] was solubilized in perfluoroheptane, and then chlorobenzene, TEMPO, and 4-nitrobenzyl alcohol were added to the reaction mixture. The reaction started at  $90^\circ\text{C}$  in the presence of  $O_2$ , and after 30 min, followed by cooling to room temperature, an aliquot was removed from the perfluoroheptane phase and immediately frozen at 77 K in an EPR tube. The EPR spectrum is shown in Figure 10.12-1 (spectrum a, at LNT). The spectrum shows a narrow central signal at about  $g = 2.006$ , which could be associated with the TEMPO radical. This was further demonstrated by measuring this radical in perfluoroheptane at 77 K, together with a  $\text{Cu}^{II}$  signal, with  $g_{||} = 2.26(1)$  and  $g_{\perp} = 2.06(1)$ ,  $A_{||} = 520(5)$  MHz and  $A_{\perp} < 50$  MHz. After 3.5 h, both signals decrease (spectrum b), and after 6 h the signals have decreased further (spectrum c). After 8 h we observed a recovery of the signal corresponding to the  $\text{Cu}^{II}$  spe-

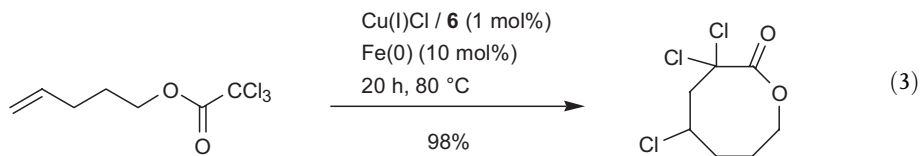


**Fig. 10.12-1.** X-band EPR spectra of the perfluoroheptane layer during the course of the oxidation of 4-nitrobenzyl alcohol with TEMPO/O<sub>2</sub>, at 90 °C, R<sub>f</sub>-TACN-R<sub>f</sub>-Cu<sup>II</sup> as precatalyst [see Eq. (2)] measured at liquid nitrogen temperature. (a) 0.5 h; (b) 3.5 h; (c) 6 h; (d) 8 h

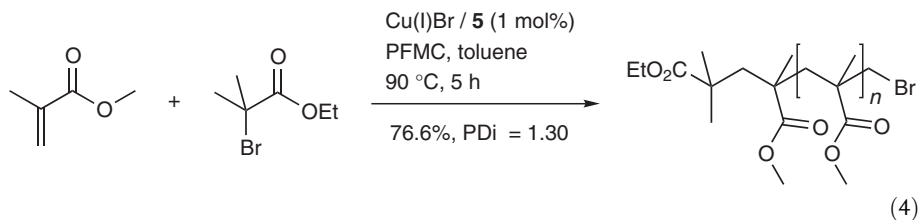
cies (spectrum d). What was clear was that the initial Cu<sup>II</sup> was reduced to the Cu<sup>I</sup> complex by virtue of a silent EPR spectrum after 3.5 h (Figure 10.12-1, spectrum c), and then was regenerated to the Cu<sup>II</sup> complex (spectrum d). This was in accordance with a mechanism proposed by Semmelhack et al. [12]. After 4 h, a 65% yield of aldehyde had been obtained; however, by leaving the reaction for longer periods of time, an ~100% yield of aldehyde was formed, concomitant with a full recovery of the initial R<sub>f</sub>-Cu<sup>II</sup> complex.

### 10.12.3.3 Atom Transfer Radical Reactions

**10.12.3.3.1 Additions** Atom transfer radical additions (ATRA) is a particularly useful radical process for the preparation of lactones and lactams through metal-catalyzed cyclization of unsaturated trichloro esters or amides [13]. One of the most efficient catalysts for both ATRA and ATRP reactions is the copper(I)/pentamethyldiethylenetriamine complex [14]. The fluorous polyamino ligands, **5** or **6**, associated with copper(I) chloride (1 mol%) and iron powder (10 mol%) catalyzed the intramolecular cyclization of the pent-4-enyl trichloroacetate in almost quantitative yields under FBC conditions [Eq. (3)] [7]. By using a ternary solvent system (perfluoroheptane/trifluorotoluene/1,2-dichloroethane), the reaction was carried out under homogeneous conditions at 80 °C, while phase separation occurred at room temperature enabling facile recycling of the catalyst and recovery of the substrate, with only 1–2% of the copper(I) leaching into the organic phase. Ensuring that no oxygen was introduced during the recycling procedure, the yield of lactone, after the fourth run, was still 91%, making the Cu<sup>I</sup>Cl/**5**, and Cu<sup>I</sup>Cl/**6** complexes highly efficient and recoverable catalysts for atom transfer radical reactions.



**10.12.3.3.2 Polymerizations** Atom transfer radical polymerization (ATRP) is a transition metal mediated living radical polymerization of vinyl monomers that is closely related to ATRA, facilitating the synthesis of well-defined and complex macromolecular architectures. The major limitation of ATRP is that the polymer is usually contaminated by the colored transition metal catalyst, thus requiring purification steps such as column chromatography or precipitation of the polymer. Catalysts grafted onto insoluble supports have been developed to lower the copper content of the final product and for recycling [15]. However, heterogeneous supported catalysts are less efficient than their homogeneous analogs leading to broader polydispersity ( $PDi = 1.4\text{--}1.5$ ) and lower initiator efficiency. Lower polydispersity and higher recycling efficiency were observed using copper(I) catalysts immobilized on poly(ethylene)-*block*-poly(ethyleneglycol), a polymer soluble in toluene above  $70^\circ\text{C}$ , but insoluble at room temperature [16]. Using the catalytic system,  $\text{CuBr}/\mathbf{5}$ , and ethyl 2-bromoisobutyrate as the polymerization initiator, Haddleton et al. have shown that living radical polymerization of methyl methacrylate can be carried out very efficiently under FBC conditions [Eq. (4)] [17]. Interestingly, PMMA was also obtained as a colorless solid after separation of the upper hydrocarbon phase and removal of the volatiles. The catalyst was recycled twice with similar results, in terms of kinetics and polydispersity, making this FBC system very attractive for further applications.



#### 10.12.4

#### Conclusion

In this chapter in this Handbook of Fluorous Chemistry, we have attempted to place our fluorous synthesis of nitrogen ligands and metal complexes that have fluorocarbon solubility, and subsequent applications in alkane, alkene, and alcohol oxidation chemistry, as well as those in ATRA and ATRP, in perspective with FBC contributions from other colleagues. We have also focused on understanding the mechanisms of these FBC reactions, along with developing new FBC applications, to ascertain any similarities or differences in comparison

with their non-fluorous reaction pathways. The major theme in all these FBC studies is still the separation factor of precatalysts from substrates and products, in comparison with the non-fluorous solvent equivalent. This separation factor, we believe, will be the seminal characteristic of all FBC contributions in this Handbook of Fluorous Chemistry.

While FBC chemistry has not been fully accepted by the industrial chemistry community, principally due to economic factors, future directions in a Green Chemistry environment will provide new opportunities for selective industrial applications, particularly specialty chemicals, as well as gas-to-liquid technology, where the gases are fluorous soluble, but the liquid, polar products are not.

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## 10.13

**Enantioselective Catalysis: Biphasic Conditions***Denis Sinou*

## 10.13.1

**Introduction**

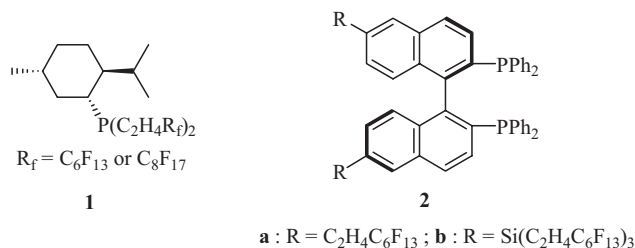
Over the last 20 years there have been very important advances in asymmetric synthesis via the use of a soluble chiral organometallic catalyst [1]. Although homogeneous organometallic catalysts have many advantages over their heterogeneous counterparts (higher activities and selectivities, mild reaction conditions), one of the major problems is the separation of the products from the soluble catalyst, which is generally an expensive and toxic transition metal; this is particularly important for industrial applications. A possible solution to this problem is the heterogenization of the chiral homogeneous catalyst on an inorganic or organic support [2]. Another approach is the use of a liquid/liquid two-phase system, the chiral catalyst being immobilized in one phase, the reactants and the products of the reaction being in the other phase. Aqueous/organic systems have been successfully applied [3], and this is due to the easy and quantitative recovery of the catalyst in the active form by simple phase separation, and also to the environmentally attractive use of water. Other two-phase systems such as ionic liquids [4] or perfluorohydrocarbons [5] in combination with an organic phase have also been proposed.

This section will focus on enantioselective catalysis performed under biphasic conditions, one phase being a fluorous solvent. Catalytic reactions performed in fluorous biphasic systems can effectively show several advantages over classical homogeneous systems or even two-phase systems. One of them is the easy product separation by simple workup techniques of liquid/liquid extraction, due to the low miscibility of fluorous solvents with common organic solvents, and hence the recycling of the catalyst. Moreover, warming the mixture renders the organic and fluorous phases miscible allowing the reaction to occur under homogeneous conditions [5], and so solving the problems of mass transfer between the two phases. Some examples performed in homogeneous systems, followed by separation of the fluorous catalyst or ligand via extraction with a fluorous solvent will also be presented, although separation of organic and fluorous compounds by solid-phase extraction with fluorous silica gel is excluded.

## 10.13.2

**Reduction of Unsaturated Substrates**

The catalytic asymmetric reduction of unsaturated compounds is now a well-used methodology in organic synthesis. Enantioselectivities higher than 95% have been obtained using molecular hydrogen or hydrogen donors in the presence of various chiral organometallic complexes [1]. If the asymmetric hydrogenation has been successfully extended to the two-phase water/organic solvent system using water-soluble catalysts [3], the observed enantioselectivities are generally lower than those obtained in normal homogeneous systems. As phosphorous-based ligands have been extensively used in catalytic hydrogenation,

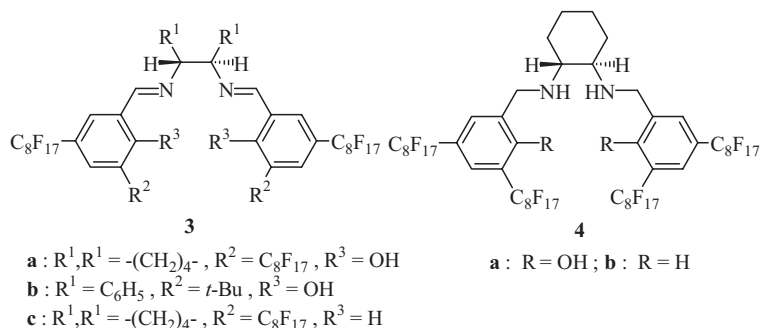


**Scheme 10.13-1.** Chiral fluororous phosphines

many efforts have been devoted to the synthesis of their fluororous analogs. Klose and Gladysz [6] described the synthesis of the chiral ligand **1** derived from menthol (Scheme 10.13-1), without any applications in catalysis. More recently, a fluororous analog of BINAP **2a** (Scheme 10.13-1) was synthesized by the group working with Hope [7], which was used as a ligand of ruthenium in the asymmetric hydrogenation of dimethyl itaconate. Although an enantioselectivity of up to 95% ee was obtained, quite similar to that observed using the original Ru-BINAP complex, recycling of the catalyst was not possible.

Asymmetric transfer hydrogenation of ketones in the presence of soluble transition metal catalysts was developed several years ago [8–10], enantioselectivities of up to 99% ee being obtained using a ruthenium catalyst bearing mono *N*-tosylated diphenylethylenediamine as the ligand. Iridium complexes associated with fluororous chiral diimines **3a–c** or diamines **4a–b** (Scheme 10.13-2) have also been shown to be effective catalysts in hydrogen transfer reduction of ketones [11, 12].

Enantioselectivities of up to 56% ee were obtained using  $[Ir(COD)Cl]_2$  associated with fluororous diimines **3a–c** at 70 °C in the reduction of acetophenone with isopropanol as the hydride source in the presence of Galden D-100 (mainly *n*-perfluorooctane, bp 102 °C) as the fluororous solvent (Scheme 10.13-3). The hydrogen transfer reduction was extended to other ketones, an enantioselectivity of 60% ee being obtained for ethyl phenyl ketone for example. However recycling of the catalyst gave lower activity and enantioselectivity, iridium leaching being very high. In order to circumvent the problem of the recycling of the fluororous catalyst, the chiral fluororous diamines **4a–b**, obtained by reduction of **3a** and **3c**, were used as ligands



**Scheme 10.13-2.** Chiral fluororous diimines and diamines



R	X	L*	Cycle	Time (h)	Yield (%)	ee (%)
CH <sub>3</sub>	H	<b>3a</b>	1	0.5	94	15
			2	0.5	95	13
CH <sub>3</sub>	H	<b>3b</b>	1	24	84	56
C <sub>2</sub> H <sub>5</sub>	H	<b>3b</b>	1	24	97	60
CH(CH <sub>3</sub> ) <sub>2</sub>	H	<b>3b</b>	1	144	99	57
CH <sub>3</sub>	H	<b>3c</b>	1	24	93	47
CH <sub>3</sub>	Br	<b>3c</b>	1	24	99	52
CH <sub>3</sub>	NO <sub>2</sub>	<b>3c</b>	1	24	98	32
CH <sub>3</sub>	OCH <sub>3</sub>	<b>3c</b>	1	24	92	11
CH <sub>3</sub>	CN	<b>3c</b>	1	24	94	1
CH <sub>3</sub>	H	<b>4a</b>	1	5	95	23
			2	25	80	17
CH <sub>3</sub>	H	<b>4b</b>	1	0.5	92	69
			2	0.5	90	79
			3	1	86	59
			4	2	69	58

**Scheme 10.13-3.** Asymmetric transfer reduction of various ketones

of [Ir(COD)Cl]<sub>2</sub> in the reduction of acetophenone in the two-phase system isopropanol/Galden D-100. Whereas ligand **3a** gave low enantioselectivity (23% ee) and a very high iridium leaching (51%) in the organic phase, ligand **3b** gave an enantioselectivity of up to 69, 79, 59, and 58% ee for the first, second, third, and fourth cycles, respectively, the iridium leaching being very low (less than 4%).

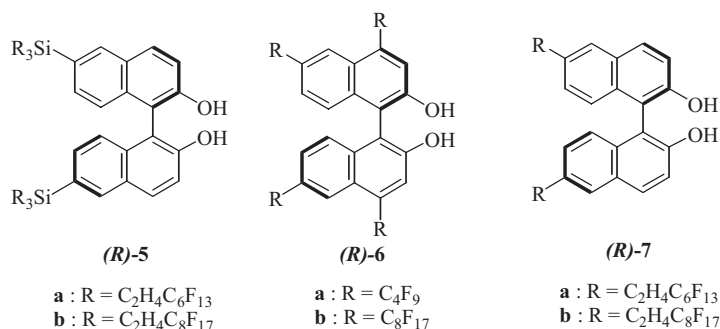
### 10.13.3

#### Carbon–Carbon Bond Formation

Carbon–carbon bond formation is one of the most important reactions in organic chemistry. Various approaches concerning the asymmetric carbon–carbon bond formation in a fluorous biphasic system have appeared in the literature.

The asymmetric 1,2-addition of diethylzinc to aromatic aldehydes catalyzed by a BINOL-Ti complex occurs with an enantioselectivity of up to 97% ee [13, 14]. Different groups reported the enantioselective carbon–carbon bond formation in a fluorous biphasic system using a titanium fluorous–BINOL complex. Various chiral fluorous BINOL **5**, **6**, and **7** complexes, bearing two –Si(C<sub>2</sub>H<sub>4</sub>C<sub>6</sub>F<sub>13</sub>)<sub>3</sub> or –Si(C<sub>2</sub>H<sub>4</sub>C<sub>8</sub>F<sub>17</sub>)<sub>3</sub> chains [15–17], four C<sub>4</sub>F<sub>9</sub> or C<sub>8</sub>F<sub>13</sub> chains [18, 19], or two –C<sub>2</sub>H<sub>4</sub>C<sub>6</sub>F<sub>13</sub> or –C<sub>2</sub>H<sub>4</sub>C<sub>8</sub>F<sub>17</sub> chains [20], respectively, have been used in this reaction (Scheme 10.13-4).

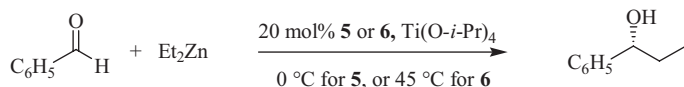
Takeuchi and collaborators reported the condensation of benzaldehyde with Et<sub>2</sub>Zn at 0 °C in the presence of the complex prepared *in situ* by mixing Ti(O-*i*-Pr)<sub>4</sub> and fluorous BINOL **5**



Scheme 10.13-4. Chiral fluorinated BINOL

[15–17] (Scheme 10.13-5). When the reaction was performed in a system toluene/hexane/FC-72, the enantioselectivity in the alcohol obtained was 80% ee, quite similar to that obtained using non-fluorous titanium-BINOL, and remained constant throughout five consecutive runs, the chemical yield being 80–89%. However about 10% of the fluorinated BINOL was recovered from the organic phase after acidic workup of the reaction mixture. Since the partial solubilization of the fluorinated catalyst in the organic phase was due to the presence of hexane, the use of the fluorinated biphasic system toluene/FC-72 gave enantioselectivities of up to 78% ee (85% yield) and 79% ee (82% yield) using ligands **5a** and **5b**, respectively; the enantioselectivity was constant during three consecutive runs, as was the chemical yields, the leaching of ligand in the organic phase being negligible (less than 1%).

The condensation of Et<sub>2</sub>Zn with other aromatic aldehydes in the presence of ligand **5a** or **5b** gave the corresponding alcohols with high enantioselectivity (76–85%) and chemical yields (73–97%).



Ligand	Solvent	Yield (%) (cycle)	ee (%) (cycle)	Ligand recovery (%) (cycle)
<b>5a</b>	toluene/hexane/ FC-72 (3:3:5)	81 (1), 89 (2), 87 (3), 87 (4), 87 (5)	83 (1), 82 (2), 82 (3), 81 (4), 80 (5)	10 (1), 12 (2), 12 (3), 11 (4), 10 (5)
<b>5a</b>	toluene/FC-72 (3:5)	85 (1), 85 (2), 80 (3)	78 (1), 78 (2), 77 (3)	<1 (1), <1 (2), <1 (3)
<b>5b</b>	toluene/hexane/ FC-72 (1:1:2)	82 (1), 82 (2), 77 (3)	79 (1), 78 (2), 78 (3)	1 (1), 1 (2), 1 (3)
<b>6a</b>	C <sub>11</sub> F <sub>20</sub> /hexane (1:0.7)	98 (1), 99 (2), 99 (3), 95 (4), 76 (5)	41 (1), 53 (2), 31 (3), 15 (4), 7 (5)	
<b>6b</b>	C <sub>11</sub> F <sub>20</sub> /hexane (1:0.7)	69 (1), 80 (2), 79 (3), 76 (4), 80 (5), 79 (6), 80 (7), 79 (8), 79 (9)	54 (1), 57 (2), 58 (3), 55 (4), 60 (5), 58 (6), 57 (7), 56 (8), 55 (9)	

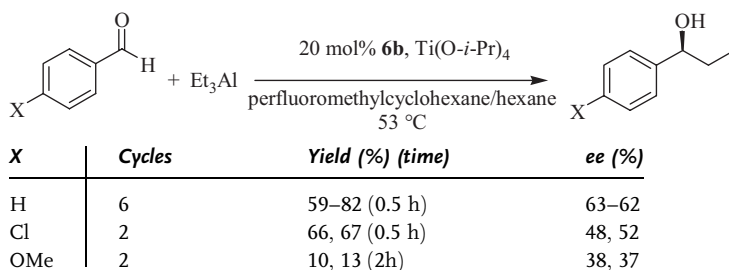
Scheme 10.13-5. Asymmetric condensation of benzaldehyde with Et<sub>2</sub>Zn

A similar approach was devised by Chan and collaborators [18, 19], who condensed  $\text{Et}_2\text{Zn}$  with benzaldehyde at 45 °C using the fluorous biphasic system hexane/perfluoro-methyl-decalin (or  $\text{C}_{11}\text{F}_{20}$ ) in the presence of the catalyst obtained by mixing  $\text{Ti}(\text{O-}i\text{-Pr})_4$  and fluorous BINOL **6** (Scheme 10.13-5). When the ligand **6a** was used, the corresponding alcohol was obtained with 98% conversion and 41% ee; however, the enantioselectivity of the reaction decreased slowly with the reaction runs, and was lost after six runs. Fortunately, when ligand **6b**, which contains 32 fluorocarbons, was used, the enantiomeric excess of the product (55–60% ee) as well as the chemical yields (76–80%) were maintained constant after nine reaction runs. The lower enantioselectivity observed using **6** as the ligand instead of **5** (55–60% ee versus 78–79% ee) is probably due to the reaction temperature; in the last case, the critical temperature was 45 °C, lower chemical yield and enantioselectivity being obtained at the lower temperature due to the heterogenization of the catalytic system. Similar enantioselectivities as well chemical yields were obtained in the condensation of  $\text{Et}_2\text{Zn}$  with other aromatic aldehydes in the presence of these ligands **6**, with the enantioselectivities remaining constant over three consecutive runs (51–54% ee for 4-chlorobenzaldehyde, and 37–40% ee for 4-methoxybenzaldehyde).

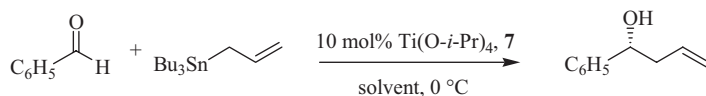
Chan and collaborators [19] used ligand **6b** in association with  $\text{Ti}(\text{O-}i\text{-Pr})_4$  in the condensation of aromatic aldehydes with  $\text{Et}_3\text{Al}$  in the biphasic system hexane/perfluoro-(methyl)decalin at 53 °C (Scheme 10.13-6). Enantioselectivities in the range of 76–88% ee and chemical yields of 77–82% were obtained during six consecutive runs when fresh titanium was added. When the reaction was extended to the electron-deficient 4-chlorobenzaldehyde, the yield was the same (59–88% for three runs) and the enantioselectivity a little lower (63–79% ee for three runs); for the electron-rich 4-methoxybenzaldehyde, only 10% of the product was obtained with an enantioselectivity of 38%.

Zhao and collaborators [20] performed the condensation of allyltributyltin with benzaldehyde in the presence of the catalyst  $\text{Ti}(\text{O-}i\text{-Pr})_4/\text{BINOL}$  **7** in various fluorous biphasic systems (Scheme 10.13-7). The highest enantioselectivities, up to 90% ee, were obtained using the hexane/FC-72 system, the yield being 85%. The ligand was recovered by continuous liquid/liquid extraction and can be reused in further experiments. The reaction was extended to other aromatic aldehydes; however only substrates with strong withdrawing groups showed good yields and enantioselectivities, when aldehydes bearing halides or electron donating groups gave rather poor yields and enantioselectivities.

van Koten and coworkers [21] synthesized fluorous chiral ethylzinc arene thiolates **8a–c** (Scheme 10.13-8). These organometallic complexes are active in the 1,2-addition of diethyl-



**Scheme 10.13-6.** Asymmetric condensation of benzaldehyde with  $\text{Et}_3\text{Al}$

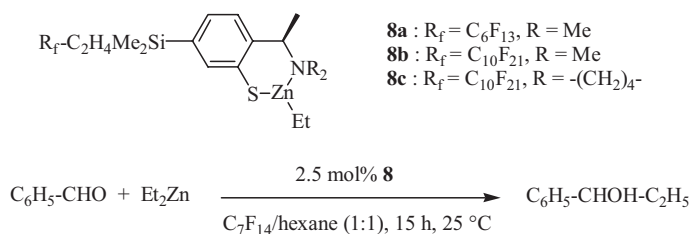


Solvents ( <b>2:1</b> )	Ligand	Yield (%)	ee (%)
CH <sub>2</sub> Cl <sub>2</sub> /C <sub>10</sub> F <sub>18</sub>	<b>7a</b>	27 (24 h)	76
	<b>7b</b>	20 (24 h)	75
hexane/C <sub>10</sub> F <sub>18</sub>	<b>7a</b>	76 (12 h)	83
hexane/C <sub>6</sub> F <sub>17</sub> CF <sub>3</sub>	<b>7a</b>	78 (10 h)	88
hexane/FC-72	<b>7a</b>	85 (10 h)	90
hexane/FC-72	<b>7b</b>	83 (5 h)	90
toluene/FC-72	<b>7a</b>	52 (12 h)	48

**Scheme 10.13-7.** Asymmetric allylation of benzaldehyde

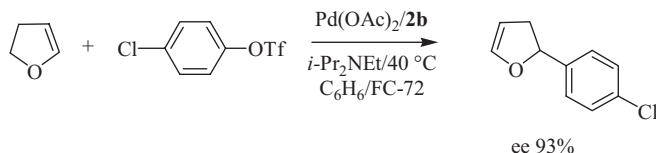
zinc to benzaldehyde in hexane, the activity and enantioselectivity being even better than that of the non-fluorous catalyst. Moreover, further experiments showed that they are also active in a two-phase medium of perfluoromethylcyclohexane/hexane. The catalyst could be recycled, although a drop in enantioselectivity was generally observed after two runs: enantioselectivities of up to 92, 92, 76, and 43% ee were obtained using ligand **1c** for four consecutive runs.

Among the organometallic catalysts used for alkylation and coupling reactions, palladium has a predominant role. Palladium catalysts are effectively used in a large number of useful transformations in organic chemistry [22]. Surprisingly there are few examples of applications of chiral palladium complexes in the literature. Nakamura et al. [23] carried out the Heck reaction between 2,3-dihydrofuran and 4-chlorophenyl triflate in the presence of Pd(OAc)<sub>2</sub> associated with ligand **2b** in the two-phase system benzene/FC-72 (Scheme 10.13-9); an enantioselectivity of up to 93% was obtained, the yield being 39%. Unfortunately recycling of the catalyst was not possible, due probably to its inactivation by ligand oxidation.



Cat.	Run 1	Run 2	Run 3	Run 4	Run 5
<b>8a</b>	84	72	37	9	3
<b>8b</b>	79	78	61	36	11
<b>8c</b>	92	92	76	43	28

**Scheme 10.13-8.** Asymmetric condensation of benzaldehyde and Et<sub>2</sub>Zn



Scheme 10.13-9.

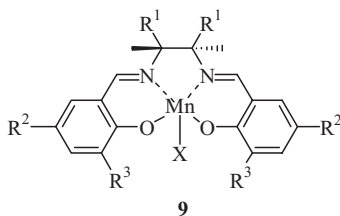
Palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenylprop-2-enyl acetate with carbonnucleophiles occurred using fluoros bisoxazolines as the ligands in benzotrifluoride or  $\text{CH}_2\text{Cl}_2$  as the solvent with ee values of up to 95% [24]; although recycling of the catalyst was not possible, extraction of the ligand allowed the recycling of the latter with the same enantioselectivity.

## 10.13.4

**Oxidation**

Pozzi's group has shown that asymmetric epoxidation of prochiral alkenes occurred under fluoros biphasic conditions using various chiral fluoros (salen)manganese complexes **9** (Scheme 10.13-10) [25, 26]. The chiral (salen)manganese complexes **9a** and **9b**, bearing fluoros alkyl substituents in the 3,3'- and 5,5'-positions in the ligand, were used in the epoxidation of indene in the two-phase system  $\text{CH}_2\text{Cl}_2/\text{D-100}$  in the dark at 20 °C under atmospheric pressure of oxygen in the presence of pivalaldehyde, giving the corresponding epoxide with 83 and 77% yield, and 92 and 90% ee, respectively (Table 10.13-1). Recycling of the catalyst was possible without loss of the enantioselectivity: ee values of up to 89 and 92% were obtained, respectively, in a second run. However, very low enantioselectivities were achieved in the epoxidation of other alkenes, such as dihydronaphthalene and benzosuberene, whose structures are very close to indene, whatever the oxidant used.

More recently, chiral fluoros second-generation Mn(salen) complexes **9c** and **9d** have been prepared [27, 28]. These complexes took into account the fact that the low ee values observed were probably due to the low steric hindrance as a result of the fluoros substituents at the 3,3'- and 5,5'-positions, as well as their electronic effects. These catalysts



**a** :  $\text{R}^1, \text{R}^1 = -\text{CH}_2)_4$ ,  $\text{R}^2 = \text{R}^3 = \text{C}_8\text{F}_{17}$ ,  $\text{X} = \text{Cl}$

**b** :  $\text{R}^1 = \text{C}_6\text{H}_5$ ,  $\text{R}^2 = \text{R}^3 = \text{C}_8\text{F}_{17}$ ,  $\text{X} = \text{Cl}$

**c** :  $\text{R}^1, \text{R}^1 = -\text{CH}_2)_4$ ,  $\text{R}^2 = \text{R}^3 = \text{C}_6\text{H}_2-2,3,4\text{-tri}(\text{OC}_2\text{H}_4\text{C}_8\text{F}_{17})_3$ ,  $\text{X} = \text{OCOC}_7\text{F}_{15}$

**d** :  $\text{R}^1, \text{R}^1 = -\text{CH}_2)_4$ ,  $\text{R}^2 = \text{C}_6\text{H}_2-2,3,4\text{-tri}(\text{OC}_2\text{H}_4\text{C}_8\text{F}_{17})_3$ ,  $\text{R}^3 = t\text{-Bu}$ ,  $\text{X} = \text{OCOC}_7\text{F}_{15}$

Scheme 10.13-10. Chiral fluoros (salen)manganese complexes

**Tab. 10.13-1.** Fluorous epoxidation of various alkenes catalyzed by complexes of **9**<sup>a</sup>

Substrate	Catalyst	Yield (%) (run)	ee (%) (run)
Indene	<b>9a</b>	83 (1), 73 (2)	92 (1), 89 (2)
	<b>9b</b>	77 (1), 75 (2)	90 (1), 92 (2)
	<b>9d</b>	98 (1), 95 (2), 93 (3), 76 (4)	92 (1), 92 (2), 93 (3), 79 (4)
1,2-Dihydronaphthalene	<b>9a</b>	70 (1), 70 (2)	10 (1), 9 (2)
	<b>9b</b>	70 (1), 61 (2)	13 (1), 10 (2)
	<b>9c</b>	68 (1), 68 (2), 60 (3), 30 (4)	50 (1), 48 (2), 44 (3), 31 (4)
	<b>9d</b>	77 (1), 67 (2), 63 (3), 19 (4)	50 (1), 45 (2), 46 (3), 40 (4)
Benzosuberene	<b>9a</b>	92	7
	<b>9b</b>	91	12
	<b>9c</b>	84 (1), 79 (2), 75 (3), 51 (4)	69 (1), 69 (2), 69 (3), 54 (4)
	<b>9d</b>	92 (1), 92 (2), 83 (3), 43 (4)	68 (1), 66 (2), 64 (3), 60 (4)
1-Methylindene	<b>9c</b>	96 (1), 95 (2), 92 (3), 76 (4)	70 (1), 68 (2), 66 (3), 50 (4)
	<b>9d</b>	98 (1), 99 (2), 82 (3), 52 (4)	77 (1), 77 (2), 76 (3), 57 (4)
1-Methylcyclohexene	<b>9c</b>	95 (1), 95 (2), 74 (3), 50 (4)	52 (1), 50 (2), 31 (3), 20 (4)
	<b>9d</b>	91 (1), 87 (2), 76 (3), 45 (4)	58 (1), 53 (2), 40 (3), 25 (4)
Triphenylethylene	<b>9c</b>	98 (1), 98 (2), 95 (3), 78 (4)	80 (1), 81 (2), 79 (3), 66 (4)
	<b>9d</b>	98 (1), 96 (2), 92 (3), 80 (4)	87 (1), 85 (2), 83 (3), 71 (4)

<sup>a</sup> O<sub>2</sub>/pivalaldehyde in CH<sub>2</sub>Cl<sub>2</sub>/D-100 (1:1) at 20 °C for **9a–b**. PhIO/  
PNO in CH<sub>3</sub>CN/*n*-perfluorooctane (1:1) at 100 °C for **9c–d**.

were successfully used in the asymmetric epoxidation of dihydronaphthalene system at 100 °C in CH<sub>3</sub>CN/perfluorooctane in the presence of PhIO/PNO (pyridine *N*-oxide) as the oxidant (Table 10.13-1). For example, in the case of **9d**, the highest yield was obtained above 40 °C (76% yield), although the ee increased with increasing temperature, the highest value (50% ee) was obtained at 100 °C.

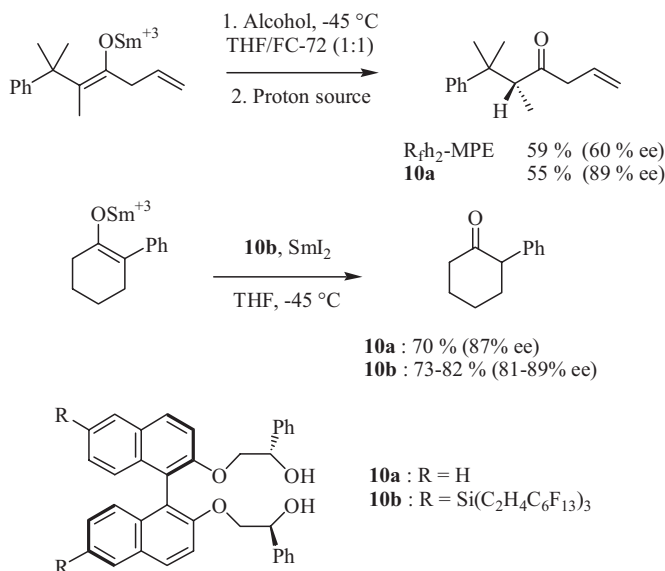
The epoxidation reaction using complexes **9c** and **9d** as the catalysts was extended to other alkenes: benzosuberene, 1-methylindene, 1-methylcyclohexene, and triphenylethylene, affording the corresponding epoxides in 68–98% yields, and 50–92% enantioselectivities, very close to the values obtained by Regen and Janda [29] using an Mn(salen) supported onto a gel-type resin. The fluorous catalysts could be efficiently recycled, the same activities and enantioselectivities being maintained for three consecutive runs. The lower activity generally observed for the fourth run was mainly due to the oxidative decomposition of the catalyst.

It should be noted that the corresponding Co(salen) complexes have also been used in the hydrolytic kinetic resolution of terminal epoxides, enantioselectivities up to 99% being obtained; however these complexes were never used in a two-phase system [30].

### 10.13.5

#### Other Reactions

The catalytic enantioselective protonation of a samarium enolate using a C<sub>2</sub>-symmetric chiral diol as the catalyst and trityl alcohol as the proton source afforded the corresponding ketone with an ee of up to 93% [31]. The use of (*S*)-2-bis[(perfluorohexyl)ethyl]-2-methoxy-1-



Scheme 10.13-11

phenylethanol (R<sub>f</sub>h<sub>2</sub>-MPE) and (C<sub>6</sub>F<sub>13</sub>C<sub>2</sub>H<sub>4</sub>)<sub>3</sub>OH (or R<sub>f</sub><sub>3</sub>COH) in a biphasic system THF/FC-72 (3:4) at -45 °C gave the ketone in 59% yield and 60% ee, although the use of **10a** as the chiral proton source increased the enantioselectivity to 89% ee (Scheme 10.13-11) [32]. This enantioselective protonation was extended to a samarium enolate derived from cyclohexanone (Scheme 10.13-11) in THF using fluorinated alcohol **10b** as the proton source [15]; enantioselectivities of up to 89% have been obtained. The fluoroalcohol was quantitatively recovered by a simple extraction with FC-72 and reused in five consecutive runs without loss of enantioselectivity.

Fache et al. used fluorinated cinchona derivatives in an asymmetric Diels-Alder reaction in CHCl<sub>3</sub>/C<sub>6</sub>F<sub>14</sub> (1:1); low enantioselectivity (13%) was obtained [33]. Moreover, due to the low fluorine content of the catalyst (45 wt% F), the reaction probably occurred in the non-fluorous phase.

#### 10.13.6

#### Conclusion

In recent years, there has been rapidly increasing interest in asymmetric catalysis in fluorinated media. Although some remarkable progress has been achieved in this field, one problem is the lack of available chiral fluorinated ligands. Another problem is the recycling of the catalyst, due probably to the low fluorine content of the chiral complex itself. In order to switch successfully from the homogeneous asymmetric catalytic reaction to its fluorinated analog, many factors have to be studied: location as well as the number of fluorinated ponytails,

presence of an appropriate spacer in order to insulate completely the metal site from the electron effect of these substituents, the nature of the counteranion, and the proper choice of the two-phase system. It is obvious that this technique will become more and more popular in the future.

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## 10.14

**Enantioselective Catalysis in Non-biphasic Conditions***Seiji Takeuchi and Yutaka Nakamura*

## 10.14.1

**Introduction**

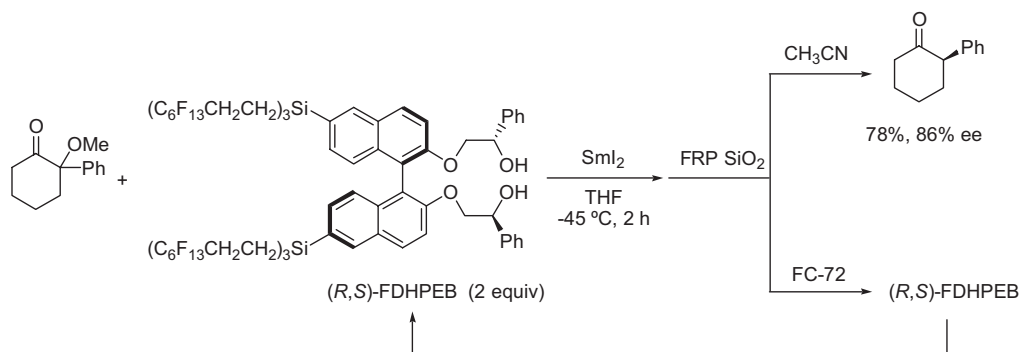
Chiral ligands that contain fluorine atoms which constitute more than 60% by weight are usually sufficiently fluorous to ensure immobilization of the catalysts in a fluorous phase. However, when the fluorous contents of the ligands are much lower than 60%, the solubilities of the ligands and/or catalysts in fluorous solvents decrease significantly. In such cases, asymmetric reactions cannot be carried out in organic and fluorous biphasic conditions but are conducted in common organic solvents or amphiphilic solvents such as BTF. The products and the ligands and/or catalysts are separated from the products for reuse by fluorous liquid/liquid extraction or solid phase extraction with a fluorous reverse phase (FRP) silica gel column [1], depending on the partition coefficients of the ligands or catalysts. Another option for such ligands is to carry out the reactions in supercritical carbon dioxide (scCO<sub>2</sub>). The catalysts are recycled successfully by separating the products with an scCO<sub>2</sub> extraction method.

## 10.14.2

**Reactions in Organic Solvents or Amphiphilic Solvents**

Takeuchi, Curran and coworkers synthesized a fluorous chiral diol, (*R*)-2,2'-bis[(*S*)-2-hydroxy-2-phenylethoxy]-6,6'-bis[tris(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)silyl]-1,1'-binaphthyl [(*R,S*)-FDHPEB] (F content = 56%, partition coefficient: benzene/FC-72 = 1/32, THF/FC-72 = 19/1) and applied it to an SmI<sub>2</sub>-mediated enantioselective protonation of 2-methoxy-2-phenyl-cyclohexanone [2]. The reaction was carried out under the same reaction conditions as those of the original non-fluorous reaction [3]. In the original reaction, the product was separated from the non-fluorous chiral proton source (2 equiv to the substrate) with preparative TLC to give the product in 70% chemical yield and 87% ee. In the fluorous version, the product and the fluorous chiral proton source were separated by FC-72 extraction (six times) and more simply by fluorous solid phase extraction with an FRP silica gel column. The recovered (*R,S*)-FDHPEB was used for the next reaction and the reaction was repeated five times. The average chemical yield and enantioselectivity were 78% and 86% ee, respectively (Scheme 10.14-1). The recovery of (*R,S*)-FDHPEB was quantitative in each run and the recovered (*R,S*)-FDHPEB after fifth reaction showed the same <sup>1</sup>H NMR spectrum as that of the pure compound. When the crude product which was obtained by FRP silica gel separation was analyzed by HPLC with CD and UV detectors, the enantioselectivity was found to reach 95% ee. The enantiomeric excess was reduced to 87% ee owing to partial racemization during purification of the crude product by preparative TLC. The quick separation of the product from (*R,S*)-FDHPEB by FRP silica gel confirmed this fact.

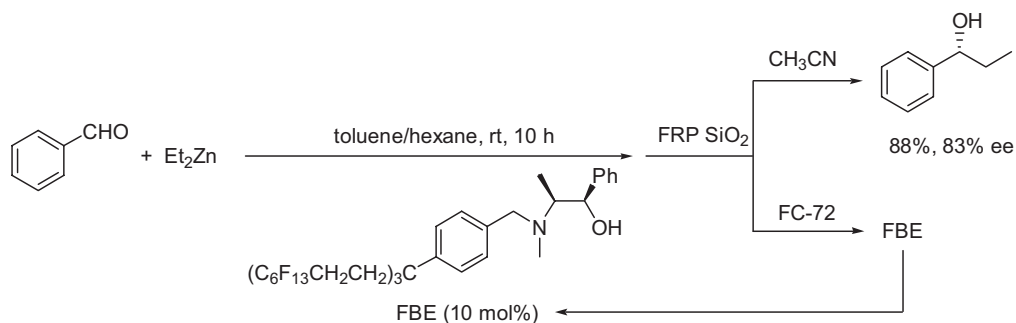
Nakamura and coworkers reported an enantioselective addition of diethylzinc to benzaldehyde using a fluorous chiral  $\beta$ -amino alcohol, (1*R*,2*S*)-*N*-[4-tris(1*H*,1*H*,2*H*,2*H*-perfluoro-



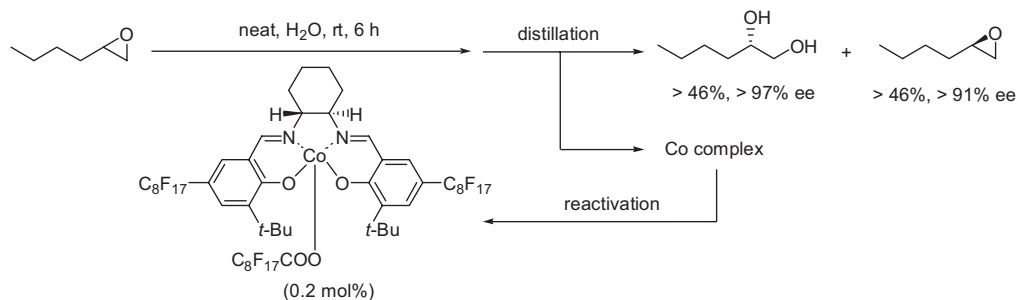
Scheme 10.14-1

octyl)silyl]benzylephedrine (FBE) (F content = 56%, partition coefficient:  $\text{CH}_3\text{CN}/\text{FC-72} = 12/88$ , toluene/ $\text{FC-72} = 41/59$ ), as a catalyst. The reaction was carried out in toluene by using  $\text{Et}_2\text{Zn}$  in hexane at room temperature [4]. The product was separated from the catalyst by an FRP silica gel column and the recovered chiral catalyst was used for the next reaction. The reaction was repeated ten times and the average chemical yield and enantioselectivity were 88% and 83% ee, respectively (Scheme 10.14-2). The recovery of the chiral catalyst was almost quantitative in each run and the enantioselectivity and chemical yield did not change significantly throughout the experiments. As for an alternative system, Soai and coworkers reported that *N*-benzylephedrine, the original of the fluororous catalysts, and the corresponding polymer supported compound at the *para*-position of the benzyl substituent gave the product in 92% ee and 89% ee, respectively [5]. They recovered another polymer-supported ephedrine catalyst and used it again without any loss in catalytic activity and enantioselectivity (using the catalyst twice).

In the two reactions described above, the chiral fluororous ligands were recovered quantitatively by FRP silica gel and reused repeatedly for the reactions. Since no significant drop was observed in chemical yield, enantioselectivity and recovery throughout the experiments, the reactions can be repeated any number of times until the chiral ligands have been consumed through mechanical losses.



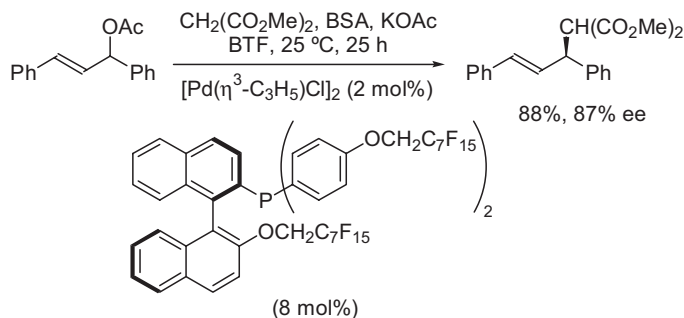
Scheme 10.14-2



Scheme 10.14-3

Pozzi and coworkers used their fluorous chiral salen compounds for the ligands of cobalt(III) complexes in a catalytic hydrolytic kinetic resolution of terminal epoxides [6]. Among them, (1*R*,2*R*)-[*N,N'*-bis(3,3'-di-*tert*-butyl-5,5'-diheptafluorooctyl)salicyliden-1,2-cyclo-hexanediamine]cobalt(III) (F content = 49%) was most effective for the reaction in the presence of counter ion C<sub>8</sub>F<sub>17</sub>COO<sup>-</sup>. The complex was soluble in neat 1-hexene oxide as well as in common organic solvents such as CH<sub>2</sub>Cl<sub>2</sub> and toluene but insoluble in perfluorocarbons at room temperature. Therefore, the reactions were carried out at room temperature without addition of any co-solvent with a sub-stoichiometric amount of H<sub>2</sub>O under aerobic conditions. In the case of 1-hexene oxide, 1,2-hexanediol and unreacted 1-hexene oxide were isolated by fractional distillation in 47% and 51% chemical yields, respectively, and in enantioselectivities higher than 99% ee (in the original non-fluorous reaction, 98% ee for both products at 50% conversion [7]). The non-volatile residue obtained after the distillation was taken up in toluene and treated with C<sub>8</sub>F<sub>17</sub>COOH in air. The recovered and reactivated catalyst was used for the next reaction and the reaction was repeated four times. Activity of the recovered catalyst was somewhat decreased at the fourth reaction, although the chemical yield and enantioselectivity of the diol were still higher than 46% and 97% ee, respectively (Scheme 10.14-3). Next, they tried to recycle the catalyst by using fluorous separation methods, liquid/liquid extraction and solid phase extraction. *n*-Perfluorooctane, BTF and CH<sub>3</sub>CN were used for the liquid/liquid extraction and the recovered catalyst resulted in 99% ee for 1,2-hexanediol although the reaction time was four times longer than the first one. The recovered catalyst by FRP silica gel provided the product in 99% ee but the reaction rate was reduced to 1/8 that of the first run.

Pozzi, Sinou and coworkers prepared a fluorous chiral phosphine, (*R*)-2-[bis[4-(1*H*,1*H*-perfluorooctyloxy)phenyl]phosphino]-2'-(1*H*,1*H*-perfluorooctyloxy)-1,1'-binaphthyl (F content = 52%, partition coefficient: *n*-perfluorooctane to toluene or CH<sub>3</sub>OH, 0.23 and 7.42, respectively), which was used as the chiral ligand of a palladium complex in an asymmetric allylic alkylation of 1,3-diphenylprop-2-enyl acetate [8]. The reaction was carried out at room temperature in BTF or toluene and gave the corresponding product in 99% and 88% chemical yields and 81% ee and 87% ee enantioselectivities, respectively (a non-fluorous MOP complex gave the product in 95% yield and 99% ee in toluene at 0 °C [9]) (Scheme 10.14-4). When toluene was used as a solvent, the simple extraction of the reaction mixture with *n*-perfluorooctane (twice) allowed the complete removal of the ligand and of the palladium

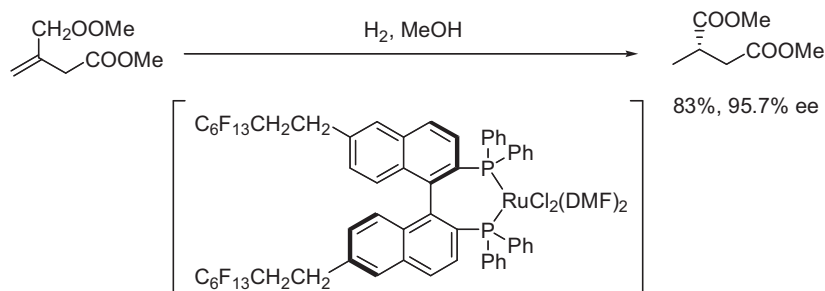


Scheme 10.14-4

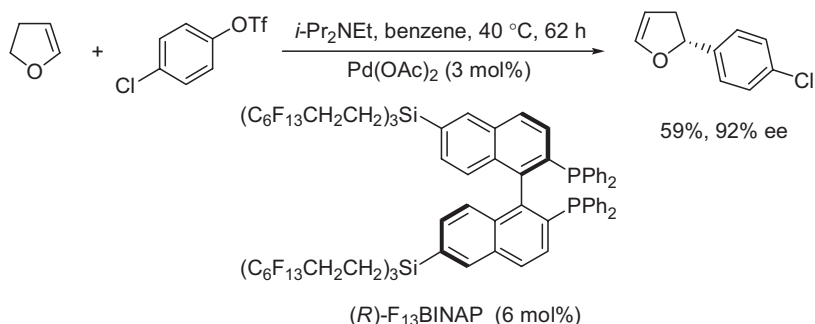
complex. However, the recovered palladium complex did not have catalytic activity for the reaction.

Stuart and coworkers reported the first synthesis of a “light” fluorous BINAP, (*R*)-6,6'-bis[1*H*,1*H*,2*H*,2*H*-perfluorooctyl]-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (F content = 38%), and application of it to a Ru-complex catalyzed asymmetric hydrogenation of dimethylitaconate [10]. The reaction was carried out at ambient temperature under the same reaction conditions as those reported by Noyori et al. [11]. The chemical yield (83%) and enantioselectivity (95.7% ee) were similar to those reported (88% and 95.4% ee, respectively) (Scheme 10.14-5). However, there was no description of the recovery of the catalyst or ligand.

Nakamura and coworkers synthesized a heavily fluorinated chiral BINAP, (*R*)-6,6'-bis[tris(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)silyl]-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl [(*R*)-F<sub>13</sub>BINAP] (F content = 54%, partition coefficient: benzene/FC-72 = 26/74, CH<sub>3</sub>CN/FC-72 = 2/98) and applied it to an asymmetric Heck reaction [12]. The reaction between 2,3-dihydrofuran and 4-chlorophenyl triflate was carried out under the same conditions as those of the original non-fluorous reaction by using F<sub>13</sub>BINAP in BTF or benzene to provide the corresponding product, 2-(4-chlorophenyl)-2,3-dihydrofuran in 59% chemical yields and in 90% ee and 92% ee, respectively (71% chemical yield and 91% ee in the original reaction in benzene [13]) (Scheme 10.14-6). The reaction rate was about one third of that in the original reaction. The products and the fluorous chiral ligand were separated by FRP silica



Scheme 10.14-5



Scheme 10.14-6

gel and about 70% of the chiral ligand was recovered. However, the recovered compound was almost all dioxide of  $\text{F}_{13}\text{BINAP}$  ( $\text{F}_{13}\text{BINAPO}$ ) and could not be reused for the next reaction.

The three examples of fluororous chiral phosphine ligands described above showed that finding a chiral phosphine ligand that can be effectively recycled by fluororous techniques is still an important challenge.

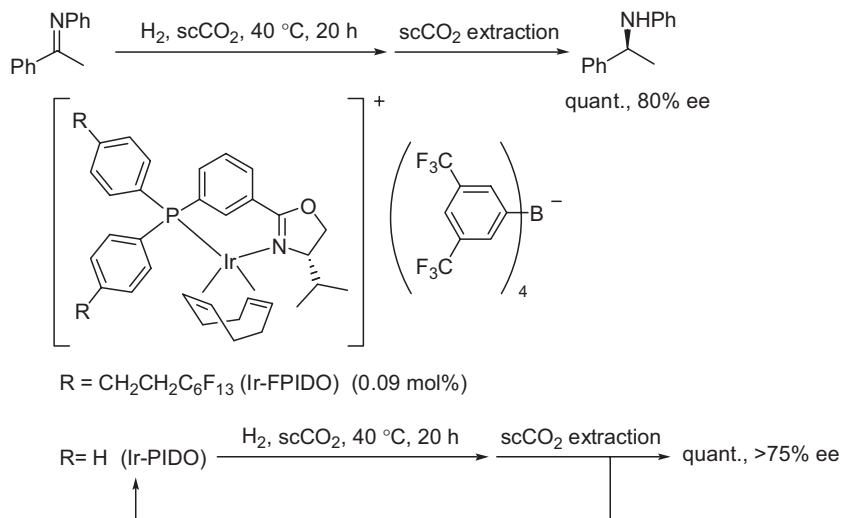
#### 10.14.3

##### Reactions in Supercritical Carbon Dioxide

The next two examples are suggestions from the viewpoint of a recyclable fluororous chiral phosphine ligand, because the fluororous complexes led to recyclable systems in supercritical  $\text{CO}_2$  ( $\text{scCO}_2$ ).

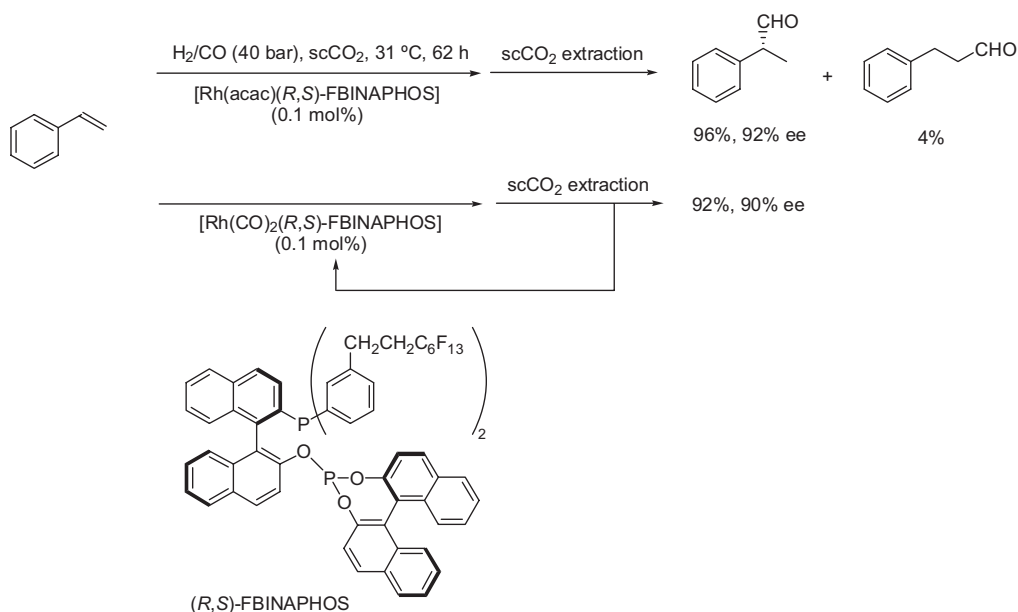
Leitner, Pfaltz and coworkers synthesized  $(4S)\text{-2-(2-[bis[4-(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)-phenylphosphanyl]phenyl]-4-isopropyl-4,5-dihydrooxazole)}$  (FPIDO) (F content = 46%) and used it as the ligand in an Ir complex that contained a “ $\text{CO}_2$ -philic” counter ion, such as tetrakis-3,5-bis(trifluoromethyl)phenylborate (BARF) (Ir-FPIDO) [14]. Asymmetric hydrogenation of  $N$ -(1-phenylethylidene)aniline was carried out under  $0.75\text{ g mL}^{-1}$   $\text{CO}_2$  density and 30 bar of hydrogen partial pressure at  $40^\circ\text{C}$  for 20 h by using Ir-FPIDO and the original non-fluororous phosphinodihydrooxazole (PIDO) Ir complex that contained BARF (Ir-PIDO). The corresponding product was obtained quantitatively in both cases and in 80% ee and 81% ee, respectively (87% ee in  $\text{CH}_2\text{Cl}_2$  for Ir-PIDO) (Scheme 10.14-7). The substrate and also  $\text{H}_2$  rendered the Ir-PIDO soluble in  $\text{scCO}_2$  but the hydrogenated product did not have such an effect. Therefore, the catalyst became insoluble in  $\text{scCO}_2$  after the reaction and the product was collected quantitatively in a cold trap by purging the reactor with compressed  $\text{CO}_2$ . The catalyst remained in the reactor and the reaction was performed by recharging the substrate and  $\text{H}_2$ . Almost identical levels of reaction rate and enantioselectivity were observed in four subsequent experiments (75–80% ee).

$(R,S)\text{FBINAPHOS}$  4-(2'-[bis-[3-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)phenyl]phosphanyl]-[1,1']-( $R$ )-binaphthalenyl-2-yloxy]3,5-dioxa-4-phosphacyclohepta[2,1-a;3,4-a']-( $S$ )-dinaphthalene (F content = 34%) was synthesized by Leitner and coworkers and used as a chiral ligand of Rh complexes for the asymmetric hydroformylation of styrene analogs in



Scheme 10.14-7

scCO<sub>2</sub> [15]. The reaction of styrene using an Rh(acac)[(R,S)-FBINAPHOS] complex under 0.8 g mL<sup>-1</sup> CO<sub>2</sub> density and 40 bar H<sub>2</sub>/CO partial pressure at 31 °C for 62 h provided the corresponding products in quantitative conversion and in 96% branched aldehyde selectivity and 92% ee (Scheme 10.14-8). *p*-*tert*-Butyl styrene, the precursor for the hydroformylation



Scheme 10.14-8

route to ibuprofen, was hydroformylated with an excellent enantioselectivity of up to 93% ee and an unprecedented high regioselectivity of 96% for the branched product. However, the very high regioselectivity was mainly due to the ligand substitution pattern rather than the reaction medium. They tried to recycle the  $\text{Rh}(\text{CO})_2[(R,S)\text{-FBINAPHOS}]$  complex in the asymmetric reaction of styrene. After the reaction the reaction mixture was cooled and  $\text{CO}_2$  was partly vented to reduce the density of the solvent. Re-heating of the mixture resulted in a two-phase system consisting of a liquid phase and a compressed gas phase. The product was distributed between both phases but the complex was contained in the liquid phase. Purging the reactor from the bottom with  $\text{CO}_2$  at constant temperature and pressure stripped away the product and left the catalyst behind for subsequent use. Eight successive runs were performed and no apparent loss in selectivity or activity occurred up to the third run. The next three runs saw a slow decrease in enantioselectivity, but regioselectivity and conversion remained uniformly high. As for an alternative system, Nozaki and coworkers reported that the reaction using an  $\text{Rh}(\text{acac})$  complex of polymer-supported BINAPHOS in benzene at 60 °C under 20 atm pressure of CO and  $\text{H}_2$  (1:1) gave the product in 85% branched aldehyde selectivity and 90% ee [16]. The catalyst was recycled three times without significant loss of regioselectivity and enantioselectivity but with a gradual decrease of catalytic activity.

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## 10.15

### Combining Lipase-Catalyzed Kinetic Resolutions of Racemic Alcohols with Fluorous Phase Labeling

*Fritz Theil, Helmut Sonnenschein, Benno Hungerhoff, and Sauda M. Swaleh*

#### 10.15.1

##### Introduction

In organic synthesis, isolation of pure products is very often the bottleneck of the whole process due to time-consuming and waste-producing separation and purification procedures such as chromatography. In an ideal case an isolation strategy of the desired product(s) should be included in the synthetic plan [1].

Fluorous phase techniques are excellent examples of the easy extractive recovery or isolation of homogeneous catalysts [2], reagents and products [3] equipped with perfluorinated auxiliary groups from non-fluorinated compounds, based on partitioning between organic and fluorous phases and avoiding chromatography.

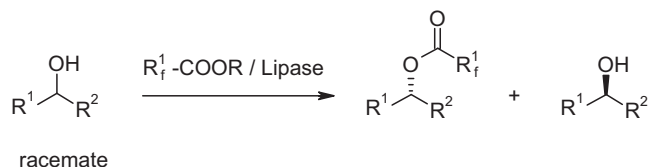
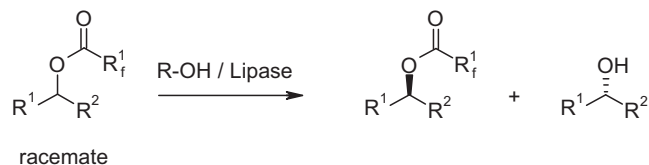
Biocatalytic methods, particularly the lipase-catalyzed kinetic resolution of racemic alcohols and their esters either by esterification, hydrolysis, or alcoholysis, are well established access routes to enantiomerically pure or enriched building blocks [4]. Lipases are inexpensive and robust biocatalysts; reactions are highly selective in many cases and can be run without any special equipment. However, there is one major drawback to this type of reaction that yields one of the enantiomers as an alcohol and the other one as a carboxylic ester: usually the products must be separated by chromatography, and therefore, on a large scale in the pharmaceutical industry or in high-throughput kinetic resolutions, the required chromatography might be the reason lipase-catalyzed resolution is not to be regarded as being useful.

To circumvent the need for chromatography, several techniques have been reported. For example, lipase-catalyzed esterification of racemic alcohols with succinic anhydride followed by an acid–base extraction separates the acidic ester from the neutral alcohol. However, acidic compounds decrease the lipase activity [5]. Transesterification of racemic esters with poly(ethylene glycol) in the presence of porcine pancreatic lipase in some cases forms crystalline poly(ethylene glycol) esters from the fast reacting enantiomer, which can be simply separated from the unreacted “normal” ester by filtration [6]. On a large scale, there are examples of the separation of esters from alcohols by distillation [7]. Finally, alcohols have been separated from esters by reaction with a polymeric acid chloride [8].

From the progress made running reactions in fluorous phases and/or improving work-up procedures by the introduction of the fluorous phase, the following question arises: is it possible to combine lipase-catalyzed acylation or deacylation reactions with the fluorous phase technique in order to replace chromatography by extraction?

To answer this question we need a fluorinated acylating reagent that fulfills the following tasks: lipase-mediated enantiomer-selective acylation of the fast reacting enantiomer and, simultaneously tagging it in order to be recognized by a fluorous phase that finally allows the separation of the fast reacting fluorinated from the non-fluorinated slow reacting enan-



**Enantiomer-Selective Acylation****Enantiomer-Selective Deacylation**

**Scheme 10.15-1.** Enantiomer-selective acylation and deacylation using fluorous labels.  $\text{R}_f^1$  = highly fluorinated residue

tiomer by liquid/liquid extraction. Alternatively, fluorinated and non-fluorinated compounds can be separated by liquid/solid extraction or fluorous chromatography [1b]. A further possibility to selectively tag one enantiomer is the lipase-catalyzed alcoholysis of a racemic ester equipped with a highly fluorinated acyl residue, whereby the fluorous tag is cleaved off from the fast reacting enantiomer (Scheme 10.15-1). Furthermore, it is known that fluorinated substrates [9] or solvents [10] do not harm lipases.

## 10.15.2

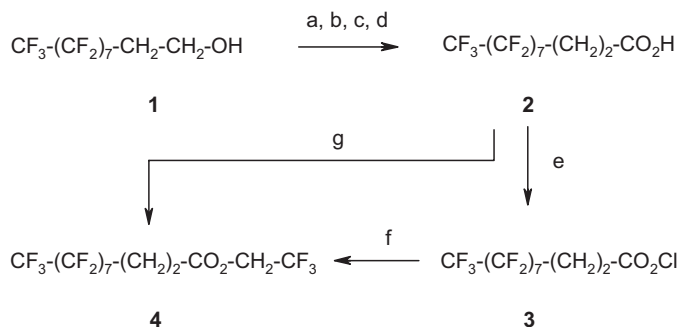
**Results and Discussion**

Initially a useful highly fluorinated acyl donor that meets all requirements with regard to reactivity, stability and fluorine content was designed and synthesized. From the point of view of reactivity, it was necessary to introduce a non-fluorinated spacer between the fluorinated alkyl and the carboxylate residue. Otherwise, acyl donors without a spacer would react non-biocatalytically in competition with the enzyme-mediated reaction, yielding products with no or with low enantiomeric excess [11].

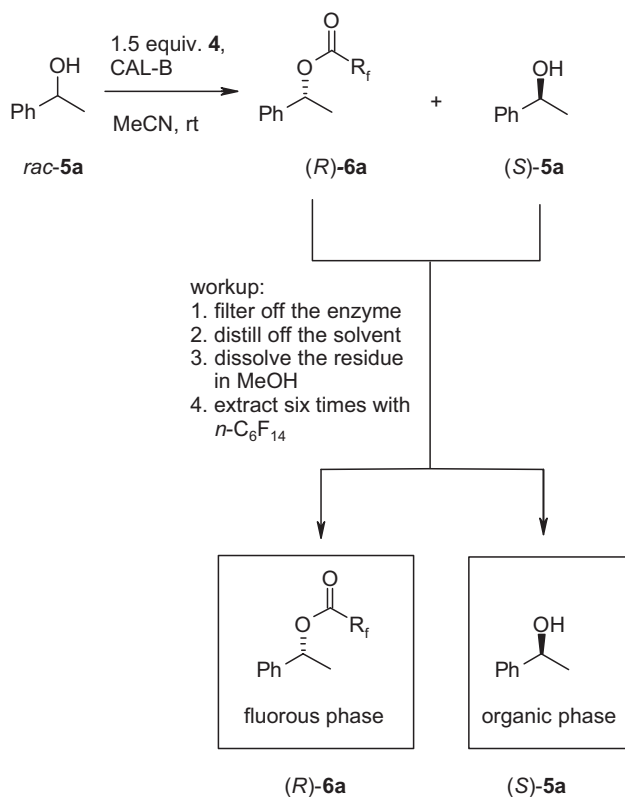
From the commercially available highly fluorinated decanol **1** the ester **4** was synthesized as an esterification agent according to Scheme 10.15-2 [12].

After the screening of lipases and solvents *Candida antarctica* B lipase (CAL-B) in acetonitrile turned out to be a useful biocatalyst employing 1.5 equiv of the ester **4** as an ideal acylating agent by resolving *rac*-**5a** into its enantiomers (*R*)-**6a** and (*S*)-**5a** with high efficacy (Scheme 10.15-3) [12].

In contrast, the corresponding fluorinated ester having only one methylene group as a spacer, synthesized by oxidation of **1** to the corresponding acid and subsequent esterification



**Scheme 10.15-2.** Synthesis of the fluorous label. (a) TsCl, (b) LiBr, (c) Mg, (d) CO<sub>2</sub>, (e) PCl<sub>5</sub>, (f) HOCH<sub>2</sub>CF<sub>3</sub>/pyridine, (g) HOCH<sub>2</sub>CF<sub>3</sub>/H<sup>+</sup>



**Scheme 10.15-3.** Kinetic resolution of *rac*-5a by enantiomer-selective fluorous labeling. R<sub>f</sub> = (CH<sub>2</sub>)<sub>2</sub>(CF<sub>2</sub>)<sub>7</sub>CF<sub>3</sub>

with 2,2,2-trifluoroethanol in analogy to a published procedure [13], was not useful. This ester was rather unstable and did not react in the appropriate manner with 1-phenylethanol (*rac*-5a) in the presence of lipases [12b].

Enantiomeric excess and yield of the products were determined after conventional workup by flash chromatography to be >99% for both enantiomers, proving that the fluorinated ester 4 is an excellent acyl donor for lipase-catalyzed esterification. In comparison, in the literature the resolution of *rac*-5a has been reported using vinyl acetate in *tert*-butyl methyl ether in the presence of *Pseudomonas* sp. lipase showing similar results [14], demonstrating that the perfluoroester 4 exhibits the same enantioselectivity as vinyl acetate.

For the separation of the products we intended to use liquid/liquid extraction as a quick and simple method. Consequently, the next step was to identify a suitable fluoruous/organic biphasic system for the extractive separation of the alcohol 5a from the fluorinated ester 6a. Therefore, as a model substance the ester *rac*-6a was synthesized in a conventional non-enzymatic way from the alcohol *rac*-5a and the acid chloride 3. After screening of several biphasic systems consisting of perfluoro-*n*-hexane and various organic solvents, methanol/*n*-C<sub>6</sub>F<sub>14</sub> turned out to be the system of choice. Distribution experiments with an equimolar mixture of *rac*-5a and *rac*-6a in methanol showed that at least five extractions with perfluoro-*n*-hexane were required for a total separation of the fluorinated from the non-fluorinated enantiomer. The remaining organic phase was contaminated with less than 1% of *rac*-6a and the combined fluoruous phases with less than 1% of *rac*-5a, whereby separation was carried out in ordinary separating funnels.

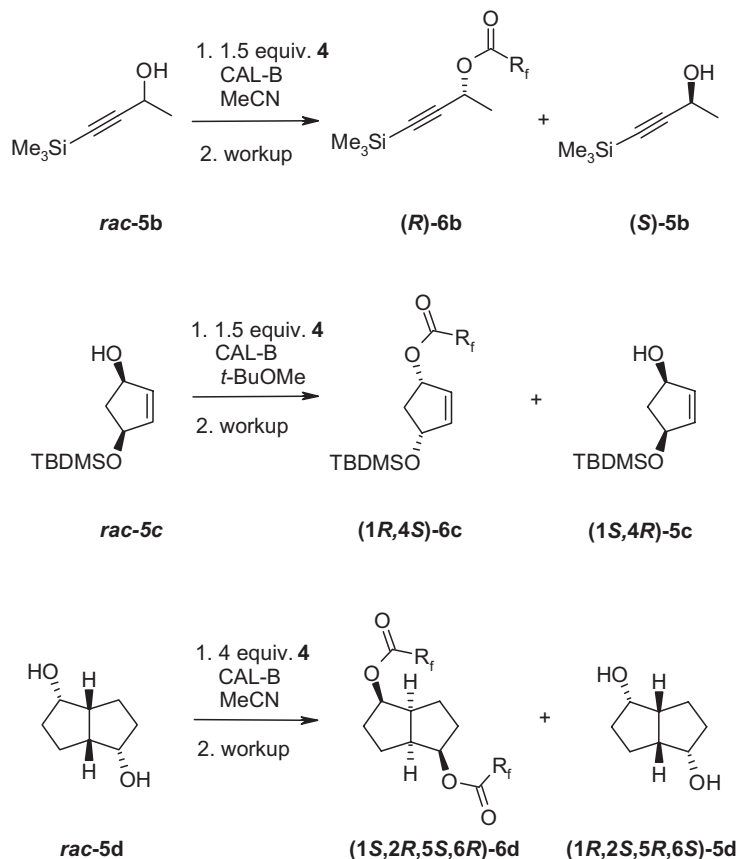
Having identified the appropriate biphasic solvent system, the products (*R*)-6a and (*S*)-5a were isolated after a lipase-mediated acylation reaction as follows (Scheme 10.15-3): removal of the enzyme by filtration, evaporation of acetonitrile, and partition between perfluoro-*n*-hexane and methanol. After extraction the organic phase contains (*S*)-5a with 99% ee and a trace of not more than 1% of (*R*)-6a, whereas (*R*)-6a with an ee of 98% [determined after hydrolysis to (*R*)-5a] and the excess of the fluoroester 4 remain in the combined fluoruous phases. The ee of 98% for (*R*)-5a represents an impurity of at most 1% of (*S*)-5a in the fluoruous phase.

Saponification of the mixture of the fluorinated esters (*R*)-6a and 4 with lithium hydroxide yielding (*R*)-5a allows the almost quantitative recovery of the fluorinated carboxylic acid as its lithium salt in solid form.

In order to prove the general usefulness of this newly developed separation methodology, it was applied to the racemic alcohols *rac*-5b, c and d (Scheme 10.15-4). These racemic alcohols and their enantiomers, known as versatile building blocks, were resolved utilizing the acylating agent 4 in the presence of CAL-B in acetonitrile (*rac*-5b, *rac*-5d) or *tert*-butyl methyl ether (*rac*-5c) as solvents and methanol/perfluoro-*n*-hexane as the fluoruous/organic biphasic system for the extractive separation of the fluorinated from the non-fluorinated enantiomer [12b].

Independently of the constitution of the products, the extractive separation of the fluorinated from the non-fluorinated enantiomer was very efficient in all cases, demonstrating that the highly fluorinated ester 4 is an efficient acyl donor and tagging agent establishing sufficient fluorine content in the fast reacting enantiomers.

The results summarized in Table 10.15-1 show that the newly developed separation principle could be applied successfully to substrates of different constitution that have already



workup: filtering off the lipase, evaporation of the solvent,  
partition between  $n\text{-C}_6\text{F}_{14}$  and MeOH

**Scheme 10.15-4.** Kinetic resolution of *rac*-**5b–d** by enantiomer-selective fluorine labeling.  $\text{R}_f = (\text{CH}_2)_2(\text{CF}_2)_7\text{CF}_3$

been resolved in the literature by lipase-catalysis using conventional non-fluorinated acyl donors and separation techniques. For example, the enantiomers of the silylated butynol *rac*-**5b** have been resolved with a comparable high enantioselectivity by using vinyl acetate in the presence of *Pseudomonas* sp. lipase [15a] or with *S*-ethylthio octanoate in the presence of *C. antarctica* B lipase [15b]. Furthermore, the resolution of the monosilylated cyclopentenol *rac*-**5c** with isopropenyl acetate in the presence of *Candida antarctica* B lipase as reported by T. T. Curran et al. [16] also proceeded with low enantioselectivity ( $E = 15$ ). The bicyclic  $\text{C}_2$ -symmetric diol *rac*-**5d** has been resolved in our laboratory with either 2,2,2-trichloroethyl acetate in the presence of pancreatin [17a] or more efficiently with vinyl acetate in the presence of lipase from *Pseudomonas cepacia* [17b].

**Tab. 10.15-1.** Lipase-catalyzed kinetic resolution of the alcohols **rac-5a–d** by acylation with the fluororous acyl donor **4**

Substrate	Time (h)	Ester			Alcohol			<i>E</i> <sup>a</sup>	<i>c</i> <sup>b</sup>
		Config. <sup>c</sup>	ee <sup>d</sup> (%)	Yield (%)	Config. <sup>c</sup>	ee <sup>d</sup> (%)	Yield (%)		
<b>rac-5a</b>	19	<i>R</i>	98 (>99)	47	<i>S</i>	>99 (>99)	48	>200	0.50
<b>rac-5b</b>	64	<i>R</i>	97 (99)	36	<i>S</i>	65	52	>200	0.40
<b>rac-5c</b>	48	1 <i>R</i> ,4 <i>S</i>	38 (39)	65	1 <i>S</i> ,4 <i>R</i>	96	25	7.6	0.72
<b>rac-5d</b>	23	1 <i>S</i> ,2 <i>R</i> ,5 <i>S</i> ,6 <i>R</i>	96 (99)	43	1 <i>R</i> ,2 <i>S</i> ,5 <i>R</i> ,6 <i>S</i>	>99	44	n.a. <sup>e</sup>	0.50

<sup>a</sup> Enantiomeric ratio. <sup>b</sup> Conversion. <sup>c</sup> Assigned on the basis of the known  $[\alpha]_D$ -values of the free alcohols. <sup>d</sup> The numbers in parentheses correspond to the ee values determined after separation by flash-chromatography. <sup>e</sup> The *E*-value calculation according to Chen and Sih [4a] is not applicable because it is a sequence of two enantioselective reactions.

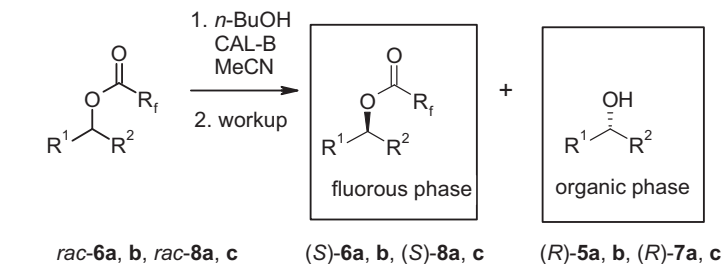
After having demonstrated that lipase-catalyzed acylation under kinetic resolution simultaneously labels the fast reacting enantiomer with a fluororous tag very efficiently, our next aim was to investigate the possibility of an enantiomer-selective detagging procedure by subjecting highly fluorinated esters of racemic alcohols to a lipase-catalyzed alcoholysis under deacylation of the fast reacting enantiomer, and leaving the slow reacting enantiomer attached to the fluororous tag [18].

The racemic fluorinated esters **rac-6a–c** and **rac-8a–c** were prepared by acylation of the corresponding alcohols **rac-5a–c** and **rac-7a–c** with the acid chloride **3** (Scheme 10.15-5), which has already been used for the synthesis of the fluororous acyl donor **4** depicted in Scheme 10.15-2.

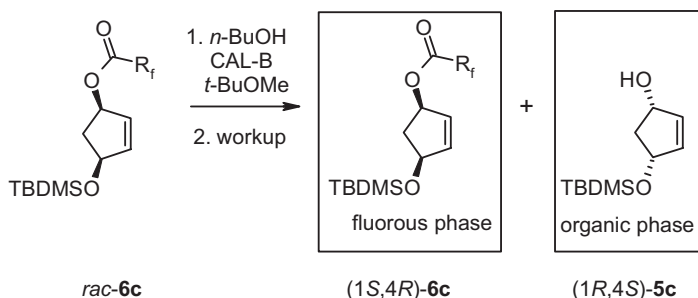
The racemic esters **rac-6a–c** and **rac-8a–c** were subjected to a lipase-catalyzed alcoholysis in acetonitrile or *tert*-butyl methyl ether for **rac-6c** in the presence of *Candida antarctica* B lipase (CAL-B) and four equivalents of *n*-butanol. Except for the non-reacting bromoindanol derivative **rac-8b** the other substrates were resolved yielding the fluorinated esters (*S*)-**6a**, **b**, (*S*)-**8a**, **c** or (1*S*,4*R*)-**6c** and the non-fluorinated alcohols (*R*)-**5a**, **b**, (*R*)-**7a**, **c** or (1*R*,4*S*)-**5c**, respectively (Scheme 10.15-6). For **rac-6c**, due to the higher rate of conversion, *tert*-butyl methyl ether was used instead of acetonitrile as the solvent. After removal of the lipase by filtration and evaporation of the solvent under reduced pressure, the ester and the alcohol were separated by partition between perfluoro-*n*-hexane and methanol. As expected the extractive separation of the esters **8** from the alcohols **7** also works very well.

The results of the kinetic resolutions are summarized in Table 10.15-2. The outcomes from these reactions confirm that apart from **rac-8b** the other fluorinated esters were accepted as substrates for CAL-B and resolved with excellent enantiomer selectivity. For all conversions the *E*-value of the reaction was >200. In a control experiment (*S*)-**8c** and (*R*)-**7c** were separated conventionally by flash chromatography, showing almost identical results compared with the extractive separation. Remarkably, the alcoholysis of **rac-6c** shows a much higher selectivity than the acylation of **rac-5c** where the *E*-value was only 7.6 (Table 10.15-1).





for  $R^1$  and  $R^2$  cf. Scheme 10.5-5.



workup: filtering off the lipase, evaporation of the solvent,  
partition between  $n\text{-C}_6\text{F}_{14}$  and MeOH

**Scheme 10.15-6.** Kinetic resolution of *rac-6a–c* and *rac-8a, c* by enantiomer-selective fluororous delabeling.  $R_f = (\text{CH}_2)_2(\text{CF}_2)_7\text{CF}_3$

**Tab. 10.15-2.** Lipase-catalyzed kinetic resolution of the esters *rac-6a–c* and *rac-8a–c* by alcoholysis with *n*-butanol

Substrate	Time/d	Ester			Alcohol			$E^a$	$c^b$
		Config.	ee (%)	Yield <sup>c</sup> (%)	Config.	ee (%)	Yield (%)		
<i>rac-6a</i>	0.8	$S^d$	97	43	$R^d$	99	48	>200	0.49
<i>rac-6b</i>	8	$S^e$	68	25 <sup>f</sup>	$R^e$	99	17 <sup>f</sup>	>200	0.41
<i>rac-6c</i>	4	1 <i>S</i> ,4 <i>R</i> <sup>e</sup>	74	42	1 <i>R</i> ,4 <i>S</i> <sup>e</sup>	99	41	>200	0.43
<i>rac-8a</i>	8	$S^d$	90	41	$R^d$	99	44	>200	0.48
<i>rac-8b</i>					no conversion				
<i>rac-8c</i>	7	$S^d$	94 (96 <sup>g</sup> )	43	$R^d$	99 (99 <sup>g</sup> )	44	>200	0.49

<sup>a</sup> Enantiomeric ratio. <sup>b</sup> Conversion. <sup>c</sup> Determined after saponification or transesterification. <sup>d</sup> Assigned by comparison with one of the commercially available enantiomers. <sup>e</sup> Assigned on the basis of the known  $[\alpha]_D$ -values of the free alcohols cf. Ref. [15a] for **5b** and Ref. [16b] for **5c**. <sup>f</sup> The yields are low due to the high volatility of the alkynol **5b**. <sup>g</sup> The numbers in parentheses correspond to the ee values determined after separation by flash-chromatography.

hydrogen in the molecule as a very rough measure for the fluorophilicity of an organic compound, it was calculated to be in the region of 1.70, as the maximum for the bicyclic diester **6d**, and 0.68 for the cyclopentenol ester **6c** as the minimum. The comparison of these ratios illustrates that the extractive separation is efficient even in the case when there is a shortage of fluorine compared with hydrogen, as in the case of the cyclopentenol derivative **6c**. In addition, the selectivity of the partition of the fluorinated esters and alcohols between perfluoro-*n*-hexane and methanol may be increased as a result of the formation of hydrogen bonds between the enantiomeric alcohols and methanol. Alternatively, for the isolation of compounds with low fluorine content solid/liquid extraction is a useful separation technique [1b].

With regard to price and availability, the highly fluorinated acyl donors **3** and **4** at present cannot compete with the frequently used inexpensive vinyl acetate, but the fluorous label can be recycled. On the other hand, perfluoro-*n*-hexane, FC-72, is a technical product. Its improper use on large scale can cause environmental problems, which could be avoided by using an appropriate extraction technique as opposed to the separatory funnels that are typical for laboratory workup.

### 10.15.3

#### Conclusion

Kinetic resolution of racemic alcohols or their corresponding esters has been performed by either enantiomer-selective fluorous phase labeling or delabeling. The highly fluorinated carboxylic ester **4** is an extremely useful and selective acyl donor for the lipase-catalyzed enantiomer-selective acylation of alcohols, whereby the fast reacting enantiomer is equipped with a fluorous tag in order to be recognized selectively by a fluorous phase. Furthermore, if highly fluorinated racemic esters, prepared from the acid chloride **3** and racemic alcohols, were subjected to lipase-catalyzed alcoholysis, the fluorous tag was selectively removed from the fast reacting enantiomer leaving the slow reacting enantiomer equipped with the fluorous label. The enantiomer-selective tagged mixture of ester and alcohol representing the two enantiomers were separated very efficiently by partition in the two-phase solvent system perfluoro-*n*-hexane/methanol, avoiding a chromatographic step. Hydrolysis of the fluorinated enantiomer allows the recovery of the fluorous tag.

These results are an example of the successful combination of fluorous techniques with lipase-catalyzed kinetic resolutions where the final separation procedure is already integrated into the initial chemical transformation. This newly developed method accomplishes existing methods for the non-chromatographic separation of enantiomeric esters from the corresponding alcohols.

In addition, the fluorous/organic liquid/liquid extractive separation can be replaced by a fluorous triphasic reaction using a U-shaped separation/reaction vessel affording both enantiomers as alcohols on the two different sides of the U-tube [19]. Typical experimental procedures can be found in a separate chapter within this book (see Chapter 11.19–21).

The kinetic resolution of racemic carboxylic acids by enantiomer-selective esterification in fluorous/organic systems with highly fluorinated alcohols can be found in the contribution by D. O'Hagan and P. Beier [20] (see Chapter 10.16).



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## 10.16

**Enantiomeric Partitioning Using Fluorous Biphasic Methodology in Lipase-mediated (Trans)Esterifications***Petr Beier and David O'Hagan*

## 10.16.1

**Introduction**

It is an extraordinary feature of lipase enzymes that they have good catalytic activity when suspended in organic solvents [1]. The catalytic efficiency of an enzyme is highly dependent on its 3D structure and the consequences of removing an enzyme from water into a hydrophobic environment are predicted to unravel the protein and destroy its catalytic prowess. However, lipases have evolved to operate between the aqueous environment of the cell and at lipid membranes and do not unravel in this destructive manner. They control this amphiphilicity by opening a “flap” when in a hydrophobic environment and exposing the active site of the protein. In water this flap closes to re-establish a hydrophobic surface [2].

This feature of lipases has resulted in their widespread utility in biotransformation reactions and in transesterifications (esters and alcohols) to generate ester products. The inherent asymmetry of lipase has offered a good strategy for the preparation of enantiomerically enriched esters and secondary alcohols [3]. The non-aqueous environment using lipases in dry organic solvents has also allowed “reverse hydrolysis” strategies to be explored. This has involved very successful esterification (carboxylic acid and alcohol) reactions to be carried out as well as condensation polymerization reactions between long chain  $\omega$ -hydroxy acids or esters [4] and also diacids and diols. These condensation reactions are generally carried out with an *in situ* drying agent added, such as molecular sieves or a dehydrated inorganic salt, both of which can absorb the water released from the condensation process [5]. The more free water that accumulates compromises the efficiency of the condensation process as the enzyme begins to catalyze the reverse hydrolytic reaction.

Another feature of such lipase reactions is that they can be carried out at much higher temperatures than enzyme reactions in an aqueous medium. Generally enzymes become less efficient above 40 °C, largely due to water burrowing through the enzyme and disrupting important intramolecular H-bonding interactions. In organic solvents, where competition for hydrogen bonding is not so significant, reactions are generally optimal at about 50 °C and reactions have been recorded in high boiling organic solvents [6] up to 100 °C.

With this background we became interested in the prospect of carrying out lipase mediated reactions in perfluorocarbon solvents, the most hydrophobic solvents available [7]. For example, hexane is a better solvent than THF or ether and acetone, acetonitrile or DMF are very poor solvents for such reactions [8]. It has been argued that this is due to the enzyme retaining “essential water” hydrated to its surface, holding the protein in a catalytically competent structure, and protecting the enzyme from being attacked by the solvent. The more polar the solvent then the greater its ability to strip the “essential water” from the surface of the protein and therefore hexane has emerged as a widely used solvent for such reactions. Perfluorocarbons are more hydrophobic than hydrocarbons [7] and thus it was tempting to speculate that this would offer a more optimal medium for lipase mediated

chemistry. Of course the prospect of carrying out lipase mediated reactions in perfluorocarbon/hydrocarbon solvent mixtures was an attractive one too as this offered a potential method for separating products after completion of a transesterification. Lipase reactions in perfluorocarbon/hydrocarbon solvent systems are rendered homogenous at temperatures which are optimal ( $\sim 50^\circ\text{C}$ ) for lipase activity in organic solvents and clearly filtering of the enzyme and subsequent cooling of the resultant solution would repartition the solvents for product separation. For these types of processes to be successful, the product esters and alcohols clearly have to be either fluorous or hydrocarbon soluble. It was particularly exciting to envisage a reaction system starting with a racemic acid or ester, which could result in a product mixture where the two enantiomeric series partitioned differentially into the hydrocarbon and fluorous phases.

In order to develop a lipase mediated enantiomeric partitioning system a number of criteria had to be met.

- (1) Identification of an enzyme with good catalytic activity in a hydrocarbon/perfluorocarbon solvent system.
- (2) Identification a carboxylic acid/ester series which resolves well during transesterification with a fluorous alcohol mediated by the lipase.
- (3) Identification of suitable fluorous alcohols or esters to ensure partitioning of the products between the two liquid phases after reaction.

In this study “organic” acids/esters were (trans)esterified using “fluorous” alcohols. Preliminary results of our investigation have been reported [9]. Another recently published study has taken the alternative approach using lipase-mediated transesterifications of “organic” alcohols with a “fluorous” ester and is discussed elsewhere [10].

#### 10.16.2

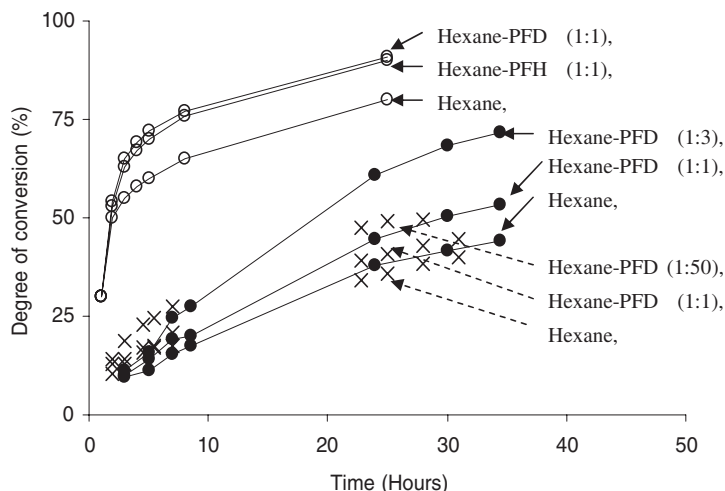
#### Results and Discussion

##### 10.16.2.1 The Efficiency and Stability of Lipase in Perfluorocarbon Media

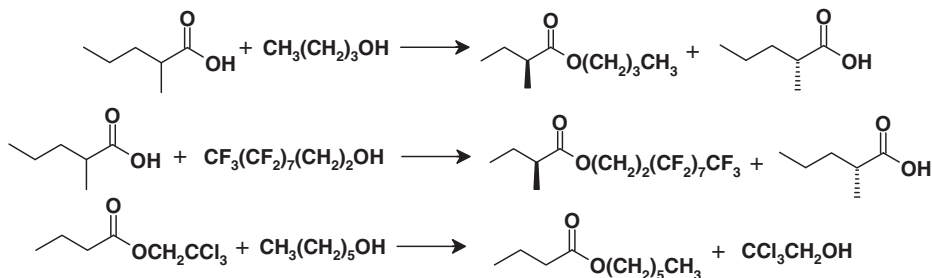
From the outset of this study it was important to establish whether certain lipases are compatible with perfluorocarbon and perfluorocarbon/hydrocarbon solvent systems. Three different lipase-mediated reactions were tested. The degree of conversion versus time for the esterification of 2-methylpentanoic acid with butanol and separately with  $\text{CF}_3(\text{CF}_2)_7(\text{CH}_2)_2\text{OH}$  catalyzed by the *Candida rugosa* lipase (CRL) was explored. Also a transesterification reaction between hexanol and 2,2,2-trichloroethyl butanoate catalyzed by the lipase from porcine pancreas (PPL) was studied and the collected data are shown in Figure 10.16-1 and Scheme 10.16-1. It can be seen that the reaction rate increased with the proportion of the perfluorinated solvent.

It emerged from these trial experiments that the mixed solvent systems provided an excellent medium in which to carry out lipase-mediated reactions.

The thermostability of the CRL in “fluorous” and “organic” solvents was investigated. The lipase was suspended in perfluorohexane or hexane and stirred at  $40^\circ\text{C}$ . After a given time the enzyme was filtered off, air dried and the activity was determined at room temperature with hexane as the solvent. It emerged that the lipase from *Candida rugosa* is more thermo-



**Fig. 10.16-1.** Time versus degree of conversion for the reaction of 2,2,2-trichloroethyl butanoate with: 1-hexanol at 45 °C, catalyzed by PPL (○); 2-methylpentanoic acid and 1-butanol at 40 °C, catalyzed by CRL (●); 2-methylpentanoic acid and  $\text{CF}_3(\text{CF}_2)_7(\text{CH}_2)_2\text{OH}$  at 40 °C, catalyzed by CRL (×). PFD, perfluorodecalin; PFH, perfluorohexane

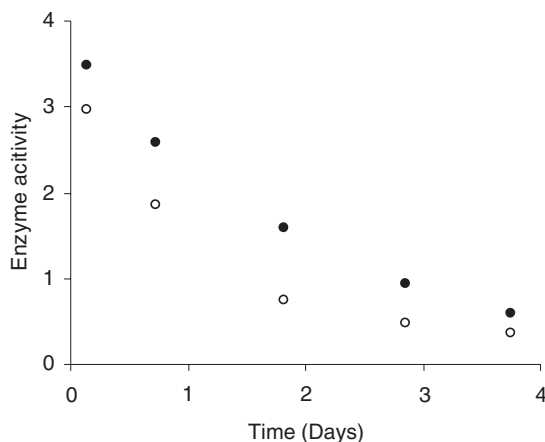


**Scheme 10.16-1.** Trial (trans)esterification reaction catalyzed by PPL or CRL in a mixed solvent system

stable in the “fluorous” solvent than in hexane (Figure 10.16-2), however the rate of deactivation is similar for both systems over several days.

#### 10.16.2.2 Transesterification Reactions with Perfluoroalkylated Substrates

In order to test the ability of lipases to mediate a reaction between a “fluorous” tagged ester and hexanol the following system was explored. A reaction between dihydroperfluorododecyl butyrate and 1-hexanol was catalyzed by CRL in a homogeneous mixed solvent system of PFD and hexane, Scheme 10.16-2. Typically reactions were run for 3–4 days to reach full conversion. After filtration of the enzyme and washing with hexane, the liquid phases separated on cooling. The hexane phase was washed with PFD to remove all “fluorous” substrates and hexyl butyrate isolated in excellent yield (98%). Contamination with “fluorous”



**Fig. 10.16-2.** Activity of CRL after treatment in PFH (●) or (○) hexane at 40 °C (μmol of converted hexanol into hexyl acetate using 3 equiv of vinyl acetate per hour and 1 mg of enzyme powder) versus time. The activity is the average of three runs in each case



**Scheme 10.16-2.** Transesterification reaction catalyzed by CRL in PFD/hexane system at 40 °C

products was less than 0.2%. In these trials there was no reaction observed without added enzyme. It was shown that these “fluorous” esters are suitably activated substrates for lipase catalyzed transesterifications and the reverse reaction is very slow as the “fluorous” alcohol is a poor nucleophile.

Conversely (trans)esterifications were explored between “organic” esters, acids or anhydrides and “fluorous” alcohols and some data are presented in Table 10.16-1. It is clear from the relatively short time required to achieve a high percentage of conversion that the perfluoroalkyl alcohol, despite its poor nucleophilicity, can intercept the acylated enzyme intermediate in the lipase mediated process. This renders the method particularly attractive.

### 10.16.2.3 Partitioning of the Products Between the Liquid Phases

The success of the approach to lipase mediated (trans)esterification reactions for product and/or stereochemical separation relies on an efficient partitioning of the reaction products between the perfluorocarbon and hydrocarbon solvents on cooling the reaction medium (−10 °C for 1 h). In order to assess this, partitioning between hexane and some perfluorocarbon solvents was evaluated for a series of alcohols, esters and carboxylic acids (Table 10.16-2).

Recent insights have revealed that the most important factors that influence miscibility of a compound in the fluorous phase are the solvent extended surface and Hildebrand solubility parameter [11],  $\delta$ . From the data in Table 11.16-2 it is apparent that the more fluorine

**Tab. 10.16-1.** Lipase (CRL) catalyzed (trans)esterification reactions between “organic” esters, acid or anhydride and “fluorous” alcohols

Acylating agent	Alcohol	Retention time (h)	Conversion (%) <sup>a</sup>	Yield of ester (%) <sup>b</sup>
Vinyl acetate	CF <sub>3</sub> (CF <sub>2</sub> ) <sub>8</sub> CH <sub>2</sub> OH	28	90	87
2,2,2-Trifluoroethyl butanoate	CF <sub>3</sub> (CF <sub>2</sub> ) <sub>7</sub> CH <sub>2</sub> CH <sub>2</sub> OH	23	96	85
Butanoic anhydride	CF <sub>3</sub> (CF <sub>2</sub> ) <sub>7</sub> CH <sub>2</sub> CH <sub>2</sub> OH	9	99.8	97
Pentanoic acid	CF <sub>3</sub> (CF <sub>2</sub> ) <sub>7</sub> CH <sub>2</sub> CH <sub>2</sub> OH	15	95	84

Typical conditions: acylating agent (2 mmol), alcohol (1 mmol), hexane (5 mL), PFH (5 mL) and the catalyst (CRL, 200 mg) were shaken at 300 rpm at 40 °C. <sup>a</sup> Determined by GC-MS. <sup>b</sup> The enzyme was filtered off, washed with hexane (5 mL) and PFH (5 mL) and liquid phases were partitioned after cooling (0 °C, 1 h). The hexane phase was washed with PFH (10 mL) and the combined fluorous phases were evaporated give the “fluorous” ester.

**Tab. 10.16-2.** Partitioning for some alcohols, esters and acids in the system hexane/perfluorohexane (PFH) and hexane/perfluorodecalin (PFD) determined at –10 °C

Compound	Solvent system	Partitioning (%) organic:fluorous	Partitioning coefficient $P = c_{\beta}/c_{\alpha}$
CF <sub>3</sub> (CF <sub>2</sub> ) <sub>8</sub> CH <sub>2</sub> OH	hexane/PFH	11 ± 1:89 ± 1	8 ± 1
	hexane/PFD	8 ± 2:92 ± 2	11 ± 2
CF <sub>3</sub> (CF <sub>2</sub> ) <sub>7</sub> CH <sub>2</sub> CH <sub>2</sub> OH	hexane/PFH	20 ± 1:80 ± 1	4 ± 0.1
	hexane/PFD	10 ± 1:90 ± 1	9 ± 0.1
EtMeCHCOOCH <sub>2</sub> CF <sub>3</sub>	hexane/PFH	74 ± 1:26 ± 1	0.36 ± 0.01
	hexane/PFD	80 ± 1:20 ± 1	0.25 ± 0.01
CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> COOCH <sub>2</sub> (CF <sub>2</sub> ) <sub>10</sub> CF <sub>3</sub>	hexane/PFH	15 ± 1:85 ± 1	6 ± 0.2
	hexane/PFD	13 ± 4:87 ± 4	7 ± 2
EtMeCHCOOCH <sub>2</sub> (CF <sub>2</sub> ) <sub>8</sub> CF <sub>3</sub>	hexane/PFH	30 ± 2:70 ± 2	2.3 ± 0.3
	hexane/PFD	20 ± 1:80 ± 1	4 ± 0.2
EtMeCHCOOCH <sub>2</sub> CH <sub>2</sub> (CF <sub>2</sub> ) <sub>7</sub> CF <sub>3</sub>	hexane/PFH	40 ± 1:60 ± 1	1.5 ± 0.1
	hexane/PFD	43 ± 1:57 ± 1	1.3 ± 0.1
PrMeCHCOOCH <sub>2</sub> (CF <sub>2</sub> ) <sub>8</sub> CF <sub>3</sub>	hexane/PFH	30 ± 1:70 ± 1	2.3 ± 0.1
	hexane/PFD	36 ± 1:64 ± 1	1.8 ± 0.1
PrMeCHCOOCH <sub>2</sub> CH <sub>2</sub> (CF <sub>2</sub> ) <sub>7</sub> CF <sub>3</sub>	hexane/PFH	49 ± 1:51 ± 1	1.0 ± 0.1
	hexane/PFD	49 ± 1:51 ± 1	1.0 ± 0.1
2-Methylbutyric acid	hexane/PFH	>99.9:<0.1	<0.001
	hexane/PFD	>99.9:<0.1	<0.001
2-Methylpentanoic acid	hexane/PFH	>99.9:<0.1	<0.001
	hexane/PFD	>99.9:<0.1	<0.001
2-Methylhexanoic acid	hexane/PFH	99 ± 0.5:1 ± 0.5	0.01 ± 0.001
	hexane/PFD	>99.9:<0.1	<0.001
1-Hexanol	hexane/PFH	98 ± 0.5:2 ± 0.5	0.02 ± 0.001
	hexane/PFD	95 ± 0.5:5 ± 0.5	0.05 ± 0.001

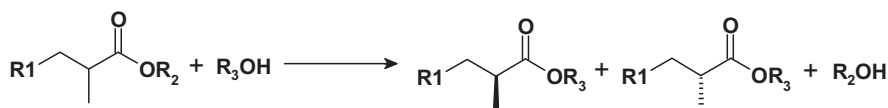
atoms within a molecule, the better the partitioning into the fluorous phase. There is some improvement of partitioning (increase of  $P$  for “fluorous” tagged molecules and decrease of  $P$  for “organic” molecules) when switching from PFH to PFD and from hexane to more polar solvents such as methanol (data not shown). However, the more polar solvents do not form a homogenous solution at lower temperatures ( $<50\text{ }^{\circ}\text{C}$ ) appropriate to the enzymatic reactions. It was also found that non-halogenated esters, acids and alcohols partition almost only to the organic phase. If a “fluorous” tagged molecule partitions 65% into the fluorous solvent, then at least four extractions of the “organic” phase are required to remove 99% of the fluorous tagged enantiomer. Conversely, if a non-tagged molecule partitions 99.8% to an “organic” phase and four extractions are performed with the same volume of the fluorous solvent, then about 1% of total mass of non-tagged molecules leaks into the combined “fluorous” phase. Clearly it is important for the success of this new lipase methodology to design substrates and products that will achieve good partitioning.

#### 10.16.2.4 Enantiomeric Partitioning After Lipase-Mediated Reactions

To exemplify enantiomeric partitioning in the mixed solvent systems the esterification reaction of racemic 2-methylalkanoic acids **1–3**, transesterification reactions of vinyl **4–5** and “fluorous” **6** esters with a range of “fluorous” and “organic” alcohols **7–9** were explored (Scheme 10.16-3). The reactions were carried out in a hexane/PFH solvent mixture and catalyzed by CRL lipase and the data are presented in Table 10.16-3.

In all of these reactions no (trans)esterification was observed without added enzyme, however after adding lipase from *Candida rugosa* (CRL) the reactions proceeded smoothly. The CRL lipase has previously been shown to mediate a kinetic resolution of 2-methyl-branched carboxylic acids and reacts faster with the *S*-enantiomer [12, 13]. The same stereochemical outcome was confirmed in this study by reference to commercially available compounds.

Activated vinyl and fluorous esters proved to be much more reactive than the corresponding acids, but the esterifications proceeded with higher enantioselectivities than the transesterifications. The longer the alkyl chain of the 2-methyl branched carboxylic acid, the slower the esterification reaction, but the better the enantiomeric discrimination. The resul-



1  $\text{R}_1 = \text{Me}$ ,  $\text{R}_2 = \text{H}$ ,

2  $\text{R}_1 = \text{Et}$ ,  $\text{R}_2 = \text{H}$ ,

3  $\text{R}_1 = \text{Pr}$ ,  $\text{R}_2 = \text{H}$ ,

4  $\text{R}_1 = \text{Me}$ ,  $\text{R}_2 = \text{CH}=\text{CH}_2$ ,

5  $\text{R}_1 = \text{Et}$ ,  $\text{R}_2 = \text{CH}=\text{CH}_2$ ,

6  $\text{R}_1 = \text{Me}$ ,  $\text{R}_2 = \text{CH}_2(\text{CF}_2)_8\text{CF}_3$ .

7  $\text{R}_3 = \text{CH}_2\text{CH}_2(\text{CF}_2)_7\text{CF}_3$ ,

8  $\text{R}_3 = \text{CH}_2(\text{CF}_2)_8\text{CF}_3$ ,

9  $\text{R}_3 = (\text{CH}_2)_5\text{CH}_3$ .

**Scheme 10.16-3.** Enantioselective esterification and transesterification reactions catalyzed by CRL in hexane/perfluorohexane solvent mixture

**Tab. 10.16-3.** Lipase-catalyzed (CRL) kinetic resolution of acids and esters **1–6** by reaction with alcohols **7–9** in hexane/perfluorohexane solvent mixture

Ester/ acid	Alcohol	Reaction time (h), (temperature °C)	Conversion (%) <sup>a</sup>	S-product ester, ee (%)	R-unreacted ester/acid, ee (%)
1	7	25 (40)	52	60 <sup>b</sup>	45 <sup>c</sup> (N = 5)
2	7	95 (40)	53	95 <sup>b</sup>	79 <sup>c</sup> (N = 5)
3	7	149 (40)	49	95 <sup>b</sup>	95 <sup>c</sup> (N = 5)
4	8	50 (30)	50	44 <sup>b</sup>	40 <sup>c</sup> (N = 1)
5	7	44 (40)	48	72 <sup>b</sup>	44 <sup>c</sup> (N = 2)
5	8	51 (30)	51	77 <sup>b</sup>	33 <sup>c</sup> (N = 2)
6	9	42 (45)	53	46 <sup>c</sup> (N = 2)	42 <sup>b</sup>

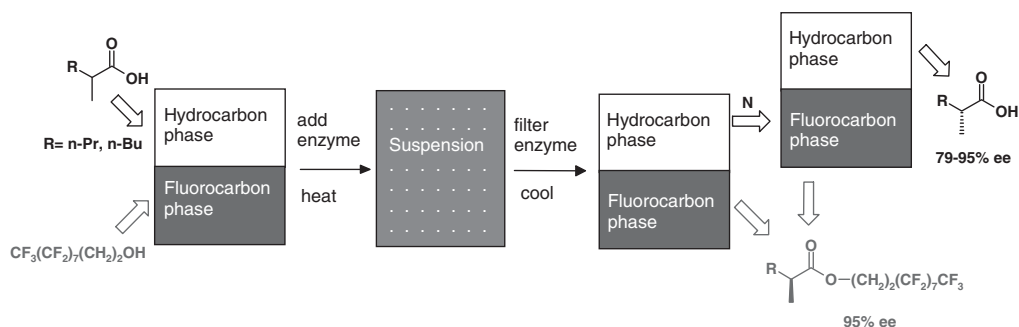
Conditions: ester/acid (1 mmol), alcohol (1 mmol), hexane (10 mL), PFH (10 mL) and the catalyst (CRL, 200 mg) were shaken at 250 rpm.

<sup>a</sup> Determined by GC-MS. The enzyme was filtered off, washed with 5 mL of hexane and 5 mL of PFH and liquid phases were partitioned after cooling (−10 °C, 1 h). The hexane phase was washed with PFH (N times with 10 mL) and the combined fluorous phases were evaporated to yield the fluorous ester. The ee values were determined by chiral GC-MS of the corresponding acid obtained by hydrolysis of:

<sup>b</sup> combined fluorous phase, <sup>c</sup> washed hexane phase.

tant enantiomeric purity of the products from each liquid phase emerges as a consequence of the inherent stereoselectivity of the enzyme with the substrate, the level of conversion of the reaction and the partitioning of the unreacted ester and the product ester between the two phases, Scheme 10.16-4.

These fluorous phase lipase-mediated reactions interestingly improved the enantioselectivity of both product and unreacted substrates compared with the reported values [13]. In that particular study, esterification reactions between acids **1–3** and various “organic” alco-

**Scheme 10.16-4.** A scheme showing the enantioselective partitioning in a lipase-mediated esterification reaction using fluorous biphasic methodology



hols in heptane at room temperature were reported. The same enzyme (CRL) was used to catalyze the reaction and the resulting esters were separated from unreacted acids by chromatography on silica gel. Our approach of introducing or removing the fluororous tag in a mixed solvent system leads to a much more straightforward separation of enantiomers. However, prolonged reaction time is needed when using less nucleophilic “fluororous” alcohols such as **7** and **8**.

To illustrate the preparative utility, a kinetic resolution of **2**, catalyzed by CRL, was conducted on a multigram (6 g) scale. Racemic **2** was esterified with **7** using a hexane/perfluorohexane solvent system and the CRL. At around 50% conversion (96 h) the enzyme was filtered off and the liquids were separated after cooling. The hexane phase was washed five times with perfluorohexane to yield unreacted (*R*)-**2** (57%, ee 79%). The product (*S*)-ester (ee 94%), together with unreacted **7**, was recovered from the combined fluororous washings and subjected to enzymatic hydrolysis in an aqueous phosphate (pH 7.0) buffer of CRL. After completion of the enzymatic hydrolysis the aqueous solution was washed with PFH to recover **7** (62%) and the residual was then acidified and extracted into ether to yield the product (*S*)-**2** (66%, ee 96%). This compound has been converted by us, using standard methods, into a natural pheromone [14].

### 10.16.3

## Conclusion

We have demonstrated that lipases operate efficiently not only in hydrophobic organic solvents, such as hexane, but also in super hydrophobic perfluorocarbons [9], such as perfluorodecalin. Owing to the extreme hydrophobicity of the perfluorocarbons with their inability to dehydrate the enzyme, lipases have been shown to be particularly active in these unnatural media. “Fluororous” alcohols and esters can act as substrates in the enzymatic reactions and it is possible to isolate the products using fluororous biphasic methodology.

Lipase-catalyzed kinetic resolutions of 2-methyl branched alkanolic acids have allowed products of opposite enantiomeric series to be separated by liquid/liquid “fluororous”/“organic” extraction. One of the main limiting factors for efficient separation of enantiomers by fluororous biphasic extraction is inefficient partitioning and care must be taken when designing good systems. The methodology was successfully applied to the multigram production of both enantiomers of 2-methylpentanoic acid. Industrial applications of this methodology will require efficient recycling protocols of the perfluororous solvents and reagents, in order to become cost effective.

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## 10.17

### Selective and Clean Reactions in Fluorinated Alcohols

Jean-Pierre Bégué, Danièle Bonnet-Delpon, and Benoit Crousse

#### 10.17.1

##### Introduction

A large number of the useful applications of fluoruous media in organic synthesis concern reactions and separation processes using perfluoroalkanes, perfluoroalkylethers or any parent non-polar solvent. Fluorinated alcohols such as hexafluoroisopropanol (HFIP) and trifluoroethanol (TFE) are not considered *stricto sensu* as fluoruous media [1]. However, the presence of one or more fluoroalkyl groups introduces specific properties to fluorinated alcohols compared with those that are non-fluorinated. They have a high ionizing power ( $Y = 1.80$  for TFE and  $3.82$  for HFIP) [2], and an "acidic" character ( $pK_a = 12.4$  for TFE and  $9.3$  for HFIP) [3]. They are strong hydrogen-bond-donors [4] and poor nucleophiles [5]. While the properties of fluorinated alcohols have been exploited in physical organic chemistry (solvolysis [5], stabilization of radical cations [6]) and for their effect on the conformation of proteins and peptides [7], it is quite surprising that they have not been exploited to any great extent for synthetic purposes. Indeed, their specific properties could induce changes in reaction courses. The objectives of our projects were thus to investigate reactions where fluorinated alcohols, used as solvents, were expected to significantly improve reaction conditions. We report here some typical examples from our investigations on oxidation reactions in fluorinated alcohols.

#### 10.17.2

##### Activation of Hydrogen Peroxide

Bearing in mind that fluorinated alcohols can be hardly oxidized [8], we initiated this project with various oxidation reactions, using hydrogen peroxide as the oxidant, with the hypothe-

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## 10.17

### Selective and Clean Reactions in Fluorinated Alcohols

Jean-Pierre Bégué, Danièle Bonnet-Delpon, and Benoit Crousse

#### 10.17.1

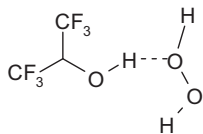
##### Introduction

A large number of the useful applications of fluorous media in organic synthesis concern reactions and separation processes using perfluoroalkanes, perfluoroalkylethers or any parent non-polar solvent. Fluorinated alcohols such as hexafluoroisopropanol (HFIP) and trifluoroethanol (TFE) are not considered *stricto sensu* as fluorous media [1]. However, the presence of one or more fluoroalkyl groups introduces specific properties to fluorinated alcohols compared with those that are non-fluorinated. They have a high ionizing power ( $\gamma = 1.80$  for TFE and 3.82 for HFIP) [2], and an "acidic" character ( $pK_a = 12.4$  for TFE and 9.3 for HFIP) [3]. They are strong hydrogen-bond-donors [4] and poor nucleophiles [5]. While the properties of fluorinated alcohols have been exploited in physical organic chemistry (solvolysis [5], stabilization of radical cations [6]) and for their effect on the conformation of proteins and peptides [7], it is quite surprising that they have not been exploited to any great extent for synthetic purposes. Indeed, their specific properties could induce changes in reaction courses. The objectives of our projects were thus to investigate reactions where fluorinated alcohols, used as solvents, were expected to significantly improve reaction conditions. We report here some typical examples from our investigations on oxidation reactions in fluorinated alcohols.

#### 10.17.2

##### Activation of Hydrogen Peroxide

Bearing in mind that fluorinated alcohols can be hardly oxidized [8], we initiated this project with various oxidation reactions, using hydrogen peroxide as the oxidant, with the hypothe-



Scheme 10.17-1

sis that the electrophilic activation of  $\text{H}_2\text{O}_2$  through a hydrogen bond could facilitate O–O bond cleavage (Scheme 10.17-1).

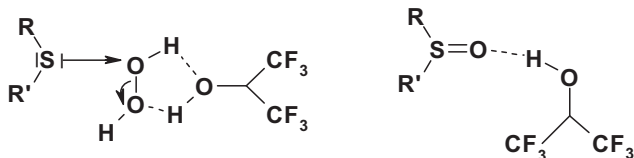
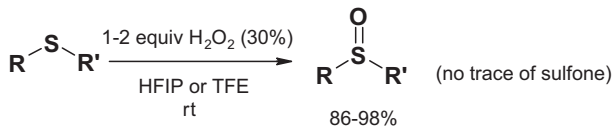
#### 10.17.2.1 Selective Oxidation of Sulfides

Among the numerous oxidizing reagents able to convert sulfides into sulfoxides, aqueous hydrogen peroxide is the cheapest and the simplest. In order to facilitate the loss of the hydroxyl group in the transition state, the reaction requires acidic conditions or the use of catalysts [9]. Conditions have to be controlled to avoid over oxidation to sulfones.

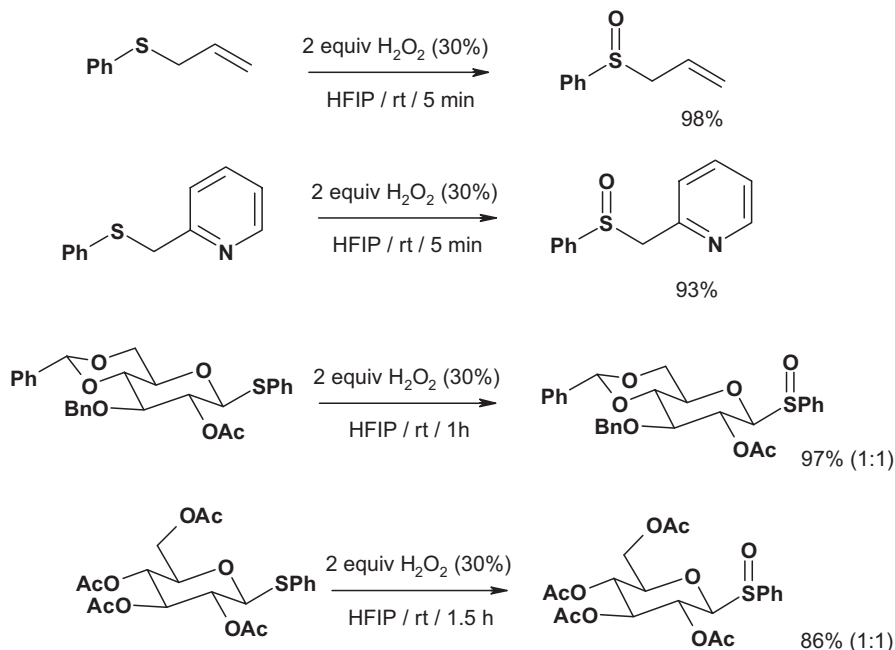
We showed that when sulfides were treated with 1 or 2 equiv of hydrogen peroxide (30%) in HFIP at room temperature, oxidation was very fast (5–15 min) and sulfoxides were obtained in quantitative yields, without any trace of sulfone [10]. The same reactions conducted in TFE were also effective and selective, but reaction times were longer.

These results clearly demonstrated the significant activation of hydrogen peroxide by fluorinated alcohols, probably due to both their high hydrogen bond donor ability and their high ionizing power. More striking is the selectivity of reactions: even when sulfoxides were again placed in the presence of 2 equiv of hydrogen peroxide (30%) in HFIP, they were recovered unchanged. This is due to the hydrogen bond between HFIP and the oxygen atom of the sulfoxide, which greatly decreases the nucleophilicity of the second available electron pair of the sulfur atom (Scheme 10.17-2) [5].

Besides the selectivity, the other great advantage of the process is the absence of any metal catalyst or salt. The reaction proceeds smoothly at room temperature, under neutral conditions and without strict control. The only effluent is water, and the solvent can be recovered by distillation. Under these conditions, a wide range of sulfides (allyl and vinyl sulfides, di-*tert*-butyl sulfide) could be selectively oxidized in high yield. The N atom of the pyridinyl group and C=C double bonds are not affected by the reagent system. Interestingly, these



Scheme 10.17-2



Scheme 10.17-3

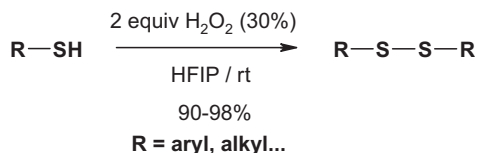
neutral conditions allowed the oxidation of the glycosyl sulfides to glycosyl sulfoxides, which was achieved in very high yield at room temperature, even when acid sensitive protecting groups are present (Scheme 10.17-3) [10b].

#### 10.17.2.2 Oxidation of Thiols to Disulfides

A large number of oxidative reagents are able to oxidize thiols to disulfides. Most of the existing methods involve the use of metal catalysts or reagents such as halogens [11]. Hydrogen peroxide is also known to oxidize some thiols to disulfides, but this requires a long reaction time and proceeds only under strong acidic or basic conditions [12].

We found that thiols were also cleanly oxidized into disulfides in quantitative yields with  $\text{H}_2\text{O}_2$ , 30% in HFIP or in TFE, without any catalyst (Scheme 10.17-4) [13]. The method presents the same advantages as for oxidation of sulfides (Scheme 10.17-4).

The oxidation reactions of sulfides to sulfoxides and of thiols to disulfides can be performed on a large scale. Fluorinated alcohols (HFIP and TFE) can be recycled by simple distillation and reused [14].



Scheme 10.17-4

## 10.17.3

**Epoxidation****10.17.3.1 With Aqueous Hydrogen Peroxide**

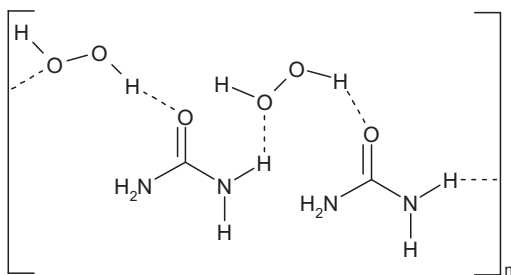
We have been interested in the epoxidation reaction by activation of hydrogen peroxide by HFIP. To our knowledge the first reports of the use of hexafluoroisopropanol as a solvent in the epoxidation reaction with  $\text{H}_2\text{O}_2$  60%, are patents [15]. A transition metal catalyst (W, As, Sb, Bi) was required.

Since then, other examples of epoxidation reactions in HFIP or TFE with hydrogen peroxide in the presence of metal catalysts have been reported ( $\text{H}_2\text{AsPhO}_3$  [16],  $\text{HReO}_4$  [16],  $\text{MeReO}_3$  [17, 18]) or non metal catalysts such as perfluoroketones [19, 20].

More recently, Neimann and Neumann [21] and Sheldon and coworkers [22] took advantage of the activation of hydrogen peroxide by fluorinated alcohols to perform epoxidation reactions in HFIP or TFE without any catalyst. In most of these examples the reaction required  $\text{H}_2\text{O}_2$  60% and were sometimes conducted under solvent reflux.

**10.17.3.2 With Urea–Hydrogen Peroxide (UHP):  $\text{H}_2\text{O}_2$  100%**

From a synthetic point of view, a search for safer conditions appeared to be essential. The urea–hydrogen peroxide complex (UHP) has been reported to be easy to handle and a safe source of anhydrous hydrogen peroxide [23]. It is a white crystalline solid, formed by strong hydrogen bonds between urea and hydrogen peroxide in a 1:1 stoichiometry (Scheme 10.17-5). However, such high stability could be a drawback to its potential chemical reactivity towards substrates. Indeed additions of anhydrides or catalysts to UHP are required to achieve oxidation reactions [23, 24]. The results described above prompted us to investigate the effect of fluorinated alcohols on the activation of hydrogen peroxide from UHP.



**Scheme 10.17-5.** UHP complex

As a preliminary study, epoxidation of the highly reactive cyclooctene was evaluated and performed using UHP in various solvents (Table 10.17-1) [25].

Among all of the solvents used, UHP was soluble only in HFIP and MeOH, and HFIP was the sole solvent where epoxidation was efficient, with a 100% conversion after 10 h at room temperature. UHP was not soluble in other commonly used reaction solvents ( $\text{CH}_2\text{Cl}_2$ , MeCN and AcOEt) and when reactions were carried out, cyclooctene remained unchanged even after 24 h. In addition, UHP was not soluble in TFE, and cyclooctene af-

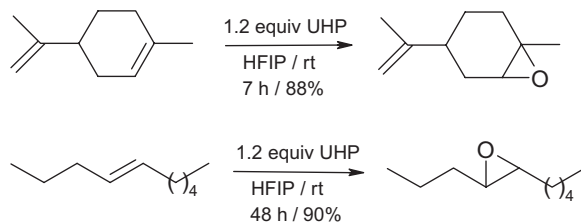
**Tab. 10.17-1.** The effect of solvent on the epoxidation<sup>a</sup> of cyclooctene with UHP

Entry	Oxidant	Solvent	Solubility of UHP	Time (h)	Conversion (%) <sup>b</sup>
1	UHP	HFIP	yes	10	100 <sup>c</sup>
2	H <sub>2</sub> O <sub>2</sub> 30%	HFIP	—	24	79
3	UHP	TFE	no	24	4
4	UHP	CH <sub>2</sub> Cl <sub>2</sub>	no	24	0
5	UHP	MeCN	no	24	0
6	UHP	AcOEt	no	24	0
7	UHP	MeOH	yes	24	0

<sup>a</sup> Conditions: cyclooctene (1 mmol), UHP or H<sub>2</sub>O<sub>2</sub> 30% aq. (3 mmol), HFIP (3 mL), 25 °C. <sup>b</sup> Epoxide; measured by GC. <sup>c</sup> Yield isolated: 91%.

forded only 4% of the epoxide after 24 h, whilst it could undergo epoxidation with aqueous H<sub>2</sub>O<sub>2</sub> in this solvent [21]. Conversely with methanol, despite the complete dissolution of UHP, cyclooctene remained unchanged, confirming that although methanol is able to dissociate the complex, it is not able to catalyze cleavage the covalent O–O bond.

HFIP has the unique ability of combining the two requirements for efficient epoxidation with UHP: solubility of the UHP complex and activation of hydrogen peroxide. Under these conditions di- and trisubstituted olefins underwent epoxidation in high yields under safe and mild conditions without a catalyst (Scheme 10.17-6) [25].

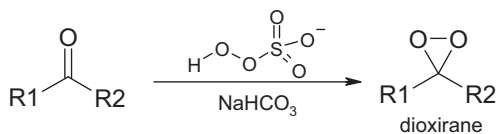
**Scheme 10.17-6**

### 10.17.3.3 Activation of Dioxirane: Epoxidation Reactions with Oxone<sup>®</sup> as Oxidant

This ability of fluorinated alcohols to cleave the O–O bond of peroxide could be applied to the activation of dioxiranes, which are excellent oxidizing reagents for the epoxidation of olefins. They are generated most often *in situ* from the parent ketone with Oxone<sup>®</sup> under basic conditions (Scheme 10.17-7) [26].

Following along these lines, fluoro analogs of acetone have been shown to be precursors of very efficient epoxidation reagents [26].

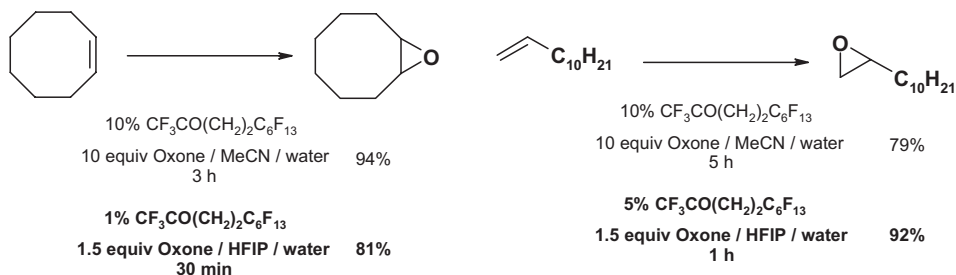
We initially designed new models of fluoroketones [27] as precursors of dioxiranes and found that the most efficient ketone for epoxidation is CF<sub>3</sub>CO(CH<sub>2</sub>)<sub>2</sub>C<sub>6</sub>F<sub>13</sub>. Epoxidation re-



Scheme 10.17-7

actions are usually conducted in an acetonitrile/water system [28], and have been investigated in this study using HFIP instead of acetonitrile as the solvent.

Both systems (HFIP/water and MeCN/water) were evaluated in epoxidation reactions of cyclooctene and the poorly reactive dodecene with this new perfluoro ketone [CF<sub>3</sub>CO(CH<sub>2</sub>)<sub>2</sub>C<sub>6</sub>F<sub>13</sub>] as the catalyst (Scheme 10.17-8) [27]. With the use of HFIP we found new conditions where the reactions were largely improved.



Scheme 10.17-8

HFIP introduced the following advantages: a decreased reaction rate, and a smaller amount of Oxone<sup>®</sup> was required (1.5 equiv instead of 10 equiv in MeCN). Since under these new conditions the fluoroketone is very stable towards Baeyer-Villiger decomposition, the catalytic amount required could be decreased to 1% for reactive olefins and 5% for poorly reactive ones. A number of olefin substrates provided epoxides in good yields (Table 10.17-2).

Besides the activation of the O–O bond cleavage by strong hydrogen bonding with HFIP, the enhanced solubility of the ketone can also be evoked to explain the efficiency of the system (Scheme 10.17-9).


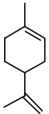
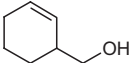
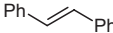
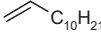
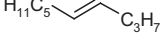
#### 10.17.3.4 With Oxygen

Fluorous solvents are known to solubilize molecular oxygen. With this in mind we investigated the influence of fluorinated solvents on aerobic epoxidation, with the hypothesis that the high solubility of molecular oxygen in fluorocarbons should favor reactions. In the course of that study, epoxidation reactions were carried out, for comparison, in various fluorinated solvents with Mn(OAc)<sub>3</sub> as the catalyst, oxygen as the oxidant, and pivalaldehyde as the co-reductant [29].

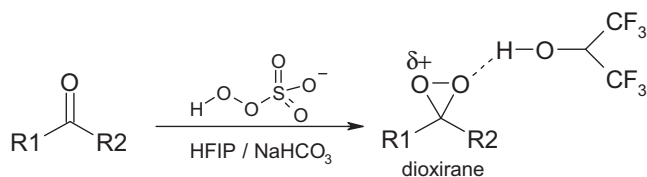
In all of the solvents used, but most efficiently in the perfluorinated tetrahydrofuran FC-75, the electron-rich di- and trisubstituted olefins readily underwent epoxidation reactions,



Tab. 10.17-2. Catalytic epoxidation reaction in HFIP/water with the ketone<sup>a</sup>

Entry	Olefin	Ketone (mol%)	Addition time (h)	Time (h) <sup>b</sup>	Epoxide (%) <sup>c</sup>
1		1	2	0.3	81
2		1	4	0.5	71 <sup>d</sup>
3		1	4	0.5	68 <sup>e</sup>
4		5	4	0.5	93
5		5	4	0.5	92
6		5	4	0.5	96

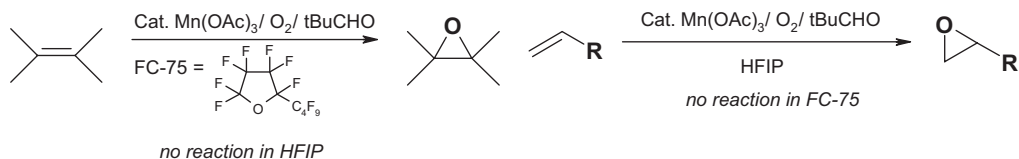
<sup>a</sup> Reactions were performed as follows: substrate (1.8 mmol), ketone 2 (1% mmol or 5% mmol) and NaHCO<sub>3</sub> (10.8 mmol) were placed in a 3/1 mL (entry 1–3, 6) or 12/4 mL (entry 4, 5) mixture of HFIP: water (EDTA 10<sup>−4</sup> mol L<sup>−1</sup>) under vigorous stirring. A solution of Oxone<sup>®</sup> (2.7 mmol) dissolved in 10 mL of water was added via a syringe pump over the time indicated above. <sup>b</sup> After addition of Oxone. <sup>c</sup> Yield of isolated product. <sup>d</sup> 10% of starting material recovered, 1:1 mixture of diastereoisomers. <sup>e</sup> 1.5:1 mixture of diastereoisomers (not determined).



Scheme 10.17-9

while terminal olefins were poorly reactive. The most striking result of this study was the opposite reactivity that olefins exhibited when aerobic epoxidation was performed in hexafluoroisopropanol: terminal olefins easily reacted to provide high yields of epoxides, while di- and trisubstituted olefins were fairly unreactive (Scheme 10.17-10).

In addition to the synthetic significance of this result for selective epoxidations, it clearly indicates that, compared with other solvents, HFIP induces a change in the mechanism of epoxidation. However, unlike the role of fluorinated alcohols on O–O bond cleavage, in this case the role of HFIP has not been elucidated.



Scheme 10.17-10

## 10.17.4

## Conclusion

We have reported that HFIP and TFE are excellent solvents that have enabled new efficient and selective processes for oxidation reactions to be developed. Their specific properties, with the combination of high hydrogen bonding donor ability, low nucleophilicity, and high ionizing power, allowed reactions to proceed under neutral and mild conditions, where the use of additive reagents or metal catalysts is usually required. Providing they are used as solvents, HFIP and, to a lesser extent TFE, are able to facilitate O–O bond cleavage of peroxides. In this way new clean processes could be described: selective oxidation reactions with oxygen, aqueous hydrogen peroxide, hydrogen peroxide complexed with urea (UHP), and Oxone. These systems were used for oxidation of sulfides to sulfoxides, of thiols to disulfides and for epoxidation reactions.

The procedures offer several advantages, such as mild and neutral reaction conditions, operational simplicity and ease of isolation of products along with good yields of the products. In most cases there are no effluents after reaction, and the fluorinated alcohols can be recovered and reused for other reactions.

## Acknowledgements

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## 10.18

### Liquid/Solid Catalyst-Recycling Method without Fluorous Solvents

Kazuaki Ishihara and Hisashi Yamamoto

#### 10.18.1

##### Introduction

Over the past 5 years or more, fluorous biphasic catalysis has emerged as an environmentally attractive alternative to traditional catalysis methods [1]. Fluorous techniques take advantage of the temperature-dependent miscibility of organic and perfluorocarbon solvents to provide easier isolation of products and recovery of a fluorinated catalyst. The large-scale use of fluorous solvents, however, has drawbacks: cost and concern over environmental persistence.

The fluorous biphasic technique involves dissolving a catalyst with long fluorinated alkyl chains in a perfluorocarbon. The reactants are added to an organic solvent that is immiscible with the perfluorocarbon at room temperature, forming a second phase. On heating, the two phases mix and the reaction occurs; on cooling, the fluorinated and organic layers separate. The organic phase can be removed and the product isolated, while the fluorinated catalyst/solvent phase can be reused.

In 2001, we [2] and Gladysz's group [3] independently reported that the fluorous solvent can be bypassed by designing fluorinated catalysts that themselves have a temperature-dependent phase miscibility, that is, solubility, in ordinary organic solvents.

#### 10.18.2

##### Fluorous Catalysis without Fluorous Solvents

We have developed a direct amide condensation catalyst, 3,5-bis(perfluorodecyl)phenylboronic acid (**1**), which can be recovered without using any fluorous solvents [2]. Arylboronic acids bearing electron-withdrawing substituents at the aryl group behave as water-, acid-, and base-tolerant thermally stable Lewis acids and can be easily handled in air. 3,5-bis-(Trifluoromethyl)phenylboronic acid (**2**) and 3,4,5-trifluorophenylboronic acid (**3**) are highly effective catalysts for the amide condensation of amines (1 equiv) and carboxylic acids (1

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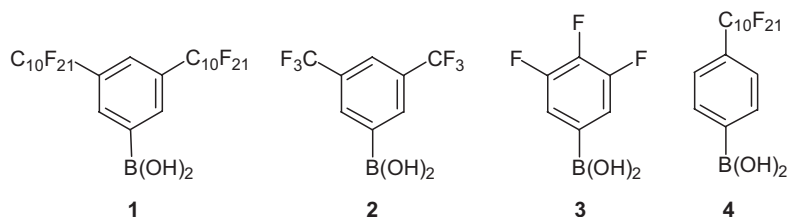
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**Scheme 10.18-1.** Amide condensation catalysts

equiv) [4]. To the best of our knowledge, this is the first example of a catalytic and direct amide condensation which does not require excess amounts of the substrates. Most of the above homogeneous catalytic reactions require relatively large quantities of arylboronic acid catalysts (1–20 mol%), and trace amounts of the catalysts must be removed from the reaction products. This hampers the application of this methodology to large-scale syntheses. Therefore, we have designed phenylboronic acids **1** and **4** bearing perfluorinated ponytails based on the direct coupling of fluoroalkyl iodides with halobenzenes. Their fluorous boronic acids can be easily recovered by the fluorous biphasic technique (Scheme 10.18-1) [2].

The catalytic activities of arylboronic acids **1–4** (5 mol%), which promote the model reaction of 4-phenylbutyric acid (1 equiv) with 3,5-dimethylpiperidine (1 equiv) in toluene at azeotropic reflux with removal of water (4 Å molecular sieves in a Soxhlet thimble) for 1 h, and their recoverabilities by extraction with perfluoromethylcyclohexane are shown in Table 10.18-1. As expected, **1** is more active than **4**, and is recovered in quantitative yield by ex-

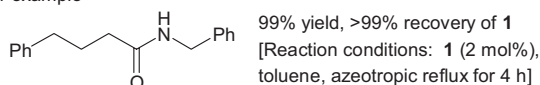
**Tab. 10.18-1.** Catalytic activities and recovery of arylboronic acid for the direct amide condensation

$\text{ArB(OH)}_2$	Yield of amide (%) <sup>a</sup>	Recovery of $\text{ArB(OH)}_2$ (%) <sup>b</sup>
<b>2</b>	59	0
<b>3</b>	60	0
<b>4</b>	39	57
<b>1</b>	47 (95) <sup>c</sup>	>99
$\text{PhB(OH)}_2$	23	0
— <sup>d</sup>	<2	—

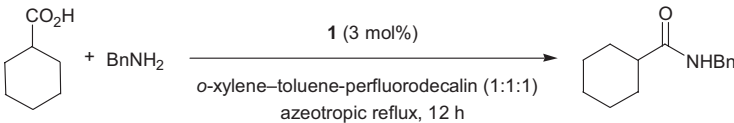
<sup>a</sup> Isolated yield. <sup>b</sup> Extraction with perfluoromethylcyclohexane. <sup>c</sup> Yield after heating at azeotropic reflux for 15 h is indicated in parenthesis.

<sup>d</sup> No catalyst was added.

Another example



**Tab. 10.18-2.** Recovery and reuse of **1** in the recyclable fluororous immobilized phase<sup>a</sup>

					
Cycle <sup>a</sup>	1	2	3	4	5 <sup>c</sup>
Conversion (%) <sup>b</sup>	>99 (99)	>99	>99	>99 (98)	>99 (99)

<sup>a</sup> Reaction conditions: *o*-xylene (2.5 mL), toluene (2.5 mL), and perfluorodecalin (2.5 mL). After the reaction, a solution of the amide in the upper phase was decanted and **1** in the lower phase was recycled successively. <sup>b</sup> Values in parenthesis refer to the isolated yields.

<sup>c</sup> Catalyst **1** was recovered in 98% yield from the perfluorodecalin phase.

traction with perfluoromethylcyclohexane. Although **2** and **3** are more active than **4**, they cannot be recovered by extraction with any of the fluororous solvents. The amide condensation proceeds cleanly in the presence of 5 mol% of **1**, the desirable amide has been obtained in 95% yield by azeotropic reflux for 15 h. In addition, the corresponding *N*-benzylamide has been obtained in quantitative yield by heating 4-phenylbutyric acid with benzylamine in the presence of 2 mol% of **1** under azeotropic reflux conditions for 4 h.

Based on the above results, the reuse of **1** has been examined for the direct amide condensation reaction of cyclohexanecarboxylic acid and benzylamine in a 1:1:1 mixture of *o*-xylene, toluene, and perfluorodecalin under azeotropic reflux conditions with removal of water for 12 h (Table 10.18-2 and Figure 10.18-1) [5]. After completion of the reaction, the homogeneous solution is cooled to ambient temperature to be separated in the biphasic mode of *o*-xylene/toluene or perfluorodecalin. The corresponding amide is obtained in quantitative yield from the organic phase. Catalyst **1** can be completely recovered from the fluororous phase and reused in the recyclable fluororous immobilized phase.

Catalyst **1** is insoluble in toluene and *o*-xylene at room temperature even in the presence of carboxylic acids, amines, and amides. However, the amide condensation catalyzed by **1** proceeds homogeneously under reflux conditions. To demonstrate this advantage of **1** with respect to solubility, we have attempted to reuse **1** (5 mol%) ten times for the amide condensation reaction of cyclohexanecarboxylic acid with benzylamine (Table 10.18-3 and Figure 10.18-2) [6]. After heating the reaction mixture at reflux with removal of water for 3 h, the mixture is allowed to stand at ambient temperature for 1 h to precipitate **1**. The liquid phase of the resultant mixture is decanted and the residual solid catalyst **1** is reused without isolation. No loss of activity has been observed for the recovered catalyst, and 26% of **1** remains in the flask in the tenth reaction. This means that 88% of **1** has been retained in each cycle. The total isolated yield of the amide which is obtained in ten reactions is 96%. Moreover, pure compound **1** can be recovered in 97% yield as a white solid from the above reaction mixture by filtration and washing with toluene [6].

Gladyś's group has also reported the temperature-dependent solubility of the solid phosphine catalyst **5** in octane [3]. Between 20–80 and 20–100 °C, **5** exhibits ca. 60- and 150-fold increases of solubility in octane. Although octane is one of the best organic solvents for dis-

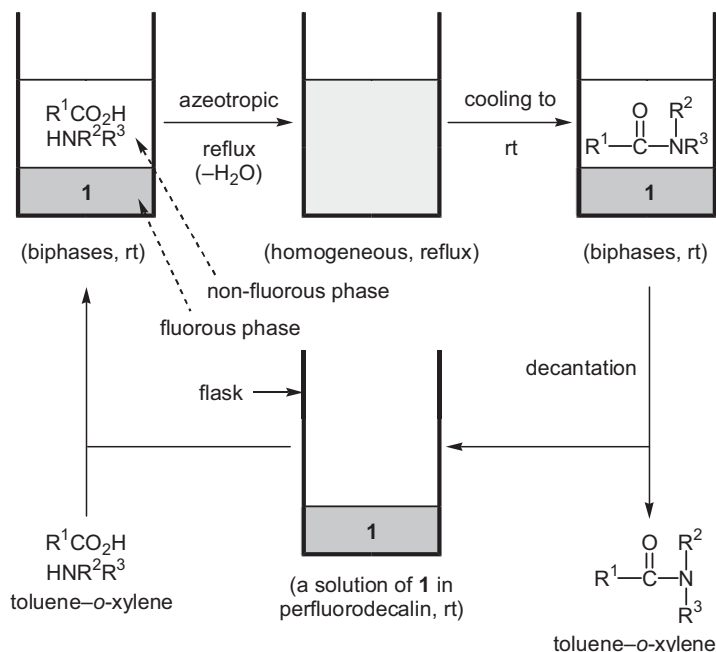
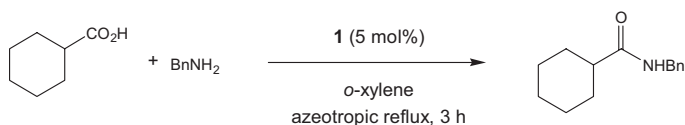


Fig. 10.18-1. Recycling system of **1** in the recyclable fluorous immobilized phase

solving nonpolar fluorous compounds, little **5** can be detected at 0 °C by GC (0.31 mM) or  $^{31}P$  NMR. At 20 °C, millimolar concentration levels are present (1.13 mM, GC; 0.97 mM, NMR). A distinct jump in solubility has been observed near the melting point (19.6 mM, 50 °C), followed by continued increases (63.4 mM, 80 °C; 157 mM, 100 °C).

Such a dramatic solubility/temperature dependence suggests an obvious catalyst method. The method has been tested by carrying out a series of additions of alcohols to methyl pro-

Tab. 10.18-3. Reuse of catalyst **1** for amide condensation of cyclohexanecarboxylic acid with benzylamine



Total (10 times): 96% isolated yield

Use of <b>1</b> <sup>a</sup>	1	2	3	4	5	6	7	8	9	10
Conversion (%)	>99	>99	>99	>99	99	>99	>99	>99	>99	>99

<sup>a</sup> Reaction conditions: **1** (0.05 mmol), cyclohexanecarboxylic acid (1 mmol), benzylamine (1 mmol), xylene (5 mL). After the reaction, the solution was decanted and the residual catalyst **1** was reused without isolation (see, Figure 9.3). <sup>b</sup> Recovered catalyst **1** was used successively (Use 2, 3, 4, ...).



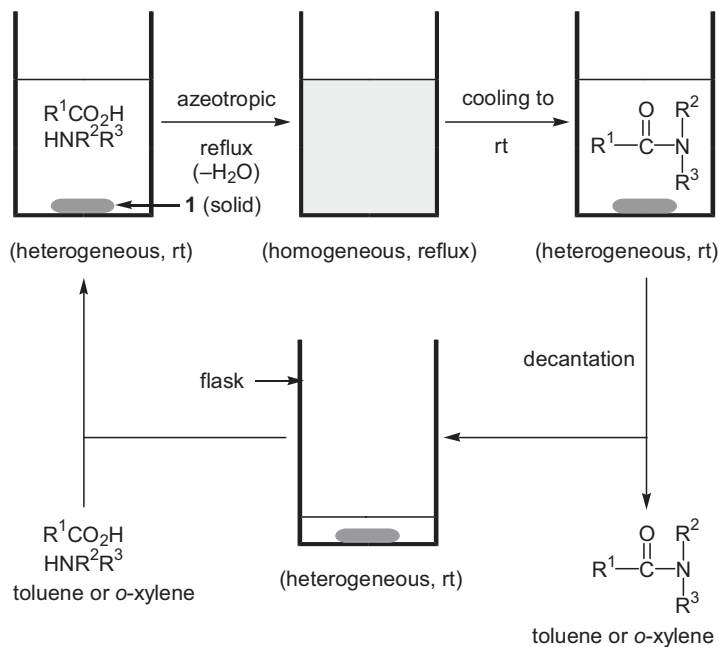


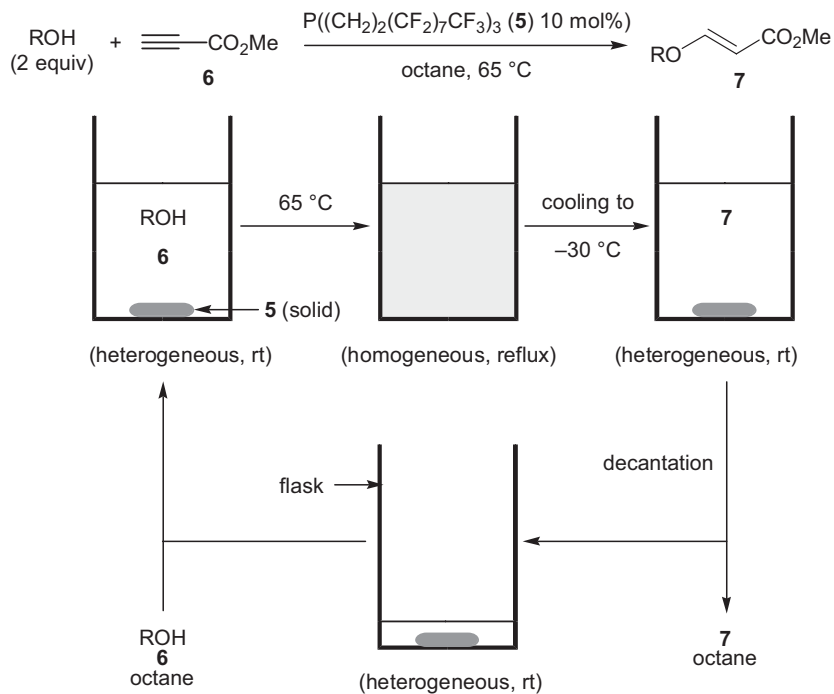
Fig. 10.18-2. Recovery of **1** by decantation and its reuse without isolation

piolate (**6**) in octane. Catalyst **5** (10 mol%), benzyl alcohol (2 equiv), and **6** are combined in octane (65 mM in **6**). The sample is kept at 65 °C (8 h) and cooled to –30 °C (arbitrary temperature of a convenient freezer). The precipitated catalyst (in some cases orange-colored) is isolated by decantation. GC analysis of the supernatant indicates an 82% yield of **7**. The recovered catalyst has been used for four further cycles without deterioration in yield, as summarized in Figure 10.18-3.

In a further refinement, Gladysz's group has shown that the above reaction of benzyl alcohol with **6** can be made even greener by not using a solvent at all [3]. Raising the temperature of a mixture of the neat reactants and solid catalyst above the catalyst's melting point of 47 °C yields the addition product. The solid catalyst can be recovered at room temperature and is recyclable with yields consistently above 95%.

We have developed a fluorous super Brønsted acid catalyst, 4-(1*H*,1*H*-perfluorotetradecanoxy)-2,3,5,6-tetrafluorophenylbis(trifluoromethanesulfonyl)methane (**8**), which can be recycled by applying liquid/solid phase separation without fluorous solvents [8] and an organic-solvent-swallowable resin-bound super Brønsted acid, polystyrene-bound tetrafluorophenylbis(trifluoromethanesulfonyl)methane (**9**) [9]. These super Brønsted acids can be synthesized by using the *para*-substitution reaction of pentafluorophenylbis(trifluoromethanesulfonyl)methane (**10**) with nucleophiles such as sodium alkoxide and alkyllithium as a key step (Scheme 10.18-2).

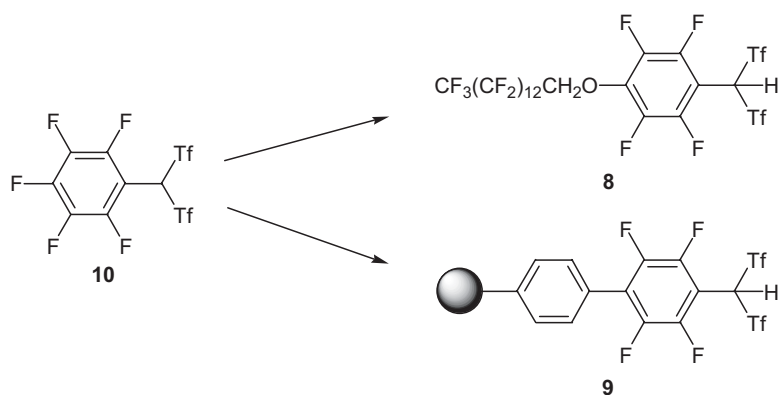
Pentafluorophenylbis(triflyl)methane **10** (47 wt% F) is soluble in most organic and fluorous solvents. However, it is possible to achieve high fluorous-phase affinity for 4-alkoxy-



The addition of  $\text{PhCH}_2\text{OH}$  to **6**:

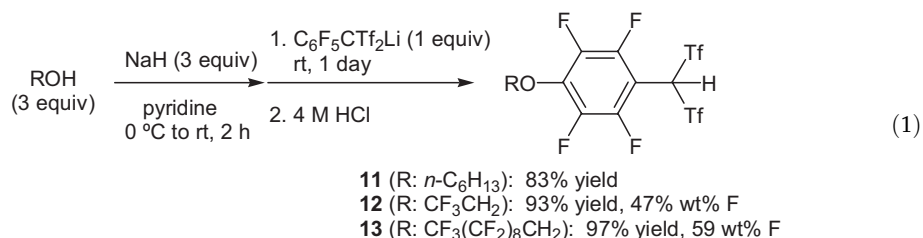
Cycle	1	2	3	4	5
Yield (%)	82	82	80	81	75

Fig. 10.18-3. Recovery of **5** by decantation and its reuse without isolation



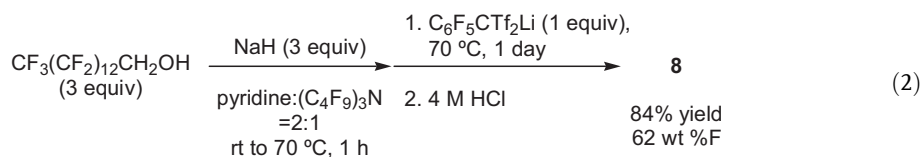
Scheme 10.18-2. Preparation of **8** and **9** from **10** via nucleophilic *para*-substitution reactions

2,3,5,6-tetrafluorophenylbis(trifluoromethanesulfonyl)methane by appending “a fluoros ponytail”,  $\text{OCH}_2(\text{CF}_2)_n\text{CF}_3$  group, to the *para*-position of **10** via the nucleophilic *para*-substitution reaction. In preliminary experiments, the preparation of 4-hexanoxo- and 4-trifluoroethanoxo-2,3,5,6-tetrafluorophenylbis(trifluoromethanesulfonyl)methanes, **11** and **12**, have been examined by reacting a lithium salt of **10** with the corresponding sodium alkoxides in pyridine at room temperature [Eq. (1)] [9]. As expected, **11** and **12** have been obtained in respective yields of 83% and 93%. Fluorous Brønsted acid **13** (59 wt% F) has been also prepared in 97% yield from a lithium salt of **10** and sodium 1*H*,1*H*-perfluorodecanoxide.



Their  $\text{pK}_a$  values in glacial acetic acid have been measured by the  $^1\text{H}$  NMR method of Schantl et al. (Table 10.18-4) [8, 10]. The Brønsted acidity of **11** is less than that of conc.  $\text{H}_2\text{SO}_4$ , while **12** is a superacid like **10**.

To obtain a higher fluorinated Brønsted acid, **3d** (62 wt% F) has been prepared in 84% yield by heating a lithium salt of **1** and sodium 1*H*,1*H*-perfluorotetradecanoxide in a 2:1 mixed solvent of pyridine and perfluorotributylamine at 70 °C [Eq. (2)]. Perfluorotributylamine has been added to partially dissolve sodium 1*H*,1*H*-perfluorotetradecanoxide.



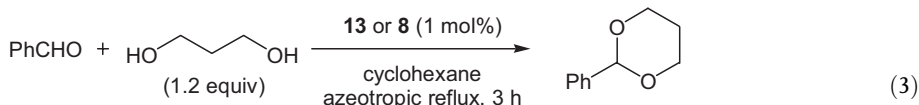
The acetalization of benzaldehyde with 1,3-propanediol has been examined in the presence of 1 mol% of a fluoros super Brønsted acid, **13** or **8**, at azeotropic reflux in cyclohexane with the removal of water for 3 h [Eq. (3)]. Both solid acids are soluble in cyclo-

Tab. 10.18-4. Brønsted acidities of arylbis(trifluoromethanesulfonyl)methanes

	<b>11</b>	<i>conc.</i> $\text{H}_2\text{SO}_4$	<b>12</b>	<b>1</b>
$^1\text{H}$ NMR (ppm) <sup>a</sup>	6.19	–	6.23	6.21 <sup>b</sup>
$\text{pK}_a$ in AcOH	11	7.5 <sup>b</sup> (7.0) <sup>c</sup>	6.6	1.5 <sup>b</sup>

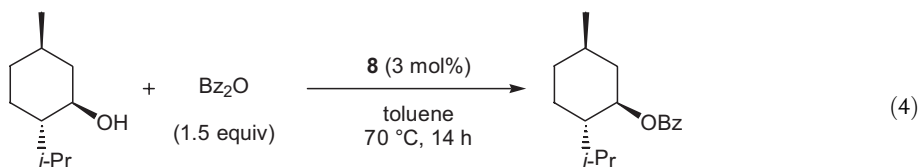
<sup>a</sup>  $^1\text{H}$  NMR chemical shift observed for an acidic proton of  $\text{ArCHTf}_2$  in  $\text{CDCl}_3$  is indicated. <sup>b</sup> Reference 8a. <sup>c</sup> Reference 10.

hexane under reflux conditions, and promote the reaction well to give the desired acetal in good yields. Post-reaction, **13** has been recovered in 96% yield by precipitation at room temperature. However, **13** can not be recovered in the same manner. Besides this acetalization, **8** is also effective as a fluorous catalyst for the acylation of *l*-menthol with benzoic anhydride [Eq. (4)] and esterification of 3-phenylpropionic acid in methanol [Eq. (5)] [11].

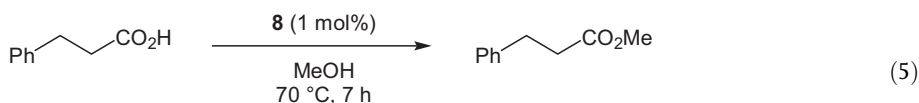


The use of **13**: Acetal: 74% yield; recovery of **13**: failed

The use of **8**: Acetal: 86% yield; recovery of **8**: 96%

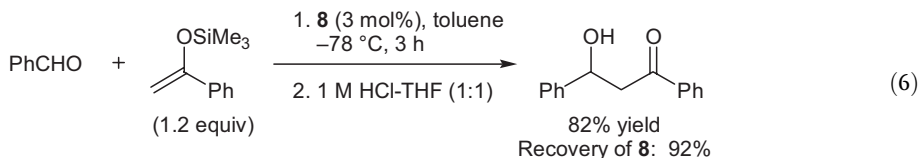


>99% yield; recovery of **8**: 70%

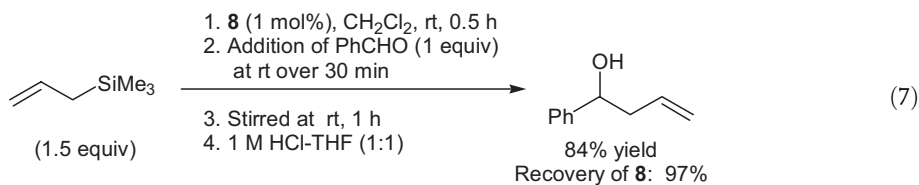


>99% yield; recovery of **8**: 68%

Fluorous solid catalyst **8** is highly effective for the Mukaiyama aldol reaction [Eq. (6)] and the Sakurai-Hosomi allylation reaction [Eq. (7)]. These reactions have been performed at  $-78^\circ\text{C}$  and rt, respectively, under heterogeneous conditions. Post-reaction, **8** has been recovered in high yield by decanting the liquids at room temperature.



82% yield  
Recovery of **8**: 92%

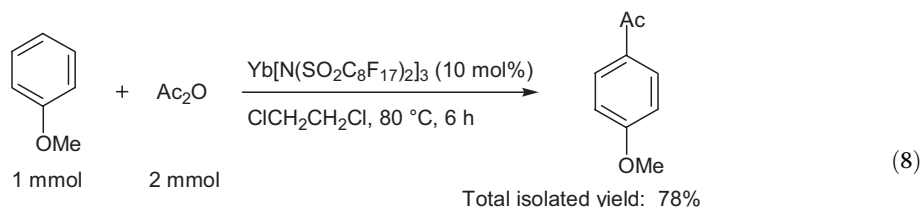


84% yield  
Recovery of **8**: 97%

Pentafluorophenylbis(trifluoromethanesulfonyl)methane **10** offers a great advantage over other analogous super Brønsted acids such as tris(trifluoromethanesulfonyl)methane, trifluoromethanesulfonimide, and trifluoromethanesulfonic acid from the perspective of synthetic modification. Barrett's group [12] and Mikami's group [13] have independently re-

ported metal tris(perfluoroalkanesulfonyl)methides as fluorous Lewis acids. Similarly, it may be possible to design pentafluorophenylbis(perfluoroalkanesulfonyl)methanes. However, it is synthetically more concise and practical to append 1*H*,1*H*-perfluoroalkoxy groups to **10** by a *para*-substitution reaction. In addition, solid acids **8** and **9** are more active catalysts than perfluoresulfonic acids such as Nafion<sup>®</sup> [8].

Mikami's group has also demonstrated the advantage of the fluorous super Lewis acids such as lanthanide tris(perfluorooctanesulfonyl)methide and perfluorooctanesulfonimide complexes with respect to temperature-dependent solubility [13b]. For example, these complexes can be reused for the Friedel-Crafts acylation reaction without fluorous solvents [Eq. (8)]. After heating the reaction mixture of anisole with acetic anhydride in 1,2-dichloroethane in the presence of ytterbium perfluorooctanedulfonimide (10 mol%) at 80 °C for 6 h, the mixture is allowed to stand at –20 °C for 30 min to precipitate the ytterbium complex. The liquid phase is decanted and the residual lanthanide complex is reused without isolation. No loss of activity is observed for the catalyst recovered. The total isolated yield of the product, which is combined from the three runs, is 78%.



Use of catalyst	1	2	3
% Conversion	>85	>85	>85

### 10.18.3

#### Outlook

One-solvent protocols of the type described above may be applicable to a wide variety of fluorous catalysts. It is probably not always necessary to traverse a melting point to achieve a sufficient solubility gradient. Nonetheless, one would expect that melting points of fluorous compounds can be engineered by shortening, lengthening, or branching the ponytails and by increasing/decreasing their numbers. The phase properties of a catalyst family could be optimized and tailored to a broad portfolio of solvents.

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- 5 Perfluorodecaline is not miscible with a non-fluorous solvent, toluene or *o*-xylene, even under reflux conditions.
- 6 For recent examples of precipitable catalysts, see: BERGBREITER, D. E.; KOSHITI, N.; FRANCHINA, J. G.; FRELS, J. D. *Angew. Chem., Int. Ed. Engl.* **2000**, 39, 1040. (b) JANDA, K. D.; REGER, T. S. *J. Am. Chem. Soc.* **2000**, 122, 6029. (c) BOSANAC, T.; YANG, J.; WILCOX, C. S. *Angew. Chem., Int. Ed. Engl.* **2001**, 40, 1875.
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- 9 BYRON, D. J.; MATHARU, A. S.; WILSON, R. C. *Liq. Cryst.* **1995**, 19, 39. Pyridine is more effective as a solvent in the *para*-substitution reaction of a lithium salt of **10** with sodium alkoxides. In contrast, this reaction does not occur smoothly in diethyl ether which is effective in the *para*-substitution reaction with alkyl-lithiums [8].
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- 11 In the case of the esterification, the resultant solution is concentrated under reduced pressure, and the crude compounds are diluted in hexane to precipitate **8**. Thus, **8** is recovered by filtration.
- 12 BARRETT, A. G. M.; BRADDOCK, D. C.; CATTERICK, D.; CHADWICK, D.; HENSCHKE, J. P.; MCKINNELL, R. M. *Synlett* **2000**, 847.
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## 10.19

### Microwave-Assisted Fluorous Chemistry

Kristofer Olofsson and Mats Larhed

#### 10.19.1

##### Introduction

Despite the fact that most of the time chemistry can be a fascinating and intellectually stimulating choice of occupation, it is no secret to the initiated that many reactions can be both time-consuming and involve tedious workup procedures. In particular, in the context of applying small-scale reactions in modern drug discovery and lead identification and optimization projects, the process of making chemical reactions faster and easier to purify is of paramount importance [1].

Microwave chemistry is a powerful and effective means of meeting the challenge to increase the speed of reactions [1–5]. The number of reports on microwave-assisted chemistry has increased rapidly during recent years [4] and as the understanding of the *in situ* superheating mechanisms behind the success of microwave heating has been clarified [6], this new technique has reached a level of acceptance in the chemical community that would have been difficult to foresee ten years ago. These achievements are followed hand in hand by the development of commercially available microwave reactors designed especially for

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  - 8 (a) ISHIIHARA, K.; HASEGAWA, A.; YAMAMOTO, H. *Angew. Chem., Int. Ed. Engl.* **2001**, 40, 4077. (b) ISHIIHARA, K.; HASEGAWA, A.; YAMAMOTO, H. *Synlett* **2002**, 1296.
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Microwave chemistry is a powerful and effective means of meeting the challenge to increase the speed of reactions [1–5]. The number of reports on microwave-assisted chemistry has increased rapidly during recent years [4] and as the understanding of the *in situ* superheating mechanisms behind the success of microwave heating has been clarified [6], this new technique has reached a level of acceptance in the chemical community that would have been difficult to foresee ten years ago. These achievements are followed hand in hand by the development of commercially available microwave reactors designed especially for

chemical synthesis, which are thus very different from the domestic microwave ovens used in the infancy of microwave chemistry. Computer controlled single-mode applicators have greatly increased the efficiency, safety and reproducibility of reactions conducted under microwave heating [7] even though the limited reaction scale is a constraint to the methodology [4]. Modern multi-mode reactors have also been applied in parallel synthesis [8].

Our own interest in homogeneous catalysis has revealed that microwave heating is advantageous in many areas of transition metal-catalyzed organic chemistry and the recent advances in this field have been reviewed [2, 5].

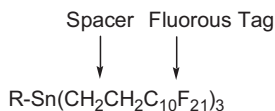
Having established that focused microwave heating is a reliable tool for increasing the speed of performing chemistry, we, together with Prof. Curran's group, undertook to investigate the combination of fluorous [9] and microwave chemistry with the aim of introducing new protocols for both fast organic transformations and uncomplicated workup procedures. The importance of having easy and reliable separation protocols should not be underestimated as today it is easy, not only in microwave chemistry but also in combinatorial and parallel synthesis, to generate vast amounts of crude products in a short time.

#### 10.19.2

#### Introducing Fluorous Groups in Microwave-Assisted Organometallic Chemistry

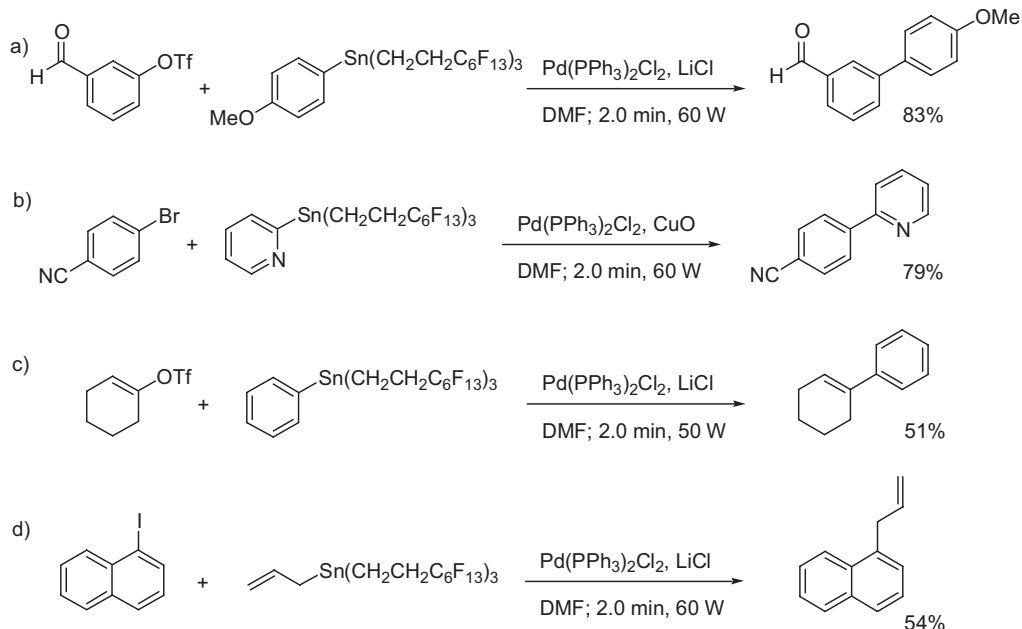
Following the rationale presented by Curran of using fluorous tags to ease the separation of organic reactions [10], a number of fluorous tags, with a varying degree of fluoricity, were evaluated in Stille- and radical mediated-reactions. These tags were introduced with the aim of inserting a fluorous handle that could be taken advantage of in the reaction phase of the synthesis and then easily cleaved or disposed of by other means in the separation phase. In the special applications of Stille-couplings [11] and stannous radical mediated reactions [12], special tin-containing fluorous reactants and reagents were designed to ease the otherwise often tedious workup procedures associated with these reactions. The fluorinated stannous compounds were envisioned to partition to a fluorous phase under workup and thus ensure a quick and reliable method of removing and isolating the tin-containing reagents from the rest of the reaction mixture.

However, the design of fluorous ligands is not without problems. It has been found that, when fluorous tags are used, the inductive power of the fluorine atoms can influence the reactivity of the tagged molecule. A spacer is often introduced between the fluorous kernel and the rest of the substrate in order to prevent inductive effects [13] (Scheme 10.19-1). The ideal length of the spacers has been the subject of several papers [14–16]. The use of longer spacers than the propylene tether does not seem to be of value and may increase the risk of micelle creation [13].



**Scheme 10.19-1.** A fluorous tin reactant





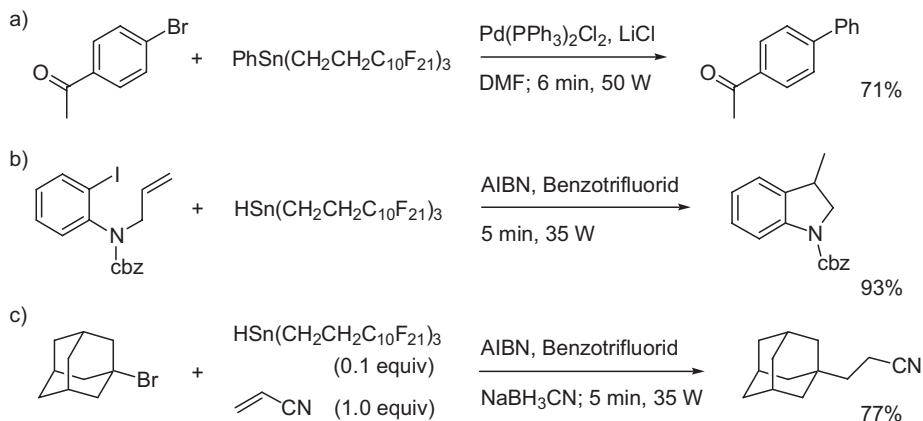
**Scheme 10.19-2.** Fluorous microwave-heated Stille-couplings with the F-13 tag

### 10.19.3

#### Fluorous Reaction Systems in Microwave Chemistry

The first report on microwave-heated fluorous palladium-catalyzed reactions was published in 1997 [17]. These Stille-couplings were performed in septa-sealed microwave transparent Pyrex vessels utilizing diverse reagents substituted with the  $\text{CH}_2\text{CH}_2\text{C}_6\text{F}_{13}$  (F-13) tag and with reaction times as short as 1.5–2.0 min (Scheme 10.19-2). A wide selection of substrates and stannous reagents could be used. The unprotected aldehyde in example a) and the pyridine in example b) both constitute reactants that have been known to present problems in palladium-catalyzed Stille cross-coupling reactions. Vinyl triflates as in example c) could be used although the yields tended to be lower, as was the case with one reported allyl substrate [example d)]. The workup procedures were simple with three-phase extractions between a perfluorinated solvent (FC-84), an organic phase (dichloromethane) and water. Almost full partitioning of the fluorinated tin compounds to the fluorous phase was achieved and only traces of fluorous reagents and byproducts could be found in the organic phase after workup.

For a few applications it was recognized that the fluorous content of the F-13 tag was not sufficient to ensure a full partitioning of the tagged compound to the liquid fluorous phase. Large compounds with a high molecular weight need a higher fluorine content in the attached tag in order to be fully distributed. Indeed, the mass percentage of fluorine atoms compared with the total amount of non-fluorous atoms can usually give a good approxima-

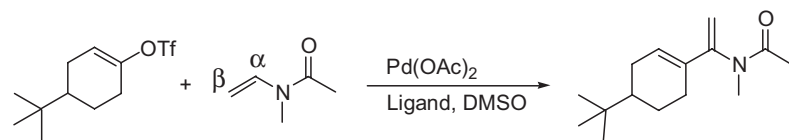


**Scheme 10.19-3.** Fluorous microwave-heated Stille- and radical mediated-reactions with the F-21 tag

tion of the solubility in fluorous media. Horváth recommended a fluorine content of at least 60% in order to ensure a good partitioning to a fluorous phase [13].

The most obvious solution to the problem of poor partitioning was to further enrich the tags with fluorine. This strategy was investigated and the tag  $\text{CH}_2\text{CH}_2\text{C}_{10}\text{F}_{21}$  (F-21) was duly introduced by Curran. However, efforts to use this ligand in oil bath heated Stille-reactions were met with disappointing and irreproducible results, plausibly caused by the insolubility of the F-21 ligand in both organic as well as perfluorinated or partly fluorinated solvents [18]. When microwave heating was applied to this reaction system it was soon evident that palladium-catalyzed couplings and radical mediated reactions could easily be carried out in single-mode reactors [18] (Scheme 10.19-3). Stille-couplings with the heavier F-21 tag were brought to full conversion within 6 min of microwave heating at 50 W power [example a)]. The radical reactions induced by AIBN in examples b) and c) also proceeded smoothly and in the case of example c) only catalytic amounts of the stannous hydride had to be used in combination with sodium cyanoborohydride. Example c) also presented an exceptionally straightforward workup procedure. The stannous byproducts that were dissolved under the high temperatures of the microwave reaction participated when brought back to room temperature and could thus easily be removed by silica filtration. No contamination of fluorous species in the organic phase was seen.

From this presentation it is possible to reach the conclusion that in order for a successful fluorous synthetic strategy to be realized, the fluorous content of the tags must be controlled. Too high a degree of fluorination may result in insoluble fluorous reactants that cannot react efficiently with non-fluorinated substrates; and a too low degree may, on the other hand, give leaching of the fluorinated content into the organic phase under a liquid/liquid separation. A different approach to exploiting fluoricity and an important and interesting application of fluorous chemistry has been developed by Curran in the use of fluorous reverse phase (FRP) chromatography [19]. Molecules with a low degree of fluorination are in this context beneficial as a good separation can be fulfilled by eluting non-fluorous com-

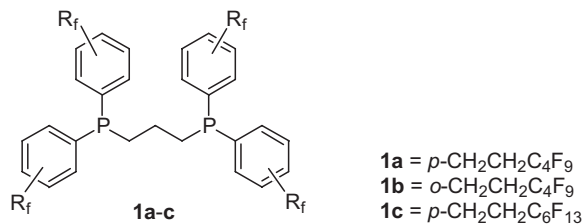


Ligand	Method of Heating	Temp. (°C)	Time	Selectivity ( $\alpha/\beta$ )	Yield (%)
dppp	Standard	60	18 h	96/4	53
dppp	MW	90	15 min	91/9	57
F-dppp (1a)	Standard	60	18 h	94/6	46
F-dppp (1a)	MW	90	15 min	90/10	46

**Scheme 10.19-4.** Heck-coupling with fluorous and non-fluorous ligands under oil-bath or controlled microwave heating

pounds with methanol and water and the fluorous compounds with acetonitrile [16, 19]. Lightly fluorinated phosphine bidentate ligands have very recently been investigated in microwave promoted and palladium-catalyzed regioselective Heck vinylations [20] (Scheme 10.19-4).

One attractive possibility when using fluorous ligands in metal catalysis is the option of recycling the often expensive ligands and catalysts used [21]. With that aim, the recyclability of the catalytic system with lightly to moderately fluorinated ligands **1a–c** was studied [20] (Scheme 10.19-5).



**Scheme 10.19-5.** Fluorous bidentate ligands (F-dppp)

Three different fluorous 1,3-bisdiphenylphosphinopropane (dppp) analogues (F-dppp) were prepared and their reactivities evaluated in an internal Heck-vinylation reaction. The *para*-substituted ligands **1a** and **1c** were found to be more widely applicable than the *meta*-substituted **1b**. The lightly fluorinated **1a** was also observed to react faster in DMSO than the more fluorinated **1c**: a finding that is reminiscent of the earlier results where the more heavily fluorinated tags reacted more sluggishly [17, 18]. The reactivities of dppp versus F-dppp (**1a**) under classic (18 h at 60 °C) as well as microwave (15 min at 90 °C) reaction conditions were compared. The isolated yields and the regioselectivities turned out to be in large identical, but there was a trend for a slightly lower regioselectivity when the fluorous ligand was used or when microwave heating was applied (Scheme 10.19-4).

The same methodology was also applied on a cyclic enamide as the olefin and, in another coupling, with a steroidal vinyl triflate as the substrate [20]. All traces of fluoruous reagents were handily removed from the reaction medium by direct solid fluoruous phase separation using a 90% methanol/10% water eluting system. However, attempts to reuse the isolated catalyst from the reaction did not result in a productive coupling: a fact that, as the authors suggest, may implicate breakdown of the catalytic system during the course of the reaction.

All in all, the outcome of the protocols has given very positive indications of the use and applicability of microwave-heated fluoruous chemistry. The reactivity of Stille- and radical mediated-reactions are maintained in the fluoruous procedures and the regioselectivity in Heck-couplings have been shown to be preserved.

#### 10.19.4

##### **Outlook**

Microwave and fluoruous chemistry are both new and up-and-coming techniques that have yet to reach their full potential. To predict the exact direction that the combination of these two methodologies will take is thus likely to be a challenge. However, a few themes could be brought up for discussion.

Fluoruous chemistry can be used to good effect in synthetic strategies if the reaction conditions and choice of reagents can be controlled to ensure a smooth separation. This has been proven to work both with heavily fluorinated tags and more recently with more lightly fluorinated tags in combination with fluoruous reverse phase chromatography (FRP). These convenient separation procedures in combination with the speed of microwave-assisted chemistry have the potential to reduce the time necessary for both synthesis and separation in modern high throughput applications [5].

When toxic compounds, for example the tin reagents used in the palladium-catalyzed Stille-reactions, have to be used; it would not only be convenient but also environmentally advantageous if the toxic compounds could be easily contained and separated from the reaction mixture. It has been shown that fluoruous chemistry fulfills this need and that microwave-assisted reactions ensure short reaction times. One further benefit of this strategy is the potential possibility of recycling expensive ligands and metal catalysts.

Despite the drawbacks of the cost of equipment and the limited availability of some reagents and solvents, the outlook for microwave-heated, fluoruous chemistry is bright, especially in the field of small-molecule drug discovery. Some keywords that easily could be associated with these techniques include High-speed synthesis, Convenient chromatography and Environmental benefits: all of which should be of great interest for industrial applications. As the number of groups and companies interested in these areas increase there is a promise for the introduction of further accomplishments and novel applications of microwave and fluoruous chemistry in the future.

##### **Acknowledgment**

We thank Knut and Alice Wallenberg's Foundation, PersonalChemistry AB and Biolipox.

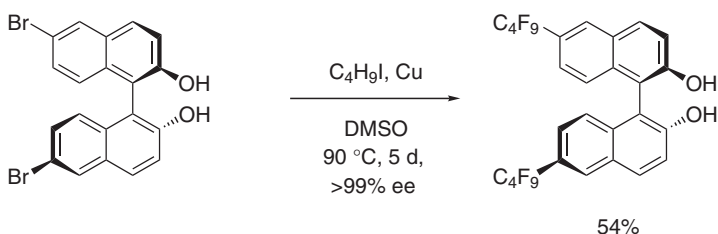
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## 11

## Preparations

## 11.1

**(*R*)-6,6'-Diperfluorobutyl-1,1'-binaphthyl-2,2'-diol. The Copper-mediated Perfluorobutylation of Dibromobinaphthol***Kin Shing Chan and Yuan Tian***Reaction 11.1-1****Experimental Procedure**

A mixture of enantiomerically pure (*R*)-6,6'-dibromo-1,1'-binaphthol (**1**) [**1**] (2.22 g, 5.0 mmol), copper bronze (3.2 g, 50 mmol) [**2**] and perfluorobutyl iodide (6.92 g, 3.44 mL, 20 mmol) in anhydrous DMSO (50 mL) is degassed three times with the freeze-pump-thaw cycles using liquid nitrogen, and is then heated to 90 °C for 5 days. After cooling to room temperature, ethyl acetate (150 mL) is added and the mixture is filtered through Celite. The filtrate is washed with 10% HCl, water, brine and dried over MgSO<sub>4</sub>. After removal of the solvent, the residue is purified by column chromatography eluting with ethyl acetate/hexane (1/6) to give the product (1.25 g, 52%) as a white solid [**3**]: mp 65–66 °C; *R*<sub>f</sub> = 0.28 (ethyl acetate/hexane/dichloromethane = 1/3/0.2); [ $\alpha$ ]<sub>D</sub><sup>20</sup> = −25.7 (c: 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  5.30 (brs, 2 H), 7.22 (d, 2 H, *J* = 8.9 Hz), 7.45 (d, 2 H, *J* = 8.8 Hz), 7.51 (d, 2 H, *J* = 9.0 Hz), 8.11 (d, 2 H, *J* = 9.0 Hz), 8.18 (s, 2 H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  110.62, 115.80 (q, *J* = 31.7 Hz), 119.29, 124.53, 124.61, 124.77, 128.33, 132.69, 135.05, 154.73; EIMS *m/z* (relative intensity) 723 ([M + H]<sup>+</sup>, 82), 704 (7), 553 (100), 525 (7), 485 (5), 333 (12); FABMS *m/z* (relative intensity) 722 (M<sup>+</sup>, 100), 704 (8), 694 (2), 584 (2), 569 (2), 553 (59); HRMS (M<sup>+</sup>). Calc. for C<sub>28</sub>H<sub>12</sub>O<sub>2</sub>F<sub>18</sub> 722.0544. Found 722.0513; >99% ee.

## Discussion

The copper is activated by adding to a suspension of copper bronze (3.18 g, 50 mmol) in acetone (20 mL) a few crystals of iodine [2]. After 30 min, the solvent is removed and the copper is washed sequentially with HCl in acetone and then acetone.

The copper mediated perfluoroalkylations of dibromobinaphthol in other polar aprotic solvents, such as DMF, HMPA and NMP, are not successful. The temperature of the reaction in DMSO needs to be well-controlled. Higher reaction temperature erodes the enantiopurity of the product.

Enantiomerically pure (*S*)-6,6'-diperfluorobutyl-1,1'-binaphthyl-2,2'-diol [3] is also obtained in the same way; mp 60–63 °C;  $[\alpha]_D^{20} = +26.1^\circ$  (c: 0.5, CHCl<sub>3</sub>). The enantiomeric purities of both isomers are determined by HPLC using a chiral Daicel OD-H column (0.46 × 15 cm). Solvent system: hexane/2-propanol = 9:1; flow rate: 1.0 mL min<sup>-1</sup>. For *R*-isomer:  $T_R = 5.51$  min; for *S*-isomer:  $T_R = 3.61$  min.

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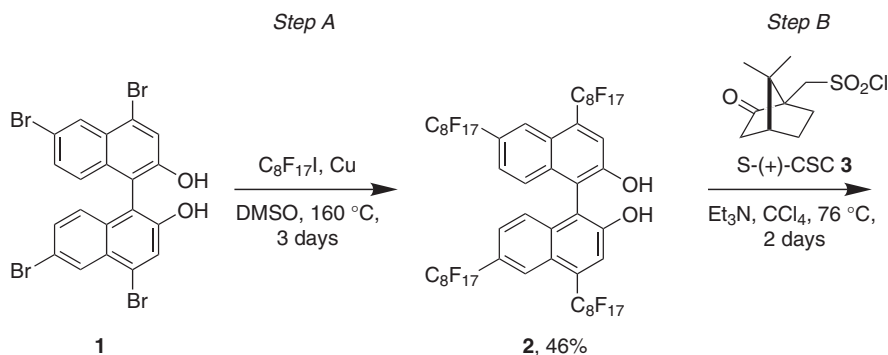
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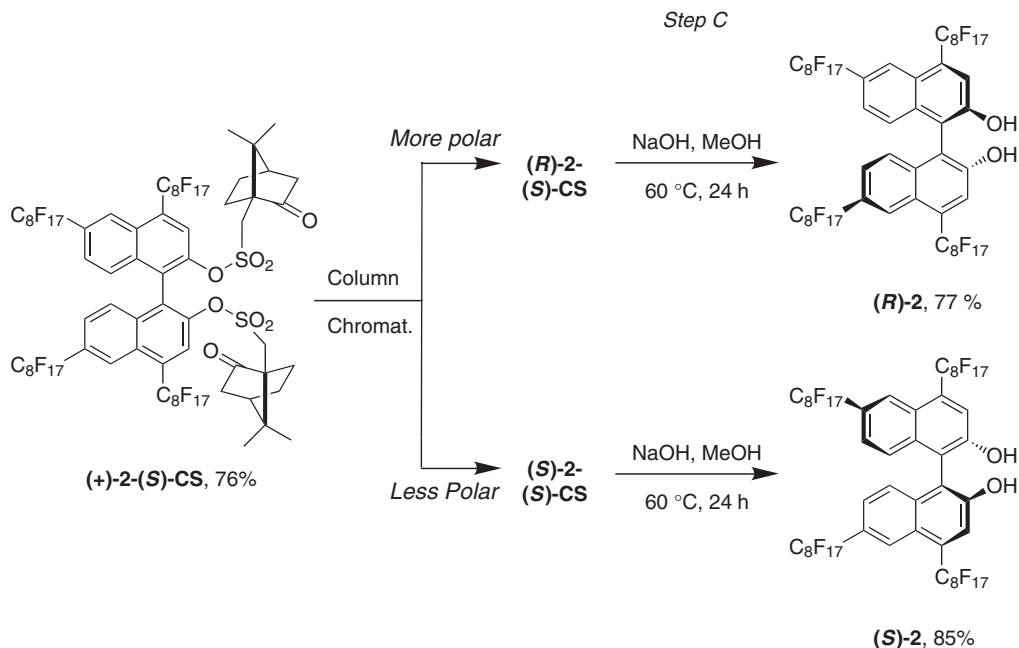
## 11.2

### (*R*)- and (*S*)-4,4',6,6'-Tetraperfluorooctyl-1,1'-binaphthyl-2,2'-diol. The Copper-mediated Perfluoroalkylation of Tetrabromobinaphthol and Resolution

Kin Shing Chan and Yuan Tian

#### Reaction 11.2-1





## Experimental Procedures

**Step A. Racemic-4,4',6,6'-tetra-perfluorooctyl-1,1'-binaphthyl-2,2'-diol 2** [1] A mixture of 4,4',6,6'-tetrabromo-1,1'-binaphthol **1** [2] (1.0 g, 1.66 mmol), copper bronze [3] (1.6 g, 25 mmol) and perfluorooctyl iodide (5.46 g, 2.6 mL, 10 mmol) in anhydrous DMSO (15 mL) is degassed three times by the freeze-pump-thaw cycles using liquid nitrogen and is then heated to 160 °C for 3 days. After cooling to room temperature, ethyl acetate (50 mL) is added and the mixture is filtered through Celite. The filtrate is washed with 10% HCl, water, brine and dried over MgSO<sub>4</sub>. After removal of the solvent, the residue is purified by column chromatography eluting with ethyl acetate/hexane (1/10) to give **2** (1.48 g, 46%) as a yellow oil: *R<sub>f</sub>* = 0.17 (ethyl acetate/hexane = 1/10); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 5.86 (brs, 2 H), 7.27 (d, 2 H, *J* = 7.6 Hz), 7.56 (d, 2 H, *J* = 8.9 Hz), 7.87 (s, 2 H), 8.55 (s, 2 H); FABMS *m/z* (relative intensity) 1159 ([*M* + *H*]<sup>+</sup>, 85), 1141 (17), 990 (100), 853 (3), 820 (19), 772 (18); SIMS *m/z* 1959 ([*M* + *H*]<sup>+</sup>). Anal. calc. for C<sub>52</sub>H<sub>10</sub>F<sub>68</sub>O<sub>2</sub>: C, 31.89; H, 0.89. Found: C, 32.02; H, 0.73.

**Step B. Diastereomers 2,2'-Di-[(1*S*)-camphor-10-sulfonyl]-4,4',6,6'-tetra-perfluorooctyl-1,1'-binaphthyl (*R*)- and (*S*)-2-(*S*)-CS** To a solution of 4,4',6,6'-tetra-perfluorooctyl-BINOL **2** (1.18 g, 0.60 mmol) at 0 °C, (1*S*)-camphor-10-sulfonyl chloride (605 mg, 2.4 mmol) in dry CCl<sub>4</sub> (20 mL) and triethylamine (304 mg, 0.57 mL, 3.0 mmol) are added. The yellow solution is refluxed for 2 days. After cooling to room temperature, water (15 mL) is added and the mixture is extracted with CCl<sub>4</sub>. The combined organic layer is washed with brine and dried over MgSO<sub>4</sub>. After evaporation of the solvents, the residue is purified by column chroma-



tography using a solvent mixture of ethyl acetate/hexane (1/6) to give a mixture of diastereomers (**±**)-2-(**S**)-CS (1.1 g, 76%) as a white solid.

Further careful column chromatography (hexane/dichloromethane = 10/7) gives a less polar diastereomer (**S**)-2-(**S**)-CS: mp 127–128 °C;  $R_f$  = 0.25 (hexane/dichloromethane = 10/7);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.60 (s, 6 H), 0.81 (s, 6 H), 1.27–1.30 (m, 4 H), 1.80 (d, 2 H,  $J$  = 18.6 Hz), 1.85–2.02 (m, 6 H), 2.22 (dd, 2 H,  $J$  = 18.6, 2.9 Hz), 2.77 (d, 2 H,  $J$  = 14.9 Hz), 3.17 (d, 2 H,  $J$  = 14.9 Hz), 7.43 (d, 2 H,  $J$  = 8.9 Hz), 7.65 (t, 2 H,  $J$  = 9.1 Hz), 8.29 (s, 2 H), 8.64 (s, 2 H);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  19.11, 19.18, 24.72, 26.58, 42.06, 42.63, 47.71, 49.77, 57.65, 107.76, 110.94, 114.87, 124.89, 125.34, 127.50, 127.94, 128.85, 129.23, 135.18, 145.86, 212.57. Anal. calcd. for  $\text{C}_{72}\text{H}_{38}\text{F}_{68}\text{S}_2\text{O}_8$ : C, 36.23; H, 1.60. Found: C, 36.12; H, 1.86. A second fraction of the more polar diastereomer (**R**)-2-(**S**)-CS is also isolated: mp 109–110 °C;  $R_f$  = 0.19 (hexane/dichloromethane = 3/5);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.58 (s, 6 H), 0.68 (s, 6 H), 1.23–1.34 (m, 4 H), 1.80 (d, 2 H,  $J$  = 18.6 Hz), 1.78–1.81 (m, 4 H), 1.98–1.99 (m, 2 H), 2.25 (dt, 2 H,  $J$  = 18.6, 2.6 Hz), 2.64 (d, 2 H,  $J$  = 14.9 Hz), 3.49 (d, 2 H,  $J$  = 15.0 Hz), 7.40 (d, 2 H,  $J$  = 8.9 Hz), 7.63 (t, 2 H,  $J$  = 9.1 Hz), 8.30 (s, 2 H), 8.64 (s, 2 H). Anal. calc. for  $\text{C}_{72}\text{H}_{38}\text{F}_{68}\text{S}_2\text{O}_8$ : C, 36.23; H, 1.60. Found: C, 36.11; H, 1.52.

**Step C.** (*S*)-4,4',6,6'-Tetraperfluorooctyl-1,1'-binaphthyl-2,2'-diol (**S**)-2 To a suspension of (**S**)-2-(**S**)-CS (239 mg, 0.10 mmol) in methanol (10 mL) and  $\text{CCl}_4$  (10 mL), NaOH (1 M, 5 mL) is added. The resulting yellow solution is stirred at 60 °C for 24 h. After cooling to room temperature, 10% HCl is added to neutralize the solution to pH 7. Methanol is removed *in vacuo* and the residue is extracted with  $\text{CCl}_4$ . The combined organic layer is washed with brine and dried over  $\text{MgSO}_4$ . After removal of the solvent, the product is purified by column chromatography eluting with ethyl acetate/hexane (1/10) to give (**S**)-2 (167 mg, 85%) as a yellow oil:  $[\alpha]_D^{20}$  = –15.7 (c 0.15, ethyl acetate). The  $^1\text{H}$  NMR spectrum is the same as the racemic compound.

(*R*)-4,4',6,6'-Tetraperfluorooctyl-1,1'-binaphthyl-2,2'-diol (**R**)-2 The same procedure is used to saponify (**R**)-2-(**S**)-CS. (**R**)-2 is obtained as a yellow oil in 79% yield:  $[\alpha]_D^{20}$  = +15.6 (c 0.96, ethyl acetate).

## Discussion

The copper is activated by adding a few crystals of iodine to a suspension of copper bronze (3.18 g, 50 mmol) in acetone (20 mL) [3]. After 30 min, the solvent is removed and the copper is washed sequentially with HCl in acetone and then acetone.

The high reaction temperature (160 °C) gives good yield in the perfluorooctylation; however, the binaphthyl chiral axis racemizes if the enantiopure precursor is used. At lower reaction temperature, little perfluorooctylation occurs. Therefore, enantiomerically pure products have to be prepared by resolution.

Commercially available (1*S*)-camphor-10-sulfonyl chloride is only 97% pure and is not pure enough for resolution. (1*S*)-(+)-Camphor-10-sulfonyl chloride is prepared from the reaction of (1*S*)-(+)-camphor-10-sulfonic acid with phosphorus pentachloride [4].

The absolute configuration of the camphorsulfonates is assigned based on proton NMR and CD spectra and the X-ray structure of the perfluorobutyl analog [1]. The enantiopurities of (**S**)-2 and (**R**)-2 are determined by the proton NMR spectra of their corresponding camphorsulfonates.

## References

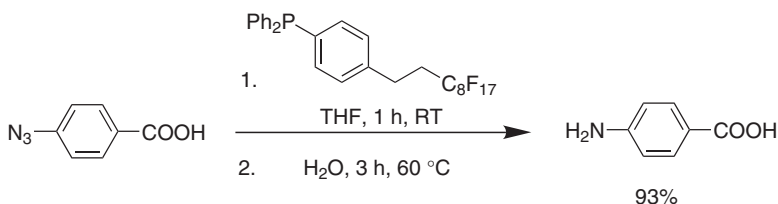
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## 11.3

## 4-Aminobenzoic Acid. The Staudinger Reduction with a Fluorous Phosphine Reagent

Craig W. Lindsley and Zhijian Zhao

## Reaction 11.3-1



## Reagents

Diphenyl-[4-(1H,1H,2H,2H-perfluorodecyl)phenyl]phosphine [462996-04-9] is commercially available from Fluorous Technologies, Inc. ([www.fluorous.com](http://www.fluorous.com)) or can be prepared according to the literature procedure [1]. FluoroFlash<sup>TM</sup> silica gel from Fluorous Technologies, Inc. was used for the solid phase extraction.

## Experimental Procedure

In a 10 mL round-bottomed flask is placed 4-azidobenzoic acid (82 mg, 0.50 mmol) and diphenyl-[4-(1H,1H,2H,2H-perfluorodecyl)phenyl]phosphine (389 mg, 0.55 mmol) in dry THF (3 mL). Immediately, gas evolution is observed. After 1 h, water (500  $\mu$ L) is added, and the reaction vessel is warmed to 60 °C for 3 h, when the solvent is then evaporated and the residue is loaded onto a 5 g FluoroFlash<sup>TM</sup> SPE cartridge using 5% aqueous methanol. Elution with 15% aqueous methanol (10 mL) and evaporation of the solvent provides analytically pure 4-aminobenzoic acid (64 mg, 93%). A second elution with THF (20 mL) provides the corresponding fluorous phosphine oxide.

## Discussion

The Staudinger reaction is a mild, chemoselective method for the reduction of functionalized azides to the corresponding amine [2]. While the reaction itself is operationally very simplistic, developing a Staudinger protocol amenable to solution phase parallel synthesis,

free from triphenylphosphine byproducts is not. Indeed, polymer-supported triphenylphosphine has been employed, but reaction and conversion rates are very poor [3, 4].

Recently, a fluororous variant of the Staudinger reduction appeared [4]. In this variant, a solution phase, homogeneous fluororous-tagged phosphine is used. Reduction rates are the same as with traditional triphenylphosphine, and 10-fold faster than with polymer-supported congeners. Solid phase extraction over FluoroFlash<sup>TM</sup> silica gel allows for the general and rapid separation of the desired amine from the spent fluororous reagents [5].

## References

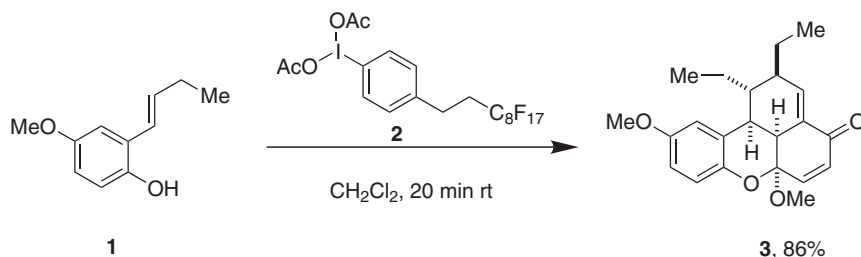
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## 11.4

### 1,2-Diethyl-6a,10-dimethoxy-1,6a,11b,11c-tetrahydro-2H-benzo[k]xanthen-4-one. $\beta,\beta$ -Phenolic Coupling Reactions to Access Unnatural Carpanone Analogs with a Fluororous Diacetoxy Iodobenzene (F-DAIB) Reagent

Craig W. Lindsley and Zhijian Zhao

#### Reaction 11.4-1



#### Reagents

4-(1H,1H,2H,2H-Perfluorodecyl)-1-(diacetoxyiodo)benzene (F-DAIB) **2** is commercially available from Fluorous Technologies, Inc. ([www.fluorous.com](http://www.fluorous.com)). FluoroFlash<sup>TM</sup> silica gel from Fluorous Technologies, Inc. was used for the solid phase extraction.

#### Experimental Procedure

In a 10 mL round-bottomed flask is placed styrenyl phenol **1** (53.4 mg, 0.3 mmol) and  $\text{CH}_2\text{Cl}_2$  (3 mL). To this solution is then added F-DAIB **2** (230 mg, 0.3 mol). The solution quickly changes from a pale yellow to a deep orange hue. After 20 min, the solvent is evaporated and the residue is loaded onto a 5 g FluoroFlash<sup>TM</sup> SPE cartridge in 5% aqueous

methanol. Elution with 20% aqueous methanol (10 mL) and evaporation of the solvent delivers unnatural carpanone analog **3** (46 mg, 86%). A second elution with THF (20 mL) gives a mixture of F-DAIB **2** and the reduced fluororous-tagged iodobenzene. The iodide can be converted back into **2**.

## Discussion

Diacetoxy iodobenzene (DAIB) is a mild, yet powerful one electron oxidant that facilitates a number of chemical transformations [1]. Often times, chromatographic separation of the desired products from excess DAIB and the iodobenzene byproduct is problematic. In short order, both “heavy” and “light” fluororous-tagged DAIB derivatives have been prepared to facilitate purification by liquid/liquid or solid phase extraction protocols, respectively [2].

Recently, DAIB has been shown to effect hetero- and homo- $\beta,\beta$ -phenolic couplings to access unnatural carpanone analogs on the solid phase [3]. A complimentary, solution phase parallel synthesis approach for the diversity-oriented synthesis of unnatural carpanone analogs takes advantage of fluororous-tagged DAIB congeners, such as **2**, to generate the carpanone core through a homo- $\beta,\beta$ -phenolic coupling reaction followed by an inverse electron demand Diels-Alder reaction. In this instance, solid phase extraction on FluoroFlash<sup>TM</sup> SPE cartridges has proven to be a general method for the purification of diverse, unnatural carpanone-like molecules such as **3**, with clean separation from the fluororous reagent [4].

## References

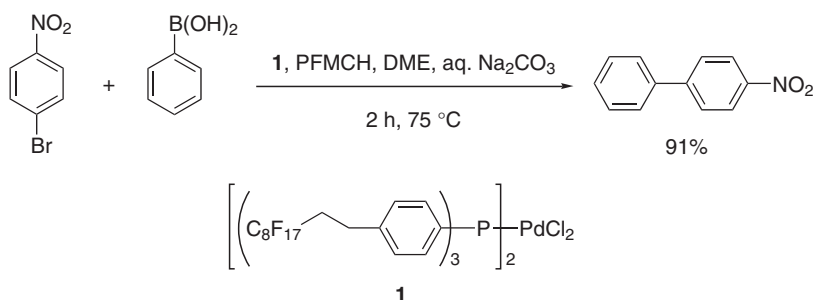
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## 11.5

### 4-Nitro-1,1'-biphenyl. Suzuki Coupling in Liquid/Liquid FBS

C. Christoph Tzschucke, Siegfried Schneider, and Willi Bannwarth

#### Reaction 11.5-1



## Reagents

Dichlorobis{tris[4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptafluorodecyl)-phenyl]phosphane}palladium **1** [326475-46-1] is commercially available from Fluka [1] or can be prepared according to the literature procedure [2, 3]. Perfluoromethylcyclohexane (PFMCH) [355-02-2] is available from Fluka.

## Experimental Procedure

A 20 mL Schlenktube with magnetic stir-bar is charged with complex **1** (10 mg, 3  $\mu$ mol, 0.015 equiv). Under argon, perfluoromethylcyclohexane (1.5 mL), stock solutions of 4-nitro-bromobenzene (0.2 M in dimethoxyethane [DME], 1.0 mL, 0.2 mmol, 1.00 equiv) and phenylboronic acid (0.44 M in DME, 0.5 mL, 0.22 mmol, 1.10 equiv) and aq. Na<sub>2</sub>CO<sub>3</sub> (2 M, 1.0 mL, 2 mmol, 10 equiv) are added. The mixture is heated to 75 °C for 2 h. After cooling to rt, the aqueous and organic phases are separated from the fluorous phase. The fluorous phase is sequentially extracted with DME (2  $\times$  1 mL), H<sub>2</sub>O (2  $\times$  1 mL) and DME (2  $\times$  1 mL). The fluorous phase containing the catalyst can be used as such for the next run. The combined aqueous and organic phases are diluted with H<sub>2</sub>O (4 mL) and extracted with diethyl ether (4  $\times$  1 mL). The combined extracts are concentrated *in vacuo*, the residue taken up in diethyl ether (1 mL) and passed through a plug of neutral alumina (activity 2–3, 2 mL) and silica gel (4 mL). The filtrate is concentrated to dryness, yielding the product as a pale yellow solid (36 mg, 0.18 mmol, 91%).

## Discussion

The Suzuki reaction is one of the most attractive possibilities for the formation of biaryls [4]. This is because a variety of functional groups are tolerated and substrates are stable, readily available and of low toxicity.

This fluorous protocol simplifies the isolation of the product significantly and offers the possibility of reusing the catalyst. The procedure was applied to several substrates, and Pd complexes with different fluorous tags were employed. The catalysts were recycled up to five times. In all cases high yields were obtained and no difference in the reactivity of the catalyst precursors was apparent [2].

## References

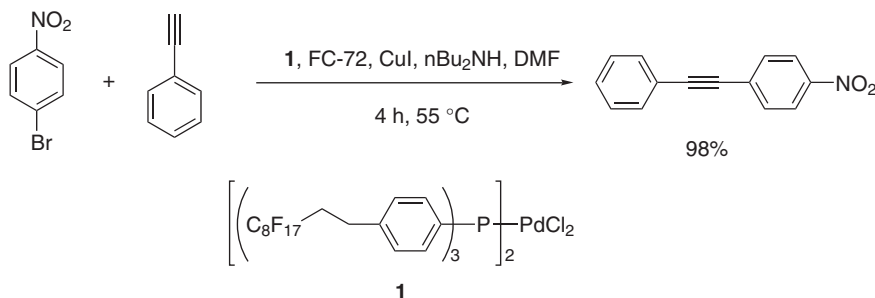
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## 11.6

## 1-(4-Nitrophenyl)-2-phenylacetylene. Sonogashira Coupling in Liquid/Liquid FBS

C. Christoph Tzschucke, Siegfried Schneider, and Willi Bannwarth

## Reaction 11.6-1



## Reagents

FC-72 is a mixture of perfluorohexane isomers [355-42-0] and can be obtained from Fluka.

## Experimental Procedure

A dry 20 mL Schlenktube with magnetic stir-bar is charged with complex **1** (20 mg, 6  $\mu\text{mol}$ , 0.02 equiv) and 4-nitro-bromobenzene (62 mg, 0.30 mmol, 1.0 equiv). The flask is evacuated and refilled with argon (3 $\times$ ). A solution of CuI (2.9 mg, 15  $\mu\text{mol}$ , 0.05 equiv) and di-*n*-butylamine (102  $\mu\text{L}$ , 0.6 mmol, 2.0 equiv) in DMF (0.4 mL) is prepared in a second Schlenktube under argon. To the reaction flask are added FC-72 (0.7 mL), phenylacetylene (40  $\mu\text{L}$ , 0.36 mmol, 1.2 equiv) and the CuI solution. The reaction mixture is heated to 55  $^{\circ}\text{C}$  for 4 h. After cooling to 0  $^{\circ}\text{C}$ , the organic phase is separated and the fluoruous phase is extracted with DMF (3  $\times$  2 mL). The fluoruous phase can be used as such for the next run. The combined organic phases are diluted with brine (40 mL) and aqueous HCl (0.5 M, 10 mL) and extracted with  $\text{CHCl}_3$  (4  $\times$  2 mL). The combined extracts are washed with saturated aqueous  $\text{NaHCO}_3$  (4 mL), the  $\text{NaHCO}_3$  solution is back-extracted with  $\text{CHCl}_3$  (5 mL) and the combined  $\text{CHCl}_3$  phases are evaporated. To completely remove the DMF, the residue is taken up in diethyl ether (5 mL), washed with brine (4 mL) and passed through a plug of silica gel (4 mL) and neutral alumina (activity 2–3, 2 mL). Removal of the solvent *in vacuo* yields the product together with excess alkyne as a brown oil. After column chromatography (silica gel, cyclohexane/ethylacetate 20:1) yellow crystals (67 mg, 0.3 mmol, 98%) are obtained.

## Discussion

The Sonogashira reaction is an efficient reaction for the catalytic coupling of aryl halides with terminal alkynes [1]. A drawback is that high catalyst loadings in the range of 5 to 10

mol% are usually used. This highlights the necessity of an efficient protocol for the separation of the catalyst. The present procedure has been applied to different alkynes and aryl halides. The yields depend very much on the reactivity of the aryl halide. While reactive substrates such as aryl iodides or electron-deficient aryl bromides gave high yields and recycling of the catalyst was possible, electron rich aryl bromides gave lower yields and catalyst recycling was not successful. Different Pd complexes were used, but no significant differences in the reactivity were observed.

During the reaction, oxygen has to be rigorously excluded to avoid homocoupling of the alkyne. Therefore all solvents have to be carefully degassed prior to use. It is also possible to use perfluoromethylcyclohexane as the fluorous phase in order to allow for higher reaction temperatures. The elaborate extraction sequence during workup is necessary to obtain the products free of DMF [2].

## References

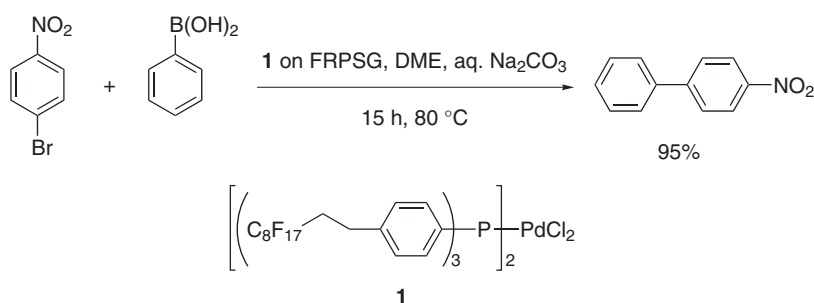
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## 11.7

### 4-Nitro-1,1'-biphenyl. Suzuki Coupling with a Catalyst on FRPSG without a Perfluorinated Solvent

C. Christoph Tzschucke, Siegfried Schneider, and Willi Bannwarth

#### Reaction 11.7-1



## Reagents

The supported complex is prepared as mentioned below. Fluorous reverse phase silica gel (FRPSG) suited for this application can be prepared according to the literature procedure [1].

### Immobilization of Pd-complexes on FRPSG

In a round-bottomed flask, complex **1** (29.8 mg) is dissolved in a sufficient amount of diethyl ether (~200 mL) and FRPSG (2945 mg) is added. The solvent is removed by rotary evaporation. To the dry FRPSG is added diethyl ether (~200 mL) and the solvent is again removed by rotary evaporation. Drying *in vacuo* gives the FRPSG-supported complex **1** as a pale yellow free flowing solid.

### Experimental Procedure

A 50 mL Schlenktube is charged with FRPSG-supported complex **1** (100 mg, containing 1 mg complex, 0.3  $\mu\text{mol}$ , 0.001 equiv), evacuated and refilled with argon (3 $\times$ ). Stock solutions of 4-nitrobromobenzene (0.3 M in DME, 1.0 mL, 0.3 mmol, 1.00 equiv) and phenylboronic acid (0.33 M in DME, 1.0 mL, 0.33 mmol, 1.10 equiv) and aqueous  $\text{Na}_2\text{CO}_3$  (2 M, 1.0 mL, 2.0 mmol, 6.7 equiv) are added. The tube is sealed with a screw cap and shaken at 80 °C for 15 h. The reaction mixture is cooled to 0 °C and the liquid phase is removed under argon with a pipette. The FRPSG is washed with DME (2  $\times$  2 mL), water (2  $\times$  2 mL) and DME (2  $\times$  2 mL). The combined liquid phases are diluted with water (40 mL) and brine (20 mL) and are extracted with *tert*-butylmethylether (3  $\times$  20 mL). The combined extracts are concentrated *in vacuo*, the residue is taken up in diethyl ether (2 mL), put on a plug of neutral alumina (activity 2–3, 3 mL) and eluted with diethyl ether (~14 mL). Evaporation of the solvent gives the product (57 mg, 0.29 mmol, 95%). The immobilized catalyst can be reused as such in further experiments.

### Discussion

The present protocol is particularly suited for automated combinatorial synthesis, since the solid support is easily separated by decantation or filtration. The dilution of the precatalyst allows for the accurate weighing of very small amounts of catalysts, which simplifies the miniaturization of the reaction setup for parallel synthesis.

With 4-nitrobromobenzene and phenylboronic acid, different Pd complexes were employed and were recycled three times without apparent loss of activity or differences between the catalysts. A maximal turnover number of 131 000 was achieved when the catalyst loading was lowered to 0.001 mol%.

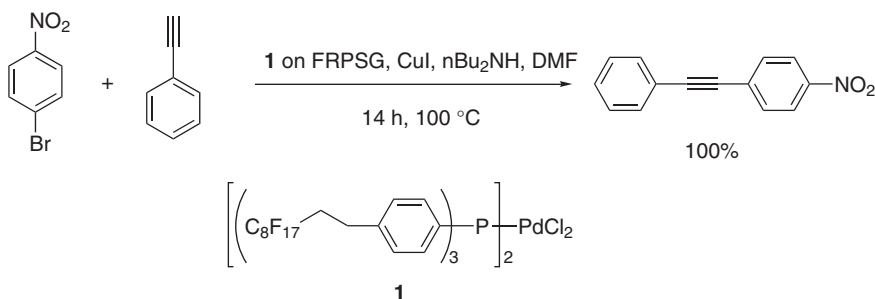
The procedure has been used for a number of different aryl bromides. With electron-deficient substrates, high yields were achieved and the catalyst was successfully recycled. With electron-rich aryl bromides, conversion was often not complete and yields dropped significantly upon recycling of the catalyst [2].

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## 11.8

**1-(4-Nitrophenyl)-2-phenylacetylene. Sonogashira Coupling with a Catalyst on FRPSG without a Perfluorinated Solvent***C. Christoph Tzschucke, Siegfried Schneider, and Willi Bannwarth***Reaction 11.8-1****Reagents**

see previous procedure.

**Experimental Procedure**

A dry 50 mL Schlenktube is charged with FRPSG supported complex **1** (200 mg, containing 2 mg complex, 0.6  $\mu\text{mol}$ , 0.002 equiv), CuI (1.0 mg, 5  $\mu\text{mol}$ , 0.02 equiv) and 4-nitro-bromobenzene (62 mg, 0.30 mmol, 1.0 equiv). The flask is evacuated and refilled with argon ( $3\times$ ). To the reaction flask are added DMF (2.0 mL), di-*n*-butylamine (102  $\mu\text{L}$ , 0.6 mmol, 2.0 equiv) and phenylacetylene (40  $\mu\text{L}$ , 0.36 mmol, 1.2 equiv). The tube is sealed with a screw cap and shaken in an oil bath at 100  $^{\circ}\text{C}$  for 14 h. After cooling to 0  $^{\circ}\text{C}$ , the liquid phase is removed under argon with a pipette and the FRPSG is washed with DMF ( $3 \times 2$  mL). The combined organic phases are diluted with brine (40 mL) and aqueous HCl (0.5 M, 15 mL) and extracted with  $\text{CHCl}_3$  ( $4 \times 4$  mL). The combined extracts are washed with saturated aqueous  $\text{NaHCO}_3$  (4 mL), the  $\text{NaHCO}_3$  solution is back-extracted with  $\text{CHCl}_3$  ( $4 \times 4$  mL) and the combined  $\text{CHCl}_3$  phases are evaporated. To remove the DMF completely, the residue is taken up in diethyl ether (5 mL), washed with brine (4 mL) and the aqueous phase is back-extracted with diethyl ether ( $4 \times 4$  mL). The combined ether phases are passed through a plug of silica gel (4 mL) and neutral alumina (activity 2–3, 2 mL), and washed down with additional diethyl ether ( $\sim 10$  mL). Removal of the solvent *in vacuo* yields the product together with excess alkyne as a brown oil. The immobilized catalyst can be reused as such in further experiments.

**Discussion**

The procedure offers similar opportunities to those mentioned previously for the Suzuki coupling [1].

## Reference

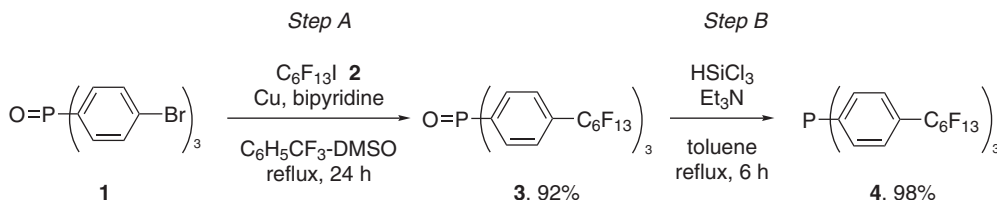
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## 11.9

**Tris(4-perfluorohexylphenyl)phosphine. Synthesis of Perfluoroalkyl Aryl Phosphines by Copper-mediated Cross Coupling**

Weiping Chen and Jianliang Xiao

## Reaction 11.9-1



## Reagents

Tris(4-bromophenyl)phosphine oxide **1** was prepared according to a published procedure [1]. Perfluorohexyl iodide **2** was purchased from Aldrich or Apollo Scientific Ltd. and used without further purification. Toluene, hexane, and triethylamine were distilled over  $\text{CaH}_2$  under nitrogen prior to use. Benzotrifluoride, DMSO, copper powder, bipyridine, and trichlorosilane were used as received.

## Experimental Procedures

**Step A. Tris(4-perfluorohexylphenyl)phosphine Oxide (3)** A mixture of **1** (515 mg, 1.0 mmol), **2** (1.405 g, 3.2 mmol), copper powder (450 mg, 7.1 mmol), 2,2'-bipyridine (34 mg, 0.2 mmol), DMSO (1.0 mL), and benzotrifluoride (10 mL) is refluxed with stirring for 24 h under nitrogen in a two-necked flask. The mixture is then cooled to room temperature, filtered through a ca. 1 cm long pad of Celite. The flask is washed with  $\text{CHCl}_3$  ( $2 \times 20$  mL) and each washing is filtered through the Celite. The combined filtrates are washed successively with 1 N HCl ( $2 \times 50$  mL), water (50 mL) and brine (30 mL), dried over anhydrous  $\text{MgSO}_4$ , and evaporated on a rotary evaporator. The resulting solid is crystallized from hot EtOH to give tris(4-perfluorohexylphenyl)phosphine oxide **3** as colorless needles (1.133 g, 92%), mp 136–138 °C:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  7.77 (dd, 6 H,  $J = 8.3, 2.1$  Hz), 7.84 (dd, 6 H,  $J = 11.4, 8.3$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  127.5 (dt,  $^3J_{\text{CP}} = 11.6, ^3J_{\text{CF}} = 6.6$  Hz), 132.3 (d,  $^2J_{\text{CP}} = 10.2$  Hz), 133.4 (td,  $^2J_{\text{CF}} = 21.1, ^4J_{\text{CP}} = 2.4$  Hz), 135.6 (d,  $^1J_{\text{CP}} = 101.7$  Hz) (the  $^{13}\text{C}$  signals of the fluorocarbon chains were too weak to be assigned);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ , 101 MHz)  $\delta$  25.6 (s). Anal. calc. for  $\text{C}_{36}\text{H}_{12}\text{F}_{39}\text{PO}$ : C, 35.09; H, 0.98. Found: C, 35.35; H, 0.97.

**Step B. Tris(4-perfluorohexylphenyl)phosphine (4)** To a mixture of **3** (2.465 g, 2.0 mmol), triethylamine (4.554 g, 45 mmol), and toluene (20 mL) in a three-necked flask is injected

trichlorosilane (4.064 g, 30 mmol) under nitrogen. The mixture is stirred at 120 °C for 6 h under nitrogen. The mixture is cooled to room temperature and further cooled with an ice bath for 10 min, to which is then added degassed, saturated NaHCO<sub>3</sub> aqueous solution (1 mL). Under nitrogen, the mixture is stirred for 10 min and filtered through a short alumina column. The flask is washed with hexane and the washings are filtered through the alumina. The combined filtrates are then concentrated on a rotary evaporator to afford tris(4-perfluorohexylphenyl)phosphine **4** as a white solid (2.384 g, 98%), mp 66–68 °C: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz)  $\delta$  7.42 (dd, 6 H,  $J_{\text{PH}} = 8.2$ ,  $J_{\text{HH}} = 7.7$ ), 7.61 (d, 6 H,  $J_{\text{HH}} = 7.7$ ); <sup>31</sup>P NMR (CDCl<sub>3</sub>, 101 MHz)  $\delta$  –6.1 (s). For other analytical details on this compound, see reference [2].

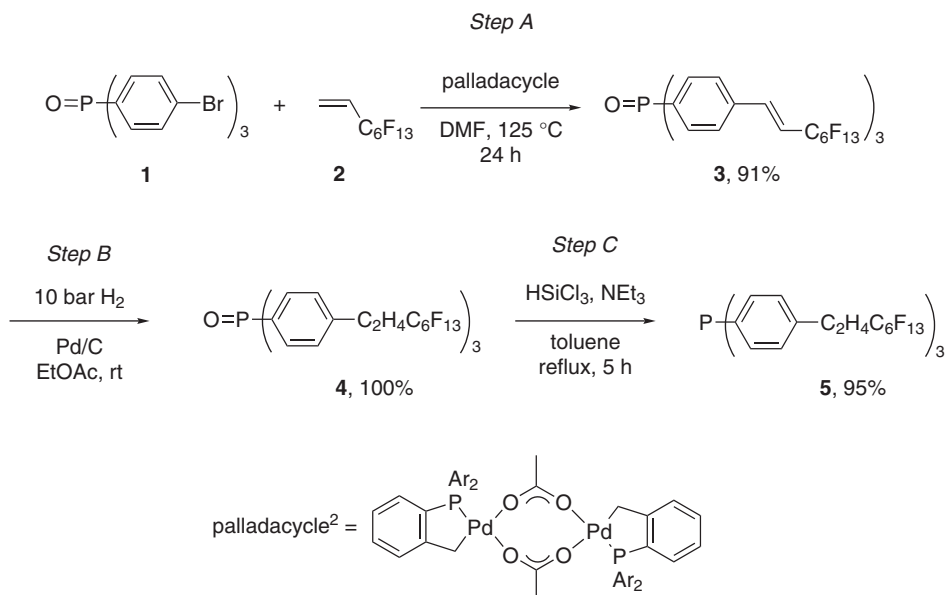
## Discussion

Perfluoroalkyl-derivatized triarylphosphines can be prepared by lithiation of perfluoroalkyl bromobenzenes followed by reaction with PAr<sub>3–n</sub>Cl<sub>n</sub> [2, 3]. This methodology involves using moisture-sensitive and pyrophoric reagents and low temperatures, and gives low yields of product relative to the perfluoroalkyl reagents used. The current method centers on copper-mediated cross coupling of bromoarylphosphine oxide **1** with a perfluoroalkyl iodide **2** and is simpler and higher yielding [4, 5]. Phosphine oxide **1** can be easily prepared from 1,4-dibromobenzene and phosphorus chloride [1]. Since the perfluoroalkylation of **1** reduces its solubility in normal organic solvents, the choice of solvent is important to ensure rapid coupling rates and high yields of **3**. For instance, longer reaction times and lower yields resulted when the reaction was performed in DMSO compared with a mixture of perfluoro-1,3-dimethylcyclohexane and DMSO (10:1, v/v). Benzotrifluoride in the presence of DMSO (10:1, v/v) is even better. This medium dissolves both the starting materials and products under the reaction conditions, and BTI is inexpensive with low toxicity and favorable environmental properties [6]. With this solvent mixture, the workup is also simpler. Thus, the pure product can be easily obtained by filtering off the excess copper and copper salts followed by washing with HCl and water to remove the remaining copper salts and DMSO prior to drying. The phosphine **4** was readily released from the oxide by reduction with trichlorosilane following normal procedures. The method described herein can be extended to the synthesis of mono-, bis-, and tris-(perfluoroalkyl)-substituted arylphosphines with either short or long fluoruous chains and with an overall yield usually close to 90% [4].

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## 11.10

**Tris[4-(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)phenyl]phosphine. Synthesis of Fluoroalkyl Arylphosphines by the Heck Reaction***Weiping Chen and Jianliang Xiao***Reaction 11.10-1****Reagents**

Tris(4-bromophenyl)phosphine oxide **1** [1] and the Herrmann-Beller palladacycle [2] were prepared according to published procedures. The palladacycle is also available from Strem (46-0290). 1*H*,1*H*,2*H*-Perfluoro-1-octene **2** was purchased from Aldrich or Apollo Scientific Ltd. and used without further purification. The Pd/C (10%) catalyst was obtained from Aldrich (20,569-9). Toluene and triethylamine were distilled over CaH<sub>2</sub> under nitrogen prior to use. DMF, NaOAc, ethylacetate, chloroform, and trichlorosilane were used as received.

**Experimental Procedures**

**Step A. Tris[4-(1*H*,2*H*-perfluorooct-1-enyl)phenyl]phosphine Oxide (**3**)** A mixture of **1** (1.03 g, 2.0 mmol), **2** (2.284 g, 6.6 mmol), palladacycle (56 mg, 0.06 mmol), NaOAc (656 mg, 8.0 mmol), and DMF (10 mL, degassed by bubbling through nitrogen for 10 min prior to use) is stirred at 125 °C under nitrogen for 24 h. After cooling to room temperature, most of the DMF is removed under reduced pressure. The residue is dissolved in CHCl<sub>3</sub> (100 mL) and water (100 mL). The organic layer is separated, washed with water (100 mL) and brine

(50 mL), dried (MgSO<sub>4</sub>), and evaporated under reduced pressure. The residue is purified by flash chromatography (SiO<sub>2</sub>, EtOAc-CHCl<sub>3</sub>, 1:8) to give tris[4-(1H,2H-perfluorooct-1-enyl)phenyl]phosphine oxide **3** as a pale yellow oil (2.385 g, 91%): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  6.31 (dt, 3 H,  $J$  = 16.2, 12.0 Hz), 7.22 (d, 3 H,  $J$  = 16.2 Hz), 7.60 (dd, 6 H,  $J$  = 8.2, 2.5 Hz), 7.73 (dd, 6 H,  $J$  = 11.6, 8.2 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  117.6 (t, <sup>2</sup> $J_{CF}$  = 23.5 Hz), 127.4 (d, <sup>3</sup> $J_{CP}$  = 12.5 Hz), 132.8 (d, <sup>2</sup> $J_{CP}$  = 10.4 Hz), 133.9 (d, <sup>1</sup> $J_{CP}$  = 103.7 Hz), 137.5, 138.5 (t, <sup>3</sup> $J_{CF}$  = 9.2 Hz) (the <sup>13</sup>C signals of the fluorocarbon chains were too weak to be assigned); <sup>31</sup>P NMR (CDCl<sub>3</sub>, 101 MHz)  $\delta$  26.8 (s). Anal. calc. for C<sub>42</sub>H<sub>18</sub>F<sub>39</sub>PO: C, 38.49; H, 1.38. Found: C, 38.24; H, 1.00; MS (CI,  $m/z$ ) 1311 ( $M^+$  + 1), 1041, 967, 926, 890, 873.

**Step B. Tris[4-(1H,1H,2H,2H-perfluorooctyl)phenyl]phosphine Oxide (4)** In a fume hood, a mixture of **3** (2.611 g, 2.0 mmol), 10% Pd/C (50 mg), and EtOAc (40 mL) in a glass liner-equipped autoclave is pressurized with 10 bar of hydrogen, which is then carefully released. After repeating this process three times, the autoclave is pressurized with 10 bar of hydrogen and the mixture is stirred for 5 h at room temperature. The hydrogen is carefully released, and the mixture is filtered through a short pad of Celite. The filtrate is evaporated under reduced pressure to give tris[4-(1H,1H,2H,2H-perfluorooctyl)phenyl]phosphine oxide **4** as a pale yellow oil (2.630 g, 100%): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  2.39 (m, 6 H), 2.98 (t, 6 H,  $J$  = 7.8 Hz), 7.33 (dd, 6 H,  $J$  = 8.1, 2.4 Hz), 7.63 (dd, 6 H,  $J$  = 11.7, 8.1 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  26.5, 32.5 (t, <sup>2</sup> $J_{CF}$  = 29.9 Hz), 128.6 (d, <sup>3</sup> $J_{CP}$  = 12.0 Hz), 131.2 (d, <sup>1</sup> $J_{CP}$  = 104.8 Hz), 132.6 (d, <sup>2</sup> $J_{CP}$  = 9.8 Hz), 143.6; <sup>31</sup>P NMR (CDCl<sub>3</sub>, 101 MHz)  $\delta$  28.0 (s). Anal. calc. for C<sub>42</sub>H<sub>24</sub>F<sub>39</sub>PO: C, 38.32; H, 1.84. Found: C, 38.46; H, 1.52; MS (CI,  $m/z$ ): 1317 ( $M^+$  + 1), 1000, 971, 909, 893, 876.

**Step C. Tris[4-(1H,1H,2H,2H-perfluorooctyl)phenyl]phosphine (5)** To a mixture of **4** (666 mg, 0.5 mmol), triethylamine (380 mg, 3.75 mmol), and toluene (10 mL) in a three-necked flask is added trichlorosilane (339 mg, 2.5 mmol) under nitrogen. The mixture is stirred at 120 °C under nitrogen for 5 h. After cooling to room temperature, degassed, saturated NaHCO<sub>3</sub> aqueous solution (0.5 mL) is added. The mixture is stirred under nitrogen for 5 min at room temperature, and then filtered through a pad of alumina. The flask is washed with toluene (3  $\times$  15 mL) and the washings are filtered through the alumina. Finally, the combined filtrates are evaporated under reduced pressure to give tris[4-(1H,1H,2H,2H-perfluorooctyl)phenyl]phosphine **5** as a white solid (630 mg, 96%): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  2.37 (m, 6 H), 2.92 (m, 6 H), 7.19 (d, 6 H,  $J$  = 7.9), 7.26 (d, 6 H,  $J$  = 7.9); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  26.6, 33.1 (t, <sup>2</sup> $J_{CF}$  = 22.1 Hz), 128.9 (d, <sup>3</sup> $J_{CP}$  = 7.0 Hz), 134.5 (d, <sup>2</sup> $J_{CP}$  = 19.8 Hz), 135.9 (d, <sup>1</sup> $J_{CP}$  = 10.8 Hz), 140.3; <sup>31</sup>P NMR (CDCl<sub>3</sub>, 101 MHz)  $\delta$  -7.6 (s) [3]. For other analytical details on this compound, see reference [4b].

## Discussion

Fluoroalkyl-derivatized aryl phosphines that contain an insulating spacer between the aryl group and the electron-withdrawing fluorine fragments can be prepared by lithiation of fluoroalkyl-substituted bromobenzenes followed by reaction with PAr<sub>3-n</sub>Cl<sub>n</sub> [3, 4]. Various methods have been developed for the synthesis of fluoroalkyl bromobenzenes; these include coupling with Grignard reagents [4a], Negishi-type coupling [4b], Wittig reactions [4c], and

the Heck reaction [5]. The method presented herein is based on the Heck coupling of **1** and provides an alternative that is easy to perform, high yielding and versatile, provided that a suitable fluorinated olefin is available [6]. Thus, the olefination of **1** with **2** by the palladacycle catalyst afforded **3** in 91% isolated yield and, as with normal Heck reactions, substitution of the vinylic protons by the arylphosphine oxide occurred at the less substituted side of the C=C double bond leading to a *trans*-olefin. The reaction did not proceed with the less-activated tris(4-bromophenyl)phosphine and the borane protected tris(4-bromophenyl)-phosphine, however. To obtain the free phosphine **5**, the substituted phosphine oxide **3** was first subjected to hydrogenation and then reduced by treatment with trichlorosilane by normal procedures; **5** was isolated in 87% overall yield. *Mono*-, *bis*- and other tris-fluoroalkylated arylphosphines have been obtained in similar yields by the same method [6], and this method has also been used to prepare 6,6'-fluoroalkylated BINAP [7].

## References

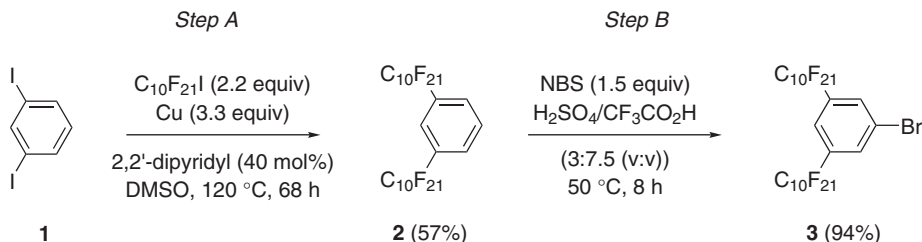
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### 11.11

#### 3,5-bis(Perfluorodecyl)phenylboronic Acid. An Easily Recyclable Direct Amide Condensation Catalyst

Kazuaki Ishihara and Hisashi Yamamoto

#### Reaction 11.11-1



the Heck reaction [5]. The method presented herein is based on the Heck coupling of **1** and provides an alternative that is easy to perform, high yielding and versatile, provided that a suitable fluorinated olefin is available [6]. Thus, the olefination of **1** with **2** by the palladacycle catalyst afforded **3** in 91% isolated yield and, as with normal Heck reactions, substitution of the vinylic protons by the arylphosphine oxide occurred at the less substituted side of the C=C double bond leading to a *trans*-olefin. The reaction did not proceed with the less-activated tris(4-bromophenyl)phosphine and the borane protected tris(4-bromophenyl)-phosphine, however. To obtain the free phosphine **5**, the substituted phosphine oxide **3** was first subjected to hydrogenation and then reduced by treatment with trichlorosilane by normal procedures; **5** was isolated in 87% overall yield. *Mono*-, *bis*- and other tris-fluoroalkylated arylphosphines have been obtained in similar yields by the same method [6], and this method has also been used to prepare 6,6'-fluoroalkylated BINAP [7].

## References

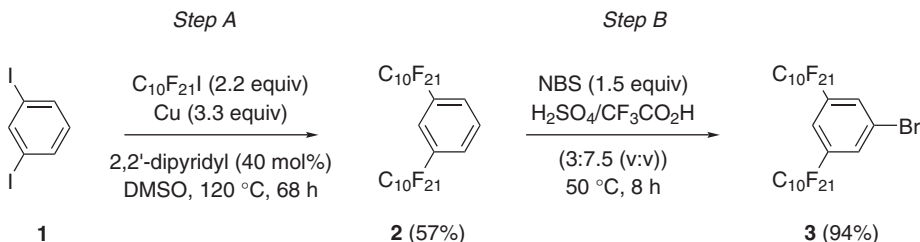
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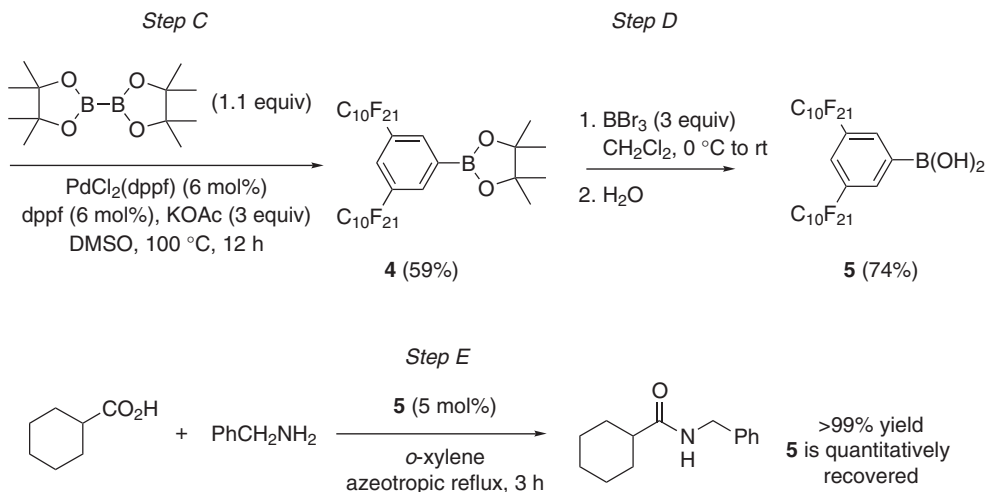
### 11.11

#### 3,5-bis(Perfluorodecyl)phenylboronic Acid. An Easily Recyclable Direct Amide Condensation Catalyst

Kazuaki Ishihara and Hisashi Yamamoto

#### Reaction 11.11-1





## Reagents

1-Iodoperfluorodecane [423-62-1] is commercially available from Lancaster Synthesis Ltd.

## Experimental Procedure

**Step A. 1,3-Bis(perfluorodecyl)benzene (2)** [1] A mixture of 1,3-diiodobenzene (**1**) (5.0 g, 15.2 mmol), 1-iodoperfluorodecane (21.6 g, 33.4 mmol), copper (powder, 3.2 g, 50.2 mmol), 2,2'-dipyridyl (940 mg, 6.0 mmol) [2] and DMSO (100 mL) is stirred at 120 °C for 68 h. After cooling to room temperature, the reaction mixture is diluted with chloroform (250 mL) and water (250 mL), filtered through a pad of Celite and washed with chloroform (100 mL  $\times$  2). The organic layer is separated, washed with 1 M HCl (100 mL  $\times$  2), water (100 mL  $\times$  2), and brine (100 mL), dried over MgSO<sub>4</sub>, and evaporated under reduced pressure (ca. 20 Torr) to give the crude product. Recrystallization from chloroform yields pure compound **2** (9.6 g, 8.6 mmol, 57% yield) as colorless needles: mp 78 °C; IR (KBr) 1210, 1152 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz, 50 °C)  $\delta$  7.69 (t,  $J$  = 7.8 Hz, 1 H), 7.82 (s, 1 H), 7.83 (d,  $J$  = 7.8 Hz, 2 H); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz, 55 °C)  $\delta$  -126.64 (s, 6 F), -123.25 (s, 4 F), -122.63 (s, 4 F), 122.25 (s, 16 F), -121.63 (s, 4 F), -111.69 (t,  $J$  = 12.1 Hz, 4 F), -81.82 (t,  $J$  = 9.3 Hz, 4 F). Anal. calc. for C<sub>26</sub>H<sub>4</sub>F<sub>42</sub>: C, 28.03; H, 3.62. Found: C, 27.98; H, 3.67.

**Step B. 1-Bromo-3,5-bis(perfluorodecyl)benzene (3)** [3] In a 100 mL round-bottomed flask, equipped with powerful magnetic stirrer, is placed trifluoroacetic acid (7.5 mL), **2** (2.0 g, 1.78 mmol), and concentrated sulfuric acid (3 mL). The mixture is stirred vigorously, and *N*-bromosuccinimide (475 mg, 2.67 mmol) is added in portions over an 8 h period. After the reaction mixture is stirred at 50 °C for 8 h, it is poured into ice water (50 mL). The reaction mixture is then stirred at room temperature for several hours, and the solid is separated by filtration. Washing with water (20 mL), drying by air and recrystallization from chloroform gives pure compound **3** with 94% yield (1.99 g, 1.67 mmol) as colorless needles: mp 109 °C;



IR (KBr) 1230, 1150  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz, 50  $^\circ\text{C}$ )  $\delta$  7.75 (s, 1 H), 7.96 (s, 2 H);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 282 MHz, 55  $^\circ\text{C}$ )  $\delta$  -126.66 (s, 6 F), -123.27 (s, 4 F), -122.29 (s, 20 F), -121.62 (s, 4 F), -111.67 (t,  $J$  = 15.2 Hz, 4 F), -81.81 (t,  $J$  = 9.0 Hz, 4 F). Anal. calc. for  $\text{C}_{26}\text{H}_3\text{F}_{42}\text{Br}$ : C, 26.17; H, 2.53. Found: C, 26.02; H, 2.55.

**Step C. 3,5-Bis(perfluorodecyl)phenylboronic Acid Pinacol Ester (4)** [4] The flask is charged with  $\text{PdCl}_2(\text{dppf})$  (32.6 mg, 0.04 mmol), dppf (22.2 mg, 0.04 mmol), KOAc (196.3 mg, 2 mmol), **3** (800 mg, 0.67 mmol), and bis(pinacolato)diboron (188 mg, 0.74 mmol), and flushed with argon. DMSO (10 mL) is added, and the resulting mixture is then stirred at 100  $^\circ\text{C}$  for 12 h. The reaction mixture is diluted with hot chloroform and hot water, then the organic layer is separated, dried over  $\text{MgSO}_4$ , filtered through glass filter (40–100  $\mu\text{m}$ ) and evaporated under reduced pressure (ca. 20 Torr). Recrystallization from hot  $\text{CHCl}_3$  yields pure compound **4** (490 mg, 59% yield) as colorless needles: mp 112  $^\circ\text{C}$ ; IR (KBr) 1341, 1240, 1220, 1200, 1152  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz, 50  $^\circ\text{C}$ )  $\delta$  1.38 (s, 12 H), 7.87 (s, 1 H), 8.21 (s, 2 H);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 282 MHz, 55  $^\circ\text{C}$ )  $\delta$  -126.67 (s, 6 F), -123.23 (s, 4 F), -122.32 (s, 20 F), -121.67 (s, 4 F), -111.56 (t,  $J$  = 15.2 Hz, 4 F), -81.82 (t,  $J$  = 9.3 Hz, 4 F). Anal. calc. for  $\text{C}_{32}\text{H}_{15}\text{F}_{42}\text{BO}_2$ : C, 30.99; H, 1.22. Found: C, 30.97; H, 1.28.

**Step D. 3,5-Bis(perfluorodecyl)phenylboronic Acid (5)** To a stirred suspension of **4** (430 mg, 0.35 mmol) in dichloromethane (10 mL) is added boron tribromide (94.5  $\mu\text{L}$ , 1.05 mmol) at -78  $^\circ\text{C}$ . The reaction mixture is stirred at 0  $^\circ\text{C}$  for 2 h and additionally at room temperature for 0.5 h. After water is added to the reaction mixture at 0  $^\circ\text{C}$ , the resulting mixture is diluted with chloroform (10 mL) and stirred vigorously for 1 h. The white solid is separated by filtration, washed with water (20 mL) and dichloromethane (20 mL), and dried under vacuum (1 Torr) to give pure **5** in 74% yield (301 mg, 0.26 mmol): mp 166  $^\circ\text{C}$ ; IR (KBr) 1375, 1841, 1293, 1225, 1150, 1096, 899  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz, 55  $^\circ\text{C}$ )  $\delta$  7.90 (s, 1 H), 8.12 (s, 2 H);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 282 MHz, 55  $^\circ\text{C}$ )  $\delta$  -127.09 (s, 6 F), -123.70 (s, 4 F), -122.78 (s, 20 F), -122.15 (s, 4 F), -112.04 (t,  $J$  = 15.2 Hz, 4 F), -81.96 (t,  $J$  = 9.0 Hz, 4 F). Anal. calc. for  $\text{C}_{26}\text{H}_5\text{F}_{42}\text{BO}_2$ : C, 26.97; H, 0.44. Found: C, 27.01; H, 0.35.

**Step E. N-Benzyl-4-phenylbutyramide** A dry, 10-mL round-bottomed flask fitted with a stir bar and a 5 mL pressure-equalized addition funnel [containing a cotton plug and ca. 2 g of 4 Å molecular sieves (pellets) and functioning as a Soxhlet extractor] surmounted by a reflux condenser is charged with cyclohexanecarboxylic acid (128.2 mg, 1.0 mmol), benzylamine (109.2  $\mu\text{L}$ , 1.0 mmol), and **5** (57.9 mg, 0.05 mmol) in *o*-xylene (5 mL). The mixture is heated at azeotropic reflux with removal of water to provide a homogeneous solution. After 3 h, the resulting mixture is cooled to ambient temperature to precipitate **5**. After 1 h, the liquid phase of the resultant mixture is decanted and the residual solid catalyst **5** is reused without isolation. Catalyst **5** remains in the flask up to the tenth reaction. Liquid phases which are obtained in each of the reactions are combined, concentrated under reduced pressure, and the residue is purified by column chromatography on silica gel (eluant: hexane–ethyl acetate = 3:1) to give the corresponding amide (2.08 g, 9.6 mmol, 96% yield) [5].

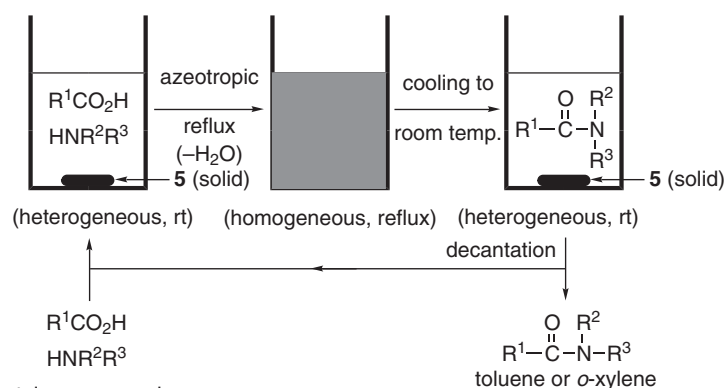
**Typical Procedure for Recovery of 5** After completing the above reaction (one cycle), the resulting mixture is cooled to ambient temperature to precipitate **5**. After 1 h, the resultant

mixture is diluted with toluene (3 mL), and **5** is separated by filtration, washed with toluene (2 mL), and dried under vacuum (1 Torr) to recover **5** (56.0 mg, 97% yield) as a pure white solid.

## Discussion

Arylboronic acids bearing electron-withdrawing substituents at the aryl group behave as water-, acid-, and base-tolerant thermally stable Lewis acids and can be easily handled in air. Ishihara et al. have found that 3,5-bis(trifluoromethyl)phenylboronic acid (**6**) and 3,4,5-trifluorophenylboronic acid (**7**) are highly effective catalysts for the amide condensation of amines (1 equiv) and carboxylic acids (1 equiv) [5]. This is the first example of a catalytic and direct amide condensation which does not require excess amounts of substrates. Most of the above homogeneous catalytic reactions require relatively large quantities of arylboronic acid catalysts (1~20 mol%), and trace amounts of the catalysts must be removed from the reaction products. This has hampered the application of this methodology to large scale syntheses.

Catalyst **5** is insoluble in toluene and *o*-xylene at room temperature even in the presence of carboxylic acids, amines, and amides. However, the amide condensation catalyzed by **5** proceeds homogeneously under reflux conditions. To demonstrate this advantage of **5** with respect to solubility, Ishihara et al. have reused **5** (5 mol%) ten times for the amide condensation reaction of cyclohexanecarboxylic acid with benzylamine. After heating the reaction mixture at reflux with removal of water for 3 h, the mixture is allowed to stand at ambient temperature for 1 h to precipitate **5**. The liquid phase of the resultant mixture is decanted and the residual solid catalyst **5** is reused without isolation. No loss of activity is observed for the recovered catalyst, and 26% of **5** remains in the flask after the tenth reaction. This means that 88% of **5** is retained in each cycle. The total isolated yield of the amide which is obtained in ten reactions is 96%. Moreover, pure compound **5** can be recovered in 97% yield as a white solid from the above reaction mixture by filtration and washing with toluene [6].



Scheme 11.11-1

## References

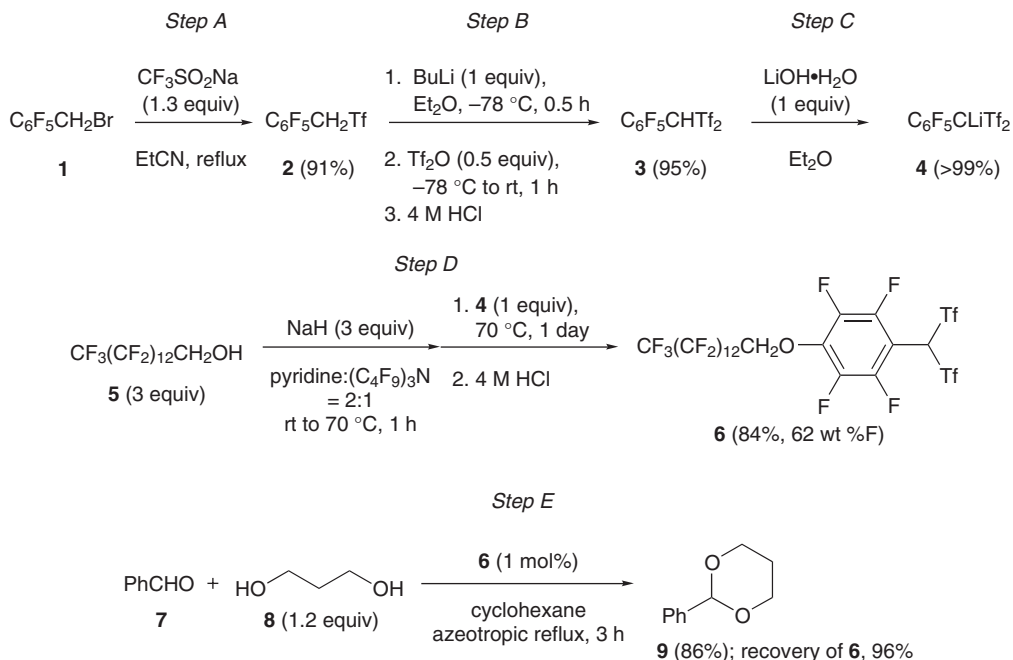
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## 11.12

## Fluorous-tagged Tetrafluorophenylbis(triflyl)methane. An Organic Solvent-swellable and Strong Brønsted Acid Catalyst

Kazuaki Ishihara and Hisashi Yamamoto

## Reaction 11.12-1



## Reagents

Sodium suifinate is commercially available from Central Glass Co., Ltd., Japan. 1*H*,1*H*-Perfluoro-1-tetradecanol [15622-57-8] is commercially available from Fluorochem Ltd., UK. Pentafluorophenylbis(triflyl) methane (**3**) is sold by TCI Co., Ltd.

## Experimental Procedures

**Step A. Pentafluorophenylmethyl Triflone (2)** [1] A solution of 2,3,4,5,6-pentafluorobenzyl bromide (**1**) (2.6 g, 10 mmol) and sodium triflinate (2.0 g, 13 mmol) in propionitrile (30 mL) is heated at reflux. After one day, the mixture is cooled, the salts are filtered and the solvent is evaporated under reduced pressure. The residue is purified by column chromatography using a linear EtOAc gradient in hexane to give **2** as a solid (2.9 g, 91% yield): IR (KBr) 1509, 1374, 1210, 1121, 995  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  4.64;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  44.3, 100.0 (dt,  $J_{\text{CF}} = 4, 17$  Hz, 1 C, *ipso*-C), 119.5 (q,  $J_{\text{CF}} = 326$  Hz, 1 C,  $\text{CF}_3$ ), 137.9 (d,  $J_{\text{CF}} = 251$  Hz, 2 C, 2*m*-C), 142.8 (d,  $J_{\text{CF}} = 258$  Hz, 1 C, *p*-C), 145.9 (d,  $J_{\text{CF}} = 252$  Hz, 2 C, 2*o*-C);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 282 MHz)  $\delta$  -160.0 (d,  $J = 15.2$  Hz, 2 F, 2*m*-F), 149.0 (s, 1 F, *p*-F), 139.4 (d,  $J = 15.2$  Hz, 2 F, 2*o*-F), -78.3 (s, 3 F,  $\text{CF}_3$ ). Anal. calc. for  $\text{C}_8\text{H}_2\text{O}_2\text{F}_8\text{S}$ : C, 30.59; H, 0.64; F, 48.38; S, 10.21. Found C, 30.49; H, 0.73; F, 48.37; S, 10.18.

**Step B. Pentafluorophenylbis(triflyl)methane (3)** [2] To a solution of **2** (157 mg, 0.5 mmol) in dry  $\text{Et}_2\text{O}$  (3 mL) is added BuLi (0.34 mL, 0.5 mmol, 1.6 M solution in hexanes) dropwise at  $-78^\circ\text{C}$ , and the resulting mixture is stirred for 10 min. Triflic anhydride (42  $\mu\text{L}$ , 0.25 mmol) is then added, and the resulting mixture is allowed to warm to room temperature over a period of 1 h, before the reaction is quenched with water. The resultant mixture is neutralized and washed with hexane. The aqueous phase is acidified with 4 M aqueous HCl and extracted with ether twice. The organic layers are dried over magnesium sulfate, filtrated and concentrated under reduced pressure to give **3** as a solid, which is purified by vacuum sublimation (0.3 Torr,  $100^\circ\text{C}$ ): mp  $86\text{--}87^\circ\text{C}$ ; IR (KBr) 1522, 1501, 1347, 1321, 1198, 1127, 1024, 988, 613  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  6.21 (brs, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  70.4, 98.0 (s, 1 C, *ipso*-C), 119.2 (q,  $J_{\text{CF}} = 330$  Hz, 2 C, 2 $\text{CF}_3$ ), 137.8 (d,  $J_{\text{CF}} = 258$  Hz, 1 C, *m*-C), 138.6 (d,  $J_{\text{CF}} = 257$  Hz, 1 C, *m*-C), 144.7 (d,  $J_{\text{CF}} = 264$  Hz, 1 C, *p*-C), 145.4 (d,  $J_{\text{CF}} = 262$  Hz, 1 C *o*-C), 147.2 (d,  $J_{\text{CF}} = 262$  Hz, 1 C, *o*-C);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$  ( $\delta$  49.0), 125 MHz)  $\delta$  56.2, 109.1 (dt,  $J = 6, 19$  Hz, 1 C, *ipso*-C), 122.4 (q,  $J_{\text{CF}} = 324$  Hz, 2 C, 2 $\text{CF}_3$ ), 138.5 (d,  $J_{\text{CF}} = 250$  Hz, 2 C, 2*m*-C), 143.0 (d,  $J_{\text{CF}} = 251$  Hz, 1 C, *p*-C), 150.0 (d,  $J_{\text{CF}} = 245$  Hz, 1 C, *o*-C),  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 282 MHz)  $\delta$  -157.9 (dt,  $J = 6.2, 21.5$  Hz, 1 F, *m*-F), -156.8 (dt,  $J = 6.2, 21.5$  Hz, 1 F, *m*-F), -142.6 (tt,  $J = 5.9, 21.5$  Hz, 1 F, *p*-F), -140.3 (br, 1 F, *o*-F), -127.7 (ddd,  $J = 5.9, 15.2, 21.5$  Hz, 1 F, *o*-F), -75.2 (s, 6 F, 2 $\text{CF}_3$ ); HRMS (EI) calc. for  $\text{C}_9\text{HO}_4\text{F}_{11}\text{S}_2$   $[\text{M}]^+$  445.9141, found 445.9137.

**Step C. Preparation of Lithium Pentafluorophenylbis(triflyl)methide (4)** A solution of **3** (1.36 g, 3.05 mmol) in diethyl ether (20 mL) is neutralized by addition of lithium hydroxide monohydrate (0.13 g, 3.05 mmol). Diethyl ether is evaporated under reduced pressure and the residual salt was dried at  $80^\circ\text{C}$  under vacuum (ca. 1 Torr) for 12 h (quantitative yield):  $^{13}\text{C}$

NMR (CD<sub>3</sub>OD, 125 MHz)  $\delta$  56.1, 109.0 (dt,  $J$  = 4, 19 Hz, 1 C, *ipso*-C), 122.3 (q,  $J_{\text{CF}}$  = 324 Hz, 2 C, 2CF<sub>3</sub>), 138.5 (d,  $J_{\text{CF}}$  = 247 Hz, 2 C, 2*m*-C), 143.0 (d,  $J_{\text{CF}}$  = 251 Hz, 1 C, *p*-C), 149.5 (d,  $J_{\text{CF}}$  = 245 Hz, 2 C, 2*o*-C).

**Step D. 4-(1*H*,1*H*-Perfluorotetradecanoxy)-2,3,5,6-tetrafluorophenylbis(triflyl)methane (6)** To a mixture of sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol) and 1*H*,1*H*-perfluoro-1-tetradecanol (5) (0.53 g, 0.75 mmol) is added pyridine (4 mL) [3] and perfluorotriethylamine (2 mL) at room temperature. The resulting mixture is heated to 70 °C and stirred at the same temperature for 1 h. Lithium salt 4 (0.11 g, 0.25 mmol) is then added at 70 °C, and the resulting mixture is stirred for an additional 1 day at the same temperature. After cooling to 0 °C, the reaction is quenched with 4 M aqueous HCl (40 mL) at 0 °C. The resultant acidified mixture is extracted with diethyl ether (40 mL  $\times$  2). The organic layers are dried over magnesium sulfate, filtered and concentrated under reduced pressure to give a brown solid. Furthermore, excess 5 which is contained in the solid is removed by vacuum sublimation (120 °C, 0.06 Torr). The residual dark-brown solid is dissolved in diethyl ether (20 mL) or perfluoromethylcyclohexane (20 mL), and some insoluble impurities are then removed by filtration. The filtrate is concentrated under reduced pressure to give 6 (0.238 g, 0.21 mmol, 84% yield) as a white solid: mp 95~96 °C; IR (KBr) 1503, 1406, 1397, 1213, 1154, 1111, 984, 646, 625, 550, 527 cm<sup>-1</sup>; <sup>1</sup>H NMR (toluene-*d*<sub>8</sub> + perfluorotoluene, 80 °C, 300 MHz)  $\delta$  4.06 (t,  $J$  = 12.5 Hz, 2 H), 6.21 (s, 1 H). Anal. calc. for C<sub>23</sub>H<sub>3</sub>O<sub>5</sub>F<sub>37</sub>S<sub>2</sub>: C, 24.53; H, 0.27. Found: C, 24.51; H, 0.31.

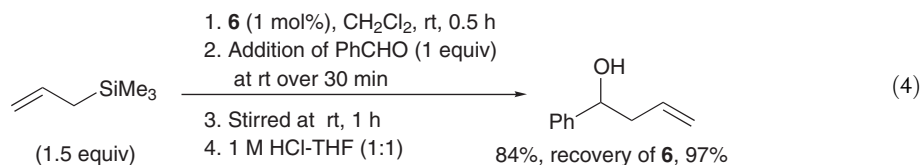
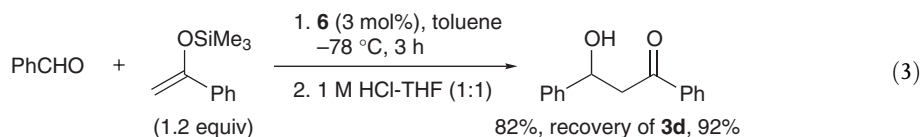
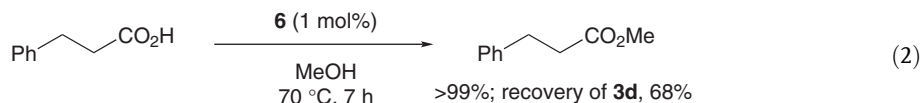
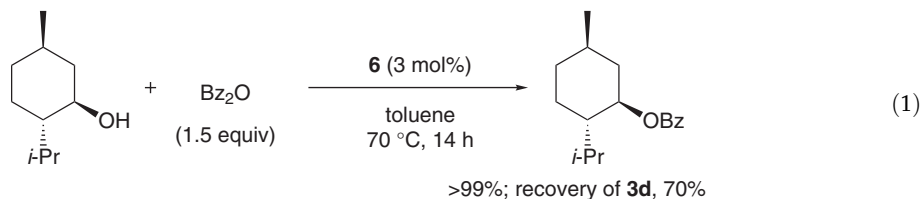
**Step E. 2-Phenyl-1,3-dioxane (9)** To a solution of 6 (33.8 mg, 0.03 mmol) in cyclohexane (6 mL) are added benzaldehyde (7) (0.30 mL, 3.0 mmol) and 1,3-propanediol (8) (0.24 mL, 3.3 mmol), and the resulting mixture is heated at azeotropic reflux with the removal of water using a Dean-Stark apparatus. After 3 h, the reaction mixture is cooled to ambient temperature to precipitate 6, which is filtered and washed with cyclohexane (2 mL) to recover 6 (32.4 mg, 0.029 mmol, 96% yield). The filtrate is concentrated under reduced pressure. The purity of the recovered catalyst is checked by <sup>1</sup>H and <sup>19</sup>F NMR analyses. The crude oil is purified by column chromatography on silica gel (eluent: hexane–EtOAc = 20:1 to 5:1) to afford the corresponding acetal 9 (0.425 g, 2.6 mmol, 86% yield).

## Discussion

Pentafluorophenylbis(triflyl)methane 3 (47 wt% F) is soluble in most organic and fluorous solvents [4]. Fluorous-phase affinity for arylbis(triflyl)methane is increased by appending, “fluorous ponytails,” OCH<sub>2</sub>(CF<sub>2</sub>)<sub>*n*</sub>CF<sub>3</sub> groups to 3. For example, 4-(1*H*,1*H*-perfluoro-1-tetradecanoxy)-2,3,5,6-tetrafluorophenylbis(triflyl)methane 6 (62 wt% F) can be recycled by using a fluorous biphasic technique [5]. Fluorous solid catalyst 6 is a more active catalyst than perfluoresulfonic acids such as Nafion<sup>®</sup>.

Fluorous solid catalyst 6 is soluble in cyclohexane under reflux conditions, and promotes the acetalization of 7 with 8 well to give the desired acetal 9 in 86% yield. After the reaction, 6 is recovered in 96% yield by precipitation at room temperature [6]. Besides this acetalization, 6 is also effective as a fluorous catalyst for the acylation of *l*-menthol with benzoic anhydride [Eq. (1)] and esterification of 3-phenylpropionic acid in methanol [Eq. (2)] [7]. Fluorous solid catalyst 6 was also used in the Mukaiyama aldol reaction [Eq. (3)] and the Sakurai-Hosomi allylation reaction [Eq. (4)]. These reactions are performed at –78 °C and rt,

respectively, under heterogeneous conditions. After the reaction, **6** is recovered in high yield by decanting the liquids at room temperature.



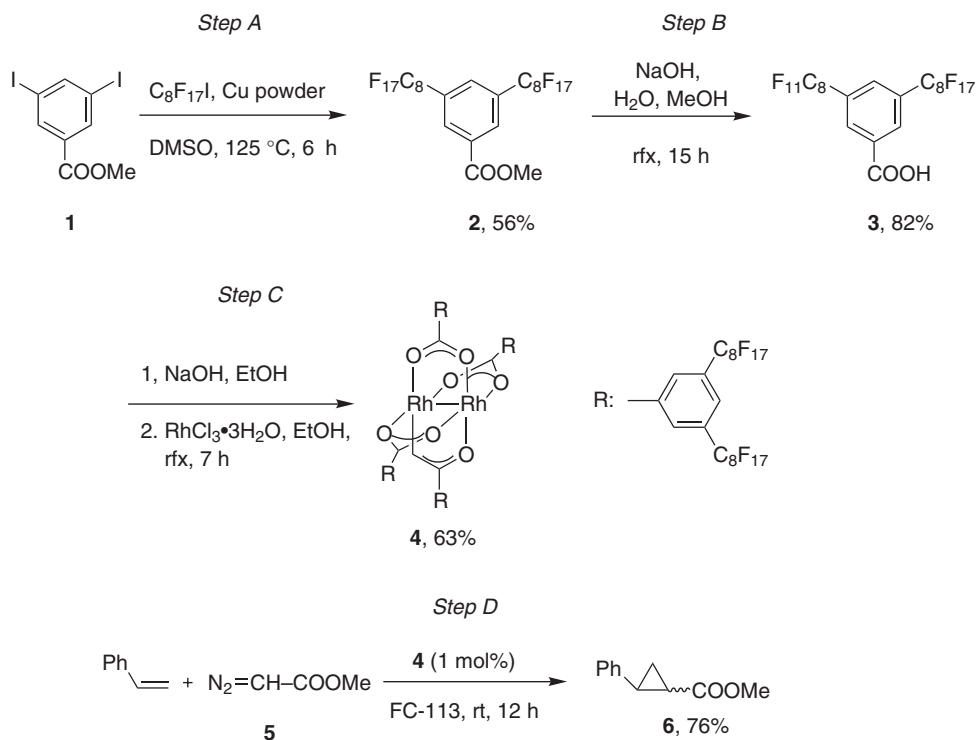
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- In the case of the esterification, the resultant solution is concentrated under reduced pressure, and the crude compounds are diluted in hexane to precipitate **6**. Thus, **6** is recovered by filtration.

## 11.13

**Tetrakis[ $\mu$ -3,5-bis(perfluorooctyl)benzoato-O,O'] Dirhodium. Application as a Recyclable Catalyst for a Carbenoid Cyclopropanation Reaction**

Gerhard Maas and Andreas Endres

**Reaction 11.13-1****Reagents**

Perfluorooctyl iodide and perfluoro(methylcyclohexane) (PFMC) were purchased from Lancaster, 1,1,2-trichloro-1,2,2-trifluoroethane (FC-113) from Riedel-de-Haen.

**Experimental Procedure [1]**

**Step A. Methyl 3,5-Bis(perfluorooctyl)benzoate (2)** A mixture of a few iodine crystals and copper dust (3.00 g) in acetone (20 mL) is stirred for 30 min. After removal of the solvent, the copper is washed with aq. HCl (6 N) in acetone (20 mL, 2:3 v/v) and acetone (2 × 10 mL) and dried *in vacuo*. The activated copper powder (819 mg, 12.89 mmol) is mixed with methyl 3,5-diiodobenzoate **1** (500 mg, 1.29 mmol), perfluorooctyl iodide (1.48 g, 2.71 mmol) and dry DMSO (9 mL). The suspension is stirred for 6 h at 125 °C. After cooling to rt, water and

ether (10 mL each) are added. The mixture is stirred for 10 min, then filtered with suction. The solid residue is washed with ether ( $2 \times 20$  mL). The filtrate (ether, water, DMSO) and the ether washings are combined, the ethereal layer is separated and kept, and the DMSO–water phase is extracted with ether ( $2 \times 20$  mL). All ether phases are combined, dried ( $\text{Na}_2\text{SO}_4$ ), and evaporated. The resulting pale-brown solid is purified by chromatography on silica gel [eluent: petroleum ether/diethyl ether (7:3)] to give colorless crystals (702 mg, 56% yield), mp 62–63 °C [2]:  $^1\text{H}$  NMR (400.1 MHz,  $\text{CDCl}_3/\text{FC-113}$ )  $\delta$  4.01 (s, 3 H, OMe), 7.98 (s, 1 H, 4- $\text{H}_{\text{ar}}$ ), 8.49 (s, 2 H, 2,6- $\text{H}_{\text{ar}}$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , FC-113)  $\delta$  53.7 (OMe), 113.5–131.5 (several m,  $\text{C}_{\text{F}}$ ), 129.4 (2,6- $\text{C}_{\text{ar}}$ ), 130.9 (3,5- $\text{C}_{\text{ar}}$ ), 131.6 (4- $\text{C}_{\text{ar}}$ ), 132.3 (C-1 $_{\text{ar}}$ ), 164.4 (C=O);  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -82.2 (t,  $^3J = 10.8$  Hz, 6 F,  $\text{CF}_3$ ), -112.38 (t,  $^3J = 14.3$  Hz, 4 F), -122.45 (m, 4 F), -123.15 (m, 16 F), -124.05 (m, 2 F), -127.45 (m, 2 F).

**Step B. 3,5-Bis(perfluorooctyl)benzoic Acid (3)** Ester 2 (250 mg, 0.26 mmol) is suspended in a mixture of methanol (2 mL) and water (4 mL), and potassium hydroxide (130 mg, 2.32 mmol) is added. A clear solution forms upon heating at reflux. After 15 h at reflux, most of the methanol is evaporated and the remaining solution is neutralized with 6 N hydrochloric acid. After extraction with ether ( $3 \times 20$  mL), drying of the combined ether phases ( $\text{Na}_2\text{SO}_4$ ) and evaporation of the solvent, the residue is recrystallized from toluene to give a white solid (205 mg, 82% yield), mp 117 °C:  $^1\text{H}$  NMR (400.1 MHz,  $\text{CDCl}_3$ )  $\delta$  7.97 (s, 1 H, 4- $\text{H}_{\text{ar}}$ ), 8.49 (s, 2 H, 2,6- $\text{H}_{\text{ar}}$ ); IR (KBr)  $\nu = 3650$ –2700 (several broad absorptions, OH), 1712 (s, C=O), 1204 (vs, CF), 1149 (vs, CF)  $\text{cm}^{-1}$ .

**Step C. Complex 4** A solution of acid 3 (100 mg, 0.104 mmol) and sodium hydroxide (4.1 mg, 0.104 mmol) in ethanol (10 mL) is added to a stirred solution of rhodium trichloride trihydrate ( $\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$ ) (9.0 mg, 34.6  $\mu\text{mol}$ ) in refluxing ethanol (3 mL). The color of the solution changes from red to yellow, yellow brown, and green. After 7 h a green waxy solid precipitates. Half of the solvent is removed at 40 °C/120 mbar and after cooling to 4 °C, the remaining solvent is decanted completely. The dark-green residue, which contains some rhodium powder, is dried at 50 °C/1 mbar, then dissolved in PFMC (2 mL). After filtration and liquid/liquid extraction with THF ( $2 \times 1.5$  mL), the fluorous layer yields a solid which is subjected to flash chromatography on silica gel [eluent petroleum ether/diethyl ether (7:3);  $R_f$  of 4 = 0.97] to remove left-overs of the sodium salt of 3. Complex 4 is obtained as a dark-green waxy solid (44 mg, 63% yield):  $^1\text{H}$  NMR (400.1 MHz,  $\text{CDCl}_3/\text{FC-113}$ )  $\delta$  7.83 (s, 1 H, 4- $\text{H}_{\text{ar}}$ ), 8.37 (s, 1 H, 2,6- $\text{H}_{\text{ar}}$ );  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -82.5 (t,  $^3J = 10.3$  Hz, 24 F,  $\text{CF}_3$ ), -112.3 (m, 16 F,  $\text{CF}_2$ ), -122.5 (m, 16 F,  $\text{CF}_2$ ), -122.7 (m, 16 F,  $\text{CF}_2$ ), -123.3 (m, 32 F,  $\text{CF}_2$ ), -124.1 (m, 16 F,  $\text{CF}_2$ ), -127.7 (m, 16 F,  $\text{CF}_2$ ); IR (KBr) 1626 (m), 1587 (s), 1408 (s), 1369 (s), 1314 (s), 1238 (vs, br), 1209 (vs, br), 1150 (vs), 1118 (s)  $\text{cm}^{-1}$ .

**Step D. Cyclopropanation of Styrene with Methyl Diazoacetate (5) Catalyzed by 4** A solution of methyl diazoacetate (5) (100 mg, 1.00 mmol) in FC-113 (0.5 mL) is added via a syringe pump over 8 h to a stirred solution of catalyst 4 (40.3 mg, 1 mol%) and a ten-fold excess of styrene (1.13 mL, 10.0 mmol) in FC-113 (1.5 mL). After 4 h at 20 °C, most of the volatiles are removed at 20 °C/1 mbar and the residue is stirred with PFMC (0.8 mL) and dichloromethane (2.5 mL) for 20 min. After phase separation, methyl 2-phenylcyclopropane-1-carboxylate 6 is found in the  $\text{CH}_2\text{Cl}_2$  phase (yield: 76.4%;  $E$ : $6$ : $Z$ : $6 = 0.88$ ; all values determined by GC). Preparative isolation and purification of 6 can be achieved by column chro-



matography (silica gel, ether–pentane) followed by bulb-to-bulb distillation (162–168 °C/16 mbar). The dark-green fluoruous phase is evaporated, and the recovered catalyst so obtained is used in a subsequent reaction cycle. A series of five subsequent reaction cycles gave the following results for yield of cyclopropane **6** and percentage of recovered catalyst relative to the amount used in the first cycle (in parentheses): 76.4% (98%), 75.9 (88), 76.1 (77), 75.6 (68), 75.1 (62). The evaporated fluoruous solvents can be collected in a cold trap and can be reused after vacuum distillation.

## Discussion

Metal-catalyzed inter- and intramolecular carbenoid reactions of diazo compounds are powerful tools in contemporary organic synthesis because they allow chemical transformations that often cannot be readily realized by other means [3]. Besides some copper-based catalysts, dinuclear rhodium(II) carboxylates and amidates currently represent the most effective and versatile catalysts for such carbenoid reactions. For various different reasons, it may be desirable to recover and to reuse the rhodium catalyst. As an alternative to polymer-supported catalysts, we investigated the fluoruous approach and found [1] that rhodium complex **4** and the related 3,5-bis(perfluorohexyl)benzoate complex serve the purpose much better than highly fluorinated rhodium(II) alkanoate complexes [4]. Owing to the insolubility of **4** in common organic solvents applicable for carbenoid reactions, the cyclopropanation reaction described above was run in the hybrid solvent [5] 1,1,2-trichloro-1,2,2-trifluoroethane in which both **4** and the organic reactants and products are soluble, in order to provide homogeneous catalysis conditions. Separation of the fluoruous catalyst from the reaction mixture was achieved by a biphasic extraction (CH<sub>2</sub>Cl<sub>2</sub>-PFMC), and the catalyst could be reused through several subsequent reaction cycles with only a slight decrease in efficiency. The observed loss after each cycle is not caused by leaching into the organic phase but appears to be due mainly to partial degradation.

The preparation of the highly fluorinated free ligand **3** and of the rhodium complex **4** (F contents are 67.4 and 64%, respectively) does not require fluoruous solvents, since the fluorinated reactants are soluble in the hydroxylic solvents at the given reaction temperatures. However, a liquid/liquid extraction using the PFMC/THF biphasic system is a convenient step in the purification procedure of fluoruous complex **4**, due to its good solubility in the fluoruous solvent.

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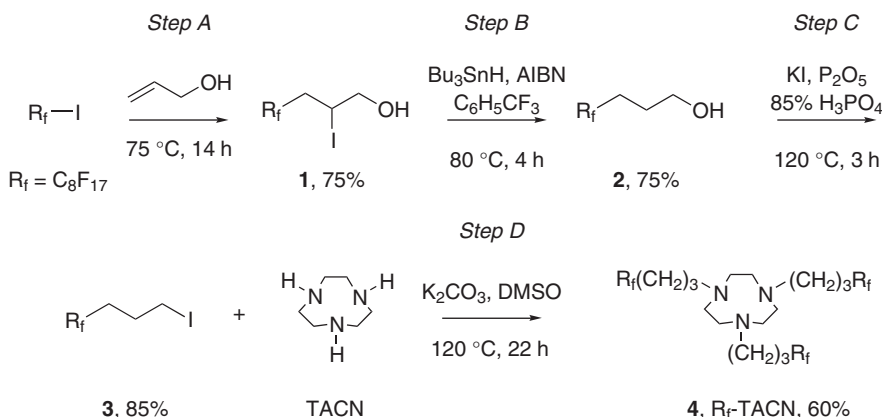
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## 11.14

**1,4,7-Tris-*N*-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecyl)-1,4,7-triazacyclononane [ $R_f$ -TACN]. A Fluorous Soluble Nitrogen Ligand via Alkylation with a Fluoroponytail,  $C_8F_{17}(CH_2)_3I$**

Jean-Marc Vincent\* and Richard H. Fish\*

## Reaction 11.14-1



## Reagents

$R_fI$  ( $R_f = C_8F_{17}$ ) and perfluoroheptane were purchased from Pierce Chemical Co., while AIBN, allyl alcohol, tributyltin hydride, trifluorotoluene, phosphorous pentaoxide, 85%, phosphoric acid, potassium iodide, and 1,4,7-triazacyclononane (TACN) were purchased from Aldrich Chemical Company.

## Experimental Procedures

**Step A. 2-Iodo-1-perfluorooctyl-3-propanol (**1**)** The  $R_fI$  ( $R_f = C_8F_{17}$ , 7 g, 12.8 mmol), allyl alcohol (1 mL, 14.7 mmol), and AIBN (84 mg, 0.51 mmol) are heated at 70–75 °C under an inert atmosphere for 14 h. Every 2 h, a new portion of AIBN is added to the reaction mixture. The pale yellow solid obtained is recrystallized from refluxing hexane (40 mL), and **1** is obtained in 75% yield, mp 93–94 °C: EIMS [ $M^+$ ] 604. Elemental anal. calc. for  $C_{11}H_6F_{17}IO$ : C, 21.87; H, 1.00. Found: C, 22.06; H, 0.97.  $^1H$  NMR (400 MHz,  $CDCl_3$ , 25 °C)  $\delta$  4.45 (m, 1 H,  $-CHI-$ ), 3.79 (m, 2H,  $-CH_2-OH$ ), 2.9 (2m, 2 H,  $R_f-CH_2$ ), 2.04 (t,  $-OH$ ).

**Step B. 3-Perfluorooctyl-1-propanol (**2**)** Compound **1**,  $R_fCH_2CHICH_2OH$  (8 g, 13.2 mmol), and AIBN (52 mg, 0.31 mmol) are partially dissolved in dry trifluorotoluene (40 mL). Tributyltin hydride (4.2 mL, 15.8 mmol) is then added dropwise and the reaction mixture is heated at 80 °C under an inert atmosphere for 4 h (reaction followed by GC analysis). After removing the solvent under vacuum, the resulting residue is partitioned between per-

fluoroheptane and toluene. After decantation, the lower phase is separated from the upper one, which mainly contains  $(\text{Bu})_3\text{SnI}$ . By removing the perfluoroheptane, compound **2** is isolated as a white powder in 75% yield. Compound **2** can be recrystallized from hexane: EIMS  $[\text{M}^+]$  477. Elemental anal. calc. for  $\text{C}_{11}\text{H}_7\text{F}_{17}\text{O}$ : C, 27.63; H, 1.46. Found: C, 27.72; H, 1.63.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , 25 °C)  $\delta$  3.75 (m, 2 H,  $-\text{CH}_2\text{-OH}$ ), 2.20 (m, 2 H,  $\text{R}_f\text{-CH}_2\text{-}$ ), 1.88 (m, 2 H,  $-\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-}$ ), 1.57 (s,  $-\text{OH}$ ).

**Step C. 3-Perfluorooctyl-1-iodopropane (3)** Phosphorous pentaoxide (3.4 g) is added to phosphoric acid (85%, 7.1 mL) in a 50 mL round-bottomed flask and then the mixture is cooled to 0 °C. The KI (1.39 g, 8.2 mmol) is added, followed immediately by  $\text{R}_f\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$  (1.5 g, 3.1 mmol). The mixture is heated at 120 °C for 3.5 h. At ambient temperature, 10 mL of water are added, and the resulting brown solution is extracted four times with 25 mL of diethyl ether. The organic layer is washed twice with 25 mL thiosulfate (0.1 M), then dried over  $\text{Na}_2\text{SO}_4$ . After removing the solvent, the iodo derivative is obtained as an oil, which solidifies at 4 °C. Compound **3** is used without further purification (yield 85%); however, **3** can be recrystallized from methanol: EIMS  $[\text{M}^+]$  588. Elemental anal. calc. for  $\text{C}_{11}\text{F}_{17}\text{H}_6\text{I}$ : C, 22.47; H, 1.02. Found: C, 22.80; H, 1.26;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , 25 °C)  $\delta$  3.26 (t, 2 H,  $\text{I-CH}_2\text{-}$ ), 2.16 (2m, 4 H,  $-\text{CH}_2\text{-CH}_2\text{-R}_f$ ).

**Step D. Tris-*N*-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptafluoroundecyl)-1,4,7-triazacyclononane (4)** TACN (88.4 mg, 0.73 mmol),  $\text{K}_2\text{CO}_3$  (423 mg, 3.1 mmol), and  $\text{R}_f\text{CH}_2\text{CH}_2\text{CH}_2\text{I}$  (1.41 g, 2.41 mmol) are dissolved in DMSO (10 mL, distilled over  $\text{CaH}_2$ ) and heated at 90 °C for 24 h. Then perfluoroheptane (20 mL) is added to the reaction mixture and the brown fluororous lower phase is separated and then filtered. After removing the solvent, compound **4** is obtained as a brown oil. After crystallization from hot hexane, compound **4** is isolated as a yellowish powder in 60% yield: FABMS  $[\text{M} + \text{H}^+]$  1510. Elemental anal. calc. for  $\text{C}_{39}\text{H}_{30}\text{F}_{51}\text{N}_3$ : C, 31.03; F, 64.20; H, 1.98; N 2.78. Found: C, 30.74; F, 64.31; H, 2.02; N, 2.70.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , 25 °C)  $\delta$  2.71 (s, 12 H,  $-\text{N-CH}_2\text{-CH}_2\text{-N-}$ ), 2.55 (t, 6 H,  $-\text{N-CH}_2\text{-CH}_2\text{-}$ ), 2.17 (m, 6 H,  $-\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-}$ ), 1.58 (m, 6 H,  $-\text{CH}_2\text{-CH}_2\text{-R}_f$ ).

## Discussion

The alkylation of aliphatic amines is a very convenient reaction for the fluorocarbon solubilization of these important ligands that are utilized with fluoroponytailed metal complexes as precatalysts in fluororous biphasic catalysis (FBC) systems [1]. Thus, by specifically using the necessary three carbon spacer, fluoroponytailed synthon, 3-perfluorooctyl-1-iodopropane, **3**, a wide variety of fluoroponytailed amine ligands, such as **4**, are now readily accessible [1b, 1c].

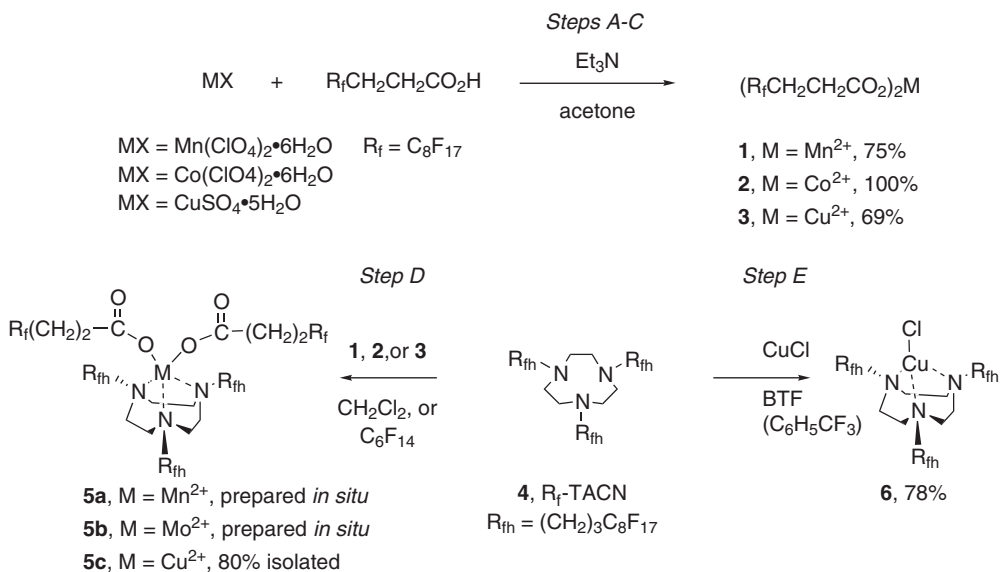
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## 11.15

**Mn<sup>2+</sup>/Co<sup>2+</sup>/Cu<sup>2+</sup>/Cu<sup>+</sup> Complexes of Fluoroponytailed R<sub>f</sub>-Tris-N-1,4,7-triazacyclononane and R<sub>f</sub>-Carboxylate, C<sub>8</sub>F<sub>17</sub>(CH<sub>2</sub>)<sub>2</sub>COOH. Precatalysts for FBC Alkane, Alkene, and Alcohol Oxidation Chemistry**

Jean-Marc Vincent\*, Maria Contel, Mariano Laguna, and Richard H. Fish\*

**Reaction 11.15-1****Reagents**

R<sub>f</sub>I (R<sub>f</sub> = C<sub>8</sub>F<sub>17</sub>) and perfluoroheptane were purchased from Pierce Chemical Co., while AIBN, allyl alcohol, tributyltin hydride, trifluorotoluene (benzotrifluoride), phosphorous pentaoxide, 85%, phosphoric acid, potassium iodide, 1,4,7-triazacyclononane (TACN), triethylamine, diethyl malonate, sodium hydride, potassium hydroxide were purchased from Aldrich Chemical Company. CF<sub>3</sub>(CF<sub>2</sub>)<sub>7</sub>CH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>H was a gift from Elf Atochem, France, but is now available from Strem Chemical Co. The non-fluorous metal complexes were purchased from Strem Chemical Co.

**Experimental Procedures**

**Step A.** *Manganese bis(2-(2-Perfluorooctylethyl)-3-perfluorooctyl Propanoate Dihydrate {Mn[C<sub>8</sub>F<sub>17</sub>(CH<sub>2</sub>)<sub>2</sub>CO<sub>2</sub>]<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>} (1)* CF<sub>3</sub>(CF<sub>2</sub>)<sub>7</sub>CH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>H (1.35 g, 2.80 mmol) is dissolved in acetone (15 mL) and triethylamine is added (380 mL, 2.80 mmol). This resulting solution is added dropwise to Mn(ClO<sub>4</sub>)<sub>2</sub>•6H<sub>2</sub>O (500 mg, 1.37 mmol) dissolved in acetone (30 mL). The sticky precipitate that forms is vigorously stirred for 2 h. After filtration, **1** is obtained

as a white powder in 75% yield. Elemental anal. calc. for  $C_{22}F_{34}H_{12}O_6Mn$ : C, 24.61; F, 60.19; H, 1.12; Mn, 5.12. Found: C, 25.37; F, 59.77; H, 0.94; Mn, 5.50.

**Step B. Cobalt bis(2-(2-Perfluorooctylethyl)-3-perfluorooctyl Propanoate Dihydrate**  $Co[C_8F_{17}(CH_2)_2CO_2]_2(H_2O)_2$  (**2**) The same procedure, as conducted with complex **1**, was used for the synthesis of **2**, except with  $Co(ClO_4)_2 \cdot 6H_2O$ . A pink precipitate formed immediately, and after filtration, a pink powder is obtained in 100% yield. Elemental anal. calc. for  $C_{22}H_{12}F_{34}CoO_6$ : C, 24.53; H, 1.11; F, 59.98; Co, 5.46. Found: C, 25.05; H, 1.27; F, 60.15; Co, 5.35.

**Step C. Copper bis(2-(2-Perfluorooctylethyl)-3-perfluorooctyl Propanoate Dihydrate**  $\{Cu[C_8F_{17}(CH_2)_2CO_2]_2\}$  (**3**)  $CF_3(CF_2)_7CH_2CH_2CO_2H$  (1.35 g, 2.80 mmol) was dissolved in acetone (15 mL), and to this solution is added triethylamine (0.39 mL, 2.80 mmol). This solution is added dropwise to a suspension of  $CuSO_4 \cdot 5H_2O$  (0.342 g, 1.37 mmol) in acetone (30 mL). After 24 h stirring at room temperature, the complex **3** precipitates as a blue powder, which is collected by filtration and washed with  $Et_2O$ . This complex is obtained in 69% yield (0.098 g). Elemental anal. calc. for  $C_{22}H_8F_{34}O_4Cu$ : C, 25.27; H, 0.77. Found: C, 25.44; H, 0.81. IR: carboxylate bands  $\nu = 1573$  and  $1420\text{ cm}^{-1}$ . UV-vis spectrum (diffuse reflectance):  $\lambda$  666 nm (28%). This complex is totally soluble in trifluorotoluene, partly soluble in dichloromethane, and insoluble in acetone,  $Et_2O$ , n-hexane, MeOH,  $H_2O$ , and perfluoroheptane.

**Step D.  $Mn[C_8F_{17}(CH_2)_2CO_2]_2(R_f\text{-TACN})$  (**5a**),  $Co[C_8F_{17}(CH_2)_2CO_2]_2(R_f\text{-TACN})$  (**5b**), and  $Cu[C_8F_{17}(CH_2)_2CO_2]_2(R_f\text{-TACN})$  (**5c**)** The complexes **5a** and **5b** are prepared [**1a**, **1b**] *in situ*, while **5c** is isolated as follows:  $R_f\text{-TACN}$  (0.218 g, 0.14 mmol) is added to a suspension of  $\{Cu[C_8F_{17}(CH_2)_2CO_2]_2\}$  **3** (0.15 g, 0.14 mmol) in 10 mL of dichloromethane. A green solid precipitates immediately and is collected by filtration. After drying under vacuum, **4** is obtained as a green powder in 80% yield (0.255 g). Elemental anal. calc. for  $C_{61}H_{38}F_{85}O_4N_3Cu$ : C, 28.67; H, 1.49; N, 1.64. Found: C, 29.01; H, 1.60; N, 2.03. LSIMS-MS:  $m/z$  2063 (75%,  $\{M - [C_8F_{17}(CH_2)_2CO_2]\}^+$ ),  $m/z$  1572 (30%,  $\{M - [C_8F_{17}(CH_2)_2CO_2]_2\}^+$ ),  $m/z$  1508 (58%,  $R_f\text{-TACN}^+$ ); IR carboxylate bands =  $1632$  and  $1403\text{ cm}^{-1}$ ; UV-vis spectra (perfluoroheptane)  $\lambda$  272 nm, (diffuse reflectance)  $\lambda$  1013 nm (62%), 700 nm (48%). This complex was totally soluble in trifluorotoluene and in perfluoroheptane, while being insoluble in acetone, dichloromethane, chloroform,  $Et_2O$ , n-hexane, MeOH, and  $H_2O$ .

**Step E.  $[Cu(R_f\text{-TACN})Cl]$  (**6**)**  $R_f\text{-TACN}$  (0.151 g, 0.1 mmol) is added to a suspension of excess  $[CuCl]$  (0.050 g, 0.5 mmol) in 5 mL of trifluorotoluene. After 3 h at room temperature, the suspension was filtered through Celite (to remove the excess of  $CuCl$ ), and the colorless solution was evaporated to 1 mL. The addition of n-hexane affords an off white powder **6** in 78% yield (0.125 g). Elemental anal. calc. for  $C_{39}H_{30}F_{51}N_3ClCu$ : C, 29.12; H, 1.88; N 2.61. Found: C, 29.45; H, 1.97; N, 2.43; LSIMS-MS  $m/z$  1573 (88%,  $[M - Cl]^+$ ),  $m/z$  1095 (100%,  $[M - Cl - (CH_2)_3C_8F_{17} - F]^+$ );  $^1H$  NMR ( $CDCl_3$ , 25 °C),  $\delta$  2.25 (m, 6 H,  $-CH_2-CH_2-CH_2-C_8F_{17}$ ), 2.10 (s, 12 H,  $-N-CH_2-CH_2-N$ ), 1.57 (m, 6 H,  $-CH_2-CH_2-CH_2-C_8F_{17}$ ), 1.20 (m, 6 H,  $-CH_2-CH_2-CH_2-C_8F_{17}$ );  $^{19}F\{^1H\}$  NMR ( $CDCl_3$ , 25 °C)  $\delta$  -80.5, -110.8, -111.2, -121.1, -121.7, -122.6 and -125.9 ppm. The  $^{19}F\{^1H\}$  NMR spectrum in  $CDCl_3$  of  $R_f\text{-TACN}$  **4**

shows the signals at  $\delta$  -81.7, -115.2, -122.9, -123.9, -124.7 and -127.3. UV-vis spectrum (perfluoroheptane)  $\lambda$  212, 260 nm (diffuse reflectance). This complex was totally soluble in trifluorotoluene and perfluoroheptane, partly soluble in dichloromethane and chloroform, and insoluble in acetone, Et<sub>2</sub>O, n-hexane, MeOH, and H<sub>2</sub>O.

## Discussion

The use of metal complexes as precatalysts in fluorous biphasic catalysis (FBC) reactions has led to the discovery that the ligands for the central metal ion needed to have appended fluoroponytails to enhance their perfluorocarbon solubility [1]. We also found that fluoroponytailed metal carboxylates, such as complexes 1–3, were not totally soluble in perfluorocarbons, but were solubilized via reaction with a fluorous soluble, fluoroponytailed organic ligand, such as ligand 4, to synthesize complexes, such as 5a–c, where M<sup>2+</sup> is Mn<sup>2+</sup>, Co<sup>2+</sup>, or Cu<sup>2+</sup> [1, 2]. Interestingly, the Cu<sup>+</sup> complex 6 was found to be fluorous soluble, without the [CuCl] complex having appended fluoroponytails [2]. Complexes 1–3, 5a–c, and 6 were used as precatalysts in the FBC oxidation of alkanes, alkenes, and alcohols [1, 2].

## References

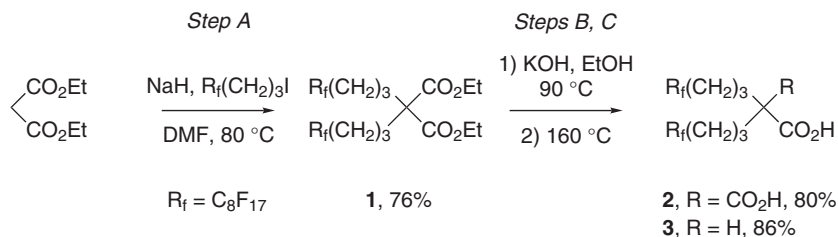
- 1 (a) J.-M. VINCENT, A. RABION, V. K. YACHANDRA, R. H. FISH, *Angew. Chem., Int. Ed. Engl.* **1997**, 36, 2346. (b) J. M. VINCENT, A. RABION, V. K. YACHANDRA, R. H. FISH, *Can. J. Chem.* **2001**, 79, 888.
- (c) R. H. FISH, *Chem. Eur. J.* **1999**, 5, 1677.
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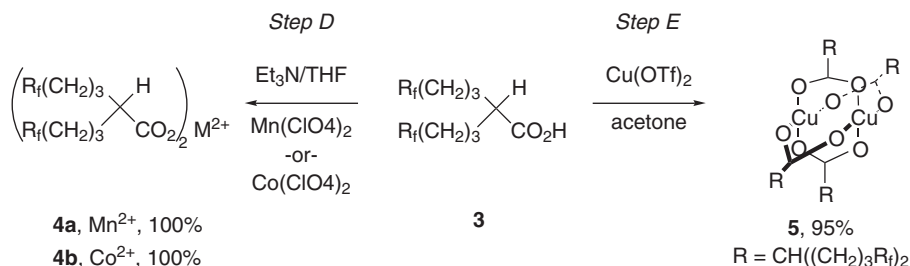
## 11.16

**6,6,7,7,8,8,9,9,10,10,11,11,12,12,13,13,13-Heptadecafluoro-2-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecyl)tridecanoic Acid (Bis-R<sub>f</sub>-carboxylate), [C<sub>8</sub>F<sub>17</sub>(CH<sub>2</sub>)<sub>3</sub>]<sub>2</sub>CHCOOH.**  
**A Fluorous Soluble Carboxylic Acid Ligand for Metal Complexes**

Jean-Marc Vincent\* and Richard H. Fish\*

### Reaction 11.16-1





## Reagents

R<sub>f</sub>(CH<sub>2</sub>)<sub>3</sub>I, R<sub>f</sub>I (R<sub>f</sub> = C<sub>8</sub>F<sub>17</sub>) and perfluoroheptane were purchased from Pierce Chemical Co., while AIBN, allyl alcohol, tributyltin hydride, trifluorotoluene (benzotrifluoride), phosphorous pentaoxide, 85%, phosphoric acid, and potassium iodide were purchased from Aldrich Chemical Company. Diethyl malonate, sodium hydride, and potassium hydroxide were purchased from Aldrich Chemical Company. The non-fluorous metal complexes were purchased from Strem Chemical Co.

## Experimental Procedures

**Step A. 2,2-bis-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoroundecyl)malonic Acid Diethyl Ester (1)** Diethyl malonate (0.72 g, 4.5 mmol) dissolved in anhydrous DMF (15 mL) is added dropwise to an NaH suspension (95%, 0.324 g, 13.5 mmol) in anhydrous DMF (30 mL) at 0 °C. After 1 h at ambient temperature, R<sub>f</sub>(CH<sub>2</sub>)<sub>3</sub>I (6 g, 10.2 mmol) dissolved in anhydrous DMF (15 mL) is slowly added, and the mixture is stirred at 80 °C for 12 h. After cooling to room temperature, perfluorohexane (20 mL) is added to extract 1. The perfluorohexane solvent is removed under reduced pressure leading to 1, as a beige oil in 76% yield: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 4.20 (q, 4 H), 1.91–2.05 (m, 8 H); 1.50–1.53 (m, 4 H), 1.23 (t, 6 H); <sup>13</sup>C NMR δ 170.6, 61.3, 56.9, 31.9, 30.7, 15.2, 13.5; MS (*m/z*, *I*%, *M* – *X*) 1080, <1, *M*; 1061, 2, *M* – 19; 1035, 4, *M* – 45; 1007, 23, *M* – 83; 620, 39, *M* – 460.

**Step B. 2,2-bis-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoroundecyl)malonic Acid (2)** The diester 1 (7 g, 6.5 mmol) is refluxed in a mixture of absolute ethanol (70 mL) and aqueous potassium hydroxide (50%, 70 mL) for 6 h. The mixture is acidified at 0 °C (pH 2–3) with concentrated HCl leading to the precipitation of 2 as a yellow powder; yield, 5.3 g (80%), mp 150–151 °C: <sup>1</sup>H NMR (THF-*d*<sub>8</sub>) δ 2.35–2.08 (m, 4 H), 2.00–1.92 (m, 4 H), 1.65–1.55 (m, 4 H); <sup>13</sup>C NMR (THF-*d*<sub>8</sub>) δ 172.3, 57.3, 33.1, 16.5; LSIMS (*m/z*, *I*%) 1025, 100, *M* + H<sup>+</sup>.

**Step C. 6,6,7,7,8,8,9,9,10,10,11,11,12,12,13,13,13-Heptadecafluoro-2-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecyl)tridecanoic Acid (3)** The diacid 2 is heated at 180 °C until the CO<sub>2</sub> evolution ceases. The monoacid 3 was recrystallized in hot toluene; yield 86%, mp 91–92 °C; <sup>1</sup>H NMR (THF-*d*<sub>8</sub>) δ 2.1–2.4 (m, 5 H), 1.55–1.72 (m, 8 H); <sup>13</sup>C NMR (THF-*d*<sub>8</sub>)

170.3, 45.3, 32.2, 31.4, 19.0; MS ( $m/z$ , I%, M – X): 980, <1, M; 961, 1, M – 19; 520, 31, M – 460. Anal. calc. for  $C_{24}H_{14}O_2F_{34}$ : C, 29.39; H, 1.43. Found: C, 29.31; H, 1.50.

*Step D. bis[6,6,7,7,8,8,9,9,10,10,11,11,12,12,13,13,13-Heptadecafluoro-2-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecyl)tridecanoyl] Manganese and Cobalt (4a,b)* A mixture of the monoacid **3** (0.2 g, 0.2 mmol) and triethylamine (28  $\mu$ L, 0.2 mmol) in THF (5 mL) is added to a solution of  $Mn(ClO_4)_2$  or  $Co(ClO_4)_2$  (0.1 mmol) in THF (2 mL) at room temperature. After 12 h, **4a,b** are recovered by filtration, the triethylammonium salt being eliminated in the filtrate. Anal. calcd. for  $C_{48}H_{26}O_4F_{68}Mn$ : C, 28.61; H, 1.29; Mn, 2.73. Found: C, 28.63; H, 1.35; Mn, 2.75%. Anal. calc. for  $C_{48}H_{26}O_4F_{68}Co$ : C, 28.57; H, 1.29; Co, 2.92. Found: C, 28.39; H, 1.29; Co, 3.15%.

*Step E. tetrakis[6,6,7,7,8,8,9,9,10,10,11,11,12,12,13,13,13-Heptadecafluoro-2-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecyl)tridecanoyl] Dicopper (5)* A solution of carboxylic acid **3** (0.2 g, 0.2 mmol) and triethylamine (30.5  $\mu$ L, 0.22 mmol) in acetone (5 mL) is added to a stirred solution of  $Cu(OTf)_2$  (36.9 mg, 0.1 mmol) in acetone (2 mL). After 3 h, an insoluble blue oil forms. After decanting off the acetone solution, the resulting oil is washed with cold acetone. The oil is dissolved in hot toluene/trifluorotoluene and the blue solution is left to stand at  $-18^\circ C$ . After 24 h, the precipitated complex **5** is collected by filtration and washed with toluene (0.194 g, 96%): FTIR ( $cm^{-1}$ , KBr) 1592 ( $\nu_{asym}CO_2$ ), 1420 ( $\nu_{sym}CO_2$ ); UV-vis (perfluorodecalin) [ $\lambda_{max}$ , nm ( $\epsilon$ ,  $M^{-1} cm^{-1}$ )] 680 (300). Anal. calc. for  $C_{96}F_{136}H_{52}O_8Cu$ : C, 28.50; F, 63.90; H, 1.29; Cu, 3.14. Found: C, 28.29; F, 62.57; H, 1.21; Cu, 3.14.

## Discussion

The use of metal complexes as precatalysts in fluorous biphasic catalysis (FBC) reactions has led to the discovery that the ligands for the central metal ion needed to have appended fluoroptynyls to enhance their perfluorocarbon solubility [1]. More importantly, it was found that the fluoroptynylated carboxylate ligands could themselves be made fluorous soluble by appending two fluoroptynyls to the carboxylic acid backbone, compound **3**, enabling their metal complexes to be concomitantly soluble in fluorous media, **4a,b** and **5** [2, 3].

## References

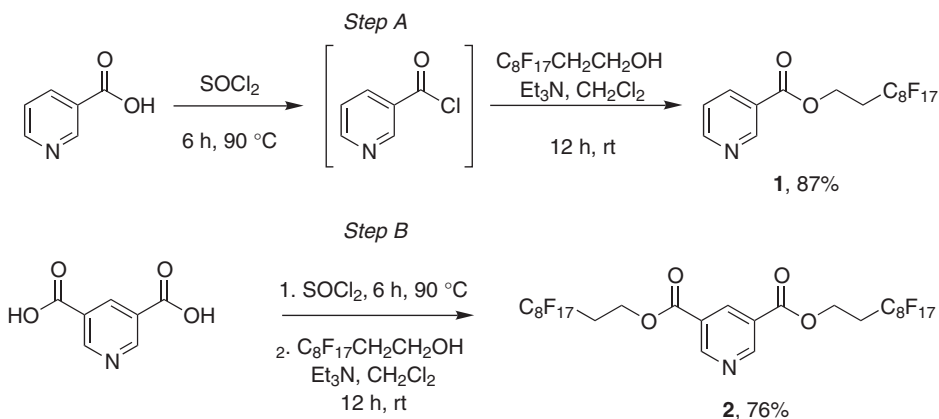
- (a) J.-M. VINCENT, A. RABION, V. K. YACHANDRA, R. H. FISH, *Angew. Chem., Int. Ed. Engl.* **1997**, 36, 2346. (b) J. M. VINCENT, A. RABION, V. K. YACHANDRA, R. H. FISH, *Can. J. Chem.* **2001**, 79, 888. (c) R. H. FISH, *Chem. Eur. J.* **1999**, 5, 1677.
- J. LOISEAU, E. FOUQUET, R. H. FISH, J.-M. VINCENT, J.-B. VERLHAC, *J. Fluorine Chem.* **2001**, 108, 195.
- M. EL BAKKARI, N. MCCLENAGHAN, J.-M. VINCENT, *J. Am. Chem. Soc.* **2002**, 124, 12942.



## 11.17

**1*H*,1*H*,2*H*,2*H*-Heptadecafluorodecyl Nicotinate (1) and Bis(1*H*,1*H*,2*H*,2*H*-heptadecafluorodecyl)pyridine-3,5-dicarboxylate (2). Esterification of Nicotinic Acid with a Fluoroalcohol**

Takahiro Nishimura and Sakae Uemura

**Reaction 11.17-1****Reagent**

1*H*,1*H*,2*H*,2*H*-Heptadecafluorodecanol [678-39-7] is commercially available from Tokyo Kasei Kogyo Co., Ltd. ([www.tokyokasei.co.jp](http://www.tokyokasei.co.jp)).

**Experimental Procedures**

**Step A.** 1*H*,1*H*,2*H*,2*H*-Heptadecafluorodecyl Nicotinate (**1**) To a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar and reflux condenser are charged nicotinic acid (1.23 g, 10.0 mmol) and thionyl chloride (5 mL) and the mixture is stirred at 90 °C under nitrogen. After 6 h, excess thionyl chloride is removed on a rotary evaporator under reduced pressure and the resulting yellow-white solid is dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 mL). The mixture is cooled to 0 °C and triethylamine (1 mL) is added. 1*H*,1*H*,2*H*,2*H*-Heptadecafluorodecanol (2.32 g, 5.0 mmol) is then added portion-wise to the mixture with stirring at 0 °C, and the resulting mixture is allowed to warm to room temperature and stirred for 12 h. After the solvent is removed on a rotary evaporator under reduced pressure, the resulting white solid is washed with water (30 mL) and dried under vacuum at room temperature. The pure compound is obtained after column chromatography on Merck silica gel 60 with hexane/ethyl acetate (6/1) as an eluent (2.48 g, 4.35 mmol, 87%) as a white solid; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.63 (tt, *J*<sub>HF</sub> = 18.2 Hz, *J*<sub>HH</sub> = 6.3 Hz, 2 H), 4.67 (t, *J* = 6.3 Hz, 2 H), 7.41 (dd, *J* = 7.9, 5.0 Hz, 1 H), 8.29 (d, *J* = 7.9 Hz, 1 H), 8.81 (d, *J* = 5.0 Hz, 1 H), 9.23 (s, 1 H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 30.7 (t, <sup>2</sup>*J*<sub>CF</sub> = 22 Hz), 57.4, 105–122 (m), 123.5, 125.7, 137.2, 151.1, 153.9, 165.0 [1].

**Step B. bis(1H,1H,2H,2H-Heptadecafluorodecyl)pyridine-3,5-dicaboxylate (2)** To a 30 mL two-necked round-bottomed flask equipped with a magnetic stirring bar and reflux condenser are charged 3,5-pyridinedicarboxylic acid (0.33 g, 2.0 mmol) and thionyl chloride (2.2 mL) and the mixture is stirred at 90 °C under nitrogen. After 6 h, excess thionyl chloride is removed on a rotary evaporator under reduced pressure and the resulting yellow-white solid is dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 mL). The mixture is cooled to 0 °C and triethylamine (1 mL) is added. 1H,1H,2H,2H-Heptadecafluorodecanol (2.04 g, 4.4 mmol) is then added portion-wise to the mixture with stirring at 0 °C, and the resulting mixture is allowed to warm to room temperature with stirring. After 12 h, water (10 mL) is added and the mixture is dissolved in CHCl<sub>3</sub> (400 mL). The organic layer is washed with water (50 mL) and dried over MgSO<sub>4</sub>. After the solvent is removed on a rotary evaporator under reduced pressure, the resulting orange solid is washed with acetone (30 mL) and dried under vacuum at room temperature. The pure compound is obtained (1.60 g, 1.52 mmol, 76%) as a white solid after recrystallization from hexane/ethyl acetate; <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>) δ 2.65 (tt, *J*<sub>HF</sub> = 18.1 Hz, *J*<sub>HH</sub> = 6.2 Hz, 4 H), 4.71 (t, *J* = 6.2 Hz, 4 H), 8.84 (s, 1 H), 9.50 (br s, 2 H) [1].

## Discussion

The reaction of carboxylic acids with alcohols is widely used for preparation of the corresponding esters. In particular, the method of preparation of esters via acid chlorides using thionyl chloride [2] is most widely employed because of high yields of products. In the case of step B, the extraction of the product with CHCl<sub>3</sub> is recommended. If the solvent is removed after the reaction and the resulting orange solid is washed with water, as in the case of step A, jelly-like solids appear and the filtration becomes quite difficult.

## References

- 1 T. NISHIMURA, Y. MAEDA, N. KAKIUCHI, S. UEMURA, *J. Chem. Soc. Perkin Trans. 1* 2000, 4301.
- 2 M. B. SMITH, J. MARCH, In *Advanced*

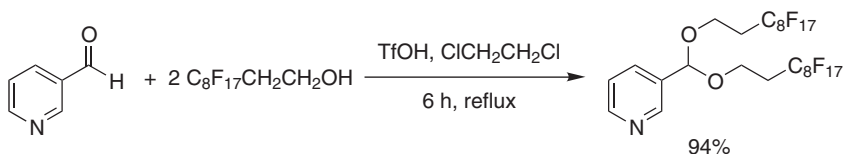
*Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th Ed. Wiley Interscience: New York, 2001.

## 11.18

### Pyridine-3-carbaldehyde Bis(1H,1H,2H,2H-heptadecafluorodecyl) Acetal. Acetalization of Pyridine-3-carbaldehyde with a Fluoroalcohol

Takahiro Nishimura and Sakae Uemura

#### Reaction 11.18-1



## Reagent

1*H*,1*H*,2*H*,2*H*-Heptadecafluorodecanol [678-39-7] is commercially available from Tokyo Kasei Kogyo Co., Ltd. ([www.tokyokasei.co.jp](http://www.tokyokasei.co.jp)).

## Experimental Procedure

A mixture of pyridine-3-carbaldehyde (0.32 g, 3.0 mmol), 1*H*,1*H*,2*H*,2*H*-heptadecafluorodecanol (4.18 g, 9.0 mmol) and trifluoromethanesulfonic acid (TfOH; 0.3 mL, 3.3 mmol) in 1,2-dichloroethane (30 mL) is stirred at reflux (bath temperature: 90 °C) in a 50 mL two-necked round-bottomed flask equipped with a magnetic stirring bar and a dropping funnel (30 mL), the top of which is attached with a reflux condenser. The 1,2-dichloroethane that condenses in the dropping funnel during the reaction is added occasionally to the reaction mixture. After 6 h, the mixture is cooled to room temperature and then triethylamine (2 mL) is added to the solution, and the mixture is diluted with diethyl ether (100 mL). The ether solution is washed with water and dried over MgSO<sub>4</sub>. The solvent is removed on a rotary evaporator under vacuum and the residue is subjected to column chromatography on Merck silica gel 60 with hexane/ethyl acetate (4/1) as an eluent to give pyridine-3-carbaldehyde bis(1*H*,1*H*,2*H*,2*H*-heptadecafluorodecyl) acetal (2.85 g, 2.81 mmol, 94%) as a colorless oil: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.46 (tt, *J*<sub>HF</sub> = 18.6 Hz, *J*<sub>HH</sub> = 6.4 Hz, 4 H), 3.77–3.81 (m, 4 H), 5.67 (s, 1 H), 7.34 (dd, *J* = 7.8, 4.9 Hz, 1 H), 7.77 (d, *J* = 7.8 Hz, 1 H), 8.62 (d, *J* = 4.9 Hz, 1 H), 8.70 (s, 1 H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ 31.4 (t, <sup>2</sup>*J*<sub>CF</sub> = 21 Hz), 57.4, 100.0, 105–122 (m), 123.3, 132.5, 134.3, 148.5, 150.3 [1].

## Discussion

Acetalization is one of the most popular protection methods of carbonyl compounds. Acetals are formed by treatment of the aldehydes or ketones with alcohols in the presence of acid catalyst. Generally, *p*-toluenesulfonic acid is used as a catalyst for this reaction, but the protection of pyridine-3-carbaldehyde with 1*H*,1*H*,2*H*,2*H*-heptadecafluorodecanol failed using this acid. In this case, the use of a small excess amount of TfOH to the substrate is efficient in giving the corresponding acetal in excellent yield [2].

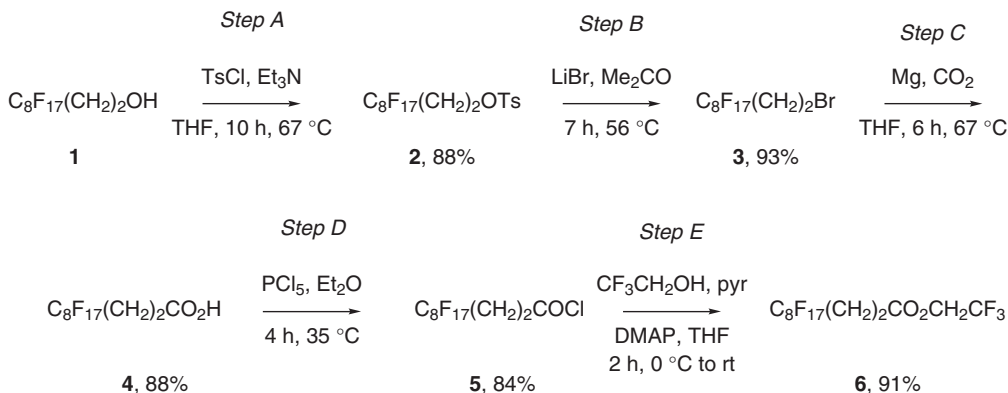
## References

- 1 T. NISHIMURA, Y. MAEDA, N. KAKIUCHI, S. UEMURA, *J. Chem. Soc. Perkin Trans. 1* **2000**, 4301.
- 2 Example of acetalization using TfOH as a catalyst, see: T. HARADA, S. TANAKA, A. OKU, *Tetrahedron* **1992**, 48, 8621.

## 11.19

**2,2,2-Trifluoroethyl 2H,2H,3H,3H-perfluoroundecanoate. A Highly Fluorinated Acyl Donor Useful for the Lipase Catalyzed Labeling of Racemic Alcohols [1]**

Fritz Theil\*, Helmut Sonnenschein, Benno Hungerhoff, and Sauda M. Swaleh

**Reaction 11.19-1****Reagents**

1H,1H,2H,2H-Perfluorodecane-1-ol (**1**) [678-39-7], 2,2,2-trifluoroethanol [75-89-8] and all other chemicals used are commercially available.

**Experimental Procedures**

**Step A. 1H,1H,2H,2H-Perfluorodecane-1-ol Tosylate (2)** To a solution of 1H,1H,2H,2H-perfluorodecane-1-ol **1** (400 g, 0.862 mol) and *p*-toluene sulfonyl chloride (TsCl, 207.0 g, 1.086 mol) in dry THF (800 mL) is added triethylamine (110.0 g, 151.3 mL, 1.086 mol) at rt within 10 min. The reaction mixture is refluxed under argon until **1** is completely consumed (~10 h). The precipitate is filtered off and washed with *tert*-butyl methyl ether (500 mL). The filtrate is evaporated under reduced pressure and the remaining residue is partitioned between a mixture of *tert*-butyl methyl ether (1000 mL)/ethyl acetate (500 mL) and 2 N HCl (500 mL). The organic phase is washed with 2 N K<sub>2</sub>CO<sub>3</sub> (2 × 100 mL), brine (100 mL) and dried (Na<sub>2</sub>SO<sub>4</sub>). Evaporation under reduced pressure (up to 95 °C bath temperature/10 mbar) yields the crude product still containing *p*-toluene sulfonyl chloride that is distilled off by rotatory evaporation (140–154 °C bath temperature, 0.08 mbar). The slightly brown oily residue crystallizes on cooling affording toluene-4-sulfonic acid 1H,1H,2H,2H-perfluorodecylester (**2**, 470.6 g, 88%), which is used in the next step without further purification: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.47 (s, 3 H), 2.51 (m, 2 H), 4.31 (t, 3 H, *J* = 6.9 Hz), 7.37 (d, 2 H, *J* = 7.8 Hz), 7.81 (d, 2 H, *J* = 7.8 Hz).

**Step B. 1-Bromo-1H,1H,2H,2H-perfluorodecane (3)** A suspension of the above described toluene sulfonate **2** (470.0 g, 0.76 mol) and dry LiBr (132.0 g, 1.52 mol) in acetone (380 mL)

is refluxed for 7 h turning into a fluffy suspension. After this time a complete conversion of the starting material takes place [3]. The reaction mixture is cooled down to rt, cyclohexane (1000 mL) is added and the precipitate is filtered off, washed with a mixture of cyclohexane (100 mL) and acetone (20 mL) and finally with pure cyclohexane ( $3 \times 100$  mL). The filtrate is concentrated under reduced pressure and the oily residue is distilled affording 1-bromo-1*H*,1*H*,2*H*,2*H*-perfluorodecane (**3**, 371.8 g, 93%, bp 68–72 °C at 0.1 mbar) as a colorless liquid that crystallized at  $\sim 6$  °C:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.70 (tt, 2 H,  $J_1 = 8.1$  Hz,  $J_2 = 8.4$  Hz), 3.51 (t, 2 H,  $J = 8.4$  Hz).

**Step C. 1*H*,2*H*,3*H*,3*H*-Perfluoroundecanoic acid (**4**)** Mg (wire, 3.16 g, 130 mmol) is heated with iodine ( $\sim 100$  mg) under argon [4]. After cooling down to rt dry THF (10 mL) is added. Then the mixture is heated to 60 °C and 1-bromo-1*H*,1*H*,2*H*,2*H*-perfluorodecane (**3**, 0.53 g, 1 mmol) is added to start the Grignard reaction. Subsequently, a solution of the bromo compound **3** (52.0 g, 98.7 mmol) in dry THF (150 mL) is slowly added over 1.25 h keeping the reaction under gentle reflux. The mixture is refluxed for another 4.5 h and cooled down in an ice/NaCl bath to  $-6$  °C. Dry carbon dioxide is bubbled through the reaction mixture whereby the temperature rises up to 24 °C and a brown solid precipitates (15 min). 2 N HCl (75 mL) is added slowly at 0 °C. The aqueous mixture is extracted with *tert*-butyl methyl ether ( $1 \times 200$  mL,  $2 \times 50$  mL). The combined organic layers are washed with brine (50 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure affording crude 2*H*,2*H*,3*H*,3*H*-perfluoroundecanoic acid (**4**, 42.9 g, 88%) as a brown solid that is used in the next step without further purification. (If required, **4** can be recrystallized from  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR ( $\text{CD}_3\text{COCD}_3$ )  $\delta$  2.57 (m, 2 H), 2.69 (t, 2 H,  $J = 8.1$  Hz), 11.0 (broad s, 1 H).

**Step D. 2*H*,2*H*,3*H*,3*H*-Perfluoroundecanoyl chloride (**5**)** A solution of **4** (43.7 g, 88.8 mmol) in dry diethyl ether (150 mL) is treated with  $\text{PCl}_5$  (37.0 g, 177.6 mmol) and refluxed under argon (4 h). After cooling with an ice bath the reaction mixture is filtered and the filter cake (excess  $\text{PCl}_5$ ) is washed with *n*-hexane (100 mL). The filtrate is concentrated under reduced pressure and the resulting brown oily residue is distilled under reduced pressure affording 2*H*,2*H*,3*H*,3*H*-perfluoroundecanoyl chloride (**5**, 38.0 g, 84%, bp 95–97 °C at 0.5 mbar) as a colorless liquid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.53 (m, 2 H), 3.24 (t, 2 H,  $J = 7.8$  Hz);  $^{19}\text{F}$  NMR [ $\text{CDCl}_3$ ;  $\delta$  ( $\text{CFCl}_3$ ) = 0]  $\delta$   $-80.5$ ,  $-113.7$ ,  $-120.9$ ,  $-121.2$  (2 signals),  $-122.0$ ,  $-122.6$ ,  $-125.4$ .

**Step E. 2,2,2-Trifluoroethyl 2*H*,2*H*,3*H*,3*H*-Perfluoroundecanoate (**6**)** To an ice-cold solution of the above described acid chloride **5** (25.5 g, 50.0 mmol) and 2,2,2-trifluoroethanol (5.2 g, 3.7 mL, 52.5 mmol) in dry THF (50 mL) containing a catalytic amount of DMAP (200 mg) is added dry pyridine (4.15 g, 4.24 mL, 52.5 mmol) dropwise within 5 min. The cooling bath is removed and the solution is allowed to reach rt. After stirring for 1 h at rt, the precipitate is filtered off. The filtrate is concentrated under reduced pressure and the remaining residue is partitioned between *tert*-butyl methyl ether (100 mL) and 2 N HCl (25 mL). The organic layer is washed with water (25 mL), dried ( $\text{Na}_2\text{SO}_4$ ), concentrated under reduced pressure and distilled under reduced pressure affording 2,2,2-trifluoroethyl 2*H*,2*H*,3*H*,3*H*-perfluoroundecanoate (**6**, 26.2 g, 91%, bp 58–60 °C at  $1 \times 10^{-3}$  mbar) as a colorless liquid that crystallized at 4 °C [5, 6]:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.51 (tt, 2 H,  $J_1 = 8.4$  Hz,  $J_2 = 8.0$  Hz), 2.77 (t, 2 H,  $J = 8.4$  Hz), 4.52 (t, 2 H,  $J = 8.4$  Hz);  $^{19}\text{F}$  NMR [ $\text{CDCl}_3$ ;  $\delta$  ( $\text{CFCl}_3$ ) = 0]  $\delta$   $-73.7$ ,  $-80.5$ ,  $-114.1$ ,  $-120.9$ ,  $-121.1$  (2 signals),  $-121.9$ ,  $-122.7$ ,  $-125.3$ .

## Discussion

A highly fluorinated acyl donor is obtained in a five step synthesis starting from 1*H*,1*H*,2*H*,2*H*-perfluoro-decane-1-ol. Two of the four intermediates of the synthesis are already, as the crude product, of sufficient purity and can be used in the next step without further purification.

## References and Notes

- 1 B. HUNGERHOFF, H. SONNENSCHN, F. THEIL, *J. Org. Chem.* **2002**, 67, 1781–1785.
- 2 Caution: The obtained bromide is a lachrymator.
- 3 The progress of the reaction was followed by  $^1\text{H-NMR}$ .
- 4 All reagents and glassware are dried rigorously.
- 5 Prior to use of the substance in enzymatic reactions, the pH of **6** should be tested on wet pH paper after waiting for 5 min. If necessary, traces of acid that decrease enzyme activity are to be removed by simple silica gel filtration (80.0 g of **6** through a layer of 4 cm in height, 13 cm in diameter with cyclohexane/ethyl acetate, 10:1).
- 6 An alternative procedure to obtain **6** directly from **4** is conducted as follows: to a solution of the acid **4** (11.8 g, 24 mmol) in 2,2,2-trifluoroethanol (30 mL) is added

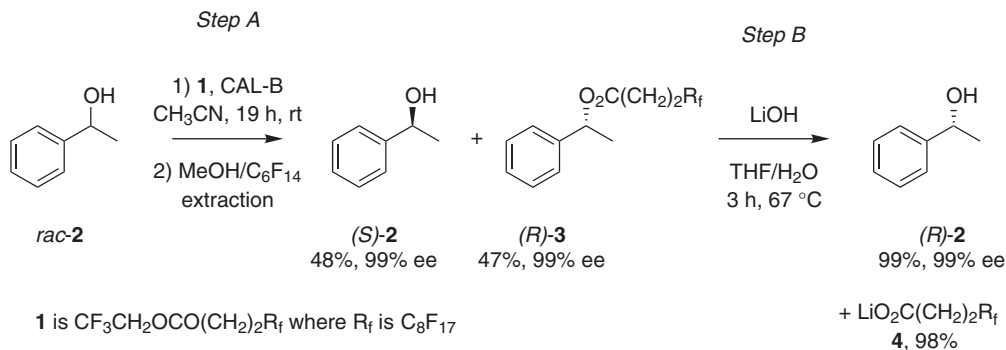
sulfuric acid (2 mL) and the mixture is refluxed for 6 h. The solvent is distilled off under reduced pressure and the residue is partitioned between *tert*-butyl methyl ether (60 mL) and water (20 mL). The aqueous layer is re-extracted with *tert*-butyl methyl ether (60 mL). The combined organic layers are washed with water (10 mL), 5% aqueous  $\text{NaHCO}_3$  (10 mL) and dried ( $\text{Na}_2\text{SO}_4$ ). Evaporation yields a crude liquid that is distilled by Kugelrohr distillation (oven temperature:  $88^\circ\text{C}/1 \times 10^{-3}$  mbar) affording pure **6** (10.2 g, 74%). The reaction also works with the dry crude lithium salt **4a** obtained as a byproduct of resolution of racemic alcohols by use of **6** (see reaction described in Section 11.20 in connection with the resolution of racemic 1-phenyl-ethanol).

## 11.20

### (*R*)- and (*S*)-1-Phenylethanol. Kinetic Resolution of the Racemic Alcohol by Lipase Catalyzed Enantiomer-Selective Fluorous Phase Labeling

Fritz Theil\*, Helmut Sonnenschein, Benno Hungerhoff, and Sauda M. Swaleh

#### Reaction 11.20-1



## Reagents

The synthesis of 2,2,2-trifluoroethyl 2*H*,2*H*,3*H*,3*H*-perfluoro-undecanoate (**1**) [1, 2] is described in the preceding procedure (Section 11.19). *Candida antarctica* B lipase (CAL-B, Chirazyme L-2, c.-f., lyo., Roche Diagnostics, Mannheim), 1-phenyl-ethanol [98-85-1] and the other chemicals used are commercially available. The enantiomeric excess of the enantiomeric alcohols was determined by HPLC on Chiralcel OJ<sup>®</sup> (250 × 4.6 mm); mobile phase: *n*-heptane/*n*-propanol (95:5); flow rate: 1 mL/min; temperature: 22 °C; detection: UV at 254 nm [1].

## Experimental Procedures

**Step A. (S)-1-Phenylethanol ((S)-2) and (R)-1-Phenylethyl 2*H*,2*H*,3*H*,3*H*-Perfluoroundecanoate [(R)-3]** A solution of (*R,S*)-1-phenylethanol (*rac*-2, 1.22 g, 10 mmol) in acetonitrile (65 mL) is treated with 2,2,2-trifluoroethyl 2*H*,2*H*,3*H*,3*H*-perfluoro-undecanoate [2] (**1**, 8.61 g, 15 mmol) and CAL-B (2.00 g). The reaction mixture is stirred at ambient temperature until the conversion reaches about 50% (19 h). The enzyme is filtered off and the solid residue is washed with acetone (2 × 40 mL). The combined filtrates are evaporated under reduced pressure. The residue is dissolved in MeOH (25 mL). The resulting solution is extracted with *n*-C<sub>6</sub>F<sub>14</sub> (6 × 25 mL). The organic phase is concentrated to dryness yielding (*S*)-2 (0.59 g, 48%) with an ee of 99% containing ca. 1% of (*R*)-3. From the fluorous phase a mixture (8.50 g) of (*R*)-3 (ee 98%) [1] and the excess of **1** is obtained.

**Step B. (R)-1-Phenylethanol [(R)-2]** For saponification of (*R*)-3 to (*R*)-2 the mixture of (*R*)-3 and **1** obtained in step A is dissolved in a 1:1 mixture of THF/water (40 mL) containing LiOH (0.64 g, 26.7 mmol) and refluxed for 3 h. Subsequently, the reaction mixture is diluted with cyclohexane (100 mL), cooled to 0 °C and filtered. The filter cake is washed with a mixture of cyclohexane (100 mL) and *tert*-butyl methyl ether (30 mL). The filtrate is concentrated to dryness yielding (*R*)-2 (0.57 g, 47% related to *rac*-2) with an ee of 98%.

The solid filter cake (7.35 g, 98%) consists of the lithium salt of 2*H*,2*H*,3*H*,3*H*-perfluoroundecanoic acid **4** [3].

## Discussion

The highly fluorinated carboxylic ester **1** is an extremely useful and selective acyl donor for the lipase-catalyzed enantiomer-selective acylation of alcohols, thus the faster reacting enantiomer is equipped with a fluorous tag in order to be recognized selectively by a fluorous phase. The enantiomer-selective labeled mixture of ester and alcohol representing the two enantiomers can be separated very efficiently by partition in the two-phase solvent system perfluoro-*n*-hexane/methanol avoiding a chromatographic step. Hydrolysis of the fluorinated enantiomer allows the quantitative recovery of the fluorous tag.

Kinetic resolutions by use of the highly fluorinated ester **1** are a useful alternative to existing methods for the non-chromatographic separation of enantiomeric esters from the corresponding alcohols [4–9].

## References and Notes

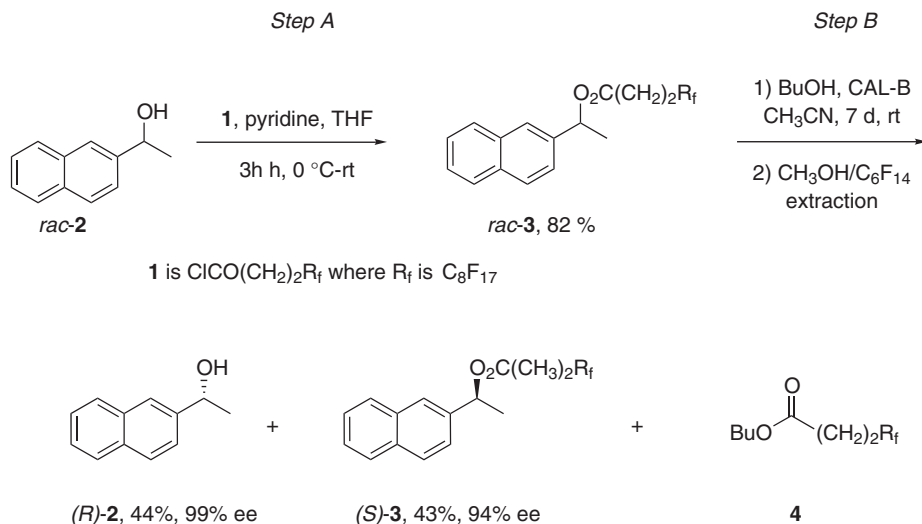
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- 2 The pH of **6** should be tested on wet pH paper after waiting for 5 min. If necessary, traces of acid that decrease enzyme activity are to be removed on a large scale by simple silica gel filtration [see synthesis of 2,2,2-trifluoroethyl 2*H*,2*H*,3*H*,3*H*-perfluoroundecanoate (11.19)].
- 3 Before its use in esterification, the salt **4a** has to be dried under reduced pressure over P<sub>2</sub>O<sub>5</sub>.
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## 11.21

(R)- and (S)-1-Naphthalen-2-yl-ethanol. Kinetic Resolution of the Racemic Alcohol by Lipase Catalyzed Enantiomer-Selective Fluorous Phase Delabeling of a Corresponding Highly Fluorinated Ester

Fritz Theil\*, Helmut Sonnenschein, Benno Hungerhoff, and Sauda M. Swaleh

## Reaction 11.21-1





## References and Notes

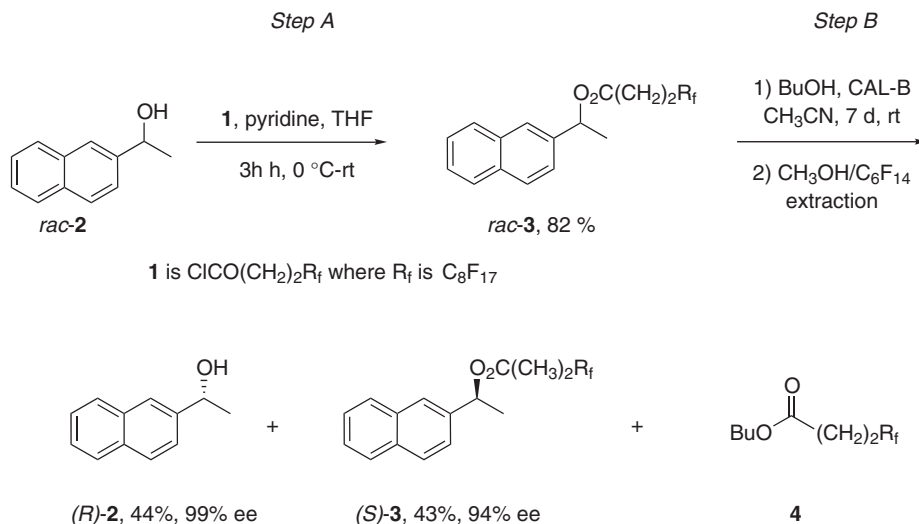
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- 2 The pH of **6** should be tested on wet pH paper after waiting for 5 min. If necessary, traces of acid that decrease enzyme activity are to be removed on a large scale by simple silica gel filtration [see synthesis of 2,2,2-trifluoroethyl 2*H*,2*H*,3*H*,3*H*-perfluoroundecanoate (11.19)].
- 3 Before its use in esterification, the salt **4a** has to be dried under reduced pressure over P<sub>2</sub>O<sub>5</sub>.
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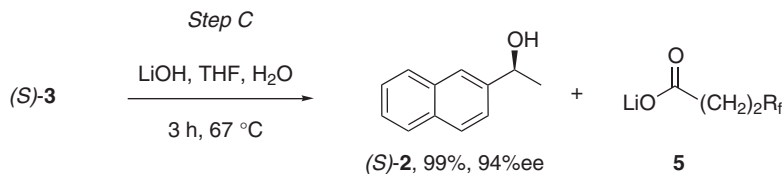
## 11.21

(R)- and (S)-1-Naphthalen-2-yl-ethanol. Kinetic Resolution of the Racemic Alcohol by Lipase Catalyzed Enantiomer-Selective Fluorous Phase Delabeling of a Corresponding Highly Fluorinated Ester

Fritz Theil\*, Helmut Sonnenschein, Benno Hungerhoff, and Sauda M. Swaleh

## Reaction 11.21-1





## Reagents

The synthesis of 2*H*,2*H*,3*H*,3*H*-perfluoroundecanoyl chloride (**1**) [1] is described above in connection with the preparation of 2,2,2-trifluoroethyl 2*H*,2*H*,3*H*,3*H*-perfluoro-undecanoate (Section 11.19). *Candida antartica* B lipase (CAL-B, Chirazyme L-2, c.-f., Iyo., Roche Diagnostics, Mannheim), (*R,S*)-1-naphthalen-2-yl-ethanol [52193-85-8] and the other chemicals used are commercially available. The enantiomeric excess of the alcohols was determined by HPLC on Chiracel OJ<sup>®</sup> (250 × 4.6 mm); mobile phase: *n*-heptane/2-propanol (90:10); flow rate: 1.5 mL/min; detection: UV at 254 nm [2].

## Experimental Procedures

**Step A. (*rac*)-1-Naphthalen-2-yl-ethyl 2*H*,2*H*,3*H*,3*H*-perfluoroundecanoate (**3**)** To an ice-cold solution of the 2*H*,2*H*,3*H*,3*H*-perfluoroundecanoyl chloride (**1**; 5.10 g, 10.0 mmol) and the (*R,S*)-1-naphthalen-2-yl-ethanol (*rac*-**2**, 1.81 g, 10.5 mmol) in anhydrous THF (10 mL) containing a catalytic amount of DMAP (20 mg) is added dropwise anhydrous pyridine (0.83 g, 10.5 mmol) within 5 min. The cooling bath is then removed. After reaching rt, the mixture is stirred for another 2 h. The precipitate is filtered off, the filtrate is concentrated under reduced pressure and the residue is partitioned between *tert*-butyl methyl ether (20 mL) and 2 N HCl (5 mL). The organic layer is washed with water (5 mL), dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. Flash chromatography [cyclohexane/ethyl acetate (10:1)] of the residue on silica gel yields the pure 2*H*,2*H*,3*H*,3*H*-perfluoroundecanoic acid-1-naphthalen-2-yl-ethylester (*rac*-**3**, 5.30 g, 82%) as a white powder with a melting point of 66–67 °C [2].

**Step B. (*R*)-1-Naphthalen-2-yl-ethanol [(*R*)-**2**] and (*S*)-1-Naphthalen-2-yl-ethyl 2*H*,2*H*,3*H*,3*H*-perfluoroundecanoate [(*S*)-**3**]** A solution of the ester *rac*-**3** (3.23 g, 5 mmol) in acetonitrile (120 mL) is treated with *n*-butanol (1.48 g, 1.83 mL, 20 mmol) and CAL-B (8.0 g). The reaction mixture is stirred at ambient temperature until the conversion reaches ca. 50% (7 days, estimated by TLC). The lipase is removed by filtration and washed with acetone (2 × 40 mL). The combined filtrates are evaporated under reduced pressure. The residue is dissolved in MeOH (25 mL). The resulting solution is extracted with *n*-C<sub>6</sub>F<sub>14</sub> (6 × 25 mL). The organic phase is concentrated to dryness yielding pure (*R*)-**2** (0.379 g, 44%) with an ee of 99%. From

the fluorous phase a mixture (2.97 g) of (S)-3 and the butylester of 2H,2H,3H,3H-perfluoro-undecanoic acid (4) is obtained.

**Step C. (S)-1-Naphthalen-2-yl-ethanol [(S)-2]** For saponification of (S)-3 to (S)-2 the mixture, obtained from the fluorous phase of step B [2.97 g, (S)-3 and 4] is dissolved in a 1:1 mixture of THF/water (40 mL) containing LiOH (0.36 g, 15 mmol) and refluxed for 3 h. Subsequently, the reaction mixture is diluted with cyclohexane (70 mL) and *tert*-butyl methyl ether (30 mL), and the two distinct phases are separated. The aqueous phase containing 5 is washed with a mixture of cyclohexane (7 mL) and *tert*-butyl methyl ether (3 mL). The combined organic phases are dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to dryness to yield the alcohol (S)-2 (0.367 g, 99%, ee 94%).

## Discussion

The example demonstrates that highly fluorinated carboxylic esters of racemic alcohols are substrates for lipase B from *Candida antarctica*. The enantiomer-selective alcoholysis of 2H,2H,3H,3H-perfluoroundecanoic acid-1-naphthalen-2-yl-ethyl ester selectively cleaves the fluorous label from the fast-reacting enantiomer affording a mixture of an alcohol and the corresponding enantiomeric fluorinated ester. The products can be separated very efficiently by partition in the biphasic solvent system methanol/perfluoro-*n*-hexane avoiding chromatography. These results represent an example for the successful combination of fluorous techniques with lipase catalyzed kinetic resolutions where the final separation procedure is already integrated into the initial chemical transformation.

This technique is a useful alternative to existing methods for the non-chromatographic separation of enantiomeric alcohols [3–8].

## References

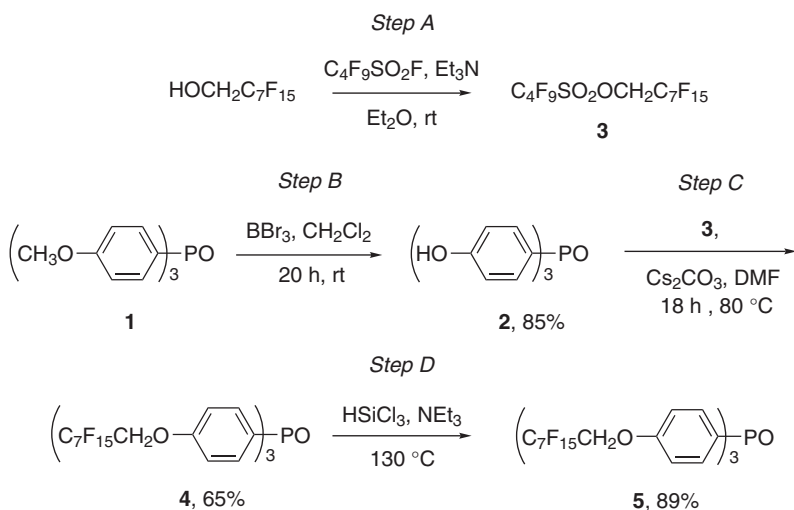
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## 11.22

Tris[4-(1*H*,1*H*-pentadecafluorooctyloxy)phenyl]phosphane

Denis Sinou and David Maillard

## Reaction 11.22-1



## Reagents

Nonafluorobutane sulfonyl fluoride  $\text{C}_4\text{F}_9\text{SO}_2\text{F}$  [375-72-4], and tris(4-methoxyphenyl)-phosphane **2** [855-38-9] are commercially available from Aldrich, and 1*H*,1*H*-pentadecafluorooctan-1-ol [307-30-2] is from Fluka.

## Experimental Procedures

**Step A.** 1*H*,1*H*-Pentadecafluorooctyl Nonafluorobutanesulfonate (**3**)  $\text{C}_4\text{F}_9\text{SO}_2\text{F}$  (3.4 g, 11 mmol) is slowly added under argon to a solution of 1*H*,1*H*-pentadecafluorooctan-1-ol (4 g, 10 mmol) and  $\text{NEt}_3$  (1.55 mL, 11 mmol) in  $\text{Et}_2\text{O}$  (20 mL). After stirring for 24 h at room temperature, the solution is treated with  $\text{H}_2\text{O}$  (10 mL) and  $\text{Et}_2\text{O}$  (20 mL). Evaporation of the solvent affords butaflate **3** as a solid (6.2 g, 95%).

**Step B.** Tris(4-hydroxyphenyl)phosphane Oxide (**2**) A solution of  $\text{BBr}_3$  (1 M in  $\text{CH}_2\text{Cl}_2$ , 67 mmol, 67 mL) is slowly added at  $-10^\circ\text{C}$  to a solution of the methoxyphosphane oxide **1** (4.9 g, 13.3 mmol) in  $\text{CH}_2\text{Cl}_2$  (50 mL) under argon. After stirring for 20 h at room temperature, the solution is slowly poured into cold water (200 mL). After partial evaporation of the solvent, the aqueous phase is filtered and extracted with ethyl acetate ( $3 \times 120$  mL). The combined organic phases are washed with a saturated aqueous solution of  $\text{NaCl}$  ( $2 \times 80$  mL) and

dried over Na<sub>2</sub>SO<sub>4</sub>. Evaporation of the solvent gives a solid which is recrystallized from ethyl acetate to give hydroxyphosphane oxide **2** (3.69 g, 85%).

**Step C. Tris[4-(1H,1H-pentadecafluorooctyloxy)phenyl]phosphane Oxide (4)** A mixture of hydroxyphosphane oxide **2** (653 mg, 2 mmol), 1H,1H-pentadecafluorooctyl nonafluorobutane-sulfonate **3** (5.45 g, 8 mmol), and Cs<sub>2</sub>CO<sub>3</sub> (1.63 g, 10 mmol) in DMF (25 mL) is stirred at 80 °C under N<sub>2</sub> for 18 h. The suspension is then cooled to 25 °C and poured into H<sub>2</sub>O (30 mL). The aqueous solution is extracted with Et<sub>2</sub>O (3 × 50 mL), the combined organic phases are washed with a saturated aqueous solution of NaCl (2 × 50 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. Evaporation of the solvent gives a residue which is purified by column chromatography over silica eluting with Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub> (1:1) to give fluorine phosphane oxide **3** as a white solid (1.91 g, 65%); *R*<sub>f</sub> = 0.55 (diethyl ether/CH<sub>2</sub>Cl<sub>2</sub> 1:1); mp 103–104 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 4.51 (t, <sup>3</sup>*J*<sub>HF</sub> = 12.1 Hz, 6 H, CH<sub>2</sub>), 7.03 (dd, <sup>3</sup>*J*<sub>HH</sub> = 8.8, <sup>4</sup>*J*<sub>HP</sub> = 1.8 Hz, 6 H, H<sub>arom</sub>), 7.62 (dd, <sup>3</sup>*J*<sub>HH</sub> = 8.8, <sup>3</sup>*J*<sub>HP</sub> = 11.4 Hz, 6 H, H<sub>arom</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, partial) δ 65.0 (t, <sup>2</sup>*J*<sub>CF</sub> = 27 Hz, CH<sub>2</sub>), 114.9 (d, <sup>3</sup>*J*<sub>CP</sub> = 13.6 Hz, C<sub>arom</sub>), 127.1 (d, <sup>1</sup>*J*<sub>CP</sub> = 110.2 Hz, C<sub>arom</sub>), 134.1 (d, <sup>2</sup>*J*<sub>CP</sub> = 11.6 Hz, C<sub>arom</sub>), 160.1 (s, C<sub>arom</sub>); <sup>19</sup>F NMR (CDCl<sub>3</sub>) δ –126.7 (s, 6 F), –123.6 (s, 6 F), –123.3 (s, 6 F), –122.5 (s, 12 F), –119.9 (s, 6 F), –81.3 (t, <sup>3</sup>*J*<sub>FF</sub> = 9.5 Hz, 9 F); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 27.9 (s).

**Step D. Tris[4-(1H,1H-pentadecafluorooctyloxy)phenyl]phosphane (5)** HSiCl<sub>3</sub> (832 μL, 8.24 mmol) is cautiously added under argon at room temperature to a mixture of phosphane oxide **4** (3.1 g, 2.1 mmol), and freshly distilled triethylamine (1.24 mL, 8.9 mmol) in dry toluene (15 mL). The mixture is warmed to 130 °C and stirred for 5 h. After being cooled to 5 °C, the solution is treated with precooled deaerated 2 N NaOH (50 mL). The aqueous layer is extracted with deaerated Et<sub>2</sub>O (3 × 50 mL), and the combined organic layers are washed with deaerated water (2 × 40 mL) and then dried over Na<sub>2</sub>SO<sub>4</sub>. Evaporation of the solvent gives the corresponding fluorine phosphane **5** as a white solid (2.72 g, 89%), mp 82–83 °C: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 4.46 (t, <sup>3</sup>*J*<sub>HF</sub> = 12.9 Hz, 6 H, CH<sub>2</sub>), 6.93 (dd, <sup>3</sup>*J*<sub>HH</sub> = 8.8, <sup>4</sup>*J*<sub>HP</sub> = 0.7 Hz, 6 H, H<sub>arom</sub>), 7.25 (dd, <sup>3</sup>*J*<sub>HH</sub> = 8.8, <sup>3</sup>*J*<sub>HP</sub> = 7.0 Hz, 6 H, H<sub>arom</sub>); <sup>19</sup>F NMR (CDCl<sub>3</sub>) δ –126.6 (s, 6 F), –123.6 (s, 6 F), –123.2 (s, 6 F), –122.5 (s, 12 F), –119.9 (s, 6 F), –81.3 (t, <sup>3</sup>*J*<sub>FF</sub> = 10 Hz, 9 F); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ –9.5 (s).

## Discussion

Organometallic complexes containing phosphanes are now commonly used as homogeneous catalysts in organic transformations. One of the major problems is the separation of the organometallic catalyst from the product(s) of the reaction. Although chromatography can be used as a standard purification method, another approach is the use of a non-miscible two-phase system of organic solvent/fluorous solvent, the organometallic complex being immobilized in the fluorous phase by association with fluorous phosphanes.

Several fluorous phosphanes have recently been prepared [1–5]. In our case [6], tris[4-(1H,1H-pentadecafluorooctyloxy)phenyl]phosphane is conveniently obtained from commercially available tris(4-methoxyphenyl)phosphane. The fluorous organometallic catalyst can be very easily separated by simple decantation and the fluorous phase eventually recycled. This

fluorous phosphane has been successfully used in hydrogenation [7], alkylation reactions [8], as well as non-catalyzed reactions such as the Wittig reaction [9]

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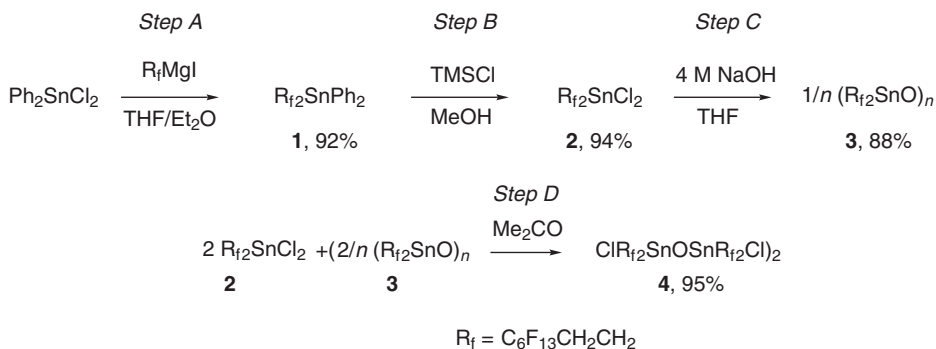
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### 11.23

**Bis(1*H*,1*H*,2*H*,2*H*-perfluorooctyl) Tin Oxide and 1,3-Dichloro-tetra(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)distannoxane. Synthesis and Applications of Fluorous Distannoxanes**

*Junzo Otera*

#### Reactions 11.23-1 [1]



#### Reagents

$\text{Ph}_2\text{SnCl}_2$  and  $\text{C}_6\text{F}_{13}\text{CH}_2\text{CH}_2\text{I}$  ( $\text{R}_f\text{I}$ ) are commercially available.

## Experimental Procedures

**Step A. Bis(1H,1H,2H,2H-perfluorooctyl)diphenyltin (1)** A flask containing Mg turnings (1.27 g, 52.5 mmol) is heated by flame *in vacuo*. Dry Et<sub>2</sub>O (30 mL) is added and the mixture is stirred at ambient temperature for 1 h to activate the surface of the Mg turnings. An Et<sub>2</sub>O solution (30 mL) of 1H,1H,2H,2H-perfluorooctyl iodide (R<sub>f</sub>I) (21.33 g, 45 mmol) is slowly added at 0 °C. The mixture is stirred at ambient temperature for 3 h, and Et<sub>2</sub>O (20 mL) is added. A THF solution (30 mL) of Ph<sub>2</sub>SnCl<sub>2</sub> (5.15 g, 15 mmol) is slowly added and the mixture is stirred at ambient temperature for 24 h. Water is added and the mixture is filtered through a Celite pad and the pad is washed with hexane. The combined filtrate is extracted with ethyl acetate. The organic layer is washed with water and brine. After drying (MgSO<sub>4</sub>) and evaporation, the residue is subjected to column chromatography on silica gel (hexane) to give pure R<sub>f</sub>SnPh<sub>2</sub> (1) (13.3 g, 92%) [2].

**Step B. Bis(1H,1H,2H,2H-perfluorooctyl)tin Dichloride (2)** To a CCl<sub>4</sub> solution (15 mL) containing 1 (4.83 g, 5 mmol) and dry MeOH (1.0 mL, 25 mmol) is added TMSCl (1.45 mL, 11.5 mmol) at 0 °C and the solution is stirred at ambient temperature overnight. The reaction mixture is evaporated and the residue is subjected to column chromatography on silica gel (hexane) to give pure R<sub>f</sub>SnCl<sub>2</sub> (2) (4.15 g, 94%) as a white solid [3]: mp 90–92 °C; <sup>1</sup>H NMR δ 1.96 (t, 4 H, <sup>2</sup>J<sub>SnH</sub> = 64 Hz), 2.62 (t, 4 H, J<sub>FH</sub> = 16 Hz, <sup>3</sup>J<sub>SnH</sub> = 111 Hz); <sup>119</sup>Sn NMR δ –42.7; <sup>19</sup>F NMR δ –82.00 (m, 6 F), –116.71 (m, 4 F), –123.10 (m, 4 F), –124.10 (m, 4 F), –124.56 (m, 4 F), –127.39 (m, 4 F).

**Step C. Bis(1H,1H,2H,2H-perfluorooctyl)tin Oxide (3)** To a THF solution (70 mL) of 2 (8.82 g, 10 mmol) is added 4 N NaOH solution (7.5 mL, 30 mmol) and the solution is stirred at ambient temperature for 6 h. The solution is evaporated and acetone (20 mL) is added to the residue. Heating with a heatgun results in homogeneous solution. Upon addition of water (40 mL), a viscous oil separates on the bottom of the flask. After decantation of the water, the residue is pumped *in vacuo*. The resulting oil is washed with water and pumped again. These operations are repeated until the pH of the water becomes 7 [4]. Then, the oil is washed with CH<sub>2</sub>Cl<sub>2</sub> and pumped to give a white solid of (R<sub>f</sub>SnO)<sub>n</sub> (3) (7.2 g, 88%) [2]. In case the oil does not solidify however, the oil is dissolved in a small amount of FC-72 and evaporation of this solution under reduced pressure affords a solid; <sup>1</sup>H NMR (300 MHz, FC-72 with acetone-*d*<sub>6</sub> as external lock) δ 1.30–1.95 (br, 4 H), 2.41–2.95 (br, 4 H); <sup>13</sup>C NMR (75 MHz, acetone-*d*<sub>6</sub>) δ 10.0–14.0 (br, 2 C), 25.0–27.0 (br, 2 C); 104.0–123.0 (12 C); <sup>119</sup>Sn NMR (112 MHz, acetone-*d*<sub>6</sub>) δ –168~–233 (complex pattern).

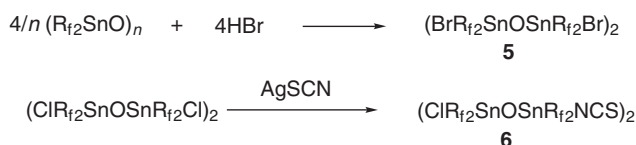
**Step D. 1,3-Dichloro-tetra(1H,1H,2H,2H-perfluorooctyl)distannoxane (4)** An acetone solution (25 mL) of 2 (8.83 g, 10 mmol) and 3 (8.29 g, 10 mmol) is heated under reflux for 8 h. The solution is evaporated and the residue was recrystallized from 2:1 FC-72/hexane to give (ClR<sub>f</sub>SnOSnR<sub>f</sub>Cl)<sub>2</sub> (4) (16.2 g, 95%): mp 71–72 °C; <sup>1</sup>H NMR (300 MHz, FC-72

with  $\text{CDCl}_3$  as external lock)  $\delta$  1.87–2.35 (m, 16 H), 2.65–3.05 (m, 16 H);  $^{13}\text{C}$  NMR (75 MHz, acetone- $d_6$ )  $\delta$  13.7 (4 C), 15.2 (4 C), 25.8 ( $^2J_{\text{CF}} = 23.2$  Hz, 4 C), 26.0 ( $^2J_{\text{CF}} = 23.2$  Hz, 4 C), 106.3–122.3 (complex pattern, 48 C);  $^{119}\text{Sn}$  NMR (112 MHz, acetone- $d_6$ )  $\delta$  –178.3, –202.5.

## Discussion

Distannoxane **4** can also be prepared by treating **3** with aqueous HCl solution at ambient temperature [5], but this procedure suffers from some problems arising from the difficulty in adjusting the amount of HCl. Thus, occasionally the yield of **3** is not satisfactory. However, this route must be invoked for synthesis of the 1,3-dibromo derivative,  $(\text{BrR}_{f2}\text{SnOSnR}_{f2}\text{Br})_2$  (**5**) because treatment of  $\text{R}_{f2}\text{SnBr}_2$  with **3** does not give rise to a satisfactory outcome [5]. Reaction of **4** with AgSCN results in replacement of non-bridging chlorines exclusively to give  $(\text{ClR}_{f2}\text{SnOSnR}_{f2}\text{NCS})_2$  (**6**).

## Reaction 11.23-2



These distannoxanes catalyze (*trans*)esterification under fluorous biphasic conditions [6–8]. Of particular interest is attainment of the 100% yield of the desired esters even by use of equimolar amounts of reactants. Apparently, the equilibrium is completely shifted to the product side by virtue of the biphasic reaction conditions.

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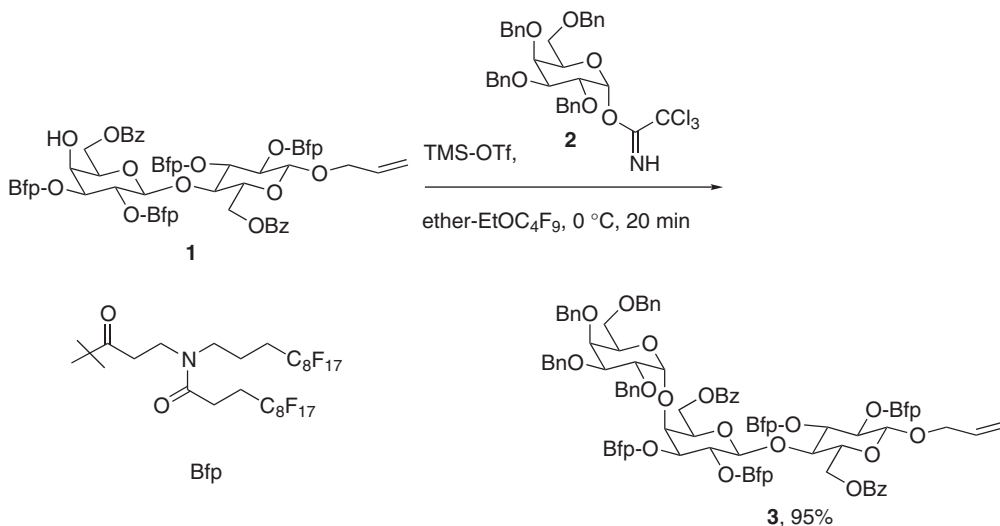


## 11.24

## Gb3 Oligosaccharide Derivative. Fluorous Synthesis of an Oligosaccharide

Tsuyoshi Miura and Toshiyuki Inazu

## Reaction 11.24-1



## Reagents

Compounds **1** [1] and **2** [2] can be prepared according to the literature procedure. EtOC<sub>4</sub>F<sub>9</sub> is a commercially available fluorocarbon solvent (Novec HFE-7200<sup>TM</sup>) from 3 M Tokyo.

## Experimental Procedure

A molecular sieve (4 Å) powder (2 g) is added to a solution of compound **1** (510 mg, 0.11 mmol) and compound **2** (530 mg, 0.77 mmol) in dry ether (12 mL)/EtOC<sub>4</sub>F<sub>9</sub> (12 mL) under an argon atmosphere. After stirring for 3 h at room temperature, TMS-OTf (60 μL, 0.33 mmol) is slowly added to the reaction mixture at 0 °C. After stirring for 20 min at 0 °C, saturated NaHCO<sub>3</sub> (5 mL) is added. The reaction mixture is filtered. The filtrate is added to water, and extracted three times with AcOEt. The AcOEt layers are washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and evaporated. Methanol is added to the residue, and this is extracted three times with FC-72. The FC-72 layers are evaporated to give compound **3** (540 mg, 95%) as colorless oil, *R*<sub>f</sub> = 0.6 (hexane/AcOEt = 2:1): <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 1.68–2.07 (16 H, m), 2.35–2.69 (24 H, m), 3.20–3.90 (21 H, m), 4.08 (5 H, m), 4.28 (4 H, m), 4.40 (1 H, m), 4.52 (4 H, m), 4.70–4.98 (10 H, m), 5.17 (4 H, m), 5.80 (1 H, m), 7.22 (18 H,

m), 7.40 (4 H, m), 7.50 (2 H, m), 7.59 (2 H, m), 7.99 (4 H, m). MALDI-TOF-MS calc. for  $C_{163}H_{120}F_{136}N_4O_{26}Na$  ( $M + Na^+$ ): 5155.6. Found: 5157.5.

## Discussion

The oligosaccharides on cell surfaces play important roles in biological processes such as cell–cell interaction, cell adhesion, and immunogenic recognition; however, the synthesis of an oligosaccharide is not easy. Although the solid phase synthesis of oligosaccharides has been actively studied, the usual solid phase method suffers from some serious disadvantages, such as the difficulty of large scale synthesis, reduced reactivity, and the inability to monitor the reaction by TLC, NMR, and MS. The use of the Bfp (bisfluorous chain type propanoyl) group as a fluorous protective group made possible the rapid synthesis of the Gb3 oligosaccharide derivative by a fluorous/organic extraction purification without column chromatography [1]. Because synthetic intermediates containing the Bfp group can be monitored by TLC, NMR, and MS, the reaction conditions are optimized rapidly. The fluorous intermediates can also be purified by silica gel column chromatography if necessary. Therefore, fluorous oligosaccharide synthesis using the Bfp group is an excellent strategic alternative to solid phase oligosaccharide synthesis, and removes some of the disadvantages of the solid phase method. Recently, oligosaccharide synthesis on the fluorous support Hfb (hexakisfluorous chain type butanoyl group) has also been developed [3].

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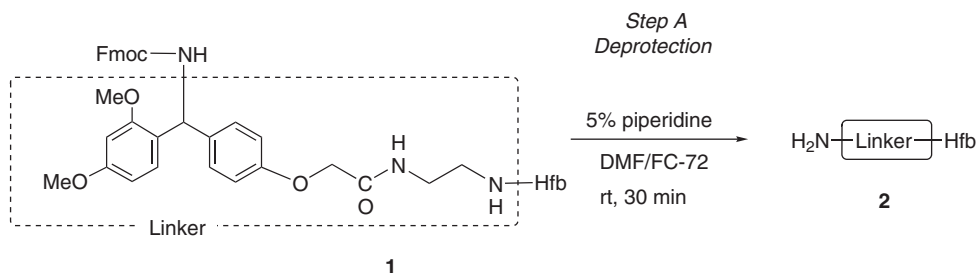
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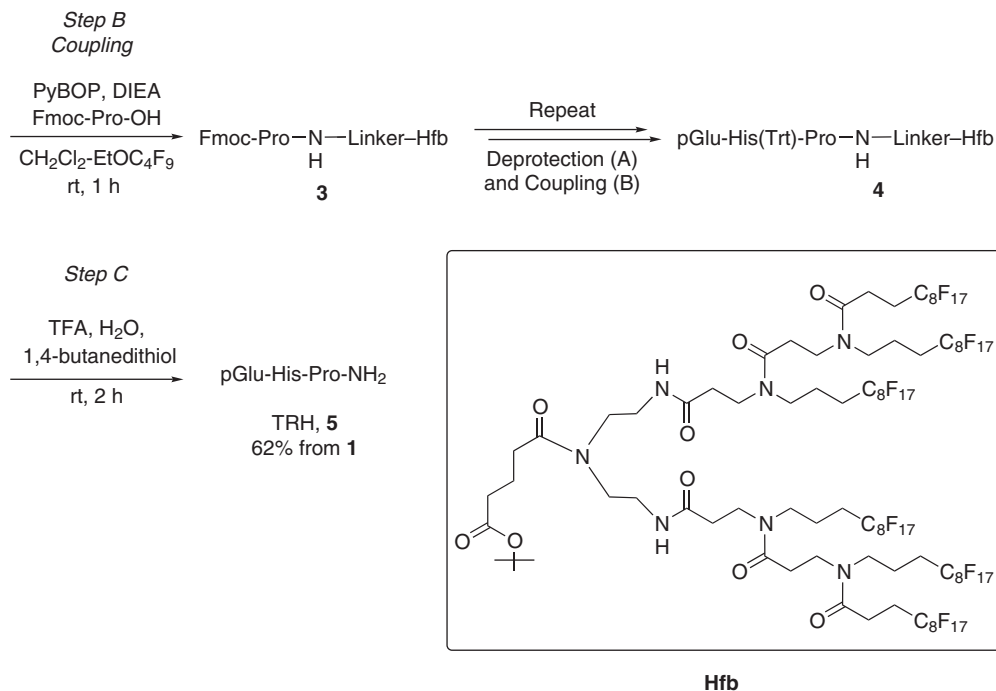
### 11.25

#### Thyrotropin-Releasing Hormone [1] (TRH). Peptide Synthesis on a Fluorous Support

Mamoru Mizuno, Kohtaro Goto, Tsuyoshi Miura, and Toshiyuki Inazu

#### Reaction 11.25-1





## Reagents

Benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP) is commercially available from Novabiochem. EtOC<sub>4</sub>F<sub>9</sub> is a commercially available fluorocarbon solvent (Novec HFE-7200™) from 3 M Tokyo.

## Experimental Procedures

**Step A. Deprotection of Fmoc Group** To a solution of Fmoc protected fluorous support **1** [2] (575 mg, 0.15 mmol) in FC-72 (10 mL) is added 10% piperidine in DMF (10 mL). After stirring for 30 min at room temperature, MeOH (30 mL) is added and the mixture is extracted with FC-72 (3 × 30 mL). The combined FC-72 layer is washed with 5% citric acid and saturated NaHCO<sub>3</sub>, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated to provide the compound **2**.

**Step B. Coupling Reaction** Fmoc-Pro-OH (202 mg, 0.60 mmol) and **2** are dissolved in a mixed solution of CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and EtOC<sub>4</sub>F<sub>9</sub> (5 mL). PyBOP (344 mg, 0.66 mmol) and DIEA (0.16 mL, 0.90 mmol) are added, and the mixture is stirred at room temperature for 1 h. The reaction mixture is concentrated to approximately 1/3 volume, and MeOH (30 mL) is added. The mixture is extracted with FC-72 (3 × 30 mL), and concentrated to give compound **3** in 97% (two steps: deprotection and coupling). Repeating the coupling reaction and the deprotection for Fmoc-His(Trt)-OH and pGlu-OH, the peptide with a fluorous support is obtained **4** (518 mg, 83% over six steps).

**Step C. Deprotection and Tag Removal** The peptide derivative **4** is treated with TFA (19 mL), H<sub>2</sub>O (0.5 mL), and 2.5% 1,4-butanedithiol (0.5 mL) at room temperature for 2 h. After concentration, FC-72 (50 mL), H<sub>2</sub>O (50 mL), and toluene (50 mL) are added to the residue, and the layers are separated. The water layer is washed with EtOC<sub>4</sub>F<sub>9</sub>, and lyophilized to give the crude peptide (65 mg). This is purified by RP-HPLC [3] [0.1% TFA/H<sub>2</sub>O–0.1% TFA/MeCN 98:2–60:40 (40 min)] to yield TRH [4] (**5**) (53 mg, 76  $\mu$ mol, 62% from **1**) after lyophilization. MALDI-TOF MS calc. for C<sub>16</sub>H<sub>23</sub>N<sub>6</sub>O<sub>4</sub> [M + H]<sup>+</sup>: 363.39. Found [M + H]<sup>+</sup>: 363.41.

## Discussion

Normally peptides are easily prepared by solid phase synthesis, which allows for a very simple product isolation by filtration. However, the solid phase method suffers from some serious disadvantages, such as reduced reactivity and the inability to monitor the reaction progress by TLC, NMR, or mass spectrometry. Similarly to solid phase synthesis, fluorous synthesis does not resort to chromatography. Since a fluorous compound is soluble not only in fluorous solvents but also in common organic solvents, the fluorous reaction can be carried out in such organic solvents [5]. Therefore, the strategy of “fluorous synthesis” is designed to combine the advantages of solid phase synthesis with those of traditional organic synthesis in the liquid phase. Thus fluorous synthesis is very useful in peptide synthesis, and has become an excellent strategic alternative to solid phase synthesis.

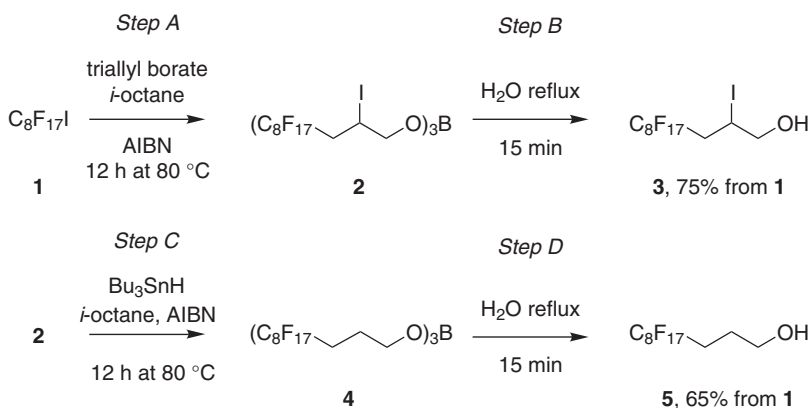
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## 11.26

**Perfluorooctylpropyl Alcohol. Radical Addition of Perfluorooctyl Iodide to Triallyl Borate, Followed by Reductive Dehalogenation and Aqueous Deprotection**

József Rábai, István Kövesi, and Ana-Maria Bonto

**Reaction 11.26-1****Reagents**

Perfluorooctyl iodide **1** [507-63-1], tributyltin hydride [668-73-3], silica gel 60, azobisisobutyronitrile (AIBN) [78-67-1] are commercially available, while triallyl borate [1693-71-6] can be prepared according to the literature procedure [1].

**Experimental Procedure**

**Step A. tris(3-Perfluorooctyl-2-iodopropyl)borate (2)** A 500 mL three-necked flask with a teflon-coated magnetic stirrer bar is equipped with a pressure equalizing dropping funnel, a thermometer and a reflux condenser connected to an argon bypass. The assembled glassware is carefully dried in a flow of argon using a hot air gun and allowed to cool to room temperature. It is then charged with isooctane (125 mL), **1** (100 g, 183 mmol) and triallyl borate (11.1 g, 61 mmol) [1]. Powdered AIBN (0.25 g) is added and the mixture is heated to 80 °C for 3.5 h. The addition of AIBN is repeated three times (0.25 g, with further heating at 80 °C for 3 h) for complete conversion of **1** to **2**. The reaction mixture solidifies at room temperature.

**Step B. 3-Perfluorooctyl-2-iodo-1-propanol (3)** Borate **2** is refluxed in water (100 mL) for 15 min. Evaporation of the separated organic phase and recrystallization of the crude product from benzene (1.3 mL g<sup>-1</sup>) gives pale yellow crystals, mp 93 °C, lit. mp 93–94 °C [4]: <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 4.11–4.49 (m, 1 H, CHI), 3.75–3.89 (m, 2 H, CH<sub>2</sub>OH), 2.65–3.14 (m, 2 H, C<sub>8</sub>F<sub>17</sub>CH<sub>2</sub>), 2.08 (t, 1 H, OH).

**Step C. tris(3-Perfluorooctylpropyl)borate (4)** AIBN (0.25 g) is added in one portion to the above melted borate and the mixture is stirred at 70–73 °C, with dropwise addition of tributyltin hydride (53 g, 182 mmol) over 2 h. The addition of AIBN and the heating process is repeated three times (0.25 g at 80 °C for 3 h) to complete the reduction.

**Step D. 3-Perfluorooctylpropyl alcohol (5)** After addition of water (100 mL) the mixture is stirred and heated to reflux for 15 min using an 120 °C oil bath. This results in the complete hydrolysis of ester 4. The mixture is cooled in an ice–water bath and the resulting crystalline product is isolated by suction filtration on a medium porosity glass funnel. The filter cake is pressed well and washed with ice-cold isooctane (2 × 50 mL) and dried on filter paper sheets in a stream of air under the hood. Then the crude product (70 g, GC: 88%) is recrystallized from isooctane (500 mL) to afford 57.0 g (65% from C<sub>8</sub>F<sub>17</sub>I, GC: 98+%) of alcohol 5 as white crystals with characteristic “tin” odour, mp 40–41 °C; selected spectral data [2]: <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 3.64 (t, 2 H, <sup>3</sup>J<sub>HH</sub> = 6.0 Hz, H<sub>2</sub>-1), 2.15–2.37 (m, 2 H, H<sub>2</sub>-3), 1.76–1.86 (m, 2 H, H<sub>2</sub>-2); <sup>19</sup>F NMR –81.3 (CF<sub>3</sub>), –114.2, –121.7, –122.5, –123.3, –126.1; FT-IR (CCl<sub>4</sub>) ν (cm<sup>–1</sup>) 3640.3 (OH). HRMS (*m/z*) calc. for C<sub>11</sub>H<sub>7</sub>F<sub>17</sub>O, M<sup>+</sup> = 478.0225. Found M<sup>+</sup> = 478.0224. Last traces of tin can be removed from this product (1 g, 98+%) by boiling it with a mixture of 50% aqueous NaOH (2 mL) and ether (20 mL) for 5 h, then filtering the separated and dried (Na<sub>2</sub>SO<sub>4</sub>) ether phase over SiO<sub>2</sub> (2 g).

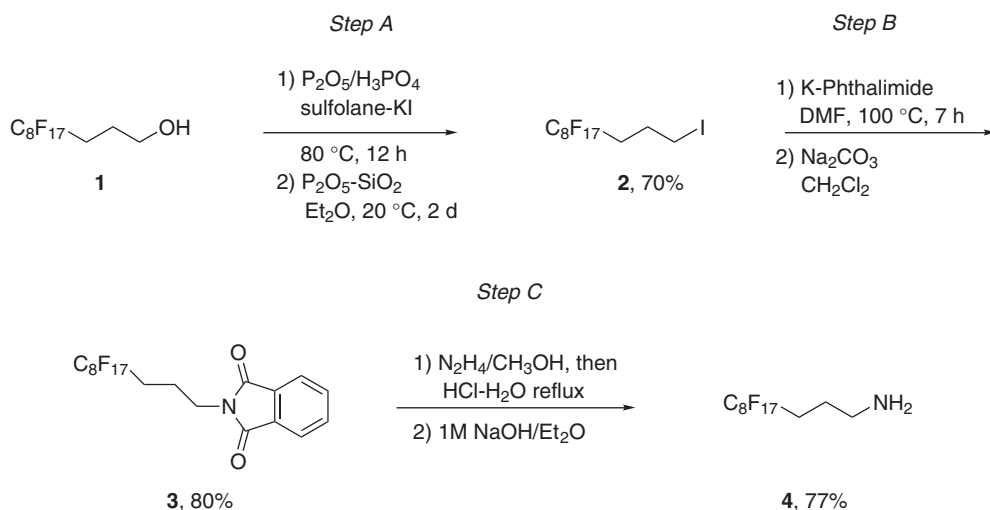
## Discussion

The addition of perfluoroalkyl iodides to alkenes is a valuable method for the introduction of linear perfluoroalkyl groups into organic molecules [1]. The best procedures for the synthesis of perfluoroalkylated iodohydrins rely on the use of protected unsaturated alcohols [2]. These radical reactions can be initiated by different means, including but not restricted to azobisisobutyronitrile, organic peroxides and transition metals, the synthetic utility of which has been commented on [3]. Furthermore, perfluoroalkyl substituted iodohydrins are versatile synthetic intermediates, for example they can be used for the synthesis of fluorine oxiranes [4, 5]. Although tributyltin hydride used above allows the selective reduction of carbon–iodine bonds, the toxicity of the organotin compounds involved calls for appropriate measures to be taken during procedures for the reaction, the workup and the disposal of side products [6].

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## 11.27

**Perfluorooctylpropyl Amine. Use of Perfluorooctylpropyl Iodide for a Gabriel Synthesis of a Fluorophilic Amine***József Rábai, Abudurexiti Abulikemu, and Dénes Szabó***Reaction 11.27-1****Reagents**

Perfluorooctylpropyl alcohol **1** [1651-41-8], perfluorooctylpropyl iodide **2** [200112-75-0] and the title perfluorooctylpropyl amine **4** [139175-50-1] are commercially available from Fluorous Technologies, Inc. ([www.fluorous.com](http://www.fluorous.com)) or can be prepared according to literature procedures [1–3].

**Experimental Procedures**

**Step A. Perfluorooctylpropyl Iodide (2)** Under an  $\text{N}_2$  atmosphere,  $\text{P}_2\text{O}_5$  (115 g, 0.81 mol) is added first at room temperature to a stirred mixture of 85%  $\text{H}_3\text{PO}_4$  (240 mL, 3.33 mol) and sulfolane (40 mL), followed by powdered potassium iodide (47 g, 0.283 mol) and **1** (50.2 g, 0.105 mol) at  $0^\circ\text{C}$ . The mixture is heated and stirred at  $120^\circ\text{C}$  for 6 h then cooled to room temperature and extracted with water (300 mL) and ether ( $4 \times 100 \text{ mL}$ ). The combined ether phases are washed consecutively with 5%  $\text{NaHSO}_3$  solution ( $2 \times 100 \text{ mL}$ ) and water ( $2 \times 50 \text{ mL}$ ) and dried ( $\text{Na}_2\text{SO}_4$ ). Distillation yields 51.5 g (83%) of the crude product of bp  $95^\circ\text{C}/0.1 \text{ mmHg}$ . It is a mixture of 94% **2** and 6% **1** (GC), and difficult to separate by distillation. The unreacted **1** can be scavenged with  $\text{P}_2\text{O}_5/\text{SiO}_2$ . Thus, a solution of the crude iodide (50 g) in ether (80 mL) is mixed with SicaPent® (8 g, Merck) and kept at room temperature for 2

days. It is filtered and washed with ether and the solvent is removed by atmospheric distillation. The residue is distilled *in vacuo* from Raschig rings to yield the pure iodide **2** as a colorless liquid, 42 g (GC: 99.5+%), bp 111 °C/16 mmHg, or shining crystals at room temperature, mp 33–34 °C:  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$  3.24 (t, 2 H,  $\text{CH}_2\text{I}$ ), 2.08–2.33 (2 m, 4 H,  $\text{C}_8\text{F}_{17}\text{CH}_2\text{CH}_2$ );  $^{19}\text{F}$  NMR  $\delta$  –81.9 (t, 3 F), –114.5 (2 F), –122.7 (6 F), –123.5 (2 F), –124.2 (2 F), –127.0 (2 F);  $^{13}\text{C}$  NMR  $\delta$  32.30 (t,  $\text{C}_8\text{F}_{17}\text{CH}_2$ ); 24.66 (t,  $\text{CH}_2\text{CH}_2\text{I}$ ); 3.65 (s,  $\text{CH}_2\text{CH}_2\text{I}$ ).

**Step B. *N*-(3-Perfluorooctylpropyl)phthalimide (**3**)** To a stirred suspension of potassium phthalimide (11.8 g, 64.0 mmol) in DMF (100 mL), **2** (18.8 g, 32.0 mmol) is added and the mixture heated at 100 °C for 7 h. The mixture is poured into 0.5 N  $\text{Na}_2\text{CO}_3$  (400 mL), extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 100$  mL) and the combined organic phases are filtered through Celite, washed with water ( $3 \times 200$  mL) and dried ( $\text{Na}_2\text{SO}_4$ ). After evaporation of the solvent, the residue is recrystallized from methanol (140 mL) to yield 15.4 g (80%) of pure **3** as pale yellow needles, mp 93.0–93.8 °C (GC: 99.4%);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.72–7.84 (m, 4 H, ArH's), 3.77 (t, 2 H,  $J = 7.0$  Hz, N- $\text{CH}_2$ ), 2.02 (qi, 2 H,  $J = 7.0$  Hz,  $\text{NCH}_2\text{CH}_2$ ), 2.16 (m, 2 H,  $\text{CH}_2\text{C}_8\text{F}_{17}$ ). HRMS ( $m/z$ ) calc. for  $\text{C}_{19}\text{H}_{10}\text{F}_{17}\text{NO}_2$ ,  $\text{M}^+ = 607.0440$ . Found  $\text{M}^+ = 607.0449$ .

**Step C. Perfluorooctylpropyl Amine (**4**)** Hydrazine hydrate (98%, 1.20 mL, 24 mmol) is added to a stirred solution of **3** (13.4 g, 22 mmol) in methanol (50 mL) and the mixture is refluxed for 1 h. This results in the formation of a voluminous crystalline precipitate. After addition of 6 N hydrochloric acid (50 mL), the mixture is refluxed for 1 h and filtered at room temperature. Then the filter cake is stirred with a mixture of 1 N NaOH (100 mL) and ether (100 mL) for 3 h to afford a clear solution of phthalylhydrazide in the water phase, while **4** is in the ether layer. The phases are separated and the water phase washed with more ether ( $2 \times 50$  mL). The ether solution is dried ( $\text{Na}_2\text{SO}_4$ ) and distilled to yield 8.1 g (77%) of pure amine **4** as a colorless liquid (GC: 98+%), bp 140–141 °C/100 mmHg:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.19 (s, br, 2 H,  $\text{NH}_2$ ), 1.71–1.78 (m, 2 H,  $\text{CH}_2\text{CH}_2\text{NH}_2$ ), 2.09–2.21 (m, 2 H,  $\text{C}_8\text{F}_{17}\text{CH}_2$ ), 2.80 (t, 2 H,  $\text{CH}_2\text{CH}_2\text{NH}_2$ );  $^{19}\text{F}$  NMR  $\delta$  –81.3 (F-11), –114.6 (F-4), –122.1 (F-6), –122.4 (F-7 and F-8), –123.2 (F-9), –123.9 (F-5), –126.6 (F-10). HRMS ( $m/z$ ) calc. for  $\text{C}_{11}\text{H}_7\text{F}_{17}\text{N}$ ,  $[\text{M} - \text{H}]^+ = 476.0307$ . Found  $[\text{M} - \text{H}]^+ = 476.0302$ . This is a fluorophilic amine, since its fluorophilicity is larger than zero:  $f = \ln P_{\text{FBS}} = 0.79$  [3b].

## Discussion

Perfluorooctylpropyl amine is a nucleophilic scavenger, which has been prepared by multiple step syntheses using perfluorooctylpropyl alcohol as a precursor [3]. In the former procedure this alcohol is first oxidized to the corresponding aldehyde, which is then used for *N*-monoalkylation of benzylamine and the obtained intermediate on hydrogenolysis affords the title amine in excellent yield [3a]. The latter procedure relies on the conversion of this alcohol into the corresponding alkyl iodide, which on reaction with excess liquid ammonia/THF under pressure, yields a separable mixture of the primary amine and the corresponding secondary amine [2, 3b]. However, the substitution of potassium phthalimide for ammonia



results in an improved procedure, which increases the yield since only primary amine is formed, and eliminates the hazards associated with the use of pressurized ammonia solutions [3c].

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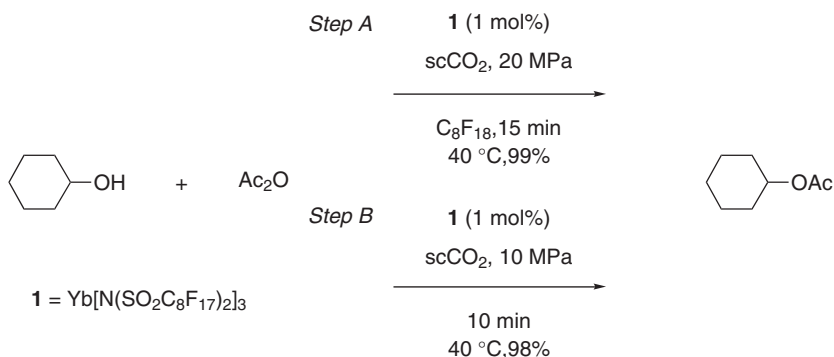
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## 11.28

### Cyclohexyl Acetate. The Acylation Reaction with a Fluorous Lanthanide Catalyst in Supercritical Carbon Dioxide with or without a Fluorous Solvent

Koichi Mikami, Hiroshi Matsuzawa, Joji Nishikido, and Mayumi Kamishima

#### Reaction 11.28-1



#### Reagents

Perfluorooctane is commercially available (Aldrich). Ytterbium(III) bis(perfluorooctanesulfonyl)amide **1** is prepared by the published procedure [1].

## Experimental Procedures

**Step A. Acylation of Cyclohexanol with Acetic Anhydride by Using  $scCO_2$  and Fluorous Solvent** A 20 mL stainless steel autoclave equipped with magnetic stirring bar is charged with cyclohexanol (0.20 g, 2 mmol), acetic anhydride (0.22 g, 2.2 mmol), and the ytterbium(III) complex 1 (1 mol% based on cyclohexanol) as a Lewis acid catalyst in perfluorooctane (5 mL). Carbon dioxide is added and a pressure of 20 MPa is applied to the autoclave. The reaction mixture is stirred for 15 min at 40 °C. After cooling below 0 °C, the pressure in the autoclave is slowly released. The autoclave is opened at room temperature, and dichloroethane (5 mL) is added. After stirring for 15 min and standing for 5 min, the mixture separates into an upper organic phase and a lower fluoruous phase. Cyclohexyl acetate is obtained from the dichloroethane layer after evaporation under reduced pressure and silica gel chromatography (0.280 g, 98% isolated yield). After removing the dichloroethane layer, fresh cyclohexanol (0.20 g, 2 mmol) and acetic anhydride (0.22 g, 2.2 mmol) are added. Carbon is added and the reaction and separation cycle is repeated with similar results. The cycle is repeated a further three times, and the yields of cyclohexyl acetate are 99%, 99% and 99%, respectively.

**Step B. Acylation of Cyclohexanol with Acetic Anhydride Using  $scCO_2$  without Fluorous Solvent** A 20 mL stainless steel autoclave equipped with magnetic stirring bar is charged with cyclohexanol (0.20 g, 2 mmol), acetic anhydride (0.22 g, 2.2 mmol), and the ytterbium(III) complex 1 (1 mol% based on cyclohexanol) as a Lewis acid catalyst. After adding carbon dioxide and applying a pressure of 10 MPa to the autoclave, the reaction mixture is stirred for 10 min at 40 °C. After cooling to -20 °C, liquid carbon dioxide is successively introduced at a flow rate of 1 mL min<sup>-1</sup> for 1 h under 6 MPa. The product is extracted with dichloroethane (5 mL). Cyclohexyl acetate is obtained from the dichloroethane layer after evaporation under reduced pressure and silica gel chromatography (0.279 g, 98% isolated yield). After successive introduction of liquid carbon dioxide, the pressure in the autoclave is released to give the catalyst, to which cyclohexanol (0.20 g, 2 mmol) and acetic anhydride (0.22 g, 2.2 mmol) were added for a second and a third cycle with similar results (98% yields).

## Discussion

We have developed the strong Lewis acids lanthanide(III) tris(perfluorooctanesulfonyl)methide and bis(perfluorooctanesulfonyl)amide in order to decrease the amount of a Lewis acid complex used in a reaction and to enable recycling to be utilized. Thus, numerous and sufficiently long (perfluorooctyl, C<sub>8</sub>F<sub>17</sub>) perfluoroalkyl ligands [2] can be attached directly without any hydrocarbon spacers to increase the Lewis acidity. These lanthanide catalysts can be employed for fluoruous biphasic catalysis (FBC) to be solubilized in fluoruous solvent [3]. FBC has the features of an environmentally benign reaction system, having the advantage that fluoruous catalysts are immobilized in the fluoruous solvent and recycled. However, the FBC method is not a completely green reaction system because organic solvents such as 1,2-dichloroethane and toluene are present. To solve this drawback, we investigated the use of supercritical carbon dioxide ( $scCO_2$ ) in place of an organic solvent. The replacement of conventional liquid solvents by supercritical fluids as the reaction media for homogeneous

catalysis provides the opportunity to control a reaction in terms of the reactivity and selectivity, because of high gas miscibilities, greater diffusivities, clustering effects, and tunable solvent power by changing their densities along with the pressure [4]. Supercritical fluids have been employed as an environmentally benign reaction media in late transition metal catalysis for hydroformylation [5] and hydrogenation [6]. By contrast, the design and immobilization of strong Lewis acid catalysts have remained a challenging problem in this unorthodox non-polar media [7]. Since fluororous compounds are soluble in  $\text{scCO}_2$  [5a, 5f, 6c, 6e, 7a, 7e], a homogeneous phase with a fluororous solvent immobilizes fluororous lanthanide catalysts. After the reaction, the fluororous solvent remains in the reaction vessel, the liquid carbon dioxide being released with the product. In addition, we tried to reuse the lanthanide catalysts by changing from  $\text{scCO}_2$  to liquid carbon dioxide. Lanthanide catalysts are insoluble in liquid carbon dioxide even in the presence of the reaction substrate or product. Our procedure features the completely recyclable use of lanthanide(III) tris(perfluorooctanesulfonyl)methide and bis(perfluorooctanesulfonyl)amide complexes in  $\text{scCO}_2$  with or without fluororous solvent.

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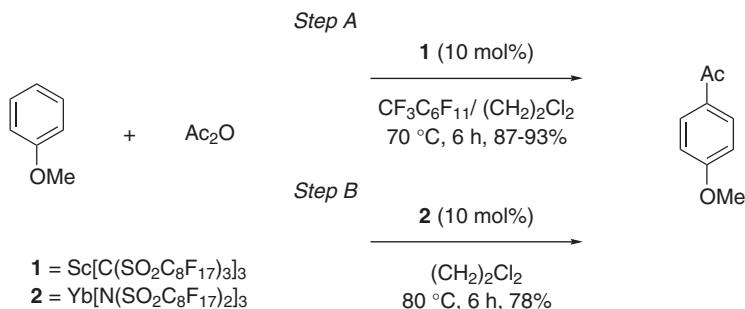
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## 11.29

***p*-Methoxyacetophenone. The Friedel-Crafts Acylation with a Fluorous Lanthanide Catalyst**

Koichi Mikami, Hiroshi Matsuzawa, and Joji Nishikido

**Reaction 11.29-1****Reagents**

Perfluoromethylcyclohexane is commercially available (Aldrich). Scandium(III) tris(perfluorooctanesulfonyl)methide **1** and ytterbium(III) bis(perfluorooctanesulfonyl)amide **2** are made by literature procedures [1–3].

**Experimental Procedures**

**Step A. The Friedel-Crafts Acylation of Anisole with Acetic Anhydride under Biphasic Conditions** Anisole (0.22 mL, 0.22 g, 2 mmol) and acetic anhydride (0.38 mL, 0.41 g, 4 mmol) are added to a mixture of perfluoromethylcyclohexane (6 mL) and 1,2-dichloroethane (6 mL). To the resultant mixture is added 10 mol% of scandium(III) complex **1** (0.89 g, 0.2 mmol). The solution is stirred at 70 °C for 6 h. After cooling to room temperature (20 °C), the mixture separates into an upper 1,2-dichloroethane phase and a lower

perfluoromethylcyclohexane phase. Each phase is individually analyzed by GC. *p*-Methoxyacetophenone is obtained from the upper phase after evaporation under reduced pressure and silica gel chromatography (0.261 g, 87% isolated yield). To the lower phase containing the catalyst is again added 1,2-dichloroethane (6 mL), anisole (0.22 mL, 0.22 g, 2 mmol), and acetic anhydride (0.38 mL, 0.41 g, 4 mmol) followed by stirring at 70 °C for 6 h. Two phases again separate on cooling, and each phase is analyzed by GC. The overall yield of *p*-methoxyacetophenone is 93%. Substantially the same procedure as mentioned above was repeated twice. The overall yields of *p*-methoxyacetophenone were 93% and 92%, respectively.

**Step B. The Friedel-Crafts Acylation Catalyzed by Ytterbium bis(Perfluorooctanesulfonyl)amide as a Solid** 10 mol% of ytterbium(III) complex **2** (0.31 g, 0.1 mmol), anisole (0.11 mL, 0.11 g, 1 mmol) and acetic anhydride (0.19 mL, 0.20 g, 2 mmol) are added to 1,2-dichloroethane (5 mL). The solution is stirred at 80 °C for 6 h. The resultant mixture is allowed to stand at –20 °C to precipitate the ytterbium complex. After 30 min, the liquid phase of the resultant mixture is decanted and the residual solid catalyst is reused without isolation. The catalyst still remains in the vessel after the third reaction. Liquid phases are combined, and concentrated under reduced pressure. *p*-Methoxyacetophenone is purified by silica gel chromatography (0.354 g, 78% isolated yield).

## Discussion

In fluorous biphasic catalysis (FBC), phosphine or phosphite ligands with fluorous ponytails and hydrocarbon spacers have been developed to immobilize late transition metal catalysts for hydroformylation [4], hydrogenation [5], alkene epoxidation [6], and hydroboration [7] in non-polar fluorous media. However, the design and immobilization of strong Lewis acid catalysts have remained as challenging problems in this unorthodox non-polar media. Numerous (nine) and sufficiently long (perfluorooctyl, C<sub>8</sub>F<sub>17</sub>) fluorous ponytails can be attached directly without any hydrocarbon spacer to increase the Lewis acidity of lanthanide catalysts and for fluorous phase immobilization. The key to the success is the powerful electron-withdrawing effect of the perfluoroalkanesulfonylmethide or -amide group [8] without any hydrocarbon spacers. The lanthanide tris(perfluorooctanesulfonyl)methide and bis(perfluorooctanesulfonyl)amide complexes are insoluble in organic solvents such as toluene and 1,2-dichloroethane at room temperature or below, even in the presence of reaction substrates. However, these complexes are soluble in organic solvents at high temperatures. We have thus reported the reuse of these fluorous lanthanide complexes as solids for the F–C acylation reaction without a fluorous solvent.

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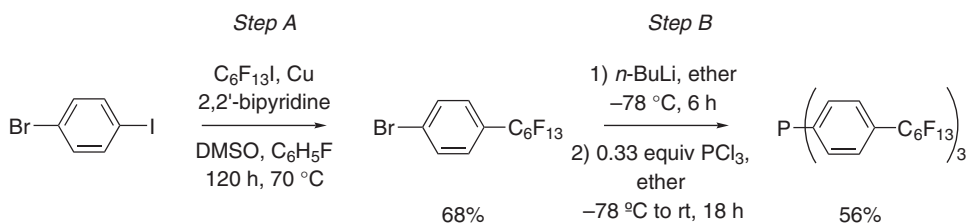
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### 11.30

#### Tris(4-tridecafluorohexylphenyl)phosphine. Versatile Ligand Synthesized via Copper Catalyzed Cross Coupling with a Perfluoroalkyl Iodide, Lithiation and Condensation Reactions

Dave J. Adams, Eric G. Hope\*, Alison M. Stuart, and Andrew J. West

#### Reaction 11.30-1



#### Reagents

All starting reagents were purchased from Aldrich Chemical Company or Fluorochem. Perfluoro-*n*-hexyl iodide [355-43-1] was stored in a fridge upon receipt before use. Anhydrous diethyl ether was prepared by distillation under dinitrogen from sodium benzophenone ketyl and was freeze/pump/thaw degassed three times before use. Phosphorus trichloride was heated at reflux for 3 h and then distilled under dinitrogen before use.

## Experimental Procedure

**Step A. 4-(Tridecafluorohexyl)bromobenzene [149068-56-4]** A 500 mL, three-necked round-bottomed flask is equipped with a magnetic stirring bar, pressure-equalizing dropping funnel, thermometer and condenser and purged for 10 min with dinitrogen. The flask is charged with 4-bromiodobenzene (25.0 g, 88.34 mmol), copper bronze (12.36 g, 193.13 mmol) [1], 2,2'-bipyridine (0.98 g, 6.36 mmol), DMSO (200 mL) and fluorobenzene (150 mL). The pressure-equalizing dropping funnel is charged with perfluoro-*n*-hexyl iodide (39.42 g, 88.39 mmol) and fluorobenzene (50 mL). The flask is purged with dinitrogen for a further 20 min whilst the suspension is stirred vigorously. The mixture is then heated to exactly 70 °C and the perfluoro-*n*-hexyl iodide added dropwise over 7 h, with the temperature of the mixture being maintained at exactly 70 °C throughout. The mixture is then stirred for a further 120 h at 70 °C. After cooling the reaction mixture to room temperature, it is added to water (250 mL) and diethyl ether (500 mL) in a 1 L conical flask. The solids that precipitate are removed by filtration through a Buchner funnel and are washed with two 50 mL portions of diethyl ether. The organic layer is separated in a 1 L separating funnel and washed five times with 250 mL water, dried over magnesium sulfate, filtered and concentrated under reduced pressure using a rotary evaporator to give a brown oil. This oil is heated in a Kugelröhr oven at 65 °C at 0.01 mmHg to remove residual 4-bromiodobenzene and, subsequently, the temperature of the oven is increased to 100 °C to distill the 4-(tridecafluoro)bromobenzene and 1,4-bis(tridecafluoro)benzene as a clear oil away from the residual copper complexes, which remain in the base bulb as a dark brown tar. The clear oil is then distilled in a microfine distillation apparatus to give 28.56 g (68%) of 4-(tridecafluoro)bromobenzene as a colorless oil (bp 89–92 °C at 10 mbar). NMR analysis showed that this sample is >98% pure and contained less than 2% of 1,4-bis(tridecafluoro)benzene. Material of this purity is acceptable for use in step B. <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 7.90 (2 H, d, <sup>3</sup>J<sub>HH</sub> = 8.5 Hz, ArH), 7.70 (2 H, d, <sup>3</sup>J<sub>HH</sub> = 8.5 Hz, ArH); <sup>19</sup>F NMR (235 MHz, CDCl<sub>3</sub>) δ –81.80 (3 F, t, <sup>4</sup>J<sub>FF</sub> = 9.3 Hz, CF<sub>3</sub>), –111.72 (2 F, t, <sup>4</sup>J<sub>FF</sub> = 14.6 Hz, α-CF<sub>2</sub>), –122.10 (2 F, m, CF<sub>2</sub>), –122.63 (2 F, m, CF<sub>2</sub>), –123.63 (2 F, m, CF<sub>2</sub>), –126.90 (2 F, m, CF<sub>2</sub>); *m/z* (EI) 474/6 (M<sup>+</sup>). Anal. calc. for C<sub>12</sub>H<sub>4</sub>BrF<sub>13</sub>: C, 30.3; H, 0.8; F, 52.0. Found C, 30.2; H, 0.8; F, 51.7.

**Step B. tris(4-Tridecafluorohexylphenyl)phosphine [193197-68-1] [2]** A 500 mL, three-necked round-bottomed flask is equipped with a magnetic stirring bar, pressure-equalizing dropping funnel, low-temperature thermometer, and Rotaflo stopcock adaptor and attached to a Schlenk line. After flame-drying under high vacuum, the flask is cooled and filled with dinitrogen. The flask is charged with 4-(tridecafluorohexyl)bromobenzene (24.0 g, 50.53 mmol) and degassed again under high vacuum for 20 min. The apparatus is again filled with nitrogen before adding dry diethyl ether (300 mL) to the main flask. Dry diethyl ether (30 mL) and a 1.6 M hexane solution of *n*-butyllithium (31.5 mL, 50.40 mmol) are both added to the dropping funnel and the flask is cooled to –78 °C using a dry ice/acetone bath. The *n*-butyllithium solution is added dropwise over 60 min with the internal temperature never allowed to warm above –75 °C. The mixture is then stirred for 5 h at –78 °C. The dropping funnel is rinsed with a 10 mL portion of dry diethyl ether and then charged with dry diethyl ether (30 mL) and phosphorus trichloride (2.29 g, 16.72 mmol). The phosphorus trichloride solution is added dropwise over 60 min with the internal temperature never al-

lowed to warm above  $-75^{\circ}\text{C}$ . The solution is then allowed to warm to room temperature and stirred overnight. A 10% ammonium hydroxide solution (100 mL) is then added [3] and the mixture is stirred for 20 min. The organic solution is then transferred into a flame-dried Schlenk flask under dinitrogen containing magnesium sulfate via a cannula. After stirring for 20 min, the solution is transferred to a flame-dried Schlenk flask under dinitrogen and the solvent removed *in vacuo* to give a yellow oil. This oil is distilled in a Kugelröhr oven to give a clear oil (bp  $210^{\circ}\text{C}$  at 0.01 mmHg). This is transferred to a glove box where it slowly solidifies to give a white solid (10.98 g, 56%). NMR analysis showed that this sample is >98% pure, mp  $63\text{--}64^{\circ}\text{C}$ .  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$  7.53 (6 H, d,  $^3J_{\text{HH}} = 8.0$  Hz, 3- $\text{C}_6\text{H}_4$ ), 7.35 (6 H, vt,  $^3J_{\text{HH}} \approx ^3J_{\text{HP}} = 8.0$  Hz, 2- $\text{C}_6\text{H}_4$ );  $^{19}\text{F}$  NMR (235 MHz,  $\text{CDCl}_3$ )  $\delta$   $-81.32$  (9 F, t,  $^4J_{\text{FF}} = 9.6$  Hz,  $\text{CF}_3$ ),  $-111.48$  (6 F, t,  $^4J_{\text{FF}} = 14.2$  Hz,  $\alpha\text{-CF}_2$ ),  $-121.90$  (6 F, m,  $\text{CF}_2$ ),  $-122.24$  (6 F, m,  $\text{CF}_2$ ),  $-123.24$  (6 F, m,  $\text{CF}_2$ ),  $-126.59$  (6 F, m,  $\text{CF}_2$ );  $^{31}\text{P}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$   $-6.3$ ;  $m/z$  (FAB) 1216 ( $\text{M}^+$ ). Anal. calc. for  $\text{C}_{36}\text{H}_{12}\text{F}_{39}\text{P}$ : C, 35.5; H, 1.0; P, 2.5. Found C, 35.8; H, 0.9; P, 2.5.

## Discussion

Reaction A is also suitable for the preparation of *ortho*- [4], *meta*- [5], and bis-*meta*-perfluoroalkylated bromobenzenes [6]. tris(4-Tridecafluorohexylphenyl)phosphine was first reported in the patent literature as a potentially useful oil additive in 1970 [7] and, more recently, has been successfully used as a modifying ligand for the hydroformylation of long chain alkenes under fluorous biphasic conditions [8] and in perfluorinated solvents [9]. It is commercially available from Fluka and Fluorous Technologies Inc. The ligand partitions 88:12 in a perfluoro-1,3-dimethylcyclohexane:toluene biphasic system and, although sensitive to oxidation in solution, can be handled as a solid in the open laboratory. Reaction B is also suitable for the preparation of tris(4-heptadecafluorooctylphenyl)phosphine via 4-(heptadecafluorooctyl)bromobenzene. However, the yield for stage B is only 26% due to the low solubility of the bromobenzene in ether at  $-78^{\circ}\text{C}$ . This tris(4-heptadecafluorooctylphenyl)-phosphine has been used successfully as a modifying ligand for palladium-catalyzed Stille [10] and Suzuki [11] coupling reactions under fluorous biphasic conditions. This procedure is also suitable for the preparation of other perfluoroalkylated aryl phosphine ligands by the replacement of phosphorus trichloride by other phosphorus-chloride reagents, e.g., 1,2-bis(dichlorophosphino)ethane [12] or diethylphosphoramidous dichloride [4].

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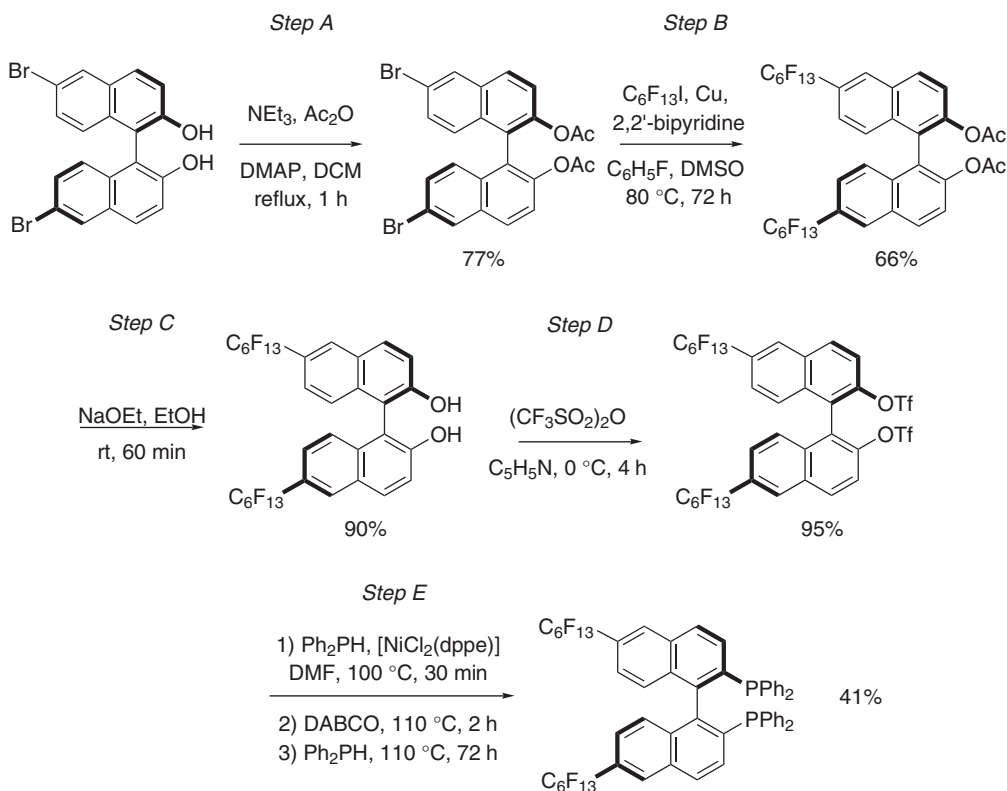
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## 11.31

**(R)-6,6'-Bis(tridecafluoro-n-hexyl)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl ((R)-Rf-BINAP).**  
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## Reaction 11.31-1



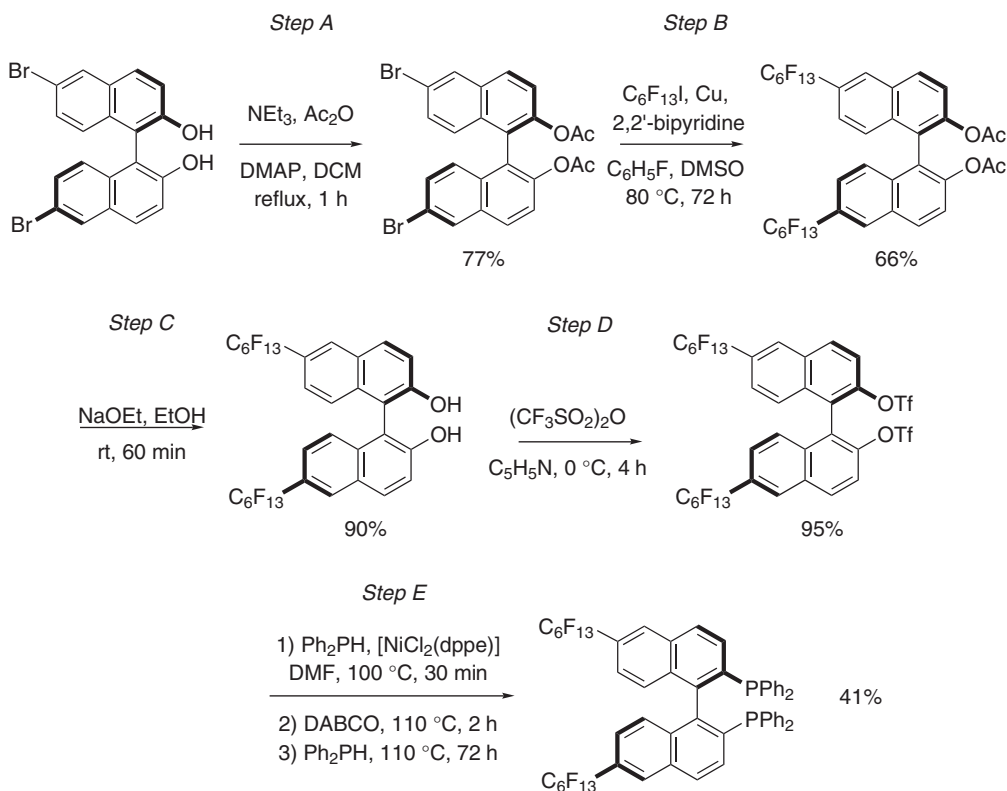
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**(R)-6,6'-Bis(tridecafluoro-n-hexyl)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl ((R)-Rf-BINAP).**  
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## Reaction 11.31-1



## Reagents

Perfluoro-*n*-hexyl iodide [355-43-1] was purchased from Fluorochem Ltd., stored in a refrigerator and used without further purification. All solvents were dried under dinitrogen. Dry dichloromethane was prepared by refluxing 1 L of the solvent over calcium hydride (approximately 15 g) for 3 days, followed by distillation from calcium hydride and transfer of the solvent to a 1 L ampoule sealed with a Youngs tap. Dry pyridine was prepared by refluxing 150 mL of the reagent over calcium hydride (approximately 10 g) for 1 day, followed by distillation from calcium hydride and transfer to a flame-dried 200 mL ampoule sealed with a Youngs tap. Anhydrous DMF was transferred from a SureSeal™ bottle to a dried ampoule containing 4 Å molecular sieves. The dichloromethane, DMF and pyridine were all freeze/pump/thaw degassed until no bubbles of gas were visible during thawing. The [NiCl<sub>2</sub>(dppe)] can be prepared easily by stirring equimolar quantities of [NiCl<sub>2</sub>]-6H<sub>2</sub>O and 1,2-bis(diphenylphosphino)ethane for 30 min in methanol followed by filtration of the suspension. The red-orange solid can then be used in the preparation. Storage of the material leads to degradation of the catalyst and unsuccessful reaction, and so the material should be freshly prepared before each synthesis. All other chemicals in this synthesis were obtained and used as supplied from Aldrich Chemical Company Inc.

## Experimental Procedures

**Step A. (R)-6,6'-Dibromo-2,2'-diacetoxy-1,1'-binaphthyl [179866-78-5]** A 250 mL, round-bottomed flask is equipped with a magnetic stirrer bar and charged with (R)-6,6'-dibromo-1,1'-bi-2,2'-naphthol (5.0 g, 11.2 mmol) [65283-60-5] [1], triethylamine (9.4 mL, 66.6 mmol), (4-*N,N*-dimethylamino)pyridine (DMAP; 100 mg, 10 mmol), acetic anhydride (2.1 mL, 22.4 mmol) and dichloromethane (100 mL). A reflux condenser is fitted to the flask and the mixture is heated to reflux for 1 h with vigorous stirring. Upon cooling, 1 M hydrochloric acid (100 mL) is slowly added and the mixture transferred to a separating funnel. The organic layer is separated and washed with saturated sodium carbonate solution (100 mL), brine (100 mL) and water (100 mL) before being dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure using a rotary evaporator to yield the crude product as a yellow semi-solid. Recrystallization from ethanol yields 8.4 g (77%) of (R)-6,6'-dibromo-2,2'-diacetoxy-1,1'-binaphthyl as white needles: <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 1.84 (6 H, s, COCH<sub>3</sub>), 7.05 (2 H, d, <sup>3</sup>J<sub>HH</sub> = 9.0 Hz, ArH), 7.49 (2 H, dd, <sup>3</sup>J<sub>HH</sub> = 9.0 Hz, <sup>4</sup>J<sub>HH</sub> = 1.8 Hz, ArH), 7.64 (2 H, d, <sup>3</sup>J<sub>HH</sub> = 9.0 Hz, ArH), 8.14 (2 H, d, <sup>3</sup>J<sub>HH</sub> = 9.0 Hz, ArH), 8.32 (2 H, d, <sup>4</sup>J<sub>HH</sub> = 1.8 Hz, ArH); <sup>13</sup>C{<sup>1</sup>H} NMR (63 MHz, CDCl<sub>3</sub>) δ 20.91, 120.48, 123.50, 123.62, 128.15, 129.24, 130.50, 130.69, 132.11, 133.01, 147.44, 169.53, *m/z* (FAB) 529 (MH)<sup>+</sup> (14%), 486 (MH-COCH<sub>3</sub>)<sup>+</sup> (14%). [ $\alpha$ ]<sub>D</sub> 33.8 (CDCl<sub>3</sub>, *c* 6.4).

**Step B. (R)-6,6'-Bis(tridecafluorohexyl)-2,2'-diacetoxy-1,1'-binaphthyl [410523-70-5]** A 250 mL, round-bottomed flask is equipped with a magnetic stirrer bar, thermometer and condenser and purged for 10 min with dinitrogen. The flask is charged with (R)-6,6'-dibromo-2,2'-diacetoxy-1,1'-binaphthyl (3.5 g, 6.6 mmol), perfluoro-*n*-hexyl iodide (8.9 g, 20 mmol), cop-

per bronze (2.6 g, 39.7 mmol) [2], 2,2'-bipyridine (0.2 g, 1.5 mmol), fluorobenzene (50 mL) and DMSO (100 mL). The flask is purged with dinitrogen for a further 15 min before heating the resulting mixture at 80 °C for 72 h with constant stirring. The mixture is then transferred to a 1 L conical flask and diethyl ether (300 mL) and water (200 mL) added. The suspension is filtered using a Buchner funnel and the solids are washed with two 25 mL portions of diethyl ether. The filtrate is transferred to a 1 L separating funnel and the organic layer is separated. This is washed with 1 M hydrochloric acid (100 mL) and five portions of water (100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure using a rotary evaporator to give 4.4 g (66%) of (R)-6,6'-bis(tridecafluorohexyl)-2,2'-diacetoxy-1,1'-binaphthyl as a yellow oil. The sample was shown to be >95% pure by  $^1\text{H}$  NMR spectroscopy. Material of this purity is acceptable for use in the third step. The yellow oil can be solidified by addition of hexane (30 mL) followed by removal of the solvent under reduced pressure using a rotary evaporator three times, followed by prolonged drying under high vacuum:  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$  1.81 (6 H, s,  $\text{COCH}_3$ ), 6.93 (2 H, d,  $^3J_{\text{HH}} = 9.0$  Hz, ArH), 7.24 (2 H, d,  $^3J_{\text{HH}} = 9.0$  Hz, ArH), 7.41 (2 H, d,  $^3J_{\text{HH}} = 9.0$  Hz, ArH), 7.85 (2 H, d,  $^3J_{\text{HH}} = 9.0$  Hz, ArH), 8.08 (2 H, s, ArH);  $^{19}\text{F}$  NMR (235 MHz,  $\text{CDCl}_3$ )  $\delta$  -81.31 (6 F, t,  $^4J_{\text{FF}} = 10.6$  Hz,  $\text{CF}_3$ ), -110.70 (4 F, m,  $\alpha\text{-CF}_2$ ), -121.89 (4 F, m,  $\text{CF}_2$ ), -121.95 (4 F, m,  $\text{CF}_2$ ), -123.17 (4 F, m,  $\text{CF}_2$ ), -126.52 (4 F, m,  $\text{CF}_2$ );  $^{13}\text{C}\{^1\text{H}\}$  NMR (63 MHz,  $\text{CDCl}_3$ )  $\delta$  19.44, 121.95, 122.52, 122.77 (t,  $^3J_{\text{CF}} = 6.1$  Hz), 125.38 (t,  $^2J_{\text{CF}} = 24.0$  Hz), 125.70, 127.04 (t,  $^3J_{\text{CF}} = 6.8$  Hz), 129.40, 129.85, 133.63, 147.69, 168.07;  $m/z$  (FAB) 1007 ( $\text{MH}^+$ ) (8%). Anal. calc. for  $\text{C}_{36}\text{H}_{16}\text{F}_{26}\text{O}_4$ : C, 42.9; H, 1.6. Found: C, 42.8; H, 1.75;  $[\alpha]_{\text{D}}^{25}$  2.7 ( $\text{CHCl}_3$ , c 0.6).

**Step C. (R)-6,6'-Bis(tridecafluorohexyl)-1,1'-bi-2,2'-naphthol [410523-71-6]** A 100 mL, round-bottomed flask, equipped with a magnetic stirrer bar, is charged with (R)-6,6'-bis(tridecafluorohexyl)-2,2'-diacetoxy-1,1'-binaphthyl (2.1 g, 2 mmol) and ethanol (65 mL). The resulting suspension is stirred rapidly and sodium ethoxide (0.34 g, 5 mmol) is added. The resulting brown solution is stirred for 1 h at room temperature. The magnetic stirrer bar is removed from the mixture and the ethanol is then removed under reduced pressure using a rotary evaporator. Dichloromethane (50 mL) is added to the brown oil and the liquid is transferred into a 250 mL separating funnel. The organic solution is washed with 1 M hydrochloric acid (100 mL) and water (100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure using a rotary evaporator to yield a yellow-brown oil. Methanol (30 mL) is added to the oil and the solution is filtered. The solvent is removed again using a rotary evaporator to yield a yellow oil. This oil is triturated with hexane and recrystallized from hexane to give 1.6 g (90%) of (R)-6,6'-bis(tridecafluorohexyl)-1,1'-bi-2,2'-naphthol as a yellow solid, mp 81–83 °C:  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$  5.21 (2 H, s, OH), 7.18 (2 H, d,  $^3J_{\text{HH}} = 9.0$  Hz, ArH), 7.37 (2 H, d,  $^3J_{\text{HH}} = 9.2$  Hz, ArH), 7.44 (2 H, d,  $^3J_{\text{HH}} = 9.0$  Hz, ArH), 8.11 (2 H, d,  $^3J_{\text{HH}} = 9.0$  Hz, ArH), 8.24 (2 H, s, ArH);  $^{19}\text{F}$  NMR (235 MHz,  $\text{CDCl}_3$ )  $\delta$  -81.22 (6 F, t,  $^4J_{\text{FF}} = 10.2$  Hz,  $\text{CF}_3$ ), -110.98 (4 F, m,  $\alpha\text{-CF}_2$ ), -121.88 (8 F, m,  $2 \times \text{CF}_2$ ), -123.21 (4 F, m,  $\text{CF}_2$ ), -126.59 (4 F, m,  $\text{CF}_2$ );  $^{13}\text{C}\{^1\text{H}\}$  NMR (63 MHz,  $\text{CDCl}_3$ )  $\delta$  110.96, 119.69, 124.95 (t,  $^3J_{\text{CF}} = 6.1$  Hz), 125.13, 125.15 (t,  $^2J_{\text{CF}} = 24.4$  Hz), 128.69 (t,  $^3J_{\text{CF}} = 7.1$  Hz), 128.74, 133.10, 135.41, 155.13;  $m/z$  ( $\text{ES}^-$ ) 922 ( $\text{M}^-$ ) (33%), 921 ( $\text{M-H}^-$ ) (100%). Anal. calc. for  $\text{C}_{32}\text{H}_{12}\text{F}_{26}\text{O}_2$ : C, 41.65; H, 1.3. Found: C, 41.7; H, 1.3;  $[\alpha]_{\text{D}}^{25}$

−17.4 (CHCl<sub>3</sub>, *c* 1.2). The <sup>13</sup>C{<sup>1</sup>H} NMR analysis reports no carbon signals for the perfluoroalkyl groups as these are coupled extensively to the fluorine nuclei and so are not distinguishable.

**Step D.** *(R)*-6,6'-Bis(tridecafluorohexyl)-2,2'-di-trifluoromethanesulfonyloxy-1,1'-binaphthyl [410523-72-7] A 100 mL, three-necked, round-bottomed flask is equipped with a magnetic stirrer and flame-dried under high vacuum. Once cool, the flask is filled with dinitrogen. (*R*)-6,6'-bis(Tridecafluorohexyl)-1,1'-bi-2,2'-naphthol (2.0 g, 2.2 mmol) is added to the flask against a positive flow of dinitrogen and the removed glass stopper is replaced with a rubber septum. Dry dichloromethane (50 mL) is added to the flask through the septum via a cannula and dry pyridine (0.15 mL, 3.2 mmol) is added via syringe. The mixture is cooled in an ice bath to 0 °C and trifluoromethanesulfonic anhydride (0.44 mL, 2.6 mmol) is added dropwise via syringe through the septum. The resulting orange solution containing a white precipitate is allowed to warm to room temperature over 4 h under nitrogen. 1 M Hydrochloric acid (50 mL) is added and the mixture transferred to a separating funnel. The organic layer is separated, washed with saturated sodium carbonate solution (50 mL) followed by water (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure using a rotary evaporator. The crude brown product is recrystallized from hexane to yield 1.2 g (95%) of (*R*)-6,6'-bis(tridecafluorohexyl)-2,2'-di-trifluoromethanesulfonyloxy-1,1'-binaphthyl as a white crystalline solid, mp 120–122 °C: <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 7.29 (2 H, d, <sup>3</sup>J<sub>HH</sub> = 9.0 Hz, ArH), 7.51 (2 H, d, <sup>3</sup>J<sub>HH</sub> = 9.2 Hz, ArH), 7.70 (2 H, d, <sup>3</sup>J<sub>HH</sub> = 9.2 Hz, ArH), 8.24 (2 H, d, <sup>3</sup>J<sub>HH</sub> = 9.0 Hz, ArH), 8.26 (2 H, s, ArH); <sup>19</sup>F NMR (235 MHz, CDCl<sub>3</sub>) δ −74.92 (6 F, s, OSO<sub>2</sub>CF<sub>3</sub>), −81.24 (6 F, t, <sup>4</sup>J<sub>FF</sub> = 10.7 Hz, CF<sub>2</sub>CF<sub>3</sub>), −111.00 (4 F, m, α-CF<sub>2</sub>), −121.88 (4 F, m, CF<sub>2</sub>), −121.93 (4 F, m, CF<sub>2</sub>), −123.18 (4 F, m, CF<sub>2</sub>), −126.54 (4 F, m, CF<sub>2</sub>); <sup>13</sup>C{<sup>1</sup>H} NMR (63 MHz, CDCl<sub>3</sub>) δ 121.34, 123.45, 125.41 (t, <sup>3</sup>J<sub>CF</sub> = 6.2 Hz), 127.70, 128.73 (t, <sup>3</sup>J<sub>CF</sub> = 7.1 Hz), 128.96 (m), 131.68, 133.79, 134.80, 147.35; *m/z* (FAB) 1186 (M)<sup>+</sup> (82%). Anal. calc. for C<sub>34</sub>H<sub>10</sub>F<sub>32</sub>O<sub>6</sub>S<sub>2</sub>: C, 34.4; H, 0.8. Found: C, 34.4; H, 0.8; [α]<sub>D</sub> 5.7 (CHCl<sub>3</sub>, *c* 2.3). The <sup>13</sup>C{<sup>1</sup>H} NMR analysis reports no carbon signals for the perfluoroalkyl groups as these are coupled extensively to the fluorine nuclei and so are not distinguishable.

**Step E.** *(R)*-6,6'-Bis(tridecafluorohexyl)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl [410523-73-8] A 100 mL, three-necked, round-bottomed flask is fitted with a magnetic stirrer bar and reflux condenser and flame-dried under high vacuum. Once cool, the flask is filled with dinitrogen. Freshly prepared [NiCl<sub>2</sub>(dppe)] (44 mg, 8.3 × 10<sup>−5</sup> mol) is added to the flask against a positive flow of dinitrogen and the removed glass stopper is replaced with a rubber septum. A 100 mL, Schlenk flask is equipped with a magnetic stirrer bar and flame dried under high vacuum. Upon cooling, this flask is also filled with dinitrogen. (*R*)-6,6'-bis(tridecafluorohexyl)-2,2'-di-trifluoromethanesulfonyloxy-1,1'-binaphthyl (0.84 mmol) is added to the Schlenk flask against a positive flow of dinitrogen and a rubber septum is placed in the mouth of the flask. Dry DMF (50 mL) is then added to each flask via a cannula. To the round-bottomed flask, diphenylphosphine (120 μL, 1.1 mmol) is added through the septum via syringe and the mixture of phosphine and nickel stirred at 100

°C for 30 min. The solution of (R)-6,6'-bis(tridecafluorohexyl)-2,2'-di-trifluoromethanesulfonyloxy-1,1'-binaphthyl in the Schlenk flask is then added to the phosphine via a cannula. The septum is removed and 1,4-diazabicyclo[2,2,2]octane (DABCO; 0.4 g, 3.3 mmol) is added against a positive flow of dinitrogen and the septum is replaced. The resulting green solution is stirred at 110 °C for 2 h. An additional portion of diphenylphosphine (120 µL, 1.1 mmol) is then added via syringe, the septum is replaced with a stopper and the solution stirred at 110 °C for a further 72 h. Upon cooling, the DMF is removed under high dynamic vacuum at 70 °C by trap-to-trap distillation using a round-bottomed flask trap cooled in liquid nitrogen. The resulting dark brown solid is stirred in methanol (50 mL) for 30 min and filtered to yield an off-white crude product. This is recrystallized from dichloromethane/methanol to yield 0.4 g (41%) of (R)-6,6'-bis(tridecafluorohexyl)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl as a white powder, mp 241–244 °C: <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 6.69 (2 H, d, <sup>3</sup>J<sub>HH</sub> = 9.1 Hz, ArH), 6.85 (2 H, d, <sup>3</sup>J<sub>HH</sub> = 8.9 Hz, ArH), 7.02 (8 H, m, ArH), 7.25 (12 H, m, ArH), 7.59 (2 H, d, <sup>3</sup>J<sub>HH</sub> = 8.5 Hz, ArH), 8.00 (2 H, d, <sup>3</sup>J<sub>HH</sub> = 8.5 Hz, ArH), 8.05 (2 H, s, ArH); <sup>19</sup>F NMR (235 MHz, CDCl<sub>3</sub>) δ –81.18 (6 F, t, <sup>4</sup>J<sub>FF</sub> = 10.2 Hz, CF<sub>3</sub>), –110.68 (4 F, m, α-CF<sub>2</sub>), –121.77 (8 F, m, 2 × CF<sub>2</sub>), –123.15 (4 F, m, CF<sub>2</sub>), –126.49 (4 F, m, CF<sub>2</sub>); <sup>31</sup>P{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ –13.6 (s); *m/z* (ES<sup>+</sup>) 1259 (MH)<sup>+</sup> (5%). Anal. calc. for C<sub>56</sub>H<sub>30</sub>F<sub>26</sub>P<sub>2</sub>: C, 53.4; H, 2.4. Found: C, 53.3; H, 2.3; [α]<sub>D</sub> 104.2 (C<sub>6</sub>H<sub>6</sub>, *c* 0.1).

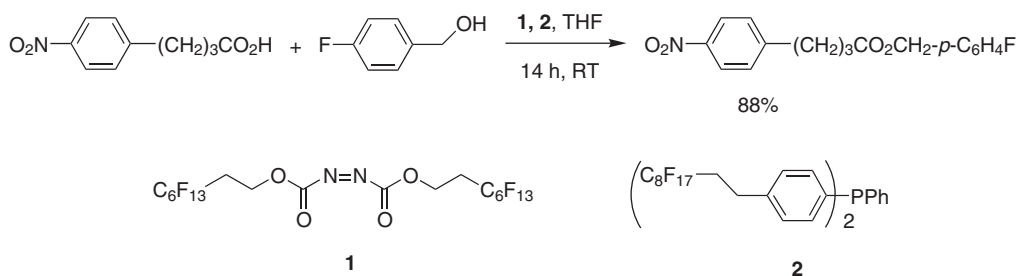
## Discussion

This perfluoroalkylated ligand is insoluble in perfluorinated cycloalkane solvents, e.g., perfluoro-1,3-dimethylcyclohexane, but has been used in the ruthenium-catalyzed asymmetric hydrogenation of dimethyl itaconate in methanol and supercritical CO<sub>2</sub>. In methanol, the perfluoroalkylated BINAP gave similar enantioselectivity but slightly lower conversion than the non-fluorous parent BINAP [3], but in supercritical CO<sub>2</sub> both the reaction rates and enantioselectivity were lower than those obtained in methanol [4]. The –C<sub>8</sub>F<sub>17</sub> analog can be prepared by a similar route using perfluoro-*n*-octyl iodide in place of perfluoro-*n*-hexyl iodide.

## References

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## 11.32

**4-Fluorobenzyl 4-(4-Nitrophenyl)butyrate. The Mitsunobu Reaction with a Fluorous Phosphine and a Fluorous Dead Reagent***Dennis P. Curran and Sivaraman Dandapani***Reaction 11.32-1****Reagents**

Bis(1*H*,1*H*,2*H*,2*H*-perfluorooctyl) azodicarboxylate (<sup>F</sup>DEAD) **1** [452912-11-7] and bis[4-(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)phenyl] phenylphosphine **2** [290827-94-0] are commercially available from Fluorous Technologies, Inc. [1] ([www.fluorous.com](http://www.fluorous.com)) or can be prepared according to the literature procedure [2]. Fluorous silica gel can be made by the literature procedure [3], but commercially available FluoroFlash<sup>TM</sup> silica gel from Fluorous Technologies, Inc. is recommended for higher loading and better reproducibility.

**Experimental Procedure**

A solution of <sup>F</sup>DEAD **1** (85 mg, 0.105 mmol) in THF (0.5 mL) is slowly added to a solution of fluorous phosphine **2** (100 mg, 0.105 mmol) in THF (0.5 mL) at 0 °C. 4-Fluorobenzylalcohol (12 μL, 0.105 mmol) is added neat. Then 4-(4-nitrophenyl)butyric acid (15 mg, 0.07 mmol) is added. After stirring overnight, the solvent is evaporated and the residue is loaded on to 2 g of fluorous silica [4] using methanol. Elution with 80% MeOH (10 mL) and evaporation of the solvent provides 4-fluorobenzyl 4-(4-nitrophenyl)butyrate (20 mg, 88%). A second elution with ether (20 mL) gives a mixture of the fluorous phosphine oxide and the fluorous hydrazine.

**Discussion**

The Mitsunobu reaction is frequently used for substitution because of its generality and because its precursors, alcohols, are readily available and can be displaced without a separate activation step [5]. While conducting Mitsunobu reactions is easy, purifying the products often is not. Chromatography is the standard purification method, but all too often one of the spent Mitsunobu reagents is difficult to separate from the target product.

Several fluorous variants of the Mitsunobu reaction have recently appeared [2, 6]. In this variant [2], a standard alcohol and nucleophile are used, and both of the reagents are fluorous. Solid phase extraction [7] over FluoroFlash silica gel allows rapid separation of the target products from the spent fluorous reagents. If desired, the spent fluorous reagents can be separated and reconverted into the starting reagents for reuse. The procedure is especially convenient for small scale reactions such as those used in natural products synthesis, medicinal chemistry or solution phase parallel synthesis.

## References

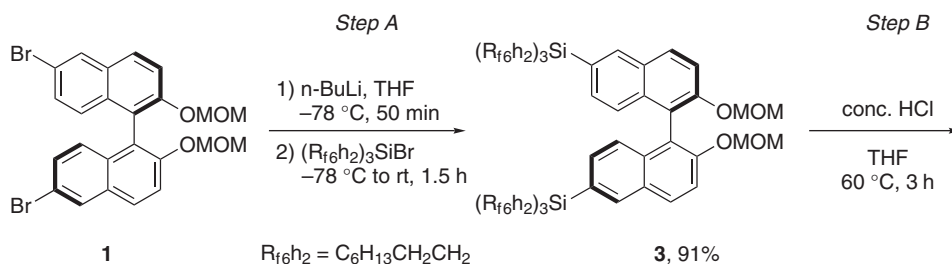
- 1 DPC holds an equity interest in Fluorous Technologies, Inc.
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## 11.33

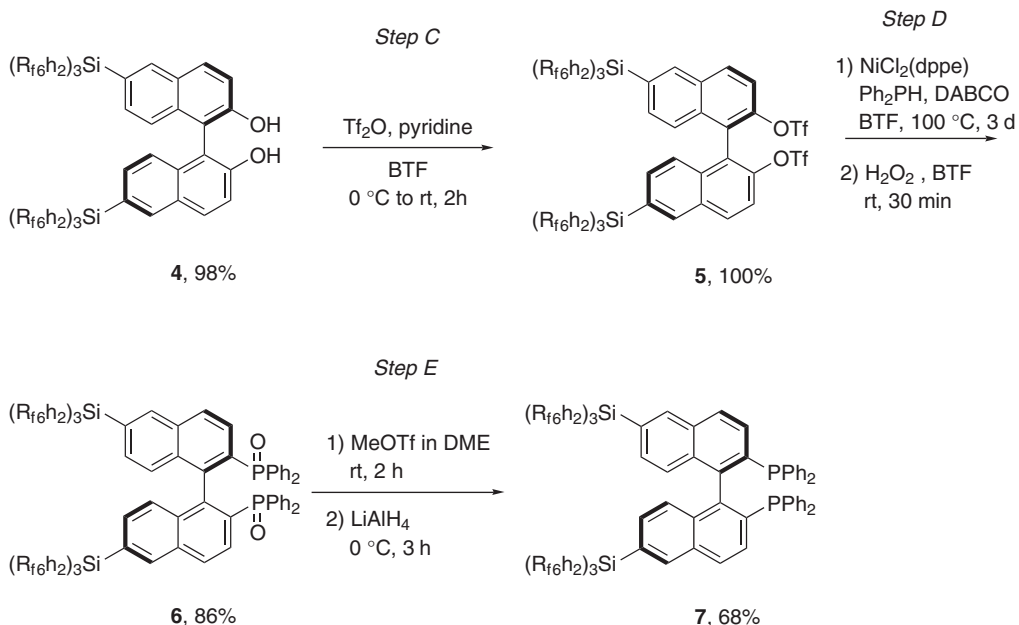
(R)-6,6'-Bis[tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)silyl]-1,1'-binaphthalene-2,2'-diol and (R)-6,6'-Bis[tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)silyl]-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene

Seiji Takeuchi and Yutaka Nakamura

## Reaction 11.33-1







### Reagents

(*R*)-6,6'-Dibromo-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene **1** [179866-74-1] and bromo tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)silane **2** [201740-57-0] can be prepared according to the literature procedures [1].

### Experimental Procedures

**Step A.** (*R*)-6,6'-Bis[tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)silyl]-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl (**3**) (*R*)-6,6'-Dibromo-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene **1** (2.00 g, 3.76 mmol) is dissolved in THF (20 mL) and cooled to  $-78^{\circ}\text{C}$  under argon. *n*-BuLi (1.55 M in hexane, 5.4 mL, 8.3 mmol) is added dropwise, and the resulting solution is stirred at that temperature for 50 min. A solution of bromo tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl) silane **2** (10.6 g, 9.22 mmol) in ether (50 mL) is added via a cannula to the reaction mixture. The reaction mixture is allowed to warm to room temperature, stirred for 1.5 h, and then quenched with a saturated aqueous  $\text{NH}_4\text{Cl}$  solution (50 mL). The volatiles are removed *in vacuo* and  $\text{CH}_2\text{Cl}_2$  (80 mL) is added. The mixture is extracted with FC-72 (30 mL  $\times$  5) and the combined FC-72 layer is concentrated *in vacuo*. The resulting syrup is purified by flash column chromatography on silica gel (400 g, hexane-EtOAc = 20/1) to afford fluorine BINOL bis MOM ether **3** as a colorless syrup (8.6 g, 91%) [2].

**Step B.** (*R*)-6,6'-Bis[tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)silyl]-1,1'-binaphthalene-2,2'-diol (**4**) A mixture of fluorine BINOL bis MOM ether **3** (399 mg, 0.159 mmol), concen-

trated HCl (4 mL) and THF (8 mL) is stirred vigorously at 60 °C for 3 h. After addition of CH<sub>2</sub>Cl<sub>2</sub> (10 mL), the cloudy biphasic mixture is extracted with FC-72 (10 mL × 5). The combined FC-72 layer is concentrated *in vacuo* to give a syrup, which is purified by flash column chromatography on silica gel (30 g, hexane/EtOAc = 10/1) to afford (R)-FBINOL **4** as a colorless syrup that gradually crystallizes (379 mg, 98%, >99% ee); mp 80–81 °C; IR (KBr) cm<sup>-1</sup>: 3500, 2946, 1614, 1470, 1207, 1144, 1071, 1019, 900, 844, 746, 708; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 1.10–1.30 (m, 12 H), 1.80–2.20 (m, 12 H), 5.14 (s, 2 H), 7.22 (d, 2 H, *J* = 8.3 Hz), 7.31 (d, 2 H, *J* = 8.3 Hz), 7.47 (d, 2 H, *J* = 9.0 Hz), 7.99 (s, 2 H), 8.04 (d, 2 H, *J* = 9.0 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 1.6, 25.5 (t, *J*<sub>FC</sub> = 24.0 Hz), 105.6–121.5 (m), 110.4, 118.7, 124.6, 126.5, 129.2, 130.8, 132.0, 134.5, 135.6, 154.1; MS (EI) *m/z* 2422 (M<sup>+</sup>). Anal. calc. for C<sub>68</sub>H<sub>36</sub>F<sub>78</sub>O<sub>2</sub>Si<sub>2</sub>: C, 33.71; H, 1.50; F, 61.16. Found: C, 33.12; H, 1.25; F, 60.93; [ $\alpha$ ]<sub>D</sub><sup>20</sup> –16.9° (c 0.463, FC-72).

**Step C.** (R)-6,6'-Bis[tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)silyl]-2,2'-bis(trifluoromethanesulfonyloxy)-1,1'-binaphthalene (**5**) A solution of (R)-FBINOL **4** (1.0 g, 0.41 mmol) and pyridine (0.10 mL, 1.24 mmol) in BTF (10 mL) is treated with trifluoromethanesulfonic anhydride (280 mg, 0.991 mmol) at 0 °C under argon. The reaction mixture is allowed to warm to room temperature and stirred for 2 h. The mixture is diluted with ether (30 mL) and washed with water (20 mL), saturated aqueous NaHCO<sub>3</sub> solution (20 mL), and brine (20 mL). The organic layer is dried over anhydrous MgSO<sub>4</sub> and then concentrated *in vacuo*. The residual syrup is purified by flash column chromatography on silica gel (50 g, hexane/ether = 20/1) to afford fluororous BINOL bis Tf **5** as a colorless syrup (1.12 g, quantitative) [3, 4].

**Step D.** (R)-6,6'-Bis[tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)silyl]-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (**6**) A mixture of [1,3-bis(diphenylphosphino)propane]nickel(II) chloride (133 mg, 0.245 mmol) in BTF (3 mL) is treated with diphenylphosphine (65 mg, 0.349 mmol) at 100 °C under argon. After stirring for 1 h, a solution of fluororous BINOL bis Tf **5** (1.12 g, 0.417 mmol) and DABCO (187 mg, 1.67 mmol) in BTF (5 mL) is added via a cannula to the reaction mixture. The green suspension is stirred at 100 °C and two additional portions of diphenylphosphine (65 mg, 0.349 mmol each) are added after 3 h and 6 h. After stirring at that temperature for 3 days, the reaction mixture is diluted with ether (50 mL). The mixture is washed with water (20 mL), brine (20 mL) and dried over anhydrous MgSO<sub>4</sub>. After the solvent is removed *in vacuo*, the residue is dissolved with BTF (20 mL). 30% H<sub>2</sub>O<sub>2</sub> (0.5 mL) is added and the mixture is stirred vigorously at room temperature for 30 min, and then excess H<sub>2</sub>O<sub>2</sub> is decomposed with MnO<sub>2</sub> (ca. 0.1 g). The mixture is dried over anhydrous MgSO<sub>4</sub> and concentrated *in vacuo*. The resulting syrup is purified by flash column chromatography on silica gel (40 g, hexane/ether = 2/1) to afford fluororous BINAP oxide **6** as a white powder (1.0 g, 86%, >99% ee) [3].

**Step E.** (R)-6,6'-Bis[tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)silyl]-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (**7**) A solution of fluororous BINAP oxide **6** in 1,2-dimethoxyethane (DME) (2 mL) is treated with methyl trifluoromethanesulfonate (MeOTf) (35 mg, 0.21

mmol) at ambient temperature for 2 h under argon. To the solution is added a solution of  $\text{LiAlH}_4$  (0.5 M in DME, 0.72 mL, 0.36 mmol) at 0 °C and then the reaction mixture is stirred at that temperature for 3 h. The reaction mixture is quenched with a few drops of saturated aqueous  $\text{Na}_2\text{SO}_2$  solution. The mixture is loaded on a column of silica gel (5 g) and then eluted with hexane-THF (20/1) [5] to afford fluorous BINAP **7** as a colorless viscous syrup which gradually crystallizes (134 mg, 68%); mp 98–101 °C; IR (KBr)  $\text{cm}^{-1}$ : 3056, 2947, 1438, 1363, 1144, 1120, 1070, 906, 813, 745, 698;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.08–1.18 (m, 12 H), 1.95–2.11 (m, 12 H), 6.79 (d, 2 H,  $J = 9.0$  Hz), 6.81 (d, 2 H,  $J = 9.0$  Hz), 7.01–7.36 (m, 20 H), 7.52 (d, 2 H,  $J = 8.5$  Hz), 7.91 (s, 2 H), 7.92 (d, 2H,  $J = 8.5$  Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  1.6, 25.5 (t,  $J_{\text{FC}} = 24.0$  Hz), 107.2–120.8 (m), 127.5–138.1 (m), 128.0, 128.4, 128.6, 129.4, 144.0 (d,  $J_{\text{PC}} = 20.0$  Hz);  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ )  $\delta$  –14.1. HRMS (ESI-TOF) calc. for  $\text{C}_{92}\text{H}_{55}\text{F}_{78}\text{Si}_2\text{P}_2$  ( $[\text{M} + \text{H}]^+$ ): 2759.2066. Found: 2759.1995;  $[\alpha]_{\text{D}}^{25} +21.2^\circ$  ( $c$  0.897, THF).

## Discussion

(*R*)-FBINOL **4** is prepared in two steps in good yield by using Curran's tagging method [6] and the procedures are applicable to a preparation of a 6,6'-bis( $\text{C}_8\text{F}_{17}\text{CH}_2\text{CH}_2$ )<sub>3</sub>Si-tagged analog [7]. The FBINOL synthetic method has a benefit that the fluorous products in each step are easily separable from organic and inorganic byproducts by FC-72/organic solvent/water three phase extraction. Fluorous BINAP [(*R*)-FBINAP] **7** is prepared in four steps from (*R*)-FBINOL **4** in moderate yield. However, operations under nitrogen or argon should be carried out carefully in order to avoid an oxidation of (*R*)-FBINAP, for example, during a column chromatography purification.

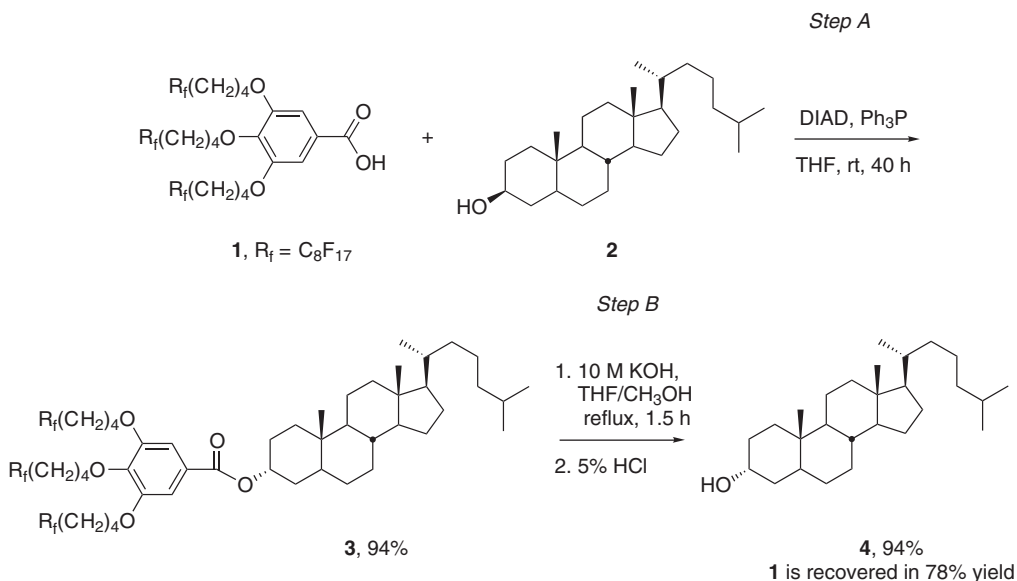
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## 11.34

**5 $\alpha$ -Cholestan-3 $\alpha$ -ol. Inversion of Configuration via the Mitsunobu Reaction with a Fluorous Gallic Acid**

Roman Dembinski and Marcin W. Markowicz

**Reaction 11.34-1****Reagents**

[CAS Registry Number]: 5 $\alpha$ -Cholestan-3 $\beta$ -ol (dihydrocholesterol) [80-97-7], diisopropyl azodicarboxylate [2446-83-5], and triphenylphosphine [603-35-0] are commercially available. 3,4,5-tris(5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-heptadecafluorododecan-1-yloxy)benzoic acid [172701-34-7] was prepared from methyl 3,4,5-trihydroxybenzoate (methyl gallate) [99-24-1] and 5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-heptadecafluorododecyl bromide [99324-99-9] or iodide [38565-62-7] by a literature method [1]. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone.

**Experimental Procedures**

*Step A.* 5 $\alpha$ -Cholestan-3 $\alpha$ -yl 3,4,5-tris(5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-heptadecafluorododecan-1-yloxy)benzoate (**3**) [477935-28-7] A round-bottomed flask (100 mL) is charged under nitrogen atmosphere with fluorous benzoic acid **1** (0.478 g, 0.300 mmol), triphenylphosphine (0.213 g, 0.812 mmol), and tetrahydrofuran (10 mL). The mixture is stirred at room temperature. 5 $\alpha$ -Cholestan-3 $\beta$ -ol **2** (0.155 g, 0.399 mmol) is added, followed by diiso-

propyl azodicarboxylate (0.15 mL, 0.76 mmol). The stirring is continued for 40 h. The solvent is removed by rotary evaporation [2] and the residue is recrystallized from chloroform/methanol (1:1 v/v, ca. 15 mL). The white solid of ester **3** is isolated by filtration (medium porosity frit) and dried over phosphorus pentoxide under an oil pump vacuum (0.556 g, 0.283 mmol, 94%), mp 117–119 °C: IR (cm<sup>-1</sup>, KBr)  $\nu_{\text{C=O}}$  1712 s; MS (EI, 70 eV) 1962 (M<sup>+</sup>, 100%), 1591 [(M - C<sub>27</sub>H<sub>47</sub>)<sup>+</sup>, 24%], 1118 [(M - C<sub>27</sub>H<sub>47</sub> - C<sub>12</sub>F<sub>17</sub>H<sub>8</sub> + 2)<sup>+</sup>, 21%]; no other peaks above 200 of >7%; <sup>1</sup>H NMR (CDCl<sub>3</sub>) 7.29 (s, 2 H, C<sub>6</sub>H<sub>2</sub>COO), 5.23 (m, 1 H, OCH), 4.20–3.90 (m, 6 H, CH<sub>2</sub>OC<sub>6</sub>H<sub>2</sub>), 2.30–0.65 (m, 64 H, remaining hydrogens); <sup>13</sup>C NMR 165.6 (COO), 152.7 (m-C<sub>6</sub>H<sub>2</sub>COO), 141.9 (p-C<sub>6</sub>H<sub>2</sub>COO), 126.6 (i-C<sub>6</sub>H<sub>2</sub>COO), 108.3 (o-C<sub>6</sub>H<sub>2</sub>COO), 72.9 (4-CH<sub>2</sub>OC<sub>6</sub>H<sub>2</sub>), 71.3 (COOCH), 68.6 (3,5-CH<sub>2</sub>OC<sub>6</sub>H<sub>2</sub>), 56.9, 56.6, 55.1, 42.8, 40.9, 40.3, 39.7, 36.3, 36.13, 36.06, 35.7, 33.6, 33.2, 32.4, 30.8 (t, *J* = 22.0 Hz, CF<sub>2</sub>CH<sub>2</sub>), 29.9 (4-CH<sub>2</sub>CH<sub>2</sub>OC<sub>6</sub>H<sub>2</sub>), 28.9 (3,5-CH<sub>2</sub>CH<sub>2</sub>OC<sub>6</sub>H<sub>2</sub>), 28.6, 28.4, 28.2, 26.5, 24.3, 24.1, 23.0, 22.7, 21.1, 18.8, 17.6 (m, CF<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 12.3, 11.7.

**Step B. 5 $\alpha$ -Cholestan-3 $\alpha$ -ol (**4**) (Epidihydrocholesterol) [516-95-0]** A round-bottomed flask (100 mL) is charged with ester **3** (0.500 g, 0.255 mmol), tetrahydrofuran/methanol (1:1 (v/v), 30 mL), and 10 M potassium hydroxide (0.6 mL). The mixture is refluxed for 1.5 h, cooled, and acidified with 5% hydrochloric acid (ca. 2 mL). The solvent is removed by rotary evaporation [2]. The solid residue is extracted with methylene chloride (2  $\times$  25 mL) and filtered through a silica gel pad (3 cm). The solvent is removed from the filtrate by rotary evaporation to give 5 $\alpha$ -cholestan-3 $\alpha$ -ol **4** as a white solid that was dried over phosphorus pentoxide under an oil pump vacuum (0.093 g, 0.24 mmol, 94%). The silica gel pad with the remaining solid is washed with tetrahydrofuran (2  $\times$  15 mL). The solvent is removed from the filtrate by rotary evaporation and the residue is crystallized from chloroform/methanol (1:1 v/v, ca. 15 mL). The white solid is isolated by filtration (medium porosity frit) and dried over phosphorus pentoxide under an oil pump vacuum to recover the fluororous benzoic acid **1** (0.317 g, 0.199 mmol, 78%) [3].

## Discussion

The conversion of asymmetric secondary alcohols into esters, with inversion of configuration, is of considerable importance in synthesis. The Mitsunobu reaction is well suited to accomplish this transformation [4]. In this reaction an alcohol is treated with dialkyl azodicarboxylate, triphenylphosphine and a carboxylic acid to provide an ester with inversion of configuration.

Inversion of configuration on C-3 of the cholestanol can be achieved by several methods and/or reagents. These include, among others, classical [5] and fluororous [6] Mitsunobu protocols, treatment with (chloromethylene)dimethylammonium chloride [7], Pd/benzoquinone [8], a Ni catalyst [9], reaction of isourea ethers with carboxylic acids [10], or reaction of sulfonates with cesium acetate [11]. Synthesis of 5 $\alpha$ -cholestan-3 $\alpha$ -ol **4** by other methods also includes a large number of references and patents. Stereocontrolled reduction of the carbonyl precursor is one of the most common approaches [12].

The side products of the Mitsunobu reaction, triphenylphosphine oxide and dialkyl hydrazinedicarboxylate are of substantial mass and may cause isolation of the product to be tedious. Several fluororous approaches addressing this issue have been recently reported (short review in Chapter 10.3). The present fluororous variant of the Mitsunobu reaction pro-

vides for facile, chromatography-free separation of the ester **3** [13] and due to the hydrophobicity of cholestanol esters has an advantage over solid phase extraction [6]. Saponification of **3** with retention of configuration gives, after workup, an alcohol **4**, and a fluororous gallic acid **1** that can be reused without any additional treatment. Other esters can also be synthesized by this method (Table 10.3-2 in Chapter 10.3).

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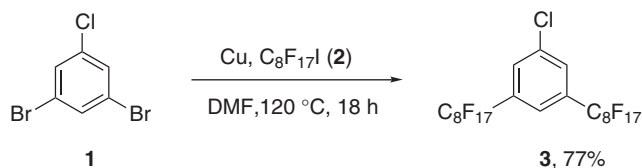
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## 11.35

### 1,3-Bis(heptadecafluorooctyl)-5-chlorobenzene. Synthesis of Perfluoroalkylarenes from Aryl Bromides

Gianluca Pozzi, Marco Cavazzini, and Ian Shepperson

#### Reaction 11.35-1



## Reagents

1,3-Dibromo-5-chlorobenzene **1** [14862-52-3] and 1-heptadecafluoro-1-iodooctane **2** [507-63-1] are available from commercial sources. Copper powder 99% for organic synthesis, commercially available from Aldrich, is used as obtained.

## Experimental Procedure

Copper powder (2.42 g, 38.1 mmol) and solid 1,3-dibromo-5-chlorobenzene **1** (1.03 g, 3.8 mmol) are suspended under nitrogen in 20 mL of dry, degassed DMF in a flame-dried Schlenk tube stoppered with a rubber septum. The mixture is vigorously stirred at 70 °C and the first portion of 1-heptadecafluoro-1-iodooctane **2** (1.11 mL, 4.2 mmol) is added dropwise with a syringe. The temperature is then increased to 120 °C and the reaction stirred for 1 h before adding the second portion of **2** (1.11 mL, 4.2 mmol). After 18 h, the reaction mixture is cooled to room temperature. Water (20 mL) and diethyl ether (50 mL) are added and the mixture is filtered using a Büchner funnel to remove insoluble inorganic compounds. The solid is then washed on the filter with diethyl ether (5 × 30 mL). The filtrate is poured into a separatory funnel, the aqueous layer is separated and extracted with diethyl ether (2 × 20 mL). The combined ethereal extracts are washed with water (40 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and the solvent and volatile byproducts are removed at reduced pressure. The crude product is washed with boiling dichloromethane (3 × 10 mL) affording pure **3** (2.70 g, 77%) as a white solid [**1**], mp 51–52 °C: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>/CCl<sub>2</sub>FCF<sub>2</sub>Cl)  $\delta$  7.69 (br s, 1 H), 7.81 (br s, 1 H). GC analysis: column HP-5 (5% phenyl methyl siloxane), carrier He = 2.7 mL min<sup>-1</sup>, split ratio = 50:1, detector *T* = 280 °C, injector *T* = 180 °C, oven *T* = 50 °C (5 min) to 70 °C (rate = 5 °C min<sup>-1</sup>) (1 min) to 220 °C (rate = 15 °C min<sup>-1</sup>), retention time = 15.4 min.

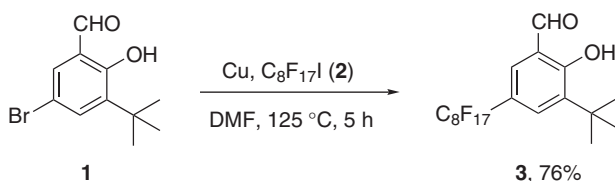
## Discussion

A discussion of copper coupling procedures accompanies the following preparation (11.36): 3-*tert*-butyl-5-heptafluorooctyl-2-hydroxybenzaldehyde.

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- |   |   |
|---|---|
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|---|---|

## 11.36

**3-*tert*-Butyl-5-heptadecafluorooctyl-2-hydroxybenzaldehyde. Synthesis of Perfluoroalkylarenes from Aryl Bromides***Gianluca Pozzi, Marco Cavazzini, and Ian Shepperson***Reaction 11.36-1****Reagents**

5-Bromo-3-*tert*-butyl-2-hydroxybenzaldehyde **1** [153759-58-1] is prepared by bromination of 3-*tert*-butyl-2-hydroxybenzaldehyde [24623-65-2] according to a literature procedure [1]. 1-Heptadecafluoro-1-iodooctane **2** [507-63-1] is available from commercial sources. Copper powder 99% for organic synthesis (Aldrich) is used as obtained.

**Experimental Procedure**

Copper powder (1.91 g, 30.0 mmol) is added under nitrogen to a solution of bromosalicylaldehyde **1** (1.54 g, 6.0 mmol) in dry, degassed DMF (30 mL) in a flame-dried Schlenk tube stoppered with a rubber septum [1]. The suspension is heated at 125 °C under stirring. 1-Heptadecafluoro-1-iodooctane **2** (3.2 mL, 12.1 mmol) is added dropwise with a syringe in four equal portions (0.80 mL each); the reaction is stirred for 40 min after each addition and then left for a further 2 h. The suspension is allowed to cool to room temperature, treated with water (30 mL) and diethyl ether (40 mL), and filtered using a Büchner funnel. The solid residue is washed with diethyl ether (3 × 20 mL). The aqueous phase is extracted with diethyl ether (3 × 15 mL). The combined organic layers are washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent removed under reduced pressure. The residue is purified by column chromatography (silica gel, petroleum ether/diethyl ether 9/1), affording **3** (2.72 g, 76%) as a white solid, mp 54 °C: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.43 [s, 9 H, C(CH<sub>3</sub>)<sub>3</sub>], 7.57 (d, *J* = 2.5 Hz, 1 H), 7.66 (br s, 1 H), 9.93 (s, 1 H, CHO), 12.13 (s, 1 H, OH); <sup>19</sup>F NMR (CDCl<sub>3</sub>) δ -81.1 (t, *J* = 10 Hz, 3 F), -111.2 (t, *J* = 13 Hz, 2 F), -121.8 (br s, 2 F), -122.3 (br s, 6 F), -123.0 (br s, 2 F), -126.4 (br s, 2 F); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 28.9, 35.2, 104–119 (m, C<sub>8</sub>F<sub>17</sub>), 120.1, 131.0, 131.5, 139.8, 163.7, 196.5.

**Discussion**

Perfluoroalkyl-substituted aromatic compounds are useful intermediates in the synthesis of more complex fluorinated molecules. Several methods have been developed to introduce one



or more perfluoroalkyl ( $R_f$ ) groups into aromatic substrates, among which are free-radical reactions promoted by light, heat or various initiators [2], the use of electrophilic perfluoroalkylating agents [3] and coupling reactions of perfluoroalkyl organometallic reagents [4]. The coupling reaction of perfluoroalkylcopper reagents with aromatic halides is particularly useful for the preparation of fluorous building-blocks because it occurs exclusively at the halogen site(s) and is compatible with the presence of a wide range of functional groups [5].

Perfluoroalkylcopper reagents are easily obtained when perfluoroalkyl iodides are heated with finely divided copper metal in coordinating solvents such as DMF or DMSO. The coupling reactions can be conveniently carried out by using perfluoroalkylcopper species generated *in situ* when a mixture of  $R_fI$ , Cu and aromatic halide in the appropriate solvent is heated to 110–130 °C. Since reactivity of aromatic halides follows the order  $ArCl \ll ArBr < ArI$ , the iodides are often chosen as starting materials for the preparation of fluorous aromatic building-blocks [6]. However, aryl (poly)iodides bearing additional functional groups are often expensive or not commercially available and the preparation of these compounds can be non-trivial. They can be usefully replaced by the corresponding, more easily accessible aryl (poly)bromides as exemplified here and in literature reports [1, 7]. Longer, but still reasonable, reaction times are required to bring the coupling to completion, as expected on the basis of the reactivity order. A slight excess of  $R_fI$  is necessary, and its addition is staggered so that there is full conversion of the aryl (poly)bromides into the corresponding perfluoroalkyl derivative. When more than one bromine atom is present in the aromatic substrate, a careful choice of the reaction conditions allows introduction of the desired number of perfluoroalkyl substituents, as in the case of the copper-mediated coupling reaction between 1,3,5-tribromobenzene and 2 equiv of **2** to give 3,5-bis(heptadecafluorooctyl)-1-bromobenzene as the main product in 60% yield [1]. The presence of substituents other than halides (e.g. -COOR, -R, -OR, OCOR, COR) is well-tolerated, but aromatic aldehydes usually give perfluoroalkylation products in very low yields because of extensive decomposition under the reaction conditions [8]. When the carbonyl group is both sterically hindered and hydrogen bonded to an *ortho*-substituent, as in the case of aldehyde **3**, the reaction proceeds in good yields and selectivities.

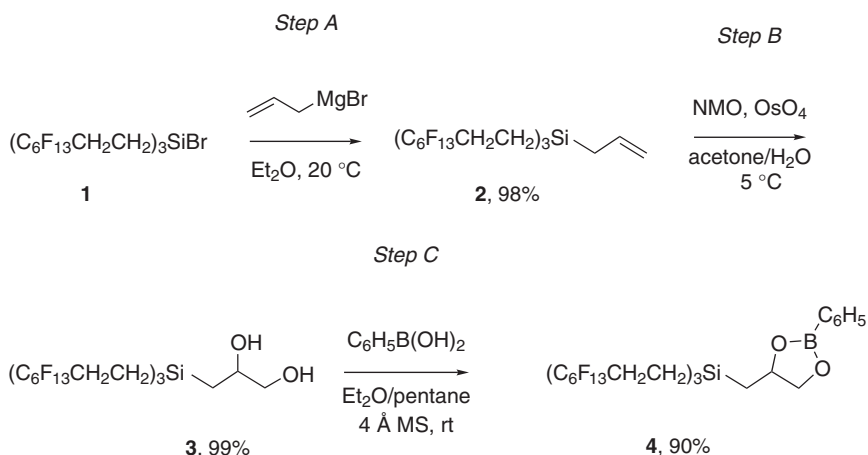
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## 11.37

**2-Phenyl-4-[[[tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)silyl]methyl]-1,3,2-dioxaborolane.**  
**The Immobilization of Boronic Acids with a Fluorous Diol**

Feng-Ling Qing

**Reaction 11.37-1****Reagents**

Bromotris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)silane **1** [201740-57-0] can be prepared according to the literature procedure [1]. FC-77 [86508-42-1] (mainly perfluoro-2-n-butyltetrahydrofuran) is commercially available from 3 M.

**Experimental Procedure**

**Step A.** 2-Propenyltris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)silane (**2**) To a freshly prepared allyl Grignard reagent (30 mmol) in ether (40 mL), a solution of fluorous bromosilane **1** (9.1 g, 7.4 mmol) in ether (30 mL) is slowly added at 20 °C under nitrogen atmosphere. The reaction mixture is allowed to reflux overnight, cooled to room temperature, and quenched with aqueous  $\text{NH}_4\text{Cl}$ . The aqueous phase is further extracted with ether, and the combined organic layer is dried over  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo*. Purification of the residue by flash column chromatography (silica gel, hexane) afford pure fluorous allylsilane **2** (8.6 g, 98%):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  5.73 (m, 1 H), 4.97 (m, 2 H), 2.08 (m, 6 H), 1.70 (d,  $J = 8.1$  Hz, 2 H), 0.9 (m, 6 H);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ ,  $\text{CF}_3\text{COOH}$ , 282 MHz)  $\delta$  -81.43 (s, 9 F), -116.69 (m, 6 F), -122.52 (s, 6 F), -123.48 (s, 6 F), -123.84 (s, 6 F), -126.77 (m, 6 F); IR (thin film) 1635, 1363, 1240, 1208, 1146, 1074, 908  $\text{cm}^{-1}$ ; MS (EI, 70 eV,  $m/z$ ) 639, 309, 289, 239. Anal. calc. for  $\text{C}_{27}\text{H}_{17}\text{F}_{39}\text{Si}$ : C 28.19; H 1.53; F 66.76. Found: C 28.61; H 1.61; F 66.28.

**Step B.** 3-[tris(3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctyl)silyl]-1,2-propanediol (**3**) In a three-necked flask, NMNO (1.48 g, 11 mmol) and compound **2** (8.5 g, 7.7 mmol) are dissolved in acetone (20 mL) and H<sub>2</sub>O (2 mL). The mixture is cooled to 0–5 °C, and 4% aqueous solution of OsO<sub>4</sub> (0.64 mL) is added via a syringe. After stirring for 1 h, the mixture is warmed to room temperature, and the stirring is continued until TLC indicated complete conversion of **2** into **3**. Saturated aqueous NaHSO<sub>4</sub> (5 mL) was added. The mixture is extracted with FC-77 (3 × 10 mL). The combined fluoruous layer is washed with H<sub>2</sub>O and evaporated to give pure compound **3** (8.7 g, 99%): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 3.88 (m, 1 H), 3.68 (dd, *J*<sub>1</sub> = 10.5 Hz, *J*<sub>2</sub> = 3.0 Hz, 1 H), 3.38 (dd, *J*<sub>1</sub> = 10.5 Hz, *J*<sub>2</sub> = 8.0 Hz, 1 H), 2.13 (m, 6 H), 1.93 (br, 2 H), 0.95 (m, 6 H), 0.82 (m, 2 H); IR (thin film) 3383, 2949, 1443, 1240, 1208, 1145, 904, 707 cm<sup>-1</sup>; MS (EI, 70 eV, *m/z*) 721, 289, 239, 69. Anal. calc. for C<sub>27</sub>H<sub>19</sub>O<sub>2</sub>F<sub>39</sub>Si: C 28.32; H 1.66; F 64.77. Found: C 28.43; H 1.72; F 65.72.

**Step C.** 2-Phenyl-4-[[tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)silyl]methyl]-1,3,2-dioxaborolane (**4**) A solution of compound **3** (0.46 g, 0.40 mmol) in anhydrous ether (2 mL) is added to a mixture of 4 Å molecular sieve (0.3 g) and phenylboronic acid (55 mg, 0.45 mmol). Then anhydrous pentane (8 mL) is added, and the mixture is stirred at room temperature. When the reaction is complete, as detected by TLC, the mixture is filtered, concentrated *in vacuo*, and dissolved in FC-77 (5 mL). The fluoruous solution is washed with anhydrous acetonitrile (1 mL), and evaporated to afford the fluoruous boronates **4** (0.44 g, 90%): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 7.73 (d, *J* = 8.1 Hz, 2 H), 7.46 (m, 1 H), 7.36 (t, *J* = 8.1 Hz, 2 H), 4.72 (m, 1 H), 4.54 (t, *J* = 8.1 Hz, 1 H), 3.92 (t, *J* = 8.1 Hz, 1 H), 2.14 (m, 6 H), 1.17 (m, 2 H), 1.02 (m, 6 H); IR (thin film) 2908, 1605, 1502, 1443, 1240, 1212, 1145, 1096, 904, 746 cm<sup>-1</sup>; MS (EI, 70 eV, *m/z*) 1230 (M<sup>+</sup>), 527, 367, 227. Anal. calc. for C<sub>33</sub>H<sub>22</sub>O<sub>2</sub>F<sub>39</sub>SiB: C 32.02; H 1.79; F 60.24. Found: C 31.84; H 1.60.

## Discussion

Boronic acids are important intermediates in organic synthesis. For example, boronic acids are widely used in Suzuki cross-coupling reactions [2]. However, the isolation and purification compounds containing a boronic acid functionality by conventional methods can prove to be notoriously troublesome, as a result of their amphiphilic character. To facilitate the synthesis and separation of functionalized boronic acids, several groups have recently reported the preparation of several types of polymer-bound diols that can be used as linkers to immobilize boronic acids [3]. Fluoruous phase synthesis is developing into a viable alternative to solid-phase techniques in organic synthesis. The synthesis performed in homogeneous media overcomes some drawbacks of heterogeneous reactions associated with solid-phase synthesis. In principle, any solid-phase synthetic technology has a counterpart in fluoruous synthesis. Thus, we have prepared the fluoruous diol **3**. A series of boronic acids are attached to a fluoruous diol **3** by esterification. We have carried out the Suzuki reaction of fluoruous boronates **4** as a detagging process. Although normal boronic acids or esters were replaced by fluoruous boronates, we do not find any retarding effect for the Suzuki-coupling reaction from perfluoroalkyl chains. The fluoruous diol **3**, which partitions into FC-77, is completely recovered from repeated FC-77/CH<sub>2</sub>Cl<sub>2</sub> extractions. The coupling product is obtained by the concentration of the CH<sub>2</sub>Cl<sub>2</sub> layer followed by flash chromatography.

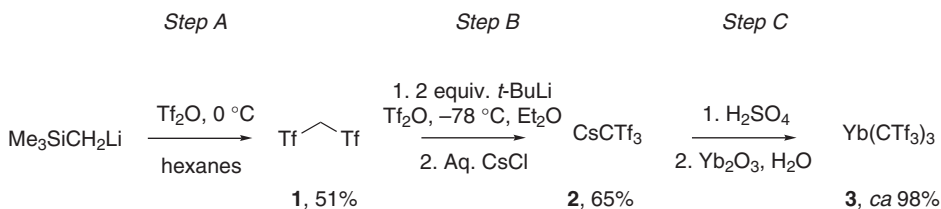
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## 11.38

**Ytterbium(III) Tris(trifluoromethylsulfonyl)methide. Preparation of a Highly Active Lanthanide Catalyst**

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**Reaction 11.38-1****Reagents**

(Trimethylsilylmethyl)lithium [1822-00-0] solution in hexane can be prepared according to the literature procedure [1] or is commercially available typically as a 1.0 M solution. Methylene ditriflone [428-76-2] is prepared according to the procedure reported below but can also be purchased from ABCR GmbH ([www.abcr.de](http://www.abcr.de)).

**Experimental Procedure [2]**

**Step A. Methylene Ditriflone (1) [428-76-2]** [3] By means of a syringe pump, freshly distilled (from  $\text{P}_4\text{O}_{10}$ ) triflic anhydride (7.9 mL, 46.9 mmol) is added over 1 h to a solution of (trimethylsilylmethyl)lithium (0.78 M, 120 mL, 93.8 mmol) in hexane at  $0^\circ\text{C}$  taking care not to let the internal temperature rise above  $5^\circ\text{C}$ . After stirring a further 1 h at  $0^\circ\text{C}$ , the solution is allowed to warm to room temperature, stirred for 2 h and quenched with saturated aqueous  $\text{NaHCO}_3$  solution (100 mL). The organic layer is separated and the aqueous layer is extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 75$  mL), acidified with concentrated HCl (12 M, 50 mL) and re-

extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 75$  mL). The latter combined  $\text{CH}_2\text{Cl}_2$  extracts are dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated under vacuum. The residual yellow oil (crystals may appear) is sublimed (0.1 mmHg, water cooled cold finger, heating  $\sim 70^\circ\text{C}$ ) to give methyleneditriflone **1** (3.4 g, 11.8 mmol, 51%) as a white solid, mp  $33\text{--}35^\circ\text{C}$  (lit. [3b]  $35^\circ\text{C}$ );  $^1\text{H}$  NMR (300 MHz;  $\text{CDCl}_3$ )  $\delta$  4.98 (br s, 2 H);  $^{13}\text{C}$  NMR (75 MHz;  $\text{CDCl}_3$ )  $\delta$  118.7 (q,  $J = 327$  Hz), 64.0;  $^{19}\text{F}$  (376 MHz;  $\text{CDCl}_3$ )  $\delta$   $-75.1$ .

**Step B. Cesium(I) tris(trifluoromethylsulfonyl)methide (2)** [114395-68-5] [4] A solution of *t*-butyl lithium (8.1 mL, 1.82 M, 14.7 mmol) in hexanes is added over 40 min to a solution of methyleneditriflone **1** (2.0 g, 7.0 mmol) in  $\text{Et}_2\text{O}$  (55 mL) at  $-78^\circ\text{C}$  to make the dianion. After stirring for 30 min at  $-78^\circ\text{C}$ , freshly distilled triflic anhydride (1.8 mL, 10.5 mmol) is added dropwise over 40 min. After 40 min at  $-78^\circ\text{C}$ , the solution is allowed to warm to room temperature over 2 h. The solution is concentrated under vacuum and saturated aqueous  $\text{NaHCO}_3$  solution (60 mL) is added to the residue. The aqueous layer is extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 60$  mL), acidified with concentrated HCl (12 M, 50 mL) and re-extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 75$  mL). The aqueous layer is further extracted with  $\text{Et}_2\text{O}$  ( $3 \times 60$  mL), and the combined extracts are dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated to give a yellow oil consisting of lithium triflate and lithium tris(trifluoromethylsulfonyl)methide. The oil is taken up in water (4 mL) and a solution of CsCl (2.1 g, 12.3 mmol) in water (3 mL) is added to precipitate cesium(I) tris(trifluoromethylsulfonyl)methide **2**. The beige precipitate obtained is isolated by filtration and concentrated sulfuric acid (98%, 4 mL) is added. Sublimation of the resultant slurry (0.1 mmHg, acetone/dry-ice cooling, heating  $\sim 100\text{--}110^\circ\text{C}$ ) gives free acid tris(trifluoromethylsulfonyl)methane,  $\text{HCTf}_3$ , [60805-12-1] as a low melting white solid. The solid is taken up in  $\text{H}_2\text{O}$  (4 mL) and a solution of CsCl (2.1 g, 12.3 mmol) in water (3 mL) is added. The precipitate obtained is isolated by filtration and recrystallized from water ( $\sim 10$  mL) to obtain cesium(I) tris(trifluoromethylsulfonyl)methide **2** (2.5 g, 4.6 mmol, 65%) as white platelets, mp  $324\text{--}326^\circ\text{C}$ ;  $^{13}\text{C}$  NMR (75 MHz;  $\text{CD}_3\text{CN}$ )  $\delta$  121.7 (q,  $J = 326$  Hz), 83.8;  $^{19}\text{F}$  (376 MHz;  $\text{CD}_3\text{CN}$ )  $\delta$   $-76.6$ ; MS (electrospray, negative ions) 410.9 ( $\text{Tf}_3\text{C}^-$ ).

**Step C. Ytterbium(III) Tris(trifluoromethylsulfonyl)methide (3)** [224317-61-7] [2] Concentrated  $\text{H}_2\text{SO}_4$  (sp. gr. 1.835, 0.7 mL, approx. 10 equiv) is added to cesium salt **2** (0.744 g, 1.37 mmol) in a sublimation pot and the slurry is sublimed (1.5 mmHg,  $100^\circ\text{C}$  rising to  $160^\circ\text{C}$ ). The liberated free acid is taken up in  $\text{H}_2\text{O}$  (2 mL) and treated with a saturated aqueous solution of  $\text{BaCl}_2$  (6 mL) to remove sulfate impurities. The resulting white precipitate in a colorless solution is extracted with  $\text{Et}_2\text{O}$  ( $3 \times 50$  mL) and the aqueous component is saturated with solid NaCl and re-extracted with  $\text{Et}_2\text{O}$  (50 mL). The combined ethereal extracts are concentrated and the residue is sublimed (1.5 mmHg,  $100^\circ\text{C}$ ). The resultant purified free acid is taken up in  $\text{H}_2\text{O}$  (25.00 mL) and titrated ( $4 \times 0.2$  mL aliquots) against a standard NaOH solution (0.9995 M, phenolphthalein indicator). In a series of separate experiments the titrations reveal that aqueous solutions of the free acid are produced in 88–98% yield from **2**.

Solid  $\text{Yb}_2\text{O}_3$  (100 mg, 0.25 mmol) is added in one portion to a titrated aqueous solution of tris(trifluoromethylsulfonyl)methane (0.057 M, 1.27 mmol, 22.4 mL). The milky suspension is heated at reflux for 24 h and the resultant colorless solution is filtered [to remove traces of

unreacted ytterbium(III) oxide]. The filtrate is concentrated and the white solid obtained dried under vacuum (0.1 mmHg, 24 h) to give ytterbium(III) tris(trifluoromethylsulfonyl)methide **3** (0.59 g, 0.42 mmol, 100%) as a white powder:  $^{13}\text{C}$  NMR (100 MHz;  $\text{D}_2\text{O}$ )  $\delta$  122.7 (q,  $J = 325$  Hz), 84.1;  $^{19}\text{F}$  NMR (376 MHz;  $\text{CD}_3\text{CN}$ )  $\delta$  -76.5.

## Discussion

The described procedure allows for the gram scale preparation of ytterbium(III) tris(trifluoromethylsulfonyl)methide (referred to as ytterbium “triflide”). Scandium triflide may also be prepared by substituting  $\text{Sc}_2\text{O}_3$  for  $\text{Yb}_2\text{O}_3$  in the last step [2]. It is to be expected that this methodology could also be applied to the synthesis of all the remaining lanthanide(III) triflides. A bismuth(III) salt has also been prepared [5]. Ytterbium and scandium triflides have been used as catalysts (10 mol% loading) for the nitration of electron deficient aromatics (e.g., *o*-nitrotoluene) using 1 equiv of nitric acid where the only side product is water [2]. In these instances, the related ytterbium and scandium triflates are essentially ineffective under the same conditions where the relative  $\text{p}K_{\text{a}}$ 's of the conjugate acids (ca. -18 [6] versus -12, respectively) are held to be ultimately responsible [7]. This superior activity is expected to translate to all reactions where the triflate salts have been employed. Additionally, the triflide catalysts may be recovered from the nitration reactions and re-used by a simple evaporative procedure. They have also been applied to the nitration of fluoroaromatics where problems of HF liberation (via  $\text{S}_{\text{N}}\text{Ar}$  displacement of fluoride) do not arise, and again recycling and re-use was demonstrated [8]. Ytterbium triflide is the parent compound of perfluorinated homologs  $\{\text{Yb}[\text{C}(\text{SO}_2\text{C}_n\text{F}_{2n+1})_2(\text{SO}_2\text{C}_m\text{F}_{2m+1})_1]_3\}$ :  $n = m = 4$ ;  $n = m = 6$ ;  $n = 6, m = 8$  which are prepared by modification of the above procedure [9]. These compounds have been employed for the first fluororous biphasic catalytic Friedel-Crafts acylation reactions [10], and (in benzotrifluoride) at catalyst loadings as low as 1% [11]. The ytterbium and scandium salts,  $\text{M}[\text{C}(\text{SO}_2\text{C}_8\text{F}_{17})_3]_3$  ( $\text{M} = \text{Yb}, \text{Sc}$ ), have been reported as recyclable fluororous catalysts for the acetylation of alcohols, Diels-Alder cycloadditions and the Mukaiyama aldol reaction [12, 13]. The scandium salt has also been employed for the same reactions in supercritical carbon dioxide with recycling by tuning the supercritical versus liquid phase [14].

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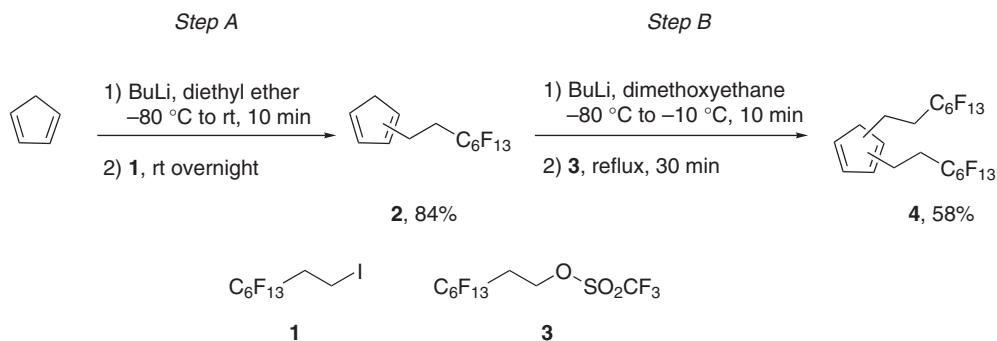
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## 11.39

**Bis(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)cyclopenta-1,3-diene. Preparation from Cyclopenta-1,3-diene, 1,1,1,2,2,3,3,4,4,5,5,6,6-Tridecafluoro-8-iodooctane and 3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctyl Triflate**

Tomáš Bříza, Jaroslav Kvíčala, and Oldřich Paleta

## Reaction 11.39-1



## Reagents

Cyclopentadiene [542-92-7] is prepared by distillation of commercially available (Aldrich) dicyclopentadiene [77-73-6] [1]. 1,1,1,2,2,3,3,4,4,5,5,6,6-Tridecafluoro-8-iodooctane (**1**) [2043-57-4] is commercially available from Aldrich or Fluorochem. 3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctyl triflate (**3**) [78522-69-7] can be prepared according to the literature procedure [2] from commercially available (Aldrich, Fluorochem) 1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluorooctan-1-ol [647-42-7] and triflic anhydride [358-23-6].

## Experimental Procedures

**Step A.** 3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctyl Cyclopenta-1,3-diene (**2**) A flask equipped with a magnetic stirbar is charged with THF (50 mL), freshly distilled cyclopentadiene (1.00 g, 15.1 mmol) and cooled to  $-80\text{ }^{\circ}\text{C}$ , followed by the addition of butyllithium solution (6.85 mL, 2.2 M in hexanes, 15.1 mmol) by a syringe. The reaction mixture is then allowed to warm to rt while stirring and polyfluoroiodooctane **1** (7.20 g, 18.2 mmol) in THF (10 mL) are added. The mixture is then stirred overnight at rt. The reaction is quenched by dropwise addition of ammonium chloride solution (20%, 20 mL) and extracted with diethyl ether ( $3 \times 50\text{ mL}$ ). The combined organic layers are dried with anhydrous magnesium sulfate. The drying agent is filtered and the dissolved salts are removed on a chromatographic column (silica,  $10 \times 5\text{ cm}$ , eluent hexane). Removal of solvents on a rotary vacuum evaporator affords mono(fluoroalkylated) cyclopentadiene **2** (5.27 g, 84.2%, light-yellow liquid).

**Step B.** bis(3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctyl)cyclopenta-1,3-diene (**4**) A flask is charged with fluorocyclopentadiene **2** (1.50 g, 3.63 mmol) and 1,2-dimethoxyethane (50 mL). The mixture is cooled to  $-80\text{ }^{\circ}\text{C}$  while stirring and butyllithium solution (1.78 M in hexanes, 2.2 mL, 3.9 mmol) is added by syringe. The mixture is then warmed to  $-10\text{ }^{\circ}\text{C}$  and stirred for 10 min. Then it is cooled again to  $-80\text{ }^{\circ}\text{C}$  and a solution of fluoroalkyl triflate **3** (2.30 g, 4.63 mmol) in 1,2-dimethoxyethane (10 mL) is added dropwise. The mixture is then heated to reflux for 30 min and cooled to room temperature. Solvents are removed on a vacuum rotary evaporator, followed by a removal of salts on a chromatographic column ( $10 \times 2.5\text{ cm}$ , eluent hexane). After evaporation of the solvent on a vacuum rotary evaporator, bis(polyfluoroalkylated) cyclopentadiene **4** (1.59 g, 58.0%, colorless liquid) is obtained by column chromatography ( $15 \times 2.5\text{ cm}$ , eluent hexane) of the residue as a mixture of four regioisomers (1,2-, 1,3-, 1,4- and 2,3-disubstituted) in the 21:40:23:16 ratio (1D and 2D  $^1\text{H}$  NMR): IR (neat) 2937, 1460, 1365, 1317, 1239, 1202, 1145  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300.1 MHz,  $\text{CDCl}_3$ ) regioisomer **4A** (1,2-**4**),  $\delta$  2.23 (4 H, m), 2.56 (4 H, m), 2.88 (2 H, t,  $J = 1.2\text{ Hz}$ ), 6.26 (1 H, d,  $^3J_{\text{HH}} = 5.5\text{ Hz}$ ), 6.28 (1 H, d,  $^3J_{\text{HH}} = 5.5\text{ Hz}$ ,  $J = 1.2\text{ Hz}$ ); regioisomer **4B** (1,3-**4**),  $\delta$  2.23 (4 H, m), 2.56 (4 H, m), 2.84 (2 H, quintet,  $J = 1.8\text{ Hz}$ ), 5.87 (1 H, sextet,  $J = 1.6\text{ Hz}$ ), 6.04 (1 H, m); regioisomer **4C** (1,4-**4**),  $\delta$  2.23 (4 H, m), 2.56 (4 H, m), 2.79 (2 H, t,  $J = 1.1\text{ Hz}$ ), 6.02 (2 H, quintet,  $J = 0.9\text{ Hz}$ ); regioisomer **4D** (2,3-**4**),  $\delta$  2.23 (4 H, m), 2.56 (4 H, m), 2.83 (2 H, sextet,  $J = 1.8\text{ Hz}$ ), 6.04 (2 H, m);  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ ) regioisomer **4A** (1,2-**4**),  $\delta$  17.9 (s), 21.3 (s), 30.4 (2 C, m), 43.2 (s), 108.3–121.5 (12 C, m), 131.7 (s), 133.7 (s), 138.1 (s), 143.9 (s); regioisomer **4B** (1,3-**4**),  $\delta$  20.6 (s), 21.3 (s), 30.4 (2 C, m), 42.9 (s), 108.3–121.5 (12 C, m), 125.0 (2 C, s), 143.9 (s), 147.2 (s); regioisomer **4C** (1,4-**4**),  $\delta$  21.3 (2 C, s), 30.4 (2 C, m), 44.7 (s), 108.3–121.5 (12 C, m), 127.3 (2 C, s), 143.9 (2 C, s); regioisomer **4D** (2,3-**4**),  $\delta$  18.5 (2 C, s), 30.4 (2 C, m), 39.5 (s), 108.3–121.5 (12 C, m), 127.9 (2 C, s), 143.8 (2 C, s);  $^{19}\text{F}$  NMR (376.5 MHz,  $\text{CDCl}_3$ )  $\delta$   $-81.5$  (6 F, t,  $^3J_{\text{FF}} = 10\text{ Hz}$ ),  $-115.2$  (4 F, m),  $-122.4$  (4 F, m),  $-123.4$  (4 F, m),  $-124.0$  (4 F, m),  $-126.7$  (m, 4 F). Anal. calc. for  $\text{C}_{21}\text{H}_{12}\text{F}_{26}$ : C, 33.62%; H, 1.60%. Found: C, 33.80%; H, 1.76%.

## Discussion

Although cyclopentadienes belong to the most common ligands employed in organometallic chemistry, surprisingly little attention has been paid to the preparation of fluoros cyclo-



pentadienes. The first such ligands synthesized were cyclopentadienes directly substituted by an electron-attracting perfluoroalkyl chain, which results in poor ligand properties [3, 4]. Cyclopentadienes containing one polyfluorinated ring with an insulating spacer between the ring and perfluorinated chain displayed insufficient fluorophilic properties due to the low content of fluorine, which should exceed 60% [5].

Bis(polyfluorinated) cyclopentadienes [2, 6] which display both sufficient complexing and fluorophilic properties [7], can be synthesized by the stepwise nucleophilic substitution of polyfluorinated compounds with cyclopentadienide anions. Whereas commercially available 2-(perfluoroalkyl)ethyl iodides are preferably employed in the preparation of mono-substituted cyclopentadienes [3, 4], more reactive building blocks, 2-(perfluoroalkyl)ethyl triflates [6], are essential for successful second polyfluoroalkylation [2]. The bis(polyfluorinated) cyclopentadienes thus synthesized consist of four regioisomers and efficiently complex iron or rhodium cations [7].

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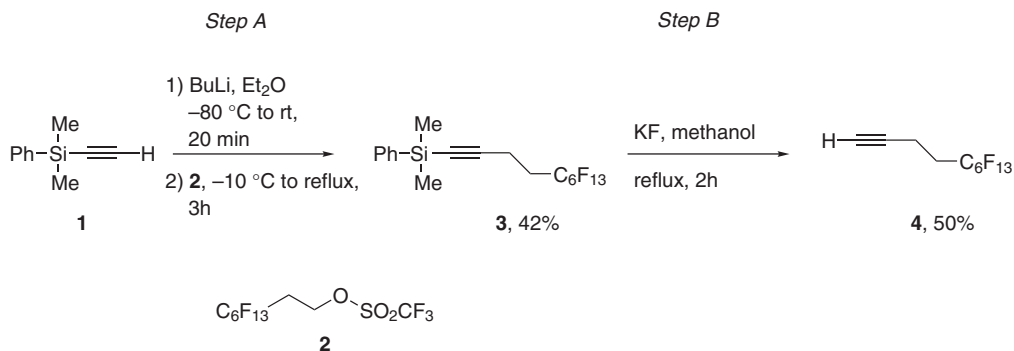
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## 11.40

### 5,5,6,6,7,7,8,8,9,9,10,10,10-Tridecafluorodec-1-yne. Preparation from Ethynyldimethylphenylsilane and 3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctyl Triflate

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#### Reaction 11.40-1



## Reagents

Ethynyldimethylphenylsilane (**1**) [17156-64-8] is synthesized from commercially available (Aldrich) ethynylmagnesium bromide [4301-14-8] (0.5 M solution in THF) and chlorodimethylphenylsilane [768-33-2] [**1**]. 3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctyl triflate (**2**) [78522-69-7] can be prepared according to the literature procedure [**2**] from commercially available (Aldrich, Fluorochem) 1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluorooctan-1-ol [647-42-7] and triflic anhydride [358-23-6].

## Experimental Procedures

**Step A. 1-(Dimethylphenylsilyl)-5,5,6,6,7,7,8,8,9,9,10,10,10-tridecafluoro-1-yne (**3**)** A 25 mL flask equipped with magnetic stirrer bar is charged with ethynyldimethylphenylsilane (**1**, 6.00 g, 37.4 mmol) and diethyl ether (20 mL). After cooling the mixture to  $-78^{\circ}\text{C}$ , butyllithium solution (16.5 mL, 2.63 g, 41.1 mmol, 2.5 M solution in hexanes) is slowly added by syringe. The mixture is then allowed to warm to room temperature while stirring for about 20 min. The second 500 mL flask equipped with a magnetic stirrer bar and reflux condenser fitted with a septum is charged with 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl triflate (**2**, 14.3 g, 28.8 mmol) and diethyl ether (150 mL). Solutions in both flasks are cooled to  $-10^{\circ}\text{C}$  and the contents of the first flask are transferred into the second flask by a capillary. After the mixing is completed, the mixture is refluxed for 3 h. After cooling the mixture it is extracted with water (100 mL). The water layer is separated and extracted with diethyl ether ( $3 \times 50$  mL). The combined organic layers are dried with anhydrous magnesium sulfate, then the drying agent is filtered and solvents are removed on a vacuum rotary evaporator. From the residue, unreacted ethynyl silane **1** and fluorotriflate **2** are distilled off (fraction boiling at  $50\text{--}80^{\circ}\text{C}/200$  Pa). The product, silylated fluoroalkyne **3**, is isolated as the main fraction (6.1 g, 42%, bp  $106\text{--}115^{\circ}\text{C}/200$  Pa, colorless liquid): IR ( $\text{CHCl}_3$ ) 3073, 2964, 2928, 2186, 1430, 1238, 1145, 1118,  $1074\text{ cm}^{-1}$ ;  $^1\text{H}$  NMR (300.1 MHz,  $\text{CDCl}_3$ )  $\delta$  0.41 (s, 6 H), 2.40 (m, 2 H), 2.60 (t, 2 H,  $^3J_{\text{HH}} = 7.2$ ), 7.39 (m, 3 H), 7.62 (m, 2 H);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$   $-1.0$  (s, 2 C), 12.0 (s, 1 C), 30.6 (t, 1 C,  $^2J_{\text{CF}} = 21.2$ ), 84.4 (s, 1 C), 104.8 (s, 1 C), 108.2–120.9 (bm, 6 C), 127.9 (s, 1 C), 129.4 (s, 2 C), 133.6 (s, 2 C), 137.0 (s, 1 C);  $^{19}\text{F}$  NMR (282.4 MHz,  $\text{CDCl}_3$ )  $\delta$   $-81.3$  (t, 3 F,  $^3J_{\text{FF}} = 10.5$ ),  $-115.7$  (t, 2 F,  $^3J_{\text{FF}} = 15.4$ ),  $-122.4$  (m, 2 F),  $-123.3$  (m, 2 F),  $-124.1$  (m, 2 F),  $-126.6$  (m, 2 F). Anal. calc. for  $\text{C}_{18}\text{H}_{15}\text{F}_{13}\text{Si}$ : C, 42.70%; H, 2.96%. Found: C, 42.30%; H, 3.14%.

**Step B. 5,5,6,6,7,7,8,8,9,9,10,10,10-Tridecafluorodec-1-yne (**4**)** A 250 mL flask equipped with a reflux condenser is charged with silylated polyfluorodecyne **3** (12.2 g, 24.0 mmol), methanol (150 mL) and anhydrous potassium fluoride (4.20 g, 72.3 mmol). The reaction mixture is then refluxed for 2 h. After cooling to rt, the mixture is diluted with water (100 mL). The aqueous layer is separated and extracted with pentane ( $2 \times 50$  mL). The combined organic layers are dried with anhydrous magnesium sulfate and the drying agent is filtered. The solvents are carefully removed on a vacuum rotary evaporator ( $40^{\circ}\text{C}/80$  kPa). Deprotected fluorodecyne **4** is isolated by fractional distillation of the residue (4.5 g, 50%, bp  $126\text{--}129^{\circ}\text{C}/$

70 kPa, colorless liquid): IR (CHCl<sub>3</sub>) 3320, 2964, 1451, 1241, 1146, 1113, 1075 cm<sup>-1</sup>; <sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  2.02 (t, 1 H, <sup>3</sup>J<sub>HH</sub> = 2.5), 2.36 (m, 2 H), 2.52 (m, 2 H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  10.6 (s, 1 C), 30.5 (t, 1 C, <sup>2</sup>J<sub>CF</sub> = 21.2), 69.7 (s, 1 C), 80.8 (s, 1 C), 108.2–120.9 (bm, 6 C); <sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -81.3 (t, 3 F, <sup>3</sup>J<sub>FF</sub> = 10.5), -115.7 (t, 2 F, <sup>3</sup>J<sub>FF</sub> = 15.4), -122.4 (m, 2 F), -123.3 (m, 2 F), -124.1 (m, 2 F), -126.6 (m, 2 F); GC-MS (EI, *m/z*) 372 (4, M<sup>+</sup>), 134 (5), 133 (5), 131 (5), 104 (52), 103 (100), 83 (21), 77 (8), 69 (14), 57 (5), 53 (28), 51 (7), 39 (37), 27 (5). Satisfactory elemental analysis could not be obtained due to the high volatility of the product.

## Discussion

To preserve the electronic character of alkynes, at least a two carbon spacer has to connect the triple bond and the perfluoroalkyl group [3]. Internal alkynes containing a phenyl and a (perfluoroalkyl)ethyl group have been prepared by palladium catalyzed coupling of alkynylstannanes with (perfluoroalkyl)ethyl iodides [4]. Neither coupling of ethynyltributylstannane, nor reaction of ethynylmagnesium bromide or ethynyllithium with 2-(perfluoroalkyl)ethyl iodides can be employed for the preparation of analogous terminal alkynes [5]. On the other hand, the lithium salt of 2-(dimethylphenylsilyl)ethynyllithium (**1**) reacts with a more reactive fluorinated electrophile, 2-(perfluorohexyl)ethyl triflate (**2**) [6], to afford silylated polyfluoroalkyne **3**, which can be deprotected by the standard desilylation protocol using potassium fluoride in methanol [7] to form the target polyfluorinated terminal alkyne **4** [5]. Fluoroalkyne **4** is a highly volatile compound and all manipulations with this compound have to be conducted with great care to prevent loss of material.

Terminal polyfluoroalkyne **4** is a useful fluorous building block, which can be employed in various cyclization reactions forming, for example, polyfluorinated cyclohexadienes, cyclopentadienes, arenes, or carboranes.

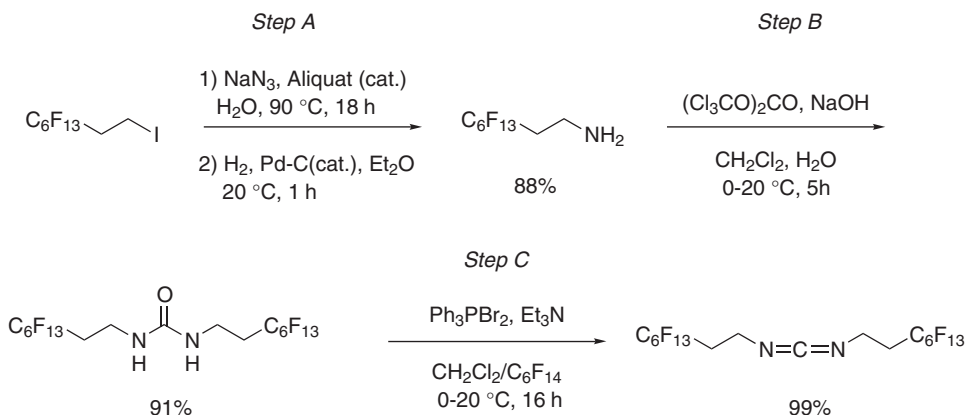
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## 11.41

***N,N'*-Bis(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)carbodiimide**

Jesús M. Aizpurua, Claudio Palomo, and Iraida Loinaz

**Reaction 11.41-1****Reagents**

1*H*,1*H*,2*H*,2*H*-Perfluorooctyl iodide [2043-57-4] was purchased from Fluka A. G. and perfluorohexane [355-42-0] from Fluorochem Ltd. Methyltriocetylammmonium chloride (Aliquat<sup>®</sup> 336) [1] [5137-55-3] was available from Acros Chemical Company. Triethylamine was distilled over calcium hydride prior to use. All reagents and solvents were used without purification.

**Experimental Procedures**

**Step A. 1*H*,1*H*,2*H*,2*H*-Perfluorooctyl Amine** A 50 mL, three-necked, round-bottomed flask equipped with a magnetic stirrer, thermometer and reflux condenser is charged with sodium azide (2.60 g, 40 mmol), water (6.00 mL), 1*H*,1*H*,2*H*,2*H*-perfluorooctyl iodide (4.89 mL, 20 mmol) and methyltridecylammmonium chloride (Aliquat<sup>®</sup> 336) (0.40 g, 1 mmol). The mixture is heated overnight to 90–100 °C (oil bath) under stirring and then is cooled to 0 °C. The lower phase, consisting of pure 1*H*,1*H*,2*H*,2*H*-perfluorooctyl azide, is separated by decantation using a pipette (7.70 g, 99%) [2] and used without purification in the next step. A high pressure hydrogenator [3] equipped with a mechanical stirrer and temperature controller is charged with diethyl ether (150 mL), 10% Pd–C (150 mg) and 1*H*,1*H*,2*H*,2*H*-perfluorooctyl azide (7.70 g, 19.8 mmol). Hydrogen pressure is set at 150 psi and the mixture is hydrogenated over 1 h at 25 °C. The hydrogenator is slowly depressurized, purged with fresh hydrogen [4] and the hydrogenation is continued at 150 psi and 25 °C for 16 h. The reactor is

depressurized again and the resulting ethereal solution is filtered through a pad of Celite in a funnel. The Celite is washed with dried diethyl ether (20 mL) and the solvent is carefully evaporated under reduced pressure (20 °C/20 mmHg) to afford the product as a colorless liquid; yield, 9.59 g (88%):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.30–1.21 ( $s_b$ , 2 H), 2.34–2.17 (m, 2 H), 3.04 (t, 2 H,  $J = 7$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  34.3 ( $s_b$ ), 34.7 (t,  $J_{\text{CF}} = 21$  Hz), 125–140 (m).

**Step B. *N,N'*-Bis(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)urea** A solution of triphosgene (2.60 g, 8.80 mmol) in  $\text{CH}_2\text{Cl}_2$  (13 mL) is added dropwise to a stirred cold (0 °C) mixture of the corresponding 2,2,2-trifluoroethylamine (9.59 g, 26.4 mmol),  $\text{CH}_2\text{Cl}_2$  (20 mL) and 6 M NaOH (26 mL). Stirring of the mixture to room temperature is continued for 5 h, while a white precipitate is observed. The  $\text{CH}_2\text{Cl}_2$  is evaporated directly from the mixture (rotavapor, carefully because of the foam) and the solid is dissolved in diethyl ether (30 mL) and washed with brine ( $5 \times 35$  mL) until neutrality. The organic layer is dried ( $\text{MgSO}_4$ ), evaporated and the product crystallized from methanol (50 mL); yield, 9.03 g (91%):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.48 (m, 4 H), 3.70 ( $s_b$ , 4 H), 6.48 ( $s_b$ , 2 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  32.8 (t,  $J_{\text{CF}} = 21$  Hz), 33.9, 159.

**Step C. *N,N'*-Bis(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)carbodiimide** A suspension of *N,N'*-bis-(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)urea (9.03 g, 12.0 mmol) in perfluorohexane (45 mL) is stirred in a dried flask under nitrogen at 0 °C and a solution of triphenylphosphine (9.44 g, 36.0 mmol) in  $\text{CH}_2\text{Cl}_2$  (90 mL) is added. Then, bromine (1.84 mL, 5.75 g, 36.0 mmol) is added dropwise until a drop gives a persistent yellow color to the upper  $\text{CH}_2\text{Cl}_2$  solution. Finally, triethylamine (8.36 mL, 60 mmol) is added dropwise and the reaction is vigorously stirred at 0 °C for 15 min and at room temperature for 16 h. The lower fluoruous colorless solution is separated with a syringe and placed in another flask under nitrogen. The remaining  $\text{CH}_2\text{Cl}_2$  brown suspension is extracted twice with perfluorohexane ( $2 \times 8$  mL) and the combined fluoruous solution is evaporated in the rotavapor to afford pure carbodiimide as a colorless liquid [5]; yield, 8.72 g (99%):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.29–2.5 (m, 2 H), 3.59 (t, 2 H,  $J = 7$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  32.3 (t,  $J_{\text{CF}} = 21$  Hz), 38.5 (s), 105–125 (m), 139.0 (s).

## Discussion

*N,N'*-Dialkylcarbodiimides are among the most popular dehydrating reagents, widely used despite the purification difficulties often met in separating the byproduct *N,N'*-dialkylureas from the polar reaction products (typically, peptides). A chromatography-free fluoruous version of the peptide synthesis, based on the use of *N,N'*-bis-(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)-carbodiimide, has been described recently as an alternative to the existing methods [6].

Although a different synthesis of *N,N'*-bis(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)carbodiimide has been reported [7, 8] in 86% yield from 1*H*,1*H*,2*H*,2*H*-perfluorooctyl azide and 1*H*,1*H*,2*H*,2*H*-perfluorooctyl isocyanate by means of triphenyliminophosphorane intermediates, the method requires a careful final distillation to purify the product. The use of *N,N'*-bis(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)urea as the carbodiimide source [9], combined with a fluoruous protocol consisting of phase separation and evaporation, circumvents such a problem and ensures the reuse of spent fluoruous materials [10].

## References

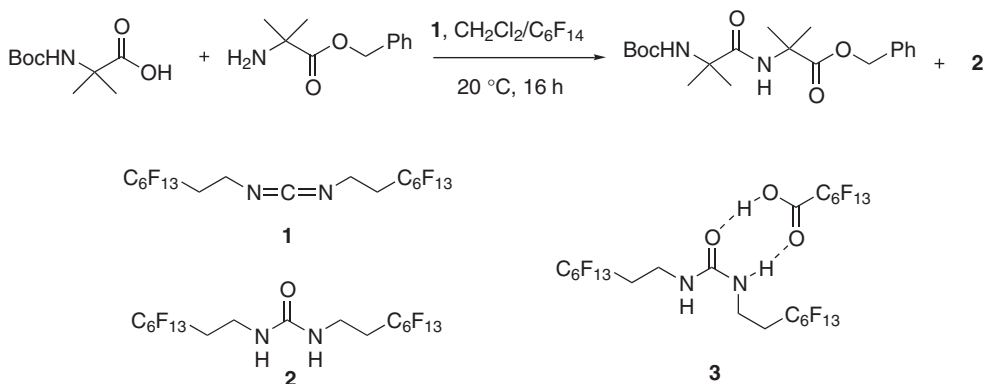
- 1 Phase transfer-catalyst presented as a liquid mixture of C<sub>8</sub> and C<sub>10</sub> chains with C<sub>8</sub> predominant.
  - 2 <sup>1</sup>H NMR (CDCl<sub>3</sub>): 3.62 (t, 2 H, *J* = 7.0), 2.5–2.3 (m, 2 H). The presence of trace amounts of Aliquat® 336 in the product is irrelevant for subsequent reactions.
  - 3 Model Parr-4842 from Parr Instrument Company. Volume: 350 mL, max. pressure 3000 psi.
  - 4 An increase of pressure may be observed due to the nitrogen evolved during the reaction. To attain a complete transformation to the amine it is necessary to purge the nitrogen formed during the reaction periodically.
  - 5 Storable under nitrogen for several months at –20 °C.
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- See also the accompanying procedure.
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  - 10 Several runs of reaction C using recovered *N,N'*-bis(1*H*,1*H*,2*H*,2*H*-perfluorooctyl) urea afforded carbodiimide yields above 95%.

## 11.42

***tert*-Butoxycarbonyl- $\alpha$ -aminoisobutyryl- $\alpha$ -aminoisobutyric Acid Benzyl Ester (Boc-Aib-Aib-OBn). Peptide Synthesis with a Fluorous Carbodiimide Reagent**

Jesús M. Aizpurua, Claudio Palomo, and Iraida Loinaz

## Reaction 11.42-1



## Reagents

*N,N'*-bis(1*H*,1*H*,2*H*,2*H*-Perfluorooctyl)carbodiimide [133600-23-4] is prepared from urea **2** following the method described in the accompanying procedure and  $\alpha$ -aminoisobutyric acid benzyl ester (H-Aib-OBn) [55456-01-1] is prepared according to the literature procedure [1]. Perfluoroheptanoic acid [375-85-9] and perfluorohexane [355-42-0] are commercially available from Fluorochem Ltd. All compounds are used without purification.

## Experimental Procedure

A flame-dried 50 mL round-bottomed flask equipped with a magnetic stirrer is charged with dry CH<sub>2</sub>Cl<sub>2</sub> (10 mL), benzyl  $\alpha$ -aminoisobutyrate (0.48 g, 2.5 mmol) and  $\alpha$ -*tert*-butoxycarbonylaminoisobutyric acid (0.51 g, 2.5 mmol) under a nitrogen atmosphere. A solution of bis(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)carbodiimide **1** (1.97 g, 2.7 mmol) in perfluorohexane (10 mL) is added and the biphasic mixture is vigorously stirred for 24 h at room temperature. Perfluoroheptanoic acid (0.91 g, 2.5 mmol) is added to the resulting suspension, the mixture is stirred for 5 min [2], and the fluoruous phase (lower) is separated with a syringe. The washing is repeated using successively a solution of perfluoroheptanoic acid (0.36 g, 1.0 mmol) in perfluorohexane (5 mL) and perfluorohexane (5 mL). Evaporation of the dichloromethane solution provides the pure product, yield: 0.70 g (74%): <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.42 (s, 12 H), 1.55 (s, 9 H), 4.97 (s, 1 H), 5.15 (s, 2 H), 7.33 (m, 5 H). <sup>13</sup>C NMR (CDCl<sub>3</sub>): 24.5, 25.4, 28.2, 56.2, 56.7, 67.0, 72.1, 128.0, 128.1, 128.4, 135.7, 154.8, 173.8, 174.3.

**Recovery of Urea 2** The fluoruous solutions are combined and evaporated in a 20 mL flask to give a syrup consisting of the impure urea/perfluorohexanoic complex **3**. Kugelrohr distillation is carried out cooling the collecting bulb tubes with an acetone/dry ice bath (−78 °C). After 3 h heating at 110 °C/0.02 Torr, perfluoroheptanoic acid is separated (1.16 g, 91% recovery). The solid residue in the oven flask is crystallized from methanol to afford pure urea, yield: 1.76 g (87% recovery).

## Discussion

The noncoded peptide sequence -Aib-Aib- occurring, for example, in peptaibol antibiotics [3] is a prototypical case of a difficult coupling between hindered  $\alpha,\alpha$ -disubstituted  $\alpha$ -amino acids [4].

Dehydration reactions using fluoruous carbodiimide **1** [5] are conducted under standard peptide synthesis conditions, as exemplified by the preparation of building block Boc-Aib-Aib-OBn [4, 6]. An important advantage of the method is the easy removal of the urea **2** byproduct by the simple addition of perfluoroheptanoic acid to the reaction mixture, followed by perfluorohexane/dichloromethane phase separation. Under these conditions, hydrogen bonded complex **3**, and the subsequent traces of the starting carbodiimide, partition

with great preference into the fluorous phase, leaving almost pure peptide in the dichloro-methane layer.

## References

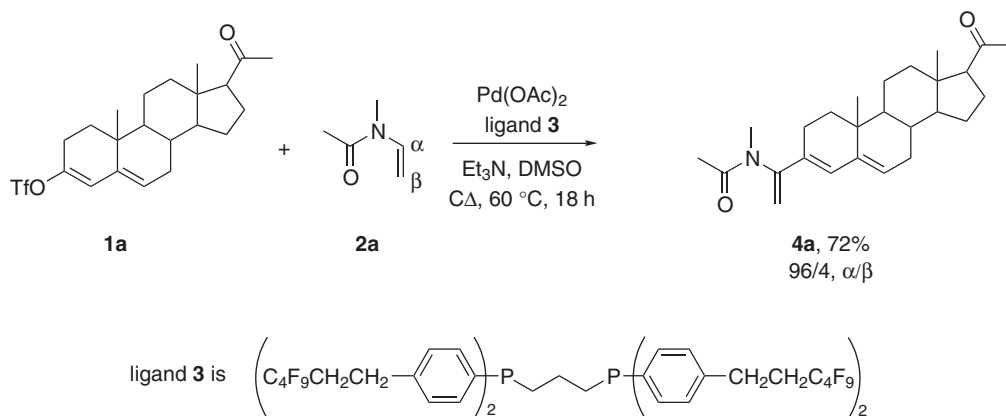
- 1 D. LEIBFRITZ, E. HAUPT, N. DUBISCHAR, H. LACHMANN, R. OEKONOMOPU, G. JUNG, *Tetrahedron* **1982**, 38, 2165–2168.
- 2 A white precipitate of *N,N'*-bis(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)urea **2** is gradually formed during the reaction, which dissolves immediately in the presence of perfluoroheptanoic acid to form the fluorous-soluble complex **3**.
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## 11.43

### *N*-Methyl-*N*-[1-(20-oxopregna-3,5-dien-3-yl)vinyl]acetamide. Regioselective Heck Coupling Reactions with a Fluorous Tagged Bidentate Ligand to Make 2-Acylamino-1,3-butadienes

Karl S. A. Vallin

#### Reaction 11.43-1



## Reagents

17- $\beta$ -Acetylandrosta-3,5-dien-3-yl triflate **1a** [95667-43-9], 4-*tert*-butylcyclohex-1-enyl triflate **1b** [77412-96-5] and 1,3-bis[bis-[4-(3,3,4,4,5,5,6,6,6-nonafluorohexyl)phenyl]-phosphino]pro-



pane **3** (F-dppp) can be prepared according to literature procedures [1–3]. *N*-methyl-*N*-vinyl acetamide **2a** [3195-78-6], 1-vinyl-2-pyrrolidone **2b** [88-12-0], the triethylamine, Pd(OAc)<sub>2</sub> and dry DMSO are obtained from commercial sources and used without further purification. Fluorous silica gel can be prepared by the literature procedure [4], but commercially available FluoroFlash<sup>TM</sup> silica gel from Fluorous Technologies, Inc. is recommended for higher loading and better reproducibility (www.fluorous.com) [5]. Controlled microwave heating is performed with a Smith Synthesizer from Personal Chemistry (the Biotage group).

## Experimental Procedure

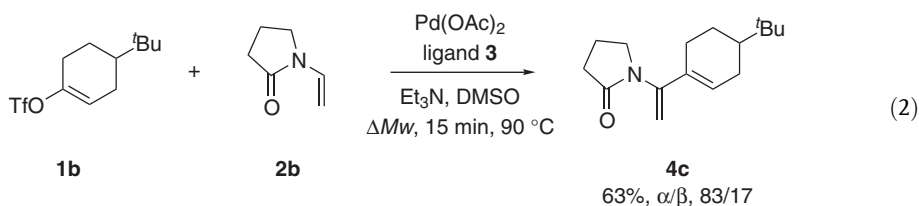
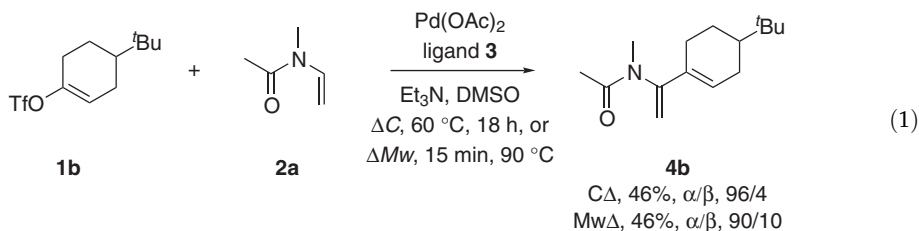
A mixture of the vinyl triflate **1a** (1.0 mmol), enamide **2a** (2.5 mmol), triethylamine (0.121 g, 1.2 mmol), Pd(OAc)<sub>2</sub> (0.0067 g, 0.030 mmol) and ligand **3** (0.090 mmol) is stirred in 4.0 mL dry DMSO under N<sub>2</sub> in a sealed 2.0–5.0 mL process vial at 60 °C for 18 h. After complete conversion of the starting vinyl triflate, as analyzed by GC/MS or LC/MS, the reaction mixture is allowed to cool. The reaction mixture is then charged directly on to the fluorous reverse phase silica gel and the organic mixture is eluted with 200 mL, 90% methanol/10% water, to give an organic fraction. Resonances from the phosphine-based ligand could not be detected in either <sup>31</sup>P or <sup>1</sup>H NMR spectra of the crude product. The methanol is thereafter removed under reduced pressure and the salts are removed by water/ether extraction. The combined ether layers are washed with brine, dried over potassium carbonate and concentrated. A second elution of the fluorous silica gel with 50 mL 100% methanol provided some of the homocoupled byproducts and subsequent elution with THF provided a complicated phosphine mixture according to <sup>31</sup>P NMR analysis. The  $\alpha$ -vinylated product **4a** is finally purified by column chromatography (hexane/ethyl acetate).

## Discussion

The carbon–carbon bond forming Heck coupling is a powerful tool in both organic and medicinal chemistry and new applications and protocols are being reported continuously [6–9]. Thus, the Heck coupling of vinyl halides (or pseudohalides) with olefins, to provide 1,3-dienes, comprise a convenient approach in the synthesis of functionalized cyclohexane derivatives by cycloaddition reactions [6, 10, 11]. The described highly regioselective Heck route from vinyl triflates and enamides constitutes a valuable new method to form 2-acylamino-1,3-butadienes [3]. In addition, controlled heating by microwave irradiation [12, 13] accelerates these palladium-catalyzed internal vinylations, and full conversions were achieved after reaction times of only 15 min.

The vinylations of **1b** with enamides **2a** and **2b** [Eqs. (1) and (2)] show that these reactions can be performed equally well with conventional heating ( $\Delta C$ ) or in a microwave oven ( $\Delta Mw$ ). The microwave method is much speedier (15 min versus 18 h). The  $\alpha$ -vinylations of the enamides **2a** and **2b** with the F-dppp ligand **3** (with a fluorine content of 49%) rendered essentially the same  $\alpha$ -selectivity and catalytic activity as in those vinylations where non-fluorous dppp ligands were employed. Furthermore fluorous solid phase purification

completely removed the fluororous-tagged phosphine ligand before subsequent product isolation. This conventional and microwave-heated procedure is convenient for rapid small-scale reactions such as those used in medicinal chemistry or solution phase parallel synthesis.



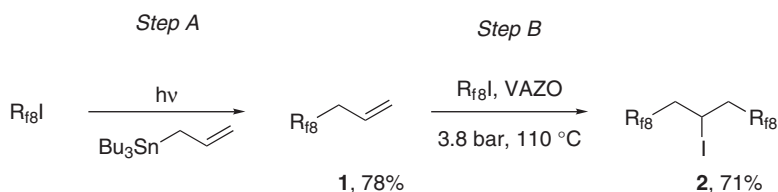
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## 11.44

**10-Iodo-9H,9H,10H,11H,11H-perfluorononadecane. Free Radical Chain Reactions of Fluorous Primary Alkyl Iodides**

Marc Wende and J. A. Gladysz\*

**Reaction 11.44-1****Reagents**

$\text{R}_{f8}\text{I}$  (Lancaster, 97%), allyl tri(*n*-butyl)tin (Lancaster, 97%), and VAZO (1,1'-azobis(cyclohexanecarbonitrile); Fluka,  $\geq 97\%$ ) were used as received.

**Experimental Procedure**

**Step A. 1H,1H,2H,3H,3H-Perfluoroundec-1-ene (1)** [1] A UV-photolysis apparatus (immersion well, Pyrex glass) [2] is charged with allyltributyltin (17.5 mL, 18.9 g, 57.0 mmol),  $\text{R}_{f8}\text{I}$  [ $\text{CF}_3(\text{CF}_2)_7\text{I}$ ; 10.0 mL, 20.7 g, 37.9 mmol] and  $\text{CH}_2\text{Cl}_2$  (100 mL) [3], and wrapped with protective aluminum foil. The mixture is irradiated with an Original Hanau TNN 15/32 lamp for 4 h [2], and then stirred overnight. The volatiles are removed by rotary evaporation, giving a cloudy or biphasic mixture. Subsequent Vigreux distillation (0.020 bar, 54–56 °C) gives **1** as a clear liquid (13.5 g, 29.4 mmol, 78% based upon  $\text{R}_{f8}\text{I}$ ) [4]: NMR ( $\delta$ ,  $\text{CDCl}_3$ )  $^1\text{H}$  5.81 (ddt,  $^3J_{\text{HH}} = 17, 11, 7$  Hz,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.35 (dm,  $^3J_{\text{HH}} = 11$  Hz,  $=\text{CH}_\text{E}\text{H}_\text{Z}$ ), 5.33 (dm,  $^3J_{\text{HH}} = 17$  Hz,  $=\text{CH}_\text{E}\text{H}_\text{Z}$ ), 2.85 (dtm,  $^3J_{\text{HH}} = 7$  Hz,  $^3J_{\text{HF}} = 18$  Hz,  $\text{CH}_2\text{CH}=\text{CH}_2$ );  $^{13}\text{C}$  ( $\delta$ ,  $\text{CDCl}_3$ , partial) 125.4 (d,  $^1J_{\text{CH}} = 158$  Hz), 122.6 (t,  $^1J_{\text{CH}} = 160$  Hz), 36.1 (td,  $^1J_{\text{CH}} = 130$  Hz,  $^2J_{\text{CF}} = 22$  Hz);  $^{19}\text{F}$  NMR ( $\delta$ ,  $\text{CDCl}_3$ ) –81.5 (t,  $J_{\text{FF}} = 8$  Hz,  $\text{CF}_3$ ), –113.8 (pseudopentet, 2 F), –122.4 (m, 6 F), –123.3 (m, 2 F), –123.6 (m, 2 F), –126.8 (m, 2 F); IR ( $\text{cm}^{-1}$ ,  $\text{CHCl}_3$ )  $\nu_{\text{C}=\text{C}}$  1649 m.

**Step B. 10-Iodo-9H,9H,10H,11H,11H-perfluorononadecane (2)** [5] A Fisher-Porter bottle is charged with **1** (12.00 g, 26.08 mmol),  $\text{R}_{f8}\text{I}$  (14.24 g, 26.08 mmol) and VAZO (1,1'-azobis(cyclohexanecarbonitrile)) (0.510 g, 2.09 mmol), briefly evacuated and refilled with nitrogen (3 $\times$ ), and then pressurized with nitrogen (3.8 bar or 55 psig). The mixture is stirred at 110 °C for 4 h and allowed to cool. The bottle is vented and the off-white solid is dissolved in refluxing hexane (ca. 75 mL). The solution is cooled to 0 °C and gels. The gel is filtered and dried by oil pump vacuum to give **2** as soft, sublimable white flakes (18.60 g, 18.49

mmol, 71%), mp 55.7 °C. In some cases, a second gel precipitation from acetone is required for purification. Although the solid product is light-stable, solutions show decomposition after several hours: NMR ( $\delta$ , 1:4 v/v  $\text{CF}_3\text{C}_6\text{F}_5/\text{CDCl}_3$ )  $^1\text{H}$  4.63 (quint,  $J_{\text{HH}} = 6.6$  Hz,  $\text{CHI}$ ), 3.01 (m, 2  $\text{CH}_2$ );  $^{13}\text{C}\{^1\text{H}\}$  (partial) 36.6 (t,  $J_{\text{CF}} = 23.0$  Hz,  $\text{CH}_2$ ),  $-1.2$  (s,  $\text{ICH}$ ). Calc. for  $\text{C}_{19}\text{H}_5\text{F}_{34}\text{I}$ : C, 22.68; H, 0.50. Found: C, 22.99; H, 0.37.

## Discussion

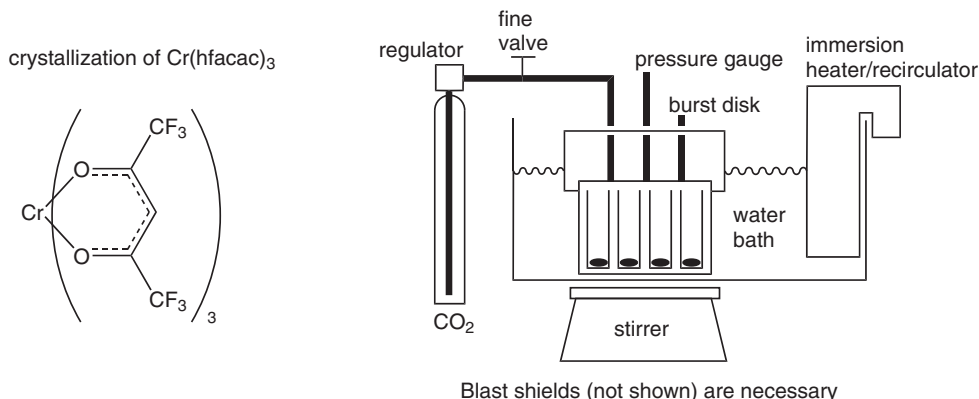
There is an extensive literature on free radical chain reactions of fluorous primary alkyl iodides [6]. As illustrated by the above two procedures, one a substitution and the other an addition, many types of carbon–carbon bond forming reactions can be effected. Both photochemical and thermal initiation can be employed. Starting from  $\text{R}_{\text{f}8}\text{I}$  and  $\text{H}_2\text{C}=\text{CHCH}_2\text{CH}_2\text{OH}$ , an addition/reduction/iodination sequence has been used to prepare  $\text{R}_{\text{f}8}\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{I}$  on a 40 gram scales [7].

The first reaction works equally well with the fluorous alkyl iodides  $\text{R}_{\text{f}6}\text{I}$  [1],  $\text{R}_{\text{f}10}\text{I}$  [1],  $\text{R}_{\text{f}8}\text{CH}_2\text{I}$  [1],  $\text{R}_{\text{f}8}\text{CH}_2\text{CH}_2\text{I}$  [7],  $(\text{CF}_3)_2\text{CF}(\text{CF}_2)_6\text{I}$  [6c], and  $(\text{CF}_3)_2\text{CF}(\text{CF}_2)_8\text{I}$  [6c]. This provides a family of olefins, which can be elaborated in free radical chain reactions with  $\text{PH}_3$  to various fluorous phosphines [1, 7]. The product of the second reaction, **2**, is an example of a branched fluorous building block. This can be employed in coupling reactions to give products with “split ponytails” [5].

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## 11.45

**Tris(1,1,1,5,5,5-hexafluoroacetylacetonate)chromium(III). Crystallization of A Highly Fluorinated Compound from a CO<sub>2</sub>-Expanded Liquid Solvent***Philip G. Jessop, Christopher D. Ablan, Charles A. Eckert, and Charles L. Liotta***Reaction 11.45-1****Reagents and Equipment**

Carbon dioxide (at least 99.9% purity) in a full-size pressurized cylinder with a full-length dip tube is available from Praxair, Nellcor, Air Products and other sources. CO<sub>2</sub> cylinders at room temperature typically have a pressure of 57 bar (830 psi). A fluorosolid which is to be crystallized is required; commercially available Cr(hfacac)<sub>3</sub> (hfacac = 1,1,1,5,5,5-hexafluoroacetylacetonate) is used here as an example.

The procedure requires a pressure vessel that (a) does not contain a stirring rotor, (b) is large enough to take at least one and preferably several uncapped glass vials, (c) is safe to use at pressures of 60–70 bar, and (d) is equipped with a rupture disk (to rupture at 100 to 200 bar), a pressure gauge, and an inlet/outlet valve capable of fine control rather than simply switching between open and closed. An acceptable vessel is the 160 mL Parr Model 4773 equipped with a 4316 gauge block assembly, a needle valve, and a 136 bar (2000 psi) rupture disk. Blast shields should be located between the vessel (when pressurized) and the operator. Blast shields should be made of polycarbonate or other impact-resistant material, and not glass or acrylic. Shields can be fabricated to match the size of the operator's equipment or can be purchased from I<sup>2</sup>R (Instruments for Research and Industry).

The CO<sub>2</sub> cylinder can be connected to the pressure vessel via a high pressure regulator (e.g., Matheson Model 3030-320), a fitting adapter, and a length of 1/16" stainless-steel tubing (HPLC type, available from Supelco or Alltech). The fitting adapter is required to allow the connection from the exit of the fine valve on the regulator to the 1/16" tubing; an appropriate choice is a high pressure steel 1/4" female pipe thread to 1/16" Swagelok adapter. There is no need for any pump, gas compressor, or back-pressure regulator.

Vials (4 mL, 1 dram), microstir bars (7–8 mm length), a constant-temperature water bath, and a magnetic stirrer are also required. The constant-temperature water bath can be as simple as an acrylic bath (e.g., Fisher Isotemp Model 13-873-14) fitted with an immersion circulator such as the Fisher Isotemp Model 2100. The magnetic stirrer should be sufficiently powerful to couple to the stir bars inside the steel vessel; powerful models are available from IKA.

## SAFETY WARNINGS

Operators of high-pressure equipment such as that required for these experiments should take proper precautions, including but not limited to the use of blast shields and pressure relief mechanisms, to minimize the risk of personal injury. Never heat a CO<sub>2</sub> cylinder or raise the temperature of an already-pressurized vessel. Do not perform this procedure if the CO<sub>2</sub> cylinder is at or exposed to a temperature  $\geq 30$  °C.

## Experimental Procedure

Place as many uncapped vials into the vessel as possible, so that they cannot fall over. Thirteen of the 4 mL vials will fit into the Model 4773 vessel at one time. Place into each vial a stir bar, a quantity of the fluororous solid [e.g., Cr(hfacac)<sub>3</sub>, 200 mg], and a quantity of an organic solvent (e.g., decane, 40, 100, or 200  $\mu$ L) insufficient to completely dissolve the fluororous solid. The volume of liquid should not exceed one eighth of the volume of the vials, to allow for volumetric expansion of the liquid under CO<sub>2</sub> pressure. Do not cap the vials. Close the vessel, place it in the water bath (prewarmed to 35 °C) over the magnetic stirrer, and turn on the magnetic stirrer. Place blast shields around the vessel to protect the operator and passers-by. After 30 min, open the connection between the vessel and the CO<sub>2</sub> cylinder. Open up the CO<sub>2</sub> regulator such that the vessel is exposed to the full pressure of the CO<sub>2</sub> cylinder; when the pressure in the vessel becomes constant, close the connection to the CO<sub>2</sub> cylinder. Allow the system to stir for 30 min and then turn off the stirrer and water bath immersion circulator. Disconnect the vessel from the CO<sub>2</sub> cylinder and open the fine valve on the vessel slightly so that the CO<sub>2</sub> gas escapes at a rate of approximately 1–2 mL per min. The flow rate of CO<sub>2</sub> gas can be measured with a flow meter or an upturned, water-filled graduated cylinder in a large beaker of water. Adjust the valve twice daily to maintain this rate. After the vessel has completely depressurized (approx. 1 week), open the vessel to look for crystals in the vials. Alternatively, vent the CO<sub>2</sub> at a much greater rate (40–60 mL min<sup>-1</sup>, taking around 4 h), open the vessel, cap the vials and leave them undisturbed at 1 bar for 1 week.

## Discussion

The preparation of crystals of solid fluororous compounds (i.e., having a fluorine content of greater than 50% by mass) can be very problematic, in that the compounds often precipitate as oils rather than crystals or powders. However, the described method allows one to prepare crystals of sufficient quality for X-ray crystallography [1, 2]. The method is based upon the

observation that the dissolution of CO<sub>2</sub> into an organic liquid increases the fluorophilicity of the liquid so that it becomes more capable of dissolving fluorinated compounds. Removing the CO<sub>2</sub> pressure removes the fluorophilicity, causing the complex to precipitate or creating a supersaturated solution. Variants of this method can be used for water sensitive compounds [3], for reaction and crystallization in one step [4], and for use and recovery of fluororous homogeneous catalysts [5].

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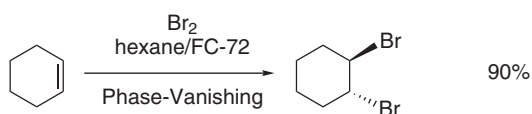
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- 3 If the fluororous solid is air- or moisture-sensitive, then the procedure must be modified in the following manner. The organic solvents must be dried and degassed before use. The CO<sub>2</sub> must have <10 ppm of O<sub>2</sub> and H<sub>2</sub>O. The loading of the vials and vessel and the unloading of the vessel should take place under a dry and inert atmosphere in a glove box. The entire exterior of the vessel should be dried before it is brought into the glove box again for unloading.
- 4 The crystallization can be combined with an *in situ* reaction by adding a liquid or soluble reagent in addition to the liquid solvent and fluororous compound. For example, put Rh<sub>2</sub>[O<sub>2</sub>C(CF<sub>2</sub>)<sub>3</sub>F]<sub>4</sub> (30 mg, prepared by the published method [6]), dimethylformamide (10 µL) and toluene (0.4 mL) in a vial, and then follow the procedure above to obtain crystals of Rh<sub>2</sub>[O<sub>2</sub>C(CF<sub>2</sub>)<sub>3</sub>F]<sub>4</sub>(DMF)<sub>2</sub> [1, 2].
- 5 Use a fluororous homogeneous catalyst that is soluble in the CO<sub>2</sub>-expanded solvent. Place fluororous silica, the catalyst, the organic solvent and the reagents for the reaction to be catalyzed in a vial in a vessel. Expand the solvent with CO<sub>2</sub>, as described above, for enough time for the reaction to proceed, then release the CO<sub>2</sub> pressure over 30 min. After depressurization, filter the catalyst-bearing fluororous silica from the product-bearing liquid phase. One can then re-use the catalyst/silica combination for further cycles [1].
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## 11.46

### ***trans*-1,2-Dibromocyclohexane. The Phase Vanishing Bromination with FC-72 as a Screen Phase**

*Ilhyong Ryu, Hiroshi Matsubara, Hiroyuki Nakamura, and Dennis P. Curran*

#### **Reaction 11.46-1**



## Reagents

All reagents including perfluorohexane (FC-72) are commercially available.

## Experimental Procedure

Bromine (2.1 mmol, 335 mg) was added slowly to FC-72 (1.5 mL) in a test tube (13 mm  $\phi \times$  105 mm) with a septum by using a glass pipette and then cyclohexene (2 mmol, 164 mg) in hexane (1.5 mL) was added slowly, forming three layers. The test tube was covered with aluminum foil in order to shield the reaction from light and kept at room temperature. Gentle stirring of the bromine layer using a magnetic stirrer was carried out, taking care not to mix the three layers. After 4 h, the bromine layer disappeared leaving two colorless layers. The upper hexane layer was taken up with a pipette. Then, additional hexane (2 mL  $\times$  4) was placed on the residual FC-72 layer, followed by decanting off. The combined hexane layer was washed with aqueous 2% Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (30 mL) and water (30 mL), dried over MgSO<sub>4</sub>, and concentrated. Purification by a short column chromatography on silica gel with hexane gave *trans*-1,2-dibromocyclohexane (1.8 mmol, 435 mg) in 90% yield [1].<sup>7</sup>

## Discussion

Generally, the bromination of alkenes requires careful slow addition of bromine and cooling to avoid heat evolution, which can cause undesirable side reactions [2]. The PV bromination method, which relies upon a diffusion of reagent through a fluoruous “liquid membrane” regulator to adjust the addition, can circumvent such a tedious reaction procedure. The PV bromination can be performed without any stirring, although it takes 2 days to finish.

The concept of the “phase-vanishing” (PV) method is applicable to other exothermic reactions, such as demethylation of aryl methyl ethers by boron tribromide [1], Friedel-Crafts acylation using tin tetrachloride [3], and bromination of alcohols by phosphorous tribromide and thionyl bromide [4]. While the original PV reaction takes advantage of the triphasic system based on the density of three layers [organic (top), fluoruous (middle), and heavier reagents (bottom)], recent efforts enabled us to apply reagents even lighter than FC-72 ( $d = 1.67$ ) by using a triphasic U-tube system [5, 6]. A U-tube holds a lower fluoruous phase that serves as a phase screen to separate the upper reagent and organic phases ( $d < 1.67$ ). The substrate added in the organic phase reacts with the reagent regularly transported through the fluoruous phase to afford a product, and the reagent phase vanishes as it is consumed. The chlorination of alcohols using thionyl chloride ( $d = 1.63$ ) and phosphorous trichloride ( $d = 1.57$ ) as a lighter reagent has been accomplished using the triphasic U-tube system [4]. It is now possible to conduct reactions with controlled addition rates of various unfluorinated reagents by the fluoruous phase-screen, independent of whether the reagent is more or less dense than the phase screen.



## References

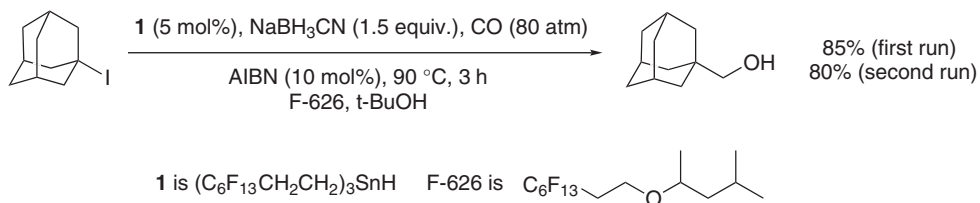
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## 11.47

### 1-Hydroxymethyladamantane. Radical Hydroxymethylation with a Fluorous Tin Hydride

Ilhyong Ryu, Hiroshi Matsubara, and Dennis P. Curran

### Reaction 11.47-1



## Reagents

1*H*,1*H*,2*H*,2*H*-Perfluorooctyl-1,3-dimethylbutyl ether (F-626) can be prepared according to the literature procedure [1]. tris(1*H*,1*H*,2*H*,2*H*-Perfluorooctyl)stannane (fluorous tin hydride, **1**) is commercially available from Fluorous Technologies, Inc. ([www.fluorous.com](http://www.fluorous.com)) or can be prepared according to the literature procedure [2]. Perfluorohexane (FC-72) is commercially available.

## Experimental Procedure

**Caution:** Carbon monoxide is highly poisonous and all operations should be carried out in a fume hood; high pressure experiments should be carried out with suitable precautions. 1-Iodoadamantane (262 mg, 1.0 mmol), fluorosulfuric acid **1** (68 mg, 0.05 mmol), sodium cyanoborohydride (94 mg, 1.5 mmol),  $\alpha,\alpha'$ -azobisisobutyronitrile (17 mg, 0.1 mmol), F-626 (1 mL), and *t*-butyl alcohol (1 mL) were placed in a 30 mL stainless-steel autoclave lined with a glass liner. The autoclave was closed and purged two times with 10 atm of carbon monoxide, pressurized with 80 atm of carbon monoxide and stirred for 3 h at 90 °C. After cooling, excess CO was discharged and the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (20 mL), washed twice with H<sub>2</sub>O and then three times with FC-72 (30 mL total). The CH<sub>2</sub>Cl<sub>2</sub> layer was dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The residue was purified by column chromatography on

silica gel ( $\phi$  8 mm  $\times$  40 mm) eluting with hexane/ethyl acetate (2:1) to afford 1-hydroxymethyladamantane (142 mg, 85%) [3]. The FC-72 solution was dried over  $\text{MgSO}_4$  and evaporated to give 1.45 g of F-626 solution containing fluororous tin hydride **1**, which was reused for the second run to give 133 mg (80%) of 1-hydroxymethyladamantane.

## Discussion

Many useful radical carbonylations of organic halides [4] employ tin reagents, such as tributyltin hydride and allyltributyltin, as radical mediators [5]. In many tin-mediated radical processes, separation of products and triorganyltin residues is often tedious. In the present case, since a catalytic amount of fluororous tin hydride is used in combination with an excess amount of  $\text{NaBH}_3\text{CN}$ , the three-phase workup procedure (aqueous/organic/fluorous), which was originally used for catalytic “Giese type” addition [2], is applicable.

BTF (benzotrifluoride) is an amphiphilic solvent available for hydroxymethylation of organic halides using a fluororous tin hydride [6]. The above procedure using a high boiling fluororous solvent F-626 [bp 80 °C (9 Torr)] has an advantage of convenient reuse of the solution containing fluororous tin hydride for the second experiment. The method of recycling of both fluororous solvents and reagents can be generalized to other fluororous reactions.

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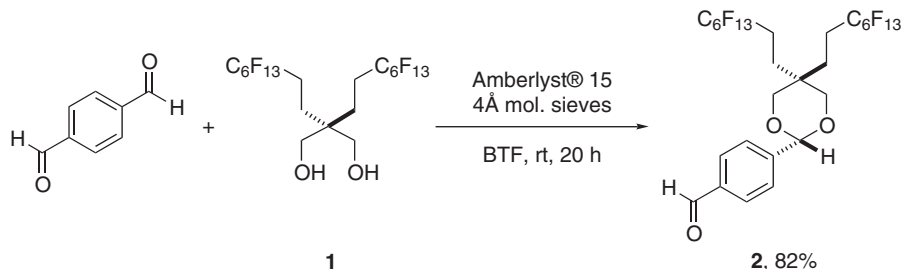
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## 11.48

### 5,5-Bis(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)-2-(4-formylphenyl)-1,3-dioxane. Selective Acetal Formation with Fluorous 1,3-Diol Reagents and its Use in Multistep Synthesis

Roger W. Read and Chutian Zhang

#### Reaction 11.48-1



## Reagents

2,2-Bis(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)-1,3-propanediol **1** can be prepared according to the literature procedure [1, 2]. Fluorous silica gel can be prepared by the literature procedure [3], but commercially available FluoroFlash<sup>TM</sup> silica gel from Fluorous Technologies, Inc. (www.fluorous.com) is recommended for higher loading and better reproducibility.

## Experimental Procedure

Diol **1** (1.101 g, 1.43 mmol), Amberlyst<sup>®</sup> 15 ion exchange resin (0.150 g) and 4 Å molecular sieves (6.1 g) are added sequentially to a solution of terephthalaldehyde (0.385 g, 2.87 mmol) in benzotrifluoride (BTF) (25 mL) and the mixture is stirred vigorously for 20 h at ambient temperature. The mixture is filtered under suction, the solid residue is washed well with Et<sub>2</sub>O (ca. 300 mL), and the combined filtrate and washings are evaporated to dryness under vacuum. The resulting solid is loaded on to a FluoroFlash silica gel column (10 g). Elution with 70:30 MeOH/H<sub>2</sub>O (200 mL) gives unreacted dialdehyde, while further elution with pure MeOH (200 mL) gives 5,5-bis(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)-2-(4-formylphenyl)-1,3-dioxane **2** (1.036 g, 82%). Elution with Et<sub>2</sub>O (200 mL) gives 1,4-bis[5,5-bis(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)-1,3-dioxane]benzene (0.144 g, 12%).

## Discussion

Acetal (used here to include the older term ketal) formation is frequently used in organic synthesis in the protection of alcohols and, in a reciprocal sense, of aldehydes and ketones [4]. The acetal group is generally stable to basic conditions, but is prone to cleavage under a variety of acidic conditions, and can in some cases be partly cleaved to yield useful intermediates for further transformations. In its fluororous modification, in addition to protection, acetal formation can provide a means of tagging appropriate substrates with fluororous groups that can then be used in efficient fluororous solid phase extraction. Normally, 1,3-alkanediols react more rapidly with aldehydes than with ketones to form 1,3-dioxanes, and this is also observed in the reactions with fluororous 1,3-diols, as for example the selective reaction of the aldehyde group in 4-formylacetophenone [2b, 2c].

In this procedure a two-fold excess of terephthalaldehyde is reacted with fluororous diol to selectively tag one aldehyde group, leaving the remaining aldehyde group to undergo further reaction. Solid phase extraction over FluoroFlash silica gel allows rapid separation of the fluororous acetal from excess dialdehyde and other organic contaminants. Subsequent chemistry has provided a route to 4-formylacetophenone and various ketone derivatives through sequential Grignard reaction, pyridinium dichromate oxidation, ketone modification (as appropriate, including hydrazone formation and aldol condensation), and acetal cleavage [2c.5].

Fluorous diols have not been used previously as reagents in acetal formation.

## References

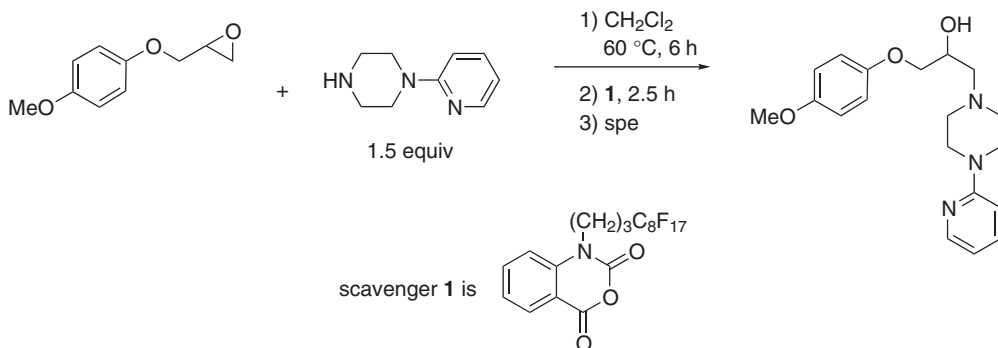
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## 11.49

### 1-(4-Methoxyphenoxy)-3-(4-pyridin-2-yl-piperazin-1-yl)-propan-2-ol. The Amination Reaction Using a Fluorous Isatoic Anhydride Scavenger to Remove Excess Amine

Wei Zhang and Christine Hiu-Tung Chen

#### Reaction 11.49-1



## Reagents and Materials

Fluorous isatoic anhydride **1** [1-(1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoroundecyl)-1*H*-benzo[d]-[1,3]oxazine-2,4-dione] is commercially available from Fluorous Technologies, Inc. (www.fluorous.com) or can be prepared by *N*-alkylation of isatoic anhydride with 1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoroundecyl iodide using sodium hydride as a deprotonation agent. FluoroFlash<sup>TM</sup> cartridges from Fluorous Technologies, Inc. are used for solid-phase extraction (SPE).

## Experimental Procedure

To a solution of glycidyl 4-methoxyphenyl ether (18 mg, 0.10 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL) is added 1-(2-pyridyl)piperazine (23 mg, 0.15 mmol) [1]. After stirring at 60 °C for 6 h, fluorous isatoic anhydride **1** (43 mg, 0.07 mmol) is added and the reaction mixture is stirred at 60 °C for an additional 2.5 h. The reaction mixture is concentrated to ~0.3 mL and loaded onto a 5 g FluoroFlash<sup>TM</sup> cartridge pre-conditioned with 80:20 MeOH/H<sub>2</sub>O on an SPE manifold. Initial elution with 80:20 MeOH/H<sub>2</sub>O (10 mL) and evaporation of the solvent provides 1-(4-methoxyphenoxy)-3-(4-pyridin-2-yl-piperazin-1-yl)-propan-2-ol (34 mg, 100%). Further elution with MeOH (20 mL) gives a mixture fluorous compounds containing the scavenged amine species.

## Discussion

Unwanted species can be quenched with fluorous scavengers and removed from a reaction mixture by fluorous solid-phase extraction [2]. Both the reaction and the scavenging process are performed in a homogeneous solution-phase environment. The scavenged species can be recovered from the fluorous silica gel if necessary. In addition to fluorous isatoic anhydride **1**, other fluorous scavengers such as 1*H*,1*H*,2*H*,2*H*-perfluorodecyl isocyanate [1] (electrophilic scavenger) and 1*H*,1*H*,2*H*,2*H*-perfluorodecane-1-thiol [3] (nucleophilic scavenger) have been developed. This technique has a potential utility in the solution-phase parallel synthesis of small molecules and natural products.

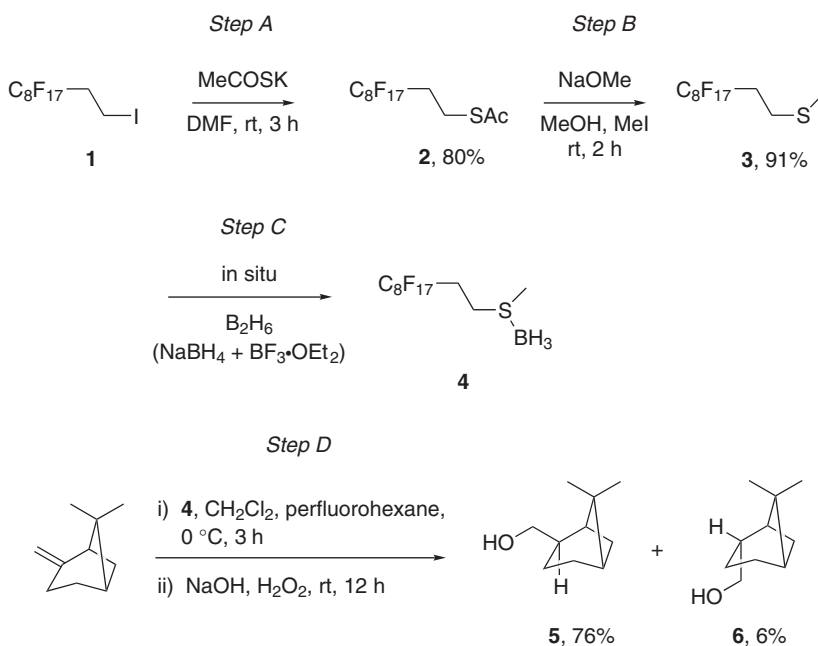
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## 11.50

**Borane-(1*H*,1*H*,2*H*,2*H*-Perfluorodecyl) Methyl Sulfide Adduct. Preparation of a Borane-Fluorous Dialkyl Sulfide and its Application to the Hydroboration of  $\beta$ -Pinene**

David Crich, Mitesh Patel, and Santhosh Neelamkavil

**Reaction 11.50-1****Reagents**

(1*H*,1*H*,2*H*,2*H*-Perfluorodecyl) Iodide **1** [2043-53-0] and perfluorohexane [355-42-0] are widely available commercially.

**Experimental Procedures**

**Step A. S-(1*H*,1*H*,2*H*,2*H*-Perfluorodecyl) Thioacetate (**2**)** A dry 1 L round-bottomed flask is charged with a stir bar, potassium thioacetate (4.0 g, 35.1 mmol), and DMF (400 mL). The mixture is stirred at room temperature until a homogeneous solution is obtained before **1** (20.0 gm, 34.8 mmol) is added. After stirring at room temperature for 3 h, diethyl ether (400 mL) is added and stirring is continued for 15 min. The reaction mixture is then transferred into a separating funnel, and is washed successively with saturated aqueous NH<sub>4</sub>Cl (120 mL), brine (100 mL), water (100 mL), and again with brine (50 mL). The ethereal solution is dried over Na<sub>2</sub>SO<sub>4</sub>, then concentrated at room temperature by rotary evaporation. Purification of the residue by chromatography over silica gel (EtOAc/hexane, 1:40) gives **1** (14.6 g,

80%) as a colorless solid [1], mp 31 °C:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.11–3.06 (m, 2 H), 2.47–2.29 (m, 2 H), 2.36 (s, 3 H).

**Step B. (1H,1H,2H,2H-Perfluorodecyl) Methyl Sulfide (3)** Thioacetate **2** (10.0 g 19.1 mmol) is dissolved under a nitrogen atmosphere in dry MeOH (100 mL) in a 250 mL round-bottomed flask, then cooled to 0 °C in an ice bath. Freshly prepared NaOMe in MeOH (20 mL of 2.4 M) is then added over 5 min. Stirring is maintained for 45 min then methyl iodide (3.0 mL, 47.9 mmol) in dry MeOH (15 mL) is added over 10 min while the temperature is maintained at 0 °C. The reaction mixture is allowed to warm to room temperature and is then stirred for 2 h before ice water (100 mL) is added. The reaction mixture is extracted with  $\text{CH}_2\text{Cl}_2$  (200 mL), and the extracts are washed with brine (100 mL), then dried over  $\text{Na}_2\text{SO}_4$  before concentration by rotary evaporation at water aspirator vacuum below 30 °C [2]. Purification of the concentrate by chromatography over silica gel (hexane) provides **3** (8.7 g, 91%) as a colorless oil [1]:  $^1\text{H}$  NMR ( $\text{C}_6\text{D}_6$ )  $\delta$  2.28 (m, 2 H), 2.10–1.95 (m, 2 H), 1.55 (s, 3 H).

**Step C. Borane-(1H,1H,2H,2H-perfluorodecyl) Methyl Sulfide Adduct (4)** A steady stream of diborane gas [generated by dropwise addition at room temperature of  $\text{BF}_3 \cdot \text{OEt}_2$  (10.3 mL, 81 mmol) to a stirred solution of  $\text{NaBH}_4$  (2.7 g, 71 mmol) in 2-methoxyethyl ether (20 mL)] is passed, over 15 min, into neat **3** (5.0 g, 10.2 mmol) in a two-necked pear-shaped flask, that had been well flushed with nitrogen, until complete solidification is achieved. Excess diborane is purged with nitrogen to give a white solid (5.1 g) comprised of a mixture of adduct **4** and the sulfide **3**, which may be manipulated in air and which is best stored under nitrogen in the refrigerator [1]. Analysis of this mixture by  $^1\text{H}$  NMR spectroscopy in  $\text{C}_6\text{D}_6$  shows it to be a 1:1 mixture of **3** and **4**:  $^1\text{H}$  NMR of **4** ( $\text{C}_6\text{D}_6$ )  $\delta$  2.10–1.90 (m, 4 H), 1.29 (s, 3 H).

**Step D. Hydroboration of  $\beta$ -pinene** A 1:1 solid mixture of **3** and **4** (0.64 g, 0.64 mmol of **4**) is added over 5 min under nitrogen to a stirred solution of  $\beta$ -pinene (0.20 mL, 1.3 mmol) in a biphasic mixture of dry  $\text{CH}_2\text{Cl}_2$  (9.0 mL) and dry perfluorohexane (9.0 mL) at 0 °C. The reaction mixture is then stirred at 0 °C for 3 h, before it is allowed to warm to room temperature. The lower perfluorohexane layer is removed with a pipette and fresh perfluorohexane (9.0 mL) is added, followed by stirring for 10 min. After separation of the phases, the perfluorohexane layers are combined and concentrated by rotary evaporation at water aspirator vacuum below 30 °C [2] to give recovered **3** (0.55 g, 88%). 3 M NaOH (0.24 mL) and 30%  $\text{H}_2\text{O}_2$  (0.12 mL) are added to the  $\text{CH}_2\text{Cl}_2$  phase followed by stirring at room temperature for 12 h. The reaction mixture is then diluted with water (10 mL) and stirred for a further 1 h. The organic layer is then run off and the aqueous layer is extracted with  $\text{CH}_2\text{Cl}_2$  (20 mL). The combined organic layers are washed with brine (10 mL), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated at room temperature [2]. Purification of the concentrate by chromatography on silica gel (0–15% ethyl acetate in hexane) gave further recovered **3** (0.03 g, 5%), *trans*-myrtanol **6** (0.01 g, 6%), and *cis*-myrtanol **5** (0.15 g, 76%).

## Discussion

The solid mixture of **3** and **4** presents numerous advantages over the familiar borane-dimethyl sulfide complex [1]. Firstly, the white solid shows no tendency to ignite sponta-

neously and only deliquesces slowly over a matter of days in air; it may, therefore, be readily handled and weighed in the open laboratory. Secondly, the mixture is readily assayed by integration of the  $^1\text{H}$  NMR spectrum recorded in deuteriobenzene solution; the ability to accurately weigh the mixture coupled with the convenient NMR assay greatly facilitates the dispensation of accurate amounts of borane. Thirdly, in addition to hydroborations, the mixture of **3** and **4** performs all the standard reductions typically conducted with borane/dimethyl sulfide, including those of ketones catalyzed by oxazaborolines. Fourthly, the sulfide carrier **3** is easily recovered in high yield, ready for reuse. Last, but not least, thioacetate **2**, sulfide **3**, and sulfide-borane **4** are all completely odorless.

## References

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- 2 Care should be taken in the concentration of solutions of **3** to avoid evaporation. At room temperature with a water aspirator vacuum losses are minimal.



## 12

## Applications of Fluorous Compounds in Materials Chemistry

## 12.1

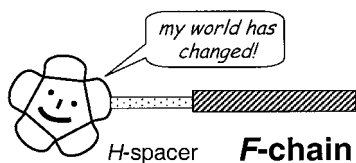
### Basic Principles and Recent Advances in Fluorinated Self-Assemblies and Colloidal Systems

Marie Pierre Krafft

## 12.1.1

#### Introduction

A clear understanding of the basic properties of fluorinated self-assembled systems and interfaces should be valuable to chemists using fluorous phases for syntheses as these properties determine phase separations, the development of large size interfaces and the possible constitution of micro- or nanoreactors and templates. Many reagents, catalysts and substrates used in fluorous chemistry, once fitted with perfluorinated chains (*F*-chains [1]), are likely to become amphiphilic or to experience enhanced amphiphilic character (Scheme 12.1-1). Hence, they become susceptible to adsorption at interfaces and to self-association into colloidal systems, including spherical and worm-like micelles, vesicles and hollow fibers, emulsions, microemulsions or other more or less complex self-assemblies. In addition, fluorinated compounds (*F*-compounds), due to their combined hydro- and lipophobia and consequent tendency to phase separate from both aqueous and hydrocarbon media, can generate compartmentalization in molecular systems. These phenomena may often account



#### The Molecule

**Scheme 12.1-1.** Grafting one or more *F*-chains on essentially any (non-fluorinated) molecule endows that molecule with amphiphilic character. This means that the molecule consists of at least two parts that have low affinity for each other. Beware of possible modifications of the microstructure and, hence, the properties of their solutions.

for unexpected kinetics or reaction pathways when *F*-amphiphilic reactants, products or even byproducts are involved. Interface-driven parameters, which depend largely on the length of the *F*-chain, can then complicate apparently simple chemistry.

Molecular and macromolecular compounds with *F*-chains have distinctive properties [2–4]. They are chemically and thermally more stable, and have lower intermolecular interactions, hence display lower surface tensions and higher vapor pressures than their *H*-counterparts. The unique properties of their colloidal systems are the basis of a wealth of applications [5]. In both materials and biological sciences, a key objective has become the design and development of materials and devices based on multiscaled subunits. *F*-compounds provide valuable tools for generating organization and segregation of molecular systems into nano- to meso-scale phases with controlled sizes and specific properties. Examples of such systems include arrangements mimicking living organisms or nano-patterned surfaces destined for microfluidics, nanolubrication and molecular sensing. Another exciting field in which fluorinated surfactants (*F*-surfactants) are instrumental is the development of biphasic reactions and industrial processes in liquid or supercritical CO<sub>2</sub>. Polymers with *F*-moieties have found new potential applications in wastewater treatment, oil recovery, control of surface erosion, and antibacterial activity.

In the biomedical area, injectable microbubbles stabilized by gaseous fluorocarbons (FC) have recently provided new contrast agents for effective diagnosis of disease by ultrasound imaging [6, 7]. Therapeutic uses of such microbubbles are also being investigated. Direct and reverse *F*-emulsions are being developed as oxygen carriers and drug delivery systems [8, 9].

After a brief reminder of the basic physicochemical properties of FC and *F*-surfactants, this review will focus on the most recent advances on self-assemblies and colloidal systems, e.g., micelles, vesicles, tubules, monolayers, emulsions and polymers that comprise *F*-chemicals. Their present and potential applications, primarily in materials science, will also be mentioned; their biomedical applications are reviewed by Riess in Chapter 13 of this Handbook [10]. The more classical, highly diverse industrial uses of *F*-surfactants and *F*-polymers, such as in textile and plastic manufacturing, fire fighting, surface cleaning, emulsion polymerization, etc., will generally not be considered here.

## 12.1.2

### Basic Physicochemical Properties

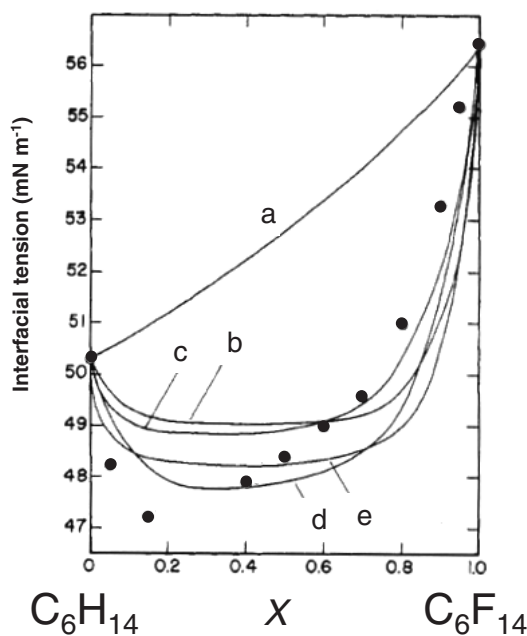
#### 12.1.2.1 Fluorocarbons

Fluorine is the most electronegative of all elements, has a high ionization potential and a very low polarizability [2, 4]. This relatively small atom is, nevertheless, significantly larger than hydrogen (van der Waals radius 1.47 Å versus 1.20 Å) [11]. Consequently, *F*-chains (C<sub>*n*</sub>F<sub>2*n*+1</sub>) are bulkier than *H*-chains (cross sections: 30 Å<sup>2</sup> versus 20 Å<sup>2</sup>) [12]. Another consequence of the large size of the fluorine atom is the greater stiffness of *F*-chains as compared with *H*-chains [13], which is accompanied by a loss of *gauche/trans* freedom. The *gauche/trans* energy differences are of ca. 2.0 kJ mol<sup>−1</sup> and 4.6 kJ mol<sup>−1</sup> for *H*- and *F*-chains, respectively [12]. In order to minimize steric hindrance, *F*-chains adopt a helical conformation.

Owing to effective overlapping of orbitals, the C–F bond is the most stable single bond

found in organic chemistry ( $\sim 485 \text{ kJ mol}^{-1}$  as compared with  $\sim 425 \text{ kJ mol}^{-1}$  for a standard C–H bond) [2]. As a consequence, FCs are thermally and chemically very stable. Furthermore, the dense electron cloud of the fluorine atoms provides a repellent sheath that protects *F*-chains against reagents [14]. FCs are also inert biologically.

The low polarizability of fluorine results in low van der Waals interactions between *F*-chains and low cohesive energy densities in liquid FCs [4, 14, 15]. These low intermolecular interactions are responsible for many of the most valuable properties of FCs, such as very low surface tensions, excellent spreading properties, high fluidity, low dielectric constant, high vapor pressure, high compressibilities and high gas solubilities [3, 14, 16]. The weak interactions between FCs also explain that they usually do not mix with hydrocarbons (HCs) that have a higher cohesive energy density. In fact, FCs are surface active in HCs both at the air/oil and the water/oil interfaces (Figure 12.1-1) [17]. The larger surface presented by the *F*-chains, in conjunction with the low polarizability of the fluorine atoms results in enhanced hydrophobicity. *F*-chains thus combine two characteristics that are commonly considered antinomic: they are extremely hydrophobic and in addition have a pronounced lipophobic character.



**Fig. 12.1-1.** Interfacial tensions of mixtures of hexane and *F*-hexane against water at 25 °C ( $X$  = mole fraction of  $\text{C}_6\text{F}_{14}$ ). Very pronounced deviations from ideal behavior have been observed. The experimental data (circles) indicate a reciprocal interfacial activity of FCs as dilute solutions in HCs and of HCs as dilute solutions in FCs. In model a, the solution is assumed to be ideal. In model b, the solution is assumed to be regular. In model c,

volume fractions have been used to calculate the activity coefficients, as the molar volumes of HCs and FCs are very different. In model d, an approach based on a monolayer at the surface has been used, as the partial molar areas of FCs and HCs are different. In model e, the activity coefficients have been calculated directly from vapor pressure data. From [17].

### 12.1.2.2 Fluorinated Surfactants

The strong hydrophobic interactions and low van der Waals interactions displayed by *F*-chains dramatically increase the tendency for *F*-amphiphiles to self-assemble in water and to collect at interfaces [3, 4]. *F*-surfactants can decrease the superficial tension of water down to values ( $15\text{--}20\text{ mN m}^{-1}$ ) that cannot be reached by *H*-surfactants ( $30\text{--}40\text{ mN m}^{-1}$ ) [18]. The interfacial tensions between an aqueous solution of an *F*-surfactant and an *F*-phase are usually extremely low (typically  $0\text{--}5\text{ mN m}^{-1}$ ). The incremental changes in the free energy of adsorption for the transfer of a  $\text{CF}_2$  group from water to the air/water interface are about twice those of a  $\text{CH}_2$  group ( $-5.1$  versus  $-2.6\text{ kJ mol}^{-1}$ ) [19]. The free energies of transfer of a  $\text{CH}_2$  group from an HC phase to an FC phase and of a  $\text{CF}_2$  from an FC phase to an HC phase are  $1.1$  and  $1.4\text{ kJ mol}^{-1}$ , respectively [20]. These values are about one third of the energy needed to transfer a  $\text{CH}_2$  from an HC phase to water.

Owing to their increased hydrophobic character, *F*-surfactants have lower critical micellar concentrations (cmc) than *H*-surfactants, with cmc values being roughly equivalent to those of *H*-surfactants with a 50% longer chain. For example, the contribution of a  $\text{CF}_2$  group toward micellization of metal salts of *F*-carboxylic acids or *F*-sulfonates [21], or of *F*-alkylated poly(oxyethylene) surfactants [22] is roughly equivalent to 1.6 times that of a  $\text{CH}_2$  group. However, it was shown that this “ $1\text{ CF}_2 \cong 1.5\text{ CH}_2$ ” rule is not necessarily valid when the chains are only partially fluorinated. In this case, the *H*-spacer inserted between the polar head and the *F*-chain does not contribute fully to the micellization and adsorption processes, which are essentially controlled by the *F*-chain length [23]. Replacing the terminal  $\text{CF}_3$  group of an *F*-surfactant by a  $\text{CF}_2\text{H}$  group strongly reduces its surface activity properties [22, 24].

Among the notions that provide tools to chemists using *F*-surfactants one should mention the hydrophilic lipophilic balance (HLB), which, for example, is a useful index for selecting a suitable surfactant for emulsification [18]. Phase diagrams are also basic to the understanding of *F*-surfactant behavior [22, 25].

*F*-surfactants cannot, however, be simply considered as more hydrophobic analogs of *H*-surfactants; they have specific properties of their own. Their self-assembly behavior is characterized by a strong tendency to form vesicles and lamellar phases rather than micelles, primarily due to the bulkiness of the *F*-chain that tends to decrease the curvature of the aggregates they form in solution. Thus, micelles of *F*-surfactants tend to be rod-shaped at concentrations where they are spherical for *H*-surfactants [12]. Single-chain *F*-phosphocholines readily form stable, heat-sterilizable vesicles while their *H*-analogs form micelles [26, 27]. Further examples of bilayer aggregates and vesicles from single chain *F*-surfactants have been reported [28]. The phase diagrams of *F*-surfactants tend to exhibit larger domains of the fluid lamellar phase ( $L_\alpha$ ) and more restrained domains of the micellar phase ( $L_1$ ) than *H*-surfactants, which also supports their strong proclivity to form vesicles [22, 29]. Vesicles made from *F*-amphiphiles are characterized by higher organization of their bilayer and improved stability (see Section 12.1.3.1).

Fluorinated cationic gemini surfactants were shown to exhibit a slow exchange rate of the molecule between the monomeric and the micellar states on the NMR time scale [30]. In addition, *F*-surfactants are characterized by slower kinetics of dissolution from the solid state while forming aggregates in solution, and longer residence times in micelles as compared with *H*-surfactants [31].

The hydrophobic effect is not the only driving force that can lead to *F*-self-assemblies. Halogen molecules ( $I_2$ ,  $Br_2$ , ...), alkyl(aryl) halides, and more recently *F*-alkyl(aryl) halides [32] can act as electron acceptors and form complexes with atoms that have lone pairs. This non-covalent interaction has been named a “halogen bond” by analogy with the hydrogen bond with which it has similarities. The attractive  $N \cdots I-F$ -alkyl(aryl) chain interaction was shown to be specific, directional and strong enough to overcome the low affinity that exists between *F*- and *H*-modules and to drive their self-assembly into oligomeric structures in the liquid phase, as well as into crystalline networks [32]. Halogen bonding thus adds a novel assembling element to the toolbox of supramolecular engineers.

### 12.1.2.3 Semifluorinated Alkanes: a Class of Special Amphiphiles

Semifluorinated alkanes  $C_nF_{2n+1}C_mH_{2m+1}$  (FnHm diblocks) consist of a lipophobic *F*-alkyl block (*F*-block) and an *H*-alkyl block (*H*-block). The mutual antipathy of these blocks results in a tendency for them to demix, which can lead FnHm diblocks to self-organize both in the bulk and in solutions. In the bulk, FnHm diblocks crystallize in a variety of smectic phases, depending on block lengths and temperature [33]. This complex phase behavior is still a matter of debate [34]. At high temperatures, solid FnHm form a lamellar structure with ordered *F*-blocks, while the *H*-blocks are in a liquid-like state [34]. In suitable solvents, FnHm form gels made of long networked fibers [35]. In solutions FnHm form micelles in both HCs and FCs [36]. Their aggregation number is, however, lower than in the case of conventional micelle-forming surfactants in water [20]. FnHm diblocks exhibit a “surface freezing” phenomenon, that is, the formation of a crystalline monolayer at their free surface melts a few degrees above the freezing point of the bulk material [37].

FnHm diblocks thus constitute a new class of non-conventional surfactants that are active at the interface between an *F*-phase and an *H*-phase. FnHm diblocks were recently used in combination with phospholipids in vesicles, monolayers and emulsion films (Sections 12.1.3.1 and 12.1.5.1). They also allowed stable HC-in-FC emulsions to be obtained.

## 12.1.3

### Self-Assembly Behavior of *F*-Amphiphiles

*F*-amphiphiles have a much stronger tendency to self-assemble into supramolecular aggregates when dispersed in water and other solvents than their *H*-analogs (Figure 12.1-2).

#### 12.1.3.1 Vesicles

The first examples of *F*-bilayers and vesicles were reported by the groups of Kunitake [38] and Ringsdorf [39]. Stable, often heat-sterilizable *F*-vesicles have since been elaborated from numerous single, double and triple-chain amphiphiles [40, 41]. The amphiphiles used include a large variety of non-ionic, cationic, anionic, or zwitterionic head groups. Liposomes made from *F*-phospholipids have been extensively investigated and reviewed by Riess and coworkers [40, 41]. *F*-phospholipids are characterized by higher gel-to-fluid transition temperatures, as compared with *H*-analogs, which indicate increased ordering of the bilayer membrane. The strongly hydrophobic and lipophobic *F*-chains form an internal *F*-film within the bilayer that decreases the permeability of the vesicles and slows down the

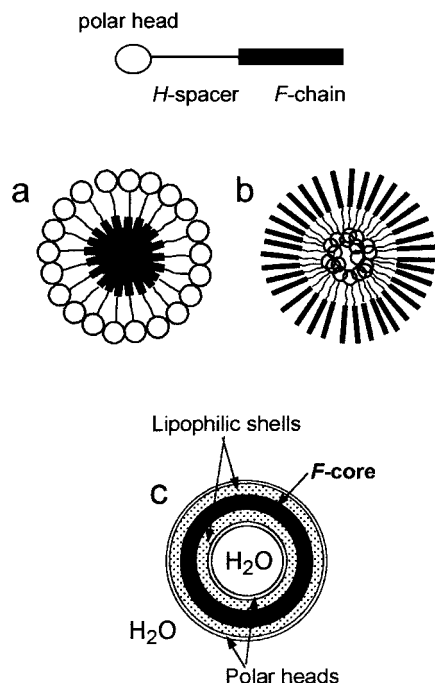


Fig. 12.1-2. Schematic representation of: a, a direct *F*-micelle; b, a reverse *F*-micelle; and c, an *F*-vesicle.

release of an encapsulated probe, as compared with *H*-vesicles. Additional *F*-vesicles were prepared from further examples of *F*-phospholipids [42] as well as from various glycolipids and glycopospholipids [43]. See Chapter 13 for the biological properties of such vesicles.

*F*-colloids can be used as templates for reactions. For example, *F*-vesicles allowed polymerization of hydrophobic monomers within their bilayer [44], while, in the case of *H*-vesicles, a phase separation between the polymer chain and the lipid matrix occurred, which led to the formation of a latex bead.

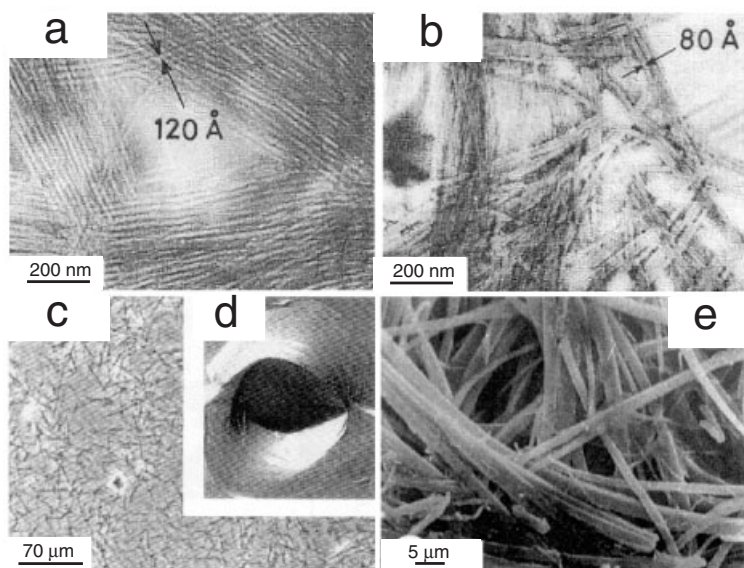
*F*-gemini surfactants form unilamellar vesicles, while the coexistence of unilamellar vesicles and threadlike micelles was observed in the case of mixed *F*-alkyl/*H*-alkyl gemini surfactants [30]. Spontaneously forming vesicles were also obtained from mixtures of an *F*-propylether surfactant and *n*-dodecylbetaine [45].

Additionally, *F*-vesicles have been obtained by combining standard phospholipids and FnHm diblocks. These *F*-vesicles are more stable and less permeant than vesicles made from the phospholipid alone [46]. The Ca<sup>2+</sup>-induced fusion kinetics of these vesicles were slowed down as compared with those of *H*-vesicles [47]. Direct experimental evidence for the diblock's presence and organization within the bilayer has recently been provided [48].

## 12.1.3.2 Tubules and Fibers

Hollow nano- and microtubules made from rolled-up bilayers of amphiphiles have received substantial attention since the 1990s because of their potential applications [49]. Recently, nanotubules are being investigated as nanocontainers for the elaboration of metal nanowires [50] and as templates for molecular recognition-driven protein controlled self-assembly [51].

Prior to using *F*-amphiphiles, the presence of a chiral center and/or the ability to form hydrogen bonds between polar heads were deemed necessary for the inception of the rolling-up process that leads to the tubular structures. However, very stable and sturdy rigid microtubules and flexible fibers were obtained from non-chiral, non-hydrogen bound single-chain *F*-amphiphiles derived from dimorpholinophosphate in water and other polar solvents, leading to the formation of gels [52, 53]. Nanotubules have also been obtained from mixed *F*-alkyl/*H*-alkyl double-chain anionic *F*-glucolipids [54]. The introduction of an *F*-chain had a significant impact on tubule diameter. Examples of tubules and fibers formed by *F*-surfactants in polar solvents are depicted in Figure 12.1-3. Amphiphiles with two *F*-chains and one *H*-chain grafted on the chiral L-glutamate residue were reported to form very viscous turbid dispersions in organic solvents [55]. Optical and electron microscopy studies revealed the presence of fibers (Figure 12.1-3).



**Fig. 12.1-3.** Examples of tubules and fibers formed by *F*-amphiphiles in various media. Formation of a, aligned rods and b, tube-like aggregates from a glutamate derivative containing two *F*-chains and one *H*-chain, in benzene and chlorocyclohexane, respectively (negative staining electron microscopy) from [55]. c, Formation of hollow tubules from a

partially fluorinated derivative of dimorpholinophosphate (optical microscopy); the insert d shows the hollow core of a tubule (freeze fracture electron microscopy) from [53]. e, Fibers formed by a partially fluorinated alcohol in methanol (scanning electron microscopy; courtesy Dr. F. Giulieri, University of Nice).

## 12.1.4

**Bi-dimensional Films****12.1.4.1 Langmuir and Gibbs Monolayers**

Langmuir films (spread monolayers that are compressed with a barrier in a trough) and Gibbs monolayers (spontaneously adsorbed monolayers at an air/liquid or liquid/liquid interface) are valuable tools for studying chain–chain interactions and the formation and structure of interfacial films. Monolayers of *F*-amphiphiles present specific structures and properties, due to differences in chain cross-section, stiffness and molecular interactions between the *F*- and *H*-amphiphiles [56]. A stable Langmuir monolayer was formed from a non-amphiphilic *F*-alkane,  $C_{20}F_{42}$ , at room temperature [57], while such behavior was only seen, subsequently, for alkanes one and a half times longer. A specific feature of monolayers of *F*-amphiphiles having a polar head smaller than the chain cross section of the hydrophobic chain (e.g., *F*-acids and *F*-alcohols, or acids and alcohols with short, one or two  $CH_2$  group *H*-spacers between the polar head and the *F*-chains) is that, due to the stiffness of the *F*-chain, they undergo a direct transition from the gas phase to an untilted liquid condensed (crystalline) phase upon compression, without occurrence of the liquid expanded phase usually found for *H*-analogs [58]. In the liquid condensed phase, *F*-surfactant molecules are vertical and packed in a well-organized 2D hexagonal lattice [59]. The introduction of an *H*-spacer in carboxylic *F*-acids results in a decrease in the ordering due to the combined effects of the *F*-chain and *H*-spacer cross-sections mismatch and of repulsive interactions between the dipoles associated with the  $CF_2-CH_2$  linkage. This leads then to the appearance of a liquid phase in addition to the gas and liquid condensed phases [58].

Precise control of the shape, size and molecular organization of colloids is necessary to master the construction of supramolecular 2D architectures. Patterned surfaces with lateral phase separations were achieved by mixing *F*- and *H*-surfactants that form liquid condensed and liquid expanded monolayers, respectively [59], or two liquid condensed phases [60]. Monolayers can also be compartmentalized vertically. This was achieved by compressing mixed Langmuir monolayers of a phospholipid and an *F**n**H**m* diblock, resulting in the expulsion of the diblock molecule at high surface pressures and the formation of segregated layers of lipid and diblock [61]. Monodisperse two-dimensional surface micelles were formed in monolayers of partially fluorinated carboxylic acids [62], as well as from nonpolar *F**n**H**m* diblocks [63], after transfer onto solid substrates.

**12.1.4.2 Self-Assembled Monolayers**

Thin *F*-films have been proposed as alternative materials for coatings in order to compensate for certain inherent drawbacks of *F*-polymers that are related to the cost of *F*-monomers, certain processing difficulties and poor stability against UV radiation. Since the first studies of films of adsorbed partially fluorinated acids pioneered by Zisman and co-workers [64], extensive research has focused on self-assembled monolayers (SAM) of *F*-alkanethiols and partially fluorinated alkanethiols adsorbed on gold and, particularly, on the relations between the structure of the hydrophobic chain and the corresponding interfacial properties [65]. The lattice spacing of *F*-SAMs and partially fluorinated SAMs with a short *H*-spacer is larger than that of *H*-SAMs and the former adopt more ordered structures [66]. The tail chain lattice is tilted by  $30^\circ$  with respect to the underlying gold lattice [67]. Increas-



ing the length of the *H*-spacer increases disorder. The wettability of totally and partially fluorinated SAMs appears to be dictated primarily by the interactions of the dipoles orientated along the  $\text{CF}_3\text{--CH}_2$  axis with the molecular dipoles of the solvent [68]. As a consequence, replacing the terminal  $\text{CH}_3$  group of an *H*-SAM by a  $\text{CF}_3$  group increases the wettability of the monolayer by polar solvents [69]. Likewise, the wettability of a partially fluorinated SAM decreases, for a given *H*-spacer, with decreasing degree of fluorination due to the progressive burying of the  $\text{CF}_3\text{--CH}_2$  dipole within the SAM. The frictional properties of *F*-SAMs appear to be primarily controlled by the size of the terminal group.

#### 12.1.5

### Emulsions and Microemulsions Containing a Fluorocarbon or a Fluorinated Surfactant

#### 12.1.5.1 Fluorocarbon Emulsions and Microemulsions

FC-in-water emulsions are the focus of extensive research and development efforts with a view to providing injectable oxygen carriers and for other biomedical applications, including diagnostic [9]. They have been extensively reviewed [8] along with the basic properties of FCs relevant to oxygen transport. Details on emulsion engineering have also been provided [70]. Efforts have focused on the protection of concentrated emulsions against aging, that is, primarily molecular diffusion (Ostwald ripening). Ostwald ripening was successfully reduced by adding to the primary FC small amounts of an FC that is slightly heavier, which lowers the solubility of the *F*-phase in water [70]. Particle size increase was slowed down even more effectively by adding small amounts of an *F*-alkyl/*H*-alkyl diblock. The latter was shown to have a synergetic interfacial activity with phospholipids at the FC/water interface [71] in addition to their potential contribution to lowering the solubility of the *F*-phase. Use of diblocks also allowed smaller-sized *F*-emulsions to be obtained. Such *F*-emulsions could be used as reservoirs for gases other than  $\text{O}_2$ , for example NO and Xe. *F*-emulsions offer large interfaces for reactivity. Water-in-FC emulsions and non-polar HC-in-FC emulsions can also be obtained using *F*-surfactants.

Microemulsions of FCs and *F*-polyethers stabilized by *F*-alkanoic surfactants [72] or *F*-polyether surfactants [73] have been widely investigated. Depending on composition, these microemulsions consist either of discrete droplets dispersed in a continuous phase or of bicontinuous phases. *F*-microemulsions have been used for the production of polyfluoroolefins [74] and of magnetic oxide particles of controlled characteristics in aqueous dispersions. The effect of pressure on the phase behavior of microemulsions of an *F*-olefin in water, stabilized by an *F*-alkanoate and an *F*-alcohol has been reported [75]. *F*-microemulsions have also been used to control chemical reactivity. Thus, the microstructure of microemulsions based on  $\text{C}_8\text{F}_{17}\text{CH=CHR}$  ( $\text{R} = \text{H}$  or  $\text{C}_{10}\text{H}_{21}$ ) and formamide has been reported to control the yield and regioselectivity of photoamidation [76]. Some mixed *F*-alkyl/*H*-alkyl catanionic surfactants, i.e.,  $\text{C}_n\text{F}_{2n+1}\text{COO}^- + \text{NR}(\text{C}_m\text{H}_{2m+1})_3$ , were shown to form microemulsion phases with hydrofluoroethers, and to form an acid/soap complex that can easily be recovered and recycled [77, 78]. These compounds may provide an alternative to *F*-alkanoyl surfactants.

#### 12.1.5.2 Water-in- $\text{CO}_2$ Microemulsions

The scope of industrial processes using supercritical or liquid  $\text{CO}_2$  is rapidly expanding. Indeed,  $\text{CO}_2$  provides a cheap, non-toxic, non-flammable and bio-recyclable solvent alternative

to conventional volatile organic compounds. Commercial processes include decaffeination of coffee, supercritical fluid chromatography, and fluoropolymer synthesis. The challenge was to identify surfactants that are capable of stabilizing water-in-CO<sub>2</sub> microemulsions to replace the water-in-HC microemulsions stabilized by aerosol-OT (sodium bis-2-ethylhexyl sulfosuccinate, AOT) that are widely used for chemical synthesis and extraction processes. *F*-surfactants (and, to a lesser extent, silicone surfactants) were shown to be the best candidates for this purpose, due to the favorable solubility of *F*-chains in CO<sub>2</sub>. *F*-surfactants able to form water-in-CO<sub>2</sub> microemulsions include *F*-polyether carboxylates [79], *F*-analogs of AOT [80], *F*-phosphates [81], and surfactants with mixed *F*-alkyl and *H*-alkyl chains [82]. The structure of the resulting microemulsions has been determined, and the effects of the *F*-surfactant's chain structure (terminal CF<sub>2</sub>H group versus CF<sub>3</sub>, in particular) on the formation of water-in-CO<sub>2</sub> microemulsions have been investigated [83]. The relations established between the aqueous surface tension of *F*-surfactants and their ability to stabilize CO<sub>2</sub> microemulsions should facilitate the rational design of highly efficient, low cost CO<sub>2</sub>-philic surfactants [84].

#### 12.1.5.3 Fluorocarbon Microbubbles

Injectable aqueous dispersions of FC-stabilized gaseous micron-size bubbles, most of which can be considered as emulsions of gases in water, have recently been developed as contrast agents for ultrasound imaging [6, 7]. By providing a more accurate and reliable diagnosis at relatively low cost with respect of other imaging techniques, these agents are likely to play a significant role in patient care. The role of FCs in these products was to oppose the rapid dissolution of the gaseous microbubbles in the blood due to the combined action of Laplace pressure, arterial pressure, oxygen metabolism, and ultrasound waves. FCs provide the unique combination of low solubility in water and high vapor pressure that was needed to achieve bubble stabilization.

#### 12.1.6

##### Fluorocarbon Polymers

Fluorine-containing polymers are widely used for their uniquely low friction, high thermal and electrical insulation properties and chemical inertness. They can be applied to a variety of surfaces or manufactured into thin films. In order to improve the solubility of *F*-polymers in solvents or to promote their self-association, as well as for cost-effectiveness reasons, hybrid polymers with non-fluorinated moieties have been synthesized. The most recent investigations on the rheological and colloidal properties of a variety of fluorinated homopolymers and block copolymers have been reported [85, 86]. The synthesis, self-assembly and rheological properties in aqueous solutions of *F*-side-chain and *F*-end-capped associative polymers have also been recently reviewed [87].

A range of fluorinated dendrimers has recently been developed [88]. These “molecular colloids” have potential applications as nanoreactors, in catalysis and for biomedical applications. One particular dendrimer has been used to extract a polar ionic dye from water into supercritical CO<sub>2</sub> [89].

The behavior of living organisms, proteins, cell organelles and cells is based on the cooperation of specialized and miniaturized functional subunits. The concept of multicompart-

ment polymerized micelles was devised in the mid-1980s by Ringsdorf as a simple model of complex natural systems. The various approaches to these multicompartment polymerized micelles have recently been analyzed [90].

#### 12.1.7

### Conclusions and Perspectives

Highly fluorinated compounds provide behavior that is not seen and performances that are not reached by *H*-analogs. Most unique is the antipathy between FC and HC molecules or moieties that allows phase separation (macro, micro and nano) and endows colloidal systems with special properties. These properties may be exploited to control syntheses in fluorous phases. The presence of *F*-amphiphiles in a medium, including in the form of *F*-alkylated substrates, reagents or byproducts can significantly alter the structure of this medium, hence its properties.

Further fundamental work in *F*-colloid chemistry is needed in order to improve control of the properties of self-assemblies and adaptation of them to specific applications. Despite unmatched performances, the obstacles on the path to the development of highly fluorinated materials are numerous. They include a number of economical and environmental issues and, when use in living organisms is contemplated, a perceived *alien* character. The still limited knowledge of the *in vivo* behavior of *F*-surfactants and lipids certainly hinders the development of fluorinated micelles, liposomes, emulsions or dendrimers for therapeutic uses. The approval by health authorities of injectable FC-based microbubbles for diagnosis may help change this situation. Minimizing the number of fluorine atoms needed to achieve the targeted material properties, such as for applications related to self-assembled monolayers or chemistry in supercritical CO<sub>2</sub>, is a definite trend as it reduces cost.

Fluorine chemistry provides unique building blocks and components for materials and biomedical sciences, whether for research or applications in industry and medicine. Conversely, *F*-self-assemblies and *F*-colloids represent for fluorine chemistry a logical and inescapable step towards increased complexity, thus participating in the evolution of chemistry from molecules to molecular assemblies, from designing structures to seeking specialized functions.

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## 12.2 Fluorous Nanoparticles

*Marcial Moreno-Mañas and Roser Pleixats*

### 12.2.1 Introduction

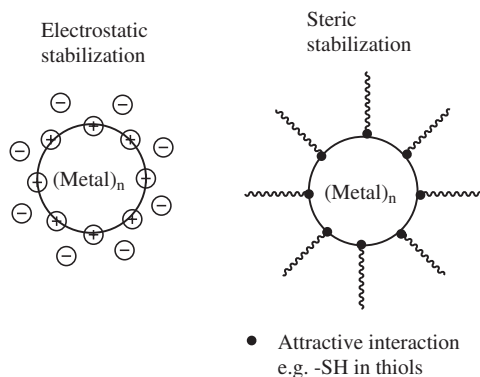
The preparation, structure determination, and possible applications of metallic nanoparticles have attracted a great deal of attention in the last ten years [1]. In general metallic nanoparticles are defined as having: (1) a diameter of 1 to 50 nm, and (2) a surrounding shell of a suitable agent that prevents their agglomeration [1b]. Nanoparticles are in the size realm where metals and their oxides, halides, and chalcogenides can show size-dependent properties. Thus, physicists wonder what is the minimal size of a fragment of metal (e.g., how many atoms) necessary for the metal to lose its known bulk properties, and which new properties are to be found. On the other hand, the smaller the cluster of atoms, the higher is the percentage of atoms in the surface (high specific surface), and this renders nanoparticles very interesting in catalysis [1f, k].

Two key issues arise when thinking about nanoparticles. The first is how nanoparticles are formed and the second is why they do not agglomerate to form higher aggregates with bulk metal properties. Metal nanoparticles, not binary combinations, can be formed by: (1) chemical reduction of a metal salt; (2) thermal, photochemical, or sonochemical decomposition of a metal(0) complex; (3) hydrogenation of an unsaturated ligand, the metal being liberated upon saturation of the coordinating olefinic moiety; and (4) vapor phase deposition. To this list proposed by Bradley [1b] should be added (5), electrochemical reduction of higher valence species of the metal [1i, 2].

Nanoparticles are formed by a process consisting of the following steps: (1) generation of atoms; (2) nucleation to form a cluster of atoms; (3) growing of the cluster to reach a certain volume; and (4) surrounding by a protecting shell that prevents agglomeration.

Of course size and dispersity are significant properties, which are usually determined by transmission electron microscopy (TEM).

Therefore, the nanoparticles ought to be generated in the presence of one such protecting agent. The protecting agents can be broadly divided into two categories: those that provide electrostatic and those that provide steric stabilization. The electrostatic stabilization is based upon the double electric layer formed when some ions of the same sign are adsorbed at the nanoparticle surface (the charges in Figure 12.2-1 could be inverted). The counterions form a second layer that repels the neighboring nanoparticle; for example sodium citrate acts by this mechanism. In other cases protecting molecules of considerable length interact in an attractive manner with the surface of the nanoparticle. The volume of the surrounding molecules prevents mutual approximation of metal surfaces at bonding distance. Popular protecting agents are polymers [for example polyvinylpyrrolidone, (PVP)], cyclodextrines, dendrimers, and so forth. Particularly well known is the mechanism of stabilization by large molecules possessing a functional group with high affinity for the metal: thiols, sulfides, amines, phosphanes. Other common stabilizers are some cationic and anionic surfactants,



**Fig. 12.2-1.** Possible mechanisms of nanoparticle stabilization

for example, lauryltrimethylammonium chloride and sodium dodecylsulfate. They protect nanoparticles by both electrostatic and steric mechanisms (Figure 12.2-1).

Organic compounds heavily or totally (per) fluorinated can also stabilize metallic nanoparticles. This is intriguing since perfluorinated carbon chains are reputable because of their low affinity towards many materials and towards themselves. Thus, non-stick pans are often coated with poly(tetrafluoroethylene) (PTFE) commonly known as Teflon®. As another example it should be recalled that the boiling point of perfluoroheptane (82 °C) is lower than the boiling point of heptane (92 °C) [3].

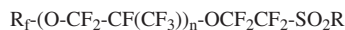
Examples have been reported of metallic nanoparticles (pure metal or binary combinations) stabilized by heavily fluorinated compounds. In some cases the fluorinated compounds also possess a functional group with high affinity for the metal (for example, thiols). In these cases the stabilization probably takes place mainly by attractive interaction of the sulfur atom with the metal surface, the poly- or perfluorinated chains playing a steric role as well as contributing repulsive interactions with the surroundings. In cases in which the ancillary functional group, thiol or others, are absent, it is more difficult to understand how the protecting agent sticks to the metal surface. This chapter deals with such a curious situation of metal (and binary combinations) nanoparticles being protected by heavily fluorinated compounds. By heavily we mean something more than a simple  $\text{CF}_3$  group in a molecule or in a polymer.

This chapter deals with a multidisciplinary field; papers frequently focus on many different topics but not specifically on the protecting fluorine-containing shell. Therefore, it is possible that the “less chemical papers” could have escaped our attention. A prudent “and references cited therein” should be added to the cited works. Small clusters with well-defined stoichiometry, such as,  $\text{Ru}_3(\text{CO})_{12}$ ,  $\text{Au}_{55}(\text{PPh}_3)_{12}\text{Cl}_6$ , and the like will not be considered.

### 12.2.2

#### Metal Nanoparticles

Table 12.2-1 contains examples found in our literature search dealing, in one form or another, with “perfluor”, “fluoro” or “fluorinated” “nanoparticle”, “cluster”, or “colloid”.



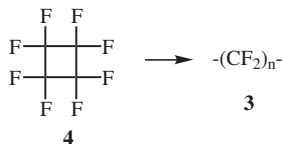
**1a**, R = OH: Nafion™; **1b**, R = NHSO<sub>2</sub>CF<sub>3</sub>

Polymers used in entries 1-7 of Table 12.2-1

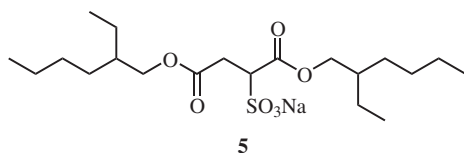


**2**: Polytetrafluoroethylene (PTFE)

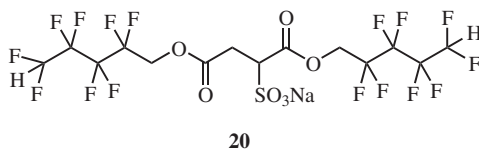
Polymers used in entries 8,9, and 12 of Table 12.2-1



Generation of polymer in entry 10



Surfactants used for nanoparticles in water-in-CO<sub>2</sub> emulsions  
Entries 13-15 in Table 12.2-1



Surfactant used for CdS and ZnS nanoparticles in Ref. [53]

**Scheme 12.2-1.** Some heavily fluorinated compounds used for metal nanoparticle stabilization

Nafion®, **1a**, (Scheme 12.2-1) has been extensively used as a stabilizer of metal nanoparticles. Nafion® is a strong sulfonic acid made of a polymer of perfluoropropylene oxide. It forms ionomeric films that permit protons to cross through. Some examples are in entries 1–7 of Table 12.2-1.

Evolution of hydrogen by oxidation of chromium(II) with protons can be achieved under catalysis by colloidal silver anchored in Nafion® resin (entry 1 in Table 12.2-1) [4]. The silver nanoparticles were formed by hydrogenation of Ag<sup>+</sup> in the presence of water.

In 1993 Mills and coworkers reported the preparation of silver nanoparticles by reduction of silver nitrate with isopropanol in basic media (entry 2) [5]. If Nafion® is present in the preparation procedure the particles were deposited on it. This silver is oxidized to Ag<sub>2</sub>O in the presence of air and upon exposure to UV light. The same group described the preparation of gold nanoparticles on Nafion® by reduction of chloroaurate (AuCl<sub>4</sub><sup>−</sup>) with basic methanol (entry 3) [6].



Tab. 12.2-1. Metal nanoparticles stabilized by heavily fluorinated compounds

Entry	Main author	Ref.	Catalyzed reaction	Metal (diameter nm)	Generation. Protecting shell	Observations
1	Lee, Meisel	[4]	$\text{Cr}^{2+} + \text{H}^+ \rightarrow \text{Cr}^{3+} + \frac{1}{2}\text{H}_2$	Ag (7)	Hydrogenation of Ag(I), Nafion®, 1a	Non-electrochemical production of hydrogen
2	Mills	[5]	none	Ag (7.4)	Reduction.	Cubic silver. It is oxidized to $\text{Ag}_2\text{O}$ by air/ $h\nu$ 290 nm
3	Mills	[6]	none	Au (57)	Nafion®, 1a (MW 1100) Reduction.	Kinetics of particles formation
4	Aberdam	[7]	$\text{CO} \rightarrow \text{CO}_2$	$\text{Pt}_{50}\text{Ru}_{50}$ (2)/ C	Nafion®, 1a (MW 1100) Nafion®, 1a (MW 1100)	Bimetallic composite deposited over Nafion® to prepare working electrodes
5	Antoine, Durand, Gloaguen	[8–10]	$\text{O}_2 \rightarrow \text{H}_2\text{O}_2$ methanol oxidation	Pt/C (1.2–4.4)	Electrochemical reduction. Nafion®	Composite of Pt/C deposited over Nafion® to modify electrodes
6	Solorza-Feria	[11]	$\text{O}_2 \rightarrow \text{H}_2\text{O}$	Ru (5–15)	Thermal decomp of $\text{Ru}_3(\text{CO})_{12}$ .	Composite of Ru/C deposited over Nafion® on a carbon rotating disk electrode
7	Sun	[12]	none	Ag (13)	Reduction. Nafion® (MW 1100), 1a, and 1b	Silver hosted in the structural cavities of Nafion®
8	Foss	[14]	none	Au	Reduction $\text{C}_{12}\text{H}_{25}\text{SH}$	Thiol-protected nanoparticles embedded in PTFE
9	Smirnov	[15]	isomerization of dichlorobutenes	Fe	Thermal decomp. of $\text{Fe}(\text{CO})_5$ , PTFE	
10	Dalacu, Martinu	[16]	none	Au	Gold sputtering. 3, polymer from 4	Spectroellipsometric characterization. Plasma polymerization of $\alpha\text{-C}_4\text{F}_8$ , 4
11	Kay	[17]		Co (5–25) Al	Metal and $\text{C}_3\text{F}_8$ cosputtering. Polymer from $\text{C}_3\text{F}_8$	Size depends on the $\text{C}_3\text{F}_8/\text{Ar}$ ratio
12	Torsi, Convertino	[18]	none	Au	Gold and PTFE sputtering	Analysis of chemical composition of shell

13	Wai	[20]	none	Ag (5–15)	Reduction. 5 + 6	Nanoparticles in the water core of a water-in-CO <sub>2</sub> emulsion
14	Wai	[21]	none	Ag (5–15) Cu (5–15)	Reduction. 5 + 6	Nanoparticles in the water core of a water-in-CO <sub>2</sub> emulsion
15	Wai	[22]	Hydrogenation of alkenes and of nitrobenzene to aniline	Pd (5–10)	Hydrogenation. 5 + 6	Nanoparticles in the water core of a water-in-CO <sub>2</sub> emulsion
16	Johnston, Korgel	[25]	none	Ag (5.5)	Reduction. C <sub>8</sub> F <sub>17</sub> CH <sub>2</sub> CH <sub>2</sub> SH	
17	Yonezawa, Kimizuka	[26]	none	Ag (2.5)	Reduction. C <sub>8</sub> F <sub>17</sub> CH <sub>2</sub> CH <sub>2</sub> SH	Careful description of the purification procedure
18	Yonezawa, Kimizuka	[27]	none	Au (2.5)	Reduction. C <sub>n</sub> F <sub>2n+1</sub> CH <sub>2</sub> CH <sub>2</sub> SH ( <i>n</i> = 6, 8)	As for entry 17.
19	Kim	[28]	none	Ag (5)	Thermal decomp. of R <sub>f</sub> COOAg (C <sub>12</sub> –C <sub>18</sub> )	See text
20	Crooks	[32]	Hydrogenation of alkene	Pd	Reduction. 8 ≡ PAMAM + 9	Recovered 12 times in a biphasic solvent system toluene/FC75 (fluorinert, 10)
21	Crooks	[34]	Heck reaction	Pd (2.1)	Reduction. Dendrimer 11	Recovered in a biphasic solvent system heptane/FC75 (fluorinert, 10)
22	Crooks	[35]	Hydrogenation of alkene; Heck reaction	Pd	Reduction. Dendrimers 8 and 11	Review articles covering also non-fluorous nanoparticles
23	Klabunde	[36]	none	Au (3.4–5)	Metal atom vapor deposition on N(C <sub>4</sub> F <sub>9</sub> ) <sub>3</sub>	Precursors for thin films
24	Moreno-Mañas	[37]	Heck reaction	Pd (4–5)	Reduction. 12	Recovery in biphasic solvent systems
25	Moreno-Mañas	[38]	Suzuki coupling	Pd (see text)	Reduction. 13–16	
26	Gladysz	[41]	Heck reaction	Pd	Formation from 19. Possibly R <sub>3</sub> NH <sup>+</sup>	Full paper in entry 27 Remarkable high TON values
27	Gladysz	[42]	Heck reaction Suzuki coupling	Pd	Formation from 19 and from 20. Possibly R <sub>3</sub> NH <sup>+</sup>	Remarkable high TON values

Owing to its ionomeric character Nafion® has found extensive application in the stabilization of metal nanoparticles used in the construction of electrodes for electrochemical reactions requiring the transfer of protons. Thus, Aberdam et al. reported the preparation of working electrodes made from carbon-supported Pt<sub>50</sub>Ru<sub>50</sub> nanoparticles deposited in Nafion® for the electro-oxidation of carbon monoxide (entry 4) [7].

Electrochemical reduction of platinum(IV) [8] produced nanoparticles supported on carbon and inside Nafion® that have been used for the electrochemical reduction of oxygen [9] and for the electrocatalytic oxidation of methanol [10] at the metal/ionomer interface (entry 5). The last studies have implications in the construction of methanol fuel cells.

Ruthenium nanoparticles prepared by thermal decomposition of Ru<sub>3</sub>(CO)<sub>12</sub> were deposited on Nafion® and the thin layer so prepared was deposited on a glassy carbon rotating disk electrode for studies on the electrochemical four-electron reduction of oxygen (entry 6) [11].

Owing to the beneficial properties of electrodes modified by nanoparticles embedded in Nafion®, it is important to know how metal nanoparticles are bound to Nafion® membranes. The answer can be found in a paper by Sun et al. who have prepared silver nanoparticles by reduction of silver nitrate with sodium borohydride (NaBH<sub>4</sub>) as well as silver sulfide nanoparticles (*vide infra*) (entry 7) [12]. They reported that structural cavities in ionomer membranes serve as excellent templates for the formation of nanoparticles, or, in other words, nanoscale silver particles are hosted in the structural cavities of Nafion® membranes. The related sulfonimide ionomer **1b** behaves similarly.

A patent related to noble metal-containing nanoparticles deposited in ionomeric fluorinated polymers for producing membrane electrode assemblies has been published [13].

Poly(tetrafluoroethylenes) (PTFE) **2** (Scheme 12.2-1), have been used for stabilization or deposition of metal nanoparticles. Thus, Foss et al. have reported that dodecylthiol (C<sub>12</sub>H<sub>25</sub>-SH) stabilized gold nanoparticles can be embedded in PTFE (entry 8) [14]. In this case the SH termination of the thiol is responsible of the particle stabilization rather than the perfluorinated support. The gold particles were prepared by the classical reduction of chloroauric acid (HAuCl<sub>4</sub>) with sodium borohydride.

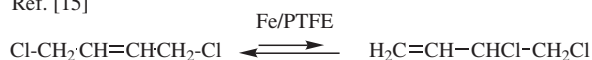
Smirnov et al. have reported iron-containing composites made by the thermal decomposition of Fe(CO)<sub>5</sub> on a solution-melt of PTFE. The resulting metallopolymeric material was tested as a catalyst for the isomerization of dichlorobutenes (entry 9, Scheme 12.2-2) [15].

Dalacu and Martinu have used another perfluoro-stabilizer for gold. It can be better described as -(CF<sub>2</sub>)<sub>n</sub>-, **3**, or -(CF<sub>2</sub>)<sub>4n</sub>- since it is formed by plasma polymerization of perfluorocyclobutane, **4** (Scheme 12.2-1). The composite films are formed by simultaneous plasma polymerization of **4** and gold sputtering onto glass substrates (entry 10) [16]. The authors described an ellipsometric characterization of the material as an alternative to the classical transmission electron microscopy (TEM) for determining the size and dispersion of the nanoparticles.

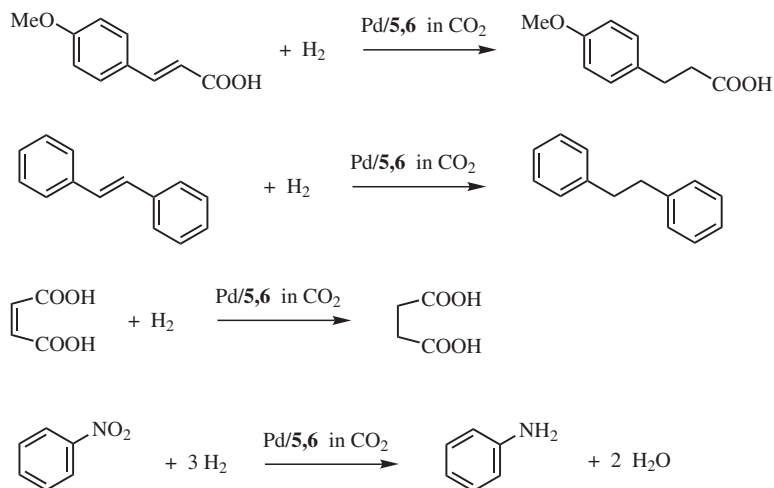
Cobalt or aluminum clusters can be formed in plasma polymerized fluorocarbon films by co-sputtering the metal and a mixture of perfluoropropane and argon (entry 11) [17]. The size of the particles depends on the [C<sub>3</sub>F<sub>8</sub>]/[argon] ratio. At higher ratios cobalt(II) fluoride particles are also formed together with cobalt.

Torsi and Convertino et al. have prepared another example of gold-PTFE nanocomposite [18]. CF<sub>x</sub>Au samples were deposited on silicon substrates by co-sputtering PTFE and gold

Entry 9  
Ref. [15]



Entry 15  
Ref. [22]



**Scheme 12.2-2.** Some reactions catalyzed by metal nanoparticles stabilized by fluoruous compounds

targets with Ar<sup>+</sup> ion beams at room temperature and a pressure of 10<sup>-4</sup> mbar (entry 12). The X-ray photoelectron spectroscopy of the fluorocarbon polymer revealed that it contains not only CF<sub>2</sub> and CF<sub>3</sub> groups but also CF, C=CF, C-CF, and C-C in a fluorinated environment. Therefore, a PTFE target can suffer alterations on co-sputtering with a gold target with Ar<sup>+</sup> ion beams.

A review on the properties of metal nanoparticle-polymer composites, including PTFE has been published [19].

Wai and coworkers have reported an interesting method for stabilization of metal nanoparticles in liquid and supercritical CO<sub>2</sub>. The particles are kept in the water core of a water-in-CO<sub>2</sub> microemulsion. The stabilizing shell is made of two surfactants, the conventional sodium bis(2-ethylhexyl)sulfosuccinate, **5**, and the polyfluorinated polyether-phosphate **6** (Scheme 12.2-1). The role of **6** seems to be two-fold: it renders the system soluble in CO<sub>2</sub>, and it provides the nanoparticles with a shell that reduces the interdroplet attractive interactions. This method has permitted the preparation of silver (entries 13 and 14) [20, 21] and copper [21] (entry 14) nanoparticles by reduction of silver nitrate with modified sodium borohydrides [NaBH(OAc)<sub>3</sub> or NaBH<sub>3</sub>CN] or *N,N,N,N*-tetramethyl-*p*-phenylenediamine (TMPD) and of copper nitrate with TMPD.

The group of Wai has also reported the preparation of palladium nanoparticles in the same water-in-CO<sub>2</sub> system by hydrogenation of palladium(II). The formed nanoparticles catalyze the hydrogenation of several olefins such as *p*-methoxycinnamic acid, *trans*-stilbene and maleic acid as well as the hydrogenation of nitrobenzene to aniline (entry 15, Scheme 12.2-2) [22].

Thiols are classical stabilizers of transition-metal nanoparticles [23]. Brust and co-workers have determined by <sup>1</sup>H NMR the fate of the sulfur-bound hydrogen in dodecylthiol-stabilized gold particles and concluded that intact thiols are adsorbed to the gold clusters [24].

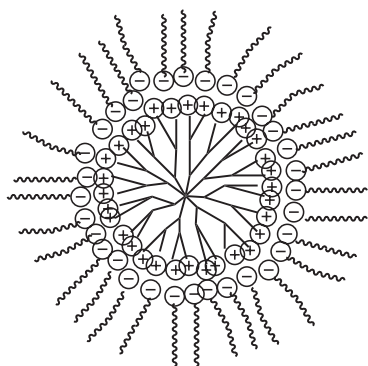
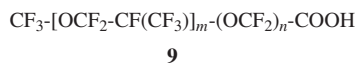
Fluorinated thiols C<sub>8</sub>F<sub>17</sub>CH<sub>2</sub>CH<sub>2</sub>-SH and C<sub>6</sub>F<sub>13</sub>CH<sub>2</sub>CH<sub>2</sub>-SH have been successfully applied to the preparation of silver (entries 16 and 17) [25, 26] and gold (entry 18) [27] nanoparticles. The description of the careful purification procedure by the group of Yonezawa and Kimizuka is noteworthy [26, 27]. The same group recommended the use of HCFC-225 or AK-225 (mixture of CF<sub>3</sub>CF<sub>2</sub>CHCl<sub>2</sub> and CF<sub>2</sub>ClCF<sub>2</sub>CHFCl, 7), fluid of low surface tension, as dispersal medium for TEM determinations. In the three cases the metal(0) was generated by reduction of silver nitrate [25] or perchlorate [26] and of chloroauric acid [27] with sodium borohydride.

The thermal decomposition of silver perfluoroalkancarboxylates [AgOCO(CF<sub>2</sub>)<sub>*n*</sub>CF<sub>3</sub>, *n* + 2 = 12, 14, 16, 18] produced silver nanoparticles. The exact nature of the silver/shell interface is not clear although the authors suggested that carboxylate groups are symmetrically bound to the surface of silver via their two oxygen atoms (entry 19) [28].

The high specific surface of nanoparticles renders these materials potentially useful in catalysis [1f, k]. Two examples of catalysis by nanoparticles have already been mentioned in this chapter [15, 22]. More have been reported by Crooks and coworkers, who have encapsulated palladium nanoparticles, generated by reduction of palladium(II) with sodium borohydride, in the interior of fourth-generation amine-terminated poly(amidoamine) PAMAM dendrimers [29, 30]. The metal is simply entrapped within the branches of the dendrimer. Moreover, this fourth generation dendrimer has 32 amino groups in periphery and it is soluble in toluene and in heptane containing dodecanoic acid since an acid-base self-assembly is formed featuring the dodecanoic acid lipophilic moiety. This material is active in the hydrogenation of olefins [31] although recovery was not mentioned. The recovery problem was addressed by proton transfer between the PAMAM dendrimer and perfluoroacid **9** (Scheme 12.2-3). The palladium nanoparticles entrapped inside assembly **8** catalyze hydrogenation of olefins and were recovered in the fluorine layer of a biphasic solvent system toluene/perfluoro-2-butyltetrahydrofuran, **10** (Fluoroinert FC-75) and reused 12 times (entry 20) [32, 33].

A further step by the group of Crooks is the modification of 4th and 5th generation of poly(propylene imine) PPI dendrimers (32 and 64 amino groups in periphery) as amides with perfluoroacid **9** to give structure **11** (Scheme 12.2-3), fully covalent as opposed to **8** (entry 21) [34]. Structure **11** encapsulates palladium nanoparticles and the assembly catalyzes Heck reactions of iodoarenes with butyl acrylate. The palladium-in-dendrimer was recovered in the fluorine layer of the biphasic solvent system heptane/**10**, but the recovered material showed decreased catalytic activity upon successive recovery/catalysis cycles. Reviews on the palladium-in-dendrimer work by Crooks' group, both fluorine and non-fluorine, have been published (entry 22) [35].

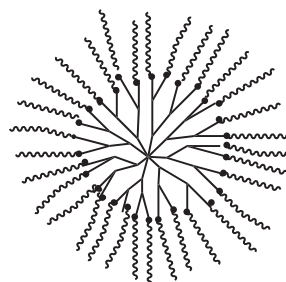
Entries 20-22  
References [32], [34], [35]



= anion of 9

8

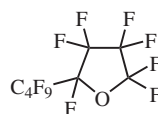
4th Generation PAMAM dendrimer  
has 32 amino groups in periphery.



amides from 9  
and PPI

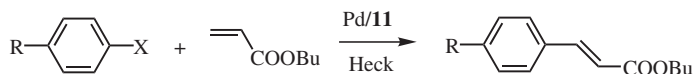
11

4th Generation PPI dendrimer  
has 32 amino groups in periphery.



10: FC-75

Hydrogenation of several alkenes  $\xrightarrow{\text{Pd/8}}$



R = H, NO<sub>2</sub>; X = I, Br

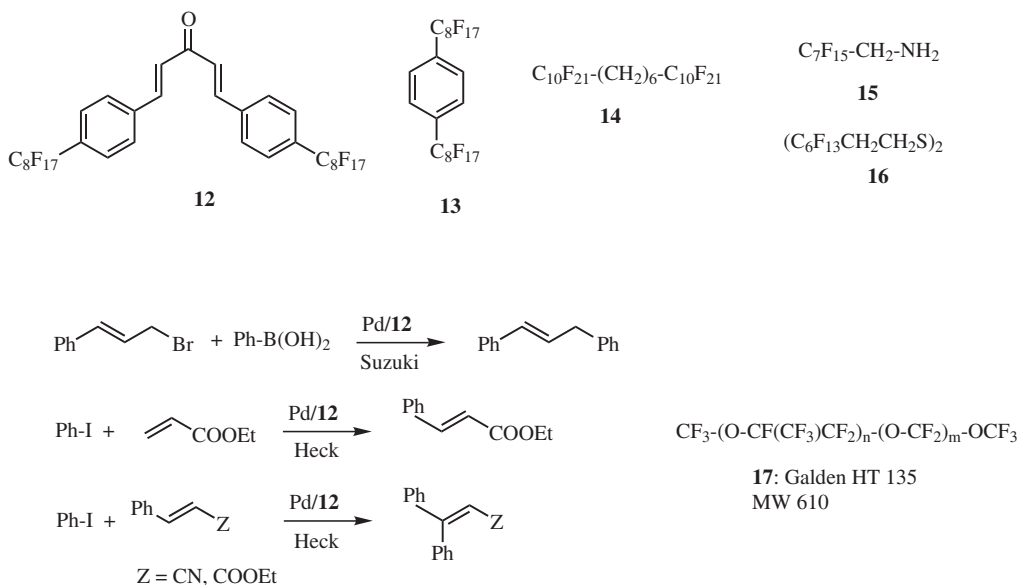
**Scheme 12.2-3.** Reactions catalyzed by palladium nanoparticles entrapped in dendrimers 8 and 11

Klabunde et al. reported the clustering of gold atoms in perfluorotributylamine (entry 23) [36]. The method is conceptually very simple. It consists of the thermal vaporization of the metal and depositing the atoms in the perfluoroamine at 77 K. The infrared and the <sup>19</sup>F NMR spectra of the particles revealed that the perfluorotributyl amine had been altered despite the mild method of preparation. These particles are soluble in acetone and when recovered the elemental analysis showed that the solvent had been incorporated into the protecting shell, together with the amine.

Our group reported the generation of palladium nanoparticles stabilized by ketone 12 by reduction of PdCl<sub>2</sub> with methanol (entry 24, Scheme 12.2-4) [37]. This method, when

Entries 24,25

References [37], [38]

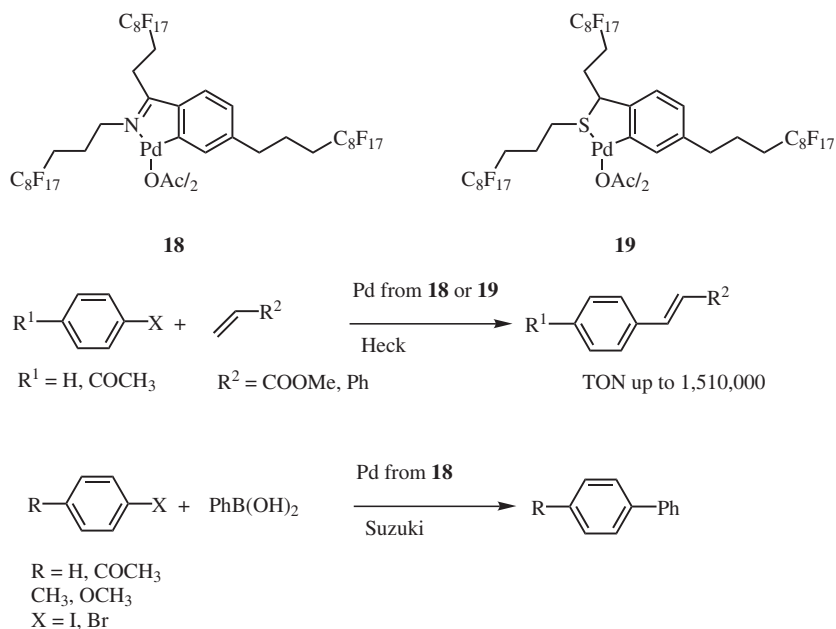
**Scheme 12.2-4.** Suzuki and Heck reactions catalyzed by palladium nanoparticles stabilized by **12**

applied to bis(dibenzylidene)acetone (H instead of  $\text{C}_8\text{F}_{17}$  in **12**), produces a discrete palladium(0) complex  $[\text{Pd}(\text{dba})_2]$  that is used as a precatalyst in many palladium-catalyzed reactions. The nanoparticles catalyzed Suzuki-type couplings and Heck reactions and could be recovered and reused without loss of activity in the biphasic solvent systems benzene/1-bromoperfluorooctane (Suzuki coupling) or acetonitrile/Galden HT 135 (**17**) (Heck reactions).

Compounds **13–16** also stabilized palladium nanoparticles (entry 25) [38]. Although stabilization by **15** and **16** can be attributed to the functional groups, this is not possible for **13** and especially for **14**. It is noteworthy that the *ortho*- and *meta*-isomers of **13** did not stabilize nanoparticles under identical experimental conditions for palladium(II) reduction. No clear explanation for these observations can be offered so far. The same type of compounds also stabilize gold nanoparticles [39].

Gladysz et al. have investigated the use of complexes of palladium(II) with fluorous dialkyl sulfides [40] as well as fluorous imine [41] and thioether [40, 42] palladacycles **18** and **19** as precatalysts for the Suzuki coupling and Heck reaction (entries 26 and 27, Scheme 12.2-5). They presented evidence that palladium nanoparticles are the actual catalysts, but these nanoparticles are soluble in DMF rather than in fluorous solvents. Therefore, **18** acts mainly as a steady-state source of extremely reactive, soluble-in-DMF palladium nanoparticles, plausibly non-fluorous in nature and stabilized by ammonium ions during the Heck reactions. The high TON are remarkable.

Entries 26,27  
References [41], [42]



**Scheme 12.2-5.** Catalysis by nanoparticles generated from palladacycles **18** and **19**

### 12.2.3

#### Nanoparticles of Metal Oxides, Halides, and Chalcogenides

Many of the fluorinated agents discussed above for the protection of metal nanoparticles are useful also for metallic oxides, halides, and chalcogenides. The methods of preparation of these new particles are, of course, different.

Thus, Nafion® has been used extensively. Sun and coworkers, in a paper already commented upon [12], described the formation of silver sulfide ( $\text{Ag}_2\text{S}$ ) nanoparticles hosted in the structural cavities of Nafion®. They were formed by immersion of the Nafion® film first in aqueous silver nitrate and, after drying, in aqueous sodium sulfide (entry 1 in Table 12.2-2, Scheme 12.2-6).

The same preparation technique was adopted by Nagamura et al. to prepare cadmium sulfide ( $\text{CdS}$ ) nanoparticles by immersion of the Nafion® film in cadmium chloride, drying, and immersion in sodium sulfide in the indicated order. Alternatively, the sodium sulfide immersion can be replaced by exposure to ammonia and hydrogen sulfide [43]. The authors found size-dependence in the ultra-fast dynamics of transient photobleaching upon excitation with a femtosecond laser at 400 nm (entry 2).

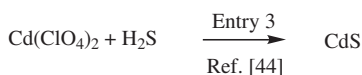
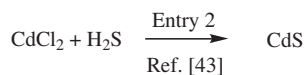
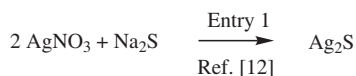
Size-dependence was also observed in photoetching with  $\text{CdS}$  nanoparticles made by immersion of Nafion® in  $\text{Cd}(\text{ClO}_4)_2$  solution, drying, and exposure to  $\text{SH}_2$  (entry 3) [44].



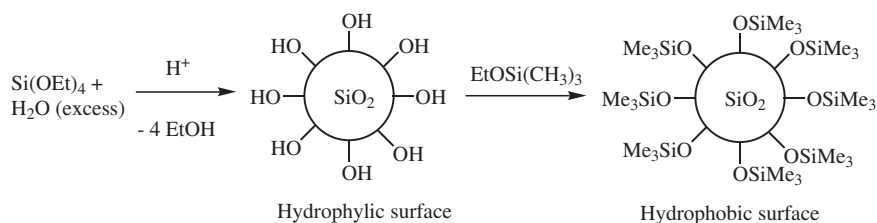
Tab. 12.2-2. Oxides, halides and sulfides nanoparticles stabilized by heavily fluorinated compounds

Entry	Main author	Ref.	Metal (diameter nm)	Protecting shell	Observations
1	Sun	[12]	Ag <sub>2</sub> S (10.5)	Nafion® (MW 1100), <b>1a</b> , and <b>1b</b>	Silver sulfide hosted in the structural cavities of Nafion®
2	Nagamura	[43]	CdS (2.7–4.9)	Nafion® (MW 1100), <b>1a</b>	Ultra-fast dynamics of transient bleaching of CdS nanoparticles
3	Yoneyama	[44]	CdS (8.9–24)	Nafion®, <b>1a</b>	Size-selective photoetching for particles of <12 nm
4	Mauritz	[45]	SiO <sub>2</sub>	Nafion®, <b>1a</b>	Sol–gel preparation by hydrolysis of Si(OEt) <sub>4</sub> (TEOS)
5	Mauritz	[46]	SiO <sub>2</sub> –TiO <sub>2</sub> and SiO <sub>2</sub> –Al <sub>2</sub> O <sub>3</sub>	Nafion®, <b>1a</b>	Simultaneous or successive hydrolysis of TEOS and Ti(OBu) <sub>4</sub> or Al(O-s-Bu) <sub>3</sub>
6	Several	[47–49]	Several metal oxides	PTFE, <b>2</b>	PTFE filled with metal oxides shows modified mechanical and other properties
7	Kim	[50]	TiO <sub>2</sub>	Copolymer of CH <sub>2</sub> =CF <sub>2</sub> /CF <sub>3</sub> CF=CF <sub>2</sub>	
8	Lamparth, Szabó	[51]	Several metal oxides	Compounds in Scheme 12.2-7 or derived polymers	Microwave Plasma Process of nanoparticle generation
9	Wai	[52, 53]	AgCl, AgBr, AgI, ZnS, CdS	<b>5 + 6</b> or <b>20</b>	Nanoparticles in a water-in-CO <sub>2</sub> emulsion
10	Johnston, Korgel	[54]	CdS (1.8–3.6)	<b>21</b>	Semiconductor nanoparticles have size-dependent properties. Nanoparticles in a water-in-CO <sub>2</sub> emulsion
11	Johnston	[55]	TiO <sub>2</sub> (9–18)	<b>21</b> and <b>22</b>	Sol–gel preparation by hydrolysis of Ti(O-isoPr) <sub>4</sub>

Mauritz et al. have described the growth of SiO<sub>2</sub> by the sol–gel procedure within or over Nafion® films (entry 4) [45]. This method consists of hydrolysis of tetraethyl orthosilicate (TEOS) to form the network of SiO<sub>2</sub> *in situ*. The peripheral silicon contains free OH groups that by reaction with excess diethoxydimethylsilane [(CH<sub>3</sub>)<sub>2</sub>Si(OEt)<sub>2</sub>] or ethoxytrimethylsilane (CH<sub>3</sub>)<sub>3</sub>SiOEt are capped as silicon ethers. The uncapped free OH groups



Sol-gel procedure; Entries 4, 5; Ref. [45], [46]



**Scheme 12.2-6.** Some reactions performed on Nafion® films

give hydrophilicity to the surface whereas the capped ones confer hydrophobicity (Scheme 12.2-6).

The simultaneous or consecutive sol-gel process can be applied to TEOS and a second alkoxide of a different metal. This is the method of Mauritz to prepare perfluorosulfonate ionomer/[SiO<sub>2</sub>-TiO<sub>2</sub>] or [SiO<sub>2</sub>-Al<sub>2</sub>O<sub>3</sub>] nanocomposites (entry 5) [46].

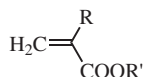
Composites of PTFE, **2**, with metal oxides have been described. The materials are considered as PTFE filled with the metal oxide and in general, they are prepared by mechanical mixing. Thus, PTFEs filled with the following oxides have been prepared for studying the indicated properties: with zinc oxide powder (50 nm) for their friction and anti-wear properties [47]; with Al<sub>2</sub>O<sub>3</sub>, and with SiO<sub>2</sub>, TiO<sub>2</sub>, Al<sub>2</sub>O<sub>3</sub>, and ZrO<sub>2</sub> for their mechanical properties [48]; with TiO<sub>2</sub> for their exceptional diffuse reflectivity (entry 6) [49].

A related polymer, poly(vinylidene fluoride-co-hexafluoropropylene) (from CH<sub>2</sub>=CF<sub>2</sub> and CF<sub>3</sub>CF=CF<sub>2</sub>) has been filled with TiO<sub>2</sub> and its properties pertinent for application to rechargeable lithium batteries have been studied (entry 7) [50].

A different method for coating nanoparticles with polymers is the Karlsruhe Microwave Plasma Process. This consists of introducing a vaporized metal precursor into an argon/oxygen microwave plasma where metal oxide particles are formed. The coating is achieved by introducing the coating or coating precursor after the plasma zone [51]. This method has been successful in preparing nanoparticles of ZnO, ZrO<sub>2</sub>, HfO<sub>2</sub>, Al<sub>2</sub>O<sub>3</sub>, TiO<sub>2</sub>, SnO<sub>2</sub>, and WO<sub>x</sub> coated by the fluorinated products indicated in Scheme 12.2-7 or derived polymers. Enhanced thermal and chemical stabilities, fluorescence, and permittivity of these materials have been measured (entry 8).

Two different groups have made halides and chalcogenide nanoparticles in the water-in-CO<sub>2</sub> medium. Thus, Wai and coworkers have prepared silver iodide (3.4 nm), bromide (3.0 nm), and chloride (size not determined) nanoparticles by mixing two water-in-CO<sub>2</sub>

## Acrylates

R = H, CH<sub>3</sub>R' = CH<sub>2</sub>C<sub>3</sub>F<sub>7</sub>, CH<sub>2</sub>CH<sub>2</sub>C<sub>8</sub>F<sub>17</sub>,  
CH<sub>2</sub>CH<sub>2</sub>C<sub>10</sub>F<sub>21</sub>

## Perfluoroalkanes

*n*-C<sub>12</sub>F<sub>26</sub>*n*-C<sub>20</sub>F<sub>42</sub>

PTFE

## Others

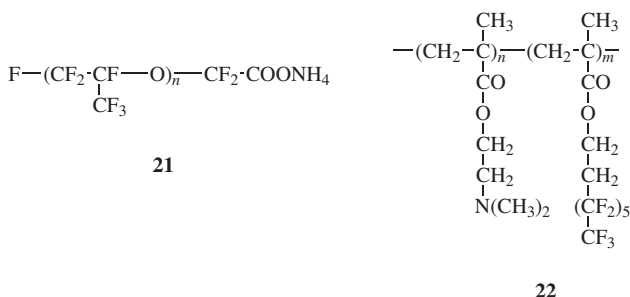
*n*-C<sub>11</sub>F<sub>23</sub>-COOCH<sub>3</sub>*n*-C<sub>10</sub>F<sub>21</sub>CH<sub>2</sub>CH<sub>2</sub>-I**Scheme 12.2-7.** Compounds used in reference [51] for coating metal oxide nanoparticles

emulsions, one containing silver nitrate and the other sodium halide [52]. The mixture of surfactants made with **5** and **6** stabilizes the system (entry 9).

In a related work Wai et al. reported the preparation of zinc and cadmium sulfide nanoparticles by mixing emulsions containing zinc or cadmium nitrate and sodium sulfide [53]. An interesting novelty is the use of fluorosurfactant **20** (Scheme 12.2-1) for stabilization of the system (entry 9).

Korgel, Johnston et al. have described cadmium sulfide semiconductor nanoparticles (1.8–3.6 nm) by injecting aqueous sodium sulfide into a water-in-CO<sub>2</sub> emulsion containing cadmium nitrate [54]. The stabilizing surfactant is the ammonium salt **21** (Scheme 12.2-8). The exciton energies of these materials are size-dependent (entry 10).

Johnson and coworkers have prepared TiO<sub>2</sub> nanoparticles (9–18 nm) by hydrolysis of titanium tetraisopropoxide [Ti(OCH(CH<sub>3</sub>)<sub>2</sub>)<sub>4</sub>] (sol-gel method) in the presence of either **21** or the fluorinated polymer **22** (Scheme 12.2-8) (entry 11) [55].

**Scheme 12.2-8.** Compounds used in references [54] and [55] for CdS and TiO<sub>2</sub> nanoparticles stabilization

Finally, stabilization of nanoparticles of metal binary combinations has been the subject of some patents. Those not specifically mentioned above can be found in the last reference [56].

**Acknowledgements**

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## 12.3

### Self-Assembly of Hybrid Fluorous Materials

*Pierangelo Metrangolo\*, Tullio Pilati, and Giuseppe Resnati\**

#### 12.3.1

##### Introduction

Perfluorocarbon (PFC) derivatives show a unique combination of physical properties and chemical reactivities, which account for some of their useful applications. Enthalpies of interaction between PFCs and hydrocarbons (HCs) are smaller than interaction enthalpies between HCs. For this reason, PFCs usually have a very low affinity for their analogous HC parents [1]. Specifically tailored patterns of intermolecular interactions are thus required if the PFC-HC recognition process is pursued to the point of triggering the intermolecular recognition and self-assembly of the two species into stable hybrid materials.

An attractive interaction occurs between halogen atoms, which work as electron acceptor sites (Lewis acids, halogen bond donors) and lone-pair possessing atoms, which work as electron donor sites (Lewis bases, halogen bond acceptors). This interaction was first recognized as early as two centuries ago [2]. The term “halogen bond” has been proposed for this interaction in order to stress the numerous analogies between its properties and those of the hydrogen bond [3]. Carbon-bound iodine, bromine, and chlorine atoms C–X (X = I, Br, Cl) effectively work as electron acceptor motifs and give rise to halogen bonded complexes C–X⋯B (X = I, Cl, Br; B = O, N, S, Se, I<sup>−</sup>, Br<sup>−</sup>, ...) with a wide variety of neutral or anionic electron donor motifs [4]. Recently, fluorine atoms of perfluoroalkanes have also been reported to work as electron acceptors when amines are used as bases [5]. The tendency to form strong complexes (I > Br > Cl > [F]) usually parallels the order of halogen atom polarizabilities, consistent with a key role for halogen polarization in the interaction [6].

The presence of electron withdrawing groups on halocarbon modules promotes the acidity of halogen atoms and, consequently, their tendency to form strong halogen bonds [6a, 7]. Fluorine atoms and perfluorinated residues are among the most powerful electron withdrawing groups [8] so that halo-PFCs form halogen bonds definitively stronger than the corresponding halo-HC. According to quantum chemical calculations (DFT and MP2), the interaction energies for the halogen bond between trimethylamine and iodomethane and between 4,4'-bipyridyl and 1,4-diiodobenzene are 2.8 and 3.3 kcal mol<sup>−1</sup>, respectively [9]. The

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## 12.3

### Self-Assembly of Hybrid Fluorous Materials

*Pierangelo Metrangolo\*, Tullio Pilati, and Giuseppe Resnati\**

#### 12.3.1

##### Introduction

Perfluorocarbon (PFC) derivatives show a unique combination of physical properties and chemical reactivities, which account for some of their useful applications. Enthalpies of interaction between PFCs and hydrocarbons (HCs) are smaller than interaction enthalpies between HCs. For this reason, PFCs usually have a very low affinity for their analogous HC parents [1]. Specifically tailored patterns of intermolecular interactions are thus required if the PFC-HC recognition process is pursued to the point of triggering the intermolecular recognition and self-assembly of the two species into stable hybrid materials.

An attractive interaction occurs between halogen atoms, which work as electron acceptor sites (Lewis acids, halogen bond donors) and lone-pair possessing atoms, which work as electron donor sites (Lewis bases, halogen bond acceptors). This interaction was first recognized as early as two centuries ago [2]. The term “halogen bond” has been proposed for this interaction in order to stress the numerous analogies between its properties and those of the hydrogen bond [3]. Carbon-bound iodine, bromine, and chlorine atoms C–X (X = I, Br, Cl) effectively work as electron acceptor motifs and give rise to halogen bonded complexes C–X⋯B (X = I, Cl, Br; B = O, N, S, Se, I<sup>−</sup>, Br<sup>−</sup>, ...) with a wide variety of neutral or anionic electron donor motifs [4]. Recently, fluorine atoms of perfluoroalkanes have also been reported to work as electron acceptors when amines are used as bases [5]. The tendency to form strong complexes (I > Br > Cl > [F]) usually parallels the order of halogen atom polarizabilities, consistent with a key role for halogen polarization in the interaction [6].

The presence of electron withdrawing groups on halocarbon modules promotes the acidity of halogen atoms and, consequently, their tendency to form strong halogen bonds [6a, 7]. Fluorine atoms and perfluorinated residues are among the most powerful electron withdrawing groups [8] so that halo-PFCs form halogen bonds definitively stronger than the corresponding halo-HC. According to quantum chemical calculations (DFT and MP2), the interaction energies for the halogen bond between trimethylamine and iodomethane and between 4,4'-bipyridyl and 1,4-diiodobenzene are 2.8 and 3.3 kcal mol<sup>−1</sup>, respectively [9]. The

interaction energies for the corresponding halogen bonds involving trifluoriodomethane and tetrafluorodiodobenzene are 7.1 and 5.8 kcal mol<sup>-1</sup>, respectively. From the experimental point of view, the shortening of the van der Waals distances between the halogen bonded nuclei are much greater for halo-PFCs than for the corresponding halo-HC.

The halogen bond involving halo-PFCs proved to be strong enough to effectively overcome the low affinity between PFC and HC derivatives or inorganic salts (IS) [10]. A wide variety of hybrid materials were obtained where heteroatom substituted HCs or anions self-assemble with mono- and di-iodo-PFCs or their bromo-analogs. While both aliphatic and aromatic PFCs give self-assembled systems with equal success, we will discuss here only the hybrid materials formed starting from the former derivatives (i.e., *fluorous* compounds), occasional discussions also being included for the latter. Discrete aggregates, 1D infinite chains, helical structures have been obtained where *fluorous* modules alternate with HC modules.

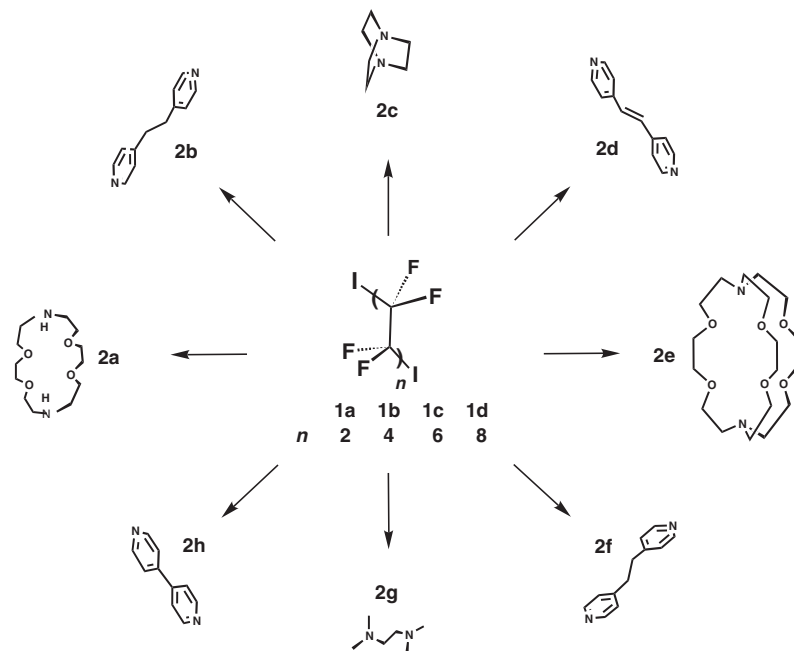
### 12.3.2

#### Neutral Two-Component PFC-HC Materials

When difunctional electron donors interact with monofunctional acceptors, or when monofunctional donors interact with difunctional acceptors, the halogen bond forms well defined trimeric adducts and starting modules are present in a 2:1 ratio in the resulting co-crystals [11]. When difunctional electron acceptors and difunctional donors are used, the interaction is doubled at either end of the modules and one dimensional (1D) infinite networks are formed where the starting modules are present in a 1:1 ratio [12]. The effectiveness of the protocol is shown by the fact that a wide diversity of highly crystalline supramolecular architectures has been obtained starting from differently sized diiodoperfluoroalkanes (acid modules) and from pyridine derivatives or dialkyl- or trialkyl-amines (basic modules) (Scheme 12.3-1).

Halogen bonded co-crystals obtained starting from iodoperfluoroalkanes and nitrogen substituted HC are typically crystalline solids stable in the air at room temperature. They usually melt definitively higher than pure starting modules. For instance, the non-covalent co-polymer formed by 1,2-diiodotetrafluoroethane and tetramethylethylenediamine (1:1 co-crystal) melts at 105 °C, while pure starting modules melt at -27 and -55 °C, respectively. Dramatic melting point increases are observed not only when non-covalent co-polymers are formed but also when the halogen bond affords discrete adducts. 1-Iodoperfluoroheptane melts at -8 °C and the trimeric adduct it gives with tetramethylethylenediamine (2:1 co-crystal) melts at 52 °C. While the correlation between intermolecular interaction strength and melting point cannot be quantified, this thermal behavior is consistent with the formation of well defined molecular aggregates due to interaction of the starting modules. It is also indirect proof of the strength that the halogen bond is responsible for such an interaction. The melting point of the co-crystals obtained starting from bromo-PFCs is usually slightly higher than or in between those of pure starting modules, consistent with bromo-PFCs being weaker acids than iodo-PFCs. Theoretical calculations [9a], experiments of competitive co-crystal formation, and different analytical techniques (<sup>19</sup>F NMR, IR, Raman, single crystal X-ray analyses) [13] all confirm this relative acidity of halo-PFCs.





Complex	References	Analytical Technique
2a + 1d	<i>New J. Chem.</i> <b>2000</b> , 24, 777	Single Crystal X-Rays
2b + 1d	<i>Adv. Mater.</i> <b>2002</b> , 14, 1197	Single Crystal X-Rays
2e + 1a, 2g + 1a	<i>J. Am. Chem. Soc.</i> <b>1998</b> , 120, 8261	Single Crystal X-Rays
2f + 1a	<i>Angew. Chem. Int. Ed.</i> <b>2000</b> , 39, 1782	Single Crystal X-Rays
2h + 1c	<i>Tetrahedron Lett.</i> <b>1999</b> , 40, 7519	Single Crystal X-Rays
2c + 1a-c	<i>J. Mol. Struct.</i> <b>2000</b> , 524, 87	Single Crystal X-Rays

For the complexes characterization with other techniques: *Tetrahedron* **2000**, 56, 5535.

**Scheme 12.3-1.** Diagram showing halogen-bonded infinite 1D chains obtained starting from structurally different dinitrogen HCs and  $\alpha,\omega$ -diiodoperfluoroalkanes

In solid hybrid materials, vibrational spectroscopies (IR and Raman) are effective techniques to check whether the PFC and HC modules are halogen bonded [12a–12c, 14]. The co-crystals spectra are the sum of the starting modules spectra, some diagnostic band shifts and band intensity changes revealing the halogen bond occurrence. Consistent with the  $n \rightarrow \sigma^*$  electron donation from the lone-pair possessing atoms to the iodine, or bromine, atoms [15], the  $\nu_{\text{CH}}$  IR stretching frequencies (2900–3100  $\text{cm}^{-1}$  region) of the basic modules show a blue shift and an intensity decrease while the  $\nu_{\text{CF}}$  stretchings (1100–1250  $\text{cm}^{-1}$  re-

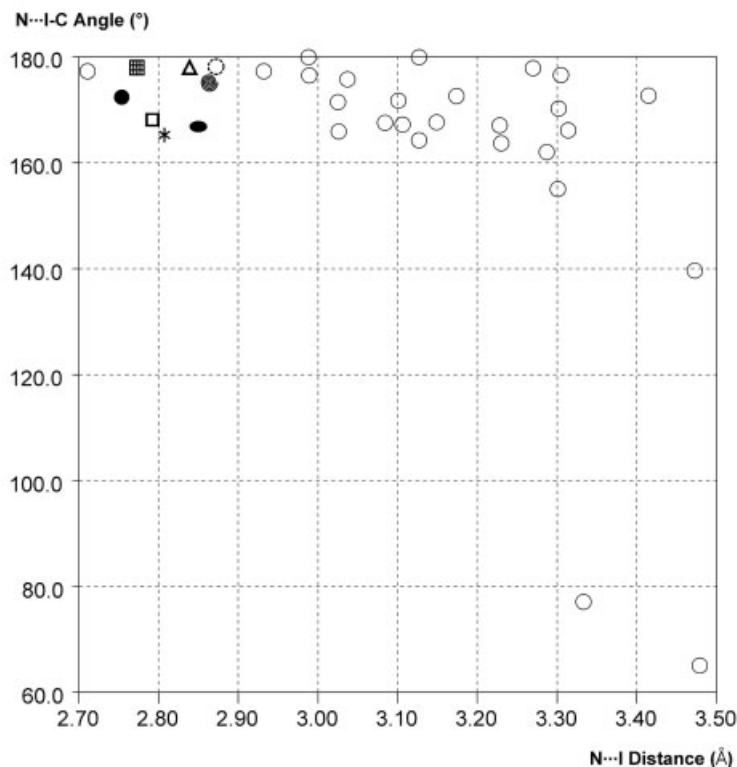
gion) of the acid modules show a red shift. The  $N \cdots I$  interactions give larger changes than the  $N \cdots Br$  ones, consistent with the relative strength of the two interactions.

$^{19}F$  NMR spectroscopy is the best tool to detect the halogen bond formation in liquid hybrid materials, or in solution. The technique is a simple, powerful, and versatile method to rank the relative acidities of different halo-PFCs and the relative basicities of different lone-pair possessing motifs [13]. Signals invariably shift upfield on halogen bond formation and shift values decrease with increasing distance from the iodine, or bromine, atoms. The stronger the halogen bond is, the larger the shifts are and shift values up to 20 ppm have been observed for fluorine atoms geminal to secondary iodine atoms. Iodo-PFCs give larger shifts than Br-PFCs and secondary halo-PFCs give larger shifts than primary halo-PFCs, consistent with the greater electron withdrawing ability of a perfluoroalkyl chain with respect to a fluorine atom.

Owing to the strong tendency of long perfluorinated chains to form waxes and act as lubricants [16], few reports exist on the single crystal X-ray structure of perfluoroalkyl substituted compounds and in most cases low temperatures were used in these studies [17]. Often, the co-crystals obtained starting from diiodo-PFCs and dinitrogen-HCs can be studied through single crystal X-ray analyses, even at room temperature. The halogen bond driven formation of PFC-HC or PFC-HC-IS hybrid materials (see later) can thus be considered as a general and reliable strategy to readily obtaining halo-PFC derivatives that are suitable for X-ray studies (Figure 12.3-1).

X-Ray structures of numerous supramolecular architectures assembled via the  $N \cdots I-R_F$  ( $R_F$  = perfluoroalkyl chain) halogen bond have been obtained so that the geometric characteristics of the interaction were determined in detail. Nitrogen atoms approach iodine atoms roughly along the elongated C–I bond axis, consistent with the  $n \rightarrow \sigma^*$  electron donation from nitrogen to iodine (Figure 12.3-1). The  $N \cdots I-R_F$  distance spans the range 2.75–2.87 Å, and is clearly longer than the average covalent N–I bond length (2.07), and approximately 0.80 times the sum of van der Waals radii (1.55 Å for nitrogen, 1.98 Å for iodine). These contractions are greater, with a single exception [18], than those reported in the Cambridge Crystallography Data Centre for intermolecular  $N \cdots I$  interactions, consistent with the ability of iodo-PFCs to form particularly strong halogen bonds. Also the  $N \cdots Br$  interactions develop along the elongated C–Br bond axis, and the  $N \cdots Br$  distances are usually 0.85 times the sum of van der Waals radii of involved atoms, this smaller shortening being consistent with the  $N \cdots Br$  halogen bond being weaker than that for  $N \cdots I$ . The C–X ( $X = Br, I$ ) covalent bond lengthens in the halogen bonded co-crystals compared with the pure halo-PFCs. Furthermore, the stronger the halogen bond, the greater the lengthening, once again consistent with an electron donation from the lone-pair possessing atoms to the iodine, or bromine, atoms [4c].

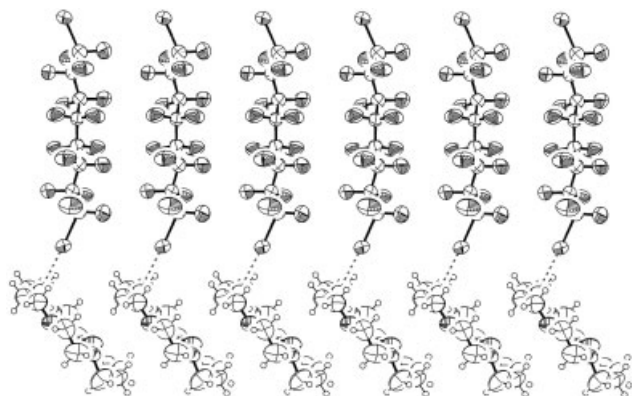
These geometric characteristics of the halogen bonds involving iodo- and bromo-PFCs are exactly analogous to those of the halogen bonds involving iodine and bromine [4a, 4b, 6]. The use of iodine for the formation of halogen bonded co-crystals has recently witnessed a renewed interest [19] as iodine easily works as a removable structural template and allows polymorphs to be isolated and interconverted. Halo-PFCs are notorious as particularly volatile compounds and they can be easily removed from their co-crystals. They could therefore function as effective alternatives for iodine as removable templates in polymorphism studies. Their removal from the co-crystal could afford nanoporous materials.



- co-crystal between 1-iodoperfluoroheptane and TMEDA.
- \* co-crystal between 1,2-diiodotetrafluoroethane and K.2.2.
- co-crystal between 1,2-diiodotetrafluoroethane and TMEDA.
- co-crystal between 1,8-diiodoperfluorooctane and K.2.2.
- co-crystal between 1,8-diiodoperfluorooctane and 1,3-di(4-pyridyl)propane.
- co-crystal between 1,2-diiodotetrafluoroethane and K.2.2.2.
- co-crystal between 1,8-diiodoperfluorooctane and 4,4'-dipyridyl.
- △ co-crystal between 1,6-diiodoperfluorooctane and 4,4'-dipyridyl.

**Fig. 12.3-1.** Scatterplot of C-I...N angles versus N...I distances for intermolecular C-I...N interactions. Only error free and non-polymeric structures showing no disorder and with  $R < 0.06$  are reported. The structures described in Scheme 12.3-1 are labeled with the following signs

In many PFC-HC co-crystals the perfluoroalkyl chains show dramatic rotational disorder not only at room temperature, but also in the cold. This disorder increases in the perfluoroalkyl chain with increasing distance from the iodine, or bromine, atoms which, on the contrary, never show any disorder. Halo-PFC molecules are clearly pinned in their position in the co-crystals through the halogen bond involving the iodine, or bromine, atoms and the perfluoroalkyl chains, reminiscent of their poor tendency to be involved in any interaction, flip as much as possible.



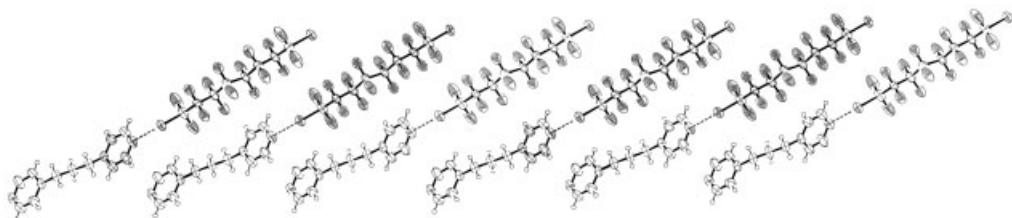
**Fig. 12.3-2.** Layer-like PFC-HC domains in the crystal matrix of the complex between of 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (Kryptofix® K.2.2.) and 1,8-diiodoperfluorooctane. Dashed lines represent halogen bonds

Single crystal X-ray analyses allowed the structural details of co-crystals to be established. For instance, with very few exceptions the perfluorinated chains adopt an all-*trans* and twisted conformation. In the hybrid materials, the halo-PFCs are present as rigid and parallel bars aligned and segregated into PFC layers alternating with HC layers (Figure 12.3-2) [13]. This arrangement persists independently of the nature and shape of the HC module, and by simply changing the metric dimensions of the PFC or HC modules, differently sized PFC-HC layer-like hybrid materials can be rationally designed and prepared (Figure 12.3-3).

### 12.3.3

#### Anionic Three-Component PFC-HC-IS Materials

The ability of halide anions to act as donors to electron-poor carbon-bound halogens may be developed as a general protocol for halide-centered supramolecular chemistry. Both PFCs and HCs have a very low affinity for inorganic salts, and it can thus be expected that *three-component heteromeric architectures* where PFCs, HCs, and ISs self-assemble are endowed with unique structures and useful properties.

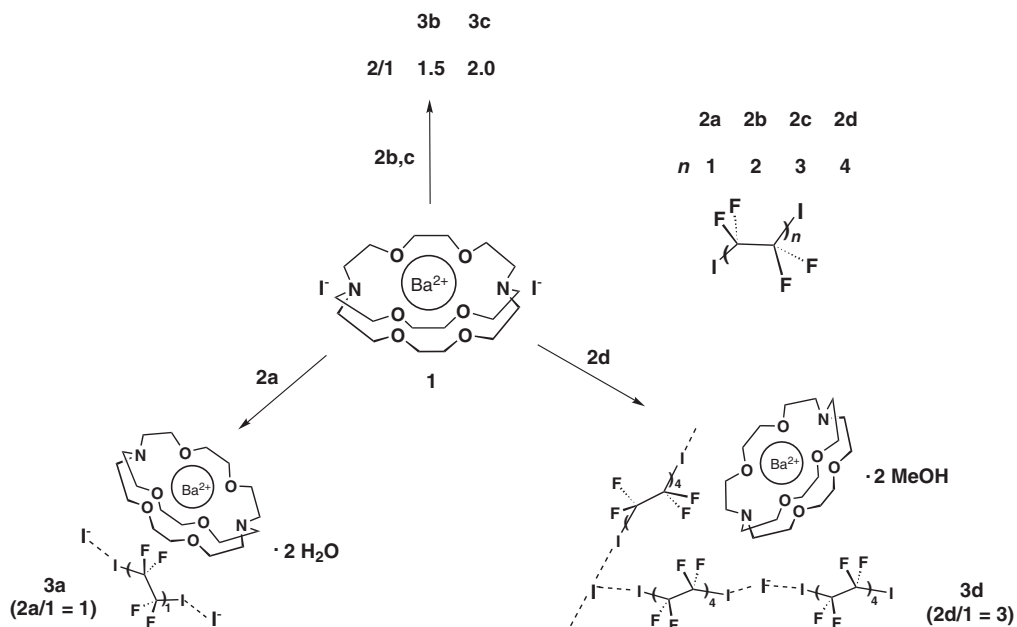


**Fig. 12.3-3.** Alternating PFC-HC layers characterizing the crystal matrix of the halogen-bonded complex obtained from 1,3-di(4-pyridyl)propane and 1,8-diiodoperfluorooctane. Dashed lines represent halogen bonds

Crystalline organic iodides represent a special group of halogen-doped organic crystals. The presence of polyiodide chains in organic materials noticeably influences their electrical properties. Polyiodides have been extensively studied in the solid and liquid state as constituents of a large number of molecular conductors and superconductors [20]. They are characterized by a strong tendency to concatenation [21] and give rise to solid structures that may contain small and discrete polyiodides or extended networks of interconnected units [22]. These important applications produced a great demand for new crystalline organic materials containing polyiodide chains [23].

We have already discussed the ability of diiodoperfluoroalkanes to mimic iodine [12c] and pseudo- or interhalogens in the halogen bond driven formation of adducts with neutral electron donors. Telechelic iodoperfluoroalkanes are also reminiscent of iodine in their tendency to self-assemble with  $I^-$  anions. In fact, fluorous polyiodide networks of different lengths and different fluorine-contents have been synthesized by varying the metric parameters of the  $\alpha,\omega$ -diiodoperfluoroalkane utilized.

When 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8,8,8]hexacosane (K.2.2.2.) is crystallized from a methanol solution of KI, the solid cryptate K.2.2.2.  $\subset$  BaI<sub>2</sub> **1** is isolated. If **1** is crystallized from methanol in the presence of 1,2-diiodotetrafluoroethane (**2a**), the naked iodide of the cryptate K.2.2.2.  $\subset$  BaI<sub>2</sub> functions as a strong electron donor towards the iodine atoms of **2a**, causing the precipitation of the three-component PFC-HC-IS architecture [Ba(K.2.2.2.)<sup>2+</sup>](C<sub>2</sub>F<sub>4</sub>I<sub>4</sub>)<sup>2-</sup> **3a** as colorless crystals (Scheme 12.3-2).

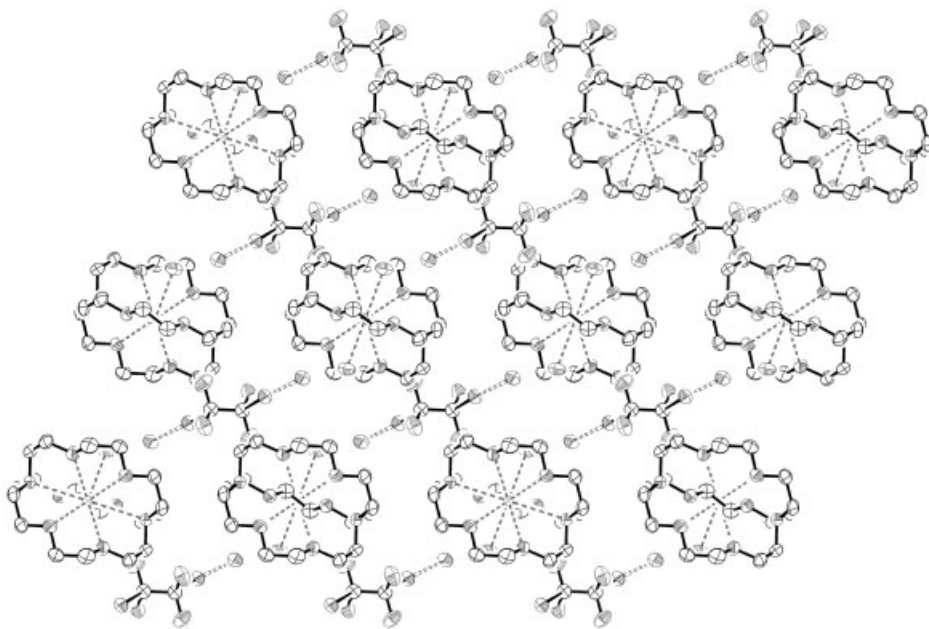


**Scheme 12.3-2.** Diagram showing the formation of fluorous polyiodide networks starting from cryptate **1** and differently-sized telechelic diiodoperfluoroalkanes **2**. The 2/1 modules ratio in the complexes is reported for each structure as

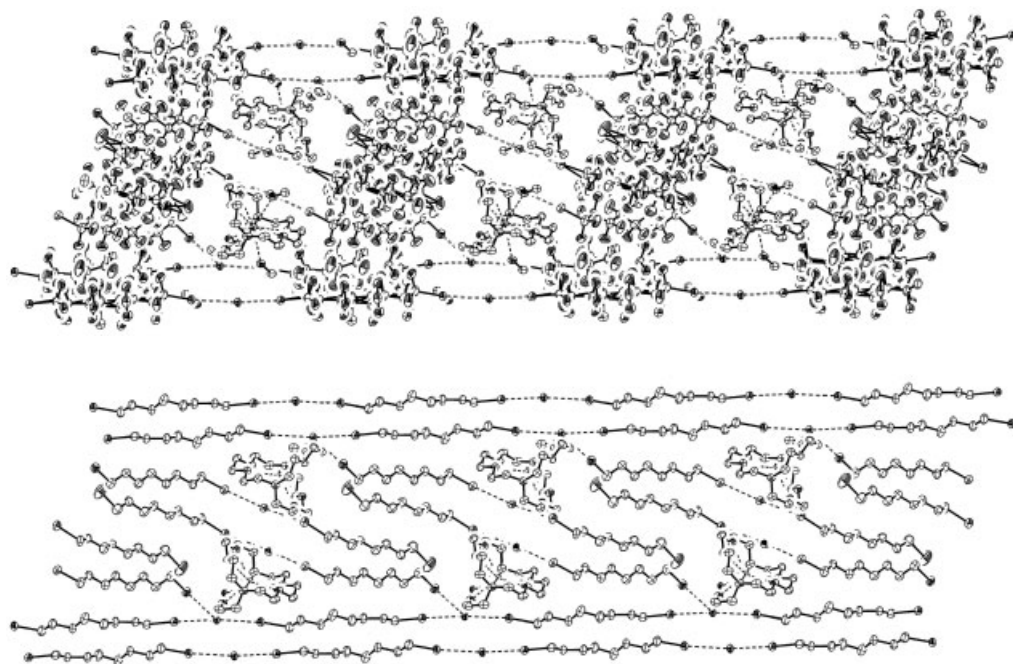
derived from single crystal X-rays analyses and <sup>1</sup>H/<sup>19</sup>F NMR experiments. For polyiodides **3a,d** the concatenation is reported as found in the crystal structures

The structural details of **3a** were established through single crystal X-ray analysis. Barium cations are embedded in the cryptand and two molecules of water are also present and complete the co-ordination sphere of the alkaline-earth metal. Diiodotetrafluoroethane works as a bidentate and telechelic electron acceptor as two distinct iodide ions are halogen bonded at either ends of the molecule. Iodide anions behave as monodentate electron donors and are located at the surface of the cryptate with a distance from the cation of 5.845 Å. This concatenation gives rise to the fluorinated polyiodide network  $[\text{C}_2\text{F}_4\text{I}_4]^{2-}$ . The  $\text{I}^- \cdots \text{I}-\text{C}-$  angle is  $177.3(1)^\circ$  and the  $\text{I}^- \cdots \text{I}-\text{PFC}$  halogen bond length is 3.391(1) Å, longer than the average covalent I-I bond (2.666 Å) but approximately 0.8 times the sum of the van der Waals radii for an iodine atom (1.98 Å) and iodide ion (2.20 Å). A strictly related crystalline organization has recently been described by Pantenburg et al. [24] for the complex  $[\text{Ba}(\text{benzo-15-crown-5})_2]^{2+}(\text{I}_3^-)_2$ . This confirms the suggestion that the supramolecular synthon  $\cdots \text{I}(\text{CF}_2)_n\text{I} \cdots \text{I}^-$  functions as a fluorous analog of the triiodide building block (Figure 12.3-4).

Naked iodide anions have been demonstrated to be strong templating agents for iodo-PFCs. This behavior, along with the great tendency of perfluoroalkyl chains to behave as rigid rod-like modules, allows one to predict the formation of higher fluorine-content polyiodide networks when using iodo-PFCs longer than **2a**. Co-crystals **3b–d** were obtained starting from  $\alpha,\omega$ -diiodoperfluorobutane (**2b**), -hexane (**2c**), and -octane (**2b**, **2c**, and **2d**, respectively), as confirmed by thermal and IR analyses. Microanalyses and  $^1\text{H}/^{19}\text{F}$  NMR revealed the PFC/cryptate ratios are 1.5:1.0, 2.0:1.0, and 3.0:1.0, in **3b–d**, respectively [25].



**Fig. 12.3-4.** Ortep III view of the crystal packing of **3a**.  $\text{I}^- \cdots \text{I}$  halogen bonds are dashed lines. For the sake of clarity hydrogen atoms have been omitted



**Fig. 12.3-5.** Crystal packing of PFC-HC-IS complex **3d**. For the sake of clarity hydrogen atoms have been omitted. Top: the high degree of segregation of perfluorinated modules from cryptated salt allows the formation of alternating nanometric layers connected only by  $R_F I \cdots I^- \cdots I R_F$  interactions.

Bottom: the same packing on top has been drawn without fluorine atoms to show the concatenation of the polyiodide network more clearly. The non-covalent comb-like fluorous polymers obtained pack facing each other and intercalating the perfluoroalkyl side chains

Single crystals of **3d** suitable for X-ray analysis were grown from methanol. Barium cations are again embedded in the cryptand and two molecules of methanol, rather than of water as in **3a**, complete the co-ordination sphere. Two different iodide ions are present in the asymmetric unit of the crystal. One of these iodide ions is tridentate, bridges two distinct and well-ordered all-*trans* diiodoperfluorooctane molecules in a linear manner, and gives rise to infinite and linear fluorous polyiodide chains (Figure 12.3-5). A third molecule of diiodoperfluorooctane is bound, with an angle of  $127^\circ$ , to the iodide ions of the infinite chains and is connected to a linear, discrete, and disordered  $\cdots I^- \cdots I(CF_2)_8 I$  unit. The overall lattice organization of the true polyiodide network thus obtained reminds one closely of the structure of a comb-like co-polymer. Each “monomer” consists of a perfluorinated octaiodide which can be described as a V-shaped pentaide unit  $C_{16}F_{32}I_5^-$  [ $I1B \cdots I1$  3.531(1) Å,  $I1 \cdots I1A$  3.584(1) Å,  $I1B \cdots I1 \cdots I1A = 126.96(2)^\circ$ ], connected to a triiodide unit  $C_8F_{16}I_3^-$  unit [ $I2A(x, y, -1+z) \cdots I2$  3.464(1) Å,  $I2 \cdots I1C(1+x, y, z)$  3.442(1) Å,  $I2A(x, y, -1+z) \cdots I2 \cdots I1C(1+x, y, z) = 174.5(2)^\circ$ ] of the same type found in **3a**. The single fluorous monomers are then connected head-to-head by  $I \cdots I$  secondary interactions of 4.167–3.999 Å with angles of  $60$ – $65.6^\circ$ . The packing of the fluorous and comb-like polymeric poly-

iodides in the crystal matrix is characterized by a strong segregation of the perfluoroalkyl chains and alternating PFC-HC layers are present as usual (Figure 12.3-5).

To the best of our knowledge, this is the first example of a comb-like fluorous polymer constructed exclusively by means of non-covalent interactions. This is also the first report of the syntheses of fluorine-rich polyiodide networks. Their formation is driven by the strength of the  $I^- \cdots I$ -PFC halogen bond, which gives rise to single comb-like co-polymer chains, and by the fluorophobic effect, which packs the single chains into a nano-segregated crystal matrix.

Fluorous polyiodide networks are a virtually unknown class of materials, but remembering the technological importance of PFCs in general, and of PFC-halides in particular, interesting properties can be anticipated for the new systems described in this section.

#### 12.3.4

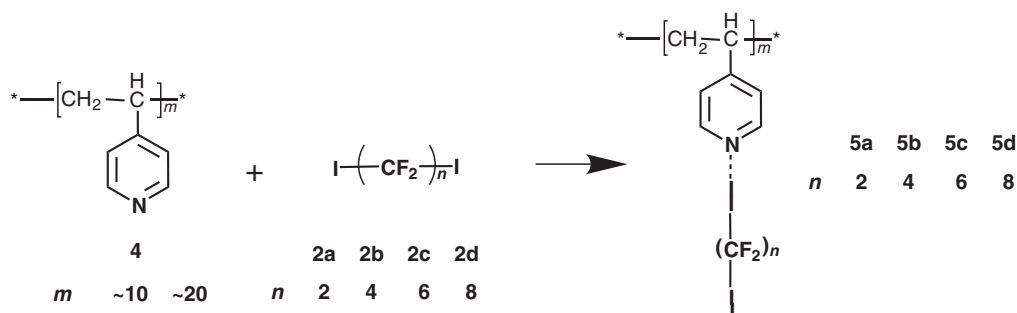
#### Polymeric PFC-HC Comb-shaped Complexes

Comb-like polymers with perfluoroalkyl side chains have recently received interest because of their unique surface behavior [26]. Random copolymers containing fluorinated segments are much more common than graft copolymers because of the greater difficulties encountered in the synthesis of a two-phase graft copolymer.

We have demonstrated above how the halogen bond is a powerful tool in crystal engineering. Owing to its high strength and specificity, this interaction also effectively drives the self-assembly of long chain halo-PFCs with HC polymers carrying appropriate electron-donor sites. This approach has been applied in the coating of surfaces with fluorinated materials [27]. The halogen bond is thus confirmed as an effective intermolecular interaction for the design of new comb-like complexes.

Poly(4-vinylpyridine) **4** (P4VP) gives 2:1 halogen-bonded comb-shaped complexes with  $\alpha,\omega$ -diiodoperfluoroalkanes **2a–d** (Scheme 12.3-3). The complexes **5a–d** have been fully characterized by FT-IR, Raman,  $^1H$  and  $^{19}F$ -NMR, CP-MAS  $^{13}C$ -NMR, DSC and thermogravimetric analyses (TGA).

IR and Raman spectroscopies effectively show the occurrence of the halogen bond on both the HC and PFC modules. The observed blue shift and intensity decrease in the 3100–



**Scheme 12.3-3.** Fluorous comb-like polymeric complexes **5** obtained from poly(4-vinylpyridine) **4** with telechelic diiodoperfluoroalkanes **2**



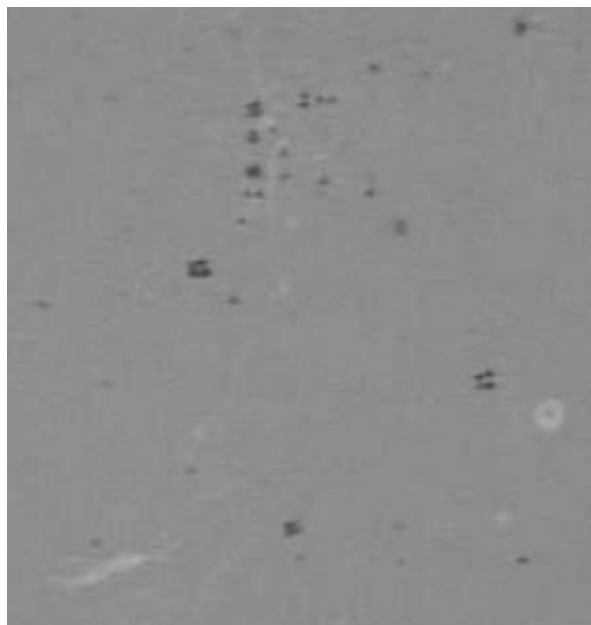
2900  $\text{cm}^{-1}$  region of the IR of P4VP is highly diagnostic of halogen bond formation, and the same holds for the blue-shift to 1001  $\text{cm}^{-1}$  of the absorption at 993  $\text{cm}^{-1}$  in pure **1** [28]. As to the acidic module, the C–I bond Raman vibration (at 277  $\text{cm}^{-1}$  in pure **2a**) underwent the typical red-shift on complex formation [14a].

TGA-FTIR experiments on complexes **5** having different stoichiometries were very informative as to the relationship between their stoichiometry and single module properties. The halogen bond dramatically decreases the volatility of the perfluorinated compound and bonded PFCs show quite different behaviors from unbonded PFCs. With this technique it was possible to establish that the 1:1 N/I stoichiometry is favored in the complexes and these results are confirmed by titration experiments with IR and Raman measurements.

While **5d** had a paste-like morphology, the complexes **3a–c** were dense oils. The features typical for a smectic-type liquid crystallinity were confirmed in complex **3c** with polarized light. The macroscopic organization also remained unchanged upon heating to 70 °C, thus suggesting the lyotropic character of this LC system (Figure 12.3-6).

Studies in which shear stress was applied to the molten complex showed a behavior typical of the lamellar organization, distinctly similar to related literature systems [29].

Thanks to the high strength and directionality of the halogen bond, and the rigid, rod-like structure of perfluoroalkyl residues, materials with a nice comb-like structure have been obtained starting from P4VP **4** and halo-PFCs **2**. The high tendency of PFCs to segregate from HCs contribute to the LC properties of such materials. The self-assembly of halo-PFCs



**Fig. 12.3-6.** Polarized light microscopy images of comb-shaped complex **3c** taken with a 100 $\times$  magnification showing the spherulitic textures with a Maltese extinction cross dispersed in the birefringent matrix, as typical for a smectic-type liquid crystallinity

with polymers carrying suitable electron-donor residues can be an alternative route to fluorinated graft co-polymers, easier and more convenient than the covalent synthesis. These non-covalent approaches could be successfully pursued as a new method to the deposition of fluorinated coatings.

### 12.3.5

#### Conclusion

It has been proven how the halogen bond can be considered as a first choice intermolecular interaction to rationally design the self-assembly of PFCs with HCs and ISs both reliably and effectively. In the resulting hybrid materials, the single modules are arranged by the halogen bond into well-defined discrete aggregates or infinite networks. The packing of these self-assembled units into the supramolecular structure of the material is heavily influenced by the low affinity which exists between PFCs and HCs or ISs. As HC and IS derivatives are *fluorophobic*, segregation of the different modules into separated nanodomains occurs and the halogen bond holds together the alternating layers of PFC and HC, or IS, modules. This nanodomain formation is largely independent of the molecular structure of single modules.

Physical and chemical properties of bulk materials are not simply the sum of the molecular properties of the constituting compound(s) and this becomes particularly true when multi-component materials are considered. Very few systems (e.g., PFC-HC emulsions or diblock and triblock compounds  $R_F-R_H$  and  $R_F-R_H-R_F$ , respectively) can be considered in an attempt to anticipate the properties of mixed PFC-HC supramolecular architectures. Nevertheless, also remembering the unique and useful properties of PFC materials (e.g., Nafion®, Teflon®, ...), the few precedents cited above allow one to state that the properties of mixed PFC-HC supramolecular architectures, while difficult to anticipate, are expected to be of great interest. Similar considerations hold for PFC-HC-IS hybrid materials.

In synthetic chemistry, the halogen bond can drag hydrocarbon reagents/catalysts into fluorous solvents thus offering an alternative to the “perfluorinated ponytail” approach in fluorous based technology [30]. The formation of PFC-HC co-crystals can also be used as a low cost and large scale approach to the separation of mixtures of PFC-halides, a class of compounds of great technological relevance.

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## 13

## Fluorous Materials for Biomedical Uses

Jean G. Riess

### 13.1

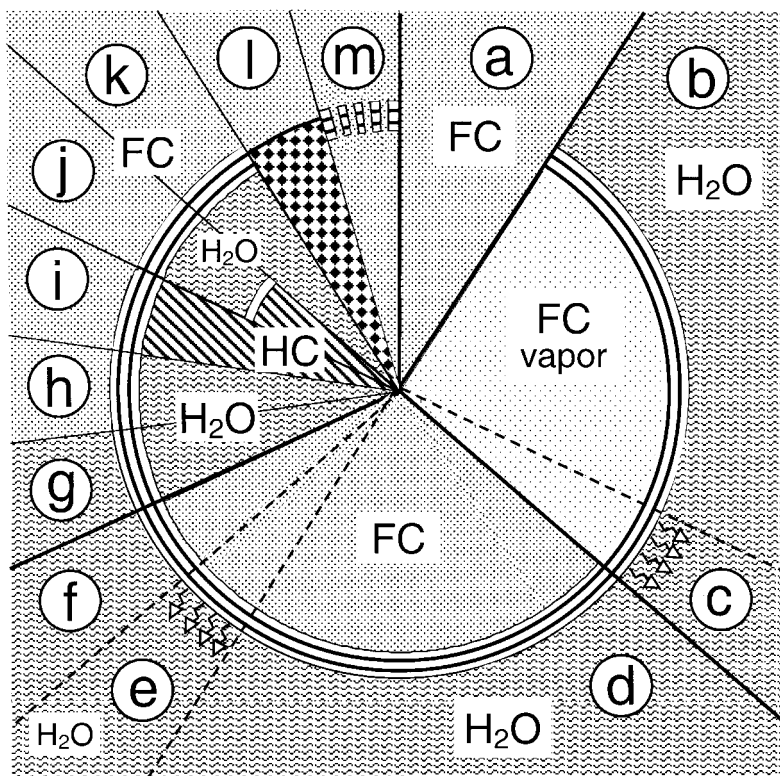
#### Introduction

This chapter reviews the uses, present and potential, of highly fluorinated compounds (*F*-compounds) and colloids with fluorous components (*F*-colloids) in medicine and biology (Figure 13-1). The IUPAC-authorized italicized prefixal symbol *F*-, meaning perfluoro, as in *F*-alkyl = perfluoroalkyl, will, by extension, be used to designate entities (*F*-chains, *F*-amphiphiles, *F*-surfactants, *F*-vesicles and *F*-colloids) that comprise a highly fluorinated moiety or phase, responsible for significant effects, different from those found for hydrocarbon (HC) analogs. Mirroring this representation, the prefix *H*- (as in *H*-alkyl) will be used for unambiguous designation of HC counterparts [1].

Several perfluorocarbon (or fluorocarbon, FC)-based contrast agents for ultrasound diagnostic imaging have recently been commercialized. Fluids for ophthalmologic applications and a magnetic resonance image enhancement device are also available. An injectable oxygen-carrier (blood substitute) is undergoing advanced clinical evaluation, while others are in the early investigation stages. Various *F*-compounds and *F*-colloids have potential for the detection of diseases by molecular imaging, and for the delivery of drugs, genes and other bioactive agents or markers. Other *F*-compounds and *F*-colloids provide valuable research tools and processing aids for the manufacture of drug delivery vehicles.

The simultaneously hydrophobic and lipophobic character of *F*-chains is a powerful driving force for FCs to phase separate and for *F*-amphiphiles to self-assemble in aqueous media as well as in standard organic solvents. FCs and *F*-amphiphiles can thus allow the formulation of an array of multicomponent, multiphase nano- and micro-compartmentalized colloidal systems and nano-objects that comprise confinement and exclusion zones with differential solubility and diffusibility characteristics, responses to sound waves, etc. These colloids have potential as gas carriers, targetable drug vehicles and microreservoirs, sound reflectors and sound-triggered cavitators, diffusion barriers and templates, useful for biomedical applications and beyond [2]. Fluorinated colloids thus participate in the ineluctable movement towards increased, yet increasingly controlled complexity that characterizes the evolution of science.

Selection of fluorous components and formulations for biomedical applications is largely determined by the target properties and constraints appropriate to their specific uses. These



**Fig. 13-1.** Schematic representation of *F*-systems investigated for biomedical applications; the components inside and outside the circle (which represents an interface) are dispersed and continuous phases, respectively: a) neat FCs; b) aqueous suspensions of FC or FC-stabilized gas bubbles; c) aqueous suspensions of targeted FC-filled or FC-stabilized gas bubbles; d) FC-in-water injectable emulsions; e) targeted FC-in-water emulsions; f) high-internal-phase-ratio gel-

emulsions; g) *F*-vesicles; h) reverse water-in-FC emulsions; i) apolar HC-in-FC emulsion; j) example of a multiple emulsion; k) gels with a continuous FC phase; l) suspensions of nanocrystalline material; m) homodispersions of hollow porous microparticles. Many of these systems can optionally be loaded with drugs and other active material or markers, or fitted with targeting devices

criteria and constraints include pharmacokinetic and side effect profiles, especially when intravascular administration is intended. Further selection criteria are dictated by the need for large-scale manufacture, extended shelf-life, user friendliness, need to abide by current Good Manufacturing Practices and strict regulatory rules, and numerous other practical considerations, including cost-effectiveness.

The scope of this chapter embraces all biomedical applications of molecular *F*-compounds. However, FC-in-water emulsions for oxygen delivery will only be briefly summarized here, as they have recently been reviewed extensively [3–6]. Likewise for *F*-component-containing gels [7] and vesicles [8]. Research directed at developing pharmaceuticals has generated numerous novel *F*-compounds, self-assemblies and other colloidal

systems, as well as a wealth of data on these compounds and systems. These data have been analyzed from the perspective of the formation, structure and behavior of fluorinated nano- and microphases in colloidal systems [2]. Fluorinated colloids and self-assemblies are reviewed in Chapter 12.1 of this Handbook [9], while *F*-colloids and interfaces are the topic of a section in *Current Opinion in Colloid and Interface Science*, edited by Krafft [10]. Fluorinated polymers and copolymers (including, for example, the Goretex® materials used in reconstructive surgery), liquid crystals and mesophases in general are excluded from the scope of this review. The reference selection is primarily intended to provide background information, illustration and literature sources, rather than exhaustiveness.

## 13.2

### Specific Properties of Highly Fluorinated Materials That Are the Basis for Their Uses in Medicine and Biology

The potential of FCs in medicine results from a unique set of strongly interrelated properties that will be briefly discussed as a reminder here (see also [5, 8, 11, 12]). The components discussed include FCs and *F*-amphiphiles, as well as *F*-alkyl/*H*-alkyl diblocks. All are characterized by extensive fluorine content, typically in the form of linear or cyclic FCs or of linear *F*-alkyl moieties.

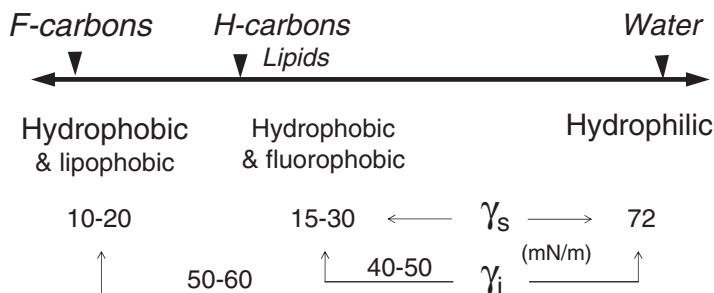
It must be emphasized that the properties and behavior of FCs and *F*-alkylated amphiphiles are nothing mysterious. They are in essence of the same nature as those of HC-derived compounds and derive directly from the electronic and dimensional characteristics of the component atoms in a generally well understood and predictable manner [2, 12]. However, swapping a substantial number (typically 7 to 20) of hydrogen atoms for fluorines in a molecule can hardly be inconsequential. The fluorine atom is larger, more electronegative and less polarizable than the hydrogen atom. *F*-chains are bulkier, stiffer, less cohesive, more hydrophobic and more electroattractive than *H*-chains. The impact of these differences on macroscopic properties can be of such amplitude that it can generate behavior that is not observed, or reach a level of effectiveness in their performances that cannot be attained, by *H*-compounds [2].

Moreover, certain combinations of properties can lead to technological feats that just cannot be achieved with non-fluorinated materials, making the fluorinated ones irreplaceable. Superior O<sub>2</sub> solubilities would not suffice to make FCs good candidate *in vivo* O<sub>2</sub> carriers; it is the combination of O<sub>2</sub> solubilities and biological inertness that creates the potential. Likewise, it is the combination of high volatility and water solubilities lower than those of any other volatile compound that allows use of FCs to stabilize injectable microbubbles for ultrasound imaging.

#### 13.2.1

##### Perfluoroalkyl Chains: Bulkier, Stiffer, Hydrophobic and Lipophobic

The element fluorine has extremely high ionization potential (just after Ne and before Ar), electroaffinity and electronegativity, and low polarizability (second to Ne). Fluorine is larger than hydrogen (van der Waals radii estimated at 1.47 Å versus 1.20 Å, respectively) and comparable in size to oxygen, but less polarizable [13, 14].



**Fig. 13-2.** A hydrophobicity scale. FCs are both more hydrophobic and lipophobic than HCs, as reflected by their surface tensions  $\gamma_s$  and their interfacial tensions with water  $\gamma_i$

Because fluorine atoms fill more space than hydrogens, *F*-alkyl chains are bulkier and more rigid than alkyl chains (*H*-chains). Their cross-section is around  $30 \text{ \AA}^2$  (compared with  $20 \text{ \AA}^2$  for *H*-chains) and they have a helical structure rather than the planar “zigzag” structure of *H*-chains. The mean volumes of  $\text{CF}_2$  and  $\text{CF}_3$  groups are estimated to be  $38 \text{ \AA}^3$  and  $92 \text{ \AA}^3$  versus  $27 \text{ \AA}^3$  and  $54 \text{ \AA}^3$  for  $\text{CH}_2$  and  $\text{CH}_3$ , respectively [15, 16].  $\text{CF}_3$  is substantially larger than  $\text{CH}(\text{CH}_3)_2$  and only marginally smaller than  $\text{C}(\text{CH}_3)_3$  [17]. The larger *trans/gauche* interchange energy of 4.6 versus  $2.0 \text{ kJ mol}^{-1}$  for *F*- and *H*-chains, respectively, strongly reduces the conformational freedom of the former. Consequently, the occurrence of *gauche* defects at equilibrium is also reduced in *F*-chains which, along with enhanced stiffness, favors their ordered stacking [18]. On the other hand, *F*-chain stiffness is a likely cause for slower dissolution and equilibration and slower exchange kinetics, as between different types of aggregates or aggregates and monomer [19–21].

On a hydrophobicity scale (Figure 13-2), *F*-alkyl chains are located on the hydrophobic side, well beyond *H*-chains of similar length and are, therefore, not only more *hydrophobic* than *H*-alkyl chains, but *lipophobic* as well. Enhanced hydrophobicity has been related primarily to larger molecular surface area for *F*-chains as compared with *H*-chains [22, 23]. These features promote self-aggregation, molecular organization, phase separation and the exclusion of non-highly fluorinated solutes [2, 9]. Hydrophobic interactions are well known to influence the availability, distribution and activity of biologically active molecules.

The powerful electron-withdrawing character of *F*-alkyl chains can generate or amplify an electric dipole, locally increase the polarity of the molecules to which they belong, and modify the surface potential of molecules adsorbed on water. *F*-alkanoic acids are more extensively dissociated in water than *H*-alkanoic acids, *F*-alcohols are substantially more acidic than *H*-alcohols, while *F*-alkyl diethers and *F*-alkyl tertiary amines generally lose all base character.

The thermal stability and chemical inertness of FCs and *F*-chains reflect a combination of the strength of the C–F bond, low polarizability and strong electroattracting character of fluorine (which reinforces the C–C backbone), and of the compact, repellent electron shield provided by the fluorine atoms. Resistance of *F*-chains to metabolism may be advantageous when enzymatic material is present.



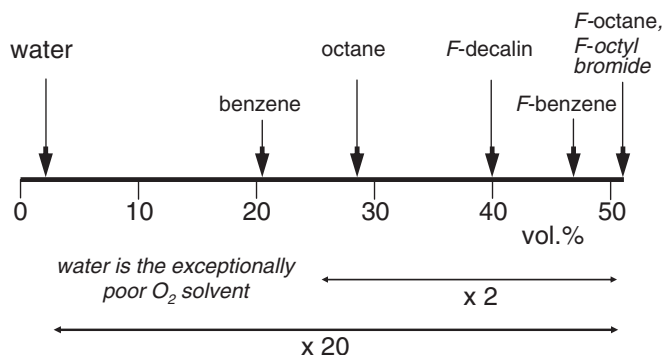
## 13.2.2

**Perfluorocarbons: Inert Liquids with Gas-like Behavior**

In sharp contrast with strong *intramolecular* covalent bonds, FCs display very low *intermolecular* cohesiveness. This originates from the low polarizability of fluorine, which results in lower van der Waals interactions between *F*-chains than between *H*-chains, hence in lesser cohesive energy density. Consequently, liquid FCs behave as nearly ideal, gas-like fluids [2, 16, 24]. Lesser chain flexibility is reflected by higher melting points than for HCs, and lesser van der Waals interactions by lower boiling points (barely higher than those of noble gases with comparable MW), translating into a narrower liquid phase domain. As compared with HCs, FCs are also characterized by much higher vapor pressures relative to their MW, exceptional chemical and biological inertness, higher gas solubilities, density, fluidity, spreading coefficients and compressibility, lower surface tensions, water solubility, refractive index and dielectric constant, and a magnetic susceptibility comparable to that of water. For example, the boiling points of *n*-*F*-octane (MW = 438) and *n*-octane (MW = 114) are 104 °C and 126 °C, respectively and their surface tensions are 13.6 and 21.6 mN m<sup>-1</sup>, respectively.

The mixing of FCs and HCs is highly non-ideal [25–27], which is the basis for fluorous biphasic chemistry [28]. The Hildebrand parameter  $\delta$ , which is related to the cohesive energy density of fluids and reflects their similarity, ranges as follows:  $\delta$  FCs <  $\delta$  HCs  $\ll$   $\delta$  water. In order for two fluids to be mutually soluble, they need to have similar  $\delta$  values. The  $\delta$  values of FCs are typically close to 6 hildebrands (cal<sup>1/2</sup> cm<sup>-3/2</sup>), as compared with 5.7 for O<sub>2</sub>, 7 to 9 for HCs, and 23.4 for water. FCs and HCs with seven carbon atoms or more are not miscible at room temperature. The calculated Hildebrand solubility parameter was used for a rough estimation of fluorophilicities within a given family of compounds [29].

The large solubility of gases in liquid FCs is well documented (Figure 13-3) [5, 30, 31]. Indeed it takes less energy to create a hole in a lesser cohesive material and also less energy to introduce a molecule of comparable cohesive energy into that hole. The large solubility of gaseous CO<sub>2</sub> in FCs, and the enhanced solubility of FCs in liquid and supercritical

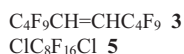
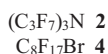
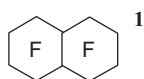


**Fig. 13-3.** Oxygen solubility is highest in the loosely interacting FC liquids and lowest in water with its highly cohesive three-dimensional network of hydrogen bonds

CO<sub>2</sub> further indicate the likeness of the two media. The solubility of O<sub>2</sub> in *F*-*n*-hexane and *n*-hexane has recently been measured precisely (51.8 and 36.8% v/v, respectively, at 37 °C) and compared with computer simulations [32].

High hydrophobicity translates into low water solubility. The solubility of FCs in water, as estimated from Ostwald ripening rate measurements in emulsions, is indeed very low (e.g.,  $3.8 \cdot 10^{-9}$  mol L<sup>-1</sup> for *n*-C<sub>8</sub>F<sub>18</sub>) [33]. It decreased by a factor of ~8 for each added CF<sub>2</sub> in a homologous series, while it increased upon cyclization and branching, in correlation with the decreasing solvent cavity surface [29, 33]. This solubility correlates well with the surface or the volume of the cavity created in water by the FC molecule [34]. The solubility of short *F*-alkanes in water has been determined experimentally as well as calculated by molecular simulation [35]. Molecular simulation of this solubility of O<sub>2</sub>, CO<sub>2</sub> and H<sub>2</sub>O in some *F*-alkyl/*H*-alkyl compounds and in *F*-octyl bromide has also been carried out [35a].

Biological constraints, especially excretion rates, have limited the number of liquid FCs that have actually undergone any significant pharmaceutical development for intravascular use. These include primarily *F*-decalin **1**, *F*-tripropylamine **2**, bis(*F*-butyl)ethene **3**, *F*-octyl bromide **4**, and *F*- $\alpha,\omega$ -dichlorooctane **5**. Volatile *F*-chemicals, including the light *F*-alkanes C<sub>*n*</sub>F<sub>2*n*+2</sub> (*n* = 3 to 6) and SF<sub>6</sub>, are being used in injectable gaseous microbubbles (Section 13.3).



The biological inertness of FCs is well documented. Clinical research on liquid ventilation involving installation of liter-size amounts of *F*-octyl bromide in the lungs uncovered no significant side effects [36–40]. Oral ingestion of liter-size doses of *F*-octyl bromide was approved by the FDA for X-ray imaging of the gastrointestinal tract. Intravascular administration of FCs in dispersed form and excretion characteristics are discussed in Sections 13.3 and 13.4.

### 13.2.3

#### Fluorinated Amphiphiles: a Predilection for Self-Assembly

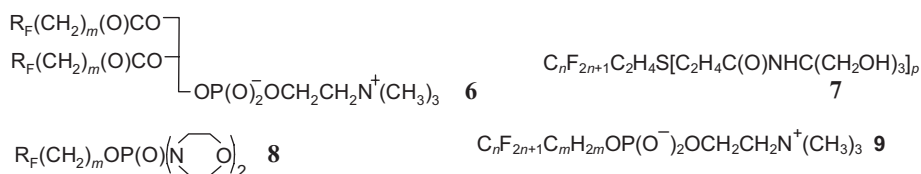
Fitting molecules with *F*-alkyl chains exacerbates the amphiphilic character of these molecules. Fluorosurfactants are particularly valuable when extreme surface activity, extreme hydrophobicity, high fluorophilicity or lipophobicity, and resistance to high temperatures, aggressive environments and detergent activity are needed [41].

A large diversity of well-defined *F*-surfactants has been synthesized with a view to providing highly surface-active components usable in pharmaceuticals and to determining the impact of *F*-chains on the structure and properties of colloids. Hydrophilic, lipophilic and fluorophilic characters, size and shape, chemical functions available for derivatization, etc. were varied extensively [11, 42, 43]. Further examples of *F*-surfactants that may provide components for biomedical applications include *F*-amphiphiles derived from carbohydrates and polyols [44–46], aminoacids and peptides [47], lipids [48], dimeric (gemini) surfactants [49], surfactants with two polar heads for one *F*-chain [50], surfactants with a “reverse” HC-

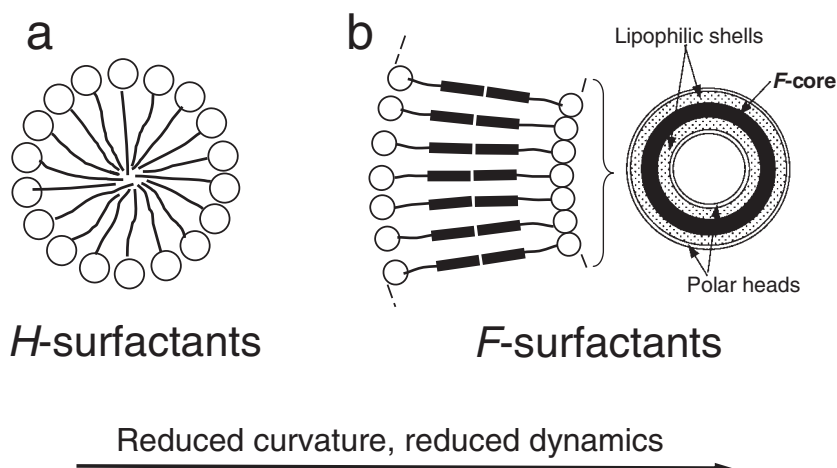
FC-polar head sequence [51–53], bolaamphiphiles with a central *F*-segment [54], amphiphilic fluorinated copolymers [55], and gel-forming amphiphilic polymers with *F*-alkyl-end-caps or side-chains [21, 56–58].

*F*-surfactants are both more effective and more efficient than their *H*-counterparts. They can decrease the surface tension of water from 72 mN m<sup>-1</sup> to typically 15–20 mN m<sup>-1</sup> versus 25–40 mN m<sup>-1</sup> for *H*-analogs. They can reduce the FC/water interfacial tension to values as low as 1 mN m<sup>-1</sup> or less. Efficiency is illustrated by critical micellar concentrations (CMC) in water that are typically one to two orders of magnitude lower than for HC analogs. The CMC of a surfactant is indeed related to the water solubility of its hydrophobic moiety [22]. Therefore, *F*-surfactants can usually be used in much smaller amounts, partially compensating for higher cost and possibly reducing any physiological burden associated with the surfactant. The CMC values for *F*-alkylated surfactants are generally considered to be roughly equivalent to those of *H*-alkylated analogs with a 50–70% longer chain [15, 34]. This rule may, however, not be applicable when the chains are only partially fluorinated, as *F*-chains tend to reduce the contribution of *H*-spacers to the adsorption and micellization energies [59]. It is also worth noting that the presence of a single hydrogen atom at the end of the hydrophobic chain (as in HCF<sub>2</sub>– versus CF<sub>3</sub>–) results in a considerable increase in surface tension and CMC [34, 60].

Despite substantially higher surface activity, *F*-surfactants were consistently found to be less hemolytic than their *H*-counterparts. Hemolytic activity was often fully suppressed [8, 46, 61]. The introduction of *F*-alkyl chains into a molecule apparently does not increase its acute toxicity. Acute lethal doses, LD<sub>50</sub>, of several grams per kg body weight (b.w.) have been reported for certain *F*-alkylated phosphatidylcholines of type **6** and *F*-alkylated telomers **7** in mice [8, 42, 62]. The cytotoxicity of the *F*-alkylated dimorpholinophosphates **8** on mouse fibroblast or human lung epithelial cells was noted to decrease with increasing *F*-chain length [63]. However, contrary to FCs, the pharmacology of *F*-surfactants is still largely unknown. With few exceptions [64], their absorption, distribution, metabolism and excretion characteristics remain to be determined, as well as their sub-acute and chronic toxicity. *F*-surfactants can influence protein adsorption onto particles and phagocytic uptake of particles by macrophages [65, 66]. The many unknowns that remain relating to their toxicity and pharmacology certainly hinders the acceptance of *F*-surfactants in pharmaceuticals.



When co-dispersed in water, *F*- and *H*-amphiphiles tend to form two types of micelles, rich in one or other of the amphiphiles [67–71]. When present simultaneously in bilayer membranes, they form phase-separated domains [72, 73]. Poor mixing also commonly leads to phase separations within Langmuir and Langmuir-Blodgett films [72, 74–76]. Application to the preparation of associative polymers [55, 77] and terpolymers [78] with mutually incompatible *F*- and *H*-domains has also been reported.



**Fig. 13-4.** The general trend for single-chain *F*-surfactants is to form bilayers ( $L_x$  phases) rather than micelles ( $L_1$  phases), which is more typical for their *H*-counterparts. For example, the single-chain *F*-alkylated phosphocholines **8** (even with short chains, e.g.,  $n = 8$ ,  $m = 2$ ) produce *F*-vesicles (b), while the *H*-analogs investigated only formed micelles (a)

The extreme hydrophobic character and, additionally, the lipophobic character of *F*-alkyl chains generate a powerful driving force for *F*-amphiphiles with *F*-chains longer than four carbon atoms to collect at interfaces, and to self-assemble into discrete compartmentalized organized molecular systems when dispersed at low concentrations in water and other solvents [2, 8]. *F*-amphiphiles display a stronger tendency to form bilayer membranes than *H*-analogs, generating well-organized stable films, bilayers, vesicles, tubules and fibers, with stability and properties generally unmatched by *H*-analogs.

The enhanced tendency for *F*-amphiphiles to self-assemble into  $L_x$  (fluid lamellar) rather than  $L_1$  (micellar) phases (Figure 13-4) and the powerful structuring and stabilizing effect provided by *F*-chains is remarkably illustrated by the formation of highly stable *F*-vesicles from *single-chain*, short (typically 10 C atoms) *F*-amphiphiles (e.g., **9**), without the need for any co-surfactant or any supplementary associative interaction, while their hydrogenated analogs only form micelles [79–81]. Such *F*-vesicles withstood heat sterilization and showed only little changes in particle size distribution after 3 months at 40 °C. This finding has since been confirmed in other systems [82, 83]. The differences in aggregation behavior of *F*- versus *H*-amphiphiles are in line with the difference in their packing parameter (which relates to the tail cross section to polar head area ratio) [80, 84–86]. The larger tail cross section of *F*-amphiphiles tends to favor formation of aggregates with lesser surface curvature; their stiffness tends to slow down aggregation kinetics.

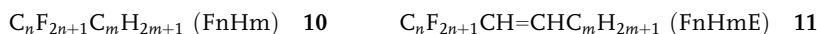
Likewise, *F*-amphiphiles have been reported to readily form hollow microtubules made of rolled-up bilayers [8, 62, 87]. While the presence of a chiral center is generally deemed necessary for the inception of the rolling-up of tubules, and hydrogen bonds are also usually involved in their formation, robust fluorinated tubules were obtained from *non-chiral*, non-hydrogen bonding single-chain *F*-amphiphiles such as **8** [87–89]. Helical fibers, several

microns in length, were obtained from *F*-alkylated glycolipids [90, 91]. *F*-tubules and fibers were also grown in ethanol, dimethylsulfoxide, formamide and dimethylformamide [50, 92] and supercritical CO<sub>2</sub> [93].

#### 13.2.4

##### Fluorocarbon–Hydrocarbon Diblocks: Fluorophilic/Lipophilic Amphiphiles

Linear *F*-alkyl/*H*-alkyl diblock compounds, such as **10** and **11** constitute a set of



*F*-amphiphiles that have mutually incompatible fluorophilic and lipophilic moieties, but are devoid of the hydrophilic polar head present in standard surfactants. These diblocks can play, with respect to fluoruous and hydrocarbonous phases, a role similar to that played by standard surfactants at a water/HC interface. They represent simple and valuable building blocks for producing and stabilizing colloids with fluoruous phases, and provide an effective means of modulating the properties of these colloids.

The synthesis of *F*-alkyl/*H*-alkyl diblocks is straightforward [94]. These diblocks can have dipole moments (primarily due to the CH<sub>2</sub>–CF<sub>2</sub> dipole), surface tensions and dielectric constants higher than those of both their totally fluorinated and totally hydrogenated analogs, and physical properties quite different from those of these analogs [2, 16, 27, 95]. *F*-alkyl/*H*-alkyl diblocks form micelles, although with low aggregation numbers, when dispersed in an HC and reverse micelles in an FC [96, 97]. They form gels in organic solvents, including FCs and HCs [98, 99]. They can reduce the surface tension of HCs [100, 101], lower the interfacial tension between an FC and water, and act as a co-surfactant that further reduces the FC/water interfacial tension in the presence of a phospholipid monolayer [102]. Langmuir films made from combinations of phospholipids and *F*-alkyl/*H*-alkyl diblocks display a unique reversible, vertical segregation phenomenon upon compression [103]. Novel, highly monodisperse, stable non-polar surface hemimicelles were obtained when a monolayer of FnHm was transferred onto a silicon wafer. The radius of the micelles was determined by the length of the *F*-chain and *H*-chain, demonstrating the possibility of decorating surfaces with molecular clusters of predetermined size in the nanometer range [104].

From the biological viewpoint, the still limited data that are available indicate a behavior close to that of FCs, including absence of hemolytic activity and effect on cell cultures, very low acute toxicity, absence of metabolism, and excretion rate dependent on block length [8, 105]. Diblocks thus appear to benefit from simplified pharmacology, which may facilitate their pharmaceutical development.

*F*-alkyl/*H*-alkyl diblocks have provided effective emulsifiers for the preparation of HC-in-FC emulsions and strong stabilization of FC-in-water emulsions when used in conjunction with an appropriate surfactant (Section 13.4.5). They have also been used as the dispersed phase of microemulsions in water [106]. Addition of diblocks to a fluoruous phase may help increase the solubility of lipophilic material. When present in a liposomal membrane, *F*-alkyl/*H*-alkyl diblocks impart to this membrane some of the properties obtained with complete *F*-surfactants (Section 13.6).

## 13.3

**Contrast Agents for Diagnostic Imaging**

Recent approval by the European or American health authorities of several contrast agents for ultrasound imaging has propelled FC-stabilized injectable microbubbles into the limelight. These agents constitute the first large market-size FC-based medical products to have become commercially available, which explains the tremendous activity that is currently focused on FC-based microbubbles. Targeted FC microbubbles and FC-in-water emulsions are now being investigated for molecular imaging, that is identifying the molecular signature (rather than anatomical signs) of disease by ultrasound or magnetic resonance (MR) imaging (Section 13.3.2).

## 13.3.1

**Gaseous Fluorocarbon-Loaded Microbubbles as Sound Reflectors for Ultrasound Imaging**13.3.1.1 **Needs and Challenges**

Worldwide echography is the most frequently used imaging modality. It is a non-invasive, portable (e.g., bedside), widespread, low-cost technique that allows diagnosis of numerous pathological conditions. However, as for any imaging technique, there are instances when contrast between tissues is not large enough to allow reliable, conclusive diagnosis. For instance, in the absence of a contrast agent, ultrasound imaging provides only limited information on the cardiovascular system, blood flow and organ perfusion. The availability of effective ultrasound contrast agents is having a considerable impact on diagnostic ultrasound imaging [107–114].

The optimal injectable sound scatterer is a tiny gas bubble, which is highly compressible and reflects sound waves several orders of magnitude more effectively than red blood cells. In the circulation this gas bubble needs to be stable long enough to provide an adequate imaging time window. It must also have minimal side effects. Its diameter, in the 1–5  $\mu\text{m}$  range, must be large enough to provide effective scattering intensity (which shows dependence to the sixth power of the bubble radius), yet small enough to easily cross capillary beds. Particle size needs to be well controlled and should not grow in the circulation. The microbubbles should preferably have a highly deformable soft shell, so as not to damp sound scattering. Their components obviously need to be safe and readily excretable, and should preferably not include proteinous material of human or animal origin.

13.3.1.2 **Principles of *In Vivo* Microbubble Stabilization: a Key Role for Perfluorochemicals**

When micron-size air bubbles are injected into the circulation, they dissolve rapidly in the blood under the combined actions of the blood pressure and the Laplace pressure ( $\Delta P = 2\sigma/r$ ) generated by surface tension (Figure 13-5). Additional contributors to bubble dissolution include oxygen metabolism and ultrasound energy. In order to hinder bubble dissolution, the gas inside the bubble must be less soluble in the blood than air. Perfluorochemical gases are obvious candidates for this role, as their water solubility is at least an order of magnitude lower than for HC analogs of similar volatility. The *in vivo* behavior of a microbubble filled only with an FC gas is depicted in Figure 13-6a. It first expands because the gases dissolved in the blood will be drawn into the bubble until the FC is diluted to

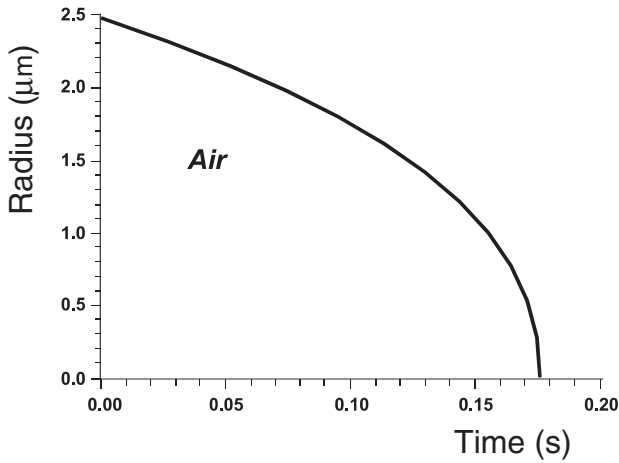


Fig. 13-5. Simulation of the dissolution of air-filled microbubbles in the blood under the combined action of surface tension and arterial blood pressure. From reference [117], with permission

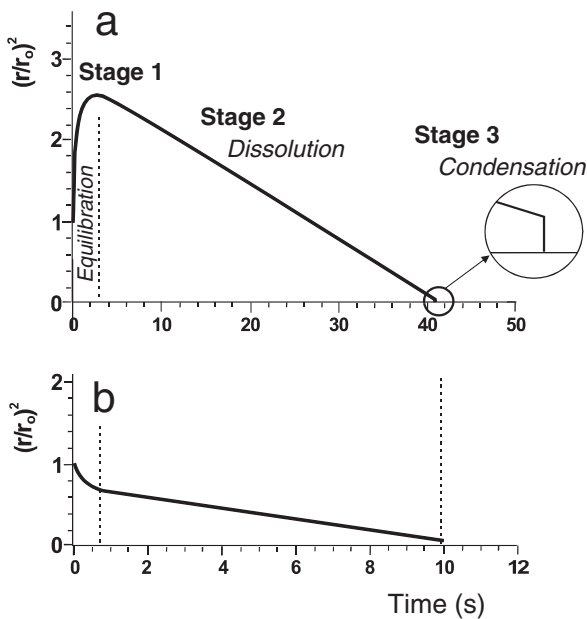
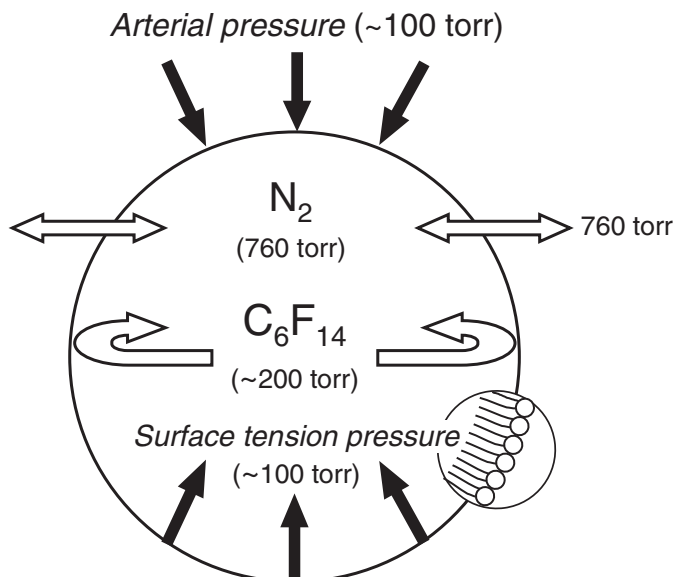


Fig. 13-6. Simulations of microbubble size changes in the circulation. a) Bubbles containing only an FC gas first expand as blood gases diffuse into the bubble, until an osmotic equilibrium is reached (stage 1); they then slowly shrink at a rate that depends on the solubility of the FC (stage 2); eventually the FC may condense and the bubble

collapse if the Laplace pressure exceeds the saturated vapor pressure of the FC (stage 3). b) In osmotically stabilized bubbles, the partial pressure of the FC gas counterbalances surface pressure and blood pressure, thus stabilizing the bubble at a predetermined size; the expansion phase is prevented. From reference [117], with permission



**Fig. 13-7.** Phospholipid-coated nitrogen microbubble osmotically stabilized by *F*-hexane vapor. At equilibrium, the rates of diffusion of the water-soluble blood gases in and out of the bubble are equal. The added partial pressure of the FC vapor counterbalances blood pressure and Laplace pressure

an osmotic equilibrium composition [115–117]. Such droplet growth in the circulation can be prevented by loading the bubble with just the amount of insoluble FC vapor needed to counterbalance the surface tension and blood pressure forces that push the gases inside the bubble towards dissolution (Figure 13-6b) [113, 117, 118]. Once osmotic equilibrium is reached, the rates of diffusion of the water-soluble gases in and out of the bubble are equal. The concentration of FC required to stabilize a microbubble at a given target diameter in the circulation (Figure 13-6b or Figure 13-7) can be calculated. The optimal FC osmotic stabilizing agent combines low water solubility and high saturated vapor pressure at body temperature [117]. An *in vivo* study indicated that *n*-C<sub>6</sub>F<sub>14</sub>, CF<sub>3</sub>(OCF<sub>2</sub>)<sub>3</sub>OCF<sub>3</sub> and CF<sub>3</sub>(OCF<sub>2</sub>CF<sub>2</sub>)OCF<sub>3</sub> are among the most effective FCs in this respect [119]. A further study of the effect of filling gases on the backscatter from microbubbles *in vivo* can be found in [120].

The bubble wall consists typically of 2–3 nm thick, highly expandable phospholipid monolayers or somewhat thicker membranes made from a heat-denatured protein or a biodegradable polymer. The properties of the bubble wall can significantly influence resonance frequency; the stiffer the shell, the higher the resonance frequency. Microbubbles a few microns in size are normally restricted to the vascular spaces, hence are essentially blood pool agents, i.e., agents that, when submitted to ultrasound, “light up” the blood, hence the blood vessels and chambers of the heart. Substantial negative surface charge (such as obtained by including palmitic acid or dipalmitoylphosphatidic acid in the lipid shell) can re-



sult in bubble retention within pulmonary and myocardial capillaries via complement-mediated attachment to the endothelium [121]. Such retention may be useful when delayed imaging is sought; it may, however, also raise some safety issues. The presence of poly-(ethylene glycol) (PEG) on the bubble's surface markedly reduced such attachment [121].

Because gas bubbles provide extremely high scattering intensity, the total dose of gas that is injected intravenously to patients is minuscule, typically 250  $\mu\text{L}$ , containing in the order of  $10^8$  microbubbles of a few  $\mu\text{m}$  in diameter. Peak blood concentrations of FC are then in the order of  $10\text{ ng mL}^{-1}$ . The total amount of material needed for effective diagnosis is in the order of milligrams as compared with grams for the contrast agents currently used in MR or X-ray imaging. The light *F*-chemicals used ultimately leave the body with the expired air. A pharmacokinetic study in humans indicated, for example, that diagnostic doses of *F*-pentane, administered in the form of an emulsion, had an elimination half-life of around 2 min; recovery of the FC in the expired air was almost complete after 2 h [122].

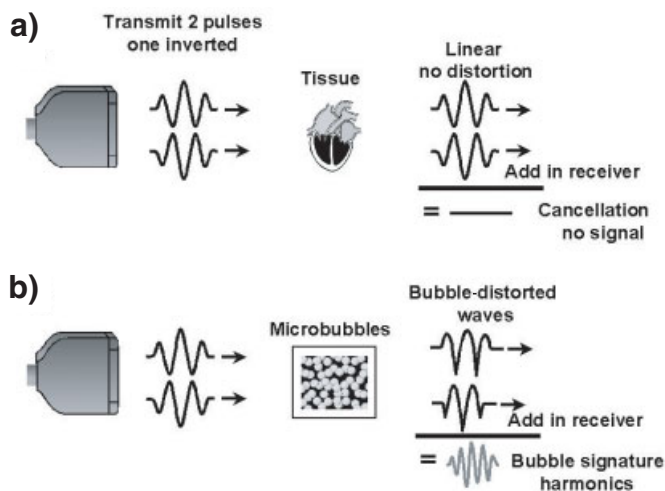
### 13.3.1.3 Bubble-Specific Imaging – Harmonics and Pulse Inversion Techniques

A unique feature of contrast echosonography as compared with any other imaging modality is that the contrast agent interacts with the sound waves [123–130]. Microbubbles rapidly expand and contract under the action of ultrasound. At a critical frequency, which depends primarily on bubble size, they resonate and become transmitters themselves. By chance, microbubbles a few microns in size resonate within the range of ultrasound frequencies used for diagnostic imaging. Moreover, when the acoustic pressure is sufficient, the microbubbles behave differently during the positive and negative pressure of the sound wave. Their oscillations being asymmetric generate non-linear echoes and a significant amount of super- and sub-harmonics of the incident sound wave [123, 129, 131]. “Harmonic imaging” can be performed by using broadband transducers that transmit between 1.3 and 3 MHz and receive at twice that frequency, while filtering the incident frequency. This way, the signals from red blood cells and tissues (which are poor resonators and do not generate much harmonics) are largely suppressed, leaving the signals at the second harmonic frequency, which originate essentially from the microbubbles. Harmonic imaging thus enhances the contrast between microbubble-containing and non-microbubble-containing tissues, hence is a *microbubble-specific* imaging mode [123, 129, 131–136].

The resolution and sensitivity of harmonic imaging have been further enhanced by using appropriate pulse sequences. In pulse inversion techniques [137, 138], two ultrasound pulses are emitted in close sequence, the second  $180^\circ$  out of phase with the first (Figure 13-8). When the received signals of the two pulses are added, the echoes from linear reflectors essentially cancel out since they are equal and opposite. On the contrary, the signals from the microbubbles, which are non-linear reflectors, do not cancel out, yielding a highly contrasted image (Figure 13-9). This technique is particularly effective at producing high contrast, high resolution imaging of blood vessels [139]. Its sensitivity is so high that a single microbubble can be monitored [140].

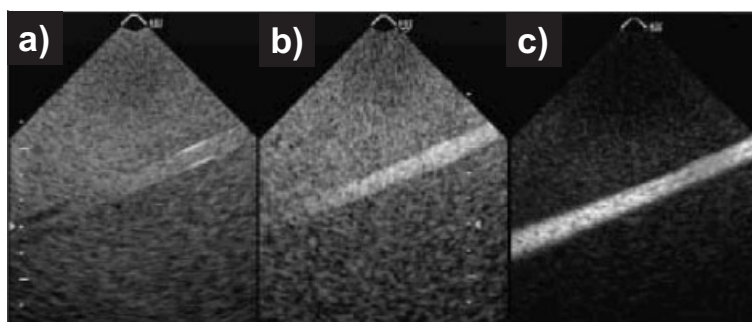
### 13.3.1.4 Controlled Bubble Destruction: Monitoring Tissue Perfusion

Another unique property of microbubble contrast agents is that the bubbles can be destroyed in a controlled fashion by ultrasound, especially at resonance. When the bubble shell is disrupted, the scattering level increases sharply for a short period of time and the scat-



**Fig. 13-8.** Phase inversion harmonic imaging. Early second harmonic imaging used band pass filters that allowed the generation of images from frequencies mostly reflected by microbubbles. However, these images still contained some signal from the tissues. The much more efficient pulse inversion modes use a pulse cancellation technique: two pulses are sent out close together in time. The second pulse is an inverted replica

( $180^\circ$  phase shift) of the first. Because tissues do not distort sound, the reflections from tissues, when added, cancel each other [panel a)]. The distortions produced when sound is reflected by microbubbles affect the two transmitted pulses differently. When added, these pulses do not cancel, producing an image that is highly sensitive to the presence of microbubbles [panel b)]. Highly contrasted high resolution images are produced



**Fig. 13-9.** *In vitro* images of a “phantom” (model) vessel containing the FC bubble contrast agent Optison surrounded by tissue-mimicking material. a) conventional, non-contrasted image; b) harmonic image with improved contrast

between agent and tissue; c) pulse inversion harmonic image; contrast is further improved by suppressing linear echoes from tissue. From reference [110], with permission

tered signal becomes highly nonlinear, hence well suited for harmonic imaging [129, 141]. This effect is irreversible and lasts until the shell-free gas microbubble is dissolved in the blood.

Controlled bubble destruction (“bleaching”) by intermittent high power pulses in a region of interest, and monitoring of bubble reappearance in the field also provides a very effective tool for kinetic studies [138, 142–145]. This technique allows the assessment of tissue blood flow velocity and fractional blood volume. Accurate determination of blood velocity supposes that the vast majority of the bubbles within the region of interest will be destroyed by an ultrasonic pulse of sufficient intensity. Different contrast agents displayed significant differences in sensitivity to acoustic pressure [146]. A phantom that mimics the microcirculation allowed standardized analysis of contrast replenishment kinetics after acoustic destruction of the microbubbles at velocities comparable to those found in capillary beds [147]. Bubble destruction depends on frequency and intensity of the ultrasound waves. At very high energy (as expressed by a “mechanical index”) destruction of microbubble-containing phagocytic cells can occur [128]. Bubble destruction can be limited by use of low acoustic power and/or intermittent insonation and increasing the time interval between pulses. The possible effects of microbubble destruction on tissues have also been investigated [148, 149]. The extremely localized, transient heating of a liquid shell of micrometer thickness around a bubble as a result of acoustic heat deposition was not deemed likely to cause severe biological damage [150].

#### 13.3.1.5 The Products

The initial commercial ultrasound contrast agents Albunex (Molecular Biosystems Inc., San Diego, CA, USA) and Echovist (Schering AG, Berlin, Germany) that were developed in the early 1990s did not contain FCs. Their intravascular persistence was limited and they did not withstand repeated passage through the pulmonary capillary beds. When injected intravenously they could not reach the left cardiac ventricle, and hence had little utility.

The first FC-based agent, Optison® (developed by Molecular Biosystems; now marketed by Amersham Health Corp., Little Chaford, UK) was launched in 1998. It consists of an aqueous suspension of *F*-propane microspheres, 2.0 to 4.5  $\mu\text{m}$  in diameter, whose shells are made of heat-denaturated human albumin. The agent effectively improves ultrasound imaging and displays minimal side effects [143, 151–155]. Definity®, developed by ImaRx (Tucson, AZ, USA) and DuPont Pharmaceutical Co. (North Billerica, MA, USA) [156–158] was licensed in the United States in 2001 and is now marketed by Bristol-Myers-Squibb (New York, USA). It is also a dispersion of *F*-propane microbubbles, 1 to 3.3  $\mu\text{m}$  in diameter, but with a phospholipid monolayer coating consisting of dipalmitoylphosphatidylcholine (DPPC), a methylPEG dipalmitoylphosphatidylethanolamine (MPEG5000 DPPE) and a minor amount of negatively charged dipalmitoylphosphatidic acid. The product comes as a vial containing the precursor components that, upon agitation by the sonographer in a calibrated mechanical shaker, yields the injectable microbubble dispersion. Both Optison and Definity have a shelf life of two years under refrigerated storage conditions.

SonoVue® (Bracco, Milan, Italy) [159–164] has been licensed in Europe. It uses  $\text{SF}_6$  as the poorly water soluble *F*-chemical and a phospholipids/PEG/palmitic acid membrane. It comes as a lyophilized powder stored under  $\text{SF}_6$ , which upon addition of a saline solution, yields the injectable agent.

Imagent™, which is based on the osmotic stabilization concept developed by Alliance Pharmaceutical Corp. (San Diego, CA, USA) and has been approved in the United State in 2002, is formulated as a heat-sterilized spray-dried powder comprising hollow, amorphous and porous microspheres under a nitrogen/*F*-hexane atmosphere. The microspheres are made of dimyristoylphosphatidylcholine (DMPC), hydroxyethylstarch (as a wall-forming agent), a poloxamer (as a wetting agent), sodium chloride and a phosphate buffer (for tonicity and pH control). Upon addition of water, a phospholipid monolayer forms that traps the gas mixture present in the headspace inside a microbubble. The amount of FC in the gas mixture was calculated to provide bubbles about 3 μm in diameter in the circulation, and ensure that these bubbles could not grow *in vivo*, but rather shrink slowly over time. The persistence of the microbubbles in the blood is controlled by their eventual dissolution rather than by clearance by the reticuloendothelial system [119]. Recent reports on the product's use and efficacy include [111, 135, 136, 165–167]. Imagent has now been licensed to and is being marketed by IMCOR Pharmaceutical Co. (San Diego, CA).

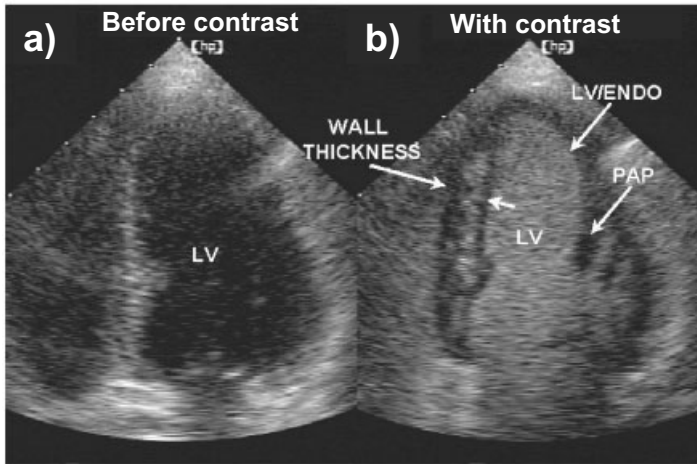
All of the above commercial agents appear to benefit from satisfactory side effect profiles. With several million injections given, no death has been reported that is attributable to the agent, nor has there been any clinically significant side effects.

A phase change from liquid at room temperature to gaseous at body temperature was the basis for an injectable *F*-pentane emulsion stabilized by an *F*-surfactant (Sonus Pharmaceuticals, Bothel, WA, USA) [122, 168, 169]. This product was, however, abandoned, possibly because bubble formation and growth in the circulation were difficult to control, and/or because of side-effects [170]. A negatively charged variant of this agent was briefly investigated [171].

Further agents and formulations under investigation include PFC-exposed sonicated dextrose albumin (PESDA) [172–175]; Acusphere's AI-700, which has a biodegradable synthetic polymer shell [176]; BR14 (Bracco), a lipid-coated *F*-butane microbubble [177–179]; Sonazoid® (Amersham Health), which consists of lipid-stabilized *F*-butane microbubbles, but whose development appears to have been interrupted [180]; and MP1950 (Mallinckrodt, St. Louis, MO, USA), a sonicated dispersion of *F*-butane in an aqueous micellar dispersion of phospholipids, pegylated phospholipid and PEG stearate [181]. Targeted microbubbles are also being developed (Section 13.3.2).

#### 13.3.1.6 Medical Imaging Applications

Being restricted to the vascular space, the present FC-based ultrasound contrast agents are ideal for echocardiography and vascular imaging. Echocardiography is extensively used to assess ischemic heart disease. The approved contrast agents have all demonstrated left ventricular opacification, significant improvement in endocardial border delineation (Figure 13-10) and assessment of wall motion during systolic contraction, hence allowing improved detection of structural and functional abnormalities, as compared with non-contrasted ultrasound procedures [108–110, 112]. For example, harmonic ultrasound imaging at the bedside with Optison allowed determination of left ventricular wall motion and ejection fraction (the percentage of the blood in the left ventricle that is ejected during a heart beat), hence ventricular function, in 91% of patients, as compared with 56% with standard imaging, and prevented misinterpretations in 44% of studies [182]. Contrast-echocardiography during stress is even more effective than imaging at rest [109]. Improved image quality



**Fig. 13-10.** Left ventricular cavity opacification. a) A view of the left ventricle of a patient; b) the same view after a bolus injection of Imagent microbubbles. The left ventricle (LV), endocardial border (LV/ENDO) and papillary muscle (PAP) are now visualized, which was not the case in the

absence of contrast agent. This allowed myocardial thickening to be evaluated. When the heart is in motion, normal functioning heart muscle thickens as it contracts, abnormal functioning heart muscle moves less and does not thicken. From reference [420], with permission

results in increased diagnostic accuracy, a reduction in downstream testing, and possible improvement in patient outcome. Use of contrast agents may therefore have a significant impact on patient management in the intensive care setting [107].

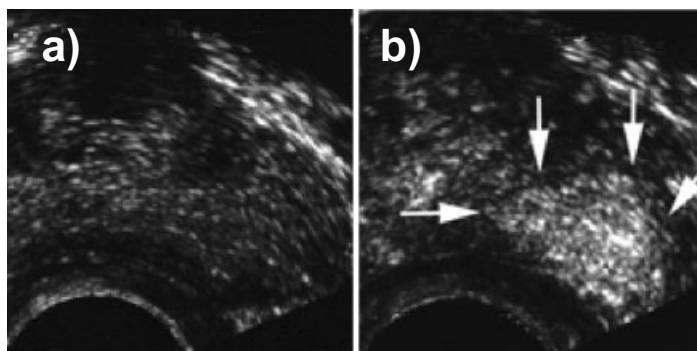
Vascular imaging is another important goal for contrast echosonography. Filling a blood vessel with a contrast agent allows detecting vessel occlusions, wall abnormalities such as atherosclerotic plaques, and assessment of their effects on blood flow. Clear visualization of blood clots can be obtained and even, because of the ability of ultrasound to monitor single microbubbles, of the tiny open channels that form as a clot begins to recanalize [183]. Accurate demonstration of plaques and plaque ulceration was reported [166, 184]. Unstable plaques are susceptible to rupture and microthrombus formation that often precede myocardial infarction, ischemic attacks and strokes. Their timely detection may allow early therapeutic intervention.

Controlled microbubble destruction (bleaching) by a high energy pulse, followed by imaging with a non-destructive pulse allows accurate imaging of tissue perfusion and detection of vascular insufficiencies, hence of vascular occlusion [135, 144, 185]. Assessment of myocardial perfusion, hence of microvascular integrity, is a key to diagnosing coronary artery disease and myocardial infarction, determining infarct area during coronary occlusion and the area at risk of necrosis, assessing coronary stenosis, and monitoring the success of thrombolytic treatment, hence guide subsequent patient management [109, 164, 167, 186–189]. Assessment of perfusion differentiated between stunning and necrosis and accurately predicted recovery of left ventricular function in patients after acute myocardial infarction [190]. Further recent papers demonstrating the utility of PFC microbubbles to assess myocardial perfusion and viability include [153, 157, 173, 174, 191]. Accuracy of myocardial

perfusion quantification was similar or superior to that provided by  $^{99}\text{Tc}$  single-photon emission computed tomography, a much more cumbersome and costly technique [112, 175]. Contrast-specific ultrasound of the myocardium may thus provide results equivalent to perfusion imaging with radionuclides with the advantages of providing real-time, direct information on both heart function and perfusion at lower cost and of eliminating the handling of radioactive materials [152, 175].

By visualizing the arterial tree and filling pattern within an organ, contrast-specific sonography can allow detection of abnormal regions. It can also improve characterization of the disease, i.e., infection versus infarction versus trauma versus cancer [155, 192], and detection and assessment of angiogenesis consequent to tumor growth [193]. Regional cerebral blood flow mapping was achieved in newborn piglets [194]. Analysis of microbubble refill kinetics in human cerebral microcirculation after bubble destruction by transcranial ultrasound allowed quantitative evaluation of cerebral blood flow [195]. Similar techniques allowed visualization and quantification of kidney [153, 196], liver [153] and tumor microvascularity [136, 197, 198]. Renal perfusion and perfusion defects in animal models were depicted [135, 199, 200]. The detection of liver lesions, including carcinoma and metastasis were substantially enhanced when contrast agent was present [201, 202]. Contrast-echosonography may help monitor the microvascular changes associated with the growth of malignant tumors and with tumor response to treatment more easily than CT or MR imaging [203]. A clinical study indicated that sonographic contrast may help identify prostate cancer based on differences in vasculature between malignant and normal tissue (Figure 13-11) [165].

Finally, contrast imaging can facilitate guidance in therapeutic procedures such as biopsies, cryo- and radiofrequency ablation of malignant tissue and metastasis, assessment of tissue destruction and detection of any residual viable tumor [204]. It can also provide a non-invasive means of monitoring the outcome of surgical intervention or drug treatment. Furthermore, microbubbles may constitute effective tools for drug development to determine the pharmacokinetics and pharmacodynamics of new molecules, establish therapeutic efficacy, dose regimen, etc.

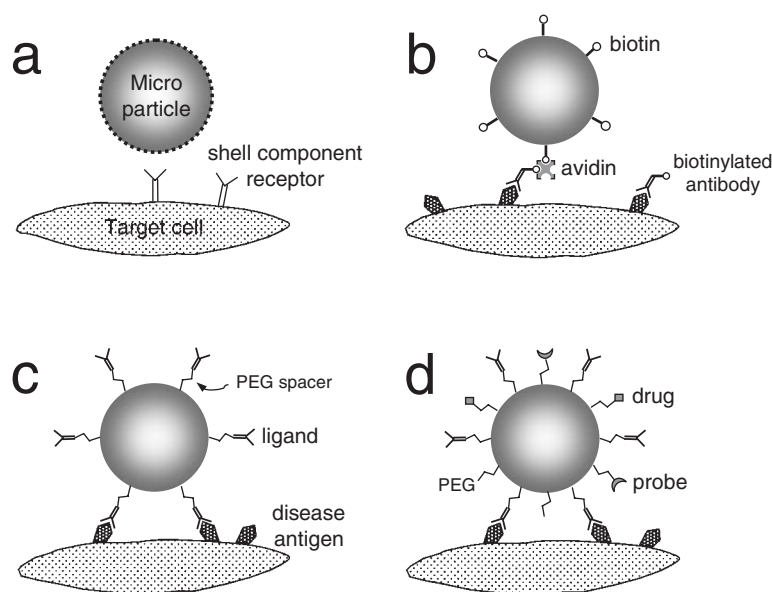


**Fig. 13-11.** Prostate echography a) before and b) after administration of Imagent. The presence of an abnormal mass is clearly seen, which was not the case in the absence of contrast agent. From reference [165], with permission

## 13.3.2

**Targeted Fluorinated Colloids for Molecular Imaging – Molecular Markers for Specific Pathologies**

Substantial efforts are now being devoted to designing FC microbubbles [205–207] and FC emulsion droplets [208] that seek the unique molecular signature of a given pathology, making diseased tissues detectable by ultrasound or MR imaging. Molecular imaging (the detection of specific molecular markers such as proteins or other cellular receptors associated with a given pathology) extends the basis for diagnosis of pathology from anatomic description to detection of biochemical changes. Site-targeted particles (Figure 13-12) that are retained by specific diseased tissues, are expected to provide higher sensitivity and specificity than standard blood pool agents, hence earlier and safer assessment of pathology. Because microbubbles and emulsion droplets normally do not escape the circulation, targeting is essentially restricted to pathologies that express specific ligands within the vascular lumen, typically endothelial cells, leukocytes and thrombi. Targeting of activated endothelial cells may thus be used to signal thrombi, areas of inflammation, atherosclerotic plaques and angiogenesis in solid tumors. Additionally, particles targeted to specific cell-surface epitopes can provide site-specific drug and gene delivery (Section 13.6).



**Fig. 13-12.** Schematic representation of FC microbubble and emulsion droplet targeting strategies for molecular imaging and drug delivery. a) Passive targeting using the intrinsic ability of certain shell components (e.g., albumin or phosphatidylserine) to bind to receptors expressed on the target cell's surface. b) Binding of the particle, through avidin–biotin interactions, to

antibodies or other ligands that recognize specific disease-related antigens. c) Covalent binding of such ligands, usually through a PEG spacer, to a microparticle shell component. d) Simultaneous binding to a targeted microparticle of stealth-providing elements, drugs and markers (e.g., a  $\text{Gd}^{+++}$  chelate). Adapted from references [205, 208], with permission

### 13.3.2.1 “Passive” Targeting of Microbubbles

Certain microbubbles provide a late phase of enhancement when, after initial enhancement of the blood pool, they highlight liver and spleen parenchyma. This can occur when bubbles are cleared from the blood stream and taken up by the reticuloendothelial system (RES) or are mechanically slowed down within the sinusoidal network [209].

Passive targeting of microbubbles relies essentially on size and shell characteristics. It allows detection of very small size liver lesions, including carcinoma and metastasis, as microbubbles highlight normal tissue, but not tumors [210]. RES accumulation also allowed evaluation of hemorrhage within the liver and spleen in dogs [180], providing potential benefit for the assessment of trauma victims.

Assessment of inflammation is another important goal for microbubble-enhanced imaging. Both albumin- and lipid-coated PFC microbubbles were found to be retained in inflamed tissue, for example after myocardial ischemia-reperfusion injury, because of  $\beta_2$ -integrin- and complement-mediated attachment to and phagocytosis by activated leukocytes that adhere to vascular endothelium [211, 212]. The phagocytosed microbubbles remained acoustically active well after microbubbles had been cleared from the blood pool [212]. These non-specific leukocyte/microbubble interactions may thus provide a means of imaging inflammation, in which leukocyte adhesion plays an important part, and monitoring treatment. Retention of *F*-butane microbubbles in areas of inflammation has been further increased by incorporating phosphatidylserine into the lipid shell [213]. This targeting procedure was used to assess the severity of myocardial inflammation after ischemia/reperfusion [214]. Phagocytosed microbubbles experience a viscous damping that increases the frequency of their echo as compared with free microbubbles [128]. The distinct signals from microbubbles inside of activated neutrophils may thus provide a unique tool for selective identification of sites of inflammation.

### 13.3.2.2 Active Site-Directed Targeting of Microbubbles

Active targeting supposes attachment to the microbubbles' surface of receptor ligands, including monoclonal antibodies, polysaccharides and peptides, which recognize disease antigens. Binding can be achieved through covalent or non-covalent (hydrophobic, avidin/biotin pairing) interactions [215]. The strength of receptor–ligand mediated adhesion between pegylated phospholipid-coated microbubbles and coated glass beads was shown to depend on bubble surface architecture [216]. Strong attachment required that the ligand be attached to the shell via an extended PEG spacer (i.e., a spacer that is longer than the PEG chains that were used as a shell stabilizer), thus projecting the ligand away from the bubble's surface and enhancing its availability.

Active targeting to inflammation sites can be achieved with FC microparticles that have antibodies to endothelium cell adhesion molecules attached on their surface. Such adhesion molecules (which are expressed on endothelial cells activated during the inflammatory response) include P-selectin, intercellular adhesion molecule-1 (ICAM-1) and certain integrins. An anti-ICAM-1 monoclonal antibody has been covalently bound to a lipid component of the shell of *F*-butane microbubbles through amide bonds [217]. These microbubbles demonstrated selective binding to activated cultured endothelial cells overexpressing ICAM-1 *in vitro*. In another approach, conjugation, via a biotin/avidin system, of antibodies against P-selectin to *F*-butane/lipid microbubbles through a PEG spacer increased their re-



tention in inflamed tissue, allowing early detection of ischemia-reperfusion injury of the kidney [218]. The binding and detachment kinetics of such microbubbles when exposed to shear stress have been investigated [218a].

Detection of blood clots is another clinically important goal. Targeting of vascular clots has been achieved with a FC microbubble (e.g., MRX-408, ImaRx Pharmaceutical Corp., Tucson, AZ, USA) having a peptide with an Arg-Gly-Asp sequence covalently attached via a PEG spacer to a lipid membrane component [219, 220]. The peptide binds selectively to the GPIIb/IIIa fibrinogen receptor on activated platelets that attach to thrombi. Detection of thrombus was demonstrated in dog and mouse models using such targeted microbubbles [221, 220].

*F*-butane/lipid microbubbles targeted to  $\alpha_v$ -integrins (which are overexpressed in neo-vascular endothelium) allowed assessment of regions of angiogenesis in mice [222]. Such agents may improve tumor imaging, as tumors promote angiogenesis for their growth, and hence help diagnose cancer at earlier stages [203]. They may also help monitor promotion of angiogenesis in chronically ischemic tissue.

### 13.3.2.3 Targeted Fluorocarbon Emulsions for Diagnosis by Ultrasound or Magnetic Resonance Imaging

Targeted FC emulsions also provide a very interesting approach to molecular imaging of pathology [208, 223, 224]. The target pathologies are the same as for microbubbles and include inflammation, thrombi, atherosclerosis and tumor-related angiogenesis, each having its specific molecular signature. Detection of these targets and differentiation from normal tissue likewise involves binding onto the droplet's surface of ligands that specifically bind to cellular epitopes and receptors characteristic of the target pathology.

While enhancement of ultrasonic scattering by an untargeted emulsion is poor, the scattering observed when the droplets attach collectively in adequate density to a surface is remarkable. This phenomenon has been accounted for by a simple acoustic transmission line model [224, 225]. In this model, a thin, contiguous layer of ligand-bound emulsion droplets, which has essentially the properties of the neat FC, creates an acoustically reflective interface between the targeted surface and its surrounding. *In vitro* acoustic reflectivity enhancement of a nitrocellulose membrane or plasma thrombi targets was inversely correlated with the acoustic impedance of the FC. The greatest enhancement, in the series investigated, was obtained for *F*-hexane. An advantage of FC emulsions over FC microbubbles may reside in their longer intravascular persistence.

Specific detection of thrombi in a canine model demonstrated the concept of molecular imaging with targeted FC emulsions [223]. In a first step, a biotinylated monoclonal anti-fibrin antibody was administered that accumulated at the target. Avidin, which attaches to the biotinylated ligand, was then infused. In a third step, an FC emulsion that had a biotinylated phosphatidylethanolamine incorporated in its lipid membrane was administered, which attached to the avidin–biotin complex, and hence to the target site. The time course of binding of site-targeted FC emulsions to human thrombi incubated with a biotinylated monoclonal antifibrin antibody and then exposed to avidin has been investigated *in vitro* [226]. The same biotin/avidin binding strategy allowed visualization of carotid artery overstretch inflammation injury in pigs after balloon angioplasty using a tissue factor-targeted emulsion (tissue factor is a transmembrane glycoprotein responsible for initiating the coag-

ulation cascade) [227]. Subsequently, a more realistic approach, from a practical and product development standpoint, used an emulsion with antibodies covalently bound to a component of the interfacial film, allowing single step administration [228, 229].

Incorporation of paramagnetic material (e.g., a gadolinium chelate-phosphatidylethanolamine) into the membrane of ligand-targeted FC emulsion droplets provided contrast agents useful with both ultrasound and MR imaging modalities [208]. For example, paramagnetic fibrin-specific FC emulsion droplets provided sensitive detection and localization of clots *in vitro* and *in vivo* (dogs), which may allow early identification of fibrin deposits in unstable atherosclerotic plaques [228]. The lipid coating of the emulsion droplets used for the *in vivo* studies had both an anti-fibrin monoclonal antibody and gadolinium diethylamine-triaminepentaacetic acid (DTPA)-phosphatidylethanolamine attached. A similar Gd-FC emulsion, with an  $\alpha_v\beta_3$  integrin (a molecular marker of angiogenic endothelium) antibody attached, allowed localization of the molecular epitopes of neovasculature in rabbits [230]. Such agents may improve detection of tumors and metastasis, and monitoring of therapy.

Further ligand-targeted FC emulsions are being investigated that combine site-directed ultrasound or MR imaging and drug delivery capacity (Section 13.6).

### 13.3.3

#### Further Uses of Fluorocarbons in Diagnosis

Neat *F*-octyl bromide has gained approval in the United States for oral use as a bowel marker during MR imaging of the gastrointestinal tract. In this case it is the absence of protons, hence of the signal, that creates the desired contrast, improving stomach and bowel wall delineation, thus facilitating the detection of pathology [231]. Fast *in vivo*  $^{19}\text{F}$  NMR imaging was used to monitor clearance of *F*-octyl bromide from the liver and spleen of rats, based on the reduction of the  $^{19}\text{F}$  spin-lattice relaxation parameter  $T_1$  by the paramagnetic  $\text{O}_2$  molecule [232]. The same technique allowed measurement of partial  $\text{O}_2$  pressure in the RES organs using bis(*F*-butyl)ethene [233]. FC emulsions allowed quantitative mapping of  $\text{O}_2$  partial pressure by NMR in organs [234] and tumors [235]. Myocardial  $p\text{O}_2$  monitoring with  $^{19}\text{F}$  MR imaging demonstrated changes with global and regional ischemia [236]. Aerosolized *F*-tributylamine was investigated as a means of analyzing lung structure and oxygenation patterns using  $^{19}\text{F}$  NMR [237]. An emulsion of *F*-15-crown-5-ether (20 magnetically equivalent  $^{19}\text{F}$  nuclei) was used to map  $\text{O}_2$  tension in tumors by analyzing  $^{19}\text{F}$  relaxation rates [238, 239]. The same emulsion, when directly infused into the interstitial/ventricular space in the rat brain, allowed investigation of the effect of hyperoxia, hypoxia and  $\text{CO}_2$  concentration on cerebral interstitial  $\text{O}_2$  tension [240]. Recently, such an emulsion was used as a “gold standard” to validate a  $^1\text{H}$  MR imaging method to assess changes in tumor oxygenation in carbogen (95%  $\text{O}_2$ /5%  $\text{CO}_2$ )-breathing rats [241]. In another example, neat *F*-benzene was directly deposited in the tumor, providing the local  $\text{O}_2$  sensor that allowed mapping of tumor  $\text{O}_2$  tension by  $^{19}\text{F}$  MR imaging techniques [242]. An *F*-octyl bromide emulsion allowed intravenous delivery of laser-polarized xenon, making *in vivo*  $^{129}\text{Xe}$  NMR studies possible [243]. However, such use appears limited by the rapid exchange of Xe with the water environment. Externally applied FC-filled pads are available commercially (SatPad®) which improve magnetic homogeneity, hence image quality, when fat saturation techniques are used during  $^1\text{H}$  MR imaging [244].

X-ray radiography allowed monitoring of FC distribution during liquid ventilation of patients with the radiopaque FC *F*-octyl bromide [36, 38, 245, 246]. Percutaneous computed tomography after subcutaneous injection of an FC emulsion effectively depicted intranodal distribution of macrophages in lymph nodes, which is important for cancer staging [247].

### 13.4

#### **In Vivo Oxygen Delivery: Fluorocarbon-in-Water Emulsions**

Considerable research and development efforts have focused on engineering and investigating FC-in-water emulsions for *in vivo* oxygen delivery (blood substitutes). These efforts have recently been analyzed in detail, including the context of blood transfusion issues: basic principles of *in vivo* O<sub>2</sub> delivery by injectable FC emulsions; formulation, engineering and characterization issues; *in vivo* behavior; potential indications and clinical development status [3–5, 248]. For recent updates on FC emulsion development see [6, 248a]. Therefore, this topic will only be briefly surveyed here. Reports on blood substitute research in Russia can be found in references [249, 250].

#### 13.4.1

##### **Objectives and Challenges**

In short, reasons for developing “blood substitutes” include: the reluctance that has developed against allogeneic (donor) blood transfusion through fear of infectious risks; the realization that banked blood is less effective than fresh blood; evidence that donor blood may reduce the immune responsiveness of the organism; shortages in blood collection to meet the augmenting needs of an aging population; and the possibility of providing the developing countries with an alternative to blood banking. Examples of recent papers on these issues include: those dealing with the change in the physicians’ attitude vis-à-vis blood transfusion [251]; the transmission of prion by blood transfusion [252]; transfusion-related acute lung injury [253]; transfusion mortality due to clerical errors [254]; and a review of immunological aspects of blood transfusions [255]. An analysis of the perceived risks of transfusion in the UK shows that, given a choice, anesthetists would more likely accept a blood substitute than donor blood [256]. Another paper concludes that mass appeal to blood donation is not an appropriate response in the case of a disaster [257].

Use of O<sub>2</sub>-carrying injectable FC emulsions during surgery is expected to provide effective O<sub>2</sub> delivery (thus preventing tissue ischemia) and reduction in exposure of patients to donor blood. Consequently, O<sub>2</sub> carriers could help mitigate the increasingly frequent blood shortages. FC emulsions could also help bridge the time gap between the moment when a critical need for increased tissue oxygenation is determined and transfusion of compatible blood becomes possible, or the time between transfusion and full effectiveness of the transfused banked blood. Trauma is one such situation. Further potential applications for FC-based O<sub>2</sub> carriers include use during cardiopulmonary bypass surgery, treatment of acute myocardial infarction and stroke, use for cardioplegia and reperfusion. Oxygenation of hypoxic tumors may improve the response of tumor cells to radio- and chemotherapy. Use of FC-enriched perfusates may help increase the availability and quality of organs suitable for transplantation. FC emulsions are also being investigated for treatment of sickle cell disease, treat-

ment of decompression sickness, as research tools for stabilizing and controlling animal models, organs and tissues, in cell culture technology, and as drug delivery systems [5, 258, 259]. Targeted FC emulsions offer potential for molecular imaging and drug delivery (Sections 13.3.2 and 13.6.1).

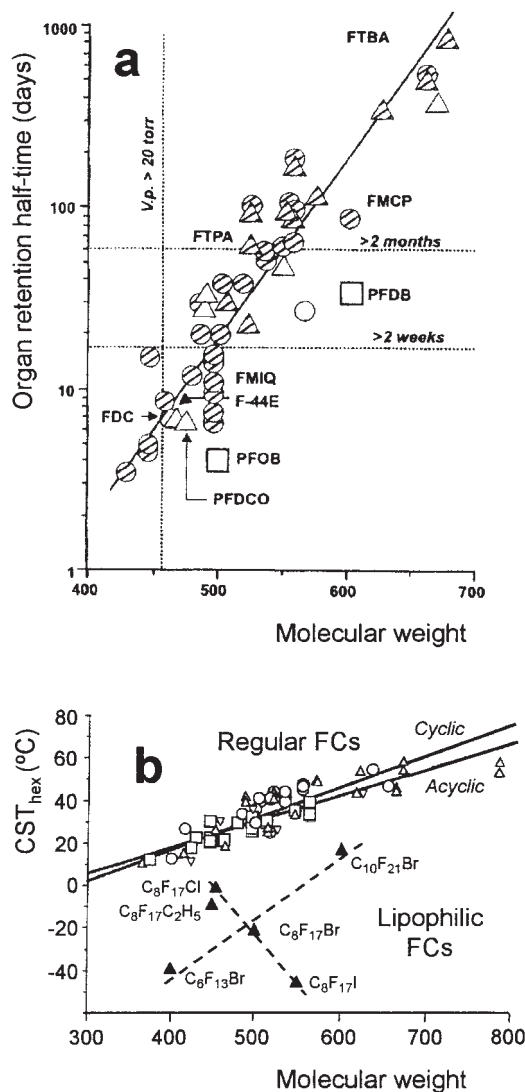
The principal challenges in the development of injectable FC-in-water emulsions included: selecting an FC that is readily excretable, easy to manufacture and to emulsify; preparing small-sized heat-sterilizable emulsions using a surfactant well accepted in the pharmaceutical industry; controlling particle size and counteracting molecular diffusion, which is responsible for particle size growth over time; understanding the *in vivo* behavior of the emulsion and minimizing its side effects; and defining conditions of use for clinical evaluation and optimal benefit to the patient. Also important are cost-effectiveness, user-friendliness, and compliance with current Good Manufacturing Practices and regulations from health authorities.

#### 13.4.2

##### Selecting a Fluorocarbon with Lipophilic Character: Perfluorooctyl Bromide

The most critical criterion for selecting an FC for intravascular use turned out to be its fluorophilic/lipophilic balance, as it largely determines the rate of excretion of the FC (unchanged, with the expired air) from the body [3, 5]. This is because the rate-determining step in the elimination process is dissolution of the FC into lipid carriers in the blood. Lipid solubility also largely determines tissue distribution and accumulation. The solubility of FCs in lipids is therefore an essential parameter for FC selection. The lipophilicity of an FC is reflected by its critical solution temperature in *n*-hexane ( $CST_{\text{hex}}$ , the temperature at which equal volumes of the FC and hexane form a single isotropic phase; Figure 13-13b).

The organ retention half-time of regular FCs turned out to be primarily an exponential function of MW, (and  $CST_{\text{hex}}$  a linear function of MW) reflecting the decreasing lipid solubility generally attached to the increasing molecular volume of the solute (Figure 13-13). Neither cyclization nor branching, or the presence of heteroatoms had any significant effect on organ retention [260–262]. On the other hand, the presence of lipophilic elements, such as Cl, Br or a  $\text{CH}_2\text{CH}_3$  moiety, causes a definite lowering of the  $CST$  and increase in excretion rate [3]. *F*-Octyl bromide was selected as an injectable  $\text{O}_2$  carrier primary because its organ half-life was shorter than that of other FCs of similar MW and vapor pressure. The lipophilic character induced by the well-exposed, polarizable terminal bromine atom in  $\text{C}_8\text{F}_{17}\text{Br}$  translates into a  $CST_{\text{hex}}$  of around  $-20^\circ\text{C}$ , i.e., about  $25^\circ\text{C}$  lower than that of  $\text{C}_8\text{F}_{18}$  (in spite of higher MW) and about  $50^\circ\text{C}$  lower than that of *F*-*N*-methyldecahydroisoquinoline ( $\text{C}_{10}\text{F}_{19}\text{N}$ ), an earlier candidate  $\text{O}_2$  carrier with a similar MW to  $\text{C}_8\text{F}_{17}\text{Br}$ . The effect of one Br on the solubility of an FC in olive oil was essentially equivalent to that of two Cl and almost comparable to that of a  $\text{C}_2\text{H}_5$  group, and the effect of two terminal Br was equivalent to that of one terminal I [263]. A too high vapor pressure was observed to cause a so-called increased pulmonary residual volume effect due to retention of air in the alveoli in certain animal species [264]. Although this phenomenon, which depends on airways size has never been reported with humans, the vapor pressure of the FC phase should probably not exceed around 10 torr.



**Fig. 13-13.** a) Organ retention of regular FCs *in vivo* is an exponential function of molecular weight. Lipophilic FCs are excreted faster than regular FCs of similar MW (FDC, *F*-decalin; FTPA, *F*-tripropylamine; FTBA, *F*-tributylamine; PFDCO, *F*- $\alpha,\omega$ -dichlorooctane; PFOB, *F*-octyl bromide; F-44E, bis(*F*-butyl)ethene; FMIQ, *F*-*N*-methyl-decahydroisoquinoline; PFDB, *F*-decyl bromide;

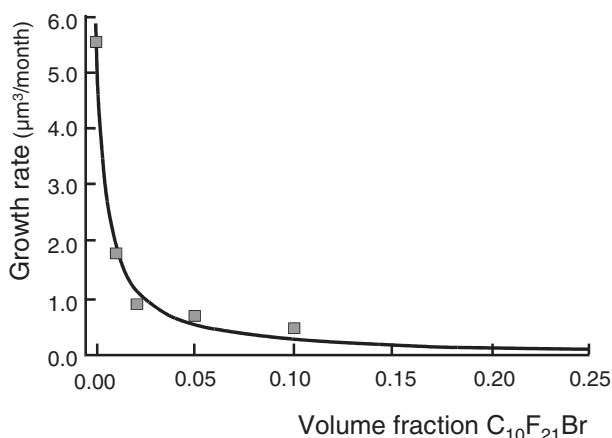
FMCP, *F*-*N*-methylcyclohexylpiperidine.

b) Assessing the lipophilicity of FCs: correlation between  $CST_{hex}$  and MW for a variety of regular ( $\Delta$  acyclic,  $\circ$  monocyclic,  $\square$  bicyclic,  $\nabla$  tricyclic) and lipophilic ( $\blacktriangle$ ) FCs. A lower  $CST$  corresponds to higher lipophilicity; dotted lines indicate trends observed for the more lipophilic FCs (taken from reference [3])

## 13.4.3

**Stabilizing Fluorocarbon Emulsions: Counteracting Molecular Diffusion**

Formulating FCs as fine ( $< 0.2 \mu\text{m}$ ) emulsions for intravascular administration requires a surfactant system capable of reproducibly ensuring homogenous dispersion, stability and biocompatibility. Phospholipids, which are commonly used in pharmaceuticals, including the fat emulsions routinely used for parenteral nutrition, are capable of fulfilling these requirements. Emulsions, however, undergo particle size growth over time, ultimately leading to phase separation. The principal mechanism for irreversible particle growth in FC-in-water emulsions was determined to be molecular diffusion (Ostwald ripening). Particle growth by molecular diffusion essentially obeys the Lifshits-Slezov theory, which states that particle volume increase is directly proportional to interfacial tension, and to solubility and diffusibility of the dispersed phase into the continuous phase [265]. Such growth can be counteracted by lowering the FC/water interfacial tension and by reducing the solubility and diffusibility of the dispersed FC phase in the aqueous phase. In the case of *F*-octyl bromide, unexpectedly low interfacial tension could be achieved using phospholipids [266]. Solubility and diffusibility of the fluorous phase in water was reduced by adding a secondary, higher molecular weight FC. *F*-decyl bromide was selected for this purpose because it is slightly lipophilic, which mitigates the increase in organ retention that normally accompanies an increase in MW (Figure 13-14) [267]. Processing conditions were optimized to produce fine and narrowly dispersed emulsions. Particle size is indeed known to affect both intravascular persistence and side effect profile. Large particles are cleared more rapidly from the circulation than smaller ones and tend to stimulate macrophage activation, resulting in “flu-like” side effects [264].



**Fig. 13-14.** Repressing Ostwald ripening in an *F*-octyl bromide emulsion by addition of the higher, less water soluble homolog *F*-decyl bromide. A few percent of *F*-decyl bromide suffice to reduce the rate of droplet growth by a factor of about 6. From reference [267] with permission

Extensive research and development efforts led to Oxygent™ AF0144 (Alliance Pharmaceutical Corp.), a submicronic (about 0.16  $\mu\text{m}$  in average diameter) 60% weight/volume-concentrated FC emulsion consisting principally of *F*-octyl bromide, emulsified with egg yolk phospholipids and stabilized against particle growth with a few percent of *F*-decyl bromide. The product is terminally heat sterilized, has a shelf life of two years at standard refrigeration temperatures (5–10 °C) and is ready for use [5].

#### 13.4.4

#### Fluorocarbon Emulsion Physiology and Clinical Trials

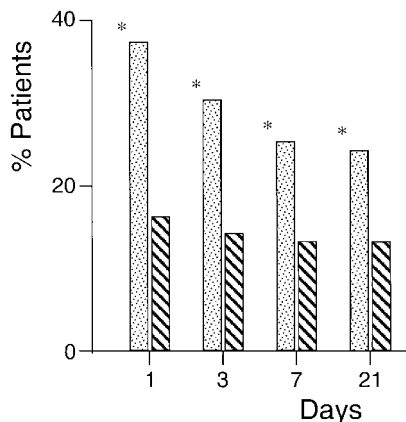
Extensive pre-clinical experimentation has investigated Oxygent's pharmacology and safety, and demonstrated O<sub>2</sub> delivery efficacy [5, 268].

During Phase I clinical safety studies in conscious volunteers with the Oxygent formulation AF0144, fever frequency (~15% of patients) and amplitude (seldom exceeding 1 °C) was not significantly different from the controls, and platelet count, although temporarily depressed with respect to the base line, remained within normal range. There were no effects on platelet function and coagulation parameters, no complement activation, immunogenic or allergic reactions, vasoconstriction or microcirculatory disturbances, abnormal changes in liver, lung or kidney function, or clinically meaningful effects on blood chemistry at the doses administered [269, 270].

Phase II trials have demonstrated that the emulsion was more effective than fresh blood in reversing the need for transfusion (transfusion triggers) during surgery [271] and led to a reduction in the number of patients who reached a transfusion trigger during surgery [272].

The recently published results of a Phase III clinical trial conducted in Europe in general surgery patients have established the ability of the emulsion to significantly reduce and avoid red blood cell transfusion during general surgery [273]. The trials were conducted using an augmented acute normovolemic hemodilution with FC emulsion protocol. In the protocol-defined target population (330 subjects with blood loss  $\geq 20 \text{ mL kg}^{-1} \text{ b.w.}$ ), significantly greater avoidance of any red blood cell transfusion (including predonated blood), as compared with controls, was gained and maintained through day 21 or day of hospital discharge (Figure 13-15,  $p < 0.05$ ). There was also a significant reduction in the number of blood units transfused ( $p < 0.001$ ). The latter result is not negligible, as each unit of blood transfused carries the same risks. The added O<sub>2</sub>-delivering capacity provided by administration of a dose of FC emulsion has been described in terms of a "hemoglobin equivalent" value [273, 274]. Using data from clinical trials, the hemoglobin (Hb) equivalent of a 1.8  $\text{g kg}^{-1} \text{ b.w.}$  dose of *F*-octyl bromide was calculated to be about 2.7 g Hb (i.e., about 1.5 g Hb per g FC) at an inspired O<sub>2</sub> fraction of 1. The intended clinical dose (4.5  $\text{mL kg}^{-1} \text{ b.w.}$  of the 60% w/v emulsion, i.e., 2.7 g of FC) would then provide an Hb equivalent of around 4  $\text{g dL}^{-1}$ , comparable to that of four units of fresh blood. Another Phase III study, conducted in cardiopulmonary bypass surgery patients was suspended because of adverse effects that were traced to protocol-related, overly aggressive autologous blood harvesting in the treatment group prior to bypass [275]. Clinical development is being pursued through a partnership between Alliance and Nycomed (Copenhagen, Denmark).

The gastric tonometric variables (which are markers of proper tissue perfusion) were preserved in surgical patients administered Oxygent [276]. FC emulsions also appear to



**Fig. 13-15.** Percentage of patients avoiding blood transfusion in the target population (blood loss  $\geq 20$  mL kg<sup>-1</sup>) after 1, 3, 7 and 21 days (or hospital discharge). First bar, Oxygen-treated patient; second bar, control group. \* $p < 0.05$  between groups. Adapted from reference [273], with permission

attenuate neutrophil activation and reduce inflammation during extracorporeal circulation [277]. A further study indicated that the emulsion was effective in reducing sickle cell vaso-occlusion caused by human sickle cells in a rat mesocecum vasculature preparation [278]. Sickle cell anemia is due to a mutation ( $\beta 6$ , Glu  $\rightarrow$  Val) in the Hb molecule that causes Hb to polymerize and the sickling of red blood cells under deoxygenated conditions. Blockage of blood vessels by the non-deformable sickle cells leads to painful vaso-occlusive crises and multiple organ damage. The FC emulsion was capable of unsickling trapped red cells in partially occluded vessels, thus decreasing peripheral resistance, probably as a result of effective O<sub>2</sub> delivery.

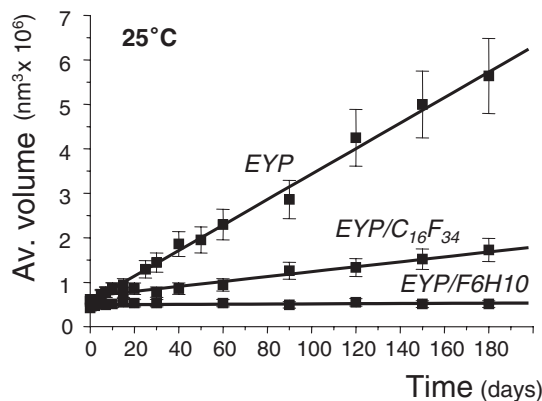
#### 13.4.5

##### Further Research on Fluorocarbon Emulsions for Oxygen Delivery

Objectives for additional emulsion improvement include further increasing emulsion stability, achieving smaller size particles and prolonging intravascular persistence. These improvements are likely to require modification of the interfacial film. Use of *F*-surfactants allowed the shelf stability of an *F*-decalin emulsion to be increased from days to years [3]. However, the physiological effects of large doses of an *F*-surfactant are, at this point, largely unknown.

*F*-alkyl/*H*-alkyl diblocks, when used in combination with phospholipids, provide a highly effective means of stabilizing small-size FC emulsions (Figure 13-16) [105, 279]. The fit between emulsifier and diblock is then critical. Thus, while incorporation of *F*-alkyl/*H*-alkyl diblocks provided very effective stabilization of an *F*-octyl bromide emulsion when phospholipids were the emulsifier, combination of diblocks with poloxamers (e.g., Pluronic® F68) was insufficient to effectively stabilize an *F*-decalin emulsion [3]. Additionally, FnHm/phospholipid mixtures allowed close control of particle size (i.e., of fluorous microdomain size) over a wide range of sizes [280].



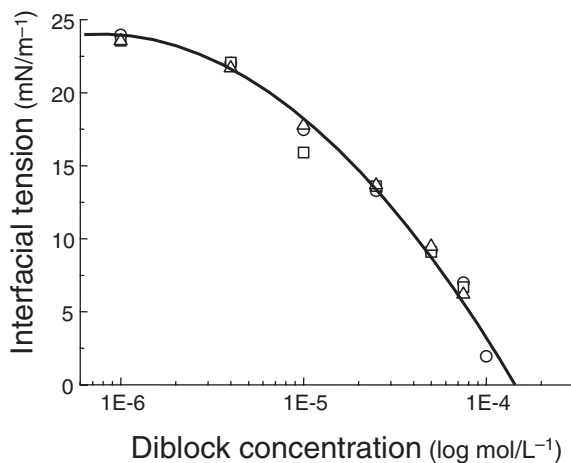


**Fig. 13-16.** Stabilization of a 60% *F*-octyl bromide-in-water emulsion emulsified with egg phospholipids upon addition of the heavier FC  $C_{16}F_{34}$ , or of diblock F6H10 ( $C_6F_{13}C_{10}H_{21}$ ) to the

formulation. The stabilizers and EYP were in equimolar amounts; note that the two additives have about the same boiling point. From reference [279], with permission

The mechanism of emulsion stabilization by *F*-alkyl/*H*-alkyl diblocks is not yet fully established. The stabilization effect could *a priori* result from a modification of the interfacial film, resulting in a reduction in interfacial tension, and/or from the effect on water solubility of less water-soluble diblock molecules homogeneously dispersed in the bulk of the FC phase (in which the diblocks may, however, also form micelles), or from an increased local concentration of the heavier, molecular diffusion-repressing material in the neighborhood of the lipidic interface.

Increasing evidence supports an involvement of the FnHm diblocks at the FC/water interface. Thus, incorporation of diblock F6H10 into an *F*-octyl bromide-in-water emulsion emulsified with egg phospholipids increased the proportion of phospholipids associated with the FC droplets relative to that present in the form of free vesicles dispersed in the aqueous phase; it also reduced the area occupied by the phospholipids' head groups at the surface of the FC droplets [281]. Reduced surface area of the polar heads reflects tighter packing of the phospholipid film. A dramatic reduction in FC/water interfacial tension (typically from about 24 to  $\sim 2$  mN m<sup>-1</sup>; pendant drop method) between an FC and an aqueous phospholipids solution was measured when increasing amounts of a diblock were added to the FC phase (Figure 13-17) [282]. The observation that the emulsion stabilization effect of a given diblock depended on the length of the lipid's fatty acid chains, while this was not so when a heavier FC (that simply reduces the solubility of the FC phase in the aqueous phase) was used as a stabilizer, further demonstrated that the diblocks were involved at the interface. On the contrary, when the fit between lipid and diblock alkyl chain length was inadequate, a droplet coalescence mechanism set in that actually led to emulsion destabilization [282]. Of course, involvement of part of the diblocks at the interface does not exclude the presence of diblocks in the bulk of the droplet and vice versa. Even a relatively small proportion of diblocks at the interface can result in a substantial reduction in interfacial tension, while the diblocks present in the bulk can contribute to increasing emulsion stability by reducing the water solubility of the dispersed FC.



**Fig. 13-17.** Synergistic lowering of the interfacial tension between *F*-octyl bromide and aqueous solutions of three phospholipids upon addition of increasing amounts of the *F*-alkyl/*H*-alkyl diblock

$C_8F_{17}C_{16}H_{33}$  (○): DLC8,  $3.72 \times 10^{-5} \text{ mol L}^{-1}$ ; □: DLPC,  $1.25 \times 10^{-9} \text{ mol L}^{-1}$ ; △: DMPC,  $1.66 \times 10^{-11} \text{ mol L}^{-1}$ ) From reference [282], with permission

Evaluation of a diblock-stabilized emulsion is in progress. Successful long-term preservation of intestine has been reported [283]. Improved tissue oxygenation was demonstrated in a rabbit model of resuscitation from acute hemorrhagic shock [284]. No perturbation of the hemodynamic or rheological parameters was induced, even at very large doses [285].

Droplet coalescence in FC and HC emulsions stabilized by water-soluble poloxamers and a bis(*F*-alkylated) PEG has been thoroughly investigated [286]. It was found that the interfacial adsorption layers of surfactant can provide an effective structural-mechanical barrier against coalescence, depending on the nature of the dispersed phase and its interaction with the hydrophobic tail of the surfactant. Droplet resistance to coalescence was enhanced by a “deficiency in affinity” between the hydrophobic moiety of the surfactant and the dispersed hydrophobic phase, which pushes the surfactant to aggregate into a compact, mechanically resistant structure. An *H*-surfactant is in this respect more effective in stabilizing an FC emulsion against coalescence than an *F*-surfactant, whose *F*-tails would tend to dissolve loosely in the FC rather than form a mechanically strong structure [286]. Phospholipids, which are used in the FC emulsions in development, are essentially insoluble in both polar and non-polar phases, and provide an effective barrier against coalescence.

An *F*-octyl bromide emulsion stabilized by phospholipids and an *F*-surfactant, and surface-modified with a distearoylphosphatidylethanolamine-poly(ethylene glycol) (DSPE-PEG) has been described briefly [287]. Its ability to deliver  $O_2$  in a cardiopulmonary bypass with hemodilution canine model was demonstrated. Phagocytosis of an FC emulsion by macrophages *in vitro* was reportedly slowed down when an *F*-alkylated PEG emulsifier was used [288].

Assays that allow detection of FCs in blood by headspace solid-phase microextraction combined with gas chromatography/mass spectrometry have been developed as part of efforts towards anti-doping in sport [289, 290].

Interestingly, the so-called “phase-shift” emulsion of *F*-pentane (bp 29 °C) that turns into

gaseous microbubbles at body temperature and was initially intended as a contrast agent for ultrasound imaging, is now being investigated for O<sub>2</sub> delivery. The theory underlying the use of FC-stabilized microbubbles for *in vivo* O<sub>2</sub> transport had been developed earlier [291, 292]. As indicated in Section 13.3.1 the fast permeating gases inside the bubble, i.e., O<sub>2</sub> and CO<sub>2</sub>, equilibrate rapidly with the gases dissolved in the plasma and surrounding tissues, allowing O<sub>2</sub> to be carried from the lungs to the tissues. The role of the FC (a slowly permeating gas) is then no longer to dissolve O<sub>2</sub>, but to stabilize O<sub>2</sub> microbubbles *in vivo*. Experimental proof of the concept includes survival of normovolemic erythrocyte-depleted rats and pigs, and of pigs with potentially lethal hemorrhagic shock and with severe right-to-left shunt [293]. Administration of the *F*-pentane emulsion, along with carbogen breathing, led to suppression of resistance to radiation of a hypoxic cell in a rat tumor model [294]. However, the mechanism for prolonged O<sub>2</sub> delivery over at least 2 h remains unclear in view of the short intravascular life of *F*-pentane [122]. A depot effect and possible bubble stabilization by serum proteins may contribute to prolonged circulation times. Emulsion formulation and stability, and *in vivo* bubble size control also warrants further research.

### 13.5

#### Fluorocarbons as Therapeutic Aids and Tissue-Sustaining Devices

The combination of FCs for fluidity, easy spreading (*F*-octyl bromide spreads spontaneously on a saline solution), density and biological inertness provides opportunities for a number of atypical biomedical uses.

##### 13.5.1

#### Pulmonary Applications – an Anti-Inflammatory Effect?

Total or partial liquid ventilation (PLV) with FCs have been investigated as a treatment of acute respiratory distress syndrome (ARDS) and other acute lung injuries. Improved oxygenation and lung function have been achieved, usually with *F*-octyl bromide, in animal models of lung injury [295–299], as well as in clinical trials with ARDS patients [36, 245, 300, 301]. Use of PLV in conjunction with high frequency ventilation improved gas exchange, decreased pulmonary vascular resistance and reversed acidosis in preterm lambs with respiratory distress syndrome and may represent an effective approach to the management of preterm infants with respiratory distress syndrome [302]. Lung lavage with FCs can help remove edema fluids while improving gas exchange and lung mechanics [303]. Bronchoscopic lavage with *F*-octyl bromide was found to be advantageous in the treatment of smoke inhalation injury in an ovine model [304]. PLV may help treat meconium aspiration [305] and may have been critical in managing a case of acute verapamil poisoning with respiratory failure [306]. Liquid ventilation with an FC may reduce lung injury associated with neonatal cardiopulmonary bypass [307].

Moreover, PLV with FCs was repeatedly reported to have an anti-inflammatory effect and to reduce oxidative damage to lipids and proteins during experimental acute lung injury [37, 308–311]. Thus, PLV with *F*-octyl bromide reduced production of oxygen free radicals and concomitant pulmonary oxidative damage, and reduced mortality in piglets with acute lung injury caused by oleic acid [310] or systemic endotoxemia [311]. FCs were shown to protect lung epithelial cells from inflammatory cell-mediated injuries and to reduce the release of

inflammatory mediators (leukotriene B<sub>4</sub> and interleukin-6) [312, 313]. They may protect the lung from acute inflammation more effectively than conventional ventilation procedures [312]. Pre-exposure to *F*-octyl bromide attenuated neutrophil adhesion to activated endothelial cells *in vitro*; infiltration of activated neutrophils into the lung is a key component of inflammation in acute lung injury [314]. Intranasal administration of *F*-octyl bromide reduced lung cellular inflammation and the expression of chemokines in mice infected with respiratory syncytial virus, the major etiologic agent of bronchiolitis in infancy [315].

More recently, delivery of vaporized or aerosolized rather than liquid FC to the bronchial tree has been investigated. Treatment of sheep with ARDS with vaporized *F*-hexane (18% vaporized *F*-hexane carried in the inspiratory gas flow during ventilation) resulted in significant and sustained improvement of gas exchange and lung compliance, possibly due to a surfactant effect [316, 317]. Exposure to *F*-hexane vapor attenuated the proinflammatory and procoagulatory responses of human activated mononuclear blood cells and isolated alveolar macrophages *in vitro*, as indicated by a reduction of expression and release of interleukin-1 $\beta$ , tumor necrosis factor  $\alpha$  and tissue factor [318]. A simpler treatment of lung surfactant-depleted pigs with aerosolized FC77 (primarily *F*-octane, from 3M) resulted in sustained improvement of oxygenation and lung mechanics, lasting for hours after the end of the intervention [319]. The treatment also suppressed an early pulmonary response in lung surfactant-depleted piglets, as indicated by reduced gene expression of proinflammatory cytokines [320].

Pulmonary infusion of cold FCs is being investigated as a means of rapidly cooling the body core and protecting the brain [321a, b]. Rapid body core and brain cooling has become an important goal of resuscitation research. It could be extremely valuable in the treatment of cardiac arrest, myocardial infarction and stroke, as well as doing neurosurgery, cardiac surgery and for organ preservations.

### 13.5.2

#### Cardiovascular Uses: Thrombolysis

FC-loaded microbubbles, in conjunction with ultrasound, have been investigated for breaking up blood clots that cause myocardial infarction. Thrombolysis was enhanced *in vitro*, with or without the presence of a thrombolytic agent (urokinase), probably as a result of cavitation [321]. Greater efficacy was found with FC- versus air-filled lipid microbubbles [321] or polymer microspheres [322]. Thrombolysis with a tissue plasminogen activator was improved by ultrasound irradiation and further improved in the presence of microbubbles [323–326].

Ultrasound was used to vaporize an *F*-pentane emulsion, of average radius 1.5  $\mu\text{m}$ , producing large microbubbles, around 100  $\mu\text{m}$  in diameter, which were suggested to have potential for tissue occlusion in cancer treatment [327].

### 13.5.3

#### Topical Applications: Fluorocarbon Gels

Fluorocarbon-based gels have recently been reviewed [7] as have concentrated emulsions in general [328]. Elastic gel-emulsions with a high water content were obtained that consisted of water in a swollen reverse water-in-FC micellar phase [34]. Investigation of the changes in rheological behavior of such a concentrated reverse emulsion [*F*-decalin emulsified with

$C_mF_{m+1}C_2H_4SC_2H_4(OC_2H_4)_2OH$ ] over time determined that coalescence was the mechanism of aging in these emulsions [329]. Complex gel-emulsion formulations also containing decane and both *H*- and *F*-surfactants have been reported [330].

Gels with a continuous FC phase have also been obtained from associations of *F*-alkyl/*H*-alkyl diblocks, phospholipids and water in FCs [331]. Generation of worm-like entangled micelles of hydrated surfactants within the continuous fluoruous phase is a likely mechanism for their formation. An *F*-alkylated gelator consisting of a bis-benzamide with two *F*-alkyl chains attached provided an *F*-tributylamine gel [332]. Gels containing twisted lamellae have been observed to form from *F*-alkylated gluconamides in formamide [50].

On the other hand, clear, highly stable high internal phase ratio emulsions (HIPRE), consisting of up to 99% FC have been produced from a wide range of FCs, from low-boiling hydrofluoroalkanes to high-boiling polycyclic FCs, using an *F*-alkylated amine oxide surfactant [333]. Structurally, these gels consist of micron-sized polyhedral fluoruous compartments enclosed within a thin hydrated film of the surfactant. Dispersion in water (the continuous phase) generates a standard FC-in-water emulsion.

PEGs with *F*-alkyl chains at both ends provided hydrogels with controlled surface erosion characteristics [334]. Phase behavior could be modulated by varying *F*-alkyl chain length relative to PEG chain length, resulting in single-phase behavior, sol-gel coexistence, or precipitation. Mechanical and erosion properties of the hydrogels could thus be tailored for use as implantable drug-release depots. *F*-alkyl end-capped polyacrylamides with pendant betaine groups provided gels that combine the surface active properties imparted by *F*-chains and the antibacterial activity of quaternary ammonium moieties [58, 335]. The enhanced hydrophobicity provided by *F*-alkylated end caps leads to larger relaxation times and higher activation energies, hence to rheological behavior that is unusual with non-fluorinated associative polymers [21].

*F*-gels may have applications in topical delivery, wound healing, and as low friction, gas-permeant, repellent protective barrier creams against toxic or aggressive media, and in cosmetic applications. A gel-emulsion of Fomblin® (a mixture of *F*-polyethers) in water showed protective efficacy against irritants such as sodium lauryl sulfate, sodium hydroxide, lactic acid and toluene [336]. Water soluble *F*-polyether PEG phosphates, when incorporated into aqueous gels, also provided prevention of irritant contact dermatitis [337].

#### 13.5.4

##### Ophthalmologic Applications

Diverse gaseous (*F*-propane, SF<sub>6</sub>) and liquid (*F*-octane, *F*-decalin, *F*-perhydrophenanthrene) *F*-compounds are being used as ocular tamponades, vitreous substitutes, intraocular washes to remove silicone oil, etc. [338, 339]. More recently investigated compounds include fluorosilicones [340], (*F*-alkyl)alkanes [341], and semifluorinated diethers of type  $[(CF_3CH_2O)_2(CH_2)_{3-6}]$  [342].

#### 13.5.5

##### Organ and Tissue Preservation, Cell Cultures

Neat liquid FCs are being investigated for the preservation of transplants using the so-called “two layer” method in which the organ lays on an O<sub>2</sub>-providing FC layer, while it is overlaid

by a nutrient-rich aqueous solution [343]. Clinical transplantation of pancreas preserved by this method achieved results at least equivalent or superior to those obtained without the FC layer [344, 345]. FC emulsions allowed preservation of organ blocks from rats [346].

Both neat FCs and FC-in-water emulsions provide effective means for facilitating and regulating the supply of O<sub>2</sub> and CO<sub>2</sub> to prokaryotic and eukaryotic (including human) cells in culture [347]. Neat FCs enhanced mitosis of isolated cells of diverse plants, thus increasing biomass production. The metabolic responses of cultured cells to oxygenated FCs has been investigated [348]. An underlying layer of oxygenated *F*-decalin stimulated cellular O<sub>2</sub> consumption, mitochondrial function and the intracellular activity of the enzymes superoxide dismutases and catalases (which scavenge deleterious oxygen radicals, thus affording protection against oxidative cell damage). Cryopreservation of agronomically important plant cells is an important storage procedure; there is evidence that FCs can improve the post-thaw viability and biomass production of frozen cultured plant cells; synergistic effects of *F*-decalin and Pluronic F-68 were also observed [349]. Use of neat *F*-decalin to supply CO<sub>2</sub> to cultured shoots of roses enhanced biomass and root production [350]. FCs have also been used to provide CO<sub>2</sub> to algae and remove excess O<sub>2</sub> from closed bioreactors, resulting in significantly enhanced growth rates (accumulation of O<sub>2</sub>, a photosynthetic byproduct of microalgae culture, severely inhibits algae growth) [351].

## 13.6

### Delivery of Bioactive Agents

*F*-colloids provide a variety of microreservoirs for drug delivery. The active components can be incorporated in aqueous or lipidic compartments inside particles, within their walls, or attached to their surface. Targeted delivery with *F*-colloids is being actively pursued. For a recent review, see [351a].

Additionally, certain *F*-amphiphiles may have biological activity by themselves. Anti-thrombogenic activity [352] and anti-HIV activity [48, 353] have, for example, been observed. *F*-alkylated polycationic lipospermins allowed DNA condensation and improved cell transfection efficiency *in vitro* [48]. *F*-amphiphile derived prodrugs have been proposed, including amphiphilic telomers that can be fitted with markers and targeting devices [354]. Fluorinated dendrimers may also serve in the controlled release of drugs adsorbed within or grafted onto the surface (e.g., 5-fluorouracil) [355] of such, usually very well defined, polymeric nanoparticles.

#### 13.6.1

##### The Parenteral Route

###### 13.6.1.1 Microbubbles and Ultrasound

Microbubbles, combined with ultrasound, offer wide possibilities in terms of carrying, targeting, delivering or facilitating and monitoring the delivery and efficacy of drugs and genes to specific tissues. Bubble destruction in a chosen tissue can facilitate local delivery of an independently administered drug; alternatively, the bubbles themselves can be loaded with the active agent; ultrasound can help trace the delivery of the active cargo; finally, ultrasound can provide the external trigger that commands bubble destruction and local release. Advantages of ultrasound include deep penetration into body tissues and the capacity to be focused into a narrow beam. However, the cargo space offered by microbubbles is generally

small, as it usually only concerns the bubble shell, meaning that only potent drugs can be delivered effectively. Microbubbles with thicker walls can be considered, the downside being that thicker, hence more rigid walls tend to dampen the scattering efficacy of the bubbles.

Delivery of colloidal particles and red blood cells through microvessel ruptures created by ultrasound-triggered microbubble destruction has been demonstrated [324]. The acoustic power required to induce sonoporation, i.e., generation of transient ultrasound-induced perforations in cell membranes, is significantly reduced when microbubbles are present [356]. *In vitro* experiments on lymphocytes indicated that sonoporation was directly related to the microbubble-to-cell ratio and to the bubble-to-cell spacing,  $r$ , and that the effects decay as  $r^{-3}$  [356].

Paclitaxel, packaged in *F*-butane microbubbles that contain soybean oil and are believed to comprise an oil layer inside a pegylated phospholipids shell, was released *in vitro* when sufficiently high-energy ultrasound was applied [357]. A prodrug of dexamethasone, with fatty chains attached for insertion into the lipid membrane of microbubbles, has been synthesized [358]. Interestingly, *F*-butane-exposed, but not air-containing, sonicated dextrose albumin microbubbles preserved albumin's ability to bind synthetic antisense oligonucleotides, indicating that the FC may have prevented albumin denaturation during sonication [359]. These oligonucleotides could be released by insonation in a target organ, in this case the kidney of a dog.

Targeted delivery of the thrombolytic agent urokinase was achieved *in vitro* using microbubbles fitted with a surface ligand that binds to the GPIIB/IIIA receptors expressed on activated platelets present in thrombi [219]. Ultrasound thrombolysis efficiency was significantly increased.

Gene delivery is another important goal for ultrasound-manipulated microbubbles. Ultrasound alone can facilitate gene transfection [360]. The presence of microbubbles significantly enhanced acoustically-induced cell transfection, probably due to enhanced sonoporation [361, 362]. Ultrasound exposure in the presence of microbubbles achieved 300-fold higher transgene expression in vascular cells *in vitro* than with naked plasmid DNA alone, and a 3000-fold increase when a polyamide transfection agent was used [363]. Intrauterine injection of naked DNA, in combination with FC microbubble-enhanced ultrasound, produced protein expression in fetal mice [364]. Luciferase expression increased  $\sim 10^3$ -fold in comparison with expression after injection of naked DNA alone or with naked DNA and ultrasound. *In vitro* ultrasound-mediated gene expression and transfection efficiency were enhanced when DNA was incorporated into albumin-coated *F*-propane microbubbles, as compared with unloaded bubbles mixed with plasmid [365]. Adenovirus delivery in rats has been promoted using an albumin-coated FC microbubble; ultrasound was used to image the delivery and disrupt the microbubbles, leading to increased myocardial gene expression [366]. Positively charged microbubbles that bind DNA have also been produced [367, 367a].

Transgene expression of  $\beta$ -galactosidase in the myocardium of rats was achieved by infusion of albumin-coated *F*-propane microbubbles having a  $\beta$ -galactosidase-containing recombinant adenoviral gene vector attached, followed by insonation of the heart [368].

#### 13.6.1.2 Targeted Fluorocarbon Emulsions

Targeted FC-in-water emulsions (Section 13.3.2.3) were designed that provide site-directed drug delivery. For example, site-directed doxorubicin and paclitaxel was delivered to vascular smooth muscle cells *in vitro* using a Gd chelate- and drug-loaded, smooth muscle-adherent

*F*-octyl bromide emulsion [369]. The targeted drug inhibited proliferation and migration of vascular smooth muscle cells and prevented restenosis after angioplasty; simultaneously, MR could allow visualization of delivery.

### 13.6.1.3 Fluorinated Vesicles and Other Self-Assembled Fluoro-Colloids

A range of *F*-vesicles has been elaborated for the purpose of determining the impact of *F*-chains on the formation, structure and properties of such *F*-colloids and to provide novel delivery vehicles for bioactive agents [2, 8, 42, 62]. At this point, however, the potential of these *F*-colloids as drug delivery systems remains largely unexploited.

The salient structural characteristic of *F*-vesicles is the presence of a well-organized highly hydrophobic, Teflon-like fluorinated core within their bilayer membrane. This modifies the thermotropic and lyotropic behavior of such vesicles, usually providing improved thermal resistance and shelf stability as compared with vesicles made from *H*-analogs, and lower membrane permeability. The ability of *F*-liposomes for withstanding heat sterilization, efficiently loading and slowly releasing diverse hydrophilic, lipophilic and amphipathic drugs, drug models and dyes has been demonstrated [8, 42, 62].

Alternatively, *F*-vesicles have been obtained by combining standard *H*-amphiphiles, in particular phospholipids, with mixed *F*-alkyl/*H*-alkyl diblocks [105, 370]. The diblocks confer to *F*-liposomes increased stability and reduced permeability. Thus, liposomes made from DMPC and diblock F4H10E **11** became heat sterilizable. Slower fusion kinetics were illustrated by the initial rates of  $\text{Ca}^{++}$ -induced fusion of *F*-vesicles made from phosphatidylserine (PS) and F6H10, being an order of magnitude slower than when PS was alone, and reduced membrane permeability by a 40-fold slower release of encapsulated carboxyfluoresceine [371]. Mixtures of *F*-alkylated phosphocholine **8** and F8H2 yielded vesicles with dramatically reduced membrane permeability than when **8** was alone [372].

The intra-bilayer *F*-film can also have repercussions on the vesicle's behavior *in vivo* or in a biological milieu, possibly by affecting the conformation and orientation of the polar groups, hence *in vivo* particle recognition and phagocytosis, leading, for example to prolonged, dose-independent intravascular persistence [373]. The presence of diblocks of type **10** in the bilayer membrane of liposomes made from DMPC or DPPC dramatically reduced the rate of hydrolysis of the phospholipid by pancreatic phospholipase  $\text{A}_2$  [374]. The dependence of the effect on *H*-alkyl chain length in the diblock and the absence of effect when there is no *F*-chain present demonstrated a key role of the latter in structuring the bilayer membrane. These observations indicate that interactions with peptides and proteins and *in vivo* recognition could be modulated by changes made *inside* the liposomal membrane.

### 13.6.2

#### The Pulmonary Route – Dispersions of Particles within a Fluorous Phase

Administration of *F*-systems through the respiratory tract deserves a special mention as FCs provide a fluid, rapidly spreading inert vehicle that may allow uniform delivery of drugs, lung surfactant, vaccines, genes and other bioactive agents. However, very few agents (besides gases and highly fluorinated compounds) are soluble in FCs; hence the interest of colloidal systems with a fluorous continuous phase incorporating aqueous, oily or solid dispersed phases (Figure 13-1, h–m) thus allowing homogeneous dispersion of both hydro-



philic and lipophilic materials within the FC carrier. Objectives include treatment of ARDS, pneumonia and pulmonary hypertension and gene delivery.

Fluorous phases are particularly apt at carrying gases. Several papers report that PLV with an FC, usually *F*-octyl bromide, combined with nitric oxide inhalation, led to augmented oxygenation, improved lung mechanics and decreased pulmonary hypertension in various models of lung injury [301, 375–378]. Halothane,  $\text{CF}_3\text{CHBrCl}$ , a fluorophilic inhalation anesthetic, can also be delivered with liquid ventilation [379].

Simple suspensions of solid drugs, for example in nanocrystalline form, usually in *F*-octyl bromide or *F*-decalin have been investigated. Combination of lung surfactant treatment with PLV with *F*-octyl bromide improved gas exchange and lung mechanics in preterm lambs with surfactant deficiency [299, 380]. Intratracheal administration of prostaglandin  $\text{E}_1$  during PLV of rabbits with oleic acid-induced lung injury resulted in sustained improvement in oxygenation and reduction in pulmonary artery pressure [381]. The feasibility of pulmonary delivery of the vasoactive drugs acetylcholine, epinephrine and prisolone during liquid ventilation was demonstrated [382]. Combination treatment of rats infected by lethal pneumococcal pneumonia with penicillin and FC liquid ventilation led to significantly improved survival as compared with treatment with penicillin alone [383]. Intratracheal delivery of a nanocrystal suspension of the antibiotic gentamycin provided effective pulmonary delivery while maintaining safe serum levels [384].

Other strategies for improving incorporation of drugs into FCs for pulmonary delivery consist in synthesizing FC-soluble prodrugs [354] or in using an *F*-alkylated solubilizing agent capable of forming hydrogen bonds with the drug [385]. In both cases, *F*-chains provide the required increase in FC solubility. As an example, FC-soluble nicotinic acid esters with *F*-chains have been synthesized [386].

Use of FCs as a vehicle could improve distribution of genes throughout the lung and facilitate their access to binding sites on distal target cells [387]. Intratracheal instillation of viral and nonviral gene transfer vectors along with neat *F*-octyl bromide resulted in increased, earlier and more uniformly distributed gene expression, including in animal models of acute lung injury [388, 389].

Reverse water-in-FC emulsions and “apolar” HC-in-FC emulsions also have potential for the delivery of bioactive material through the pulmonary route [8]. Producing reverse (i.e., water-in-FC) emulsions supposes the stabilization of a dispersion of water droplets in an extremely water-repellent medium. Highly stable water-in-FC emulsions and micro-emulsions (i.e., thermodynamically stable reverse emulsions), ranging from ca. 10 to ca. 500 nm in diameter, have been obtained using strongly fluorophilic surfactants such as the (*F*-alkyl)alkyldimorpholinophosphates **8** [390, 391]. These reverse emulsions could be loaded with a range of drugs, including antibacterial, bronchodilating, mucolytic, tuberculostatic, cholinergic, and antineoplastic agents, without loss of stability. Slower release of carboxy-fluor esceine than from water-in-HC oil emulsions was obtained [392]. The cytotoxicity towards mouse fibroblast and human lung epithelial cell cultures, of **8** dissolved in *F*-octyl bromide or as part of a reverse emulsion, was lower than with an *H*-analog of **8** and decreased with increasing *F*-chain length [63]. Reverse emulsions stabilized by **8** ( $n = 8$  or  $10$ ,  $m = 11$ ) were assessed as non-cytotoxic. Pulmonary delivery of a water-in-*F*-octyl bromide emulsion was investigated using pressurized metered-dose inhalers with light hydrofluorocarbons (e.g.,  $\text{H}_2\text{CFCF}_3$ , HFA 134a) as the propellant [393]. Homogeneous and re-

producible delivery of caffeine was demonstrated. Studies of mixed monolayers of **8** with DPPC (the main constituent of lung surfactant) in contact with *F*-octyl bromide (or of water-in-*F*-octyl bromide emulsions formulated with **8**) indicated that **8** was miscible with DPPC, which may facilitate the spreading of DPPC in the lung and the delivery of drugs [394, 395].

Water-in-HFA 134a microemulsions suitable for aerosolized delivery of water-soluble drugs have been prepared using either combinations of nonionic *F*-alkylated PEG surfactants and short-chain *H*-alcohols [396], or of *F*-acid surfactants with short-chain *F*- or *H*-alcohols [397]. Terbutaline sulfate was solubilized in such microemulsions.

Stable apolar HC-in-FC emulsions (i.e., emulsions of one hydrophobic phase dispersed in another hydrophobic phase) have also been produced [398]. The amphiphiles used for emulsification and stabilization included the *F*-alkyl/*H*-alkyl diblocks **10**. Dodecane has, for example, been dispersed in *F*-octyl bromide using F6H10 as the emulsifier. Antibiotics, corticosteroids and antitumor agents have been incorporated in these emulsions.

Multiple emulsions including three distinct, non-miscible phases (fluorous, hydrocarbonous and aqueous), the continuous phase being fluorous, have also been obtained [8]. Such systems allow simultaneous loading of fluorophilic, lipophilic and hydrophilic agents.

Finally, novel hollow and porous microparticles (PulmoSpheres<sup>TM</sup>, developed by Alliance Pharmaceutical Corp. and licensed to Nektar Therapeutics (San Carlos, CA formerly Inhale Therapeutic Systems) have been devised that have small aerodynamic diameters, which facilitate their uniform delivery throughout the lung. These particles can be delivered to the respiratory tract as dry powders or as suspensions in non-aqueous solvents, including propellants for metered dose inhalers (e.g., hydrofluoroalkanes, HFAs) and liquid FCs (e.g., *F*-octyl bromide). The particles can release their active content when reaching an aqueous environment such as a mucosa. Excellent aerosolization efficiency and dose uniformity were obtained for albuterol sulfate, cromolyn sodium, and formoterol fumarate microspheres [399]. Functional integrity of immunoglobulins formulated in PulmoSpheres for local and systemic delivery via the respiratory mucosa has been demonstrated [400]. Inhaleable tobramycin and budesonide [400a] formulations (as dry powders) and an albuterol formulation (suspended in an HFA) in PulmoSpheres are presently in clinical trials (Nektar Therapeutics) [401]. Instillation in the lungs of a gentamicin/PulmoSphere formulation in *F*-octyl bromide is also being investigated [402].

### 13.7

#### Highly Fluorinated Materials as Research Tools, Processing Aids, etc.

##### 13.7.1

##### Research Tools

FC-in-water emulsions have been used to preserve or prolong and control the viability of cells, organs, tissues and animal models for physiological experimentation [346, 351, 403]. Exchange transfusion of rats with an FC emulsion allowed the interfering hemoglobin signal to be reduced in a study of the functional organization of the brain, by analyzing optical signals evoked by peripheral nerve stimulation in the cortex [404]. Likewise, replacement of hemoglobin by a FC emulsion allowed demonstration that the response, as observed by near-infrared spectroscopy, of a mitochondrial cytochrome oxidase to anoxia was not a spectral artifact due to the presence of hemoglobin [405].

*F*-surfactants with an *F*-alkyl segment inserted between a retinoid receptor ligand and a lipidic tail have been designed for the purpose of promoting two-dimensional crystallization of membrane proteins at an air/water interface [406]. The *F*-alkyl segments stabilize the monolayer against solubilization by the detergent used for protein solubilization. The fluidity necessary for crystallization to occur is provided by branched terminal HC chains or by the presence of both *H*- and *F*-chains. The *F*-alkyl segment also forces a lipophilic ligand to stay exposed on the aqueous side of the monolayer, while its natural tendency would be to bury itself in the lipidic region of the monolayer [407].

*F*-alkylation was used to immobilize biomolecules (e.g., proteins) onto FC surfaces for applications in affinity chromatography, enzyme immobilization for bioprocessing and analytical and clinical chemistry, biosensors, immunodiagnostic and other assays [408]. Monolayers of steroidal *F*-alkylated amphiphiles with cellobiose or maltose hydrophilic heads exhibited pressure-area behavior related to, respectively, specific and nonspecific interactions with the enzyme cellulase present in the sub-phase [409].

Phase separation of *F*- and *H*-amphiphiles within bilayer membranes has been used to “drill” holes in liposomes, thus simulating a process that is believed to take place when an activated macrophage attacks a tumor cell [410]. Formation of phase-separated microdomains of *F*-alkylated crown ethers within an HC membrane resulted in faster transport of  $K^+$  through the membrane than with *H*-alkylated crown ethers; contrary to the HC carrier, transport was nearly completely suppressed below the membrane’s phase transition temperature,  $T_c$ , thus providing temperature-regulation for  $K^+$  transport [411].

Although most compounds are excluded from fluorinated domains, diffusion of small molecules and ions remains possible, offering a means for diffusion control. On the other hand, the HC shells that flank the *F*-core within the bilayer of an *F*-vesicle can dissolve and confine lipophilic material. Reverse water-in-FC microemulsions provide size-controlled insulated zones for confinement within a highly hydrophobic external medium. This feature allowed evaluation of the perturbation of water dynamics as a function of confining size [412]. This confinement system could also be used for investigation of individual proteins and other material. The apolar HC-in-FC emulsions may prove useful for confining, protecting and delivering water-sensitive lipophilic material.

Possible applications evoked for tubular self-assemblies include the elaboration of models of enzyme clefts, and of microcontainers for the controlled release of active agents [413, 414]. More recently, nanotubules have been used as templates for the molecular recognition-driven self-assembly of proteins [415] and the preparation of insulated nanowires [416].

A fluorocarbon affinity emulsion has been used for extracting proteins [417], and fluorinated gel-like network structures for electrophoretic DNA sequencing in capillary columns [418].

### 13.7.2

#### Fluorocarbons and Fluorinated Colloids as Processing Aids

FC-colloids also provide tools for the engineering of other particulate-based delivery systems. For example, segregation within the lipophilic shells that flank the *F*-core of *F*-vesicles made of phospholipid **11** provided an appropriate confinement microreactor for the polymerization of a lipophilic monomer into spherical microcapsules, a goal that had not been achieved with *H*-vesicles [419].

FC-in-water emulsions allowed production of hollow porous microparticles for delivery of bioactive agents to the respiratory tract [399, 400]. The process involved spray-drying of an *F*-octyl bromide-in-water/phospholipid emulsion along with a solution of the active component to be delivered. Evaporation of water first leaves a shell containing the bioactive agent and phospholipid on the FC droplets' surface; subsequent vaporization of the FC "blows" holes in this shell. The free-flowing powder obtained consists of amorphous microparticles, about 4–7  $\mu\text{m}$  in diameter with pore diameters in the order of 50–300 nm. They form very stable "homodispersions" in HFAs and FCs where the dispersed and continuous phases are identical, thus reducing the attractive forces between particles and the difference in density between particles and carrier medium.

### 13.8

#### Summary and Perspectives

FCs and *F*-colloids have potential in medicine and biology that includes contrast agents for diagnostic imaging, *in vivo* oxygen delivery systems, systems for controlled delivery of other bioactive material, diverse therapeutic aids, and tools for research and particle engineering.

FC-based micron-size injectable gaseous bubbles constitute effective contrast agents for ultrasound imaging and are the first major product to reach the market. These highly echogenic agents provide improved diagnostic of structural and functional cardiac abnormalities. Assessment of myocardial perfusion, blood flow and blood flow abnormalities and solid tumors has also been demonstrated. Better images enable patients to be diagnosed sooner and more accurately, thus increasing the physician's confidence in the diagnosis and reducing downstream testing. Use of ultrasound contrast agents thus provides both added clinical and economical value, which is of paramount importance in the present times of health care cost constraints. A shift from the more expensive testing modalities to ultrasound imaging can be expected, which could position echosonography as the leading diagnostic modality of the decade. Research in the field is moving rapidly towards molecular imaging, i.e., detection of molecular markers characteristic of a given pathology, using targeted microbubbles. Fine-tuning of microbubble/ultrasound interaction is also being pursued. Membrane and surface engineering are therefore likely to play a key role in optimizing control over bubble targeting and response to ultrasound waves.

FC-based injectable  $\text{O}_2$  carriers stand a good chance of providing another major application for *F*-colloids. An  $\text{O}_2$  carrying, heat-sterilized phospholipid-based emulsion of a rapidly excreted, slightly lipophilic fluorocarbon, perfluorooctyl bromide is being developed to serve as a temporary blood substitute. A Phase III clinical trial in Europe has demonstrated that use of the emulsion resulted in avoidance and reduction of blood transfusion in surgery patients. Such  $\text{O}_2$  carriers are expected to reduce exposure of patients to donor blood, thereby helping reduce blood shortages, and to provide an emergency blood substitute. Improving the understanding of FC emulsion "physiology" should allow optimization of the conditions of use of such products.

Drug delivery with *F*-colloid appears promising, both where the parenteral and pulmonary routes are concerned. It may rely on microbubbles, emulsions, vesicles and other systems. Targeting of *F*-colloids sounds particularly attractive and is rapidly progressing. As yet, this potential remains largely untapped.

*F*-amphiphiles (including *F*-alkyl/*H*-alkyl diblocks) provide unique and versatile compo-

nents for delivery systems. Their highly hydrophobic (and lipophobic) *F*-alkyl chains largely determine the ordering of molecules at interfaces and promote their self-assembly into stable *F*-vesicles and other organized molecular systems with distinctive properties. *F*-amphiphiles also allow preparation of direct, reverse, apolar and multiple FC emulsions and gels. Because *F*-chains offer the ultimate in terms of hydrophobicity, they tend to phase-separate, thereby promoting micro- and nanocompartmentation and segregation between fluororous, hydrocarbonous and aqueous compartments. FCs and *F*-colloids, can thus play a decisive role in the formulation, dispersion, encapsulation, segregation and exclusion of diverse material, thereby providing microreservoirs, microreactors, confinement zones, templates, control over reaction kinetics, etc. The diversity of components and structures available allows manipulation of the physical and biological characteristics of *F*-colloids over a wide range.

As for other colloids, *F*-colloids may, as needed, be fitted with targeting devices, or rendered pH-, pressure-, temperature-, or stimuli-sensitive, or be surface modified, as with PEG strands to hinder their *in vivo* recognition and clearance from circulation. Goals for targeted *F*-colloids include molecular imaging and drug and gene delivery. Triggering of drug release from microbubbles using ultrasound is an additional appealing feature of microbubbles.

The unique and intriguing characteristics of *F*-compounds and *F*-colloids (a fertile emerging branch of fluorine chemistry) will undoubtedly continue to inspire original research, providing novel research tools and engineering solutions, probably leading to novel uses in the medical field and beyond. Pharmaceutical development, however, involves many disciplines, extreme complexity and innumerable constraints. It requires bringing together a wide diversity of complementary skills, considerable resources, and time. Managing such complexity is a key factor in the equation for success, while advancing basic research is paramount to tomorrow's pharmaceuticals.

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## 14

## Fun and Games with Fluorous Chemistry

József Rábai

## 14.1

## Introduction: Where Does the Fun Come From?

Much of the fun emanates from the unique phase properties of fluorocarbons, which are governed by thermodynamics. The extraordinary solvent properties of fluorocarbons came to light in the late 1940s, as illustrated by the following citation [1]: “The large molal volumes of the fluorocarbons compared with the corresponding hydrocarbons leads to unusually low ‘internal pressures’ or ‘cohesive energy densities’, while their high molecular weights aid in maintaining them in the liquid state; the net result of which is to make many of their solutions with ordinary liquid hydrocarbons deviate from Raoult’s law to such an extent as to form two liquid phases, a state of affairs comparatively rare among non-polar liquids.”

The thermodynamic theory of non-electrolyte solutions, as developed by van Laar, Hildebrand, and Scatchard, in its simplest form uses solubility parameters ( $\delta$ ), molal volumes ( $V$ ), temperature, mole fractions and volume fractions to account for the molal free energy of a component in a mixture of two non-polar liquids. Furthermore, this theory allows the estimation of liquid/liquid miscibilities and critical solution (consolute) temperatures ( $T_c$ ), using Eq. (1) [2]:

$$4RT_c = (V_1 + V_2)(\delta_1 - \delta_2)^2 \quad (1)$$

Increasing differences in solubility parameters will result in higher critical solution temperatures, or in other words bring about lower miscibility. Thus,  $C_6F_{11}CF_3$  and  $CCl_4$  yield a one-phase system at 27 °C, while the more polar non-fluorous solvents benzene and chlorobenzene afford single phases at 85 °C and 127 °C, respectively. All systems were assayed easily and precisely in sealed glass tubes, as reported (Table 14-1) [2].

The above theory also predicts that the best solubility or miscibility is observed for components with similar molal volumes, provided their solubility parameters are equal. This is a simplified thermodynamic expression of the “like dissolves like” principle [3]. Consciously or not, synthetic and separation chemists make frequent use of this theory of regular solutions in selecting solvents for reactions and workups.

This chapter will describe some experiments in which three liquid phase systems are converted into two-phase systems, and with further temperature increases into one-phase systems. Since the liquid layers in these systems can be colored independently according to the wish of the person who performs the experiments, many other variations are possible.

**Tab. 14-1.** Critical (consolute) temperatures of solutions of perfluoromethylcyclohexane (component 1) [2]

<i>Solvent</i>	<i>V</i> (cm <sup>3</sup> mol <sup>-1</sup> )	<i>T</i> <sub>c,obs</sub> (K)	$\delta_2$ (cal cm <sup>-3</sup> ) <sup>1/2</sup>	$\delta_{1,calcd}$ (cal cm <sup>-3</sup> ) <sup>1/2</sup>
C <sub>6</sub> F <sub>11</sub> CF <sub>3</sub>	195	—	—	—
CCl <sub>4</sub>	97	300	8.6	5.8
CHCl <sub>3</sub>	81	323.5	9.0	6.0
C <sub>6</sub> H <sub>6</sub>	89	358.5	9.15	6.0
C <sub>6</sub> H <sub>5</sub> CH <sub>3</sub>	102	362.0	8.9	5.8
C <sub>6</sub> H <sub>5</sub> Cl	107	400.0	9.5	6.3

The experiments included here are the author's favorites, because they call attention to keywords and concepts such as solubility [4], extraction [4], partition [4, 5], solvatochromism [4], fluorophilicity [5], fluorous gold nanoclusters [6], temperature dependent miscibility [7], density [8], volatility [8], polarizability [8], lipophilicity [8], fluorine substituent effects [8] and perfluoroalkylation [9]. Owing to space limitations, experiments are described in the most compact way and references given for more detailed analyses.

This chapter also features the preparation of fluorous and organic dyes, as well as a three-component three-phase system and a four-component three-phase system. Two-phase systems are incorporated in the experiments with the four-component three-phase systems (3 → 2 → 1 or 1 → 2 → 3), which equilibrate with one-phase systems upon heating and reform three-phase systems upon cooling.

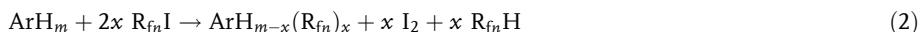
## 14.2

### Synthesis of Dyes for Fluorous and Organic Phases

#### 14.2.1

##### How to Make the “Blue Dye”: The Taming of Aromatic Perfluoroalkylations

The story of the fluorocarbon soluble blue dye is recalled by the author after a personal talk with Tiers [10], who invented the first perfluoroalkylation method for aromatic compounds [9]:



Accordingly, an aromatic compound is mixed with an excess of perfluoroalkyl iodide, sealed in a Carius tube, and heated at high temperature within a bronze protecting tube for several hours. The Carius tube is subsequently cooled in an acetone–dry ice bath, still within the bronze safety container, and then the tip is inserted into rubber tubing and cracked with the aid of a hammer (Figure 14-1). Tiers refers to this sequence as a “*brutal perfluoroalkylation*”.

In the early 1950s it was thought that perfluorocarbon based hydraulic fluids used in submarines should be colored to improve on-board safety by making them more easily distinguishable from liquid fuels. A dye had been prepared from copper phthalocyanine and perfluoroheptyl iodide under the above conditions. Since the byproducts of the above equation,  $\omega$ -hydroperfluoroalkanes and iodine, are more volatile than the educts, a significant

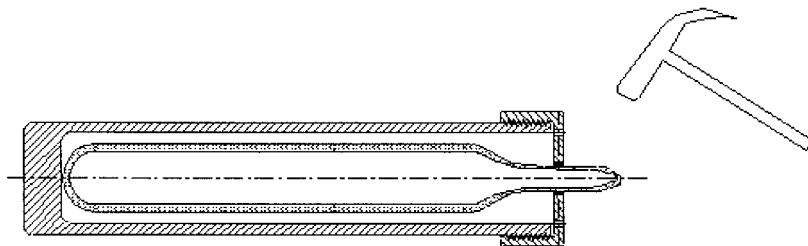


Fig. 14-1. Safe opening of a Carius tube. Redrawn from a sketch by George van Dyke Tiers [10].

pressure increase is expected at higher conversions. Accordingly, this procedure is not only brutal but hazardous.

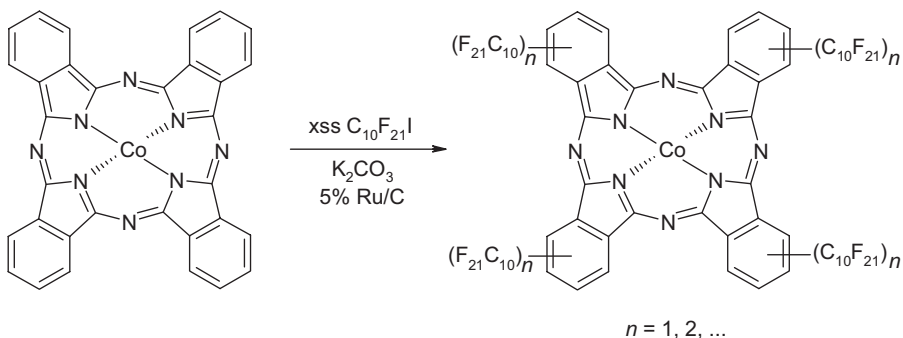
The product obtained forms brilliant blue solutions in fluorocarbons and benzotrifluoride, and is suitable for staining Teflon® at higher temperatures, near its glass transition point [9].

Other methods disclosed later provide lower reaction temperatures and higher yields based on perfluoroalkyl iodides [11–13]. However, in one of these [11] the increased yields are at the expense of the use of a peroxide reagent in stoichiometric amounts, which limits applications due to the explosion hazards associated with this compound family. The other two methods are easy to apply under standard laboratory conditions. The addition of sodium acetate or potassium carbonate to the aromatic hydrocarbon and perfluoroalkyl iodide mixture suppresses or eliminates the formation of  $\omega$ -hydroperfluoroalkanes and iodine side products, resulting in less pressure increase [12, 13].

The “blue dye” of the initial FBS paper [14] was made analogously to the original Tiers procedure. However, for the benefit of the readers a milder, safer and “*less brutal*” method is elaborated [15b]. Here melting point capillary tubes are substituted for the Carius tube, and household aluminum wrapping foil is used instead of the protecting bronze tube of Figure 14-1.

### Perfluorodecyl Cobalt(II)phthalocyanines. Direct Alkylation with Perfluorodecyl Iodide

#### Reaction 14-1



## Reagents

Perfluorodecyl iodide [423-62-1], cobalt(II)phthalocyanine [3317-67-7], and ruthenium, 5 wt.% on carbon are commercially available.

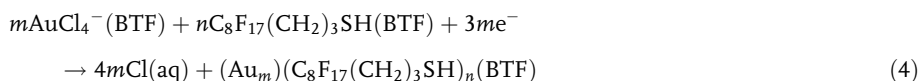
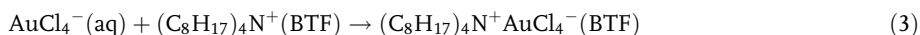
## Experimental Procedure

Cobalt(II)phthalocyanine (0.088 g, 0.154 mmol),  $C_{10}F_{21}I$  (1.0 g, 1.5 mmol),  $K_2CO_3$  (0.12 g, 0.87 mmol) and 5% Ru/C (0.026 g) were mixed in a mortar. Then five melting point capillary tubes (approximately 10 cm long and 1 mm inner diameter) were filled with this mixture to a height of ca. 2 cm and sealed in a Bunsen flame. The capillaries were bunched together and wrapped with ten turns of aluminum foil. The ends of the foil were folded back from the capillary tips. This package was heated in the oven of a “retired” gas chromatograph at 200 °C for two days. The bundle was cooled to room temperature and broken into two halves by bending at the middle. The colored pieces of the capillaries were ground in a mortar and extracted with a few mL of benzotrifluoride. The resulting blue solution was filtered through a cotton plug in a Pasteur pipette. The filtrate was treated at room temperature with an excess of  $NaBH_4$  (0.05 g) dissolved in methanol (0.5 mL) to convert the unreacted  $C_{10}F_{21}I$  (bp ~200 °C) into  $C_{10}F_{21}H$  (bp ~160 °C), which is easier to remove on evaporation. The mixture was evaporated to dryness and the residue extracted with hot FC-84. Filtration and evaporation yields approximately 0.1 g of the fluorous soluble “blue dye”. About 1 mg of this product is used to color the bottom layer of the system shown in Figure 14-2A.

### 14.2.2

#### Preparation of a Fluorophilic “Gold Dye”: $(Au_m)(HS(CH_2)_3R_{f8})_n$

#### Reaction 14-2



## Reagents

Hydrogen tetrachloroaurate(III) trihydrate [16961-25-4] and tetraoctylammonium bromide [63462-99-7] are commercially available, whereas perfluorooctylpropyl mercaptan can be prepared according to the literature procedure [16].

## Experimental Procedure

A solution of  $HAuCl_4 \cdot 3H_2O$  (0.178 g, 0.457 mmol) in water (15 mL) was mixed with a solution of  $(C_8H_{17})_4NBr$  (1.09 g, 2.0 mmol) in benzotrifluoride (40 mL). The two-phase mixture was shaken at room temperature until all the tetrachloroaurate was transferred into the organic layer. The water phase separated, and then the perfluorooctylpropyl mercaptan (0.21 g, 0.42 mmol) was added to the organic phase. A freshly prepared solution of  $NaBH_4$

(0.19 g, 5 mmol) in water (12.5 mL) was added slowly (~10 min) with vigorous stirring. After further stirring for 3 h, the organic phase was separated and washed with water ( $3 \times 5$  mL). Then it was evaporated in vacuum using a rotavap and a water bath for heating (50–60 °C). The dark residue was treated with dioxane (40–50 mL) at room temperature for 1 h to dissolve all components but the solid fluoros-thiol protected the gold nanoparticles. The latter product was isolated by suction filtration, washed with dioxane ( $2 \times 5$  mL) and dried in a vacuum desiccator over phosphorous pentoxide. Yield: 140 mg of a glittering black solid, stable to air, soluble in benzotrifluoride and fluoros solvents, insoluble in most organic solvents.

### Discussion

Using a two-phase (water/toluene) reduction of  $\text{AuCl}_4^-$  by sodium borohydride in the presence of an alkanethiol results in the formation of solutions of 1–3 nm gold particles bearing a surface coating of thiol, as described by Brust et al. [17]. The above synthesis of fluoros thiol-protected gold nanoparticles, disclosed by Rábai et al., adopted the same strategy [6a].

#### 14.2.3

#### Preparation of an Organophilic “Gold Dye” $(\text{Au}_m)(\text{HS}(\text{CH}_2)_{11}\text{CH}_3)_n$

#### Reaction 14-3

Prepared according to the literature procedure [17]. For the equations, see 14.2.2 and substitute toluene for BTF, and  $\text{CH}_3(\text{CH}_2)_{11}\text{SH}$  for  $n\text{C}_8\text{F}_{17}(\text{CH}_2)_3\text{SH}$ .

### Reagents

Dodecanethiol [112-55-0] is commercially available.

### Experimental Procedure

This preparation is conducted analogously to that in 14.2.2, but substituting toluene for BTF and 1-dodecanethiol (0.085 g, 0.42 mmol) for the fluoros thiol. The workup was altered as follows. The solvent (toluene) was evaporated in vacuum, and the residue was consecutively treated with dioxane (30 mL) and benzene ( $3 \times 30$  mL), with the evaporation of each solvent portion before the next was added. The dark residue was finally treated with acetone (50 mL), and the precipitate formed was isolated by filtration and washed with acetone ( $3 \times 5$  mL). Yield: 100 mg of glittering black solid, stable to air, soluble in benzotrifluoride and most organic solvents, insoluble in fluorocarbons.

#### 14.3

#### Fluorous Phase Systems for the Games

Any of the solvent systems displayed in Table 14-2 are easy to assemble, however, appropriate chemical safety should be practiced during demonstrations. Although these experiments were designed to be as safe as possible, eye protection is a must in all cases. To avoid overheating the systems, and as a consequence of sudden boiling (splashes) in open vials or

Tab. 14-2. Selected solvent miscibility data<sup>a,b</sup>

Entry	Solvent system	Phase	Temp. (°C)
1	FC-72/(CF <sub>3</sub> ) <sub>2</sub> CHOH	One phase	RT
2	FC-72/CF <sub>3</sub> CH <sub>2</sub> OH	Two phase	RT
		One phase	on boiling
3	FC-72/ <i>n</i> -heptane	Two phase	RT
		One phase	47 <sup>c</sup>
4	FC-72/ <i>n</i> -heptane/CH <sub>3</sub> NO <sub>2</sub> <sup>d</sup>	Three phase	RT
		Two phase	on warming <sup>b</sup>
5	FC-84/ <i>n</i> -hexane	Two phase	RT
		One phase	34 <sup>c</sup>
6	FC-84/ <i>n</i> -heptane	Two phase	RT
		One phase	54 <sup>c</sup>
7	FC-84/(CF <sub>3</sub> ) <sub>2</sub> CHOH/CF <sub>3</sub> CH <sub>2</sub> OH <sup>e</sup>	Two phase	0–RT
		One phase	26 <sup>c</sup>
8	FC-84/ <i>n</i> -hexane/(CF <sub>3</sub> ) <sub>2</sub> CHOH/CF <sub>3</sub> CH <sub>2</sub> OH <sup>f</sup>	Three phase	0 <sup>c</sup>
		Two phase	~15–30 <sup>c</sup>
		One phase	~33 <sup>c</sup>
9	<i>n</i> -hexane/(CF <sub>3</sub> ) <sub>2</sub> CHOH/CF <sub>3</sub> CH <sub>2</sub> OH <sup>e</sup>	Two phase	T < 60 <sup>c</sup>

<sup>a</sup> Reference [15a]. <sup>b</sup> All data for a 1:1 volume ratio unless otherwise stated. <sup>c</sup> Experimental observation; not a consolute temperature.

<sup>d</sup> Volume ratio 1:1:1. <sup>e</sup> Volume ratio 3:1:1. <sup>f</sup> Volume ratio 3:3:1:1.

excess pressure development in closed systems, one should check the physical properties of the solvents considered for the Games (Table 14-3). When capped vials or sealed glass tubes are warmed, the safest heat source is a water bath of ca. 60 °C.

Entries 5 and 8 in Table 14-2 constitute particularly amusing systems, since all their phase transitions can be triggered by ice water and with bare hands. All phase transitions can be observed either in warming or in cooling modes. During the experiments with entries 4 and 8, the transition temperatures can differ significantly from those listed if the experiments are performed in static mode (i.e., no rocking or shaking applied to the vials). This is caused by the screening effect of the middle phase, since the top and bottom phases should merge or equilibrate on warming. The latter unstable systems immediately merge on turning the vials. In some cases, heavy emulsions can be observed over narrow temperature ranges (not shown on Figure 14-4, but possible).

Tab. 14-3. Some physical properties of selected solvents

Solvent	Mp (°C)	Bp (°C)	Density (g mL <sup>-1</sup> )
FC-72	–90	56	1.68
FC-84	–95	80	1.73
<i>n</i> -Hexane	–95	69	0.659
<i>n</i> -Heptane	–91	98	0.684
(CF <sub>3</sub> ) <sub>2</sub> CHOH	–4	59	1.596
CF <sub>3</sub> CH <sub>2</sub> OH	–43.5	77–80	1.373
CH <sub>3</sub> NO <sub>2</sub>	–29	101.2	1.127

## 14.4

## Name of the Games

All Games are displayed in Figures 14-2 to 14-7. The standing vials shown in the photographs correspond to 30% of actual size. Figures 14-2 to 14-5 display Games with System  $3 \rightarrow 2 \rightarrow 1$ ; Figure 14-6 with System  $3 \rightarrow 2$ , middle  $\rightarrow$  up version; and Figure 14-7 with System  $3 \rightarrow 2$ , middle  $\rightarrow$  down version. Each vial is charged with appropriate amounts of the solvent mixtures shown below. Then the dyes are added and the vials sealed. More details are given under the names of the appropriate Games.

**System  $3 \rightarrow 2 \rightarrow 1$  (cf.: Entry 8, Table 14-2)**

A mixture of *n*-hexane (8.0 mL), trifluoroethanol (2.5 mL), 1,1,1,3,3,3-hexafluoro-2-propanol (2.5 mL) and FC-84 (8.0 mL) is made at room temperature. This mixture forms three layers at ice temperature, two layers at room temperature, and a one-phase system at body temperature (Table 14-2, Figures 14-2 to 14-5).

**System  $3 \rightarrow 2$ , middle  $\rightarrow$  up version (cf.: Entry 4, Table 14-2)**

A mixture of *n*-heptane (5.75 mL), nitromethane (5.75 mL) and FC-72 (5.75 mL) is made at room temperature. The top and bottom phases merge on heating, facilitated by gentle shaking, while the nitromethane layer goes up (Table 14-2, Figure 14-6).

**System  $3 \rightarrow 2$ , middle  $\rightarrow$  down version (cf.: Entry 4, Table 14-2)**

A mixture of *n*-heptane (10.5 mL), nitromethane (5.75 mL) and FC-72 (10.5 mL) is made at room temperature. The top and bottom phases merge on heating, facilitated by gentle shaking, while the nitromethane layer goes down (Table 14-2, Figure 14-7).

## 14.4.1

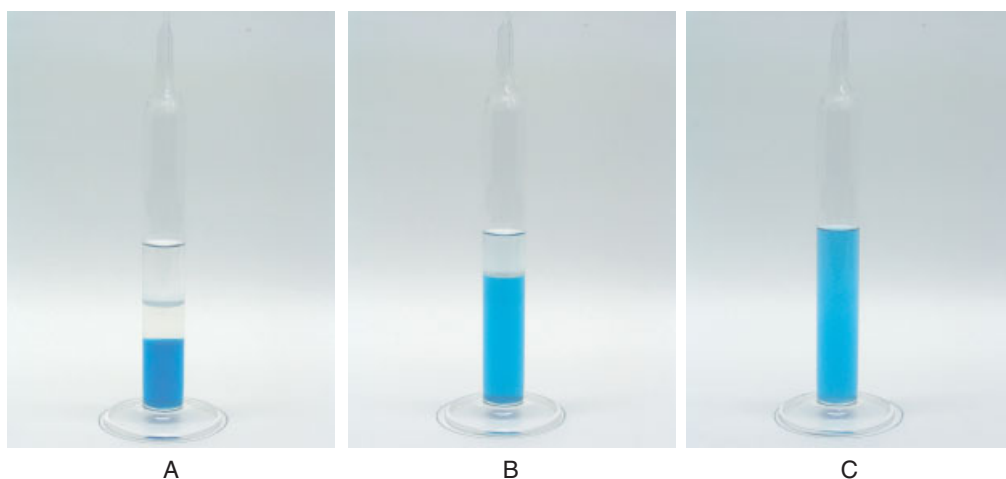
**Make Them Blue!**

Fig. 14-2. Make Them Blue!



This Game features stages of System  $3 \rightarrow 2 \rightarrow 1$  in the warming cycle (cf. entry 8, Table 2.). The FC-84 rich layer is colored with the “blue dye”, while the middle and top ones are clear and colorless (Figure 14-2A). Slight warming merges the lower layers, the blue color becomes lighter, while the hexane rich layer remains colorless (Figure 14-2B). The one-phase system formed at higher temperature is evenly dyed blue: thus the job is done (Figure 14-2C)!

#### 14.4.2

##### Purple Empire

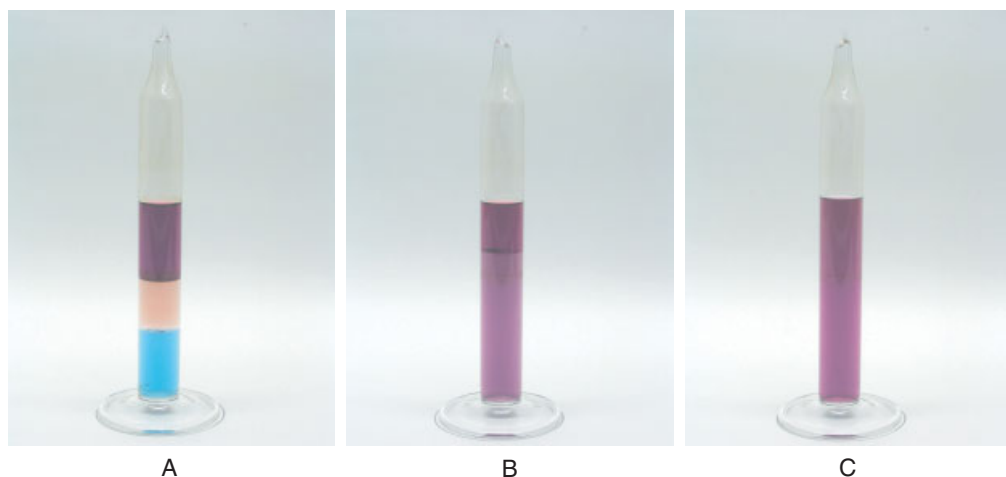


Fig. 14-3. Purple Empire.

This Game is a variant of the above (14.4.1), since besides the “blue dye” some iodine is added to make different colors at the three-phase condition: purple, orange-red and blue. At the two-layer stage, much of the iodine is still in the hexane rich top phase, while the color of the fluorous cobalt phthalocyanine is shaded or augmented by iodine (Figure 14-3B). Finally, all space is evenly dyed purple by iodine (Figure 14-3C).

#### 14.4.3

##### Which Phase to Winter?

This Game features the stages of System  $3 \rightarrow 2 \rightarrow 1$  in a cooling cycle (cf. entry 8, Table 14-2). One series of vials contains the organophilic  $(Au_m)[HS(CH_2)_{11}CH_3]_n$  dye (Figure 14-4A,B,C); the other series contains the fluorophilic  $(Au_m)[HS(CH_2)_3R_{f8}]_n$  dye (Figure 14-5A,B,C). No one can tell which is which until the three-phase stage of both series arrives. At the warm side or high temperature limit the gold nanoparticles are evenly distributed through the whole liquid volume (Figures 14-4A and 14-5A); however, at lower temperature they are completely withdrawn to the fluorine rich lower layers of the intermediate biphasic

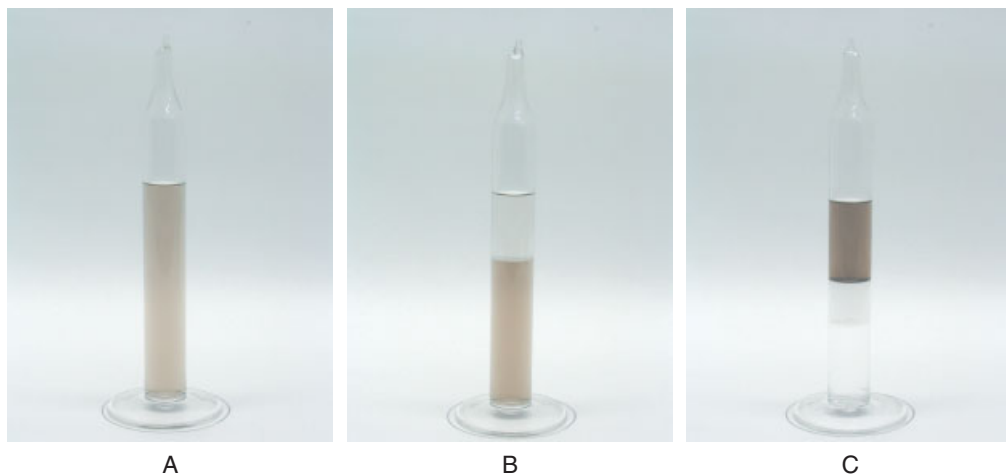


Fig. 14-4. Which Phase to Winter?

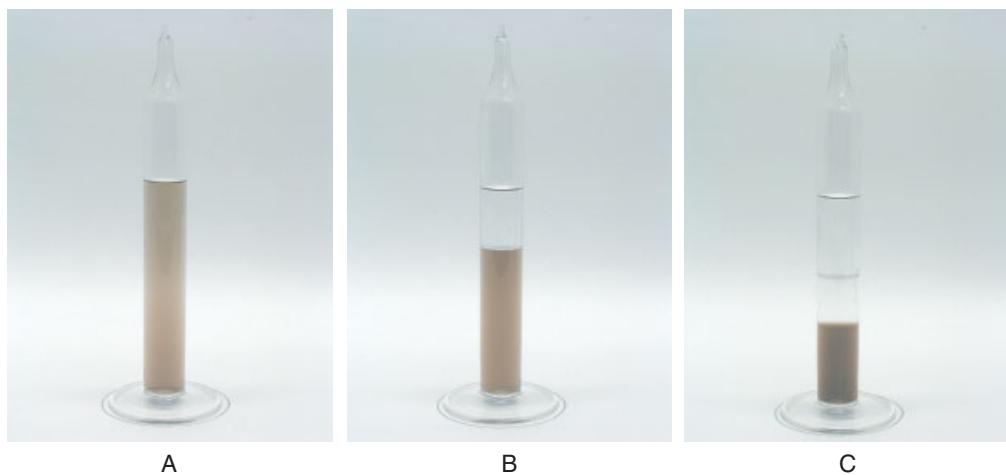


Fig. 14-5

systems (Figures 14-4B and 14-5B). Neither type of thiol protected gold nanoparticles remain in the hexane rich upper layer, an unexpected event for the organophilic dye (Figure 14-4B). The splitting of the bottom phases on further cooling yields the three-phase systems shown, and gives the solution to the puzzle: the gold particles select phases for wintering according to their coats (Figures 14-4C and 14-5C)!

## 14.4.4

## Up and Down

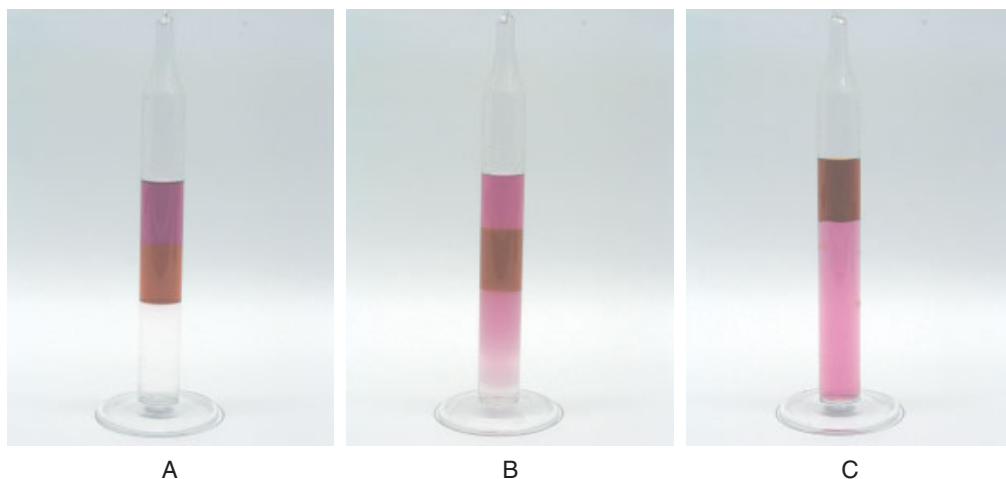


Fig. 14-6. Up and Down.

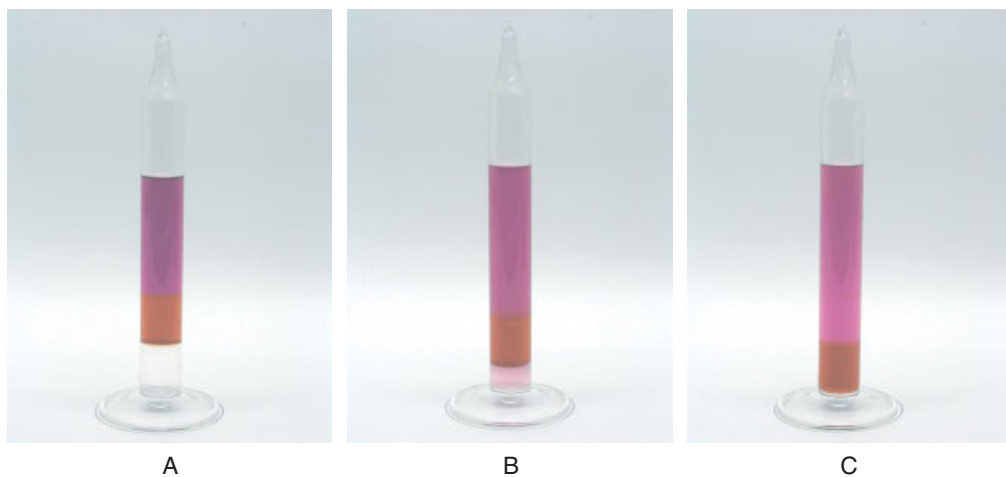


Fig. 14-7

This Game features the stages of System  $3 \rightarrow 2$ , middle  $\rightarrow$  up ( $C_7H_{16}:CH_3NO_2:FC-72 = 5.75:5.75:10.5$  v/v) and System  $3 \rightarrow 2$ , middle  $\rightarrow$  down ( $C_7H_{16}:CH_3NO_2:FC-72 = 10.5:5.75:5.75$  v/v) in their warming cycles (Figure 14-6A,B,C and Figure 14-7A,B,C; cf. entry 4, Table 14-2). The density of the merged heptane/FC-72 phases is tuned by volume ratios to be higher/lower than that of  $CH_3NO_2$ . This results in the up and down movements of

the  $\text{CH}_3\text{NO}_2$  layers upon phase transitions. The partition and the extent of solvation of the iodine used for dyeing the layers improves the beauty of the Game. Moreover, in an undisturbed cooling cycle special phenomena can be observed. The top phase releases small droplets, which penetrate through the screening  $\text{CH}_3\text{NO}_2$  phase to the bottom, until an equilibrium is established; at the same time, the droplets from the bottom phase move in the opposite direction (Figure 14-7B). A magic “F-fun” can be observed if the tubes are kept with two hands in a horizontal position and smooth waves generated by minute up and down movements (not shown).

## 14.5

### Epilogue

In the closing pages of this book, the author wishes to pay tribute to the many pioneers of organofluorine chemistry. Their contributions, brought to fruition in both academic and in industrial research laboratories, established the vast knowledge base available today and made the advances described in this book possible [18–20].

### Acknowledgements

The author thanks Ana-Maria Bonto and Dr. Peter Ivanko for their careful experimental assistance, László T. Mika for the drawings and photographs, and the European Contract of Research Training Network (“Fluorous Phase” HPRN-CT-2000-00002) for financial support.

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## Index

### **a**

ABCR 12  
 acetalization 31, 356, 386  
 acoustic pressure 533  
 acute respiratory distress syndrome 551  
 affinity chromatography 559  
 AIBN 175, 183, 187, 247, 252, 362, 419  
 AIDS chemotherapy 149  
 albumin 555  
 Albunex 535  
 alcohol resolution 325  
 alcohol oxidation 298, 302  
 aldol reaction 357, 388  
 Aldrich 12, 132  
 alkane oxidation 298, 302  
 alkene oxidation 298  
 allergic reaction 547  
 allylation 105, 109, 177, 265, 310, 357, 388, 464  
 allylic alkylation 312, 318  
 allylic oxidation 302  
 allylic substitution 265, 312, 318  
 aluminium 496  
 amide condensation catalyst 382  
 amine 421  
 amphiphiles 529  
 – fluorocarbon-hydrocarbon diblock 529  
 amphiphilic solvents 13, 316  
 angiogenesis 538f, 541  
 angioplasty 556  
 antisense oligonucleotides 555  
 Apollo Scientific Ltd. 12  
 artificial blood 13, 543  
 asymmetric synthesis 144  
 atherosclerosis 541  
 atherosclerotic plaques 537  
 atom transfer radical reactions 303  
 – addition 303  
 – polymerization 303  
 Avidin 541

### **b**

Baeyer-Villiger oxidation 207, 215  
 BBr<sub>3</sub> 152  
 benzene 13  
 benzotrifluoride (BTF) 13, 16, 131f, 157, 176, 184  
 Bfp 234, 415  
 BINAP 431, 437  
 BINOL 431, 437  
 biomedical applications of fluororous methods 521  
 biotin 539  
 blood clots 537, 541  
 blood flow velocity 535  
 blue dye 7, 575  
 bonded fluororous phases 14  
 bonded fluororous phase catalysis 35  
 Hildebrand 574  
 1-bromofluorooctane 526  
 – oral ingestion 526  
 – infusion 526  
 1-bromoperfluorooctane 12, 19, 207, 294, 302, 542, 544, 546, 550f, 556f, 560  
 brutal perfluoroalkylation 575  
 BTF 13, 16, 131f, 157, 176, 184  
 budesonide 558  
 butadiene 8  
 – telomerization 8  
 bypass surgery 543

### **c**

C<sub>8</sub>F<sub>17</sub>Br 12, 19, 207, 294, 302, 542, 544, 546, 550f, 556f, 560  
 cadmium 493, 502  
 cadmium sulphide 502  
 camphor-10-sulfonyl chloride 369  
*Candida antarctica* 151, 324, 327, 406, 408  
*Candida rugosa* 334, 338  
 carbobenzoxy 227

carbon monoxide 182  
 carboxylate 301  
 carboxylic acid 325  
 carboxylic acid amides 30, 352  
   – synthesis of 30, 352  
 carboxylic acid chloride 325  
 carboxylic acid ester 325  
 carboxylic acid halides 158  
 carcinoma 540  
 cardiopulmonary bypass 551  
 carotid artery 541  
 carpanone 371  
 catalyst inventory 38  
 catalyst precursor 24  
 catalyst rest state 24  
 CdS 493, 501  
 cell cultures 553  
 $\text{CF}_3(\text{CF}_2)_7(\text{CH}_2)_2\text{OH}$  334  
 chlorination 153  
 chromium 493  
 clinical trials 547  
 $\text{CO}_2$ -expanded solvent 466  
 coating nanoparticles 503  
 cobalt 272, 291, 294, 301, 302, 313, 318, 398, 496  
 coding  
   – analogs 147  
   – diastereomers 146  
   – enantiomers 144  
 cohesive energy densities 574  
 colon cancer 240  
 combinatorial chemistry 236  
 condensation of -diketones 34  
 consolute temperature 19, 574  
 contrast agents 560  
 copper 294, 301ff, 395, 398, 494  
 copper cross-coupling 204f, 248, 282, 366, 378, 428, 431, 443, 445  
 Corey-Kim oxidation 211, 213  
 Cornils, B. 8  
 critical micellar concentration (CMC) 481, 527  
 critical solution temperature 574  
 cryptand 509, 513  
 cryptate 513  
 crystal engineering 508, 514  
 crystal structure 509, 512, 514  
 crystallographic disorder 510  
 Curran, D. 8, 9, 101  
 cyclodextrin columns 122  
 cyclodimerization of enynes 265  
 cyclohexene 8  
   – oxidation 8  
 cyclopropanation 268, 390  
 cytochrome oxidase 558

## d

decompression sickness 544  
 Definity® 535  
 dehydrogenation 206  
 demethylation of ethers 152  
 demixing 143, 149  
 demonstrations 580ff  
 detagging 143, 149f  
 DFT calculations 50f, 507  
 Diels-Alder reaction 21, 239, 314  
 diethyl zinc 132, 265, 308, 317  
   – addition to aldehydes 132, 265, 308, 317  
 differential scanning calorimetry (DSC) 516  
 dioxirane 345  
 discodermolide 230  
 drug delivery 560  
 drug vehicles 521  
 DSC 516

## e

echocardiography 536  
 echosonography 530, 533  
 Echovist 535  
 electron donation,  $n \rightarrow \sigma^*$  509  
 emulsification 481  
 enantioselective catalysis  
   – carbon-carbon bond formation 308, 317  
   – epoxides 313  
   – hydrogenation 306, 319  
   – kinetic resolution 313  
   – kinetic resolution of epoxides 318  
   – oxidation 312  
   – protonation 313  
   – supercritical carbon dioxide 320  
   – transfer hydrogenation 307  
 endothelial cells 539  
 endothelium 542  
 endotoxemia 552  
 enthalpies of protonation 48  
 enzyme 150  
 epithelial cells 552, 557  
 epoxidation 207, 215f, 290, 292, 312, 344ff  
 epoxides 313, 318  
   – enantioselective ring opening 313, 318  
 EPR 302  
 ES Industries 103  
 esterification 357  
 ethylene 8  
   – oligomerization 8  
 Exxon 5, 8

## f

F-626 13, 184, 470  
 FC-72 12, 150, 152, 579

- FC-75 12, 21, 499
- flu 546
- Fluka 12, 132
- Fluofix® 102f, 111
- FluoMar™ reagent 137
- fluorine 479, 523
  - properties 479, 523
  - polarizability 480
- Fluorinert 12
- fluoro alkenes 161
- Fluorochem 12, 132
- FluoroFlash™ 102, 111f, 120, 134, 238, 242, 244
  - solid phase extraction 242
- Fluorophase™ 103
- fluorophilic 3
  - definition 3
- fluorophilicity 3, 56, 575
  - definition 3
- fluorophobic 3
  - definition 3
- fluorophobic effects 98
- fluorophobic interaction 21
- fluorous 2, 6
  - definition 6
- fluorous amphiphiles 526
- fluorous acac 460, 466
  - chromium complex 466
  - nickel complex 34
- fluorous acetal 147f, 300, 401, 471
- fluorous alcohol 163, 192, 198, 228, 230, 243, 300, 313, 316, 325, 334, 337, 341, 356, 386, 393, 400, 403, 410, 419, 421, 447, 471
- fluorous aldehydes 167, 243
- fluorous alkanes 157, 161
- fluorous alkenes 157, 188, 380
- fluorous alkyl bromide 403
- fluorous alkyl halides 162
- fluorous alkyl iodides 52, 109, 205, 210, 216, 248, 282, 299, 367, 379, 382, 390, 393, 419, 421, 428, 443, 452, 457, 464, 475
  - S<sub>N</sub>2 reactions 52
- fluorous alkyl zinc 248f
- fluorous alkynes 157, 161, 454
- fluorous amines 43, 47, 49, 51, 136, 159, 165, 204f, 238, 243, 249, 290, 293, 298, 300, 307, 314, 393, 421, 457, 499f, 495
  - pK<sub>a</sub> values 49
- fluorous amino acids 106
- fluorous amino alcohol 131, 316
- fluorous amino ester 138
- fluorous amphiphiles 478, 482, 521, 554, 558f, 561
- fluorous anhydrides 159
- fluorous aniline 165, 204f
- fluorous arene 161, 382, 390, 428, 443, 500
- fluorous artificial blood 521
- fluorous aryl bromide 109
- fluorous aryl halide 162, 205, 249, 382
- fluorous azodicarboxylate 191
- fluorous benzyl bromide 224, 226
- fluorous benzyl protecting group 224
- fluorous BINAP 260, 307, 311, 319, 431, 437
- fluorous BINAPHOS 283, 285
- fluorous BINOL 255, 265, 308, 310, 366f, 367, 431, 437
  - resolution 367
- fluorous biphasic chemistry 6
- fluorous biphasic system 6
- fluorous bipyridines 293
- fluorous bipyridine 300
- fluorous blood substitute 521, 543
- fluorous BOC 108, 137, 229f
- fluorous bolaamphiphiles 526
- fluorous borane-dialkyl sulfide 475
- fluorous borate 419
- fluorous boron compounds 166
- fluorous boronic acid 30, 350, 383
- fluorous boronic acid esters 263
- fluorous BPFOS 140
- fluorous Brønsted acid 31, 350, 354, 383, 386
- fluorous buckminsterfullerene 218
- fluorous C<sub>60</sub> 218
- fluorous cadmium 502
- fluorous cadmium sulphide 502
- fluorous carbobenzoxy 37, 125, 137, 146, 224, 229f, 233
- fluorous carbodiimide 179, 457, 459
- fluorous carbohydrate 129, 142, 159, 164, 211, 213, 232, 415, 475
- fluorous carbonic acid derivatives 169
- fluorous carboxylic acid 168, 179, 194, 243, 301, 318, 325, 390, 395, 397, 403, 441, 485
  - carboxylate 268, 301, 395, 398
- fluorous carboxylic acid amide 415, 417
- fluorous carboxylic acid chloride 243, 325, 403
- fluorous carboxylic acid ester 150, 158, 169, 198, 231, 300, 325, 397, 400, 403, 405, 407
- fluorous catalysis 25, 28, 34f, 35, 263, 306, 350, 354, 375, 377, 382, 386
  - biphasic 25
  - enantioselective 306
  - hybrid 25
  - liquid/liquid 25
  - liquid/solid biphasic 28, 350
  - recovery using support 35, 263, 375, 377
  - without fluorous solvents 28, 350, 382, 386
  - without solvents 34f, 354
  - without non-fluorous solvents 25



- fluorous catalysts recovery using supports 35, 123  
 fluorous CBz 37, 125, 137, 146, 224, 229f, 233  
 fluorous chemistry 4  
   – definition 4  
 fluorous chromatography 101  
 fluorous cobalt 291, 294, 301, 302, 313, 318, 398  
 fluorous colloids 478, 483, 521, 539, 554, 556, 559f  
 fluorous contrast agents 530  
 fluorous copper 294, 301ff, 395, 398, 494  
 fluorous crown ether 542  
 fluorous cycloalkanes 161  
 fluorous cyclopentadiene 452  
 fluorous DEAD 108, 191f, 196, 436  
 fluorous dendrimer 486, 498f  
 fluorous diacetoxy iodobenzene 178, 371  
 fluorous Diels-Alder adducts 112  
 fluorous diol 447, 471  
 fluorous dioxane 214, 346  
 fluorous diphosphine 135  
 fluorous dirhodium tetracarboxylate 35  
 fluorous disaccharide 142, 226, 234  
 fluorous diselenides 178, 204  
 fluorous disulfides 159  
 fluorous dyes 575  
 fluorous emulsifiers 529  
 fluorous emulsion droplet 539  
 fluorous emulsions 543, 546, 549, 554f  
   – stabilization 546, 549  
 fluorous end capping 141  
 fluorous epoxide 243  
 fluorous ether 163, 198, 241  
 fluorous fibers 484  
 fluorous flash chromatography 109, 146  
 fluorous gallic acid 194, 441  
 fluorous gels 69, 522, 552  
 fluorous glucal 226  
 fluorous glucolipids 484  
 fluorous gold 494, 496  
 fluorous gold dye 577  
 fluorous greases 14  
 fluorous Grignard reagent 412  
 fluorous heptapeptide 115  
 fluorous hollow fibers 478  
 fluorous HPLC 111, 114f  
 fluorous HPLC 118, 121, 144  
   – analysis and purification of organofluorine compounds 114  
   – demixing in fluorous mixing synthesis 115  
   – derivatization for chemical analysis 118  
   – method development for preparative fluorous chromatographies and SPEs 115  
 fluorous hybrid materials 507  
 fluorous hypervalent iodine reagents 177, 371  
 fluorous imines 159, 307  
 fluorous ionic liquid 13, 19f  
 fluorous iridium 307, 320  
 fluorous iridium carbonyl complexes 45  
 fluorous iron ruthenium 494  
 fluorous isatoic anhydride 243, 423, 473  
 fluorous isocyanate 138, 159, 243  
 fluorous ketone 122, 158, 167, 214ff, 345, 500  
 fluorous label 3, 41  
   – definition 3  
 fluorous lamellar phases 528  
 fluorous lanthanide 358, 423, 426, 449  
 fluorous Lewis acid 31, 269, 358, 412, 423, 426, 449,  
 fluorous liposomes 556  
 fluorous liquid crystal 517  
   – smectic 517  
 fluorous lithium compounds 166  
 fluorous magnesium compounds 166  
 fluorous manganese 291, 301, 302, 312, 395, 398  
 fluorous mappicine 115, 129l  
 fluorous materials 521  
   – biomedical uses 521  
 fluorous medium 3  
   – definition 3  
 fluorous metal oxide nanoparticles 501  
 fluorous micelles 96, 478  
 fluorous microbubbles 486, 530, 539, 554, 560  
 fluorous mixture synthesis 142, 232  
 fluorous molecules 545  
   – retention in organs 545  
 fluorous molybdenum 395  
 fluorous nanoparticles 259, 491, 494  
 fluorous nanoreactors 486  
 fluorous *N*-benzylmaleimide 113  
 fluorous nickel 53, 269  
 fluorous nitriles 159  
 fluorous nitrogen donor ligands 290, 298  
 fluorous *N*-phenylmaleimides 113  
 fluorous organocatalysts 297  
 fluorous palladacycle 38, 39, 259, 500  
 fluorous palladium 35, 53, 124, 136, 261, 265, 302, 311, 318, 258, 361, 372, 377, 494, 498  
 fluorous peptide 417  
 fluorous phase 6  
   – definition 6  
 fluorous phase affinity 3  
   – definition 3  
 fluorous phenol 445  
 fluorous phosphines 29, 43, 47, 48ff, 52, 96, 106, 124, 134, 135, 165, 175, 191, 196, 243, 247, 253, 258f, 261, 269, 272, 275, 307, 321, 363, 370, 372, 378, 380, 410, 428, 431, 436f, 461

- fluorous phosphines (*cont.*)
  - bidentate 253
  - chiral 253, 307
  - oxide 176, 378, 410, 437
  - pK<sub>a</sub> values 49
- fluorous phosphites 165, 281, 287, 318, 321, 493, 486
  - decomposition 287
- fluorous phosphocholines 481
- fluorous phospholipids 482
- fluorous phosphonium salt 250
- fluorous photo sensitizers 217, 296
- fluorous phthalocyanine 294, 575
- fluorous pincer complex 135, 269
- fluorous platinum 53, 107, 129, 269, 494
- fluorous p-methoxybenzyl (PMB) 148, 225, 228, 233
- fluorous polyether 493, 500
- fluorous polymer 516
  - comb-like 516
- fluorous polyoxometalate 31
- fluorous porphyrins 290, 296
- fluorous protecting groups 107, 222, 234
- fluorous pyridines 165, 300, 400f
- fluorous pyridones 116
- fluorous pyrimidine 231
- fluorous quasiracemic synthesis 144
- fluorous reaction 4
  - definition 4
- fluorous reaction component 4
  - definition 4
- fluorous rhodium 278
- fluorous rhodium carboxylate 268, 390
- fluorous Rink protecting group 225
- fluorous ruthenium 293, 307, 319
- fluorous salen complex 295, 312
- fluorous SAM 485
- fluorous scavenger 243
  - electrophiles 243
  - nucleophiles 243
- fluorous scavengers 107, 135f, 473
- fluorous selenenic acid 205, 207
- fluorous selenenyl halide 204ff
- fluorous selenide 164, 205, 207
- fluorous selenoxide 207
- fluorous self-assembled monolayers 485
- fluorous self-assemblies 478
- fluorous silane 137
- fluorous silica gel 9, 34f, 101, 106, 111, 119, 132, 238, 249, 263, 316, 375, 377
- fluorous silicon 53
- fluorous silicon compounds 166
- fluorous silver 494
- fluorous silyl bromide 140, 447
- fluorous silyl ether 116, 145, 149, 232f, 235
- fluorous silyl halide 224, 226ff
- fluorous silyl protecting group 224, 228
- fluorous silyl triflate 141, 145, 149
- fluorous solid phase extraction (FSPE) 101, 103
- fluorous solid-phase organic synthesis 36
- fluorous solvents 11, 14, 17f, 525, 579
  - boiling point 12
  - CAS numbers 11
  - cavities 15
  - densities 12, 18, 579
  - gas solubilities 17, 525
  - hydrogen solubility 17
  - miscibilities 18, 579
  - oxygen solubility 17, 525
  - polarities 14
  - solubilities in 15
  - trade names 11
  - vendors 11
- fluorous Staudinger reaction 134
- fluorous sugar 129, 142, 159, 164, 211, 213, 232, 415, 475
- fluorous sulfonates 164
- fluorous sulfonic acid 243
- fluorous sulfonimides 164
- fluorous sulfonyl halides 159
- fluorous sulfosuccinate 486, 493
- fluorous sulfoxide 164, 210
- fluorous sulfide 210, 263, 500
- fluorous supramolecular complex 96, 179, 459,
- fluorous surfactants 479, 481, 483, 521, 526, 528, 548, 559
  - gemini 481, 483, 526
- fluorous TACN 293, 299, 301, 393, 395
- fluorous tag 3, 101, 139
  - definition 3
- fluorous tags 41, 222, 231
- fluorous t-butoxy protecting group 224, 227f
- Fluorous Technologies, Inc. 102, 109, 132, 156
- fluorous tetraazamacrocyclic 293, 300
- fluorous tetrafluorophenylbis(triflyl)methane 386
- fluorous thiol 136, 139, 164, 243, 267, 310, 485, 495, 498, 577
- fluorous THP 137, 227f
- fluorous tin 30, 52, 105, 129, 176f, 177, 182, 238, 262, 360, 412, 470
- fluorous tin allylation 269
- fluorous tin compounds 166
- fluorous tin hydride 25, 32
- fluorous titanium 265, 308f, 502
- fluorous titanium dioxide 502
- fluorous TLC 108, 119
- fluorous tosylate 403

fluorous trialkoxybenzhydryl protecting group 225  
 fluorous triazamacrocyclic 293, 299  
 fluorous triazines 159  
 fluorous triflate 452, 454  
 fluorous triphasic reactions 150  
 fluorous triazolinedione 113  
 fluorous tubules 484  
 fluorous urea 179, 240, 457, 459  
 fluorous vesicles 478, 482, 521, 556, 561  
 fluorous vinyl ether 140, 224, 227, 238, 240  
 fluorous Wilkinson's catalyst 252, 278  
 fluorous Wilkinson's complex 129  
 fluorous ytterbium 269, 358, 423  
 fluorous zinc 265, 308  
 fluorous zinc compounds 166  
 FluoSep<sup>TM</sup> 103  
 Flutec 12  
<sup>19</sup>F NMR 35, 38, 43, 542, 510, 516  
 Fomblin<sup>®</sup> 553  
 four-component coupling 186  
 F-PMB 233  
 F- (prefix) 4  
 – definition 4  
 Friedel-Crafts acylation 269, 358, 426  
 FSPE 103

## g

Gabriel synthesis 421  
 gadolinium 542, 555  
 galactose 234  
 Galden 12  
 games 580ff  
 gas carriers 521  
 gas solubilities 17  
 – fluorous solvents 17  
 gastrointestinal tract 542  
 gel 96  
 Gelest 132  
 gels 50  
 gel-to-fluid transition temperature 482  
 gene delivery 561  
 gentamycin 557  
 Gibbs monolayers 485  
 Giese reaction 177, 238  
 Gladysz, J. 8f9  
 gold 493f, 496, 499

## h

haemoglobin equivalent 547  
 haemolytic activity 527  
 halogen bond 482, 507, 510  
 halothane 557  
 Hammett  $\sigma$  constants 45

harmonic imaging 533  
 heavy fluorous 4, 101, 128, 156  
 – definition 4  
 Heck reaction 38, 124, 134, 249, 311, 319, 363, 380, 461, 499f, 501  
 hemoglobin 558  
 hemorrhagic shock 550  
 hexafluorobenzene 13  
 hexafluoroisopropanol 341, 348  
 HF elimination 43  
 Hfb 224, 234, 416  
 HFIP 341, 348  
 high pressure NMR 276  
 Hildebrand, J. 5, 19, 22, 97, 336, 574  
 homodesmotic reactions 51  
 Horváth, I. 128  
 hybrid solvents 13  
 hydantoin 230  
 hydroboration 29, 475  
 hydroformylation 7, 272f, 281, 285, 321  
 – aqueous biphasic media 273, 281  
 – enantioselective 285, 321  
 – ionic liquid media 273, 281  
 – supported catalysts 274  
 – supercritical carbon dioxide 275  
 hydrogen peroxide 207, 341  
 hydrogenation 272, 277, 497  
 – aqueous biphasic media 277  
 – ionic liquid media 277  
 – supercritical carbon dioxide 278  
 – rhodium  
 hydrophile-lipophile balance 481  
 hydrophobicity 524  
 hydrostannylation 177  
 hydroxymethylation 183  
 hyperoxia 542

## i

Imagent<sup>TM</sup> 536  
 immunoglobulins 558  
 induction periods 24, 39  
 inflammation 540f, 547  
 insulating groups 6  
 interfacial tension 480  
 internal pressure 574  
 intestine 550  
 intratracheal admistation 557  
 ionic liquids 290  
 ionization potential 50  
 – VIP values 50  
 IR  $\nu_{\text{CO}}$  45  
 iridium 18, 307, 320  
 iron 494  
 ischemia 540, 542f

ischemic heart disease 536  
 isobutane oxidation 5  
 isobutyraldehyde 292

**j**

Julia olefination 147

**k**

Kaldor, A. 5  
 Keystone Scientific 103  
 Kharash addition 269  
 kidney 547, 555  
 kinetic resolution 150f, 323ff, 333, 405  
 – alcohols 323, 405  
 – carboxylic acids 334, 338  
 – esters 151, 323, 330, 338, 407

**l**

lamellar structure 482  
 Lancaster 12  
 Langmuir films 529  
 Langmuir monolayers 485  
 Laplace pressure 530  
 leaching 7, 35, 38, 276, 278, 287, 307  
 leukocyte 539f  
 libraries 142, 230, 236, 239  
 Lifshits-Slezov theory 546  
 light fluoruous 4, 101, 128, 131, 156  
 – definition 4  
 light fluoruous synthesis 106  
 lipase 323, 333f, 338, 405  
 – stability in fluoruous solvents 334  
 liposomes 482, 529, 559  
 liver 540, 542, 547  
 liver lesions 538  
 lung 547, 551  
 lung lavage 551  
 lymphocytes 555

**m**

3M 7f, 12  
 macrophages 552, 559  
 magic tricks 580ff  
 Maginot line 96  
 magnetic resonance imaging 539, 541  
 make them blue 580  
 manganese 291, 301, 302, 312, 346, 395, 398  
 mappicine 144, 149, 230, 232  
 Marshall FluoMar<sup>TM</sup> resin 231  
 matrix 132  
 Merck 12  
 metal catalyzed carbon-carbon bond forming reactions 257  
 metal chalcogenide 501

metal halide 501  
 metal oxide 501  
 methane 5  
 9-methoxyanthracene 21  
 mice 555  
 micelles 50  
 microwave 32, 135, 261, 359, 364  
 miscibility switch 20  
 Mitsunobu reaction 107, 190, 441  
 mixture libraries 143  
 mobile order and disorder theory 98  
 molal volumes 98, 574  
 molybdenum 395  
 monoclonal 540  
 murisolin 147  
 myocardial infarction 543  
 myocardial perfusion 537, 560

**n**

Nafion<sup>®</sup> 493, 496, 501  
 nanoparticles 39, 491, 503, 575  
 – coating 503  
 – fluoruous methods for formation 491  
 – mechanisms of formation 491  
 NaOCl 292  
 Negishi reaction 258  
 neural network 97  
 nickel 269, 277  
 nitrile oxide cycloaddition 239  
 non-fluoruous gold dye 578  
 non-fluoruous TLC 119  
 non-fluoruous silica gel for fluoruous separations 118

**o**

O<sub>2</sub> carrier 544  
 Oakwood Products 12  
 oligomerization 8  
 – ethylene 8  
 oligosaccharide 415  
 oligosaccharide synthesis 233  
 ophthalmology 521, 553  
 Optison<sup>®</sup> 535  
 organ preservation 553  
 organoselenium based oxidation 203  
 Ostwald ripening 546  
 oxidation 5, 8, 18, 290  
 – alcohol 290, 294  
 – aldehydes 207  
 – alkenes 290  
 – cyclohexene 8  
 – iridium 18  
 – photosensitized 217, 296  
 – sulfides 294, 342

– thiol 343  
 oxidative coupling 371  
 Oxone® 214f, 345  
 Oxychem 12  
 oxygen carrier 544  
 oxygen delivery 551, 554, 560  
 Oxygent™ 547  
 Ozark 132

## P

P *see* partition coefficients  
 paclitaxel 555  
 palladacycle 380  
 – non-fluorous 380  
 palladium 124, 135, 249, 258, 261, 277, 302, 311, 318, 361, 372, 374, 377, 380, 494, 498  
 parenchyma 540  
 partition coefficients 56ff, 61, 252  
 – alcohols 59, 337  
 – aliphatic ethers 61  
 – aliphatic halides 74  
 – alkanes 57  
 – alkenes 57  
 – amines, imines 74  
 – arenes 266  
 – arenes, aryl halides, phenols 68  
 – aryl halides 266  
 – boron compounds 84  
 – carboxylic acids and derivatives 61  
 – determination 98f  
 – – GLC 98  
 – – HPLC 98  
 – – <sup>19</sup>F NMR 99  
 – ketones and aldehydes 59  
 – phenols 266  
 – phosphorous compounds 76, 248, 252, 283  
 – prediction 97  
 – silicon compounds 82  
 – sulfur compounds 83  
 – supramolecular complexes and polymers 87  
 – temperature dependence 90  
 – tin compounds 80  
 – transition metal compounds 85  
 – trends 91, 97  
 – – fluorous solvent 97  
 – – general 95  
 – – metal complexes 94  
 – – monoarenes 92  
 – – non-aromatic hydrocarbons 91  
 – – non aromatic monofunctional compounds 91  
 – – pyridines 93  
 – – triarylphosphines 93  
 penicillin 557  
 peptide synthesis 233, 416

perfluoroalkanones 158  
 perfluoro *ωω*-diiodoalkanes 508, 513  
 perfluoro-2-butyltetrahydrofuran 12  
 perfluoroalkanecarbonitriles 159  
 perfluoroalkanecarboxylic acid halides 158  
 perfluoroalkanes 157, 507  
 perfluoroalkanesulfonyl anhydrides 159  
 perfluoroalkenes 157  
 perfluoroalkyl-caesium intermediates 160  
 perfluoroalkyl copper(I) 160  
 perfluoroalkyl halides 158  
 perfluoroalkyl iodide 186, 205, 282, 367, 379, 382, 390, 393, 419, 428, 464, 443, 576  
 perfluoroalkyl isocyanates 159  
 perfluoroalkyl-lithium intermediates 160  
 perfluoroalkylmagnesium halides 160  
 perfluoroalkylsulfides 159  
 perfluoroalkylzinc halides 160  
 perfluoroazomethines 159  
 perfluorodecalin 12, 16, 19, 337, 352, 548, 552, 554, 557  
 perfluorohexane 12  
 perfluoromethylcyclohexane 12, 16  
 perfluorothers 158  
 perfluorotributylamine 12  
 perfluoroalkynes 157  
 PFMC 12, 16  
 PH<sub>3</sub> 247  
 phagocytosis 540, 556  
 phase vanishing reaction 151, 468  
 phosphine-catalyzed addition 29, 34, 247, 353, 380, 431, 437  
 phospholipid 532, 549f, 553, 559  
 photoelectron spectra 46  
 photosensitized oxidation 217  
 phthalocyanine 7  
 pigs 541, 551  
 pigtailed 41, 95f  
 platinum 52, 107, 269, 494  
 PMCH 19  
 PMMA 304  
 polarized light microscopy 517  
 poly(methyl methacrylate) 304  
 polymers 252, 278, 486, 479  
 – fluorine-substituted 479  
 – fluorous 252, 278, 486  
 ponytail 1, 3, 6, 41f, 45f, 48ff, 53  
 – branched 42, 250  
 – computational data 50  
 – definition 3  
 – electronic effects 43, 45ff, 53, 248, 251  
 – – calorimetry 48  
 – – cyclic voltammetry 53  
 – – NMR 53

ponytail (*cont.*)  
 – – XPS 53  
 – gas phase ionization data 46  
 – IR Data 45  
 – NMR data 43  
 – solution equilibria 49  
 – spacer 42  
 – structure 41  
 porphyrin 217  
 Princeton Chromatography 103  
 PrincetonSPHER 103  
 process chemistry 24  
 prostaglandin 557  
 protective creams 553  
 proton affinity 45  
 proton affinity (PA) values 51  
 PA (proton affinity) values 51  
 ponytails 52  
 – reactivity 52  
*Pseudomonas cepacia* 327  
 PTFE 492, 496, 503  
 pulmonary capillaries 533  
 pulmonary delivery 557  
 purple empire 581  
 pyridovericin 144, 230, 233

## q

QSAR 97  
 quasienantiomers 144

## r

Rábai, J. 6, 128  
 raccoon tails 43  
 radical carbonylation 182, 186  
 radical hydroxymethylation 470  
 Raoult's law 574  
 rats 555  
 recoverability 37  
 – criteria 37  
 red blood cells 530, 555  
 Renal perfusion 538  
 reticuloendothelial system 540  
 reverse fluoros synthesis 109  
 reverse phase silica gels 102  
 Rh(CO)<sub>2</sub>(acac) 275  
 rhodium 7, 252, 272, 278, 390  
 ruthenium 293, 307, 319, 494, 496

## s

sacrificial aldehyde 292, 295  
 samarium 316  
 Samples<sup>TM</sup> 102  
 Sandmeyer reaction 204  
 scandium(III) 426

self-assembly 507  
 semifluorinated alkanes 482  
 separation of fluoros compounds on non-fluoros media 118  
 sickle cell anemia 543, 548  
 Sigma 12  
 silver 493f  
 singlet oxygen 217, 219  
 sinusoidal network 540  
 slanting data 38  
 smectic phases 482  
 SOCl<sub>2</sub> 152  
 sodium cyanoborohydride 184  
 sol gel 503  
 solid phase extraction (SPE) 34, 102, 104, 186, 223, 237  
 solubilities 29, 352, 388, 466  
 – CO<sub>2</sub>-pressure dependent 34, 466  
 – temperature dependent 29, 352, 385, 388  
 solubility parameters 574  
 solubility switch 34  
 solution-phase parallel synthesis 236  
 solvatochromism 575  
 Solvay Solexis 12  
 solvent leaching 20  
 solvent-free synthesis 34  
 solvents 25  
 Sonazoid<sup>®</sup> 536  
 Sonogashira reaction 35, 124, 263, 374, 377  
 SonoVuc<sup>®</sup> 53  
 sound reflectors 530  
 spacer groups 6  
 SPE 102, 104, 128, 134, 186, 193, 223, 227, 242, 244  
 spleen 540  
 split mixture synthesis 143  
 stabilization 491  
 Staudinger reaction 176, 370  
 Stille reaction 176, 260, 360  
 stomach 542  
 supercritical CO<sub>2</sub> 218, 275, 278, 290, 320, 423  
 surgery 547  
 Suzuki reaction 35, 124, 262, 372, 375, 500f  
 Swern oxidation 210, 211

## t

tag 237  
 tagging 143  
 Teflon 35, 124  
 Teflon shavings 35  
 Teflon<sup>®</sup> 492, 576  
 telechelic 513  
 telomerization 8  
 – butadiene 8

- temperature-dependent solubility 9
  - TEMPO 294, 302
  - tetramethylethylenediamine 508
  - thermogravimetric analysis (TGA) 516
  - thermomorphic 1
  - thermomorphic catalyst 28, 350, 352
  - thiohydantoin 230
  - thionyl chloride 153
  - thrombi 539
  - thrombogenesis 554
  - thrombolysis 552
  - thrombus 541
  - Tiers, G. 575
  - tissue perfusion 533
  - tissue preservation 553
  - titanium 265, 308f, 502
  - titanium dioxide 502
  - TLC 119
  - tobramycin 558
  - TOF as a function of cycle 37
  - tomography 543
  - TON as a function of cycle 37
  - toxicity data 527
  - transesterification 177, 335
  - transmission electron microscopy (TEM) 259, 496
  - trauma 543
  - tri(perfluoroalkyl)amines 159
  - triethylaluminum 267
    - addition to aldehydes 267, 310
  - (trifluoromethyl)-benzene 13
  - trifluoromethyl 157
  - $\alpha$ - $\alpha$ - $\alpha$ -trifluorotoluene 13, 16, 131f, 157, 176, 184
  - tris(perfluoroalkyl)triazines 159
  - tumor 541ff, 551, 559
  - tumors necrosis factor 552
  - tungsten rhenium 344
- 
- u**
  - ultrasound 560
  - ultrasound diagnostic imaging 521
  - ultrasound imaging 535
  - commercial products 535
  - ultrasound pulse sequences 533
  - up and down 583
  - upper critical solution temperature 19
  - uranium 8
  - urea 344
  - U-tube 150, 331
- 
- v**
  - vertical ionization potential (VIP) 45
  - VIP values 46, 48, 50
    - ionization potential 50
  - Vogt, M. 8
- 
- w**
  - which phase to winter 581
  - Wilkinson's catalyst 8
  - Wittig reaction 147, 175, 250, 250
  - wound healing 553
  - Wurtz coupling 249
- 
- x**
  - xenon 542
- 
- y**
  - Yamamoto, H. 9
  - yield as a function of cycle 37
  - ytterbium 269, 449, 426
- 
- z**
  - Zhu, D.W. 8
  - zinc 265, 308, 493
  - ZnS 493