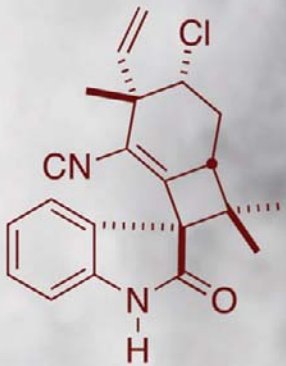
Organic Synthesis

STATE OF THE ART 2007–2009



Douglass F. Taber

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Preface

With this third volume in the series, the chapters have been grouped by topic. With this change, this volume becomes a practical field guide to recent developments in organic synthesis, from functional group transformations to complex total synthesis. The cumulative subject/transformation index that is also included as part of this volume covers all three volumes in this series. For many recent developments, such as organocatalysis, these volumes together provide a comprehensive overview of the field.

With the able assistance of Reto Mueller, webmaster of www.organic-chemistry.org, the Organic Highlights columns that are collected in this volume appeared weekly. These are still available, with active links to the journal articles cited.

The weekly Organic Highlights columns provide in-depth coverage of new developments across the field. Some topics, such as asymmetric organocatalysis and C-H functionalization, are often mentioned in the scientific press. Other topics, such as new methods for C-C bond construction, receive little popular notice, but are at least as important.

I often consult these volumes myself in my day-to-day work of teaching and research. These three volumes together (and the later biennial volumes that will follow) are a valuable resource that should be on the bookshelf of every practicing organic synthesis chemist.

Douglass F. Taber
Newark, DE
April 25, 2010

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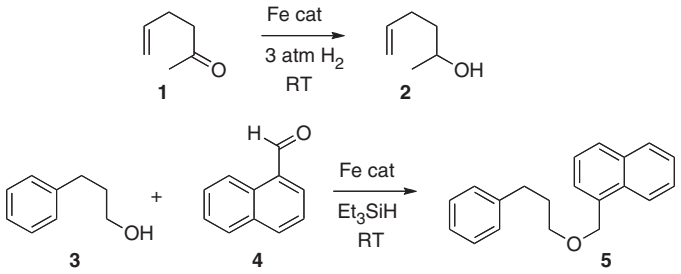
Organic Synthesis

State of the Art 2007–2009

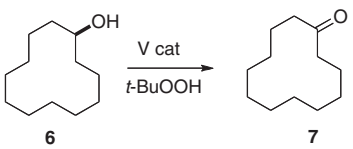
1. Best Synthetic Methods: Oxidation and Reduction

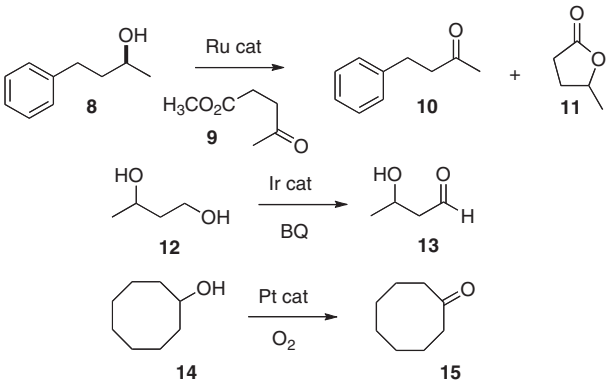
March 17, 2008

Although methods both for reduction and for oxidation are well developed, there is always room for improvement. While ketones are usually reduced using metal hydrides, hydrogen gas is much less expensive on scale. Charles P. Casey of the University of Wisconsin has devised (*J. Am. Chem. Soc.* **2007**, *129*, 5816) an Fe-based catalyst that effects the transformation of **1** to **2**. Note that the usually very reactive monosubstituted alkene is not reduced and does not migrate. Takeshi Oriyama of Ibaraki University has developed a catalyst, also Fe-based (*Chemistry Lett.* **2007**, 38) for reducing aldehydes to ethers. Using this approach, an alcohol such as **3** can be converted into a variety of substituted benzyl ethers, including **5**. Simple aliphatic aldehydes and alcohols also work well.

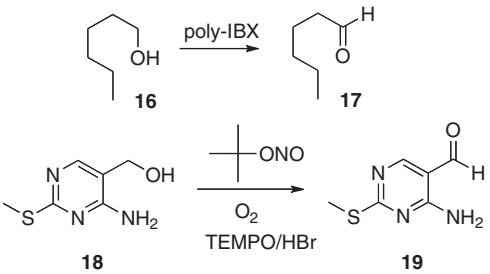


Oxidation of alcohols to aldehydes or ketones is one of the most common of organic transformations. Several new processes catalytic in metal have been put forward. Tharmalingam Punniyamurthy of the Indian Institute of Technology, Guwahati has found (*Adv. Synth. Cat*. **2007**, *349*, 846) that catalytic V(IV) oxide on silica gel, stirred with *t*-butyl hydroperoxide in *t*-butyl alcohol at room temperature smoothly oxidized **6** to **7**. After the reaction, the catalyst was separated by filtration. Another carbonyl can also serve as the hydride acceptor, but then the transfer can be reversible. Jonathan M. J. Williams of the University of Bath has shown (*Tetrahedron Lett*. **2007**, *48*, 3639) that with a Ru catalyst, methyl levulinate **9** could serve as the hydride acceptor, with the byproduct alcohol being drained off as the lactone **11**. Hansjörg Grützmacher of the ETH Zürich developed an Ir catalyst (*Angew. Chem. Int. Ed*. **2007**, *46*, 3567) with benzoquinone as the net oxidant. that showed marked preference for the oxidation of primary over secondary alcohols. Yasuhiro Uozumi of the Institute for Molecular Science, Aichi, has devised (*Angew. Chem. Int. Ed*. **2007**, *46*, 704) a nanoencapsulated Pt catalyst that worked well with O_2 or even with air. The catalyst was easily separated from the product, and maintained its activity over several cycles.

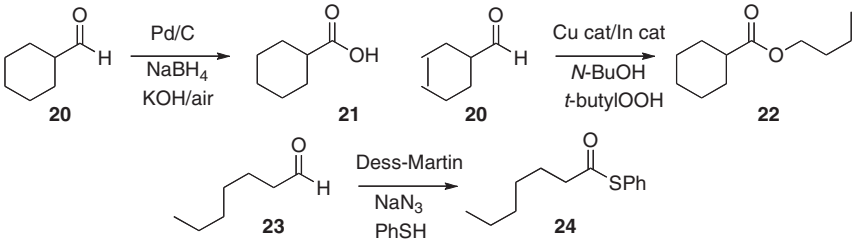




Oxidation can also be carried out without metal catalysis, but this requires stoichiometric reagent, so excess reagent and byproducts must be separated. Yoon-Sik Lee of Seoul National University has described (*Tetrahedron Lett*. **2007**, *48*, 3731) the preparation of an easily-swellable polymeric hypervalent iodine reagent that oxidized alcohols to aldehydes and ketones, including **16** to **17**. The spent reagent was removed by filtration. An alternative is to use volatile/water soluble reagents. Xinquan Hu of the Zhejiang University of Technology has devised (*J. Org. Chem*. **2007**, *72*, 4288) a combination of HBr, oxygen and *t*-butyl nitrite that, with catalytic TEMPO, oxidized **18** to **19**. This inexpensive protocol was easily scaled.



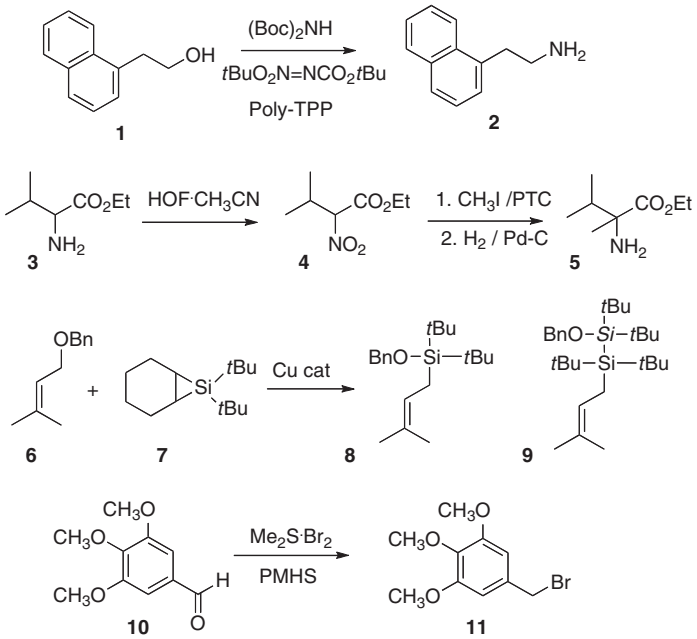
Three procedures for the oxidation of aldehydes to acids have recently appeared. Gwangil An of the Korea Institute of Radiological and Medical Sciences and Hakjune Rhee of Hanyang University have described (*Tetrahedron Lett*. **2007**, *48*, 3835) conditions leading to the carboxylic acid, Chao-Jun Li of McGill University has developed (*Tetrahedron Lett*. **2007**, *48*, 1033) an aldehyde to ester conversion that accommodated methanol as well as a range of primary and secondary alcohols, and B. P. Bandgar of Swami Ramanand Teerth Marathwada University has found (*Tetrahedron Lett*. **2007**, *48*, 1287) conditions for the oxidation of an aldehyde directly to the thioester.



2. Functional Group Transformations

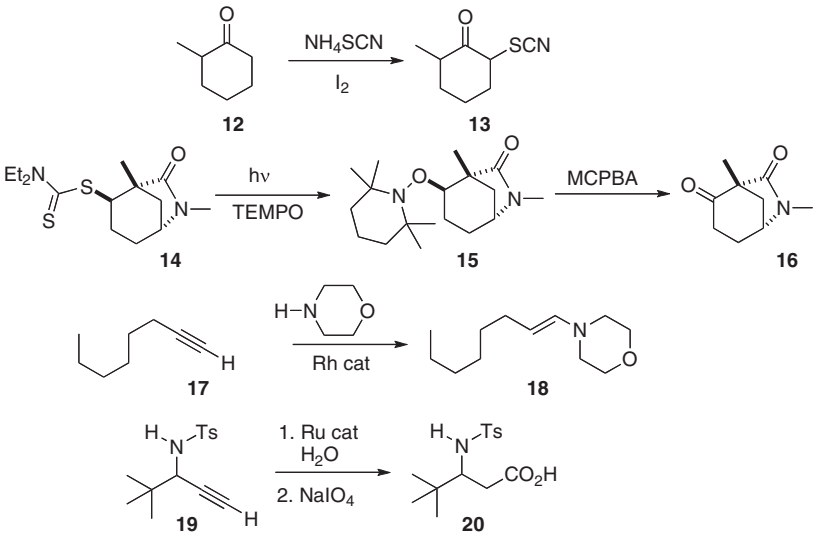
May 19, 2008

Jeffrey C. Pelletier of Wyeth Research, Collegeville, PA has developed (*Tetrahedron Lett.* **2007**, *48*, 7745) a easy work-up Mitsunobu procedure for the conversion of a primary alcohol such as **1** to the corresponding primary amine **2**. Shlomo Rozen of Tel-Aviv University has taken advantage (*J. Org. Chem.* **2007**, *72*, 6500) of his own method for oxidation of a primary amine to the nitro compound to effect net conversion of an amino ester **3** to the alkylated amino ester **5**. Note that the free amine of **3** or **5** would react immediately with methyl iodide. Keith A. Woerpel of the University of California, Irvine has uncovered (*J. Am. Chem. Soc.* **2007**, *129*, 12602) a Cu catalyst that, with **7**, effected direct conversion of silyl ethers such as **6** to the allyl silane **8**. An Ag catalyst gave **9**, which also shows arllyl silane reactivity. Biswanath Das of the Indian Institute of Chemical Technology, Hyderabad has established (*Tetrahedron Lett.* **2007**, *48*, 6681) a compact procedure for the direct conversion of an aromatic aldehyde such as **10** to the benzylic halide **11**. This will be especially useful for directly generating benzylic halides that are particularly reactive.

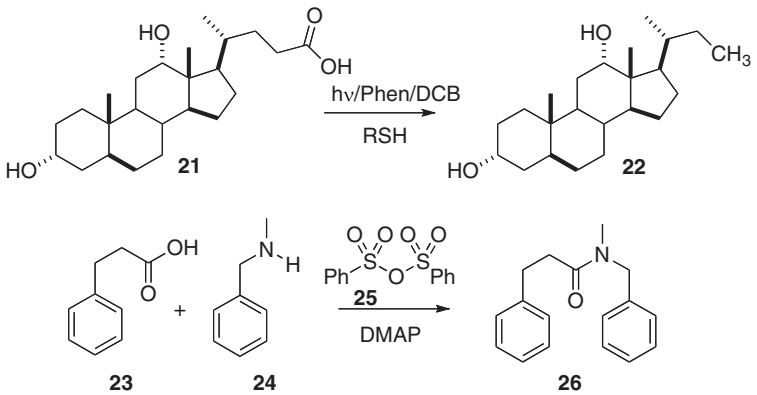


α-Sulfinylation of ketones often requires intial generation of the enolate. J. S. Yadav, also of the Indian Institute of Chemical Technology, Hyderabad, has devised (*Tetrahedron Lett.* **2007**, *48*, 5243) an oxidative protocol for installing sulfur adjacent to a ketone. In a related development, Richard S. Grainger of the University of Birmingham has established (*Angew. Chem. Int. Ed.* **2007**, *46*, 5377) a simple procedure for the conversion of thio esters

such as **14** to the corresponding ketone **16**. Yoshiya Fukumoto of Osaka University has shown (*J. Am. Chem. Soc.* **2007**, *129*, 13792) that a terminal alkyne **17** can be directly converted into the enamine **18** by Rh-catalyzed addition of a secondary amine. Lukas Hintermann and Carsten Bolm of RWTH Aachen have found (*J. Org. Chem.* **2007**, *72*, 5704) that inclusion of water gave the aldehyde, which could be oxidized with the residual Ru catalyst to the acid.



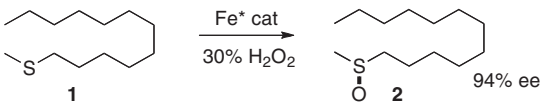
Yasuharu Yoshimi and Minoru Hatanaka of the University of Fukui have described (*Chem. Comm.* **2007**, 5244) a convenient procedure for the reductive decarboxylation of acids such as **21** to the corresponding alkane **22**. Teruaki Mukaiyama of the Kitasato Institute, Tokyo has developed (*Chemistry Lett*. **2007**, *36*, 1456) a simple protocol for the activation of carboxylic acids for amide formation. DMAP-mediated coupling of the acid with **25** gave the mixed anhydride, which combined efficiently with the amine **24** to give the amide **26**.



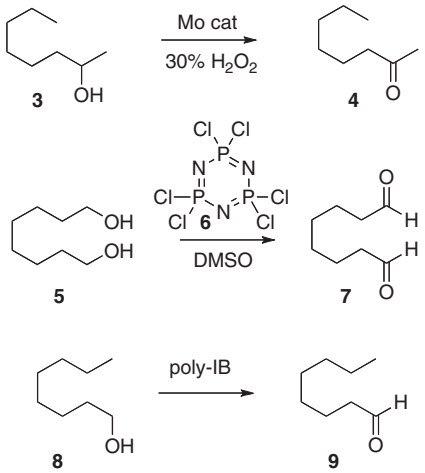
3. Best Synthetic Methods: Oxidation

May 26, 2008

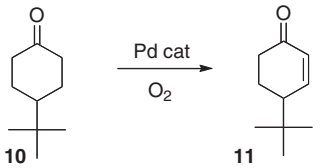
Although the enantioselective oxidation of alkyl aryl sulfides is well developed, much less is known about dialkyl sulfides. Tsutomu Katsuki of Kyushu University has designed (*J. Am. Chem. Soc.* **2007**, *129*, 8940) an Fe(salan) complex that combines with aqueous H_2O_2 to oxidize alkyl methyl sulfides in high ee.



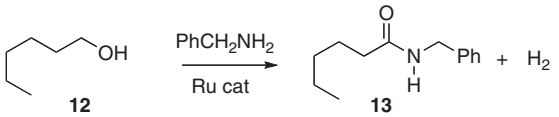
The oxidation of alcohols to aldehydes and ketones is one of the most widely practiced of synthetic transformations. Ge Wang of the University of Science and Technology in Beijing has developed (*Chem. Lett.* **2007**, *36*, 1236) a Mo catalyst that used aqueous H_2O_2 to effect this transformation. Secondary alcohols are oxidized more rapidly than primary alcohols. Vinod K. Singh of the Indian Institute of Technology, Kanpur, has found (*Synth. Comm*. **2007**, *37*, 4099) that the solid, inexpensive **6** can take the place of oxalyl chloride in the Swern oxidation. Viktor V. Zhdankin of the University of Minnesota, Duluth has devised (*J. Org. Chem.* **2007**, *72*, 8149) a polymer-bound hypervalent iodine reagent that is easily separated after use, and reoxidized for reuse.



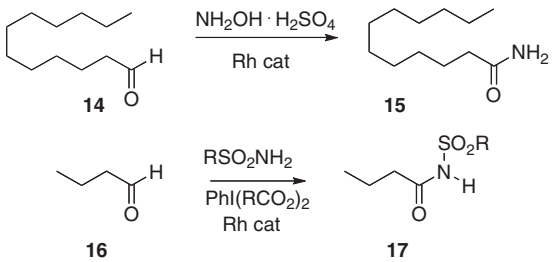
Enones such as **11** are versatile intermediates for organic synthesis. Makoto Tokunaga, now at Kyushu University, and Yasushi Tsuji, now at Kyoto University, have found (*Tetrahedron Lett*. **2007**, *48*, 6860) a Pd catalyst that, in the presence of O_2, will oxidize a cyclic ketone such as **10** to the enone.



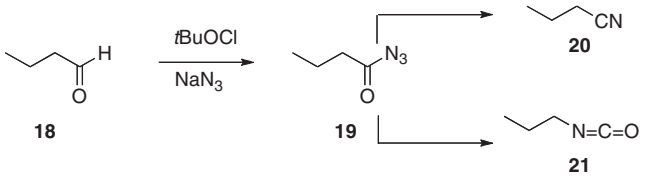
The direct oxidation of an alcohol to the acid is not always an efficient process, so the conversion of **12** to **13** would often be carried out over at least three steps. David Milstein of the Weizmann Institute of Science has devised (*Science* **2007**, *317*, 790) a Ru catalyst that effected the transformation in a single step, generating H_2 as a byproduct as the oxidation proceeded.



The oxidation of an aldehyde to the corresponding amide is also a useful transformation. Noritaka Mizuno of the University of Tokyo has designed (*Angew. Chem. Int. Ed.* **2007**, *46*, 5202) a Rh catalyst that can combine, in water, the aldehyde **14** and NH_2OH to give the primary amide **15**. Johann Chan of Amgen Inc., Thousand Oaks, CA has found (*J. Am. Chem. Soc.* **2007**, *129*, 14106) a different Rh catalyst that mediated the oxidation of a sulfonamide to the nitrene, which under the reaction conditions inserted into the aldehyde H to give the amide **17**.



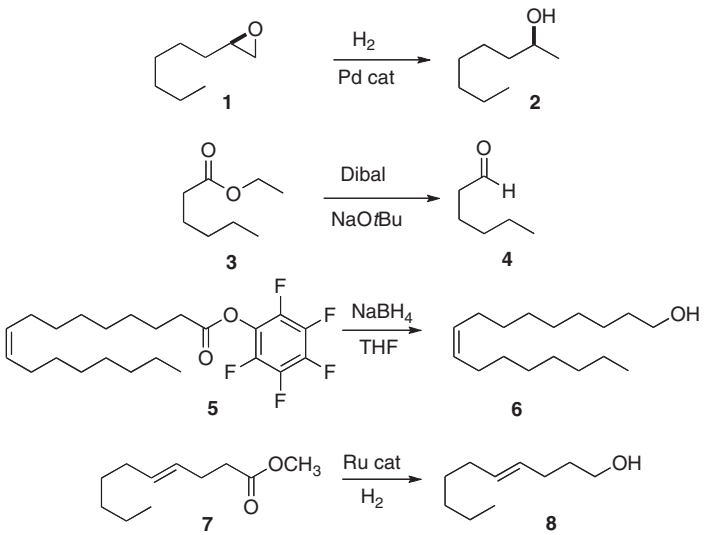
Krishnacharya G. Akamanchi of the Institute of Chemical Technology, Matunga, Mumbai has shown (*Tetrahedron Lett*. **2007**, *48*, 5661) that *t*-butyl hypochlorite and NaN_3 will convert an aldehyde **18** to the acyl azide **19**. The acyl azide **19** can be carried on to the nitrile **20**, or, on warming, to the inverted isocyanate **21**.



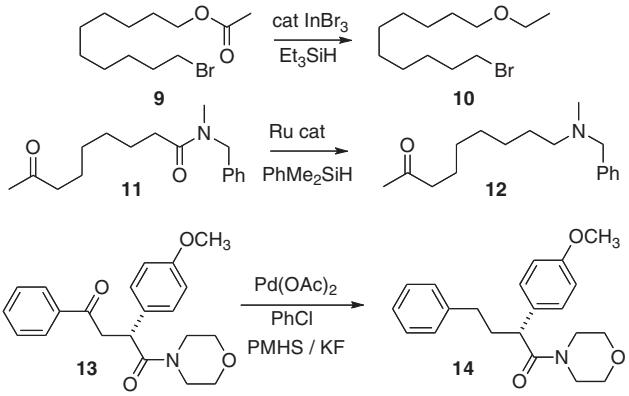
4. Best Synthetic Methods: Reduction

June 9, 2008

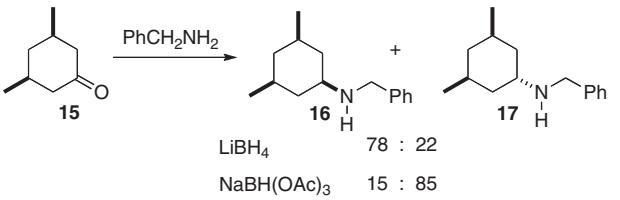
Jaiwook Park of Pohang University of Science and Technology has developed (*Org. Lett*. **2007**, *9*, 3417) a procedure for the preparation of Pd-impregnated magnetic Fe nanoparticles. This effective hydrogenation catalyst was attracted to an external magnet and so was easily separated from the reaction matrix. Duk Keun An of Kangwon National University has found (*Chem. Lett*. **2007**, *36*, 886) that by including NaO*t*Bu, Dibal reduction of an ester such as **3** can be made to reliably stop at the aldehyde **4**. By using the easily-prepared pentaflurophenyl ester **5**, Panagiota Moutevelis-Minakakis of the University of Athens was able to reduce an acid to the alcohol **6**. Lionel A. Saudan of Firmenich SA, Geneva has devised (*Angew. Chem. Int. Ed.* **2007**, *46*, 7473) a Ru catalyst that will hydrogenate an ester such as **7** to the alcohol **8** without reducing an internal alkene.



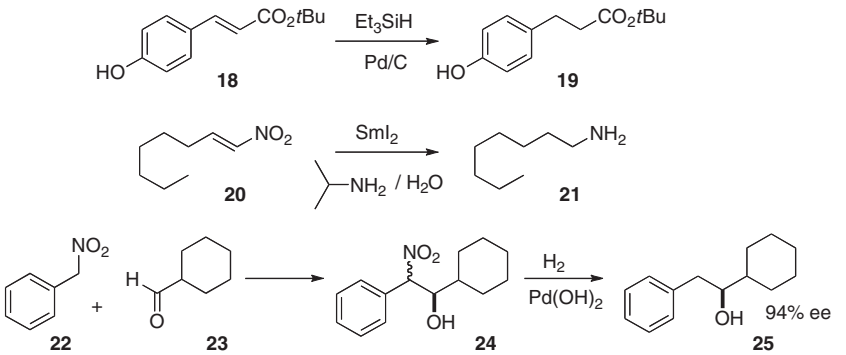
Norio Sakai of the Tokyo University of Science has established (*J. Org. Chem.* **2007**, *72*, 5920) what promises to be a general route to ethers **10**, by direct reduction of the corresponding ester **9**. Hideo Nagashima of Kyushu University has developed (*Chem. Commun.* **2007**, 4916) a Ru catalyst that effected selective hydrogenation of an amide **11** to the amine **12** without reducing ketones or esters. Alternatively, Jason S. Tedrow of Amgen Inc., Thousand Oaks, CA has found (*J. Org. Chem.* **2007**, *72*, 8870) that a protocol developed by Robert E. Maleczka, Jr. of Michigan State University was effective for reducing an aryl ketone **13** to the corresponding hydrocarbon **14** without reducing the amide.



The stereocontrolled reductive amination of cyclic ketones such as **15** has been a continuing challenge. Shawn Cabral of Pfizer, Inc. in Groton, CT has reported (*Tetrahedron Lett*. **2007**, *48*, 7134) complementary reagent combinations, leading selectively to either **16** or **17**.



To control catalytic hydrogenation, it is often desirable to control the H_2 supply. John S. McMurray of the University of Texas M. D. Anderson Cancer Center in Houston has shown (*J. Org. Chem.* **2007**, *72*, 6599) that Et_3SiH is a convenient H_2 source.

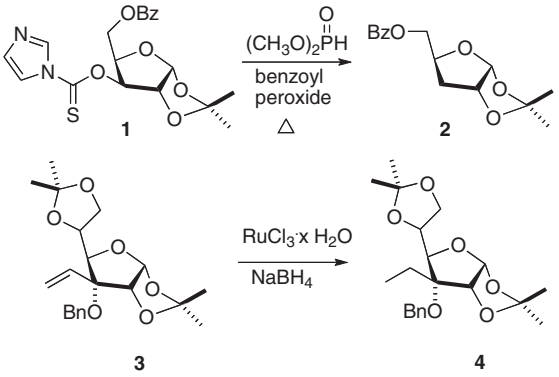


Nitro alkanes add to aldehydes to give nitro alkenes such as **20**. Göran Hilmersson of Göteborg University has developed (*Tetrahedron Lett*. **2007**, *48*, 5707) conditions for the reduction of such a nitro alkene directly to the corresponding saturated amine **21**. Erick M. Carreira of ETH Hönggerberg has coupled (*Angew. Chem. Int. Ed.* **2007**, *46*, 2078) the enantioselective addition of benzylic nitro compounds such as **22** to aldehydes with catalytic hydrogenolysis, to deliver the secondary alcohol **25** in high ee.

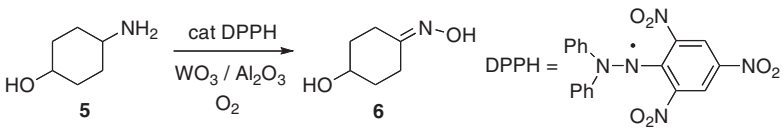
5. Best Synthetic Methods: Functional Group Transformation

October 27, 2008

François Morvan of the Université de Montpellier, using the inexpensive dimethyl phosphite, optimized (*Tetrahedron Lett*. **2008**, *49*, 3288) the free radical reduction of **1** to **2**. Pawan K. Sharma of Kurukshetra University found (*Tetrahedron Lett*. **2008**, *48*, 8704) that $NaBH_4$ in the presence of a catalytic amount of $RuCl_3{\cdot}xH_2O$ reduced monosubstituted and disubstituted alkenes, such as **3**, to the corresponding alkanes. Note that benzyl ethers were stable to these conditions.

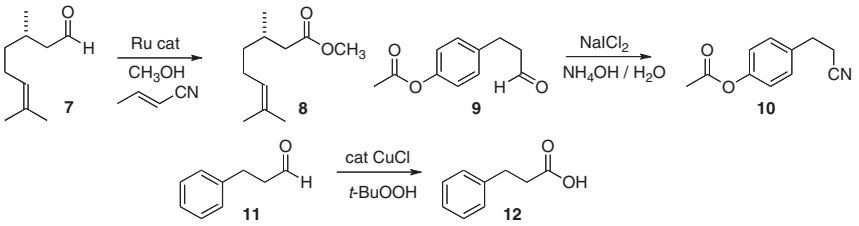


Ken Suzuki of Asahi Kasei Chemicals and Shun-Ichi Murahashi of Okayama University of Science established conditions (*Angew. Chem. Int. Ed.* **2008**, *47*, 2079) for the oxidation of primary amines such as **5** to oximes. Both ketoximes such as **6** and aldoximes were prepared using this protocol. Primary and secondary alcohols were stable to these conditions.

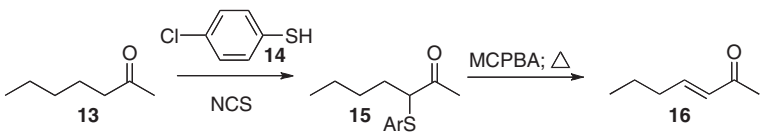


Three noteworthy procedures for the oxidation of an aldehyde to the acid oxidation state were recently reported. Jonathan M. J. Williams of the University of Bath demonstrated (*Chem. Commun.* **2008**, 624) that crotonitrile could serve as the hydrogen acceptor in the oxidation of an aldehyde **7** to the methyl ester **8**. Note that isolated alkenes were stable to these conditions. Vikas N. Telvekar the University Institute of Chemical Technology, Mumbai improved (*Tetrahedron Lett*. **2008**, *49*, 2213) the oxidative amination of an aldehyde **9** to the nitrile **10**. G. Sekar of the Indian Institute of Technology Madras effected

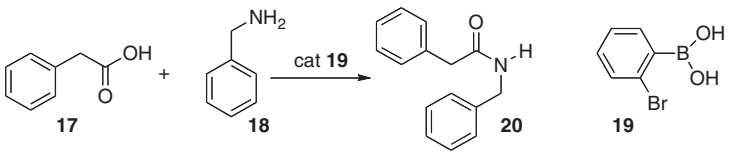
(*Tetrahedron Lett*. **2008**, *49*, 1083) oxidation of an aldehyde **11** to the acid **12**, under conditions that would be expected to not oxidize a primary or secondary alcohol.



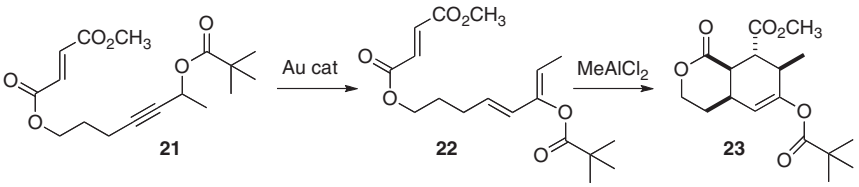
J. S. Yadav of the Indian Institute of Chemical Technology, Hyderabad observed (*Tetrahedron Lett*. **2008**, *49*, 3015) that the activation of a thiophenol **14** with N-chlorosuccimide generated a species that added regioselectively to a ketone **13** to give the thioether **15**. Oxidation of the sulfide **15** followed by heating of the resulting sulfoxide would give the enone **16**. This appears to be an easily scalable procedure.



It is well known that an acid **17** and an amine **18** will condense at elevated temperature to give the amide **20**. Dennis G. Hall of the University of Alberta has now shown (*Angew. Chem. Int. Ed.* **2008**, *47*, 2876) that a simple boronic acid **19** will catalyze this reaction *at room temperature*.



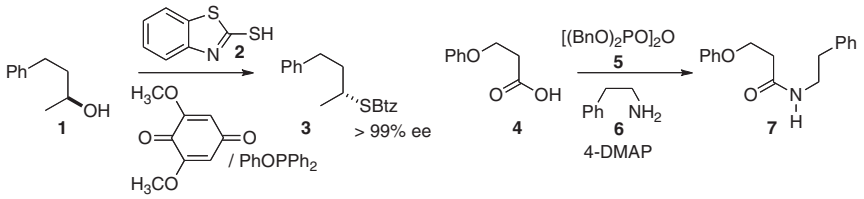
Liming Zhang of the University of Nevada, Reno devised (*J. Am. Chem. Soc.* **2008**, *130*, 3740) a new route to oxygenated dienes such as **22**, based on Au-catalyzed rearrangement of a propargylic ester such as **21**. Note that the oxygen has shifted to the adjacent carbon in the course of this transformation. The product dienes participated smoothly in Diels-Alder cycloaddition.



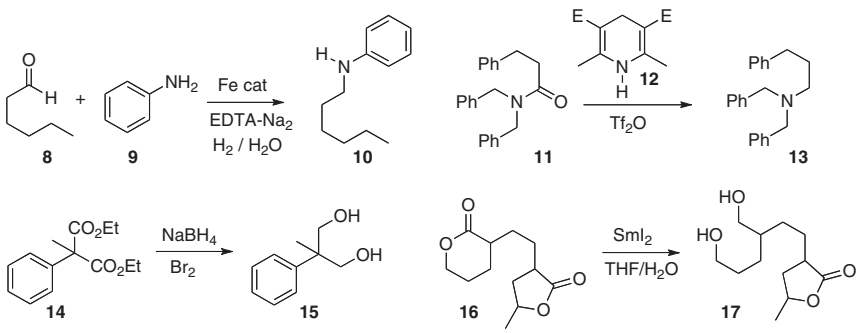
6. New Methods for Functional Group Conversion

March 23, 2009

Yujiro Hayashi of Tokyo University of Science and Teruaki Mukaiyama of the Kitasato Institute developed (*Chem. Lett.* **2008**, *37*, 592) a reduction-oxidation method for converting primary, secondary (such as **1**, with clean inversion) and tertiary alcohols to sulfides. Peter A. Crooks of the University of Kentucky found (*Chem. Lett.* **2008**, *37*, 528) that tetrabenzylpyrophosphate **5** was an effective agent for condensing an acid **4** with an amine **6** to give the amide **7**. This protocol, that runs in near quantitative yield in an hour at room temperature, with all impurities readily removable by washing with aqueous base and aqueous acid, appears to be well-suited both for scale-up, and for solid-phase synthesis.

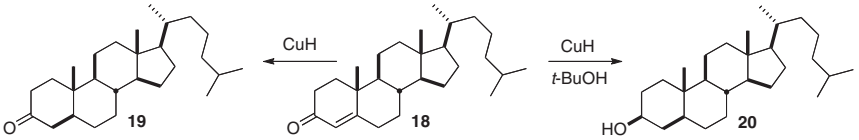


Balchandra M. Bhanage of the University of Mumbai reported (*Tetrahedron Lett*. **2008**, *49*, 965) the reductive amination of aldehydes, including **8**, and ketones to the corresponding amines, using H_2 and an inexpensive Fe catalyst. André Charette of the Université de Montréal showed (*J. Am. Chem. Soc.* **2008**, *130*, 18) that the Hantzsch ester **12**, in the presence of Tf_2O, reduced amides selectively to amines. Esters, epoxides, ketones, nitriles and alkynes were stable to these conditions.



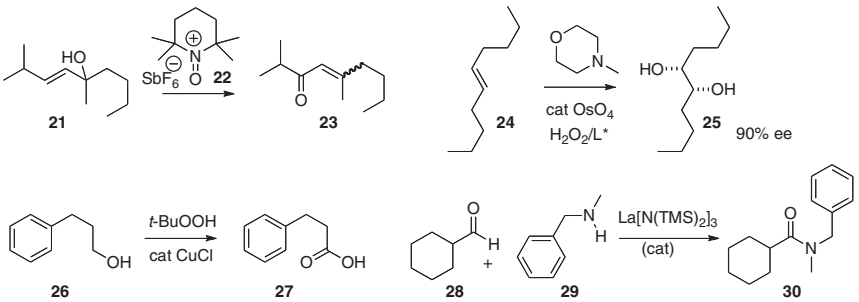
Matthew Tudge of Merck Rahway demonstrated (*Tetrahedron Lett*. **2008**, *49*, 1041) that Br_2 in DME activated $NaBH_4$, allowing facile reduction of esters, including the congested diester **14**, at ambient temperature. David J. Procter of the University of Manchester made (*J. Am. Chem. Soc.* **2008**, *130*, 1136) the remarkable observation that six-membered

ring lactones such as **16** were reduced to the corresponding diol with SmI_2. Five-membered ring and seven-membered ring lactones were not reduced under these conditions.



Bruce H. Lipshutz of the University of California, Santa Barbara devised (*Organic Lett*. **2008**, *10*, 289) a convenient and economical procedure for CuH, using Cu and an inexpensive ligand in catalytic amounts, with PMHS as the bulk reductant. The reduction of **18** presumably proceeds by electron transfer, as with dissolving metal reduction, delivering **19** with the more stable trans ring fusion. In the presence of *t*-BuOH as a proton source, the reduction goes on to the alcohol **20**. This may be the current method of choice for selectively reducing a cyclohexanone to the equatorial alcohol.

It is well known that tertiary allylic alcohols such as **21** can be oxidized to the corresponding enone **23** with chromium reagents. Yoshiharu Iwabuchi of Tohoku University observed (*J. Org. Chem.* **2008**, *73*, 4750) that the oxammonium salt **22** derived from TEMPO effected the same transformation. David E. Richardson of the University of Florida found (*Tetrahedron Lett*. **2008**, *49*, 1071) that H_2O_2 could be used to oxidize N-methylmorpholine in situ to the N-oxide, that in turn reoxidized catalytic OsO_4. In the presence of the Sharpless ligand, the dihydroxylation proceeded with high ee. This approach could offer cost and waste stream advantages over currently used oxidants.

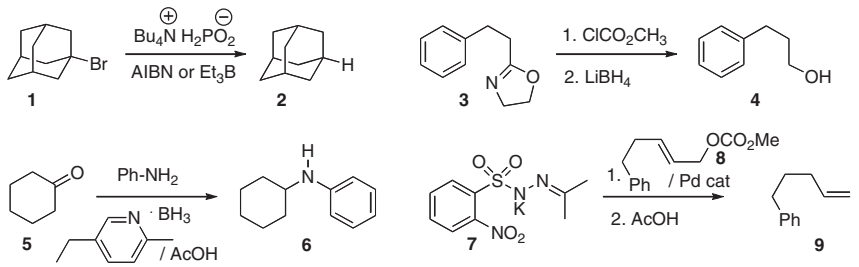


G. Sekar of the Indian Institute of Technology Madras, in Chennai, established (*Tetrahedron Lett*. **2008**, *49*, 2457) a convenient procedure for oxidizing primary alcohols such as **26** to the acid **27**. Secondary alcohols were oxidized to ketones. Allylic and benzylic alcohols could be oxidized in preference to saturated alcohols. Tobin J. Marks of Northwestern University devised (*Organic Lett*. **2008**, *10*, 317) a La catalyst for the oxidative amination of aldehydes. In its present incarnation, excess aldehyde served as the reductant. If a less expensive reductant could be found, this would be a very useful procedure, avoiding the carboxylic acid activation usually required for amide formation.

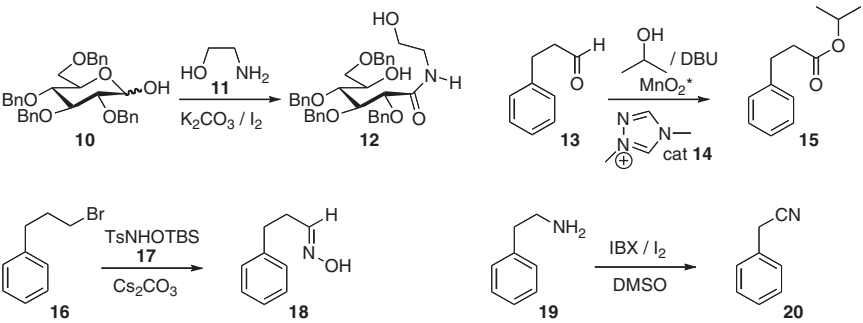
7. Organic Functional Group Interconversion: (-)-β-Conhydrine (Barua) and (+)-6'-Hydroxyarenarol (Anderson)

September 21, 2009

V. T. Perchyonok and Kellie L. Tuck of Monash University found (*Tetrahedron Lett*. **2008**, *49*, 4777) that a concentrated solution of Bu_4NCl and H_3PO_2 in water effected free radical reductions and cyclizations. Stéphane G. Ouellet of Merck Frosst demonstrated (*Tetrahedron Lett*. **2008**, *49*, 6707) that an oxazoline such as **3** could be converted to the alcohol **4** by acylation followed by reduction. Elizabeth R. Burkhardt of BASF developed (*Tetrahedron Lett*. **2008**, *49*, 5152) a protocol for scalable reductive amination using an easily metered liquid pyridine-borane complex. Mohammad Movassaghi of MIT devised (*Angew. Chem. Int. Ed.* **2008**, *47*, 8909) a strategy for conversion of an allylic carbonate **8** by way of the allylic diazene to the terminal alkene **9**.

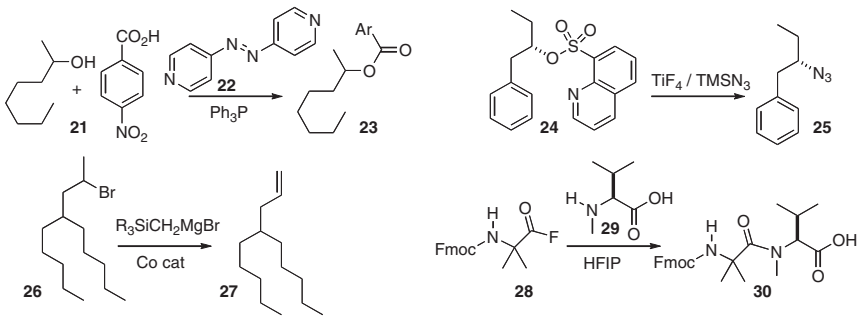


Philippe Compain of the Université d'Orleans uncovered (*J. Org. Chem.* **2008**, *73*, 8647) a practical procedure for oxidizing an inexpensive aldose such as **10** to the amide **12**, a valuable chiral pool starting material. Karl A. Scheidt of Northwestern University extended (*Organic Lett.* **2008**, *10*, 4331) activated MnO_2 oxidation to *saturated* aldehydes such as **13**, leading to the ester **15**. Tohru Fukuyama of the University of Tokyo showed (*Organic Lett.* **2008**, *10*, 2259) that halides such as **16** could be oxidized to the oxime **18** with the reagent **17**. The product oximes are readily dehydrated to the corresponding nitriles. Chutima Kuhakarn of Mahidol

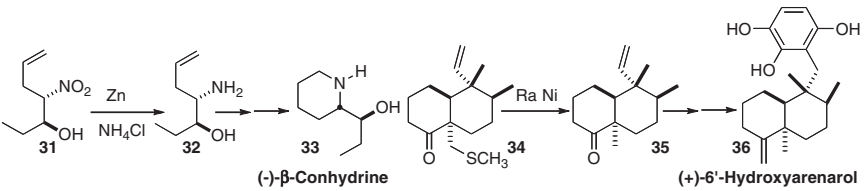


University devised (*Synthesis* **2008**, 2045) a simple protocol for the oxidation of a primary amine such as **19** to the nitrile **20**.

Nasser Iranpoor and Habib Firouzabadi of Shiraz University developed (*J. Org. Chem.* **2008**, *73*, 4882) the reagent **22** for Mitsunobu coupling. The stereochemical course of this reaction with simple acyclic secondary alcohols such as **21** was not reported. Salvatore D. Lepore of Florida Atlantic University optimized (*Angew. Chem. Int. Ed.* **2008**, *47*, 7511) the quisylate **24** for the displacement *with retention* to give the azide **25**. Hideki Yorimitsu and Koichiro Oshima of Kyoto University optimized (*J. Am. Chem. Soc.* **2008**, *130*, 11276) a Co catalyst for the conversion of a secondary halide such as **26** to the terminal alkene **27**. Base-mediated elimination gave primarily the internal alkene. Christian E. Schafmeister of the University of Pennsylvania established (*J. Am. Chem. Soc.* **2008**, *130*, 14382) that acyl fluorides such as **28** couple efficiently even with unreactive amino acids such as **29**.



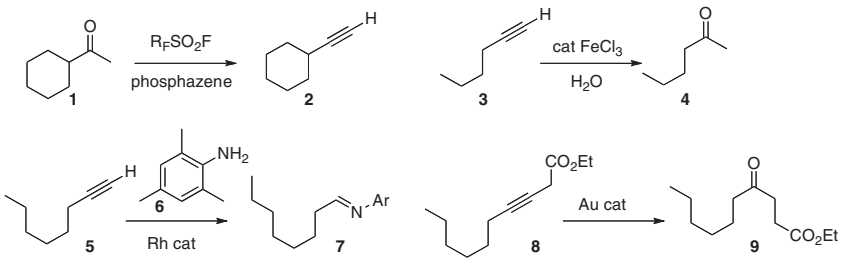
In the course of a synthesis of (-)-β-conhydrine **33** (*Tetrahedron Lett*. **2008**, *49*, 6508), Nabin C. Barua of North East Institute of Science and Technology needed to reduce the nitro group of **31** to the amine without reducing the very reactive monosubstituted alkene. Zn/NH_4Cl served well. James C. Anderson of the University of Nottingham solved (*J. Org. Chem.* **2008**, *73*, 8033) a similar problem in a synthesis of (+)-6'-hydroxyarenarol **36**. In that case, Raney Ni reduced the carbon-sulfur bond without affecting the monosubstituted alkene.



8. New Methods for Functional Group Conversion

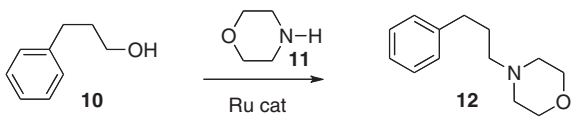
October 26, 2009

Ilya M. Lyapkalo of the Academy of Sciences of the Czech Republic, Prague, showed (*Synlett* **2009**, 558) that a ketone **1** reacted with the inexpensive nonafluorobutanesulfonyl fluoride in the presence of a phosphazene base to give first the enol sulfonate, and then the alkyne **2**. The method worked well for aldehydes also.



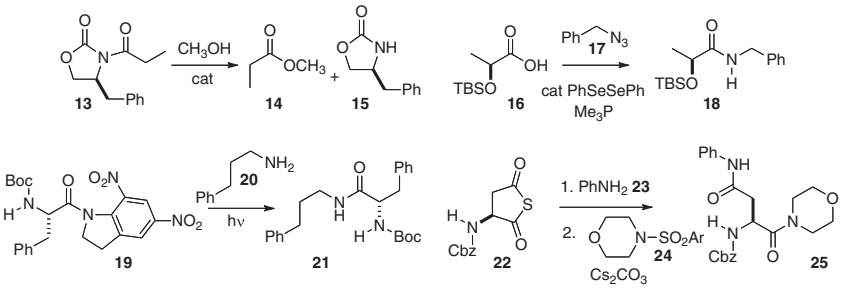
Christophe Darcel of the Université de Rennes I developed (*Adv. Synth. Cat.* **2009**, *351*, 367) an inexpensive Fe catalyst for the hydration of a terminal alkyne **3** to the ketone **4**. Carlos Alonso-Moreno and Antonio Otero of the Universidad de Castilla-La Mancha devised (*Adv. Synth. Cat.* **2009**, *351*, 881) a Rh catalyst for the complementary hydration of a terminal alkyne **5** to the aldehyde, by way of the imine **7**. Internal alkynes often give mixtures of ketones on hydration, but Bo Xu and Gerald B. Hammond of the University of Louisville found (*J. Org. Chem.* **2009**, *74*, 1640) a gold catalyst that converted an alkynyl ester **8** into the γ-keto ester **9**.

Jonathan M. J. Williams of the University of Bath developed (*J. Am. Chem. Soc.* **2009**, *131*, 1766; *Tetrahedron Lett.* **2009**, *50*, 3374) a Ru-catalyzed protocol for the alkylation of an amine **11** with an alcohol **10**. The reaction proceeded by oxidation of the alcohol to the aldehyde, imine formation, and reduction using the hydride generated by the initial oxidation. José Luis García Ruano of the Universidad Autónoma de Madrid uncovered (*Chem. Commun.* **2009**, 404) a similar conversion mediated by Raney Ni.

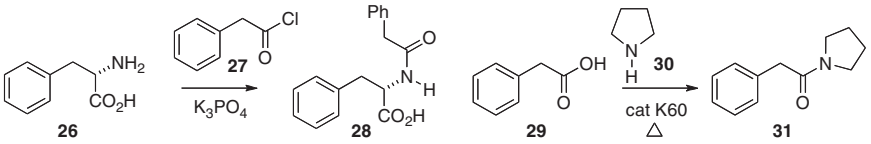


There has been a great deal of work recently on the preparation and reaction of amides. Susumu Saito of Nagoya University prepared (*J. Am. Chem. Soc.* **2009**, *131*, 8748) a diaryl boronic acid that catalyzed the methanolysis of an imide **13** to the methyl ester **14** and the oxazolidinone **15**. Jaume Vilarrasa of the Universitat de Barcelona reported (*J. Org. Chem.* **2009**, *74*, 2203) the catalyzed condensation of an acid **16** with an azide **17** to give

the amide **18**. Both aryl and aliphatic azides participated in the reaction, and the enantiomeric integrity of the amide was maintained. Christian G. Bochet of the University of Fribourg developed (*J. Org. Chem.* **2009**, *74*, 4519) the photolabile amide **19**. Long wave UV radiation, that did not disturb other photoactivatable protecting groups, then effected acylation of **20** to give **21**, with maintenance of the enantiomeric integrity of **19**.



David Crich, now at CNRS de Gif-sur-Yvette, found (*J. Org. Chem.* **2009**, *74*, 3886) that the enantiomerically-pure thioanhydride **22** could be coupled sequentially first with an amine **23** and then with an arenesulfonamide **24** to give the unsymmetrical diamide **25**. This approach was used to prepare diastereomerically-pure glycodipeptides.

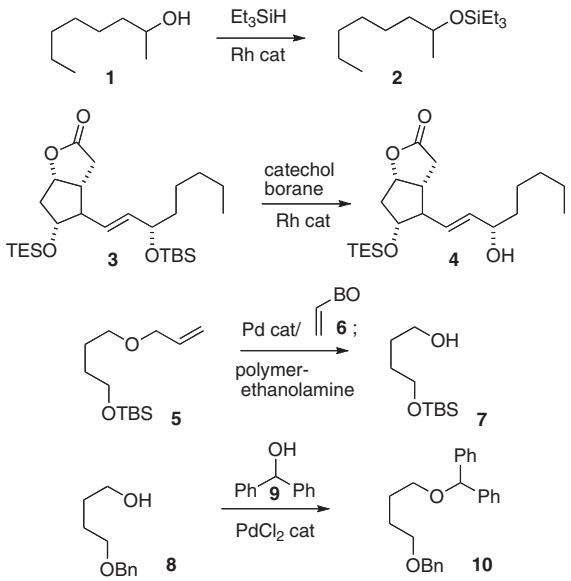


Li Zhang of Boehringer Ingelheim took (*Tetrahedron Lett*. **2009**, *50*, 2964) a simpler approach to amide construction, demonstrating that K_3PO_4 mediated the coupling of **26** and **27** to give **28** with minimal racemization. James H. Clark of the University of York established (*Chem. Commun.* **2009**, 2562) an even milder protocol, heating (toluene, reflux) the acid **29** with the amine **30** in the presence of 10 weight percent of calcined Kieselgel 60 to give the amide **31**.

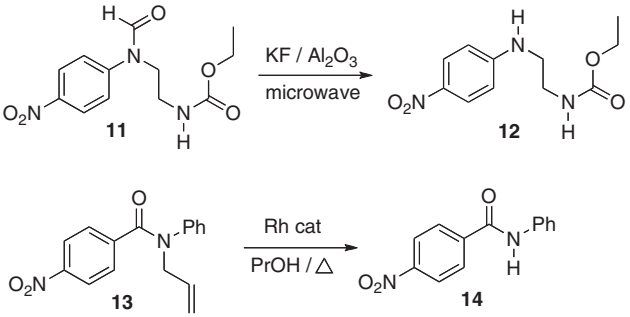
9. Protection of Organic Functional Groups

March 31, 2008

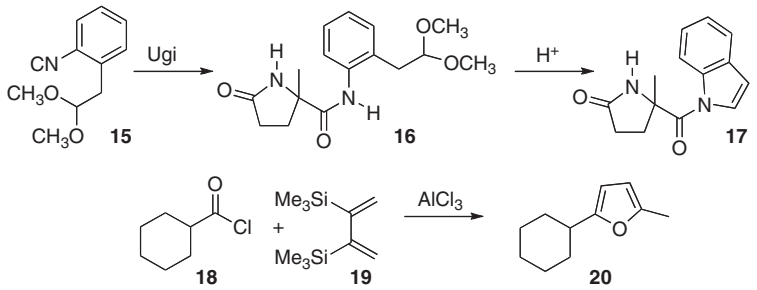
Several noteworthy new developments in the protection and deprotection of alcohols have been reported. Andrea Biffis of the Università di Padova has developed (*Adv. Synth. Catal.* **2007**, *349*, 2485) a Rh catalyst that effected silylation of alcohols such as **1** to the TES ether **2** at just 0.01% loading. Joshua Rokach of the Florida Institute of Technology has observed (*Tetrahedron Lett*. **2007**, *48*, 5289) that the reverse reaction, Rh-catalyzed desilylation of **3**, was highly selective for the less congested site, even removing the usually less reactive TBS ether of **3** and leaving the more hindered TES ether. Hirokazu Tsukamoto of Tohoku University has devised (*Tetrahedron Lett*. **2007**, *48*, 8438) an improved procedure for the deprotection of allyl ethers such as **5**. Filtration of the reaction mixture through polymer-bound diethanolamine removed > 95% of the Pd from the product. Patrick Pale of the Université Louis Pasteur has established (*Tetrahedron Lett*. **2007**, *48*, 8895) improved conditions for preparing diphenylmethyl ethers such as **10**. The protecting group was removed with the Pd catalyst and ethanol.



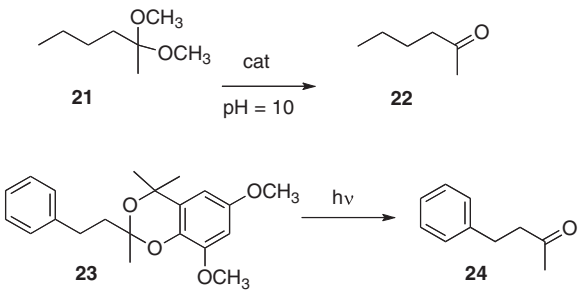
Amines can be activated for alkylation by N-formylation. Subsequent deformylation of the alkylated formamide **11** has been a challenge. Longqin Hu of Rutgers University has developed (*Tetrahedron Lett*. **2007**, *48*, 4585) microwave conditions that work well. Carbamates are stable, but esters are not. Protection of amides can also be important. Michael J. Zacuto of Merck Process in Rahway, NJ has optimized (*J. Org. Chem.* **2007**, *72*, 6298) the Rh-catalyzed deallylation of **13** to give **14**.



Carbonyl protection and deprotection is also important. Yoshihisa Kobayashi of the University of California, San Diego has devised (*J. Org. Chem.* **2007**, *72*, 3913) the isonitrile **15**. Usually, the product **16** after Ugi condensation would be very difficult to hydrolyze. In the case of **16**, mild acid effected cyclization to the acyl indole **17**, which was easy to hydrolyze. In a different approach, Francesco Naso of the Università di Bari has shown (*Chem. Commun.* **2007***,* 3756*)* that acid chlorides such as **18** condensed with **19** to give the furan **20**. Such furans are easily oxidized, liberating the starting acid.



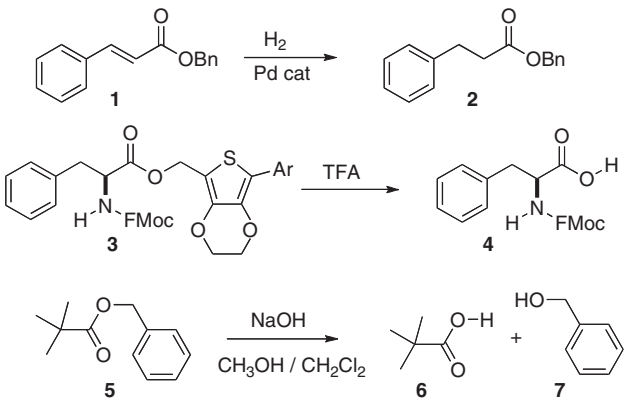
Acetals and ketals are usually removed with acid. Robert G. Bergman and Kenneth N. Raymond of the University of California, Berkeley have devised (*Angew. Chem. Int. Ed.* **2007**, *46*, 8587) a self-assembling supramolecular catalyst that hydrolysed dimethyl acetals and ketals such as **21** in water at pH = 10. Pengfei Wang of the University of Alabama, Birmingham has designed (*Organic* Lett. **2007**, *9*, 2831) a protecting group **23** for aldehydes and ketones that was efficiently removed by photolysis.



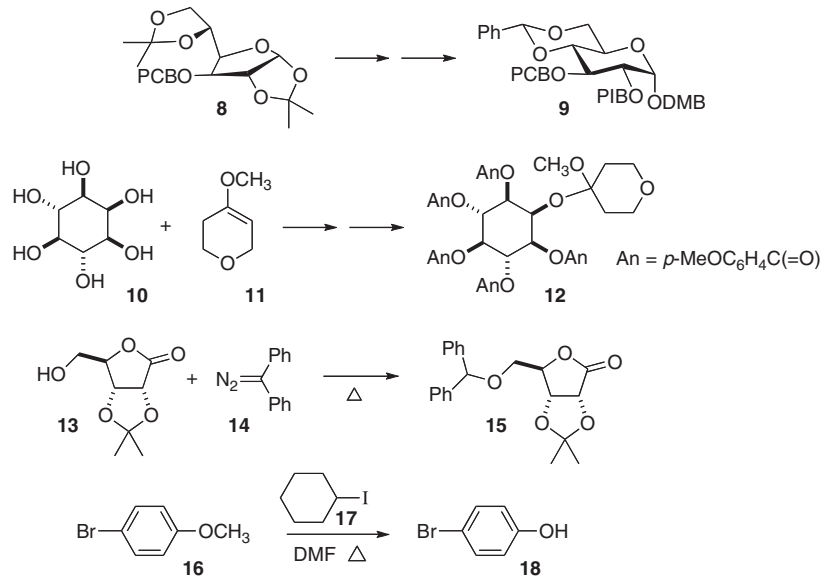
10. Best Synthetic Methods: Functional Group Protection

November 10, 2008

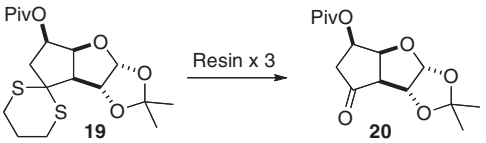
Benzyl esters are easily deprotected by hydrogenolysis. It is often observed, however, as exemplified by the conversion of **1** to **2** reported (*Adv. Synth. Catal.* **2008**, *350*, 406) by Hironao Sajiki of Gifu Pharmacutical University, that alkene hydrogenation can be carried out selectively. Fernando Albericio of the University of Barcelona has developed (*Tetrahedron Lett.* **2008**, *49*, 3304) a family of thiophene-based esters **3** that can be removed with acid in the presence of *t*-butyl esters, and that are stable to the removal of FMOC groups. Vassiliki Theodorou of the University of Ioannina has found (*Tetrahedron Lett.* **2008**, *49*, 8230) that esters were rapidly saponified by methanolic NaOH in solvent CH_2Cl_2.



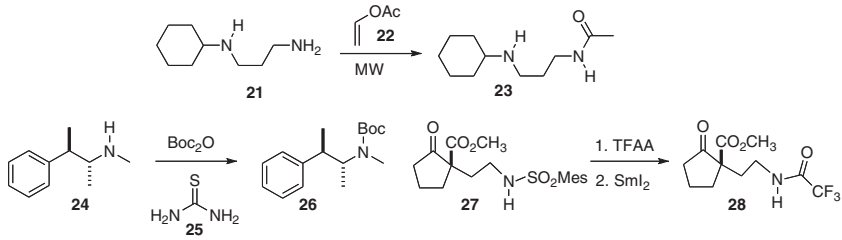
Specific oligosaccharide synthesis depends heavily on the use of orthogonal methods for alcohol protection and deprotection. This is illustrated by the work (*J. Org. Chem.* **2008**, *73*, 1008) of Carolyn R. Bertozzi of the University of California, Berkeley, who deployed *p*-methoxybenzyl (PMB), 3,4-dimethoxybenzyl (DMB), *p*-chlorobenzyl (PCB) and *p*-iodobenzyl (PIB) ethers to enable construction of a disaccharide, by way of **9**. Piers R. J. Gaffney of Imperial College London has reported (*Tetrahedron Lett.* **2008**, *49*, 1836) a practical preparation of the ether **11**, that should make this symmetrical protecting group more readily available. George W. J. Fleet of the University of Oxford and Sigthur Petursson of the University of Akureyri have found (*Tetrahedron Lett.* **2008**, *49*, 2196) that diphenyl diazomethane **14**, easily prepared from benzophenone, reacted under *neutral* conditions with primary, secondary and tertiary alcohols to form the benzyhydryl ethers. Harsh conditions have often been employed to remove aryl methyl ethers such as **16**. Wei Wang of the University of New Mexico and Wenhu Duan of the Shanghai Institute of Materia Medica have developed (*Tetrahedron Lett.* **2008**, *49*, 4054) a simple protocol to effect this transformation, by heating the ether to reflux in DMF in the presence of iodocyclohexane **17**.



Dithianes such as **19** have often been deprotected with stoichiometric heavy metals. Andreas Kirschning of Leibniz Universität Hannover has devised (*J. Org. Chem.* **2008**, *73*, 2018) a set of three anionic resins, charged, respectively, with $I(O_2CCF_3)_2^-$, HCO_3^-, and $S_2O_3^-$. Exposure of **19** to the three resins in sequence delivered the very sensitive ketone **20**.



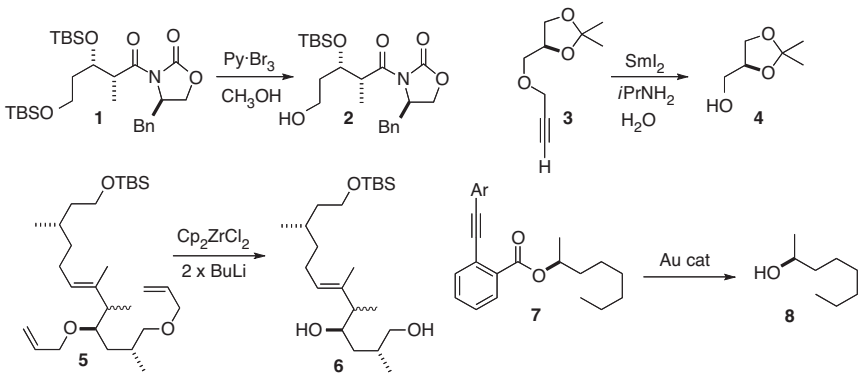
Clotilde Ferroud of the Conservatoire National des Arts et Métiers, Paris has established (*Tetrahedron Lett.* **2008**, *49*, 3004) microwave conditions for the direct acetylation of an amine such as **21** with vinyl acetate **22**. Samad Khaksar of the Islamic Azad University, Iran has found (*Tetrahedron Lett.* **2008**, *49*, 3527) that thiourea **25** catalyzed the protection of an amine **24** with Boc_2O under similarly mild conditions. Darren J. Dixon of the University of Manchester employed (*Chem. Commun*. **2008**, 2474) the protocol developed by Romo to convert the sulfonamide **27** to the trifluoracetate **28**. Uno Mäeorg of the University of Tartu showed (*Tetrahedron Lett.* **2008**, *49*, 1373) that sulfonamides can also be deprotected with the inexpensive mischmetal in the presence of $TiCl_4$.



11. Functional Group Protection

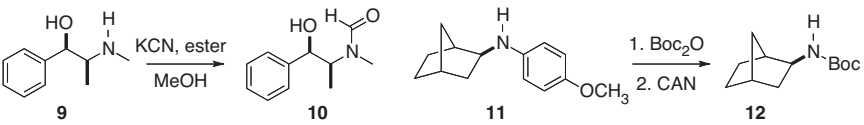
May 18, 2009

Alcohols are usually protected as alkyl or silyl ethers. Michael P. Jennings of the University of Alabama found (*Tetrahedron Lett*. **2008**, *49*, 5175) that pyridinium tribromide can selectively remove the TBS (or TES) protection from the primary alcohol of a protected primary-secondary alcohol such as **1**. Propargyl ethers are useful because they are stable, but can be selectively removed in the presence of other protecting groups. Shino Manabe and Yukishige Ito at RIKEN showed (*Tetrahedron Lett*. **2008**, *49*, 5159) that SmI_2 could reductively remove a propargyl group in the presence of acetonides (illustrated, **3**), MOM, benzyl and TBS ethers. Hisanaka Ito of the Tokyo University of Pharmacy and Life Sciences took advantage (*Organic Lett*. **2008**, *10*, 3873) of the reducing power of Cp_2Zr to selectively remove the allyl ethers from **5**, to give **6**. These conditions might also remove propargyl ethers.



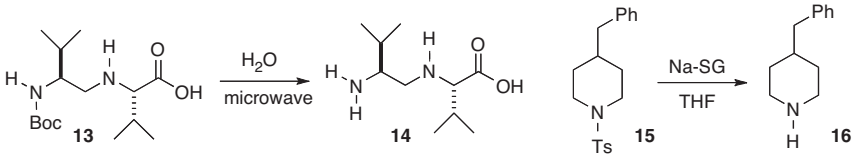
Esters can also be useful protecting groups. Naoki Asao of Tohoku University developed (*Tetrahedron Lett*. **2008**, *49*, 7046) the *o*-alkynyl ester **7**. Au catalyst in EtOH removed the ester, leaving benzoates, acetates, OTBS and OTHP intact. Alternatively, an *o*-iodobenzoate can be removed by Sonogashira coupling followed by the Au hydrolysis.

N-Formylation is usually accomplished using mixed anhydrides. Weige Zhang and Maosheng Chang of Shenyang Pharmaceutical University put forward (*Chem. Commun*. **2008**, 5429) an intriguing alternative, heating a secondary amine **9** with KCN in the presence of dimethyl malonate to give **10**.

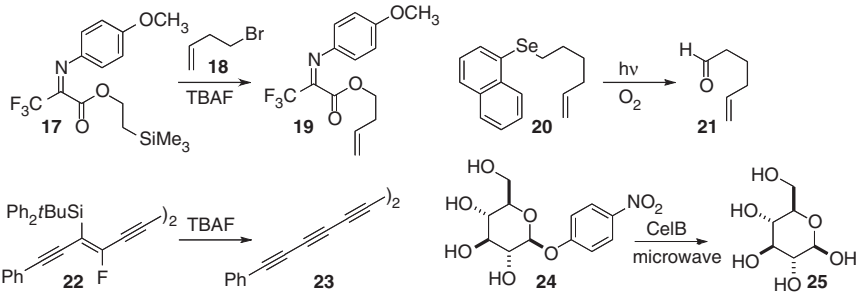


Many of the current methods for amination that have been developed deliver the aryl amine. John F. Hartwig of the University of Illinois established (*J. Am. Chem. Soc.* **2008**, *130*, 12220) that exposure of the amine **11** to Boc_2O followed by CAN led to the protected, dearylated amine **12**.

Adam McCluskey of The University of Newcastle observed (*Tetrahedron Lett*. **2008**, *49*, 6962) that microwave heating removed Boc protecting groups when there was a free carboxylic acid elsewhere in the molecule. Michael Lefenfeld of SiGNa Chemistry and James E. Jackson of Michigan State University used (*Organic Lett*. **2008**, *10*, 5441) easily-handled Na/silica gel to remove primary and secondary sulfonamides (e.g. **15** → **16**). Methanesulfonamides were also removed under these conditions.



Carboxylates are good S_N2 nucleophiles. Santos Fustero of the Universidad de Valencia took advantage of this (*J. Org. Chem.* **2008**, *73*, 5617) in developing a transesterification of TMSE esters. Exposure of **17** to TBAF in the presence of **18** gave **19**. Akihiko Ouchi of the University of Tsukuba showed (*J. Org. Chem.* **2008**, *73*, 8861) that an aryl selenide such as **20** could be unmasked by photo-oxygenation to give the corresponding aldehyde **21**. Secondary selenides gave ketones. Liam R. Cox of the University of Birmingham converted (*Tetrahedron Lett*. **2008**, *49*, 4596) halosilanes such as **22** to the corresponding alkyne **23** by exposure to TBAF.

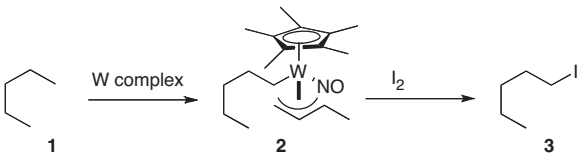


There has been much discussion about the exact role microwaves play in promoting organic reactions. It is clear that microwaves can activate peptide bond rotation. This may be a factor in the observation (*J. Am. Chem. Soc.* **2008**, *130*, 10048) by Alexander Deiters of North Carolina State University that the rate of the hydrolysis of **24** to **25** by the β-glucosidase CelB from the hyperthermophilic archaeon *Pyrococcus furiosus* increased by at least four orders of magnitude under microwave irradiation.

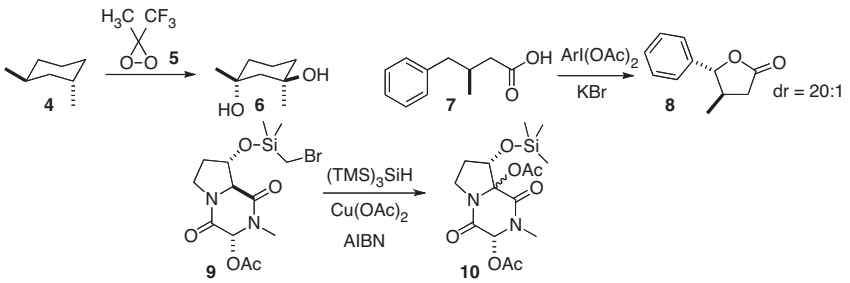
12. Intermolecular and Intramolecular C-H Functionalization

September 22, 2008

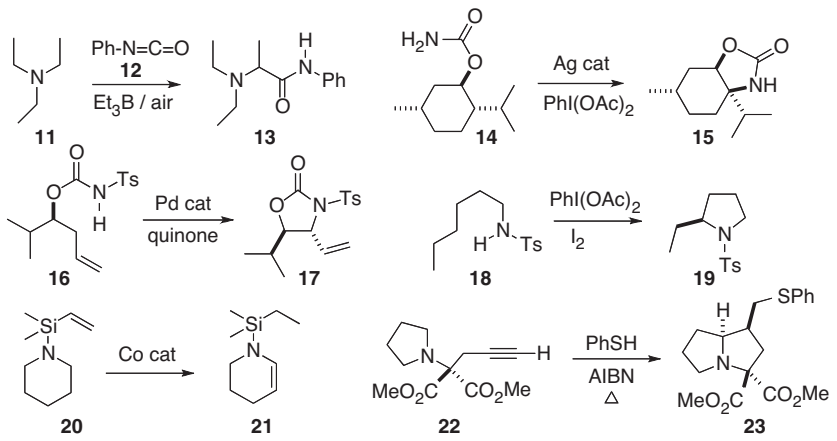
Peter Legzdins of the University of British Columbia has described (*J. Am. Chem. Soc.* **2007**, *129*, 5372) a stoichiometric tungsten complex that specifically functionalized the primary H of an alkane **1** to give the organometallic **2**. Neither the scope of the reactivity of **2** nor the functional group compatibility of this process have as yet been explored.



Ruggero Curci of the Università di Bari has reported (*Tetrahedron Lett*. **2007**, *48*, 3575) the stereospecific hydroxylation of 1,3-dimethyl cyclohexane **4** to the diol **6**. Yasuyuki Kita of Osaka University has developed (*Organic Lett.* **2007**, *9*, 3129) conditions for specific benzylic oxidation, converting **7** into **8** with high diastereocontrol. Larry E. Overman of the University of California, Irvine has established (*Organic Lett.* **2007**, *9*, 5267) that by using a slow H-atom donor, it was possible to effect intramolecular H abstraction, leading, by oxidation of the intermediate captodatively-stabilized radical, from **9** to the acetate **10**.

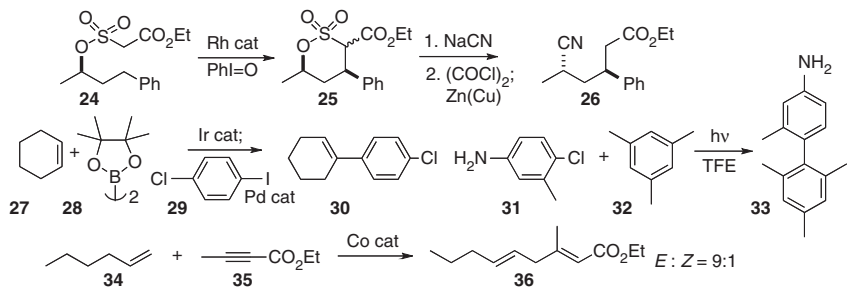


The target C-H of **9** is activated by being adjacent to the ring nitrogen. There are many other ways that nitrogen, easily oxidized, has been used to activate a C-H for bond formation. Takehiko Yoshimitsu and Tetsuaki Tanaka of Osaka University have established (*Organic Lett.* **2007**, *9*, 5115) a free-radical route for the homologation of a tertiary amine such as **11** with phenyl isocyanate **12**. Chuan He of the University of Chicago has devised (*Angew. Chem. Int. Ed.* **2007**, *46*, 5184) an Ag catalyst for the oxidative cyclization of sulfamates such as **15**. M. Christina White of the University of Illinois has developed (*J. Am. Chem. Soc.* **2007**, *129*, 7274) a ligand system that allows the diastereoselective Pd-mediated allylic oxidation of **16** to **17**.



The cyclization of **18** to **19** developed (*J. Org. Chem.* **2007**, *72*, 8994) by Renhua Fan of Fudan University is thought to be proceeding via H atom abstraction by an intermediate nitrogen radical. The oxidation of the amine **20** to the endocyclic enamine **21** reported (*J. Am. Chem. Soc.* **2007**, *129*, 14544) by Maurice Brookhart of the University of North Carolina depended on the ease of oxidative addition of an intermediate alkenyl Co complex into the C-H bond adjacent to the nitrogen. The multistep cyclization of **22** to **23** devised (*Organic Lett.* **2007**, *9*, 4375) by Philippe Renaud of the Universität Bern depended on the ease of H atom abstraction adjacent to nitrogen.

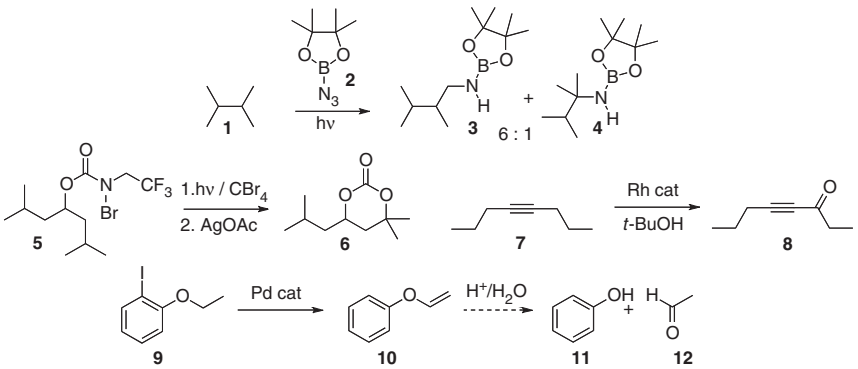
Carbon-carbon bonds can also be established by C-H functionalization. Justin Du Bois of Stanford University has shown (*Organic Lett.* **2007**, *9*, 4363) that sulfonates such as **24** can be cyclized to the sultone with high diastereocontrol. Kálmán J. Szabó of Stockholm University has found (*Angew. Chem. Int. Ed.* **2007**, *46*, 6891) that depending on conditions, either the alkenyl (illustrated) or the allylic C-H of a cycloalkene such as **27** can be activated for bond formation. Maurizio Fagnoni of the University of Pavia has delineated conditions (*Angew. Chem. Int. Ed.* **2007**, *46*, 6495) for direct biphenyl formation from easily oxidized aromatics such as **31** bearing leaving groups. Gerhard Hilt of the Philipps-Universität Marburg has established (*Angew. Chem. Int. Ed.* **2007**, *46*, 8500) a Co catalyst for the efficient Alder ene homologation of a terminal alkene **34** to the unsaturated ester **36**.



13. C-H Functionalization to Form C-O, C-N, and C-C Bonds

December 29, 2008

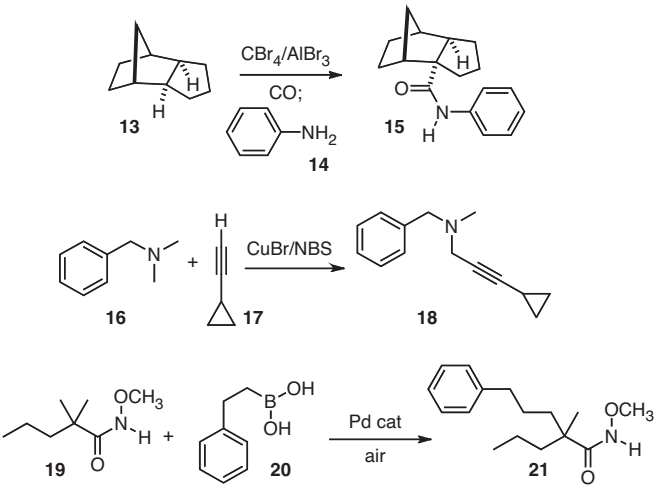
A classic example of C-H functionalization is the familiar NBS bromination of a benzylic site. Recent updates of this approach allow for direct alkoxylation (*J. Am. Chem. Soc.* **2008**, *130*, 7824) and net amination (*Organic Lett.* **2008**, *10*, 1863). For the amination of simple aliphatic H's, Holger F. Bettinger of Ruhr-Universität Bochum developed (*Angew. Chem. Int. Ed.* **2008**, *47*, 4744) the boryl azide **2**. The insertion with **1** proceeded to give a statistical mixture of the nitrene insertion products **3** and **4**. The tethered C-H functionalization devised (*J. Am. Chem. Soc.* **2008**, *130*, 7247) by Phil S. Baran of Scripps-La Jolla is selective, as in the conversion to **5** to **6**, but appears to be limited to tertiary and benzylic C-H sites.



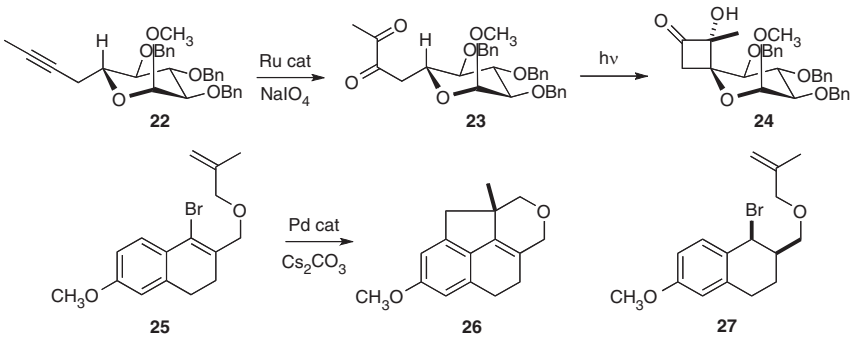
Michael P. Doyle of the University of Maryland established (*J. Org. Chem.* **2008**, *73*, 4317) an elegant protocol for the oxidation of an alkyne such as **7** to the ynone **8**. Note that the oxidation did not move the alkyne. Marta Catellani of the Università di Parma reported (*Adv. Synth. Cat.* **2008**, *350*, 565) the intriguing Pd-catalyzed conversion of **9** to **10**. Under mild conditions, it might likely be possible to hydrolyze the vinyl ether to reveal the phenol **11**. Another way of looking at this overall transformation would be to consider the ether **10** to be a protected form of the aldehyde **12**.

C-H activation can also lead to C-C bond formation. Irena S. Akhrem of the Nesmeyanov Institute, Moscow, described (*Tetrahedron Lett.* **2008**, *49*, 1399) a hydride-abstraction protocol for three-component coupling of a hydrocarbon **13**, an amine **14**, and CO, leading to the homologated amide **15**. Hua Fu of Tsinghua University, Beijing, showed (*J. Org. Chem.* **2008**, *73*, 3961) that oxidation of an amine **16** led to an intermediate that could be coupled with an alkyne **17** to give the propargylic amine **18**.

Products **15** and **18** are the result of sp^2 and *sp* coupling, respectively. C-H functionalization leading to sp^3-sp^3 coupling is less common. Jin-Quan Yu of Scripps/La Jolla found (*J. Am. Chem. Soc.* **2008**, *130*, 7190) that activation of the N-methoxy amide **19** in the presence of the *alkyl* boronic acid **20** gave smooth coupling, to **21**.



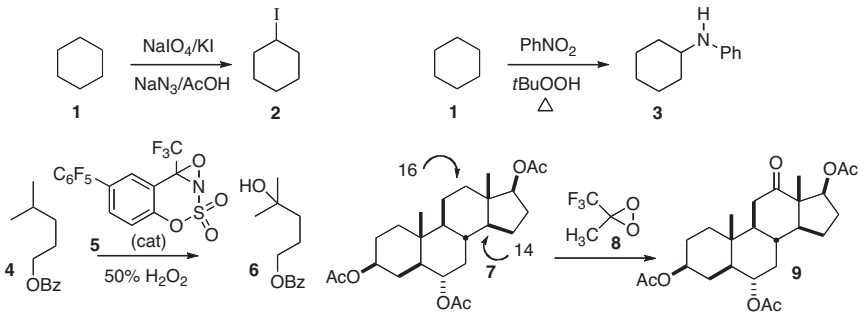
Carbocyclic rings can be constructed using intramolecular C-H functionalization. Antonio J. Herrera and Ernesto Suárez of the CSIC, La Laguna, observed (*J. Org. Chem.* **2008**, *73*, 3384) that 1,2-diketones such as **23**, easily prepared by oxidation of the corresponding alkyne, on irradation cyclized with high diastereocontrol to the cyclobutanone, in this case **24**. Jayanta K. Ray of the Indian Institute of Technology, Kharagpur found (*Tetrahedron Lett.* **2008**, *49*, 851) that exposure of **25** to a Pd catalyst initated a cascade cyclization, delivering the tetracycle **26**. It would be interesting to try the same cyclization with the bromide **27**. Cyclization might be faster than epimerization and subsequent β-hydride elimination.



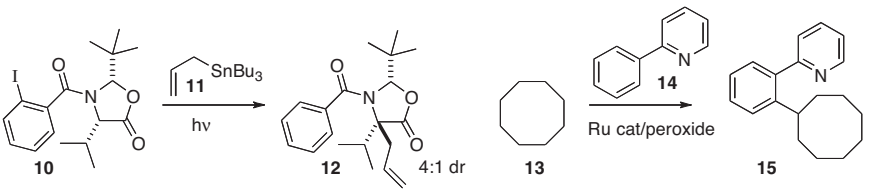
14. Functionalization of C-H Bonds: The Baran Synthesis of Dihydroxyeudesmane

September 28, 2009

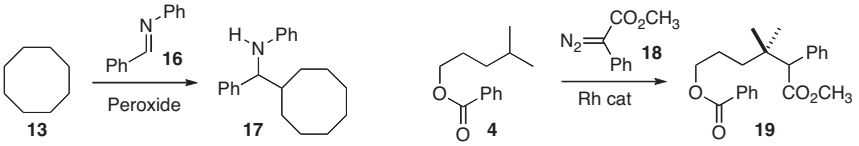
Arumugam Sudalai of the National Chemical Laboratory, Pune reported (*Tetrahedron Lett*. **2008**, *49*, 6401) a procedure for hydrocarbon iodination. With straight chain hydrocarbons, only secondary iodination was observed. Chao-Jun Li of McGill University uncovered (*Adv. Synth. Cat.* **2009**, *351*, 353) a procedure for direct hydrocarbon amination, converting cyclohexane **1** into the amine **3**. Justin Du Bois of Stanford University established (*Angew. Chem. Int. Ed.* **2009,** *48*, 4513) a procedure for alkane hydroxylation, converting **4** selectively into the alcohol **6**. The oxirane **8** usually also preferentially ozidizes methines, hydroxylating steroids at the C-14 position. Ruggero Curci of the University of Bari found (*Tetrahedron Lett.* **2008**, *49*, 5614) that the substrate **7** showed some C-14 hydroxylation, but also a useful yield of the ketone **9**. The authors suggested that the C-7 acetoxy group may be deactivating the C-14 C-H.



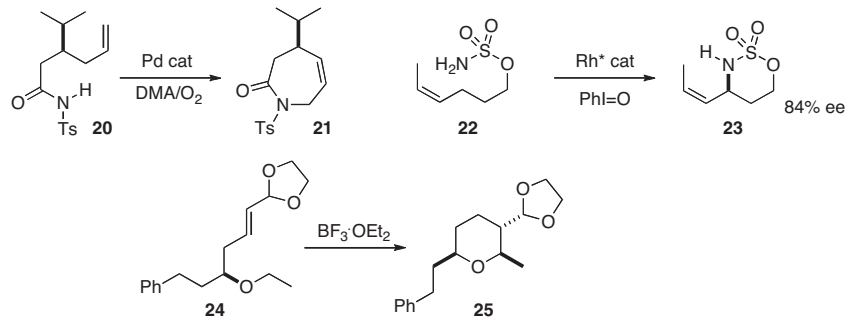
C-H bonds can also be converted directly to carbon-carbon bonds. Mark E. Wood of the University of Exeter found (*Tetrahedron Lett.* **2009**, *50*, 3400) that free-radical removal of iodine from **10** followed by intramolecular H-atom abstraction in the presence of the trapping agent **11** delivered **12** with good diastereocontrol. Professor Li observed (*Angew. Chem. Int. Ed.* **2008,** *47*, 6278) that under Ru catalysis, hydrocarbons such as **13** could be directly arylated. He also established (*Tetrahedron Lett.* **2008**, *49*, 5601) conditions for the direct aminoalkylation of hydrocarbons such as **13**, to give **17**. Huw M. L. Davies of Emory University converted (*Synlett* **2009**, 151) the ester **4** to the homologated diester **19** in



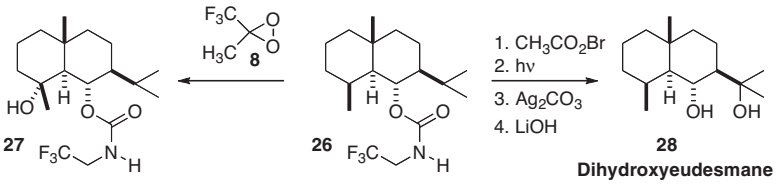
preparatively useful yield using the diazo ester **18**, the precursor to a selective, push-pull stabilized carbene.



Intramolecular bond formation to an unactivated C-H can be even more selective. Guoshen Liu of the Shanghai Institute of Organic Chemistry developed (*Organic Lett.* **2009**, *11*, 2707) an oxidative Pd system that cyclized **20** to the seven-membered ring lactam **21**. Professor Du Bois devised (*J. Am. Chem. Soc.* **2008**, *130*, 9220) a Rh catalyst that effected allylic amination of **22**, to give **23** with substantial enantiocontrol. Dalibor Sames of Columbia University designed (*J. Am. Chem. Soc.* **2009**, *131*, 402) a remarkable cascade approach to C-H functionalization. Exposure of **24** to Lewis acid led to intramolecular hydride abstraction. Cyclization of the resulting stabilized carbocation delivered the tetrahydropyan **25** with remarkable diastereocontrol.



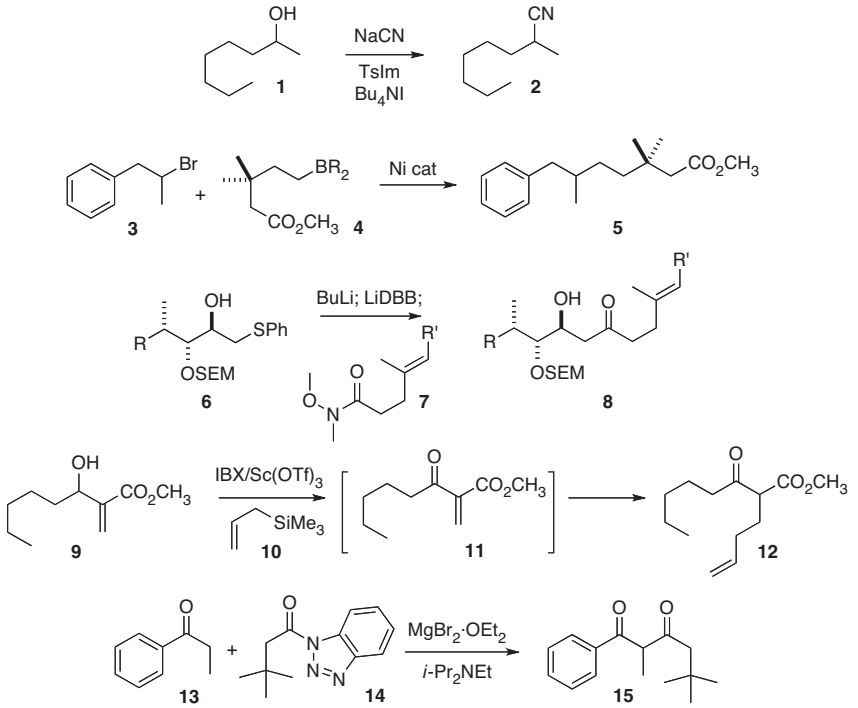
The oxidation (*Nature* **2009**, *459*, 824) of the eudesmol carbamate **26** by Phil S. Baran of Scripps/La Jolla presents an interesting case study. Direct intermolecular oxidation with the same reagent used by Professor Curci, TFDO **8**, proceeded selectively, with retention of absolute configuration, to give the equatorial alcohol **27**. In contrast, distal bromination directed by the carbamate followed by hydrolysis, using the protocol developed by the Baran group, gave the complementary diol, Dihydroxyeudesmane **28**.



15. New Methods for Carbon-Carbon Bond Construction

June 16, 2008

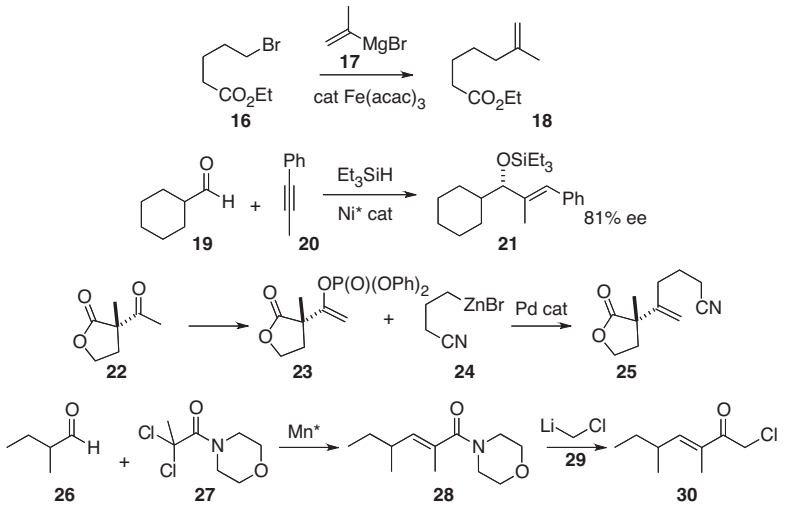
Mohammad Navid Soltani Rad of Shiraz University of Technology has shown (*Tetrahedron Lett*. **2007**, *48*, 6779) that with tosylimidazole (TsIm) activation in the presence of NaCN, primary, secondary and tertiary alcohols are converted into the corresponding nitriles. Gregory C. Fu of MIT has devised (*J. Am. Chem. Soc.* **2007**, *129*, 9602) a Ni catalyst that mediated the coupling of sp^3-hybridized halides such as **3** with sp^3-hybridized organoboranes such as **4**, to give **5**.



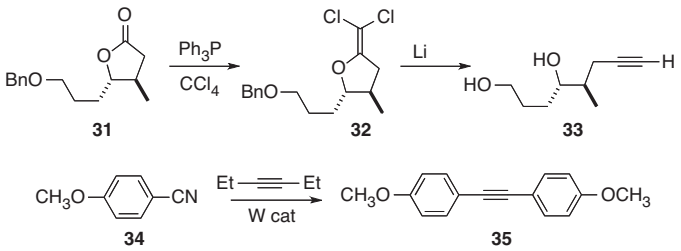
Usually, carbanions with good leaving groups in the beta position do not couple efficiently, but just eliminate. Scott D. Rychnovsky of the University of California, Irvine has found (*Organic Lett*. **2007**, *9*, 4757) that initial protection of **6** as the alkoxide allowed smooth reduction of the sulfide and addition of the derived alkyl lithium to the amide **7** to give **8**. Doubly-activated Michael acceptors such as **11** are often too unstable to isolate. J. S. Yadav of the Indian Institute of Chemical Technology, Hyderabad has shown (*Tetrahedron Lett*. **2007**, *48*, 7546) that Baylis-Hillman adducts such as **9** can be oxidized in situ, with concomitant Sakurai addition to give **12**. Rather than use the usual Li or Na or

K enolate, Don M. Coltart of Duke University has found (*Organic Lett*. **2007**, *9*, 4139) that ketones such as **13** will condense with amides such as **14** to give the diketone **15** on exposure to $MgBr_2 \cdot OEt_2$ and *i*-Pr_2NEt.

Simultaneously, Gérard Cahiez of the Université de Cergy (*Organic Lett*. **2007**, *9*, 3253) and Janine Cossy of ESPCI Paris (*Angew. Chem. Int. Ed.* **2007**, *46*, 6521) reported that Fe salts will catalyze the coupling of sp^2-hybridized Grignard reagents such as **17** with alkyl halides. John Montgomery of the University of Michigan has described (*J. Am. Chem. Soc.* **2007**, *129*, 9568) the Ni-mediated regio- and enantioselective addition of an alkynes **20** to an aldehyde **19** to give the allylic alcohol **21**. In a third example of sp^2- sp^3 coupling, Troels Skrydstrup of the University of Aarhus has established (*J. Org. Chem.* **2007**, *72*, 6464) that Negishi coupling with alkenyl phosponates such as **23** proceeded efficiently. José M. Concellón of the Universidad de Oviedo has developed (*J. Org. Chem.* **2007**, *72*, 7974) a linchpin approach to enone construction, reductive condensation of a dihalo amide **27** with an aldehyde **26** to give the amide **28**, then addition of an alkyl lithium **29** to **28** to give **30**.



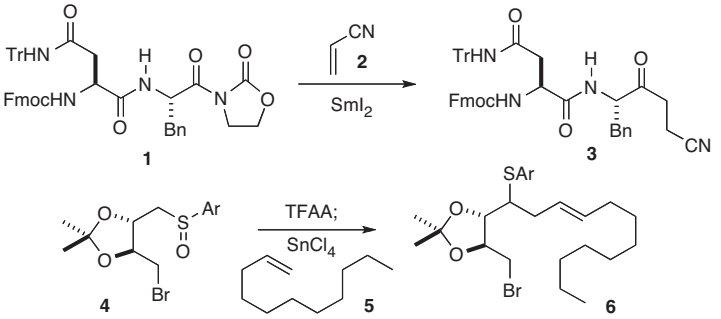
Two useful new methods for alkyne construction have been put forward. Professor Yadav has developed (*Tetrahedron Lett*. **2007**, *48*, 5335) an elegant homologation of lactones such as **31** to alkynes, and Marc A. J. Johnson of the University of Michigan has reduced to practice (*J. Am. Chem. Soc.* **2007**, *129*, 3800) the long-sought metathetical coupling of two nitriles such as **34** to form the alkyne **35**.



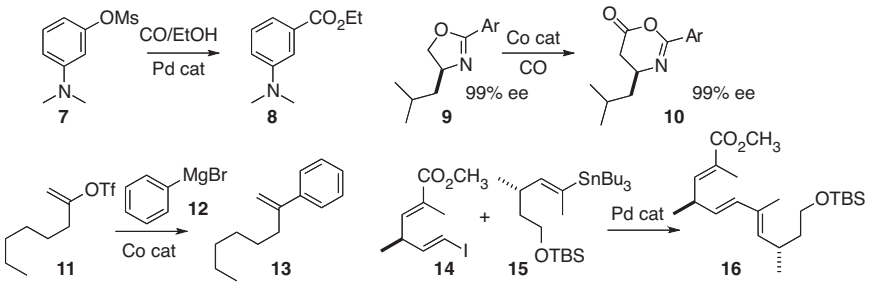
16. Best Synthetic Methods: Carbon-Carbon Bond Construction

March 16, 2009

In the context of peptidyl ketone synthesis, Troels Skrydstrup of the University of Aarhus developed (*J. Org. Chem.* **2008**, *73*, 1088) the elegant SmI_2-mediated conjugate addition of acyl oxazolidinones such as **1** to acceptors such as **2**. Sadagopan Raghavan of the Indian Institute of Chemical Technology, Hyderabad reported (*Tetrahedron Lett.* **2008**, *49*, 1601) that the addition of a Pummerer intermediate, generated by exposure of **4** to TFAA, to the terminal alkene **5** and $SnCl_4$ led to efficient C-C bond formation, to give the sulfide **6** as a single (unassigned) diastereomer.

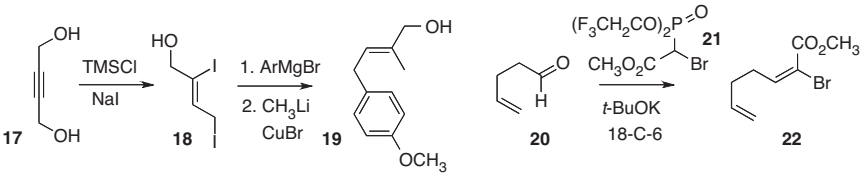


Pd-catalyzed carbonylation of aryl halides and triflates is a well-established process. Stephen L. Buchwald of MIT has now (*J. Am. Chem. Soc.* **2008**, *130*, 2754) extended this transformation to much less expensive tosylates and mesylates such as **7**. β-Amino acids have often been prepared from α-amino acids by Arndt-Eistert homologation. Geoffrey W. Coates of Cornell University has devised (*Angew. Chem. Int. Ed.* **2008**, *47*, 3979) a more practical alternative, the direct Co-catalyzed carbonylation of an oxazoline **9** to the 2-oxazine-6-one **10**.

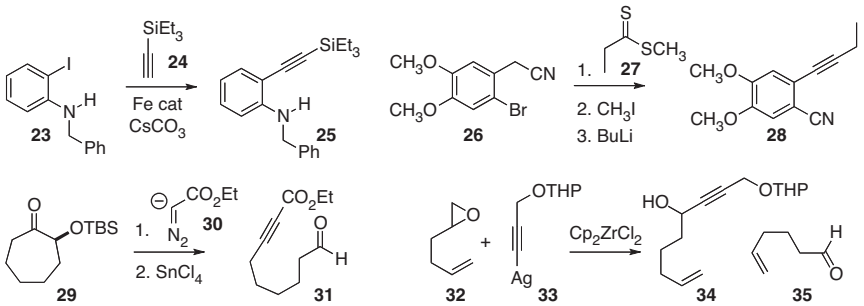


Eiji Shirakawa and Tamio Hayashi of Kyoto University also used (*Chem. Lett*. **2008**, *37*, 654) a Co catalyst to promote the coupling of aryl and alkenyl Grignard reagents with enol triflates such as **11**. Alois Fürstner of the Max-Planck-Institut, Mülheim optimized (*Chem. Commun.* **2008**, 2873) promoters for the Pd-catalyzed Stille-Migata coupling of iodo alkenes such as **14** with alkenyl stannanes such as **15** to give **16**. It is particularly noteworthy that their system is fluoride free.

The stereocontrolled construction of trisubstituted alkenes continues to be challenging. We described (*J. Org. Chem.* **2008**, *73*, 1605) the facile preparation of the diioide **18** from the inexpensive 2-butyn-1,4-diol **17**. Sequential coupling of **18** with an aryl Grignard followed by CH_3Li delivered **19**. Brian S. J. Blagg of the University of Kansas established (*Tetrahedron Lett*. **2008**, *49*, 141) that Still-Genari homologation of **20** with **21** gave (*E*)-**22** with high geometric control. Biao Jiang of the Shangahi Institute of Organic Chemistry reported (*Organic Lett*. **2008**, *10*, 593) a convenient alternative protocol to give (*Z*)-α-bromo unsaturated esters.



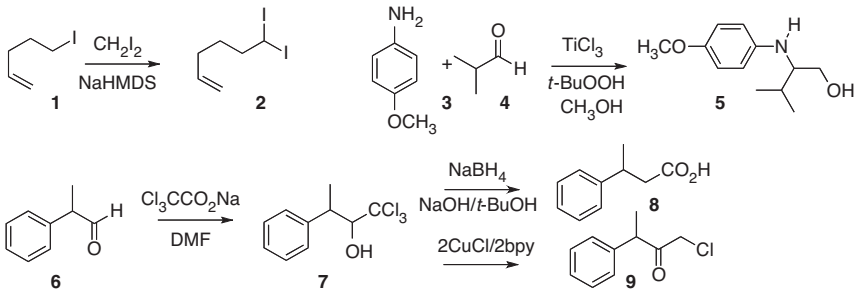
Carston Bolm of RWTH Aachen University found (*Angew. Chem. Int. Ed.* **2008**, *47*, 4862) that an inexpensive Fe catalyst could replace Pd in the Sonogashira coupling of **24** to **23**. Hiriyakkanavar Ila of the Indian Institute of Technology, Kanpur devised (*Organic Lett*. **2008**, *10*, 965) a complementary route to aryl acetylenes, with concomitant *ortho* nitrile transfer. Matthias Brewer of the University of Vermont (*J. Am. Chem. Soc*. **2008**, *130*, 3766, **29** → **31**) and Gregory B. Dudley of Florida State University (*J. Am. Chem. Soc*. **2008**, *130*, 5050 – not illustrated) devised fragmentation schemes for alkyne construction. Kazunori Koide of the University of Pittsburgh found (*J. Org. Chem*. **2008**, *73*, 1093) that exposure of an epoxide **32** to a silver acetylide **33** followed by stoichiometric Cp_2ZrCl_2 and catalytic AgOTf led to alcohol **34**. This is as though the epoxide **32** had rearranged to the aldehyde **35**, a long-sought goal of organic synthesis.



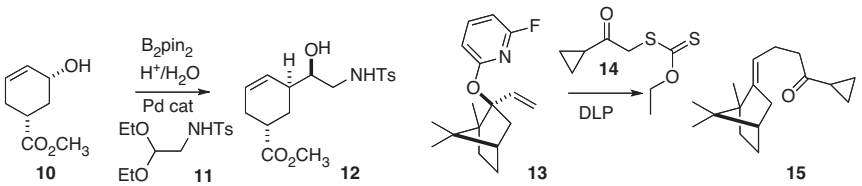
17. C-C Single Bond Construction

May 25, 2009

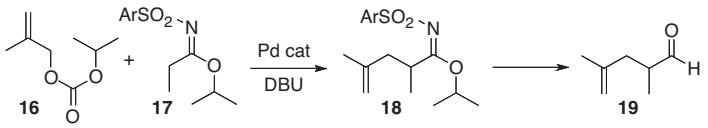
Several remarkable one-carbon homologations have recently appeared. André B. Charette of the Université de Montréal reported (*J. Org. Chem.* **2008**, *73*, 8097) the alkylation of diiodomethane with alkyl iodides such as **1**, to give the diiodoalkane **2**. Carlo Punta and the late Ombretta Porta of the Politecnico di Milano effected (*Organic Lett.* **2008**, *10*, 5063) reductive condensation of an amine **3** with an aldehyde **4** in the presence of methanol, to give the amino alcohol **5**. Timothy S. Snowden of the University of Alabama showed (*Organic Lett.* **2008**, *10*, 3853) that $NaBH_4$ reduced the carbinol **7**, easily prepared from the aldehyde **6**, to the acid **8**. Ram N. Ram of the Indian Institute of Technology, Delhi found (*J. Org. Chem.* **2008**, *73*, 5633) that CuCl reduced **7** to the chloro ketone **9**.



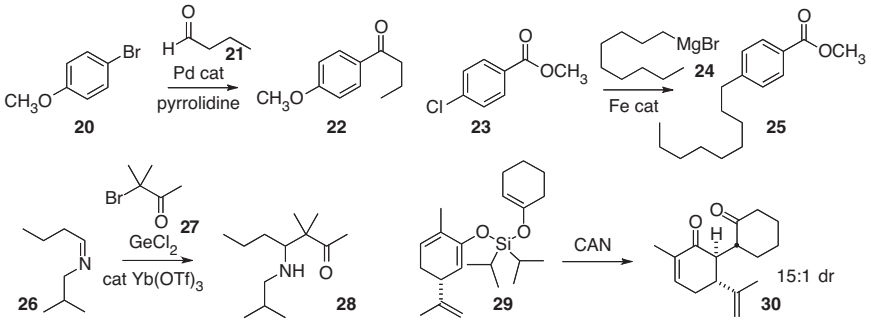
Kálmán J. Szabó of Stockholm University extended (*Chem. Commun.* **2008**, 3420) his elegant work on in situ borinate formation, coupling, in one pot, the allylic alcohol **10** with the acetal **11** (hydrolysed in situ) to deliver the alcohol **12** as a single diastereomer. Samir Z. Zard of the Ecole Polytechnique developed (*J. Am. Chem. Soc.* **2008**, *130*, 8898) the 6-fluoropyridyloxy ether of **13** as an effective radical leaving group, enabling efficient coupling with **14**, activated by dilauroyl peroxide, to give **15**.



Shu Kobayashi of the University of Tokyo established (*Chem. Commun.* **2008**, 6354) that the anion of the sulfonyl imidate **17** participated in direct Pd-mediated allylic coupling with the carbonate **16**. The product sulfonyl imidate **18** is itself of medicinal interest. It is also easily converted to other functional groups, including the aldehyde **19**.



Jianliang Xiao of the University of Liverpool found (*J. Am. Chem. Soc.* **2008**, *130*, 10510) that Pd-mediated coupling of an aldehyde **21** in the presence of pyrrolidine led to the ketone **22**. The reaction is probably proceeding via Heck coupling of the aryl halide with the in situ generated enamine. Alois Fürstner of the Max Planck Institut, Mülheim observed (*J. Am. Chem. Soc.* **2008**, *130*, 8773) that in the presence of the simple catalyst $Fe(acac)_3$ a Grignard reagent **24** coupled smoothly with an aryl halide **23** to give **25**. Akio Baba of Osaka University established (*Angew. Chem. Int. Ed.* **2008**, *47*, 6620) that the $GeCl_2$-driven Reformatsky-like addition of a halo ketone **27** to an imine **26** worked best in the presence of a catalytic Lewis acid.

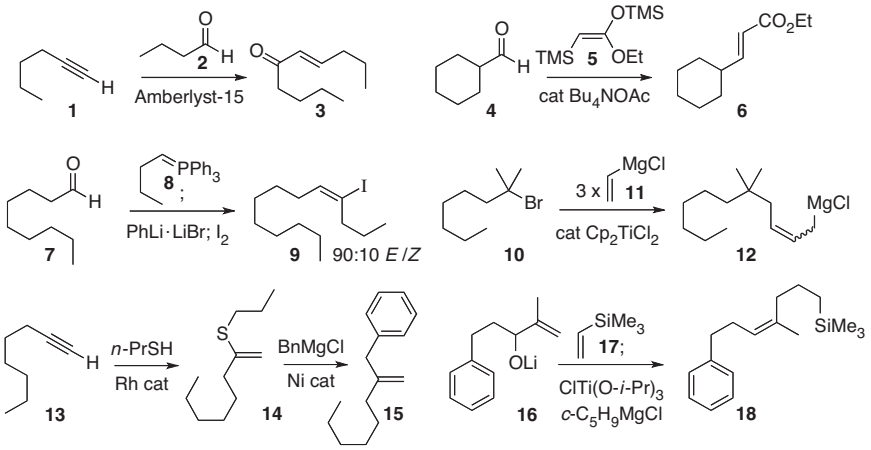


The oxidative cross-coupling of ketone enolates, leading to the 1,4-diketone, has great potential as a method for rapidly assembling molecular complexity. Attempted hetero cross-coupling, however, can also lead to the homo coupled products as contaminants. Regan J. Thomson of Northwestern University has now shown (*Organic Lett.* **2008**, *10*, 5621) that it is possible to first prepare the hetero-coupled mixed silyl enol ethers, such as **29**. Oxidation of **29** delivered **30** as predominantly a single diastereomer.

18. Construction of Alkenes, Alkynes and Allenes

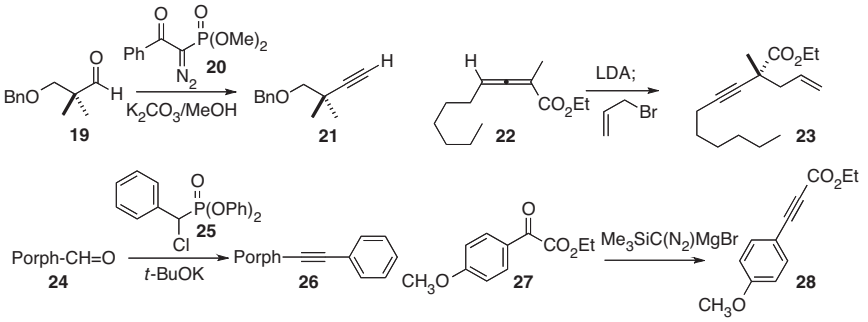
June 8, 2009

Products such as **3** and **6** are usually prepared by phosphonate condensation. J. S. Yadav of the Indian Institute of Technology, Hyderabad found (*Tetrahedron Lett*. **2008**, *49*, 4498) that the cation-exchange resin Amberlyst-15 in CH_2Cl_2 mediated the condensation of a terminal alkyne such as **1** with an aldehyde to give the enone **3**. Similarly, Teruaki Mukaiyama of Kitasato University showed (*Chemistry Lett*. **2008**, *37*, 704) that tetrabutylammonium acetate mediated the condensation of **5** with an aldehyde such as **4** to give the ester **6**. David M. Hodgson of the University of Oxford described (*J. Am. Chem. Soc.* **2008**, *130*, 16500) the optimization of the Schlosser protocol for the condensation of a phosphorane with an aldehyde **7** followed by deprotonation and halogenation, to deliver the alkenyl halide **9** with good geometric control. Jun Terao of Kyoyo University and Nobuaki Kambe of Osaka University accomplished (*Chem. Commun*. **2008**, 5836) the homologation of a halide such as **10** to the corresponding allylic Grignard reagent **12**. Primary, secondary and tertiary halides worked well. Jennifer Love of the University of British Columbia developed (*Organic Lett*. **2008**, *10*, 3941) a Rh catalyst for the addition of thiols to terminal alkynes such as **13**, and found that the product thioether **14** coupled smoothly with Grignard reagents to deliver the 1,1-disubstituted alkene **15**. Glenn C. Micalizio, now at Scripps Florida, established (*J. Am. Chem. Soc.* **2008**, *130*, 16870) what appears to be a general method for the construction of *Z*-trisubstituted alkenes such as **18**.

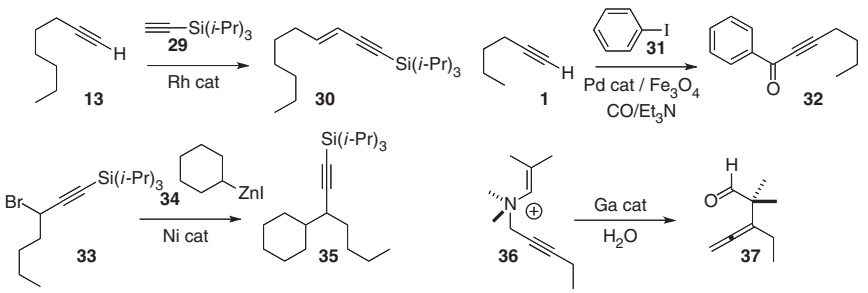


The Ohira protocol has become the method of choice for converting an aldehyde **19** to the alkyne **21**. We have found (*Tetrahedron Lett*. **2008**, *49*, 6904) that the reagent **20** offers advantages in price, preparation and handling. Bo Xu and Gerald B. Hammond of the University of Louisville observed (*Organic Lett*. **2008**, *10*, 3713) that an allene ester such as **22** is readily homologated to the alkyne **23**. Ashton C. Partridge of Massey University

extended (*Tetrahedron Lett*. **2008**, *49*, 5632) condensation with the aryl phosphonate **25** to porphyrin aldehydes, leading to alkynes such as **26**. Toyohiko Aoyama of Nagoya City University established (*Tetrahedron Lett*. **2008**, *49*, 4965) that the halomagnesium salt of TMS diazomethane was the most efficient for converting **27** to **28** [CAUTION: Two deaths were recently reported from use of TMS diazomethane without proper ventilation!].



Masahiru Miura, also of Osaka University, reported (*Chem. Commun*. **2008**, 3405) that the Rh catalyzed homologation of a terminal alkyne **13** to the enyne **30** proceeded with high geometric control. Wei Sun and Chungu Xia of the Lanzhou Institute of Chemical Physics devised (*Organic Lett*. **2008**, *10*, 3933) a magnetically-retrievable Pd catalyst, the utility of which they illustrated with the carbonylative Sonogashira coupling of **1** with **31** to give **32**. Gregory C. Fu of MIT optimized (*Angew. Chem. Int. Ed.* **2008**, *47*, 9334) the Ni catalyzed coupling of organozinc reagents such as **34** with a propargylic halide **33** to give **36**.

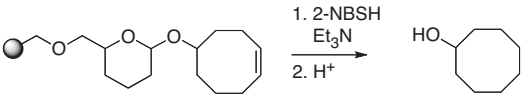


In an elegant extension of their "nanozyme" work, Robert G. Bergman and Kenneth N. Raymond of the University of California, Berkeley devised (*J. Am. Chem. Soc.* **2008**, *130*, 10977) an encapsulating Ga complex that catalyzed the rearrangement of **36** to the allene **37**. Depending on how well the quaternary ammonium salt fit in the encapsulating complex, they observed rate accelerations of more than two orders of magnitude for the rearrangement.

19. Reduction, Oxidation and Homologation of Alkenes

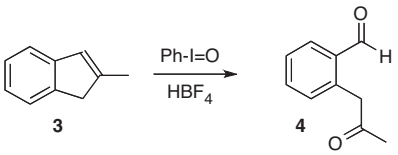
March 24, 2008

Alkenes are usually reduced by catalytic hydrogenation. Diimide reduction is a mild and neutral alternative. Keith R. Buszek, now at the University of Missouri, Kansas City, has shown (*J. Org. Chem.* **2007**, *72*, 3125) that the reduction can conveniently be carried out on resin-bound alkenes, using 2-NBSH (*o*-nitrobenzenesulfonylhydrazide) with Et_3N for convenient room temperature diimide generation.



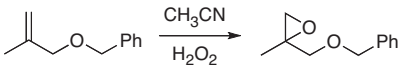
1 2

Ozone can be difficult to dispense accurately on small scale. Masahito Ochiai of the University of Tokushima has uncovered (*J. Am. Chem. Soc.* **2007**, *129*, 2772) an alternative, using acid-promoted Ph-I=O. Isolated alkenes also work well.



3 4

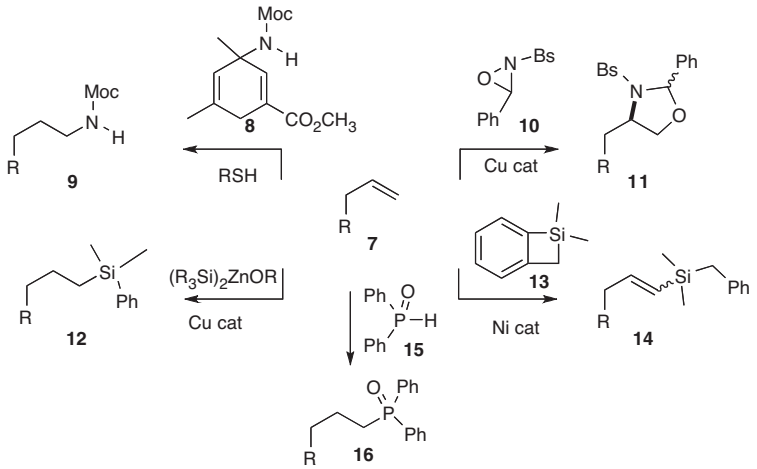
MCPBA is the reagent most commonly used for alkene epoxidation. Payne oxidation (H_2O_2 / CH_3CN) is a convenient and inexpensive alternative. In the course of a study of the enantioselective enzymatic hydrolysis of **6**, Takeshi Sugai of Keio University has described (*Tetrahedron Lett*. **2007**, *48*, 979) a practical procedure for multigram Payne epoxidation of **5**.



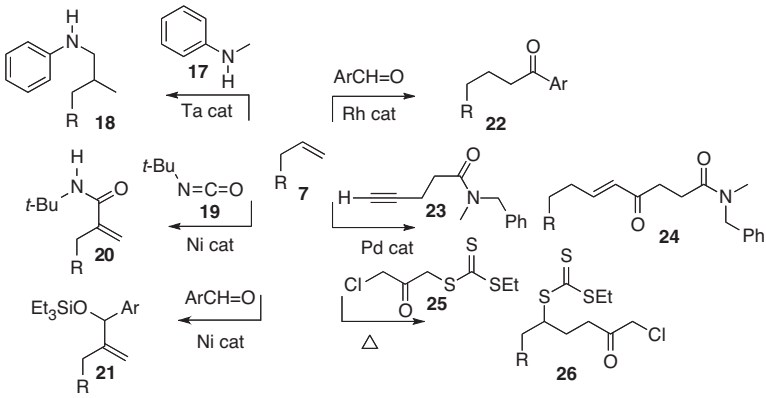
5 6

Several procedures have been put forward for functionalizing terminal alkenes, exemplified by **7**. Stefan Grimme and Armido Studer of the Universität Münster have developed (*J. Am. Chem. Soc.* **2007**, *129*, 4498) a free radical alkene amination, represented by the conversion of **7** to **9**. Tehshik P. Yoon of the University of Wisconsin has found (*J. Am. Chem. Soc.* **2007**, *129*, 1866) that Cu catalyzes the addition of oxaziridines such as **10** to alkenes, to make **11**. Shinji Nakamura of the University of Tokyo and Masanobu Uchiyama of the University of Tokyo and RIKEN have established (*J. Am. Chem. Soc.* **2007**, *129*, 28) that the anion from Cu promoted addition of the silyl zinc reagent to alkenes is long-lived enough to be trapped by electrophiles, including H+ to give **12**. Hideki Yorimitsu and Koichiro Oshima of Kyoto University have developed (*J. Am. Chem. Soc.* **2007**, *129*, 6094)

a complementary transformation, Ni-catalyzed addition of **13** to give **14**. The conversion of **7** to **15** reported (*Organic Lett.* **2007**, *9*, 53) by Li-Biao Han of the National Institute of Advanced Industrial Science and Technology, Tsukuba, is likely also a free-radical process.



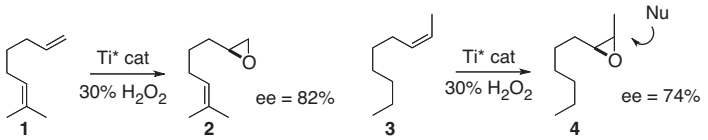
Several procedures have also been developed for homologating terminal alkenes, again exemplified by **7**. The homologation can be either branching, as with **18** [John F. Hartwig, University of Illinois (*J. Am. Chem. Soc.* **2007**, *129*, 6690)], **20** [Timothy F. Jamison, MIT (*Organic Lett*. **2007**, *9*, 875)], and **21** [Timothy F. Jamison, (*Angew. Chem. Int. Ed.* **2007**, *46*, 782)], or linear, as with **22** [Maurice Brookhart, University of North Carolina (*J. Am. Chem. Soc.* **2007**, *129*, 2082)],**24** [David R. Liu, Harvard (*J. Am. Chem. Soc.* **2007**, *129*, 2230)] and **26** [Samir Z. Zard, Ecole Polytechnique (*Organic Lett*. **2007**, *9*, 1773)]. The Liu procedure can also be used to prepare 1,5-dicarbonyl compounds. The Zard protocol is particularly noteworthy, as the product chloroketone **26** can be carried on to the xanthate, which can be added to another alkene, so **25** serves as a linchpin reagent.



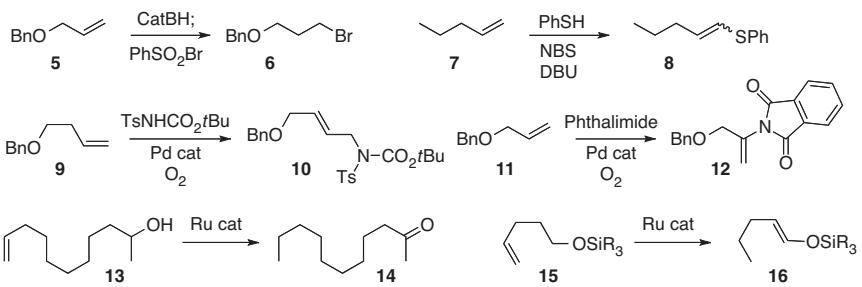
20. Reactions of Alkenes

September 29, 2008

One of the most powerful of alkene transformations is enantioselective epoxidation. Tsutomu Katsuki of Kyushu University has developed (*Angew. Chem. Int. Ed.* **2007**, *46*, 4559) a Ti catalyst that with H_2O_2, selectively epoxidized terminal alkenes with high ee. The same catalyst converted a *Z* 2-alkene such as **3** into the epoxide. This is significant, because such epoxides are opened with nucleophiles selectively at the less congested center.

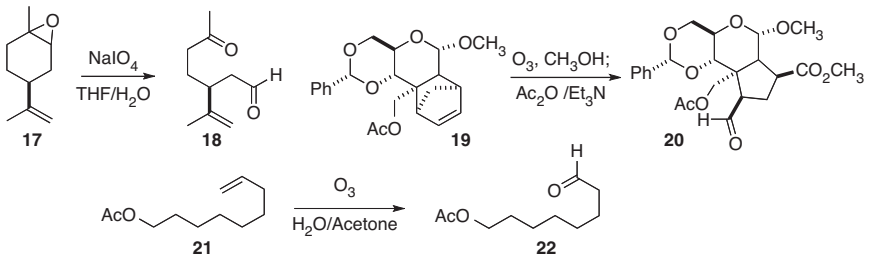


Novel procedures for alkene functionalization have been put forward. Philippe Renaud of the University of Berne has developed (*Adv. Synth. Cat.* **2008**, *350*, 1163) a simple protocol for terminal halogenation, based on catalyzed addition of catecholborane, followed by free radical substitution. Sulfides and selenides were also prepared. H. Zoghlami of the Faculty of Sciences of Tunis has devised (*Tetrahedron Lett*. **2007**, *48*, 5645) an oxidative sulfinylation, converting a terminal alkene **7** to the sulfide **8**. M. Christina White of the University of Illinois (*J. Am. Chem. Soc.* **2008**, *130*, 3316) and Guosheng Liu of the Shanghai Institute of Organic Chemistry (*Angew. Chem. Int. Ed.* **2008**, *47*, 4733) independently developed Pd catalysts for the oxidation of a terminal alkene **9** to the terminal allylic amine **10**. Shannon S. Stahl of the University of Wisconsin-Madison has established (*Organic Lett*. **2007**, *9*, 4331) conditions for the complementary transformation of a terminal alkene **11** to the enamide **12**. Douglas B. Grotjahn of San Diego State University has optimized (*J. Am. Chem. Soc.* **2007**, *129*, 9592) Ru-catalyzed alkene ("zipper") migration, effecting the conversion of **13** to **14** and of **15** to **16**.

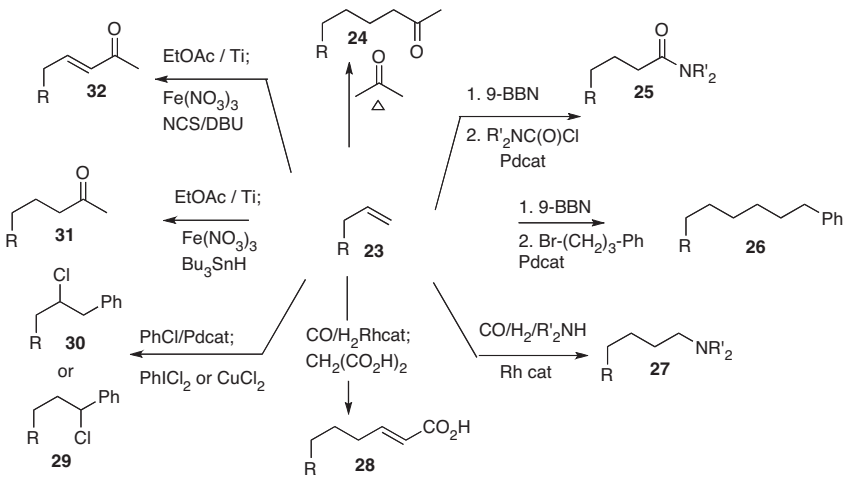


There have been several new observations on alkene cleavage. Marcus A. Tius of the University of Hawaii and Bakthan Singaram of the University of California, Santa Cruz have found (*Tetrahedron Lett*. **2008**, *49*, 2764) that epoxides such as **17** are cleaved directly by $NaIO_4$, providing a simple alternative to ozonolysis. Rolando A. Spanevello of the Universidad Nacional de Rosario has extended (*Tetrahedron* **2007**, *63*, 11410)

unsymmetrical ozonolysis to highly substituted norbornene derivatives such as **19**, observing **20** as the only product. Patrick H. Dussault of the University of Nebraska–Lincoln has established (*J. Org. Chem.* **2008**, *73*, 4688) that alkene ozonolysis in wet acetone delivered the ketone or aldehyde directly, without reductive workup.



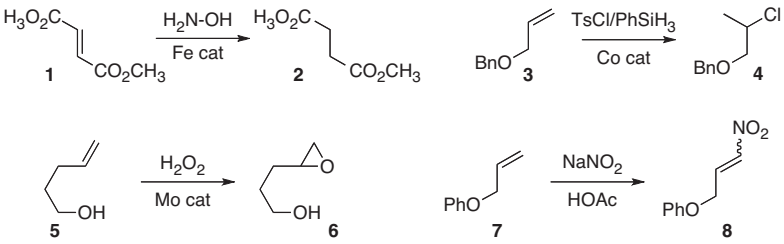
In a very simple procedure, Takashi Kamitanaka and Tadao Harada of Ryukoku University and the Industrial Research Center of Shiga Prefecture have found (*Tetrahedron Lett*. **2008**, *48*, 8460) that acetone, acetonitrile or an alcohol added without catalyst to a terminal alkene at 340 °C. Yoshiji Takemoto of Kyoto University has reported (*J. Org. Chem.* **2007**, *72*, 5898) Pd-catalyzed acylation of 9-BBN adducts, and Michael G. Organ of York University has described (*Chem. Commun*. **2008**, 735) a convenient Pd catalyst for coupling of 9-BBN adducts with primary alkyl bromides at ambient temperature. Dieter Vogt of the Eindhoven University of Technology (*Adv. Synth. Cat.* **2008**, *350*, 332) and Maurizio Taddei of the Università degli Studi di Siena (*Tetrahedron Lett*. **2008**, *48*, 8501) have reported hydroformylation in the presence of a secondary amine to give net aminomethylation, and Bernhard Breit of the Albert-Ludwigs-Universität Freiburg has found (*Adv. Synth. Cat.* **2008**, *350*, 989) that hydroformylation can be followed by Knoevenagel condensation, to give three-carbon homologation, to **28**. Melanie S. Sanford of the University of Michigan has devised (*J. Am. Chem. Soc.* **2008**, *130*, 2150) strategies for interrupting Heck arylation, to give selectively either **29** or **30**, and Andrew J. Phillips of the University of Colorado has taken advantage of Kulinkovich cyclopropanation to give selectively either **31** or **32** (*Organic Lett*. **2007**, *9*, 2717; **2008**, *10*, 1083).



21. Selective Reactions of Alkenes

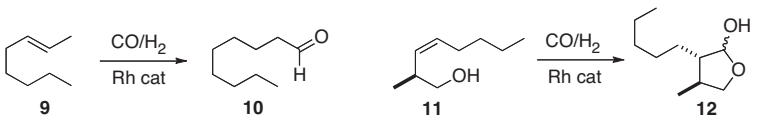
March 30, 2009

Fabio Doctorovich of the Universidad de Buenos Aires reported (*J. Org. Chem.* **2008**, *73*, 5379) that hydroxylamine in the presence of an Fe catalyst reduced alkenes such as **1**, but not ketones or esters. Erick Carreira of ETH Zürich developed (*Angew. Chem. Int. Ed.* **2008**, *47*, 5758) mild conditions for the hydrochlorination of mono-, di- and trisubstituted alkenes. Ramgopal Bhattacharyya of Jadavpur University established (*Tetrahedron Lett.* **2008**, *49*, 6205) a simple Mo-catalyzed protocol for alkene epoxidation.



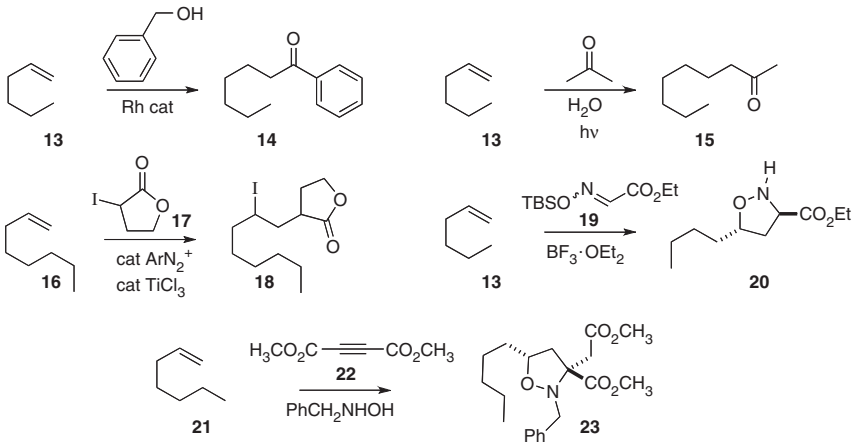
Nitro alkenes are of increasing importance as acceptors for enantioselective organocatalyzed carbon-carbon bond formation. Matthias Beller of the Universität Rostock found (*Adv. Synth. Cat.* **2008**, *350*, 2493) that an alkene such as **7** was readily converted to the corresponding nitroalkene **8** by exposure to of NO gas. The reaction could also be effected with $NaNO_2$/HOAC.

Two complementary protocols for Rh-catalyzed alkene hydroformylation have been reported. Xumu Zhang of Rutgers University devised (*Organic Lett*. **2008**, *10*, 3469) a ligand system that cleanly migrated the alkene of **9**, then terminally hydroformylated the resulting monosubstituted alkene, to give **10**. Kian L. Tan of Boston College designed (*J. Am. Chem. Soc.* **2008**, *130*, 9210) a ligand such that the hydroformylation of the internal alkene of **11** was directed to the end of the alkene proximal to the directing OH, delivering **12**.



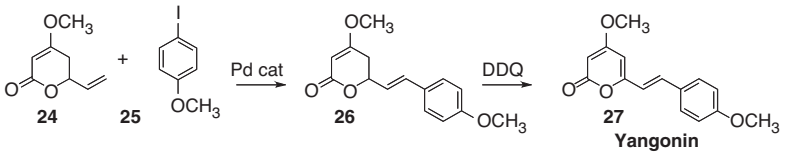
Several other methods for the functionalizing homologation of alkenes have been put forward. Chul-Ho Jun of Yonsei University assembled (*J. Org. Chem.* **2008**, *73*, 5598) a Rh catalyst that effected the oxidative acylation of a terminal alkene **13** with a primary benzylic alcohol, to give the ketone **14**. For now, this approach is limited to less expensive alkenes, as the alkene, used in excess, is the reductant in the reaction. The other procedures outlined here require only stoichiometric alkene. Yasuhiro Shiraishi of Osaka University devised (*Organic Lett*. **2008**, *10*, 3117) a simple photoprocess for adding acetone to a

terminal alkene **13** to give the methyl ketone **14**, in what is presumably a free radical reaction. Chaozhong Li of the Shanghai Institute of Organic Chemistry found (*Tetrahedron Lett.* **2008**, *49*, 7380) that reduction of a benzenediazonium salt with aqueous $TiCl_3$ generated an effective catalyst for the free radical atom transfer addition of α-iodoesters and α-iodonitriles to alkenes such as **17**, to give the adduct **18**.



Dipolar cycloaddition can also be used to homologate alkenes. Osamu Tamura of Showa Pharmaceutical University found (*J. Org. Chem.* **2008**, *73*, 7164) that exposure of **19** to BF_3OEt_2 generated a species that added to the alkene **13** with high diastereocontrol, to give **20**. Gilles Dujardin of the Université du Maine combined (*Organic Lett*. **2008**, *10*, 4493) the acetylenic ester **22** with N-benzylhydroxylamine to give a dipole, that added to the alkene **21** to give **23**, establishing a quaternary center with high diastereocontrol.

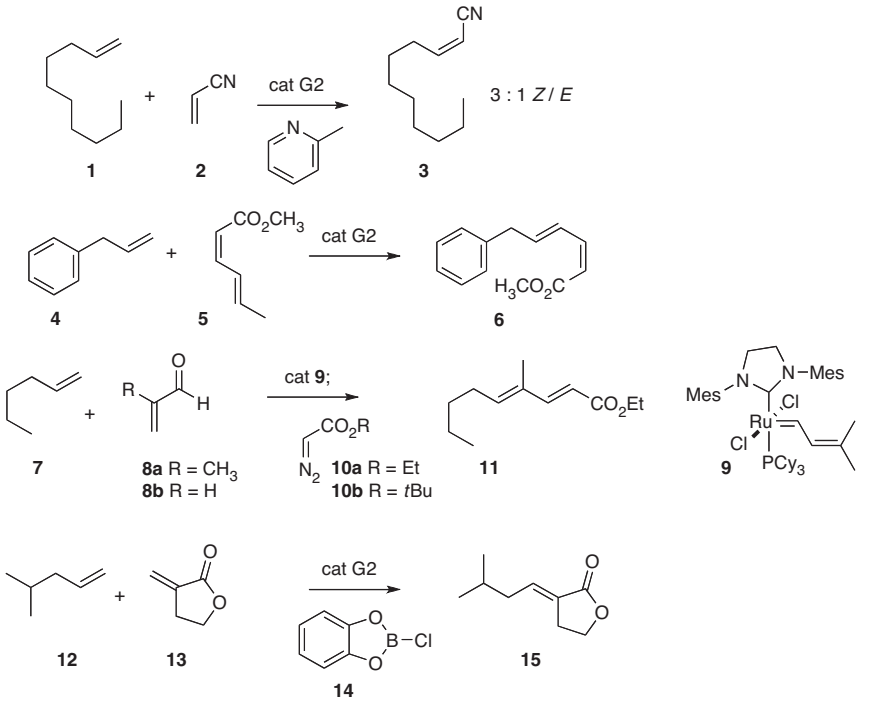
The Heck reaction has mostly been used with alkenes bearing electron-withdrawing groups, but in fact the intermediate aryl organopalladium species can insert into a wide variety of alkenes. Michèle David of the Université de Rennes1 took advantage(*Tetrahedron Lett.* **2008**, *49*, 6607) of this, adding the iodide **25** to the alkene **24**, to give **26**. DDQ oxidation of **26** gave the lactone Yangonin **27**, derived from the kava-kava root.



22. Developments in Alkene Metathesis

January 21, 2008

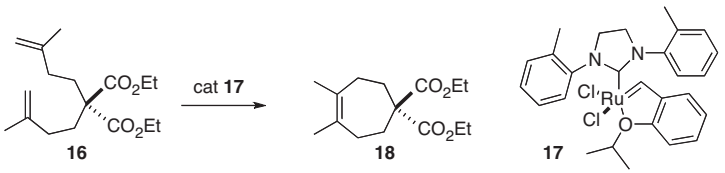
Alkene metathesis has been extended to increasingly complex starting materials and products. Nitriles are good donors to coordinatively-unsaturated transition metal centers, so tend to inhibit the reaction. Ren He of Dalian University of Technology has found (*Tetrahedron Lett*. **2007**, *48*, 4203) that inclusion of the loosely-coordinating 2-methyl pyridine in the reaction enables facile cross-coupling with acrylonitrile **2**. Although cross-coupling with (*Z*, *Z*)-sorbate is not efficient, Dennis P. Curran of the University of Pittsburgh has shown (*Organic Lett*. **2007**, *9*, 5) that cross-coupling with (*E*, *Z*)-sorbate **5** works well. For large scale work, he has developed a Hoveyda-type catalyst with a perfluoro tail, that is recoverable in 70% recrystallized yield from the reaction mixture. Shigefumi Kuwahara of Tohoku University has reported (*Tetrahedron Lett*. **2007**, *48*, 3163) a practical alternative for direct metathesis to deliver (*E*, *E*)-dienyl esters.



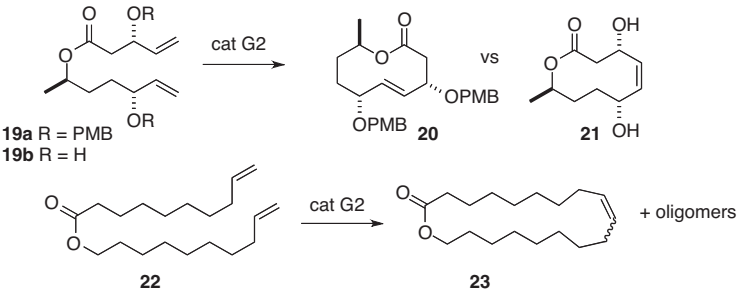
Continuing the investigation of tandem Ru-catalyzed reactions, Marc L. Snapper of Boston College effected (*Organic Lett*. **2007**, *9*, 1749) metathesis with methacrolein **8a**, then added Ph_3P and diazoacetate, to give the diene **11**. A range of common Ru catalysts worked well for this transformation. In an alternative approach to trisubstituted alkene

construction, Stellios Arseniyadis and Janine Cossy of ESPCI Paris have demonstrated (*Organic Lett*. **2007**, *9*, 1695) that inclusion of Cl-catecholborane **14** allows clean cross metathesis with the lactone **13**.

The construction of tetrasubstituted alkenes has been more challenging. Yann Schrodi of Materia, Inc. (*Organic Lett*. **2007**, *9*, 1589) has described a catalyst **17** that is particularly effective. Complex **17** was superior to a catalyst reported (*Organic Lett*. **2007**, *9*, 1339) shortly earlier by Robert H. Grubbs of Caltech.



Debendra K. Mohapatra of the National Chemical Laboratory, Pune, and Professor Grubbs, in a new approach to macrocyclic stereocontrol, have made (*Tetrahedron Lett*. **2007**, *48*, 2621) the remarkable observation that the cyclization of the bis ether **19a** gave **20** in a 9:1 *E* / *Z* ratio, while cyclization of the diol **9b** gave *only Z*-**21**. Oligomer formation can often compete in such medium ring-forming reactions. Deryn E. Fogg of the University of Ottawa has raised (*J. Am. Chem. Soc.* **2007**, *129*, 1024) the cautionary (but happy!) observation that while the cyclization, for instance, of **22** proceeded efficiently to give **23**, at an intermediate point in the transformation the product was more than half oligomer.

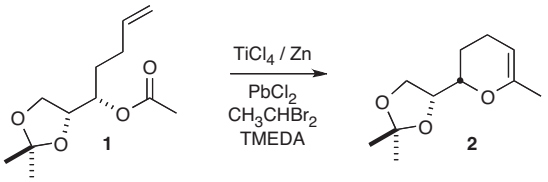


Removal of Ru residue at the end of the reaction is always an issue. Professor Grubbs has decribed (*Organic Lett*. **2007**, *9*, 1955) a PEG-based catalyst that is easy to separate from the metathesis products. Alternatively, Steven T. Diver of the University at Buffalo has shown (*Organic Lett*. **2007**, *9*, 1203) that workup of the reaction mixture from G1 or G2 with a polar isocyanide led to products having less than 5 ppm Ru.

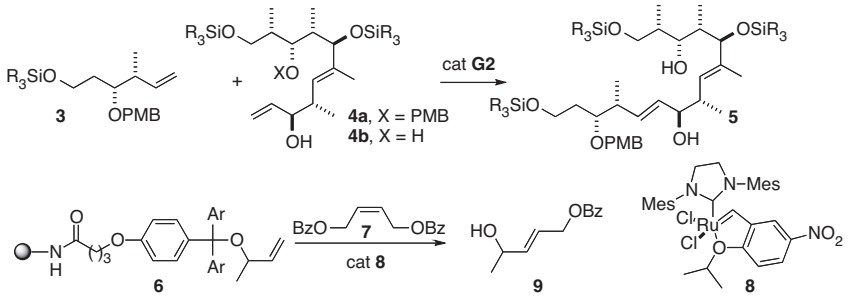
23. Developments in Alkene and Alkyne Metathesis

June 23, 2008

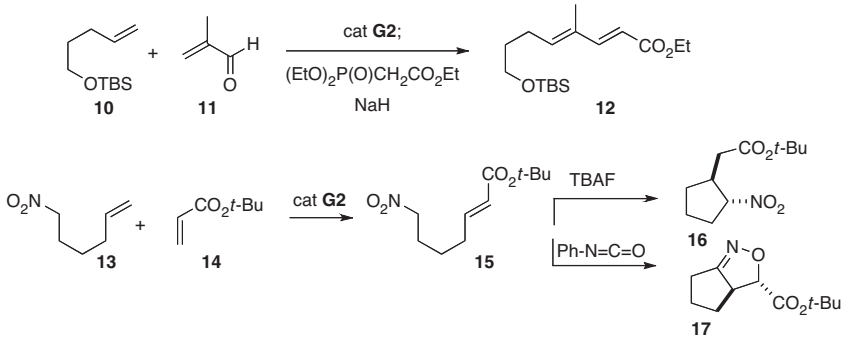
Jon D. Rainier of the University of Utah has put forward (*J. Am. Chem. Soc.* **2007**, *129*, 12604) an elegant alternative to Ru-catalyzed alkene metathesis, demonstrating that an ω-alkenyl ester such as **1** will cyclize to the enol ether **2** under Tebbe conditions.



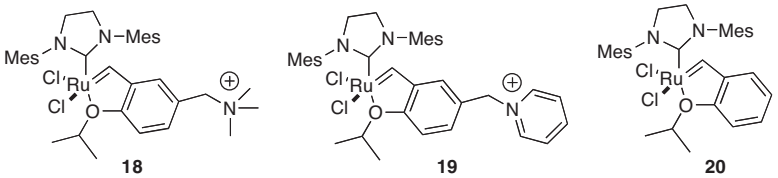
The particular reactivity of free alcohols in Ru-catalyzed alkene metathesis is underscored by the observation (*Tetrahedron Lett*. **2007**, *48*, 6905) by Javed Iqbal of Dr. Reddy's Laboratories, Ltd., Miyapur that attempted metathesis of the ether **4a** failed, but metathesis of the diol **4b** proceeded efficiently. Kazunori Koide of the University of Pittsburgh has demonstrated (*Organic Lett*. **2007**, *9*, 5235) that the yields of cross-metathesis with an alkenyl alcohol could be enhanced by binding it to a trityl resin. He observed that the Grela catalyst **8** was particularly effective in this application.



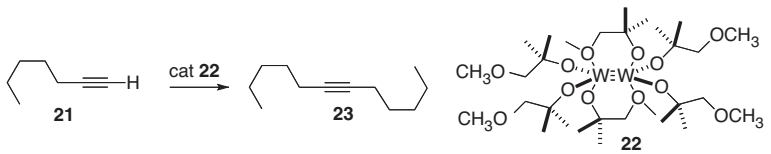
Residual Ru species do not interfere with some subsequent transformations. Rodrigo B. Andrade of Temple University has demonstrated (*Tetrahedron Lett*. **2007**, *48*, 5367) that metathesis with an α,β-unsaturated aldehyde such as **11** can be followed directly by phosphonate condensation to give the doubly-homologated product **12**. Philip J. Parsons of the University of Sussex has found (*Organic Lett*. **2007**, *9*, 2613) that the nitro functional group is compatible with the Ru catalyst. The product nitro alkene **15** could be cyclized (intramolecular Michael addition) to the cyclopentane **16**, or (intramolecular dipolar cycloaddition) to the cyclopentane **17**.



There has been much interest in carrying out the several alkene metathesis transformations (cross metathesis, ring closing metathesis, ring-opening metathesis polymerization) in water. Robert H. Grubbs of the California Institute of Technology has designed (*Angew. Chem. Int. Ed.* **2007**, *46*, 5152) the ammonium salt **18** for this purpose, and Karol Grela of the Polish Academy of Sciences in Warsaw and Marc Mauduit of ENSC Rennes have jointly(*Chem. Commun.* **2007**, 3771) put forward the pyridinium salt **19**. Remarkably, Ronald T. Raines of the University of Wisconsin has shown (*Organic Lett*. **2007**, *9*, 4885) that the Hoveyda catalyst **20** is sufficiently stable in aqueous acetone and aqueous DME to function efficiently.



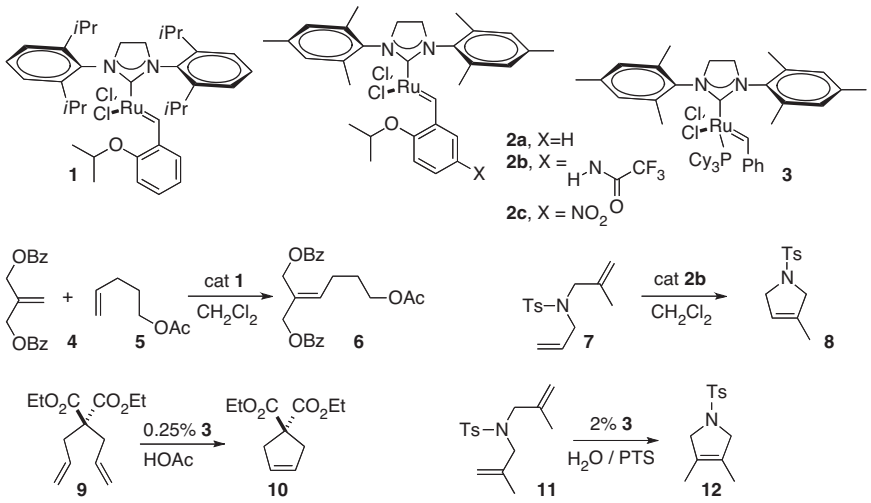
Although alkyne metathesis is now well developed as a synthetic method, it has been limited to internal alkynes. For this reason, methyl alkynes are often specially prepared to set the stage for C-C triple bond formation by metathesis. André Mortreux of ENSC-Lille has now designed (*Adv. Synth. Cat.* **2007**, *349*, 2259) a binuclear catalyst **22** that works well with *terminal* alkynes such as **21**. What remains to be determined is the functional group compatibility of **22**.



24. Advances in Alkene and Alkyne Metathesis

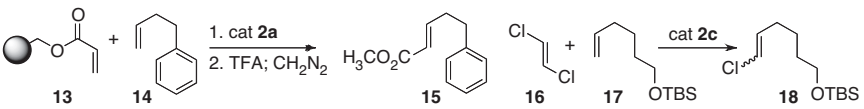
January 12, 2009

As alkene metathesis is extended to more and more challenging substrates, improved catalysts and solvents are required. Robert H. Grubbs of Caltech developed (*Organic Lett*. **2008**, *10*, 441) the diisopropyl complex **1**, that efficiently formed the trisubstituted alkene **6** by cross metathesis of **4** with **5**. Hervé Clavier and Stephen P. Nolan of ICIQ, Tarragona, and Marc Mauduit of ENSC Rennes found (*J. Org. Chem*. **2008**, *73,* 4225) that after cyclization of **7** with the complex **2b**, simple filtration of the reaction mixture through silica gel delivered the product **8** containing only 5.5 ppm Ru.

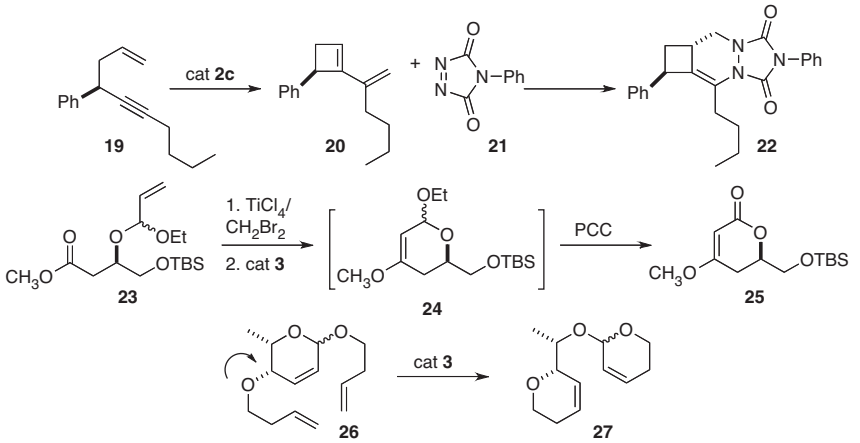


The merit of CH_2Cl_2 as a solvent for alkene metathesis is that the catalysts (e.g. **1**-**3**) are very stable. Claire S. Adjiman of Imperial College and Paul C. Taylor of the University of Warwick established (*Chem. Commun.* **2008**, 2806) that although the second generation Grubbs catalyst **3** is not as stable in acetic acid, for the cyclization of **9** to **10** it is a much more active catalyst in acetic acid than in CH_2Cl_2. Bruce H. Lipshutz of the University of California, Santa Barbara observed (*Adv. Synth. Cat*. **2008**, *350*, 953) that even water could serve as the reaction solvent for the challenging cyclization of **11** to **12**, so long as the solubility-enhancing amphiphile PTS was included.

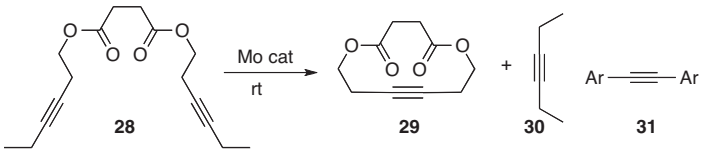
Ernesto G. Mata of the Universidad Nacional de Rosario explored (*J. Org. Chem.* **2008**, *73*, 2024) resin isolation to optimize cross-metathesis, finding that the acrylate **13** worked particularly well. Karol Grela of the Polish Academy of Sciences, Warsaw optimized (*Chem. Commun.* **2008**, 2468) cross-metathesis with a halogenated alkene **16**.



Jean-Marc Campagne of ENSC Montpellier extended (*J. Am. Chem. Soc.* **2008**, *130*, 1562) ring-closing metathesis to enynes such as **19**. The product diene **20** was a reactive Diels-Alder dienophile. István E. Markó of the Université Catholique de Louvain applied (*Tetrahedron Lett*. **2008**, *49*, 1523) the known (OHL 20070122) ring-closing metathesis of enol ethers to the cyclization of the Tebbe product from **23**. The ether **24** was oxidized directly to the lactone **25**. Jacques Eustache of the Université de Haute-Alsace observed (*Tetrahedron Lett*. **2008**, *49*, 1192) that ring-opening/ring-closing metathesis proceeded efficiently with **26**, but not with the ether epimeric at the indicated position.



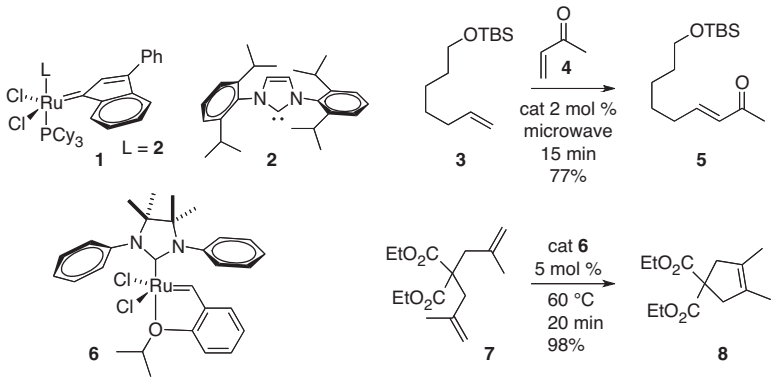
Jeffrey S. Moore of the University of Illinois prepared (*J. Org. Chem*. **2008**, *73,* 4256) a Mo alkyne metathesis catalyst on fumed silica gel that converted **28** to **29** at room temperature. The cyclization was driven by the vacuum removal of 3-hexyne **30**. In the same paper, Professor Moore used the insolubility of a product diaryl alkyne **31** to drive other cyclizations.



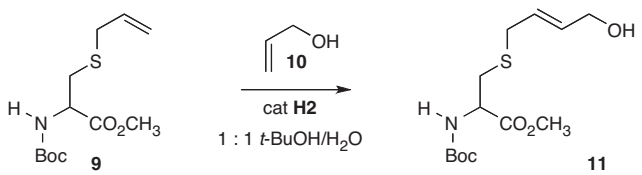
25. Developments in Alkene Metathesis

June 15, 2009

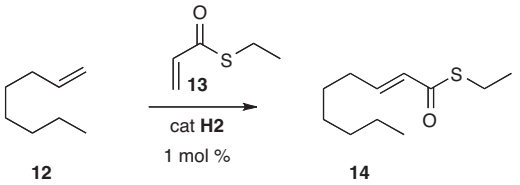
Hervé Clavier and Steven P. Nolan, now at St. Andrew's University, found (*Adv. Synth. Cat.* **2008**, *350*, 2959) that the indenylidene Ru complex **1** was an excellent pre-catalyst for alkene metathesis. A combination of **1** and the ligand **2** effected cross metathesis of **3** and **4** in just 15 minutes under microwave heating. Robert H. Grubbs of Caltech designed (*Organic Lett*. **2008**, *10*, 2693) the Ru catalyst **6** for the preparation of tri- and tetrasubstituted alkenes, as illustrated by the conversion of **7** to **8**. The catalyst **6** also worked well for cross metathesis and ring opening metathesis polymerization (ROMP).



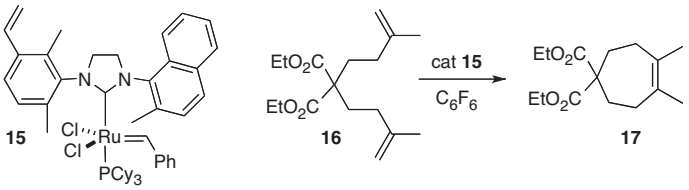
For some biological applications, it would be desirable to run alkene cross metathesis under aqueous conditions. Benjamin G. Davis of the University of Oxford observed (*J. Am. Chem. Soc.* **2008**, *130*, 9642) that allyl sulfides such as **9** were unusually reactive in cross metathesis. Indeed, aqueous cross methathesis with such an allyl sulfide incorporated in a protein worked well, although added $MgCl_2$ was required. The protein, a serine protease, maintained its activity after cross metathesis.



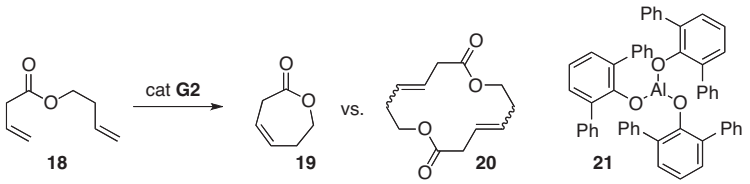
α,β-Unsaturated thioesters such as **14** are excellent substrates for, inter alia, enantioselective Cu-catalyzed conjugate addition of Grignard reagents. Adriaan J. Minnaard and Ben L. Feringa of the University of Groningen found (*J. Org. Chem.* **2008**, *73*, 5651) that the thioacrylate **13** was an excellent substrate for cross methathesis, allowing ready preparation of **14**.



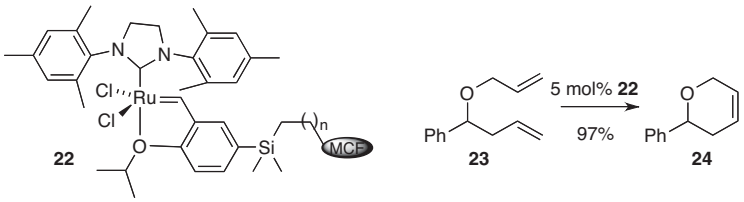
Although alkene metathesis is often run in CH_2Cl_2, benzene or toluene, these are not necessarily the optimal solvents. Siegfried Blechert of the TU Berlin established (*Tetrahedron Lett.* **2008**, *49*, 5968) that for the difficult cyclization of **16** to **17**, hexafluorobenzene worked particularly well.



The extended conformation (illustrated for **18**) of an ester is more stable than the lactone conformation by about 5 kcal/mol. It is therefore not surprising that SonBinh T. Nguyen of Northwestern University observed (*Organic Lett*. **2008**, *10*, 5613) that attempted ring-closing metathesis of **18** gave only the dimer **20**. On addition of the bulky Lewis acid **21**, which can complex **18** in the lactone conformation, the reaction delivered the desired monomer **19**. This should be a generally useful strategy for the cyclization of difficult ester substrates.



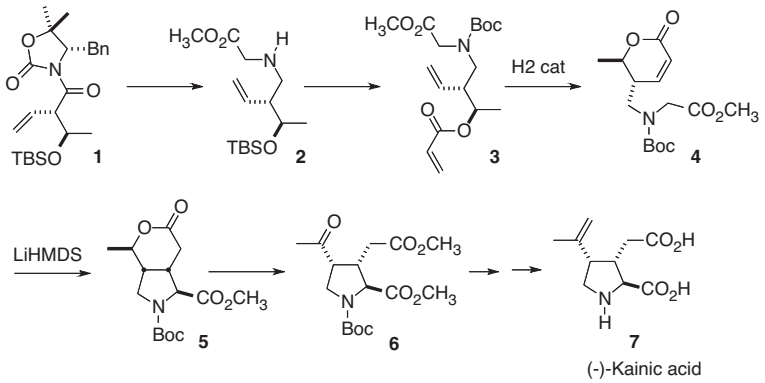
Su Seong Lee and Jackie Y. Ying of the Institute of Bioengineering and Nanotechnology, Singapore, constructed (*Chem. Commun.* **2008**, 4312) the metathesis catalyst **22**, covalently bound to siliceous mesocellular foam. At 5% catalyst loading, the tenth cycle for the cyclization of **23** to **24** gave the same yield as the first cycle, 97%. Ru residues in solution were only 5-8 ppm.



26. Alkene Metathesis: Synthesis of Kainic Acid, Pladienolide B and Amphidinolide Y

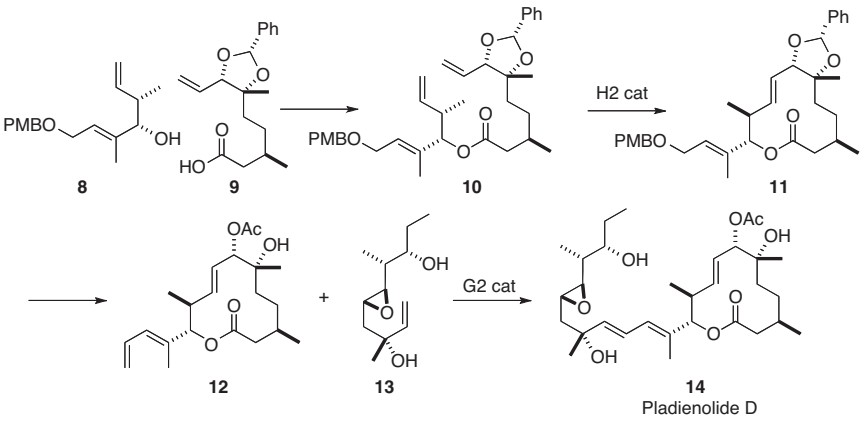
January 28, 2008

As alkene metathesis has developed into one of the tools of organic synthesis, many practical questions have arisen. In the course of a synthesis (*Organic Lett*. **2007**, *9*, 1635) of the important neuropharmacological tool (-)-kainic acid **7**, Tohru Fukuyama of the University of Tokyo prepared the key intermediate **1** by chiral auxiliary mediated coupling of crotonyl chloride with acetadehyde. Dibal reduction gave the hemiaminal, which underwent reductive amination with glycine methyl ester, leading to the alkene **2**. Alkene metathesis of the derived ester **3** to form the unsaturated lactone **4** was then examined in detail. It was found that 0.5 mol % of the second generation Hoveyda catalyst was sufficient to cyclize **3** to **4** in 92% yield. With 0.8 mol %, the yield was 99%. The key to the efficacy of this cyclization was the use of 1,2-dichloroethane at reflux as the reaction solvent.

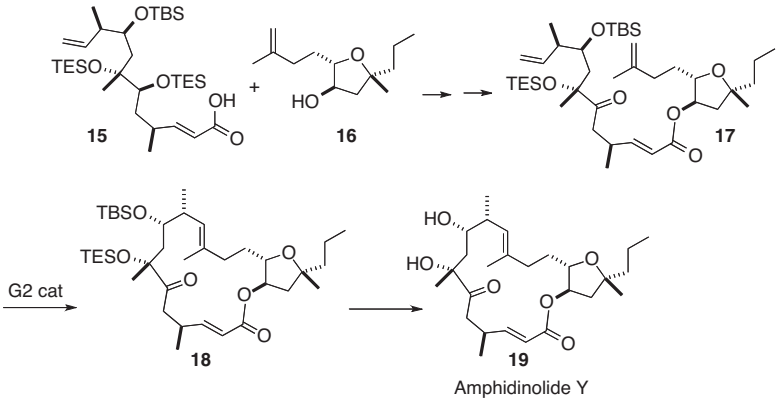


The macrolide pladienolide D **14** induces in vivo tumor regression in several human cancer xenograft models. This activity was important enough that a team at Esai Co., Ltd in Tsukuba headed by Yoshihiko Kotake undertook the total synthesis (*Angew. Chem. Int. Ed.* **2007**, *46*, 4350). Their approach used two alkene metathesis steps. To prepare the substrate for the macrolide construction, the alcohol **8** and the acid **9**, each prepared by chiral auxiliary control, were coupled to give the ester **10**. An extensive investigation led to alkene metathesis conditions that were satisfactory, the use of the second generation Hoveyda catalyst in refluxing toluene. A significant competing side reaction was the migration of the monosubstituted alkene of **10** to make the alkenyl ether.

The second alkene metathesis step was the coupling of **12** with **13**. The most effective catalyst in this case was the second generation Grubbs. Note that the free alcohol **13** participated successfully in the cross-coupling. According to the authors, this is one of just a few examples of successful cross coupling of an alkene adjacent to a quaternary center.



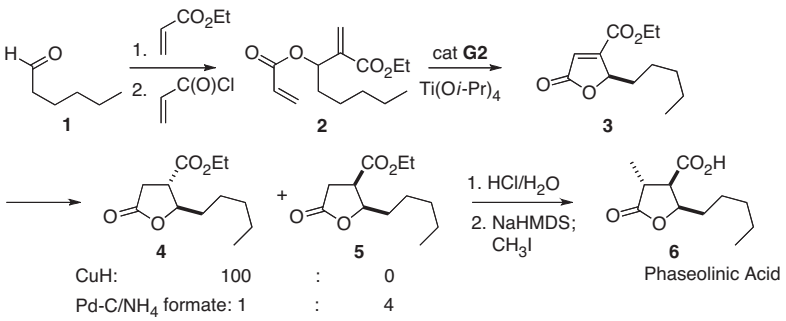
The stereocontrolled construction of trisubstituted alkenes by metathesis is a particular challenge. In his synthesis (*Organic Lett.* **2007**, *9*, 2585) of amphidinolide Y **21**, a modestly cytotoxic macrolide antibiotic, Wei-Min Dai of Zhejian University and the Hong Kong University of Science and Technology took up this challenge. The substrate for cyclization was prepared by coupling the acid **15** with the alcohol **16**, followed by selective deprotection and oxidation. Medium-ring conformational effects played an important role in this metathesis. The cyclization was also attempted with the TES ethers of the two diastereomeric secondary alcohols corresponding to the ketone of **17**. One of those diastereomers cyclized modestly well. The other diastereomer did not cyclize at all.



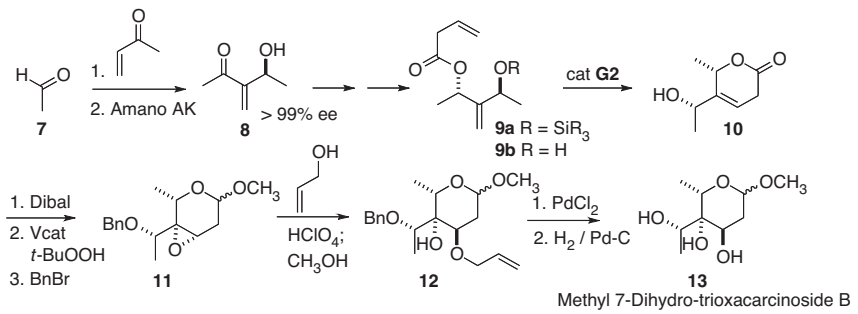
27. Alkene and Alkyne Metathesis: Phaseolinic Acid (Selvakumar), Methyl 7-Dihydro-trioxacarcinoside B (Koert), Arglabin (Reiser) and Amphidinolide V (Fürstner)

June 30, 2008

As N. Selvakumar of Dr. Reddy's Laboratories, Ltd., Hyderabad approached (*Tetrahedron Lett*. **2007**, *48*, 2021) the synthesis of phaseolinic acid **6**, there was some concern about the projected cyclization of **2** to **3**, as this would involve the coupling of two electron-deficient alkenes. In fact, the Ru-mediated ring-closing metathesis proceeded efficiently. The product unsaturated lactone **3** could be reduced selectively to either the trans product **4** or the cis product **5**.

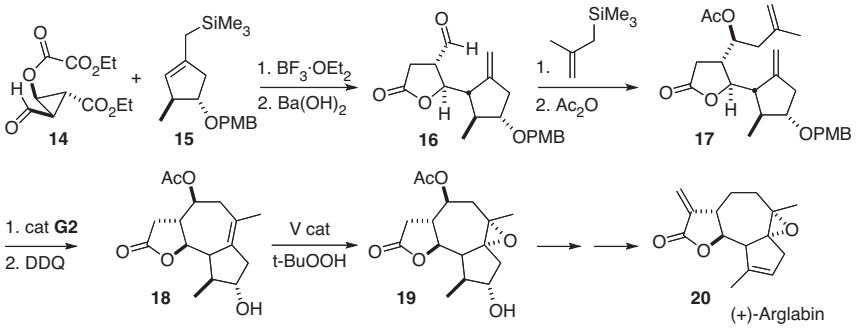


There has been relatively little work on the synthesis of the higher branched sugars, such as the octalose **13**, a component of several natural products. The synthesis of **13** (*Organic Lett*. **2007**, *9*, 4777) by Ulrich Koert of the Philipps-University Marburg also began with a Baylis-Hillman product, the easily-resolved secondary alcohol **8**. As had been observed in other contexts, cyclization of the protected allylic alcohol **9a** failed, but cyclization of the

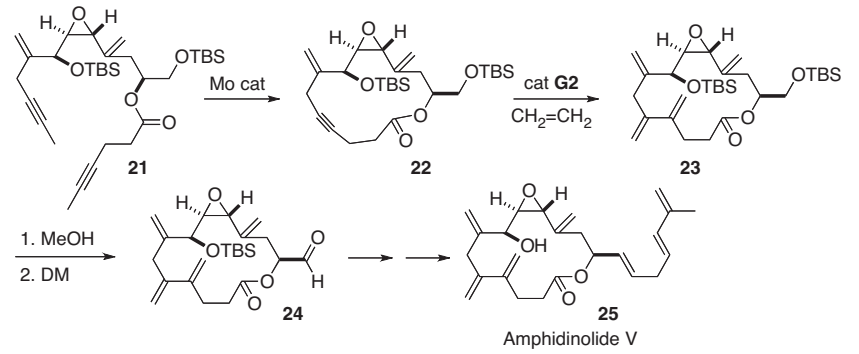


free alcohol **9b** proceeded smoothly. V-directed epoxidation then set the relative configuration of the stereogenic centers on the ring.

Ring-closing metathesis to construct tetrasubstituted alkenes has been a challenge, and specially-designed Ru complexes have been put forward specifically for this transformation. Oliver Reiser of the Universität Regensburg was pleased to observe (*Angew. Chem. Int. Ed.* **2007**, *46*, 6361) that the second-generation Grubbs catalyst itself worked well for the cyclization of **17** to **18**. Again in this synthesis, catalytic V was used to direct the relative configuration of the epoxide.



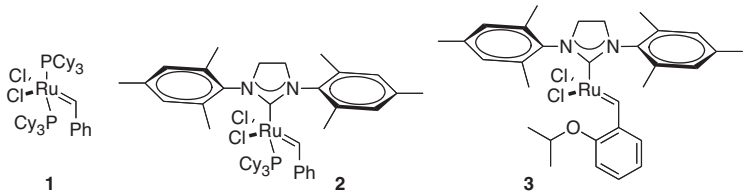
Intramolecular alkyne metathesis is now well-established as a robust and useful method for organic synthesis. It was also known that Ru-mediated metathesis of an alkyne with ethylene could lead to the diene. The question facing (*Angew. Chem. Int. Ed.* **2007**, *46*, 5545) Alois Fürstner of the Max-Planck-Institut, Mülheim was whether these transformations could be carried out on the very delicate epoxy alkene **21**. In fact, the transformations of **21** to **22** and of **22** to **23** proceeded well, setting the stage for the total synthesis of Amphidinolide V **25**.



28. Alkene Metathesis: Synthesis of Panaxytriol (Lee), Isofagomine (Imahori and Takahata), Elatol (Stoltz), 5-F_{2t}-Isoprostane (Snapper), and Ottelione B (Clive)

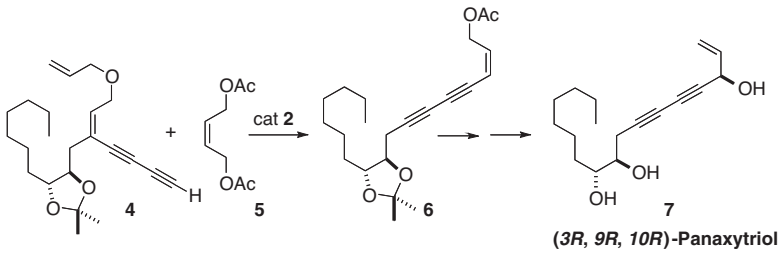
January 19, 2009

Alkene metathesis has been used to prepare more and more challenging natural products. The first and second generation Grubbs catalysts **1** and **2** and the Hoveyda catalyst **3** are the most widely used.



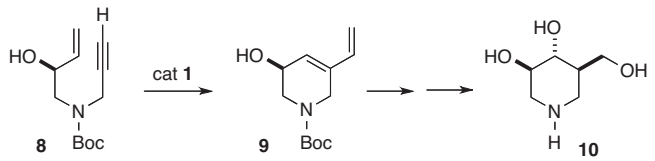
1 **2** **3**

Daesung Lee of the University of Illinois at Chicago designed (*Organic Lett.* **2008**, *10*, 257) a clever chain-walking cross metathesis, combining **4** and **5** to make **6**. The diyne **3** was carried on (*3R*, *9R*, *10R*)-Panaxytriol **7**.



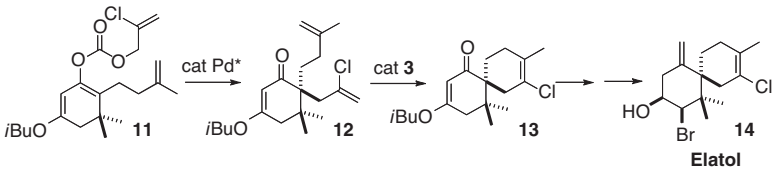
(*3R*, *9R*, *10R*)-Panaxytriol

Tatsushi Imahori and Hiroki Takahata of Tohoku Pharmaceutical University found (*Tetrahedron Lett*. **2008**, *49*, 265) that of the several derivatives investigated, the unprotected alcohol **8** cyclized most efficiently. Selective cleavage of the monosubstituted alkene followed by hydroboration delivered the alkaloid Isofagomine **10**.

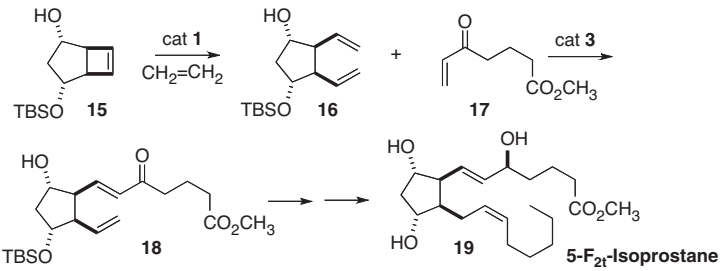


Isofagomine

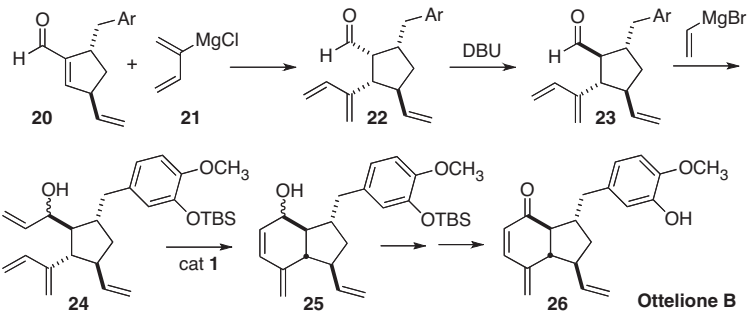
Brian M. Stoltz of Caltech established (*J. Am. Chem. Soc.* **2008**, *130*, 810) the absolute configuration of the halogenated chamigrene Elatol **14** using the enantioselective enolate allylation that he had previously devised. A key feature of this synthesis was the stereocontrolled preparation of the cis bromohydrin.



Marc L. Snapper of Boston College opened (*J. Org. Chem.* **2008**, *73*, 3754) the strained cyclobutene **15** with ethylene to give the diene **16**. Remarkably, cross metathesis with **17** delivered **18** with high regioselectivity, setting the stage for the preparation of the 5-F_{2t}-Isoprostane **19**.



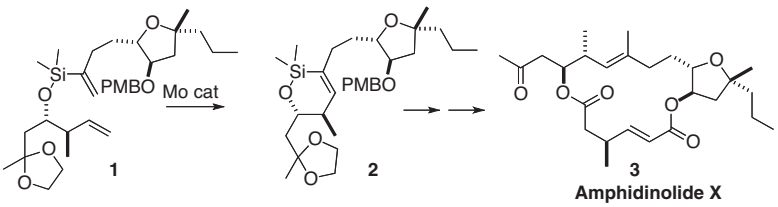
Derrick L. J. Clive of the University of Alberta assembled (*J. Org. Chem.* **2008**, *73*, 3078) Ottelione B **26** from the enantiomerically-pure aldehyde **20**. Conjugate addition of the Grignard reagent **21** derived from chloroprene gave the kinetic product **22**, that was equilibrated to the more stable **23**. Addition of vinyl Grignard followed by selective ring-closing metathesis then led to **26**.



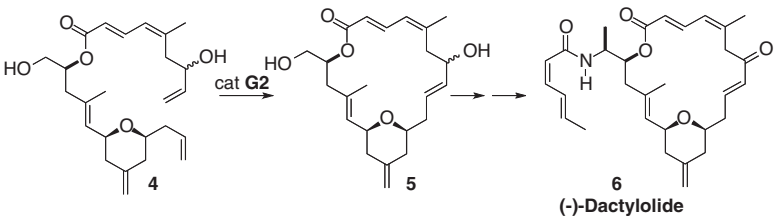
29. Total Synthesis by Alkene Metathesis: Amphidinolide X (Urpí/Vilarrasa), Dactylolide (Jennings), Cytotrienin A (Hayashi), Lepadin B (Charette), Blumiolide C (Altmann)

June 22, 2009

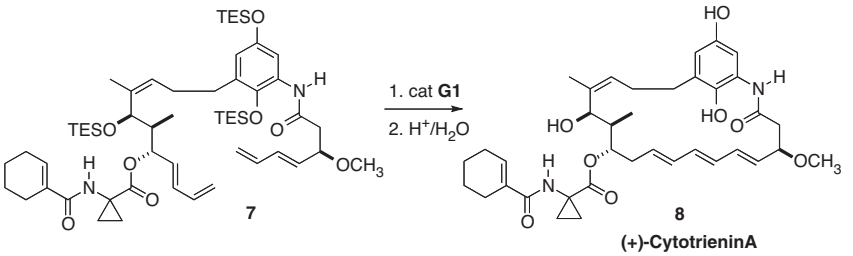
To assemble the framework of the cytotoxic macrolide Amphidinolide X **3**, Fèlix Urpí and Jaume Vilarrasa of the Universitat de Barcelona devised (*Organic Lett*. **2008**, *10*, 5191) the ring-closing metathesis of the alkenyl silane **1**. No Ru catalyst was effective, but the Schrock Mo catalyst worked well.



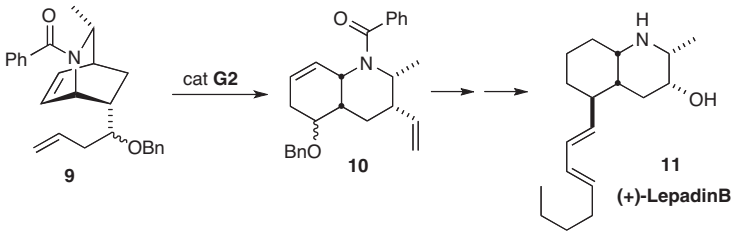
In the course of a synthesis of (-)-Dactylolide **6**, Michael P. Jennings of the University of Alabama offered (*J. Org. Chem.* **2008**, *73*, 5965) a timely reminder of the particular reactivity of allylic alcohols in ring-closing metathesis. The cyclization of **4** to **5** proceeded smoothly, but attempted ring closing of the corresponding bis silyl ether failed.



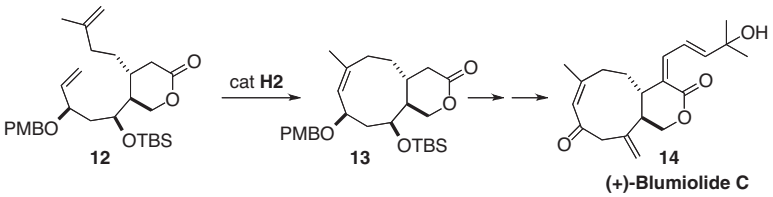
Polyenes such as (+)-Cytotrienin A **8** are notoriously unstable. It is remarkable that Yujiro Hayashi of the Tokyo University of Science could (*Angew. Chem. Int. Ed.* **2008**, *47*, 6657) assemble the triene of **8** by the ring-closing metathesis of the highly functionalized precursor **7**.



Bicyclo [2.2.2] structures such as **9** are readily available by the addition of, in this case, methyl acrylate to an enantiomerically-pure 2-methylated dihydropyridine. André B. Charette of the Université de Montréal found (*J. Am. Chem. Soc.* **2008**, *130*, 13873) that **9** responded well to ring-opening/ring-closing metathesis, to give the octahydroquinoline **10**. Functional group manipulation converted **10** into the *Clavelina* alkaloid (+)-Lepadin B **11**.



The construction of trisubstituted alkenes by ring-closing metathesis can be difficult, and medium rings with their transannular strain are notoriously challenging to form. Nevertheless, Karl-Heinz Altmann of the ETH Zürich was able (*Angew. Chem. Int. Ed.* **2008**, *47*, 10081), using the **H2** catalyst, to cyclize **12** to cyclononene **13**, the precursor to the *Xenia* lactone (+)-Blumiolide C **14**.



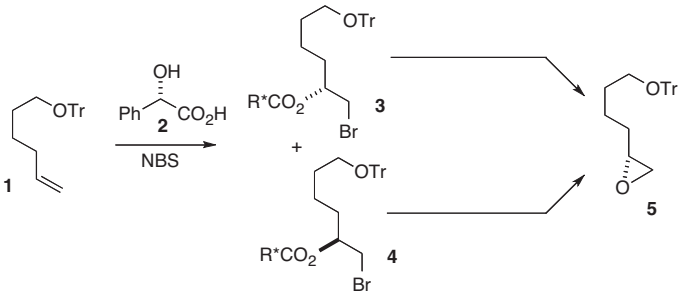
It is noteworthy that these five syntheses used four different metathesis catalysts in the key alkene forming step. For the cyclization of **7**, the use of the Grubbs first generation catalyst **G1**, that couples terminal alkenes but tends not to interact with internal alkenes, was probably critical to success. The Hoveyda catalyst **H2** is more expensive than the Grubbs second generation catalyst **G2**, but can often be effective in applications in which **G2** is sluggish. The Schrock Mo catalyst is less user friendly than the (relatively) air and moisture stable Ru catalysts, but is very reactive.

30. Enantioselective Assembly of Oxygenated Stereogenic Centers

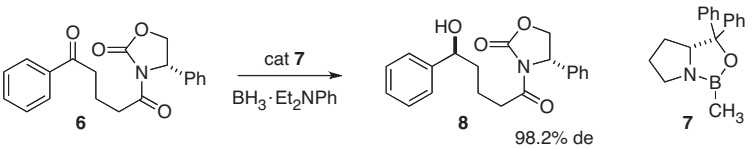
February 11, 2008

Reaction with an enantiomerically-pure epoxide is an efficient way to construct a molecule incorporating an enantiomerically-pure oxygenated stereogenic center. The Jacobsen hydrolytic resolution has made such enantiomerically-pure epoxides readily available from the corresponding racemates. Christopher Jones and Marcus Weck of the Georgia Institute of Technology have now (*J. Am. Chem. Soc.* **2007**, *129*, 1105) developed an oligomeric salen complex that effects the enantioselective hydrolysis at remarkably low catalyst loading.

Any such approach depends on monitoring the progress of the hydrolysis, usually by chiral GC or HPLC. In a complementary approach, we (*J. Org. Chem.* **2007**, *72*, 431) have found that on exposure to NBS and the inexpensive mandelic acid **2**, a terminal alkene such as **1** was converted into the two bromomandelates **3** and **4**. These were readily separated by column chromatography. Individually, **3** and **4** can each be carried on the same enantiomer of the epoxide **5**. As **3** and **4** are directly enantiomerically pure, epoxide **5** of high ee can be prepared reliably without intermediate monitoring by chiral GC or HPLC.

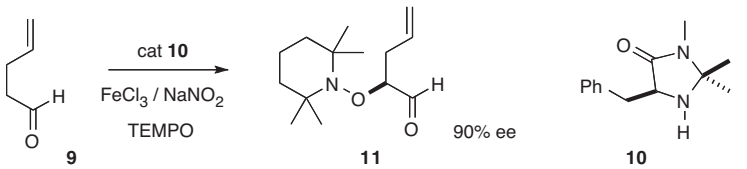


Another way to incorporate an enantiomerically-pure oxygenated stereogenic center into a molecule is the enantioface-selective addition of hydride to a ketone such as **6**. Alain Burgos and his team at PPG-SIPSY in France have described (*Tetrahedron Lett*. **2007**, *48*, 2123) a $NaBH_4$-based protocol for taking the Itsuno-Corey reduction to industrial scale.

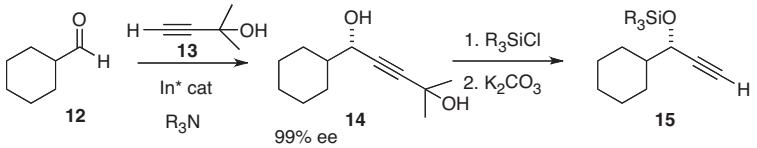


In the past, aldehydes have been efficiently α-oxygenated using two-electron chemistry. Mukund P. Sibi of North Dakota State University has recently (*J. Am. Chem. Soc.* **2007**, *129*, 4124) described a novel one-electron alternative. The organocatalyst **10** formed an

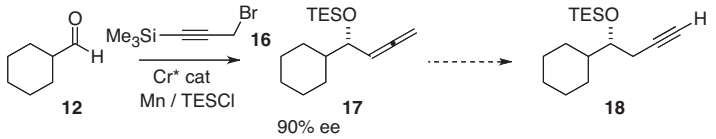
imine with the aldehyde. One-electron oxidation led to an α-radical, which was trapped by the stable free radical TEMPO to give, after hydrolysis, the α-oxygenated aldehyde **11**.



High ee oxygenated secondary centers can also be prepared by homologation of aldehydes. Optimization of the enantioselective addition of the inexpensive acetylene surrogate **13** was recently reported (*Chem. Commun.* **2007**, 948) by Masakatsu Shibasaki of the University of Tokyo. Note that the free alcohol of **13** does not need to be protected.



A protocol for enantioselective allenylation was recently developed (*J. Am. Chem. Soc.* **2007**, *129*, 496) by Hisashi Yamamoto of the University of Chicago. The conversion of **17** to **18** should be straightforward, leading to net enantioselective propargylation.

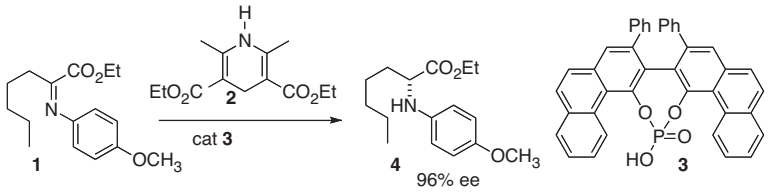


The enantioselective homologation of ketones, in particular methyl ketones, can also be accomplished. In this procedure described (*J. Am. Chem. Soc.* **2007**, *129*, 7439) by Professor Shibasaki and Motomu Kanai, also of the University of Tokyo, the alkyl group from the Zn was incorporated into the product. Alternative dialkyl zincs worked as well.

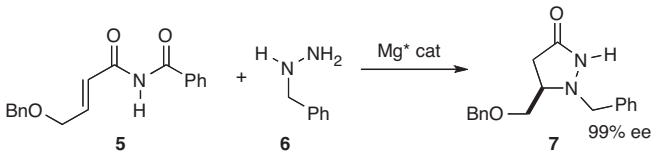
31. Enantioselective Assembly of Aminated Stereogenic Centers

February 18, 2008

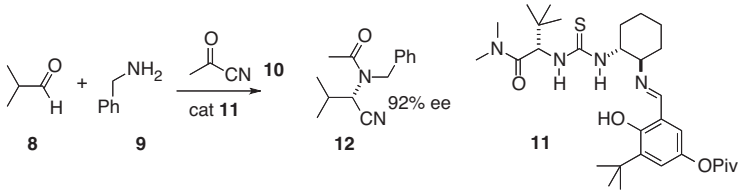
Although natural amino acids are readily available, there is a continuing need for unnatural amino acids. Jon C. Antilla of the University of South Florida has described (*J. Am. Chem. Soc.* **2007**, *129*, 5830) a promising approach, based on the enantioselective organocatalytic reduction of imines such as **1** derived from α-keto esters. The aryl group is easily removed to give the primary amine.



Mukund P. Sibi of North Dakota State University has developed (*J. Am. Chem. Soc.* **2007**, *129*, 4522) an enantioselective Mg catalyst that mediated the addition of benzyl hydrazine **6** to imides such as **5**. The initial adduct cyclized to the pyrazolidinone **7**. Karl Anker Jørgensen of Aarhus University has reported (*Angew. Chem. Int. Ed.* **2007**, *46*, 1983) a complementary protocol for the enantioselective conjugate addition of a nitrogen nucleophile.

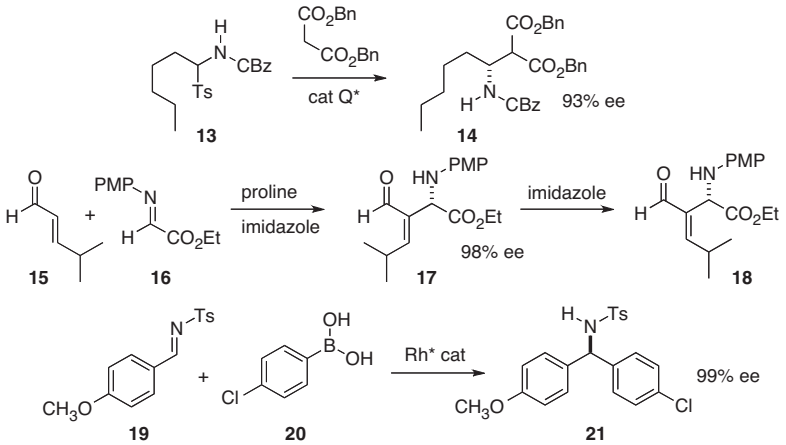


Enantioselective homologation can also be a powerful approach. Benjamin List of the Max-Planck-Institute, Mülheim has found (*Angew. Chem. Int. Ed.* **2007**, *46*, 612; *Organic Lett*. **2007**, *9*, 1149) that three-component coupling of acetyl cyanide, an aldehyde and benzylamine under the influence of the Jacobsen thiourea catalyst **10** delivered the one-carbon homologated nitrile **12** in high ee.

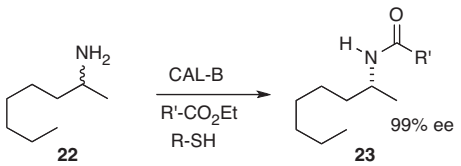


Other homologation methods are also effective. Li Deng of Brandeis University has shown (*Organic Lett*. **2007**, *9*, 603) that under the influence of cinchona-derived quaternary

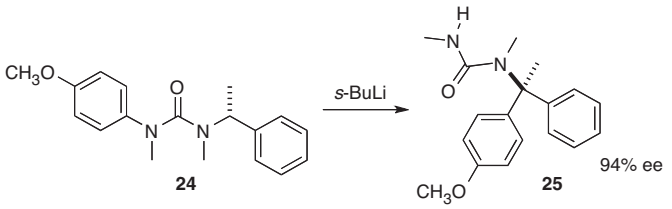
salts, malonates will add to racemic amido sulfones such as **13** to give the β-amino malonate **14** in high ee. Fujie Tanaka and Carlos F. Barbas III of Scripps/La Jolla have found (*Angew. Chem. Int. Ed.* **2007**, *46*, 1878) that the simple organocatalyst proline will mediate the aza-Baylis Hillman addition of an unsaturated aldehyde such as **15** to **16** in high ee. The alkene **17** is the kinetic product. On prolonged exposure to the reaction conditions, **17** was equilibrated to the more stable **18**. Ming-Hua Xu and Guo-Qiang Lin of the Shanghai Institute of Organic Chemistry have established (*J. Am. Chem. Soc.* **2007**, *129*, 5336) a robust protocol for the enantioselective assembly of -arylated benzylamines such as **21**.



Other routes to enantiomerically-pure amines have been put forward. Knowing that CAL-B would selectively acylate just the *R* enantiomer of the racemic α-methyl primary amine **22**, Stéphane Gastaldi, Gérard Gil and Michèle P. Bertrand of the Université Paul Cézanne devised (*Organic Lett*. **2007**, *9*, 837) a thiyl-based method for equilibrating **22**, leading to a net deracemizing acylation.



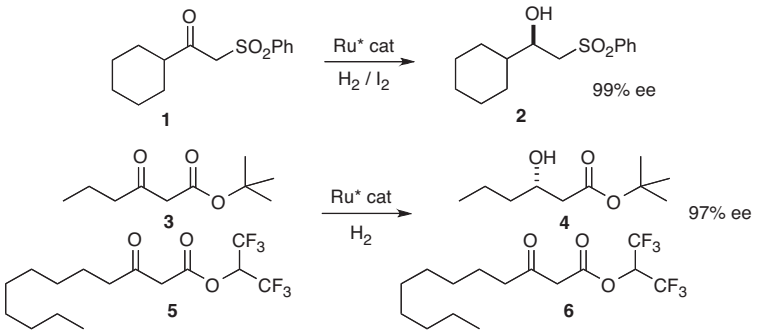
Jonathan Clayden of the University of Manchester has uncovered (*J. Am. Chem. Soc.* **2007**, *129*, 7488) a powerful enantioselective route to bis-α-aryl amines such as **25**. It is remarkable that the deprotonation and subsequent rearrangement of **24** proceeded with such high enantiocontrol.



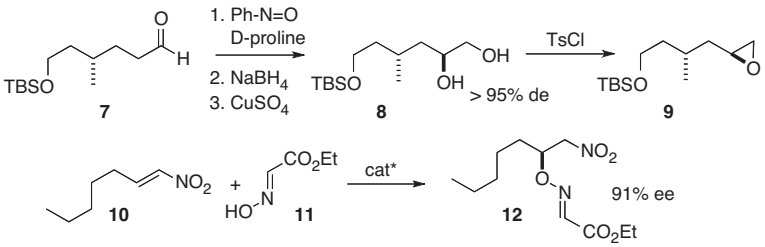
32. Enantioselective Preparation of Secondary Alcohols and Amines

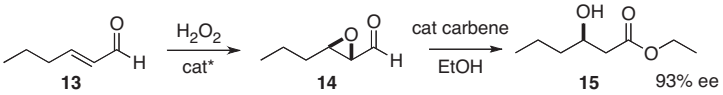
July 28, 2008

Secondary alcohols can be prepared in high enantiomeric excess by catalytic hydrogenation of ketones. Zhaoguo Zhang of Shanghai Jiaotong University has established (*Organic Lett*. **2007**, *9*, 5613) that β-keto sulfones such as **1** are suitable substrates for this hydrogenation. Reinhard Brückner of the Universität Freiburg has demonstrated (*Angew. Chem. Int. Ed.* **2007**, *46*, 6537) that the rate of hydrogenation of β-keto esters such as **3** and **5** depends on the alcohol from which the ester is derived, so **3** can be reduced to **4** in the presence of **5**.

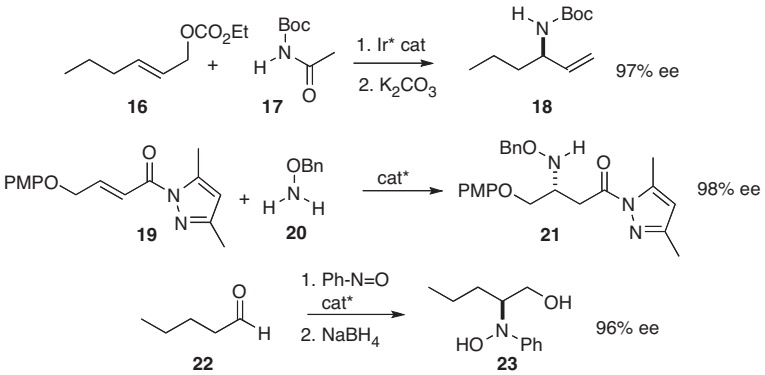


Enantiomerically-pure secondary alcohols and amines can also be prepared by adding an oxygen or a nitrogen to an existing carbon skeleton. Both Srivari Chandrasekhar of the Indian Institute of Chemical Technology, Hyderabad (*Tetrahedron Lett.* **2007**, *48*, 7339) and Arumugam Sudalai of the National Chemical Laboratory, Pune (*Tetrahedron Lett.* **2007**, *48*, 8544) have taken advantage of the previously-described enantioselective α-aminoxylation of aldehydes to establish what appears to be a robust preparative route to the enantiomerically-pure epoxides such as **9** of terminal alkenes. Karl Anker Jørgensen of Aarhus University has developed (*Chem. Commun.* **2007**, 3646) a catalyst for the enantioselective addition of **11** to nitroalkenes such as **10**. Armando Córdova of Stockholm University has shown (*Tetrahedron Lett.* **2007**, *48*, 5976) that epoxy aldehydes such as **14**, easily prepared by the protocol he developed, are converted by the Bode catalyst to β-hydroxy esters such as **15**.

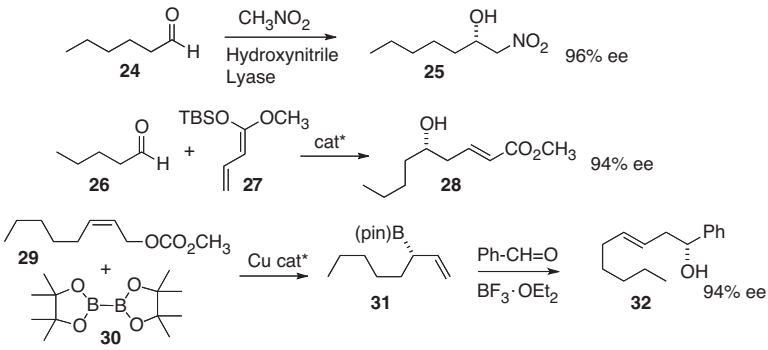




Hyunsoo Han of the University of Texas, San Antonio has described (*Tetrahedron Lett.* **2007**, *48*, 7094) an improved protocol for the enantioselective conversion of primary allylic carbonates **16** to secondary amines **17**. René Peters of ETH Zurich has used (*Angew. Chem. Int. Ed.* **2007**, *46*, 7704) a related procedure for the construction of aminated quaternary centers. Mukund P. Sibi of North Dakota State University has devised (*J. Am. Chem. Soc.* **2007**, *129*, 8064) a catalyst for the conjugate addition of the benzyloxyamine **20** to acyl pyrazoles, and Claudio Palomo of the Universidad de País Vasco has found (*Angew. Chem. Int. Ed.* **2007**, *46*, 8054) that a simple diphenyl prolinol catalyst will effect enantioselective α-amination of aldehydes.



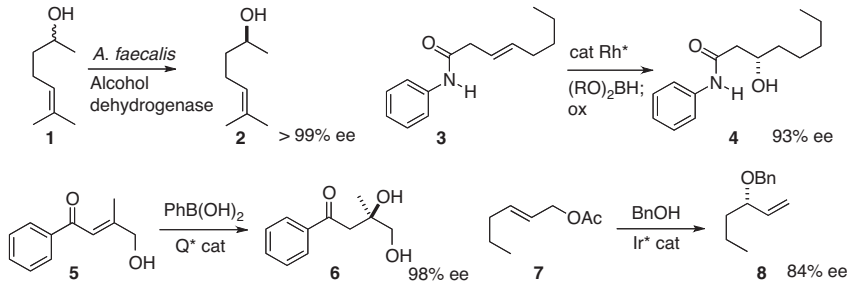
Carbon-carbon bond formation can also be used to assemble enantiomerically-pure secondary alcohols. Herfried Griengl of Graz University of Technology has found (*Adv. Synth. Cat.* **2007**, *349*, 1445) that a commercial nitrile lyase effects addition of nitromethane to an aldehyde such as **24** to give the nitro alcohol **25** in high ee. Markus Kalesse of Leibniz Universität Hannover has constructed a catalyst (*Organic Lett*. **2007**, *9*, 5637) for the enantioselective addition of the ketene silyl acetal **27** to aldehydes. Hajime Ito and Masaya Sawamura of Hokkaido University (*J. Am. Chem. Soc.* **2007**, *129*, 14856) (depicted), and Dennis G. Hall of the University of Alberta (*Angew. Chem. Int. Ed.* **2007**, *46*, 5913) have reported complementary enantioselective preparations of allyl boronates such as **31**.



33. Enantioselective Preparation of Alcohols and Amines

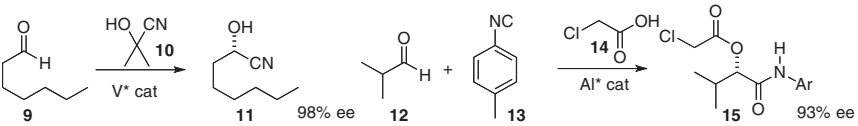
February 16, 2009

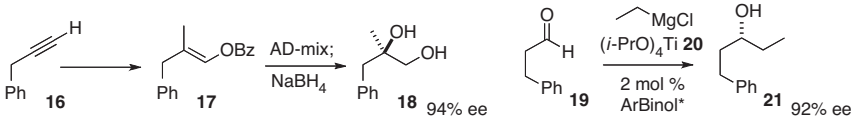
Enzymatic reduction of a ketone can proceed in high enantiomeric excess, but this would require a stoichiometric amount of a reducing agent. Wolfgang Kroutil of the Karl-Franzens-Universität Graz devised (*Angew. Chem. Int. Ed.* **2008**, *47*, 741) a protocol for preparing the alcohol **2** in high ee starting from the *racemic* alcohol. The alcohol dehydrogenase chosen was selective for the *R*-alcohol, and the microorganism reduced the ketone so produced selectively to the *S* alcohol.



James M. Takacs of the University of Nebraska established (*J. Am. Chem. Soc.* **2008**, *130*, 3734) that chiral Rh catalyzed addition of pinacolborane to a β,γ-unsaturated N-phenyl amide **3** proceeded with high enantiocontrol. The product organoborane was oxidized to the alcohol **4**. J. R. Falck of the UT Southwestern Medical Center used (*J. Am. Chem. Soc.* **2008**, *130*, 46) an organocatalyst to effect addition of phenylboronic acid to the γ-hydroxy enone **5**, to give, after hydrolysis, the diol **6**. John F. Hartwig of the University of Illinois effectively telescoped (*Angew. Chem. Int. Ed.* **2008**, *47*, 1928) alcohol formation and protection into a single step, by developing a procedure for the direct conversion of a primary allylic acetate **7** to the enantiomerically-enriched secondary benzyl ether **8**.

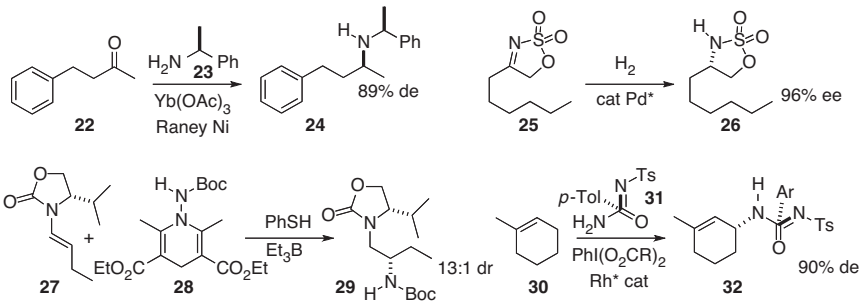
Tsutomu Katsuki of Kyushu University designed (*Chemistry Lett.* **2008**, *37*, 502) a catalyst for the enantioselective hydrocyanation of an aldehyde **9**, by HCN transfer from the inexpensive **10**. Mei-Xiang Wang of the Chinese Academy of Sciences, Beijing and Jieping Zhu of CNRS, Gif-sur-Yvette devised (*Angew. Chem. Int. Ed.* **2008**, *47*, 388) a catalyst for a complementary one-carbon homologation, the enantioselective Passerini three-component coupling of an aldehyde **12**, an isonitrile **13**, and an acid **14**.





Joseph M. Ready, also of UT Southwestern, developed (*J. Am. Chem. Soc.* **2008**, *130*, 7828) the preparation of enol benzoates such as **17** from the corresponding alkynes. Sharpless asymmetric dihydroxylation of **17** proceeded with high ee to give, after reduction, the diol **18**. Toshiro Harada of the Kyoto Institute of Technology described (*Angew. Chem. Int. Ed.* **2008**, *47*, 1088) a potentially very practical enantioselective homologation, the catalyzed addition of an alkyl titanium, prepared in situ from the corresponding Grignard reagent, to the aldehyde **19**, to give **21** in high ee.

Thomas C. Nugent of Jacobs University Bremen reported (*J. Org. Chem.* **2008**, *73*, 1297) that added $Yb(OAc)_3$ improved the de in the reductive amination of ketones such as **22** with Raney Ni and **23**. Yong-Gui Zhou of the Dalian Institute of Chemical Physics found (*Organic Lett.* **2008**, *10*, 2071) that cyclic sulfamidates such as **25** were easily prepared from the corresponding hydroxy ketone. Enantioselective hydrogenation of **25** gave **26** with high ee. Note that the cyclic sulfamidates **26** so produced will be versatile intermediates for further transformations, as the O is easily displaced by nucleophiles. Armido Studer of Westfälische-Wilhelms-Universität has been investigating (OHL March 24, 2008) the radical amination of alkenes. He has developed (*Angew. Chem. Int. Ed.* **2008**, *47*, 779) an easily-prepared N donor, **28**, and found that addition to the alkenyl oxazolidinone **27** proceeded with high de.

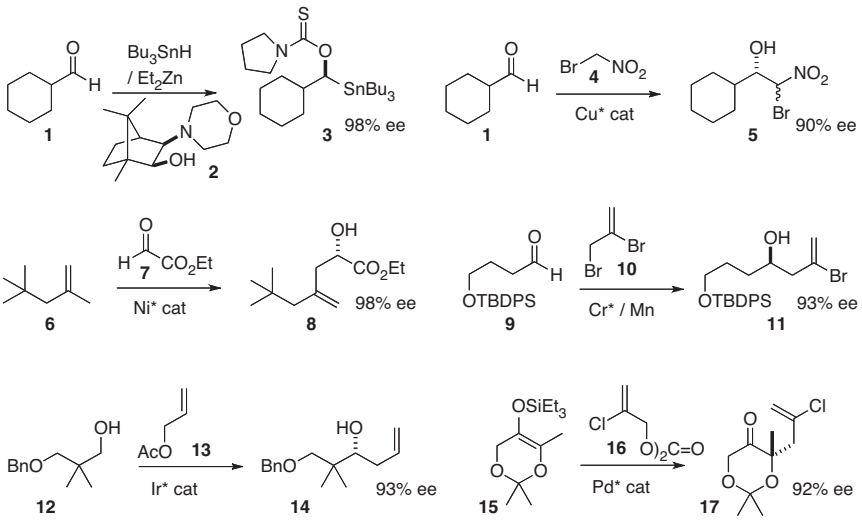


The alkene **30** has ten chemically distinct C-H bonds. Paul Müller of the University of Geneva and Robert H. Dodd and Philippe Dauban of CNRS, Gif-sur-Yvette established (*J. Am. Chem. Soc.* **2008**, *130*, 343) that insertion by a Rh nitrene proceeded with high selectivity primarily into just one of those C-H bonds, delivering **32** in high de.

34. Enantioselective Synthesis of Alcohols and Amines

July 20, 2009

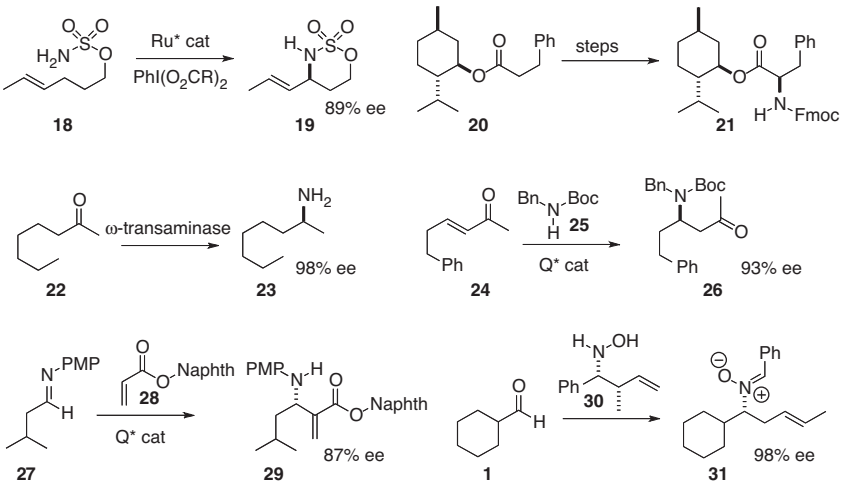
Enantiomerically-enriched alkoxy stannanes such as **3** are versatile intermediates for synthesis. John R. Falck of UT Southwestern found (*Angew. Chem. Int. Ed.* **2008**, *47*, 6586) that the simple combination of Bu_3SnH and Et_2Zn generated a reagent that added to aldehydes such as **1** under catalysis by the MIB amino alcohol introduced by Nugent (*Chem. Commun.* **1999**, 1369) to give the adduct **3** in high ee. Gonzalo Blay and José R. Pedro of the Universitat de València showed (*Chem. Commun.* **2008**, 4840) that it was possible to modulate the reactivity of the acidic **4**, allowing catalyzed formation of the high ee adduct **5** to dominate. Xiaoming Feng of Sichuan University developed (*J. Am. Chem. Soc.* **2008**, *130*, 15770) a Ni catalyst for the intermolecular ene reaction of **6** with **7** to give **8** in high ee.



Enantioselective allylation is a key transformation in current organic synthesis. Yoshito Kishi of Harvard University optimized (*Organic Lett.* **2008**, *10*, 3073) enantioselective Cr-mediated allylation, with a ligand that can be easily recovered and recycled. Michael J. Krische of UT Austin devised (*J. Am. Chem. Soc.* **2008**, *130*, 14891) a ligand-catalyst combination for effecting the enantioselective allylation of alcohols such as **12**. Brian M. Stoltz of Caltech developed (*Angew. Chem. Int. Ed.* **2008**, *47*, 6873) a protocol for the enantioselective allylation of the enol ether **15**, leading to the construction of oxygenated quaternary centers. Adducts such as **11** and **17** are of interest, *inter alia*, as direct precursors, by elimination, of the corresponding alkynes.

Simon Blakey of Emory University designed (*Angew. Chem. Int. Ed.* **2008**, *47*, 6825) a Ru catalyst that mediated enantioselective intramolecular C-H amination, converting the

simple alcohol derivative **18** into the versatile secondary amine **19** in high ee. We established (*J. Org. Chem.* **2008**, *73*, 9334) a procedure, based on diazo transfer followed by Rh-mediated intermolecular N-H insertion, for aminating menthyl esters and separating the product diastereomers. The menthyl group, easily removed (TFA) from **21**, served as a useful reporter of ee, by ^{1}H NMR of the upfield methyl doublets. Wolfgang Kroutil of the University of Graz found (*Adv. Synth. Cat.* **2008**, *350*, 2761) that ω-transaminases could effect the reductive amination of methyl ketones such as **22** in high ee. In many cases, either enantiomer of the amine could be prepared, depending on the transaminase used.

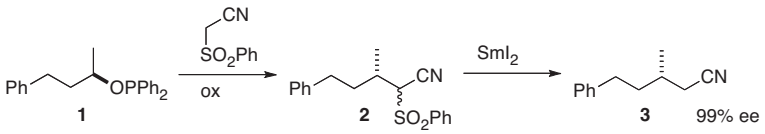


Li Deng of Brandeis University developed (*Angew. Chem. Int. Ed.* **2008**, *47*, 7710) a cinchona alkaloid derived catalyst for the enantioselective conjugate addition of **25** to enones. Manabu Node of Kyoto Pharmaceutical University reported (*Organic Lett.* **2008**, *10*, 2653) a related procedure for the addition of a recyclable enantiomerically-pure amine to α,β-unsaturated esters. Géraldine Masson and Jieping Zhu of CNRS Gif-sur-Yvette devised (*J. Am. Chem. Soc.* **2008**, *130*, 12596) a catalyst, also based on cinchona alkaloids, for the enantioselecitve aza Morita-Baylis-Hillman reaction, converting the imine **27** into **29** in substantial ee. Teck-Peng Loh of Nanyang Technological University designed (*Organic Lett.* **2008**, *10*, 2805) the enantiomerically- and diastereomerically-pure hydroxylamine **30**. The initial adduct of **30** with the aldehyde **1** rearranged to deliver **31** in high ee and as a single geometric isomer.

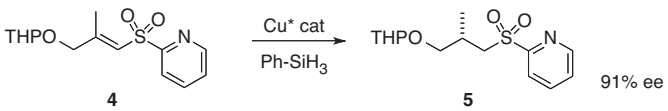
35. Enantioselective Assembly of Alkylated Stereogenic Centers

February 25, 2008

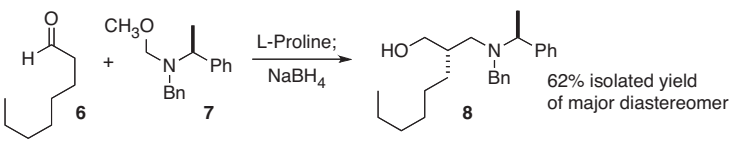
Oxygenated secondary stereogenic centers are readily available. There is a limited range of carbon nucleophiles that will displace a secondary leaving group in high yield with clean inversion. Teruaki Mukaiyama of the Kitasato Institute has described (*Chem. Lett.* **2007**, *36*, 2) an elegant addition to this list. Phosphinites such as **1** are easily prepared from the corresponding alcohols. Quinone oxidation in the presence of a nucleophile led via efficient displacement to the coupled product **2**. The sulfone could be reduced with SmI_2 to give **3.**



Enantioselective reduction of trisubstituted alkenes is also a powerful method for establishing alkylated stereogenic centers. Juan C. Carretero of the Universidad Autonoma de Madrid has found (*Angew. Chem. Int. Ed.* **2007**, *46*, 3329) that the enantioselective reduction of unsaturated pyridyl sulfones such as **4** was directed by the sulfone, so the other geometric isomer of **4** gave the opposite enantiomer of **5**. The protected hydroxy sulfone **5** is a versatile chiral building block.

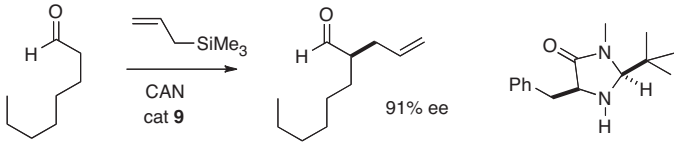


Samuel H. Gellman of the University of Wisconsin has reported (*J. Am. Chem. Soc.* **2007**, *129*, 6050) an improved procedure for the aminomethylation of aldehydes. L-Proline-catalyzed condensation with the matched α-methyl benzylamine derivavative **7** gave the aldehyde, which was immediately reduced to the alcohol **8** to avoid racemization. The amino alcohol **8** was easily separated in diastereomerically-pure form.



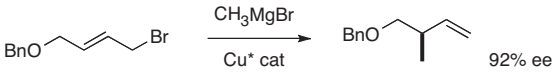
In the past, aldehydes have been efficiently α-alkylated using two-electron chemistry. David W. C. Macmillan of Princeton University has developed (*Science* **2007**, *316*, 582; *J. Am. Chem. Soc.* **2007**, *129*, 7004) a one-electron alternative. The organocatalyst **9** formed an imine with the aldehyde. One-electron oxidation led to an α-radical, which was trapped by the allyl silane (or, not pictured, a silyl enol ether) leading to the α-alkylated

aldehyde **10**. This is mechnistically related to the work reported independently by Mukund P. Sibi (*J. Am. Chem. Soc.* **2007**, *129*, 4124; OHL Feb. 11, 2008) on one-electron α-oxygenation of aldehydes.



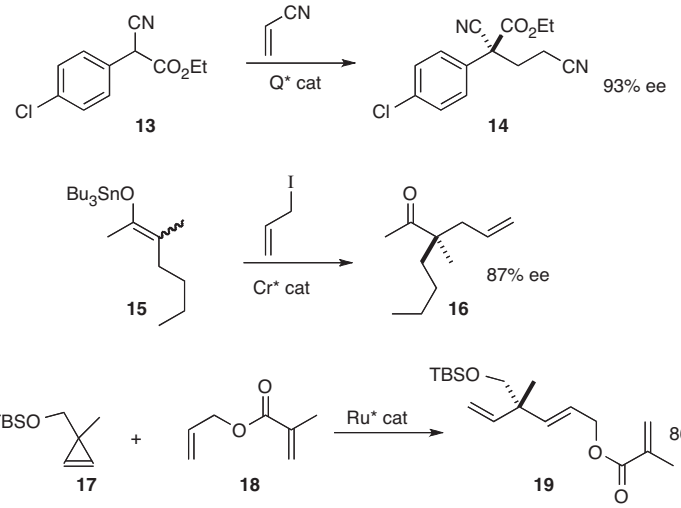
6 **10** **9**

Secondary alkylated centers can also be prepared by S_N2' alkylation of prochiral substrates such as **11**. Ben L. Feringa of the University of Groningen has shown (*J. Org. Chem.* **2007**, *72*, 2558) that the displacement proceeded with high ee even with conventional Grignard reagents. The products so formed are versatile intermediates for further transformation.



11 **12**

The enantioselective construction of *acyclic* alkylated quaternary stereogenic centers is a continuing challenge in organic synthesis. Several promising approaches have recently appeared. Li Deng of Brandeis University has established conditions (*J. Am. Chem. Soc.* **2007**, *129*, 768) for the catalyzed conjugate addition of aryl cyanoacetates such as **13** to acrylonitrile to give the adduct **14** in high ee. Eric N. Jacobsen of Harvard University has developed (*Angew. Chem. Int. Ed.* **2007**, 46, 3701) a chiral Cr catalyst that mediated the alkylation of tributyltin enolates such as **15** to give **16** in high ee. Amir H. Hoveyda of Boston College has designed (*J. Am. Chem. Soc.* **2007**, *129*, 3824) a chiral Ru metathesis catalyst that crossed **18** with the readily-prepared prochiral **17** to give **19**, also in high ee.

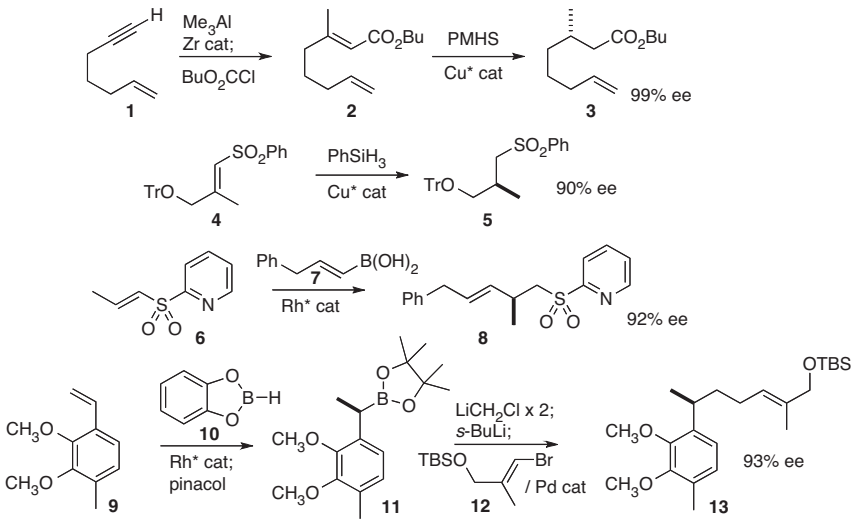


13 **14** **15** **16** **17** **18** **19**

36. Enantioselective Construction of Alkylated Stereogenic Centers

September 8, 2008

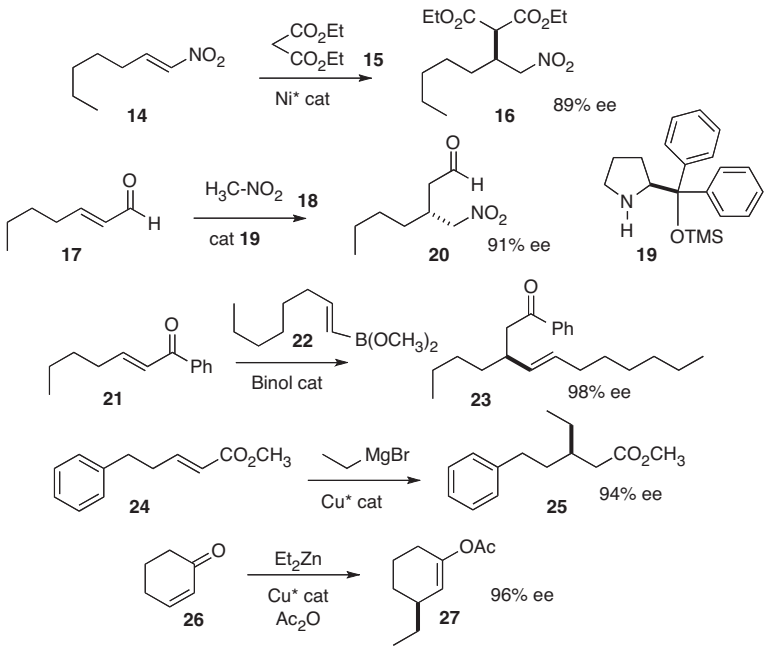
The enantioselectivity of alkene reduction usually depends on the geometric purity of the alkene. Bruce H. Lipshutz of the University of California, Santa Barbara used (*Organic Lett*. **2007**, *9*, 4713) carboalumination of the alkyne **1** to prepare **2**, which was selectively reduced to **3** in high ee. André B. Charette of the Université de Montréal reported (*Angew. Chem. Int. Ed.* **2007**, *46*, 5955) a related reduction of unsaturated sulfones such as **4**. Juan C. Carretero of the Universidad Autónoma de Madrid has developed (*J. Org. Chem.* **2007**, *72*, 9924) a complementary route to enantiomerically-enriched sulfones, by conjugate addition to the unsaturated pyridyl sulfone **6**. Specifically for styrene derivatives, Hans-Günther Schmalz of the University of Cologne has shown (*Organic Lett*. **2007**, *9*, 3555) that the product **11** from enantioselective Rh-catalyzed hydroboration can be homologated to **13**.



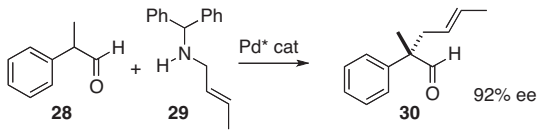
Conjugate addition of stabilized carbanions can also be carried out with high enantiocontrol. David A. Evans of Harvard University has described (*J. Am. Chem. Soc.* **2007**, *129*, 11583) the Ni-catalyzed addition of malonate **15** to nitroalkenes such as **14**. Claudio Palomo of the Universidad de País Vasco (*Angew. Chem. Int. Ed.* **2007**, *46*, 8431) and concurrently Yujiro Hayashi of the Tokyo University of Science (*Organic Lett*. **2007**, *9*, 5307) have developed organocatalytic protocols for the addition of nitromethane **18** to unsaturated aldehydes such as **17**.

J. Michael Chong of the University of Waterloo has found (*J. Am. Chem. Soc.* **2007**, *129*, 4908) that the Binol-mediated enantioselective conjugate addition of alkenylboronic acids such as **22** required the additional activation of the aryl ketone. Shun-Jun Li of

Suzhou University and Teck-Peng Loh of Nanyang Technical University have extended (*J. Am. Chem. Soc.* **2007**, *129*, 276) enantioselective conjugate to unsaturated esters such as **24** to more highly substituted Grignard reagents. Alexandre Alexakis of the University of Geneva has demonstrated (*Tetrahedron Lett*. **2007**, *48*, 7408) that Ac_2O is compatible with Et_2Zn conjugate addition conditions, leading directly to the trapped enolate **27**. Selective cleavage of **27** can then be used to prepare acyclic derivatives.



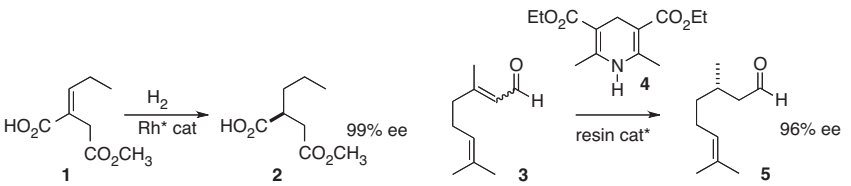
Benjamin List of the Max-Planck-Institut, Mülheim has taken advantage (*J. Am. Chem. Soc.* **2007**, *129*, 11336) of the large-small differential of the substituents on the aldehyde **28**. Enantioselective Pd-mediated rearrangement of the protonated enamine derived from condensation of **28** with **29** delivered the aldehyde **30** in high ee.



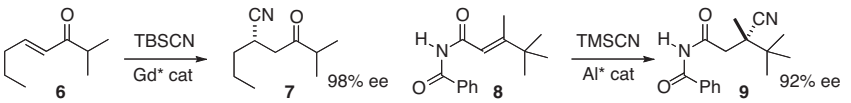
37. Enantioselective Construction of Alkylated Centers

February 23, 2009

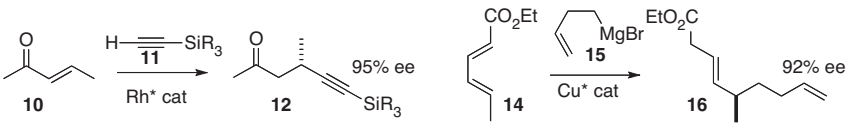
Unsaturated half acid esters such as **1** are readily prepared by Stobbe condensation between dialkyl succinate and an aldehyde. Johannes G. de Vries of DSM and Floris P. J. T. Rutjes of Radboud University Nijmegen observed (*Adv. Synth. Catal.* **2008**, *350*, 85) that these acids were excellent substrates for enantioselective hydrogenation. Kazuaki Kudo of the University of Tokyo designed (*Organic Lett*. **2008**, *10*, 2035) a resin bound peptide catalyst for the transfer reduction of unsaturated aldehydes such as **3**, using **4** as the net H_2 donor. Note that **5** was produced with high enantiocontrol from **3** that was a ~ 2:1 mixture of geometric isomers.



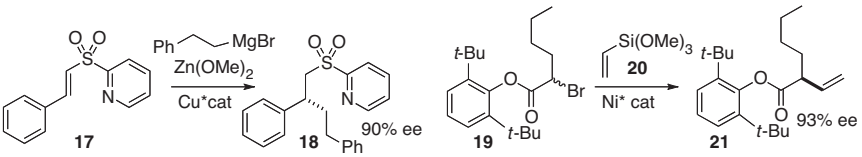
Motomu Kanai and Masakatsu Shibasaki of the University of Tokyo devised (*J. Am. Chem. Soc.* **2008**, *130*, 6072) a chiral Gd catalyst that mediated the conjugate cyanation of enones such as **6** with high ee. Eric N. Jacobsen of Harvard University prepared (*Angew. Chem. Int. Ed.* **2008**, *47*, 1762) a dimeric Al salen catalyst that showed improved activity over the monomeric catalysts. Even congested imides such as **8** could be cyanated efficiently, delivering alkylated *quaternary* stereogenic centers.



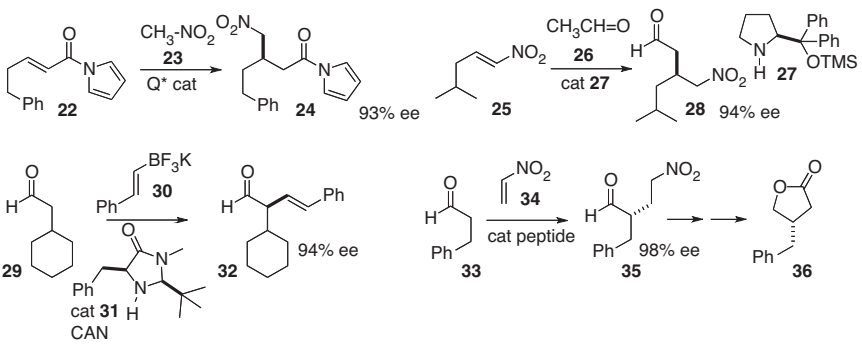
Takahiro Nishimura and Tamio Hayashi of Kyoto University optimized (*J. Am. Chem. Soc.* **2008**, *130*, 1576) the Rh*-catalyzed enantioselective conjugate addition of silyl acetylenes to enones such as **10**, to give **12**. Adriaan J. Minnaard and Ben L. Feringa of the University of Groningen devised (*Angew. Chem. Int. Ed.* **2008**, *47*, 398) conditions for the enantioselective 1,6-conjugate addition of alkyl Grignard reagents to diene esters such as the inexpensive ethyl sorbate **14**. The product **16** incorporated, in addition to the newly formed stereogenic center, a geometrically defined *E* alkene.



William S. Bechara and André B. Charette of the Université de Montréal found (*Organic Lett*. **2008**, *10*, 2315) that alkyl Grignard reagents could be induced to add with high enantioselectivity to pyridyl sulfones such as **17**. In a different approach, Gregory C. Fu of MIT developed (*J. Am. Chem. Soc.* **2008**, *130*, 3302; *J. Am. Chem. Soc.* **2008**, *130*, 2756) conditions for the enantioselective alkenylation of *racemic* bromo esters such as **19**, The latter reference is to the analogous enantioselective coupling of organozinc bromides with racemic allylic chlorides.



Organocatalyst-mediated coupling has also been used to prepare alkylated stereogenic centers. Benedek Vakulya and Tibor Soós of the Hungarian Academy of Sciences, Budapest devised (*J. Org. Chem.* **2008**, *73*, 3475) a *Cinchona* alkaloid-based catalyst for the addition of nitromethane **23** to activated amides such as **22**. Benjamin List of the Max-Planck-Institut, Mülheim showed (*Angew. Chem. Int. Ed.* **2008**, *47*, 4719) that with the versatile catalyst **27**, acetaldehyde itself could be added with high ee to nitroalkenes such as **25**. In a continuation of his work with single-electron chemistry, David W. C. MacMillan of Princeton University effected (*J. Am. Chem. Soc.* **2008**, *130*, 398) enantioselective alkenylation of aldehydes, using catalytic **31** and the stoichiometric oxidant ceric ammonium nitrate.

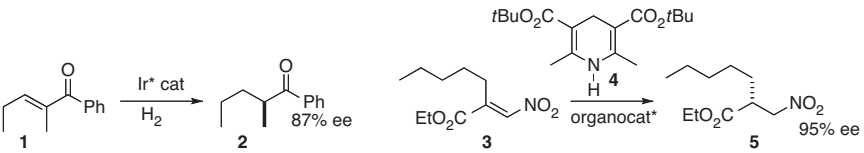


Using a designed catalytic peptide, Helma Wennemers of the University of Basel alkylated (*J. Am. Chem. Soc.* **2008**, *130*, 5610) aldehydes such as **33** with nitroethylene. Samuel H. Gellman of the University of Wisconsin effected (*J. Am. Chem. Soc.* **2008**, *130*, 5608) the same transformation using the catalyst **27**. Professor Wennemers showed that reduction of **35** followed by Mioskowski oxidation of the nitro group to the acid delivered the γ-lactone **36**. Enantiomerically-pure γ-lactones such as **36** are powerful intermediates for the enantioselective construction of natural products.

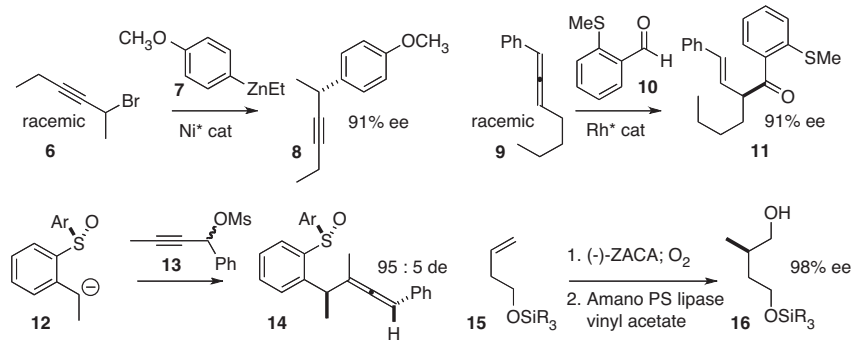
38. Enantioselective Construction of Alkylated Stereogenic Centers

July 27, 2009

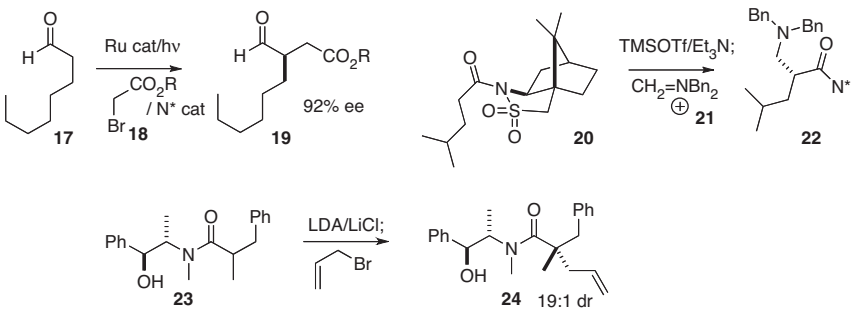
Carsten Bolm of RWTH Aachen developed (*Angew. Chem. Int. Ed.* **2008**, *47*, 8920) an Ir catalyst that effected hydrogenation of trisubstituted enones such as **1** with high ee. Benjamin List of the Max-Planck-Institut Mülheim devised (*J. Am. Chem. Soc.* **2008**, *130*, 13862) an organocatalyst for the enantioselective reduction of nitro acrylates such as 3 with the Hantzsch ester **4**.



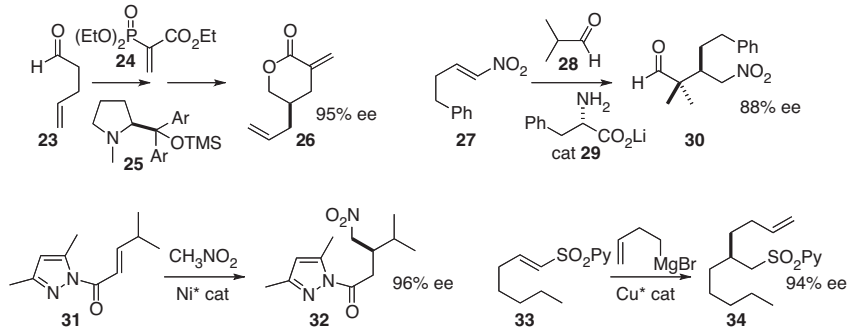
Gregory C. Fu of MIT optimized (*J. Am. Chem. Soc.* **2008**, *130*, 12645) a Ni catalyst for the enantioselective arylation of propargylic halides such as **6**. Both enantiomers of **6** were converted to the single enantiomer of **8**. Michael C. Willis of the University of Oxford established (*J. Am. Chem. Soc.* **2008**, *130*, 17232) that hydroacylation with a Rh catalyst was selective for one enantiomer of the allene **9**, delivering **11** in high ee. Similarly, José Luis García Ruano of the Universidad Autónoma de Madrid found (*Angew. Chem. Int. Ed.* **2008**, *47*, 6836) that one enantiomer of racemic **13** reacted selectively with the enantiomerically-pure anion **12**, to give **14** in high diastereomeric excess. Ei-chi Negishi of Purdue University described (*Organic Lett.* **2008**, *10*, 4311) the Zr-catalyzed asymmetric carboalumination (ZACA reaction) of the alkene **15** to give the useful chiron **16**.



David W. C. MacMillan of Princeton University developed (*Science* **2008**, *322*, 77) an intriguing visible light-powered oxidation-reduction approach to enantioselective aldehyde alkylation. The catalytic chiral secondary amine adds to the aldehyde to form an enamine, that then couples with the radical produced by reduction of the haloester.



Two other alkylations were based on readily-available chiral auxiliaries. Philippe Karoyan of the Université Pierre et Marie Curie observed (*Tetrahedron Lett*. **2008**, *49*, 4704) that the acylated Oppolzer camphor sultam **20** condensed with the Mannich reagent **21** to give **22** as a single diastereomer. Andrew G. Myers of Harvard University developed the pseudoephedrine chiral auxiliary of **23** to direct the construction of ternary alkylated centers. He has now established (*J. Am. Chem. Soc.* **2008**, *130*, 13231) that further alkylation gave **24**, having a *quaternary* alkylated center, in high diastereomeric excess.

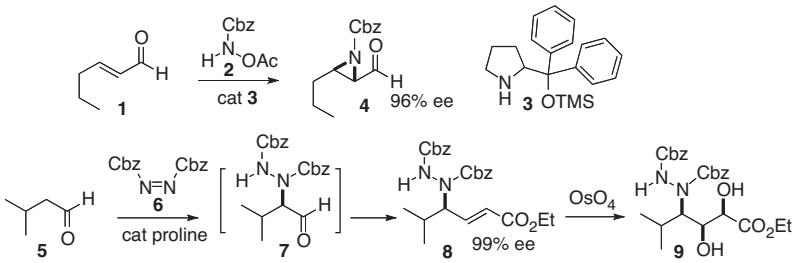


Karl Anker Jørgensen of Aarhus University developed (*J. Org. Chem.* **2008**, *73*, 8337) an enantioselective route to 4-alkyl α-methylene lactones such as **26**, based on conjugate addition of an aldehyde to the activated acceptor **24**. Masanori Yoshida of Hokkaido University found (*Chem. Commun.* **2008**, 6242) that the Li salt **29** of phenylalanine was an effective catalyst for the conjugate addition of aldehydes to nitroalkenes such as **27**. Masayuki Hasegawa and Shuji Kanemasa of Kyushu University designed (*Tetrahedron Lett*. **2008**, *49*, 5105, 5220) a Ni catalyst for the enantioselective addition of nitromethane to acyl pyrazoles such as **31**. Ben L. Feringa of the University of Groningen established (*Organic Lett.* **2008**, *10*, 4219) what may be one of the most flexible of approaches to alkylated chirons, the enantioselective conjugate addition of Grignard reagents to unsaturated sulfones such as **33**.

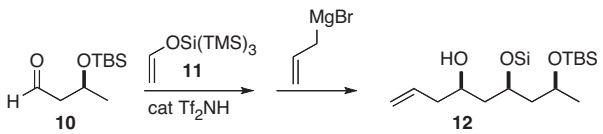
39. Stereocontrolled Construction of Arrays of Stereogenic Centers

March 10, 2008

Complex natural products and even some complex pharmaceuticals contain arrays of stereogenic centers. Sometimes, the desired array is readily available from a natural product, but usually, such arrays of multiple stereogenic centers must be assembled. Armando Córdova of Stockholm University has reported (*Angew. Chem. Int. Ed.* **2007**, *46*, 778) a simple procedure for the organocatalyst-mediated addition of the nitrene equivalent **2** to an α,β-unsaturated aldehyde to give the protected aziridine **4** in high ee. Organocatalysis was also used (*Organic Lett*. **2007**, *9,* 1001) by Arumugam Sudalai of the National Chemical Laboratory, Pune, to effect coupling of the aldehyde **5** with dibenzylazodicarboxylate **6** to give, following the List procedure, the intermediate aldehyde **7**. Osmylation of the derived unsaturated ester **8** proceeded with high diastereocontrol, to give **9**.

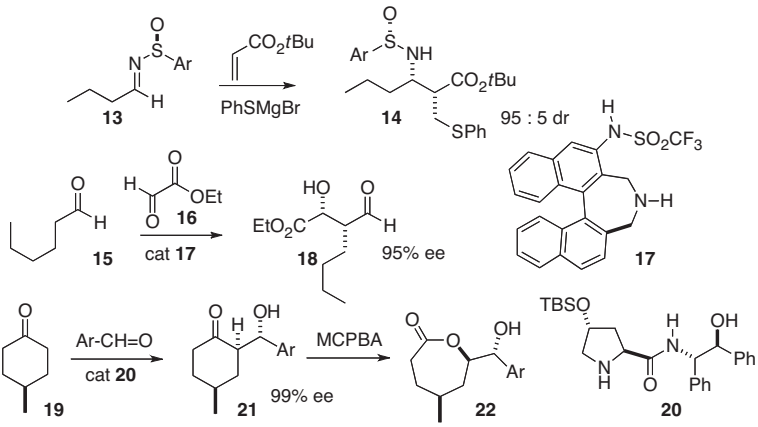


Products **4** and **9** have adjacent stereogenic centers. Hisashi Yamamoto of the University of Chicago has introduced (*J. Am. Chem. Soc.* **2007**, *129*, 2762) the linchpin reagent acetaldehyde "super"silyl enol ether **11**. Diastereoselective addition of **11** to the enantiomerically-pure aldehyde **10**, with concomitant silyl transfer, followed by the addition of allyl magnesium bromide delivered the protected triol **12** in high de and ee.

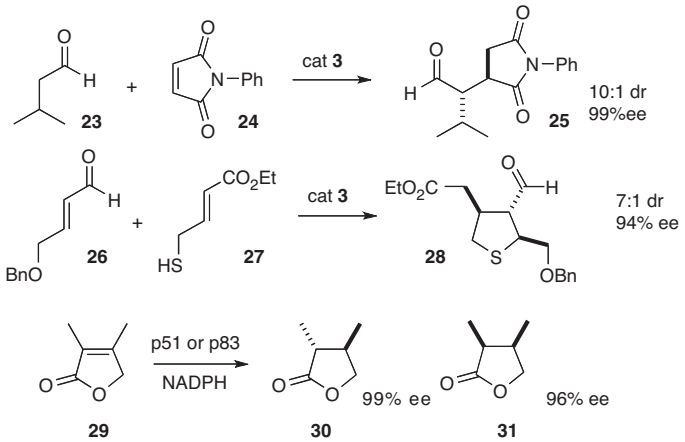


Arrays that combine alkylated and oxygenated or aminated centers are also important. Akio Kamimura of Yamaguchi University took (*J. Org. Chem.* **2007**, *72*, 3569) a Baylis-Hillman like approach, adding thiophenoxide to *t*-butyl acrylate in the presence of an enantiomerically-pure aldehyde N-sulfinimine such as **13** to give the adduct **14** with high diastereocontrol. Keiji Maruoka of Kyoto University has designed (*Angew. Chem. Int. Ed.* **2007**, *46*, 1738) the chiral amine **17**, that catalyzed the condensation of an aldehyde with ethyl glyoxylate **16** with high enantiocontrol. In a very thoughtful approach, Liu-Zhu Gong of the University of Science and Technology of China in Hefei extended (*Chem. Commun.* **2007**, 736) the now-classic aldol condensation of cyclohexanone to 4-substituted

cyclohexanones such as **19**. The product **21** could be carried in many directions, including to the Bayer-Villiger product **22**.



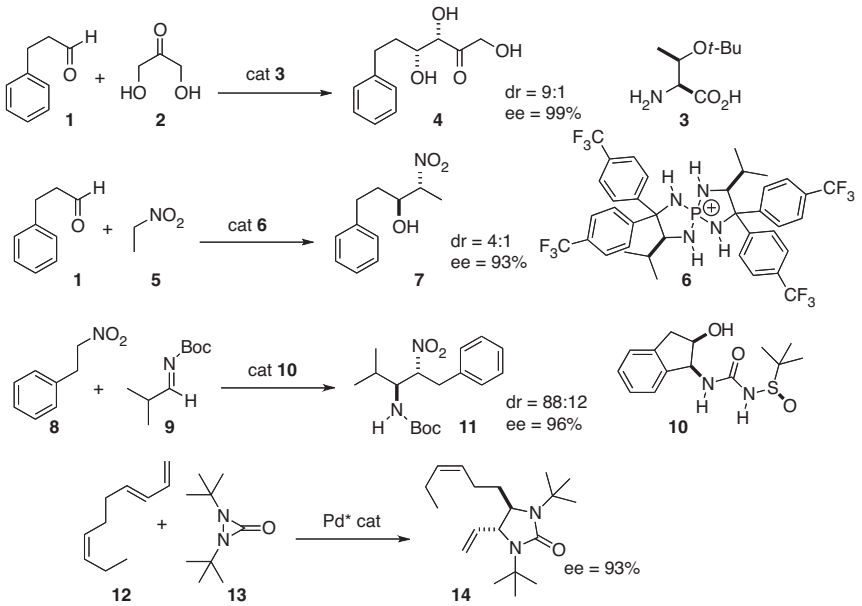
Arrays of alkylated and polyalkylated centers have been among the most challenging to prepare. Professor Córdova has established conditions (*Chem. Commun*. **2007**, 734) under which **3** will catalyze the addition of aliphatic aldehydes such as **23** to imides such as **24** with high enantio- and diastereocontrol. The two carbonyls of the imide would be easily distinguishable by reduction of the aldehyde followed by selective formation of the γ-lactone. Using the same catalyst, Wei Wang of the University of New Mexico effected (*Organic Lett*. **2007**, *9*, 1833) the addition of the mercapto ester **27** to unsaturated aldehydes such as **26**. The product **28** has three new stereogenic centers. In what may be a very general approach to this problem, Hiroki Hamada of the Okayama University of Science has observed (*Tetrahedron Lett*. **2007**, *48*, 1345) that crude purified p51 and p83 reductases from *Glycine max* showed complementary selectivity, leading to **30** and **31** respectively.



40. Enantioselective Construction of Arrays of Stereogenic Centers

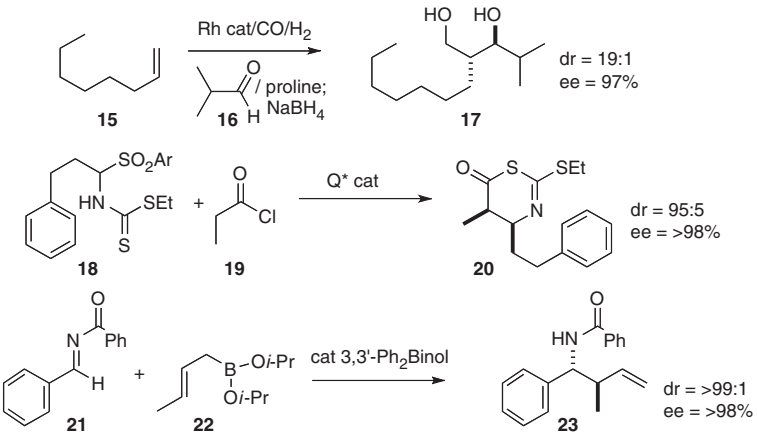
September 15, 2008

An impressive array of new catalysts for enantioselective homologation have been reported. Carlos F. Barbas III of Scripps/La Jolla has found (*Angew. Chem. Int. Ed.* ***2007****, 46,* 5572**)** that the commercial amino acid **3** mediated the addition of dihydroxyacetone **2** to an aldehyde such as **1** to give the triol **4** with high enantio- and diastereocontrol. Takashi Ooi of Nagoya University has devised (*J. Am. Chem. Soc.* **2007**, *129*, 12392) the catalyst **6** for the anti addition (Henry reaction) of nitro alkanes such as **5** to aldehydes. Takayoshi Arai of Chiba University has developed (*Organic Lett.* **2007**, *9*, 3595) a complementary catalyst (not shown) that mediated syn addition. Jonathan A. Ellman of the University of California, Berkeley has uncovered (*J. Am. Chem. Soc.* **2007**, *129*, 15110) the catalyst **10** for the aza-Henry reaction. Yian Shi of Colorado State University has found (*J. Am. Chem. Soc.* **2007**, *129*, 11688) ligands for Pd that direct the absolute sense of the addition of **13** to dienes such as **12**.

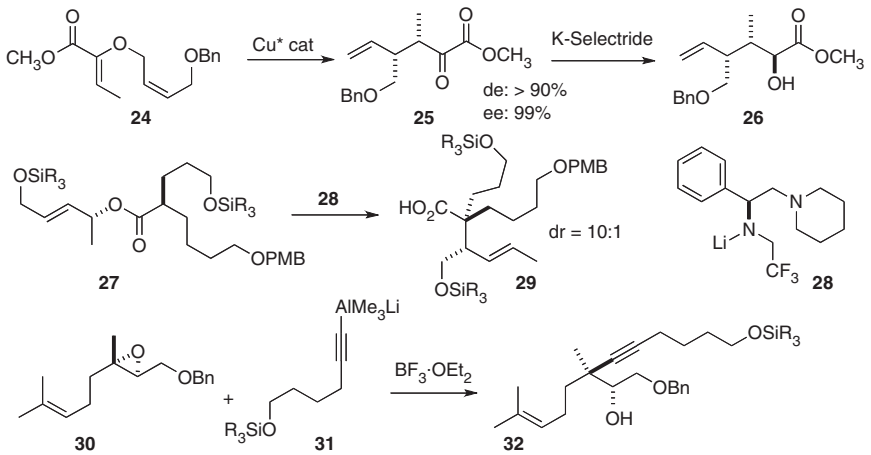


Bernhard Breit of Albert-Ludwigs-Universität, Freiburg has devised conditions (*Adv. Synth. Cat.* **2007**, *349*, 1891) for the Rh-catalyzed hydroformylation of α-olefins such as **15**, and same-pot proline-catalyzed condensation of the linear aldehyde so produced with a branched aldehyde such as **17** to give, after reductive workup, the branched diol **18**. Scott G. Nelson of the University of Pittsburgh has established (*J. Am. Chem. Soc.* **2007**, *129*, 11690) conditions, using Cinchona alkaloid derived catalysts, for the condensation of the imine surrogate **19** with the ketene precursor **20**, to give the Mannich product **21**. Scott E. Schaus of Boston University

has developed (*J. Am. Chem. Soc.* **2007**, *129*, 15398) a complementary approach, based on catalyzed addition of isolated allyl borinates such as **23** to the activated imine **22**. Kálmán J. Szabó of Stockholm University has found (*J. Am. Chem. Soc.* **2007**, *129*, 13723) that substituted allyl borinates can be prepared and reacted in situ.



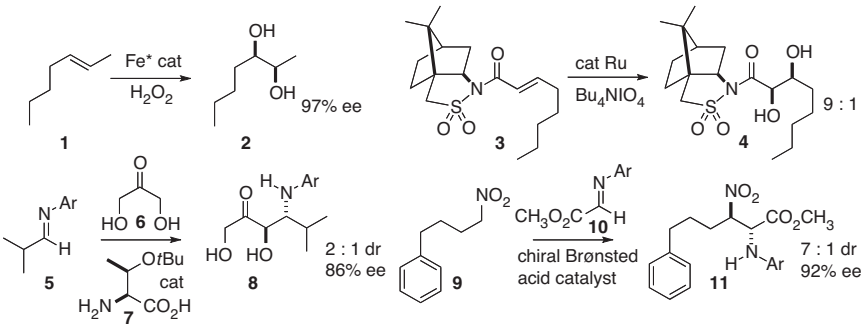
Martin Hiersemann of the Universität Dortmund has reported (*Organic Lett.* **2007**, *9*, 4979) the remarkable Cu*-catalyzed Claisen rearrangement of the prochiral **24**, leading to **25** and thus to the versatile intermediate **27**. At least as remarkable is the Claisen rearrangement, mediated by the matched enantiomerically-pure base **28**, of **27** to **30**, developed (*Angew. Chem. Int. Ed.* **2007***, 46,* 7466**)** by Armen Zakarian, now at the University of California, Santa Barbara. Brian L. Pagenkopf of the University of Western Ontario has devised (*Tetrahedron* **2007**, *63*, 8774) a general route to both cyclic and acyclic alkylated stereogenic centers, by opening trisubstituted epoxides such as **30** with alkynes.



41. Stereocontrolled Construction of Arrays of Stereogenic Centers

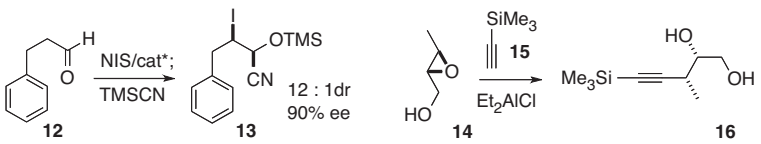
March 9, 2009

The Sharpless osmium-catalyzed asymmetric dihydroxylation is widely used. Lawrence Que, Jr. of the University of Minnesota designed (*Angew. Chem. Int. Ed.* **2008**, *47*, 1887) a catalyst with the inexpensive Fe that appears to be at least as effective, converting **1** to **2** in high ee. In an alternative approach, Bernd Plietker of the Universität Stuttgart used (*J. Org. Chem.* **2008**, *73*, 3218) chiral auxiliary control to direct dihydroxylation. The diastereomers of **4** were readily differentiated.



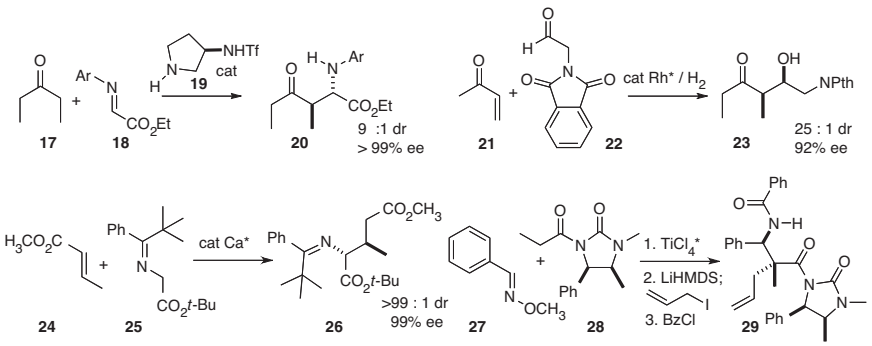
Defined arrays of stereogenic centers can also be constructed by homologation. Armando Córdova of Stockholm University condensed (*Tetrahedron Lett*. **2008**, *49*, 803) dihydroxy acetone **6** with an in situ generated imine **5** to give the amino diol **8**. In parallel work, Carlos F. Barbas III of Scripps/La Jolla described (*Organic Lett*. **2008**, *10*, 1621) a related addition to aldehydes. Magnus Rueping of University Frankfurt found (*Organic Lett*. **2008**, *10*, 1731) conditions for the addition of a nitro alkane such as **9** to the imine **10** to give **11**.

Keiji Maruoka of Kyoto University devised (*J. Am. Chem. Soc.* **2008**, *130*, 3728) a chiral amine that mediated the enantioselective iodination of aldehydes such as **12**. Direct cyanohydrin formation delivered **13** in high de and ee. The epoxide **14** is readily prepared in high ee from crotyl alcohol. Barry M. Trost of Stanford University found (*Organic Lett*. **2008**, *10*, 1893) that **14** could be opened with **15**, to give **16** with high regio- and diastereocontrol.



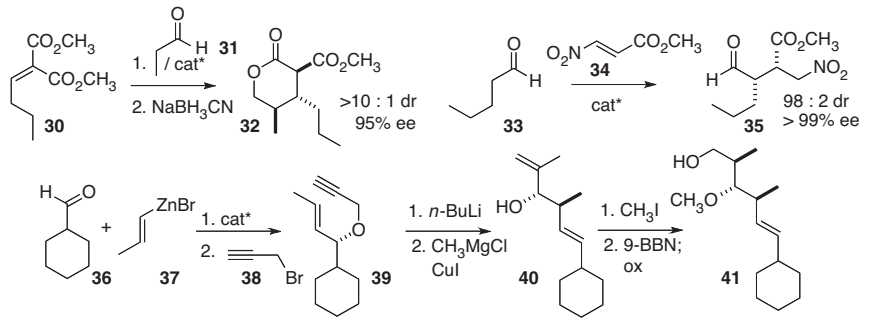
Jérôme Blanchet of the Université de Caen Basse-Normandie optimized (*Organic Lett*. **2008**, *10*, 1029) the amine **19** as a catalyst for the condensation of ketones such as **17** with the imine **18**, to give **20**. Michael J. Krische of the University of Texas has explored

(*J. Am. Chem. Soc.* **2008**, *130*, 2746) the in situ generation of chiral Rh enolates from enones such as **21**, and the subsequent aldol condensation with aldehydes such as **22**.



Shu Kobayashi of the University of Tokyo found (*Organic Lett*. **2008**, *10*, 807) that the conjugate addition of **25** to **24** mediated by a chiral Ca catalyst proceeded with high enantiocontrol at both of the newly formed stereogenic centers, to give **26**. In a chiral auxiliary based approach, Dennis C. Liotta found (*J. Org. Chem.* **2008**, *73*, 1264) that condensation of **27** with **28** gave predominantly just two of the possible four diastereomeric azetines. Alkylation of the cis diastereomer, followed by benzoylation and hydrolysis, then delivered the α-quaternary β-amino acid derivative **29** as a single enantiomerically-pure diastereomer.

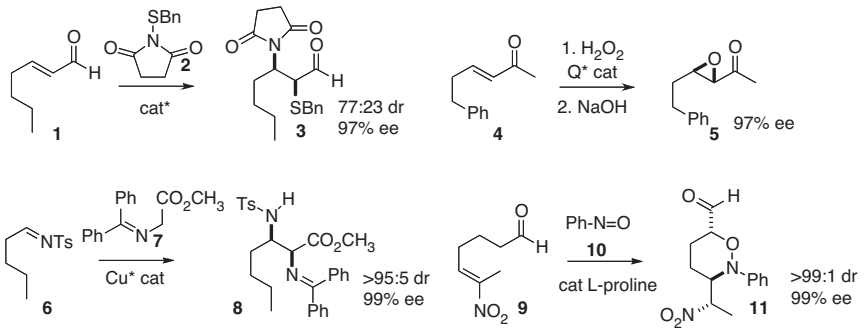
Professor Córdova showed (*Adv. Synth. Cat.* **2008**, *350*, 657) that aldehydes could be added to alkylidene malonates such as **30** to give, after reduction, the lactone **32**. Dawei Ma of the Shanghai Institute of Organic Chemistry found (*Angew. Chem. Int. Ed.* **2008**, *47*, 545) that aldehydes could also be added to nitroalkenes such as **34** with high enantio- and diasterocontrol. Kathlyn A. Parker of SUNY Stony Brook took advantage (*Organic Lett*. **2008**, *10*, 1349) of the enantioselective addition of an alkenyl zinc halide **37** to an aldehyde **36** to set the relative and absolute configuration of an extended array of stereogenic centers.



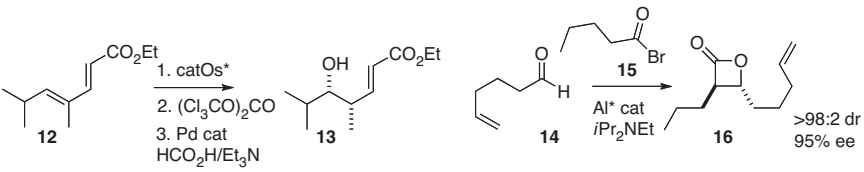
42. Practical Enantioselective Construction of Arrays of Stereogenic Centers: The Jørgensen Synthesis of the Autoregulator IM-2

September 14, 2009

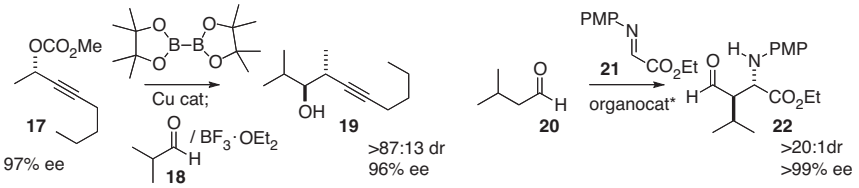
Armando Córdova of Stockholm University found (*Angew. Chem. Int. Ed.* **2008**, *47*, 8468) that the enantiomerically-enriched diastereomers from aminosulfenylation of **1** were readily separable by silica gel chromatography. Benjamin List of the Max-Planck-Institut, Mülheim developed (*Angew. Chem. Int. Ed.* **2008**, *47*, 8112) what appears to be a general protocol for the enantioselective epoxidation of enones such as **4**. Paolo Melchiorre of the Università di Bologna devised (*Angew. Chem. Int. Ed.* **2008**, *47*, 8703) a related protocol for the enantioselective aziridination of enones. Xue-Long Hue of the Shanghai Institute of Organic Chemistry and Yun-Dong Wu of the Hong Kong University of Science and Technology optimized (*J. Am. Chem. Soc.* **2008**, *130*, 14362) a Cu catalyst for enantioselective Mannich homologation of imines such as **6**. Guofu Zhong of Nanyang Technological University, Singapore established (*Angew. Chem. Int. Ed.* **2008**, *47*, 10187; *Organic Lett.* **2008**, *10*, 4585) that enantioselective α-aminoxylation of an ω-alkenyl aldehyde such as **9** could lead to defined arrays of stereogenic centers.



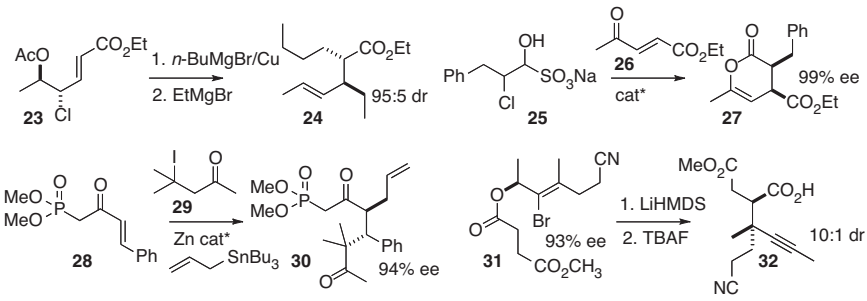
George A. O'Doherty of West Virginia University devised (*Organic Lett.* **2008**, *10*, 3149) a protocol for the enantioselective hydration of **12** to **13**. René Peters, now at the University of Stuttgart, designed (*Angew. Chem. Int. Ed.* **2008**, *47*, 5461) an Al catalyst for the enantioselective combination of an acyl bromide **15** with an aldehyde **14** to deliver the β–lactone



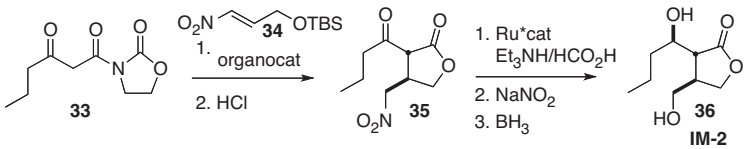
16. Hajime Ito and Masaya Sawamura of Hokkaido University established (*J. Am. Chem. Soc.* **2008**, *130*, 15774) that the allenyl borane from **17** added to aldehydes such as **18** with high ee. Keiji Maruoka of Kyoto University developed (*Tetrahedron Lett.* **2008**, *49*, 5369) an organocatalyst for the Mannich homologation of an aldehyde such as **20** to **21**.



R. Karl Dieter of Clemson University showed (*Organic Lett.* **2008**, *10*, 2087) that **23**, readily prepared in high ee, could be displaced sequentially with two different Grignard reagents, to give **24**. Jeffrey W. Bode, now at the University of Pennsylvania, found (*Organic Lett.* **2008**, *10*, 3817) that bisulfite adducts such as **25** served well for the addition of unstable chloroaldehydes to **26** to give **27**. Sunggak Kim of KAIST, Daejeon observed (*Organic Lett.* **2008**, *10*, 3149) that the radical addition of **29** to **28** with allylation of the intermediate radical delivered **30** with high diastereocontrol. Peter A. Jacobi of Dartmouth College prepared (*Organic Lett.* **2008**, *10*, 2837) the ester **31** by enantioselective reduction of the enone. Claisen rearrangement followed by TBAF elimination gave **32**.



Karl Anker Jørgensen of Aarhus University, Denmark used (*Chem. Commun.* **2008**, 5827) a *Chincona* based catalyst to effect enantioselective addition of **33** to **34**. Enantioselective reduction of the ketone **35** to the alcohol followed by conversion of the nitro group to the alcohol led to **IM-2 36**, an autoregulator derived from *Streptomyces*.

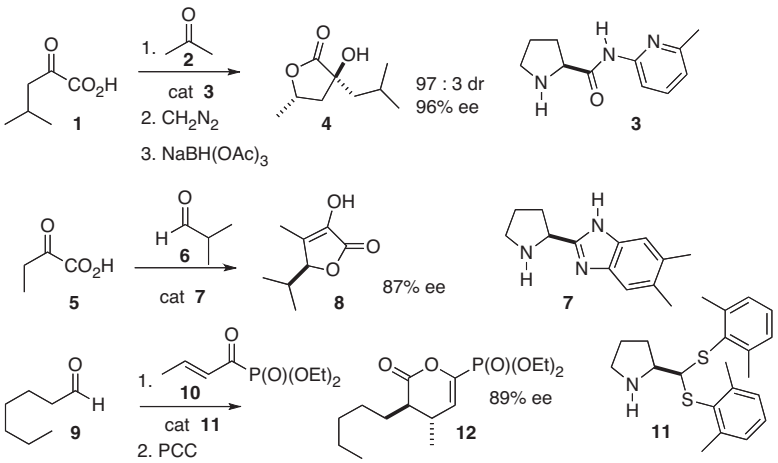


It is a measure of the progress that has been made in this area that fifteen years ago, developing a route to a family of drug products that contained two adjacent ternary alkylated stereogenic centers was a significant challenge for the process group of a major pharmaceutical company.

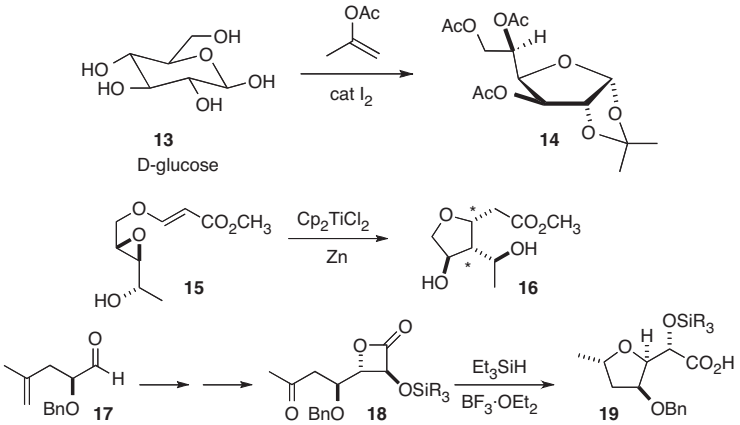
43. Enantioselective Synthesis of Lactones and Cyclic Ethers

April 14, 2008

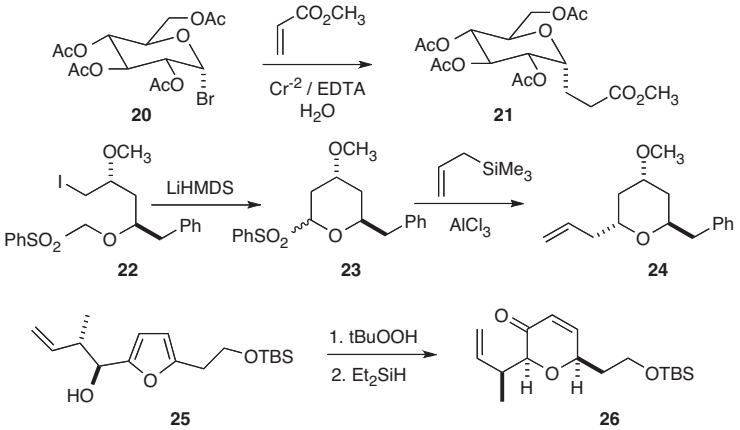
Developments in organocatalysis have turned toward the enantioselective construction of lactones. Shi-Wei Luo and Liu-Zhu Gong of the University of Science and Technology of China have found (*J. Org. Chem.* **2007**, *71*, 9905) that catalyzed addition of acetone to an α-hydroxy acid **1** proceeded with high ee. Esterification of the addition product followed by reduction and acid work-up delivered the lactone **4** with high dr and ee. In a complementary approach, Jean-Marc Vincent and Yannick Landais of the University Bourdeaux-1 showed (*Chem. Commun*. **2007**, 4782) that catalyzed condensation of an aldehyde with an α-hydroxy acid **5** delivered the tetronic acid **8** in high ee. It may be that **8** could also be reduced with useful selectivity. Cong-Gui Zhao of the University of Texas, San Antonio has devised conditions (*Organic Lett*. **2007**, *9*, 2745) for the condensation of the keto phosphonates such as **10** with aldehydes to give, after oxidation, the δ-lactone **12**.



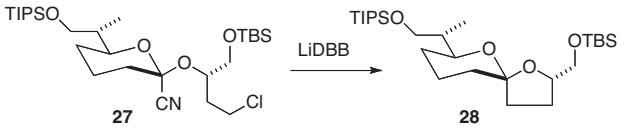
Carbohydrates such as glucose **13** are inexpensive, molecularly-complex starting materials. Subhash Chandra Taneja of the Indian Institute of Integrative Medicine, Jammu Tawi, has found conditions (*J. Org. Chem.* **2007**, *72*, 8965) for the single-step I_2-catalyzed transformation of **13** to **14**, in which each of the alcohols have been differentiated. In a complementary approach described (*Tetrahedron Lett*. **2007**, *48*, 6389) by Tushar Kanti Chakraborty of the Indian Institute of Chemical Technology, Hyderabad, Ti-mediated reduction of **15** was shown to be highly diastereoselective, setting the two new stereogenic centers (marked by ∗) in **16**. Building on work by Mead, Daniel Romo of Texas A&M has shown (*J. Org. Chem.* **2007**, *72*, 9053) that reductive cyclization of **18** also proceeded with high diastereocontrol, to give **19**.



As illustrated by the conversion of **20** to **21** reported (*Tetrahedron Lett.* **2007**, *48*, 7351) by Zsuzsa Juhász and László Somsák of the University of Debrecen, six-membered ring cyclic ethers can also be formed from carbohydrate precursors. Richard E. Taylor of the University of Notre Dame has taken advantage (*Angew. Chem. Int. Ed.* **2007**, *46*, 6874) of the "chemical chameleon" nature of a sulfone, using it both the stablilize the anion for intramolecular alkylation, to form **23**, and as a leaving group, leading to **24**. Andrew J. Phillips of the University of Colorado has oxidized (*Organic Lett*. **2007**, *9*, 5299), the enantiomerically-pure furan **25** to give, after reduction, the ring-expanded cyclic ether **26**.



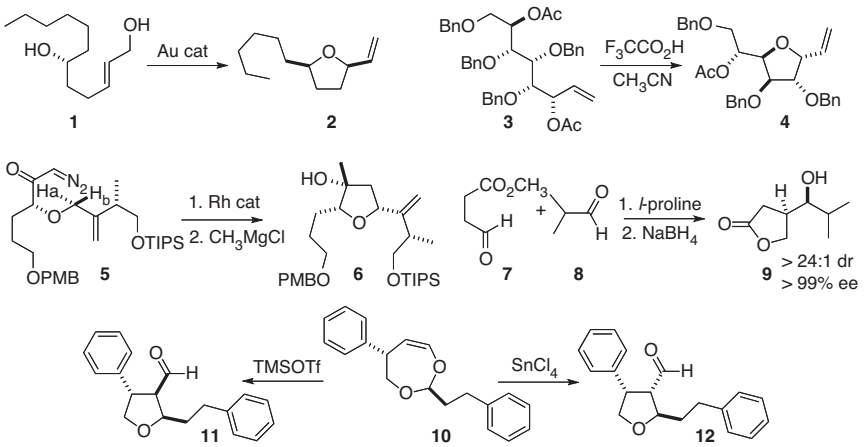
Spiroketals such as **28** are usual prepared under equilibrating conditions, leading to the most stable diastereromer. Yet, there are spiroketal natural products that are the less stable diastereomer, prepared under kinetic conditions. Scott D. Rychnovsky of the University of California, Irvine has found (*Organic Lett*. **2007**, *9*, 711) that the reductive cyclization of a halo nitrile **27** can kinetically establish the less-stable spiroketal **28**.



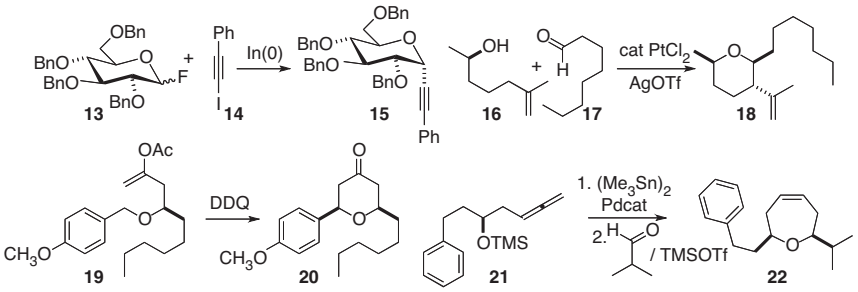
44. Stereocontrolled C-O Ring Construction: The Fuwa/Sasaki Synthesis of Attenol A

January 26, 2009

Since five-membered ring ethers often do not show good selectivity on equilibration, single diastereomers are best formed under kinetic control. Aaron Aponick of the University of Florida demonstrated (*Organic Lett*. **2008**, *10*, 669) that under gold catalysis, the allylic alcohol **1** cyclized to **2** with remarkable diastereocontrol. Six-membered rings also formed with high cis stereocontrol. Ian Cumpstey of Stockholm University showed (*Chem. Commun*. **2008**, 1246) that with protic acid, allylic acetates such as **3** cyclized with clean inversion at the allylic center, and concomitant debenzylation. J. Stephen Clark of the University of Glasgow found (*J. Org. Chem.* **2008**, *73*, 1040) that Rh catalyzed cyclization of **5** proceeded with high selectivity for insertion into H_a, leading to the alcohol **6**. Saumen Hajra of the Indian Institute of Technology, Kharagpur took advantage (*J. Org. Chem.* **2008**, *73*, 3935) of the reactivity of the aldehyde of **7**, effecting selective addition of **7** to **8**, to deliver, after reduction, the lactone **9**. Tomislav Rovis of Colorado State University observed (*J. Org. Chem.* **2008**, *73*, 612) that **10** could be cyclized selectively to either **11** or **12**.

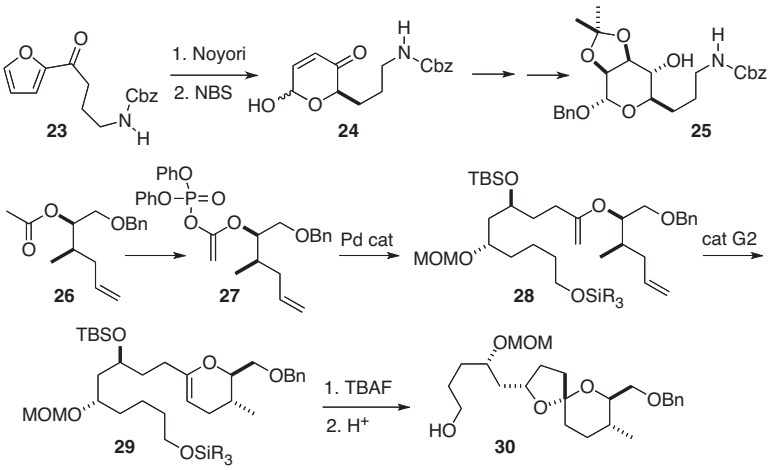


Nadège Lubin-Germain, Jacques Uziel and Jacques Augé of the University of Cergy-Pontoise devised (*Organic Lett*. **2008**, *10*, 725) conditions for the indium-mediated coupling of glycosyl fluorides such as **13** with iodoalkynes such as **14** to give the axial C-glycoside **15**. Katsukiyo Miura and Akira Hosomi of the University of Tsukuba employed (*Chemistry Lett*. **2008**, *37*, 270) Pt catalysis to effect in situ equilibration of the alkene **16** to the more stable regioisomer. Subsequent condensation with the aldehyde **17** led via Prins cyclization to the ether **18**.



Paul E. Floreancig of the University of Pittsburgh showed (*Angew. Chem. Int. Ed.* **2008**, *47*, 4184) that Prins cyclization could be also be initiated by oxidation of the benzyl ether **19** to the corresponding carbocation. Chan-Mo Yu of Sungkyunkwan University developed (*Organic Lett*. **2008**, *10*, 265) a stereocontrolled route to seven-membered ring ethers, by Pd-mediated stannylation of allenes such as **21**, followed by condensation with an aldehyde.

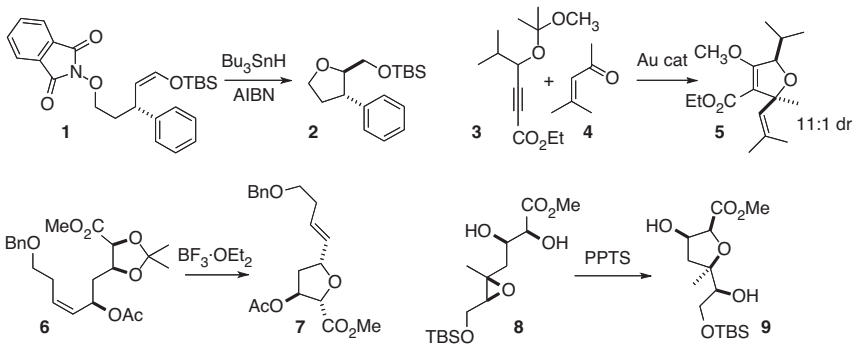
George A. O'Doherty of West Virginia University devised (*J. Org. Chem.* **2008**, *73*, 1935) an alternative route toward C-glycosides, by enantioselective reduction of the furyl ketone **23** followed by oxidative rearrangement. Haruhiko Fuwa and Makato Sasaki of Tohoku University, en route to a synthesis of Attenol A, established (*Organic Lett*. **2008**, *10*, 2549) a highly-convergent route to spiro ethers such as **30**, based on Pd-catalyzed coupling of enol phosphates such as **27**, followed by ring-closing metathesis and acid-catalyzed cyclization.



45. Stereoselective C-O Ring Construction: The Oguri-Oikawa Synthesis of Lasalocid A

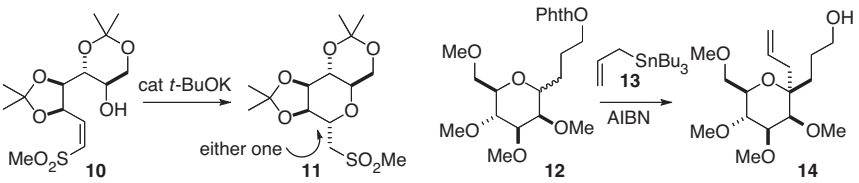
April 13, 2009

O-Centered radicals have been little used for C-O ring formation. Glenn M. Sammis of the University of British Columbia showed (*Organic Lett*. **2008**, *10*, 5083) that O-centered radicals could be generated efficiently, and that they cyclized with high diasterecontrol. Liming Zhang of the University of Nevada, Reno, continuing his studies of Au-activation of alkynes, uncovered (*J. Am. Chem. Soc.* **2008**, *130*, 12598) the bimolecular condensation of polarized alkynes such as **3** with aldehydes and ketones, including **4**, to give the dihydrofuran with high diastereocontrol.



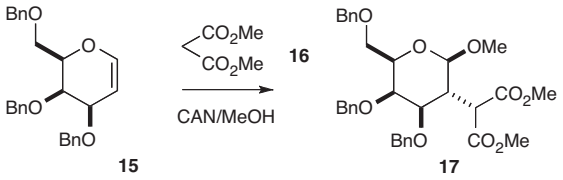
Margarita Brovetto of the Universidad de la República, Montevideo, Uruguay, prepared (*J. Org. Chem.* **2008**, 73, 5776) the precursor to the enantiomercially triol **6** by fermentation of bromobenzene with *Pseudomonas putida* 39/D. Cyclization of **6** gave **7** with high diastereocontrol. Petri M. Pihko of the University of Jyväskylä, Finland, found (*Organic Lett*. **2008**, *10*, 4179) that cyclization of **8**, prepared by Sharpless asymmetric epoxidation followed by Sharpless asymmetric dihydroxylation, also proceeded with high diastereocontrol.

Vincent Aucagne of the Université d'Orléans observed (*Tetrahedron Lett*. **2008**, *49*, 4750) that brief exposure of the sulfone **10** to *t*-BuOK at low temperature gave clean conversion to the kinetic diastereomer **11**. At room temperature, similar conditions delivered the other, more stable diastereomer. Angeles Martín and Ernesto Suárez of the C. S. I. C.,

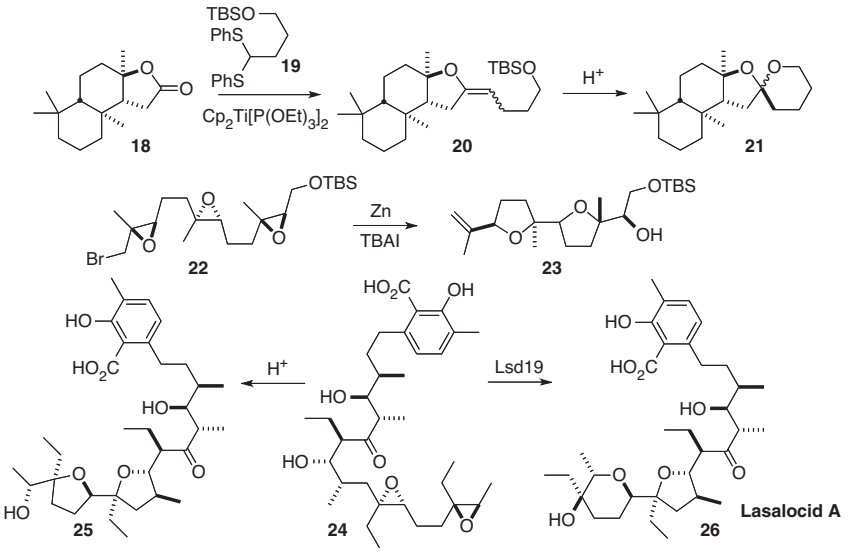


La Laguna, took advantage (*Tetrahedron Lett*. **2008**, *49*, 5179) of the facile generation of O-centered radicals in converting **12** to **14**, having a stereocontrolled quaternary center. The transformation is thought to be proceeding by H-atom abstraction, then diastereocontrolled trapping of the C-radical so formed with the allyl stannane **13**.

Much of the effort toward alkylated cyclic ether construction has been focused on alkyl group attachment adjacent to the ring oxygen. Torsten Linker of the University of Potsdam developed (*J. Am. Chem. Soc.* **2008**, *130*, 16003) a complementary approach, stereocontrolled oxidative radical addition of malonate **16** to glycals such as **15** to give the 3-alkyl substituted **17**.



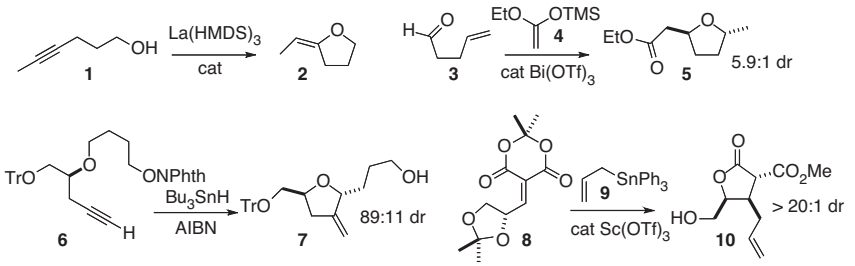
Richard C. Hartley of the University of Glasgow established (*Tetrahedron Lett*. **2008**, *49*, 4771) what promises to be a powerful strategy for the convergent assembly of spiro ketals, based on the condensation of the Ti alkylidene derived from a thioacetal such as **19** with a lactone such as **18**. James A. Marshall of the University of Virgina nicely reduced to practice (*J. Org. Chem.* **2008**, 73, 6753) the preparation and reductive cyclization of polyepoxides such as **22**. Hiroki Oguri and Hideaki Oikawa of Hokkaido University demonstrated (*J. Am. Chem. Soc.* **2008**, *130*, 12230) that overexpressed enzyme Lsd19 converted **24** to lasolacid A **26**. With acid, **24** cyclized to **25**.



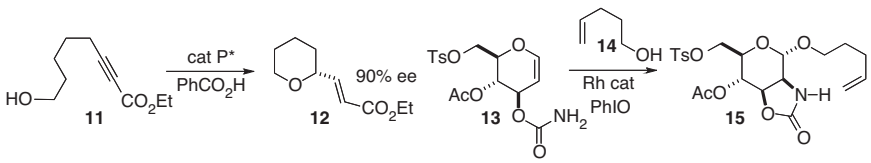
46. Stereocontrolled C-O Ring Construction: The Morimoto Synthesis of (+)-Omaezakianol

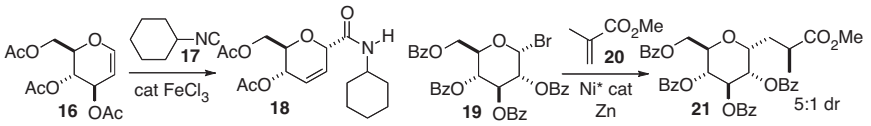
November 9, 2009

Tobin J. Marks of Northwestern University observed (*J. Am. Chem. Soc.* **2009**, *131*, 263) high geometric control in the cyclization of **1** to **2**. Tristan H. Lambert of Columbia University found (*Organic Lett.* **2009**, *11*, 1381) that Bi could catalyze both the addition of the ketene silyl acetal **4** to **3**, and the subsequent cyclization of the secondary alcohol so formed, to give the product ether **5** with high diastereocontrol. Glenn M. Sammis of the University of British Columbia devised (*Organic Lett.* **2009**, *11*, 2019) a radical relay cyclization of **6** to **7**, again with high diastereocontrol. Eric Fillion of the University of Waterloo established (*Organic Lett.* **2009**, *11*, 1919) that conjugate addition to the Meldrum's acid derivative **8** proceeded with high stereoselectivity, delivering the useful chiron **10**.

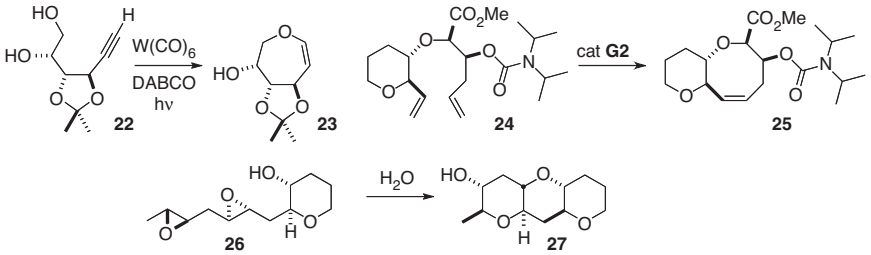


Gregory C. Fu of MIT found (*Angew. Chem. Int. Ed.* **2009**, *48*, 2225) that both five- and six-membered ring ethers could be formed with high enantiocontrol from alkyne alcohols such as **11**. The catalyst was a chiral phosphine. Christian M. Rojas of Barnard College established (*Organic Lett.* **2009**, *11*, 1527) a route to 2-amino sugars such as **15**, by Rh-mediated intramolecular nitrene addition in the presence of the trapping agent **14**. J. S. Yadav of the Indian Institute of Chemical Technology, Hyderabad devised (*Tetrahedron Lett.* **2009**, *50*, 81) a route to C-glycosides such as **18**, by condensation of a glycal **16** with an isonitrile **17**. Michel R. Gagné of the University of North Carolina developed (*Organic Lett.* **2009**, *11*, 879) a complementary route to C-glycosides such as **21**, with control of side chain relative configuration. Note that the addition to the methacrylate **20** is likely proceeding by initial one-electron reduction, since reductive β-elimination is not observed.

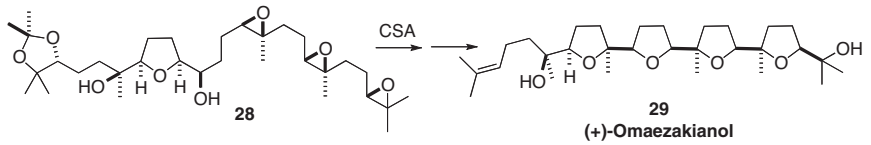




It is also possible to construct larger rings. Frank E. McDonald of Emory University devised a flexible route to protected tetraols such as **22**, and showed (*Organic Lett.* **2009**, *11*, 851) that it could be cyclized selectively to the septanoside **23**. Kenshu Fujiwara of Hokkaido University found (*Tetrahedron Lett*. **2009**, *50*, 1236) that ring-closing metathesis of **24** delivered the eight-membered ring product **25** in near quantitative yield.



For the synthesis of the ladder ethers, six-membered ring formation, as illustrated by the cyclization of **26** to **27**, is required. Timothy F. Jamison of MIT found (*J. Am. Chem. Soc.* **2009**, *131*, 6678; *Angew. Chem. Int. Ed.* **2009**, *48*, 4430) that six-membered ring formation can best be accomplished if the cyclization is carried out in water, without catalyst. The preference for six-membered ring formation is still dominant even in cases where methyl substitution would usually direct five-membered ring formation.

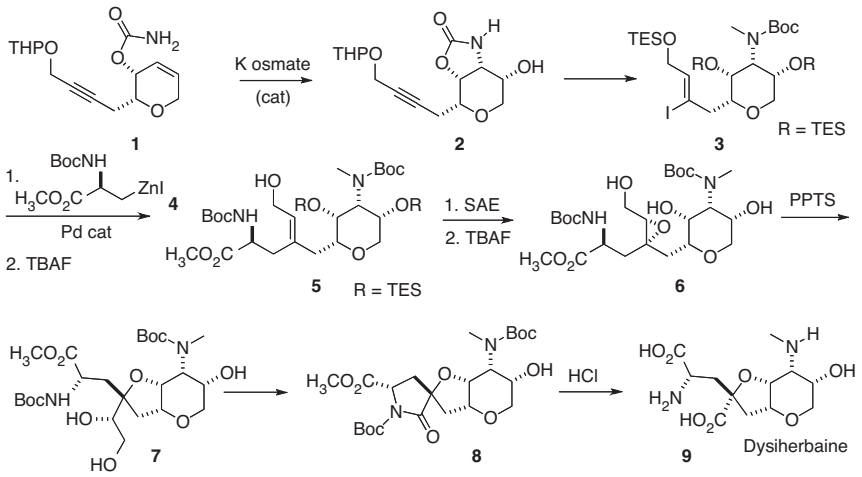


Acid-catalyzed cyclization of polyepoxides such as **28** strongly favors five-membered ring formation. In that cyclization, the central reaction in the synthesis of (+)-omaezakianol **29** reported (*Angew. Chem. Int. Ed.* **2009**, *48*, 2538) by Yoshiki Morimoto of Osaka City University, three of the four tetrahydrofuran rings of **29** are formed in a single step, each with high stereocontrol.

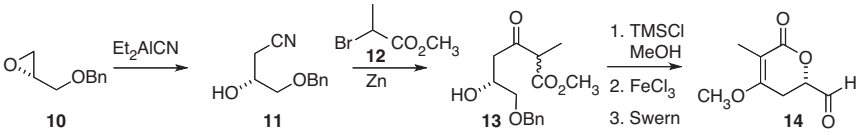
47. Synthesis of Dysiherbaine (Hatakeyama), Jerangolid D (Markó) and (+)-Spirolaxine Me Ether (Trost)

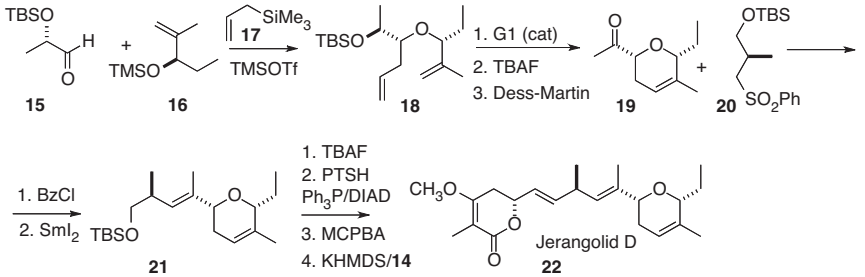
April 21, 2008

Several new developments in enantioselective C-O ring construction have been applied in the syntheses of natural products. To achieve control, the oxygenated quaternary center of dysiherbaine **9** must be established under kinetic conditions. One approach would be S_N2 opening, but this would require displacement at a fully-substituted center. Susumi Hatakeyama of Nagasaki University has shown (*Chem. Commun.* **2007**, 4158) that the epoxide **6**, prepared by the Sharpless procedure, undergoes just such an opening under mild acid catalysis.

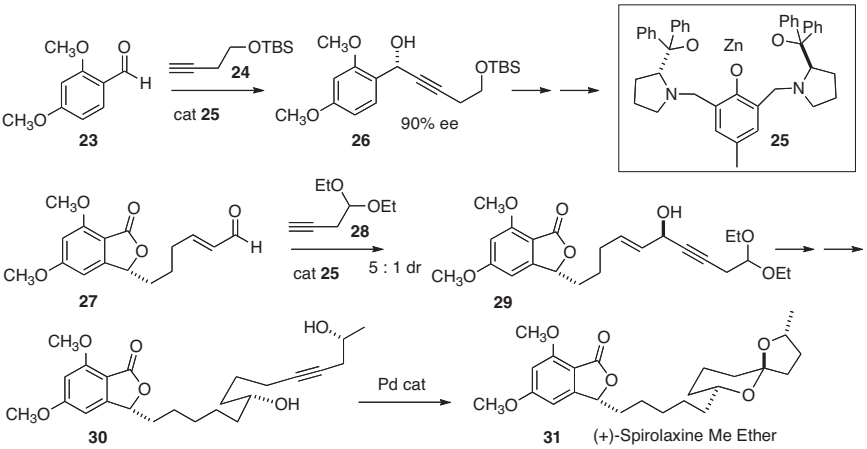


Another approach to highly-substituted tetrahydrofurans and tetrahydropyrans is to join two carbons of a preformed chiral ether, such as **18**. This is the strategy that István E. Markó employed in his recent (*J. Am. Chem. Soc.* **2007**, *129*, 3516) synthesis of jerangolid D **22**. The key step was the three-component coupling of **15**, **16**, and **17**, using a protocol recently developed in his group. Again using a procedure his group had developed, the trisubstituted alkene of **21** was prepared by modified Julia coupling of the ketone **19** with the anion of sulfone **20**, followed be esterification and reduction.





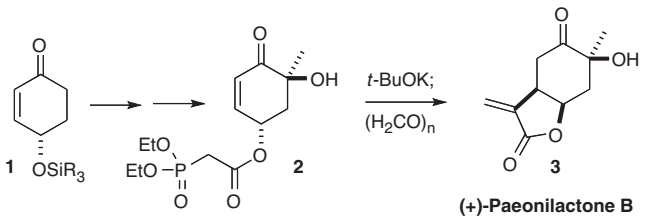
The spiroketal (+)-spiroxaline methyl ether **31** contains three secondary oxygenated stereogenic centers. In a showcase of current chiral technology, Barry M. Trost of Stanford University constructed (*Angew. Chem. Int. Ed.* **2007**, *46*, 7664) the first two of the three alcohols by the enantioselective addition of an alkyne to an aldehyde. The chiral catalyst **25** that directed the alkyne additions was derived from a commercial ligand. The last alcohol center was derived from *R*-(+)-epoxypropane. Note that the spiroketal was not prepared in the usual way, by acid-catalyzed cyclization of a dihydroxy ketone, but by Pd-catalyzed cyclization of the alkyne diol **30**.



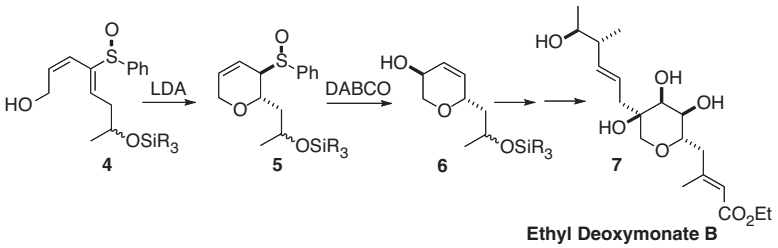
48. C-O Ring Containing Natural Products: Paeonilactone B (Taylor), Deoxymonate B (de la Pradilla), Sanguiin H-5 (Spring), Solandelactone A (White), Spirastrellolide A (Paterson)

February 9, 2009

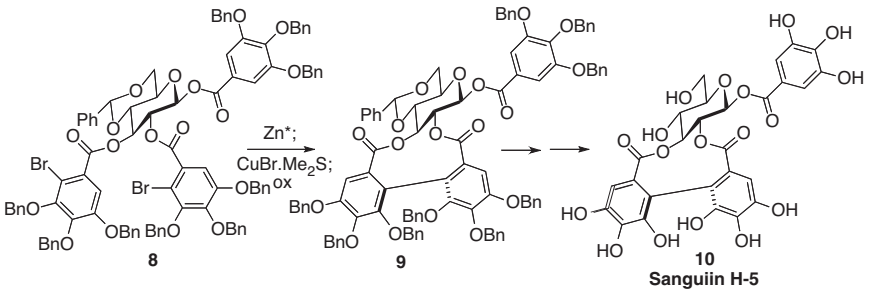
Richard J. K. Taylor of the University of York has developed (*Angew. Chem. Int. Ed.* **2008**, *47*, 1935) the diasteroselective intramolecular Michael cyclization of phosphonates such as **2**. Quenching of the cyclized product with paraformaldehyde delivered (+)-Paeonilactone B **3**.



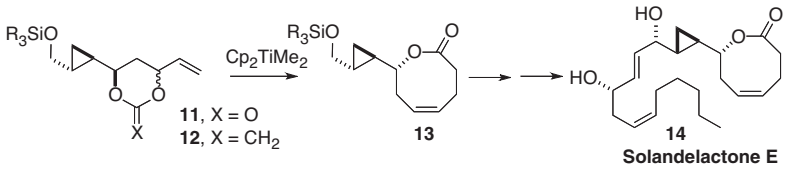
Roberto Fernández de la Pradilla of the CSIC, Madrid established (*Tetrahedron Lett.* **2008**, *49*, 4167) the diastereoselective intramolecular hetero Michael addition of alcohols to enantiomerically-pure acyclic sulfoxides such as **4** to give the allylic sulfoxide **5**. Mislow-Evans rearrangement converted **5** into **6**, the enantiomerically-pure core of Ethyl Deoxymonate B **7**.



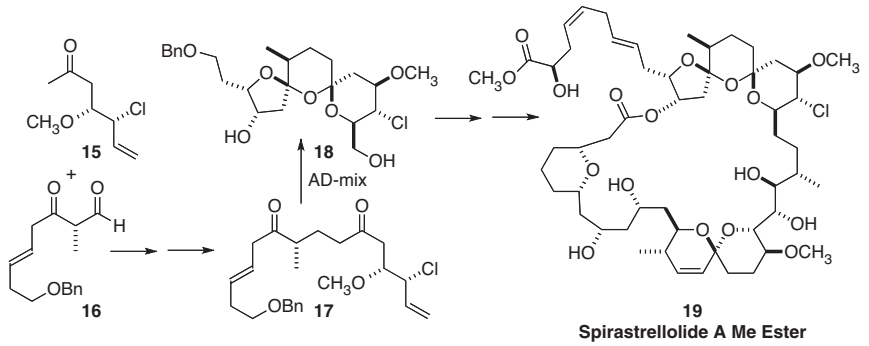
The ellagitannins, represented by **10**, are single atropisomers around the biphenyl linkage. David R. Spring of the University of Cambridge found (*Organic Lett.* **2008**, *10*, 2593) that the chiral constraint of the carbohydrate backbone of **9** directed the absolute sense of the oxidative coupling of the mixed cuprate derived from **9**, leading to Sanguiin H-5 **10** with high diastereomeric control.



A key challenge in the synthesis of the solandelactones, exemplified by **14**, is the stereocontrolled construction of the unsaturated eight-membered ring lactone. James D. White of Oregon State University found (*J. Org. Chem*. **2008**, *73*, 4139) an elegant solution to this problem, by exposure of the cyclic carbonate **11** to the Petasis reagent, to give **12**. Subsequent Claisen rearrangement delivered the eight-membered ring lactone, at the same time installing the ring alkene of Solandelactone E **14**.



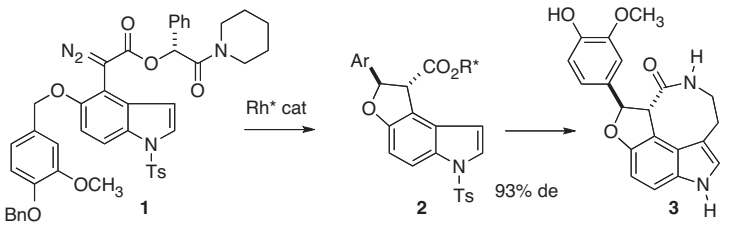
AD-mix usually proceeds with only modest enantiocontrol with terminal alkenes. None the less, Ian Paterson, also of the University of Cambridge, observed (*Angew. Chem. Int. Ed*. **2008**, *47*, 3016, *Angew. Chem. Int. Ed*. **2008**, *47*, 3021) that bis-dihydroxylation of the diene **17** proceeded to give, after acid-mediated cyclization, the bis-spiro ketal core **18** of Spirastrellolide A Methyl Ester **19** with high diastereocontrol.



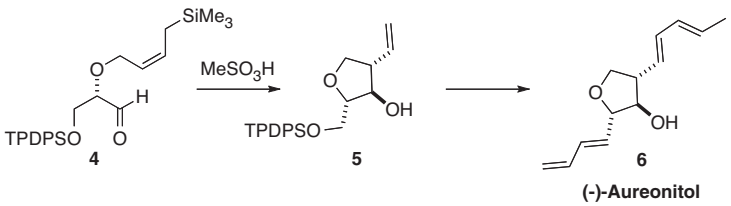
49. C-O Ring Natural Products: (-)-Serotobenine (Fukuyama-Kan), (-)-Aureonitol (Cox), Salmochelin SX (Gagné), Botcinin F (Shiina), (-)-Saliniketal B (Paterson), Haterumalide NA (Borhan)

April 20, 2009

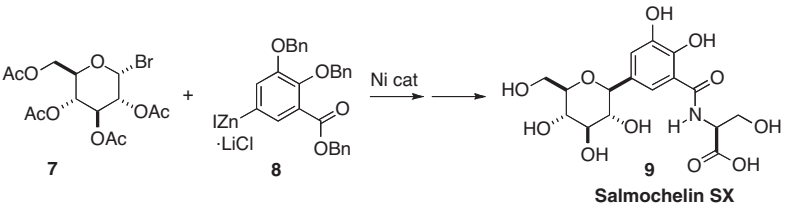
Tohru Fukuyama of the University of Tokyo and Toshiyuki Kan of the University of Shizuoka devised (*J. Am. Chem. Soc.* **2008**, *130*, 16854) the chiral auxiliary-directed Rh-mediated cyclization of **1**, setting the two stereogenic centers of **2** with high stereocontrol. The ester **2** was carried on to the indole alkaloid (-)-Serotobenine **3**.



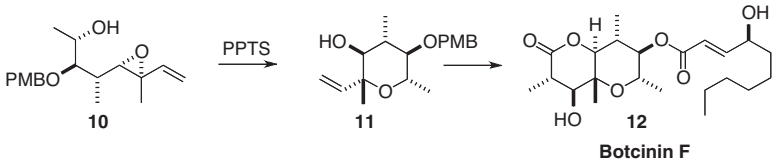
In the course of a synthesis of (-)-Aureonitol **6**, Liam R. Cox of the University of Birmingham developed (*J. Org. Chem.* **2008**, *73*, 7616) the diastereoselective intramolecular addition of an allyl silane **4** to give the tetrahydrofuran **5**. In analogy to what is known about the intramolecular ene reaction, the diastereocontrol observed for this cyclization may depend on the allyl silane being *Z*.



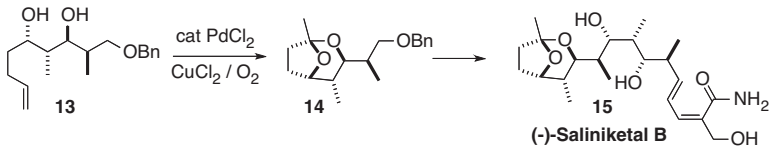
Michel R. Gagné of the University of North Carolina found (*J. Am. Chem. Soc.* **2008**, *130*, 12177) that the Ni-catalyzed coupling of organozinc halides could be extended to glycosyl halides such as **7**. This opened ready access to *C*-alkyl and *C*-aryl glycosides, including Salmochelin SX **10**.



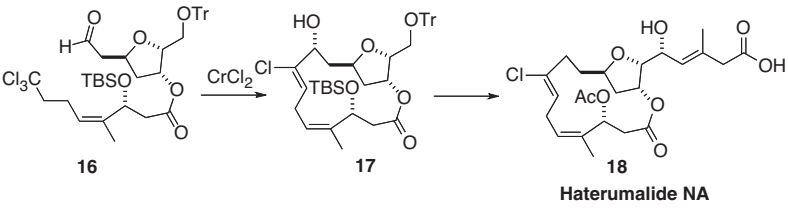
Isamu Shiina of the Tokyo University of Science established (*Organic Lett.* **2008**, *10*, 3153) that the acid-mediated cyclization of the Sharpless-derived epoxide **10** proceeded with clean inversion, to give **11**. The highly-substituted tetrahydropyran core **11** was then elaborated to the antifungal Botcinin F **12**.



Ian Paterson of Cambridge University optimized (*Organic Lett.* **2008**, *10*, 3295) the Pd-catalyzed spirocyclization of the ene diol **13**, leading to **14**, the enantiomerically-pure bicyclic core of (-)-Saliniketal B **15**.



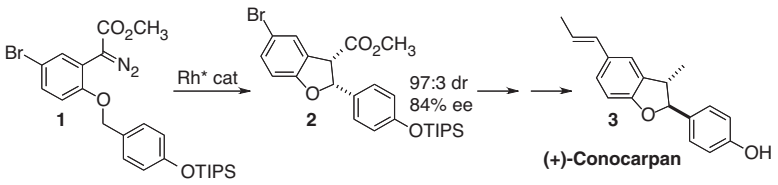
Haterumalide NA **18** presented the particular challenge of assembling the geometrically-defined chloroalkene, in addition to closing the macrolide ring. Babak Borhan of Michigan State University addressed (*J. Am. Chem. Soc.* **2008**, *130*, 12228) both of these challenges together, electing to employ a chlorovinylidene chromium carbenoid, as developed by Falck and Mioskowski, to effect the macrocyclization of **16** to **17**.



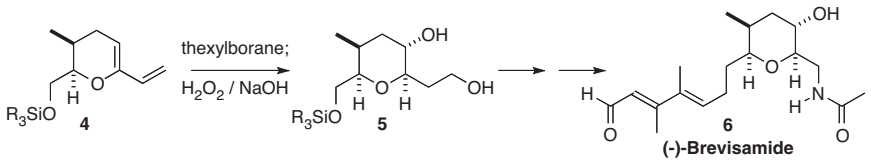
50. Complex Cyclic Ethers: (+)-Conocarpan (Hashimoto), (-)-Brevisamide (Satake/ Tachibana), (+)-Bruguierol A (Fañanás/ Rodríguez), (-)-Berkelic Acid (Snider), and (-)-Aigialomycin D (Harvey)

November 16, 2009

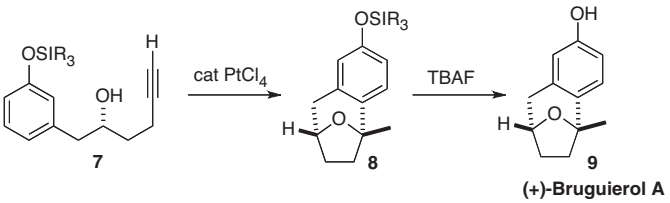
(+)-Conocarpan **3**, isolated from the wood of *Conocarpus erectus*, exhibits insecticidal, antifungal and antitrypanosomal activity. Shunichi Hashimoto of Hokkaido University developed (*J. Org. Chem.* **2009**, *74*, 4418) a chiral Rh (II) carboxylate that effected the cyclization of **1** to **2**, setting the absolute configuration of **3**.



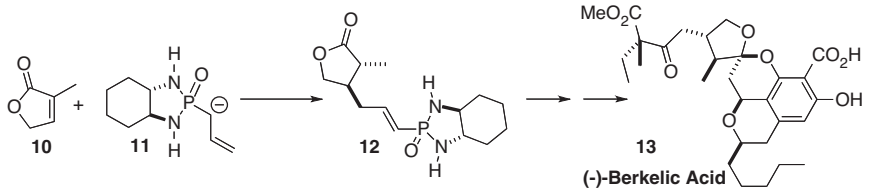
The dinoflagellate *Karenia brevis* produces the brevetoxins, a family of complex polyethers. Recently, the first N-containing cyclic ether, (-)-Brevisamide **6**, was isolated from *K. brevis*. Masayuki Satake and Kazuo Tachibana of the University of Tokyo, in their synthesis of **6** (*Organic Lett.* **2009**, *11*, 217) found it convenient to set the relative configuration around the six-membered ring by double hydroboration/oxidation of the diene **4**.



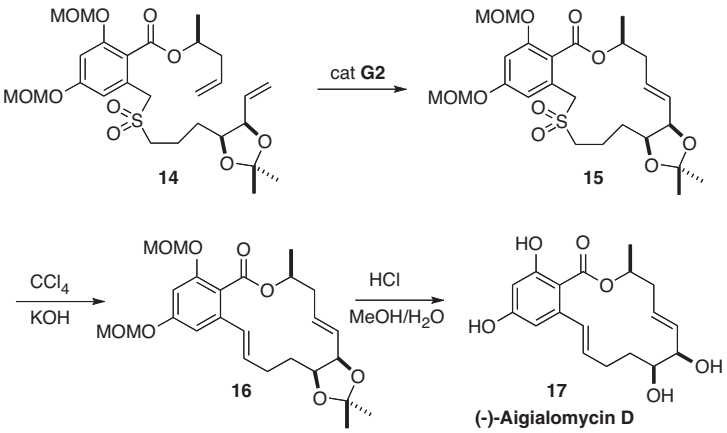
(+)-Bruguierol A **9**, isolated from the mangrove *Bruguiera gymmorrhiza*, has an unusual bridged structure. Francisco J. Fañanás and Félix Rodríguez of the Universidad de Oviedo conceived (*J. Org. Chem.* **2009**, *74*, 932) an elegant approach to the construction of **9**, based on the Pt-mediated addition of the alcohol of **7** to the alkyne to give a transient enol ether. It is not clear whether the subsequent intramolecular electrophilic addition to the aromatic ring is mediated by the Pt, or by a trace of adventitious acid. The overall transformation was remarkably efficient.



The Berkeley Pit in Butte, Montana, is an abandoned open-pit copper mine filled with 30 billion gallons of pH = 2.5 water heavily contaminated with, *inter alia*, copper, cadmium, arsenic and zinc. Remarkably, microorganisms can be cultured from that water. (-)-Berkelic Acid **13**, isolated from a *Penicillium* fungus, showed selective activity against OVCAR-3 ovarian cancer. Barry B. Snider of Brandeis University set (*Angew. Chem. Int. Ed.* **2009**, *48*, 1283) the absolute configuration of the central five-membered ring ether of **13** by conjugate addition of the enantiomerically-pure reagent **11** to the prochiral lactone **10**.



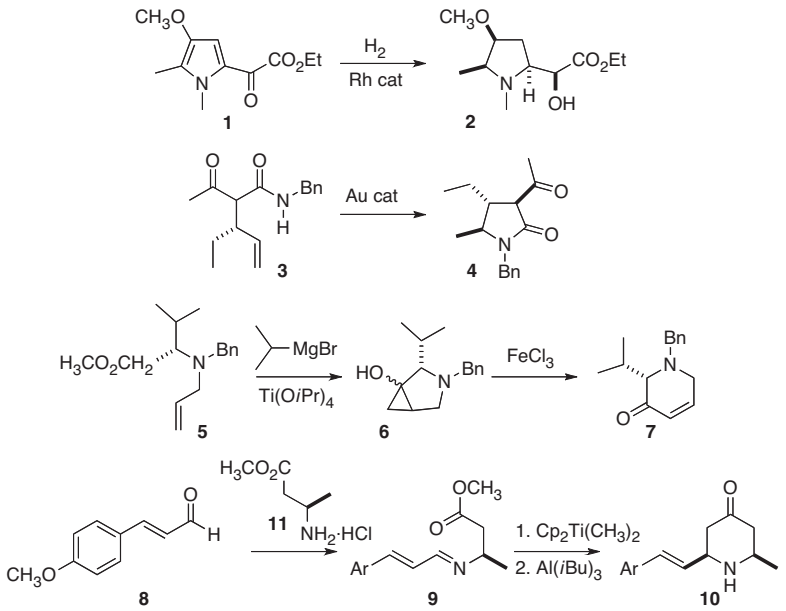
(-)-Aigialomycin D **17**, isolated from the mangrove fungus *Aigialus parvus*, was found to be a selective inhibitor of the kinases CDK1, CDK5 and GSK3. The synthesis of **17** reported (*J. Org. Chem.* **2009**, *74*, 2271) by Joanne Harvey of Victoria University of Wellington illustrated the power of the Ramberg-Bäcklund reaction for the closure of medium rings. Three-component coupling allowed the facile assembly of the sulfone **14**. Ring-closing metathesis gave **15**, that on oxidative SO_2 extrusion followed by deprotection gave (-)-Aigialomycin D **17**.



51. New Methods for the Stereoselective Construction of N-Containing Rings

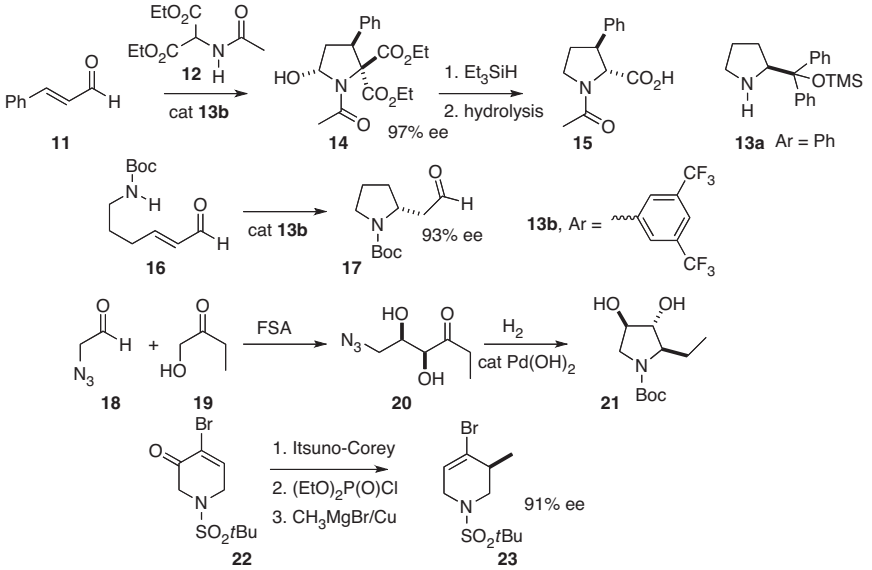
April 28, 2008

Several methods have been reported for the stereocontrolled preparation of pyrrolidine and piperidine derivatives. Alison J. Frontier of the University of Rochester has observed (*Organic Lett.* **2007**, *9*, 4939) that hydrogenation of acyl pyrroles such as **1** gave good control not just around the ring, but also on the sidechain. Chi-Ming Che of the University of Hong Kong has devised (*J. Am. Chem. Soc.* **2007**, *129*, 5828) a catalyst that converted amides such as **3** into the cyclized product **4**, also with high diastereocontrol. Jean Ollivier of the Université de Paris-Sud, following the Sato procedure, has applied (*Tetrahedron Lett.* **2007**, *48*, 8765) the Kulinkovich reaction to allylated amino acid esters such as **5**, to give, after Fe-mediated fragmentation, the enantiomerically-pure piperidone **7**. Richard C. Hartley of the University of Glasgow has reported (*J. Org. Chem.* **2007**, *72*, 10287) what are, remarkably, the first examples of the aza-Petasis-Ferrier reaction, converting an ester such as **9**, by carbonyl methylenation followed by Mannich cyclization, into the piperidone **10**.

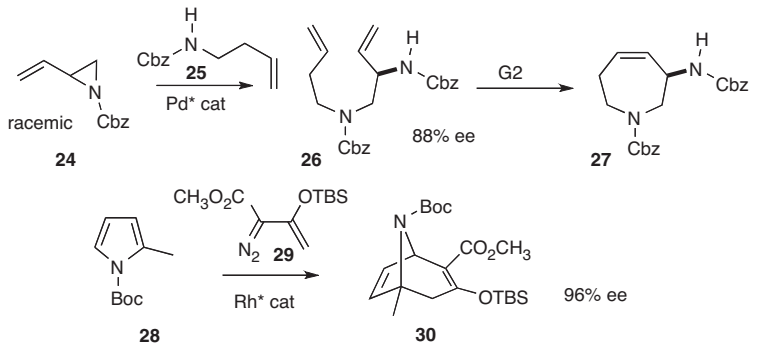


Procedures for *catalytic* enantioselective C-N ring construction have also been developed. Armando Córdova of Stockholm University has shown (*Tetrahedron Lett.* **2007**, *48*, 8695) that condensation of **11** with **12** led to **14**, which on reduction and hydrolysis delivered the 3-aryl proline **15**. In an even simpler case, Santos Fustero of the Universidad de Valencia found (*Organic Lett.* **2007**, *9*, 5283) that the aldehyde **16** could cyclize to **17** with

high ee. In a different approach (*J. Am. Chem. Soc.* **2007**, *129*, 14811), William E. Greenberg and Chi-Huey Wong of Scripps/La Jolla harnessed the power of an enzyme to mediate the addition of **19** to **18**, leading to the pyrrolidine **21**. Daniel P. Furkert of the University of Bath has applied (*Organic Lett.* **2007**, *9*, 3769) the powerful Itsuno-Corey reduction to the piperidone **22**, leading, after S_N2' displacement, to the alkene **23**.



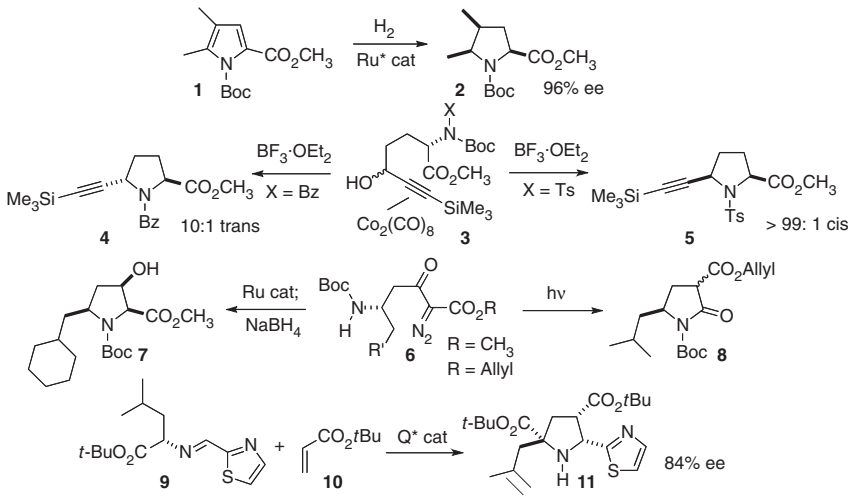
To construct larger rings, Barry M. Trost of Stanford University has employed (*Angew. Chem. Int. Ed.* **2007**, *46*, 6123) his powerful Pd catalyst to effect opening of the racemic aziridine **24**, leading, after metathesis, to the amine **27**. Huw M. L. Davies of the University at Buffalo used the Rh catalyst he has devised (*J. Am. Chem. Soc.* **2007**, *129*, 10312) to mediate the addition of **29** to the pyrrole **28**, giving the bicyclic **30** in high ee.



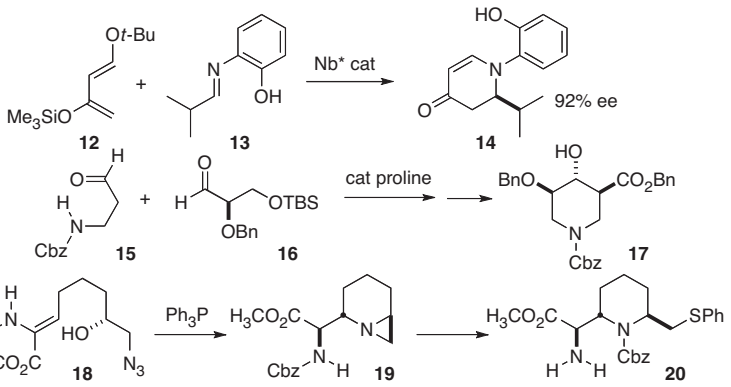
52. Stereoselective C-N Ring Construction

November 17, 2008

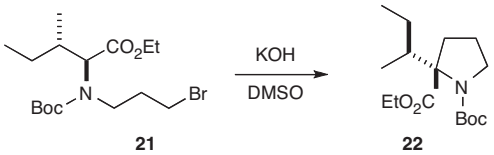
Ryoichi Kuwano of Kyushu University showed (*J. Am. Chem. Soc.* **2008**, *130*, 808) that diastereomerically and enantiomerically pure pyrollidines such as **2** could be prepared by hydrogenation of the corresponding pyrrole. Victor S. Martín of Universidad de la Laguna found (*Organic Lett*. **2008**, *10*, 2349) that the stereochemical outcome of the pyrrolidine-forming Nicholas cyclization could be directed by the protecting group on the N. Jianbo Wang of Peking University established (*J. Org. Chem.* **2008**, *73*, 1971) a convenient route to diazo esters such as **6**. N-H insertion led to the pyrrolidine, which Zhen-Jiang Xu of the Shanghai Institute of Organic Chemistry and Chi-Ming Che of the University of Hong Kong showed (*Organic Lett*. **2008**, *10*, 1529) could be reduced with high diastereoselectivity to the hydroxy ester **7**. Alternatively, Professor Wang found that photochemical Wolff rearrangement of **6** delivered the pyrrolidone **8**. Martin J. Slater and Shiping Xie of GlaxoSmithKline optimized (*J. Org. Chem.* **2008**, *73*, 3094) the hydroquinine catalyzed enantioselective 3+2 cycloaddition of **9** and **10**, leading to the pyrrolidine **11** with high diastereocontrol.



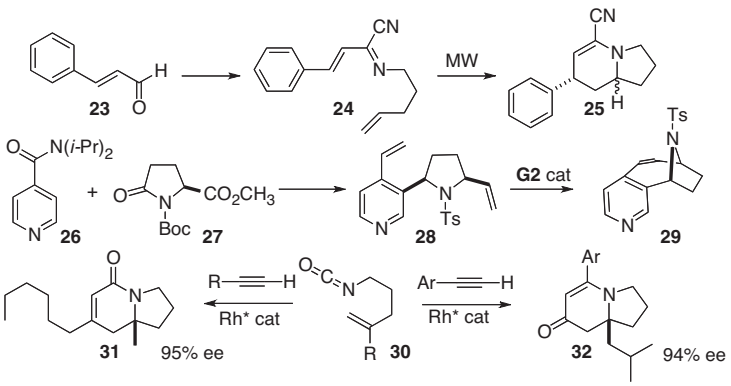
Shu Kobayashi of the University of Tokyo developed (*Adv. Synth. Cat.* **2008**, *350*, 647) a practical protocol for the aza Diels-Alder construction of enantiomerically-pure piperidines such as **14**. Biao Yu of the Shanghai Institute of Organic Chemistry cyclized (*Tetrahedron Lett.* **2008**, *49*, 672) the product from the proline-catalyzed enantioselective aldol of **15** and **16**, leading to the substituted piperidine **17**. Michael Shipman of the University of Warwick described (*Tetrahedron Lett.* **2008**, *49*, 250) the cyclization of the aziridine derived from **18**, that proceeded to give **19** as a single diastereomer, apparently via kinetic side-chain protonation.



Takeo Kawabata of Kyoto University found (*J. Am. Chem. Soc.* **2008**, *130*, 4153) that intramolecular alkylation to form four, five and six-membered rings from amino esters such as **21** proceeded with remarkable enantioretention.



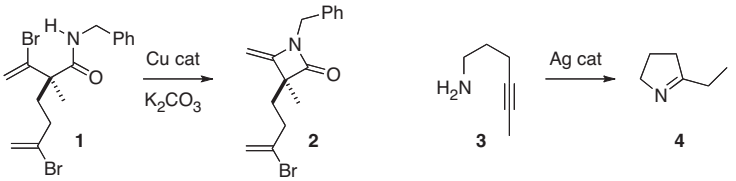
Géraldine Masson and Jieping Zhu of CNRS, Gif-sur-Yvette, condensed (*Organic Lett*. **2008**, *10*, 1509) cinnamaldehyde **23** with cyanide and an ω-alkenyl amine to give the intramolecular aza-Diels-Alder substrate **24**. Hongbin Zhai of the Shanghai Institute of Organic Chemistry acylated (*J. Org. Chem.* **2008**, *73*, 3589) **26** with **27**, leading to the ring-closing metathesis precursor **28**. Tomislav Rovis of Colorado State University developed (*Organic Lett*. **2008**, *10*, 1231) the Rh-catalyzed condensation of the isocyanate **30** with alkyl alkynes to give **31**, and with aryl alkynes to give **32**.



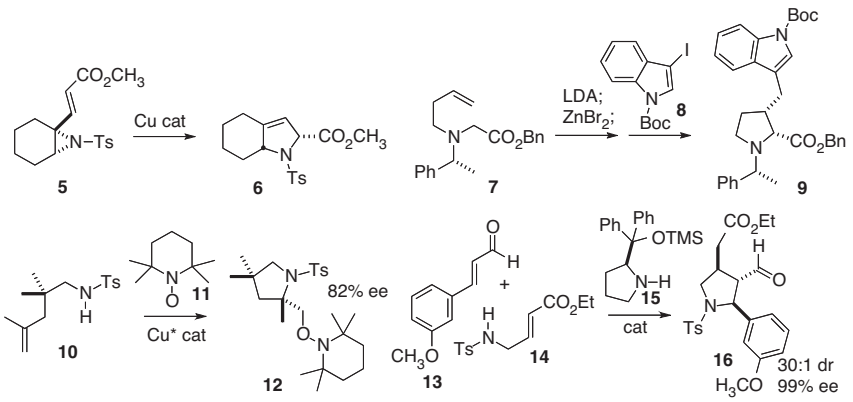
53. New Methods for C-N Ring Construction

April 27, 2009

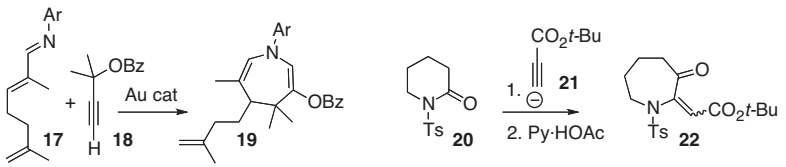
Chaozhong Li of the Shanghai Institute of Organic Chemistry demonstrated (*Organic Lett*. **2008**, *10*, 4037) facile and selective Cu-catalyzed β-lactam formation, converting **1** to **2**. Paul Helquist of the University of Notre Dame devised (*Organic Lett*. **2008**, *10*, 3903) an effective catalyst for intramolecular alkyne hydroamination, converting **3** into the imine **4**. Six-membered ring construction worked well also.



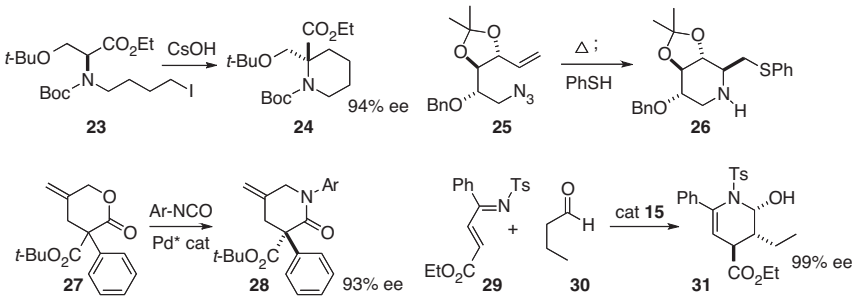
Jon T. Njardarson of Cornell University found (*Organic Lett*. **2008**, *10*, 5023) a Cu catalyst for the rearrangement of alkenyl aziridines such as **5** to the pyrroline **6**. Philippe Karoyan of the UPMC, Paris developed (*J. Org. Chem.* **2008**, *73*, 6706) an interesting chiral auxiliary directed cascade process, converting the simple precursor **7** into the complex pyrrolidine **9**. Sherry R. Chemler of the State University of New York, Buffalo devised (*J. Am. Chem. Soc.* **2008**, *130*, 17638) a chiral Cu catalyst for the cyclization of **10**, to give **12** with substantial enantiocontrol. Wei Wang of the University of New Mexico demonstrated (*Chem. Commun.* **2008**, 5636) the organocatalyzed condensation of **13** and **14** to give **16** with high enantio- and diastereocontrol.



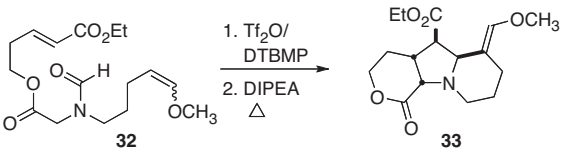
Two complementary routes to azepines/azepinones have appeared. F. Dean Toste of the University of California, Berkeley showed (*J. Am. Chem. Soc.* **2008**, *130*, 9244) that a gold complex catalyzed the condensation of **17** and **18** to give **19**. Frederick G. West of the University of Alberta found (*Organic Lett*. **2008**, *10*, 3985) that lactams such as **20** could be ring-expanded by the addition of the propiolate anion **21**.



Takeo Kawabata of Kyoto University extended (*Organic Lett*. **2008**, *10*, 3883) "memory of chirality" studies to the cyclization of **23**, demonstrating that **24** was formed in high ee. Paul V. Murphy of University College Dublin took advantage (*Organic Lett*. **2008**, *10*, 3777) of the well-known intramolecular addition of azides to alkenes, showing that the intermediate could be intercepted with nucleophiles such as thiophenol, to give the cyclized product **26** with high diastereocontrol. Ryo Shintani and Tamio Hayashi, also of Kyoto University, found (*J. Am. Chem. Soc.* **2008**, *130*, 16174) that a chiral Pd catalyst effected condensation of racemic **27** with an aryl isocyanate to give, via decarboxylation, the lactam **28** in high ee. Ying-Chun Chen of Sichuan University optimized (*Angew. Chem. Int. Ed*. **2008**, *47*, 9971) the organocatalyst-mediated condensation of **29** with **30** to give **31** with high enantio- and diastereocontrol.



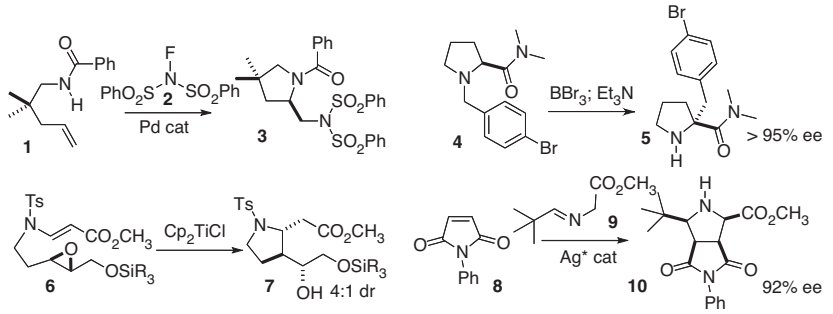
Guillaume Bélanger of the Université de Sherbrooke devised (*Organic Lett*. **2008**, *10*, 4939) an elegant cascade dipole formation and cycloaddition, converting **32** into **33** as a single diastereromer.



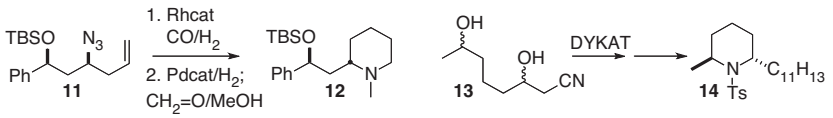
54. Stereocontrolled Construction of C-N Rings: The Vanderwal Synthesis of Norfluorocurarine

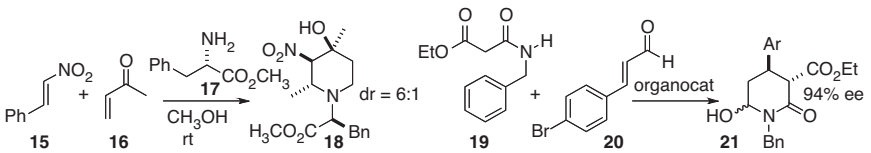
November 23, 2009

Forrest E. Michael of the University of Washington described (*Organic Lett.* **2009**, *11*, 1147) the Pd-catalyzed aminative cyclization of **1** to the differentially-protected diamine **3**. Peter Somfai of KTH Chemical Science and Engineering observed (*Organic Lett.* **2009**, *11*, 919) that [1,2]-rearrangement of **4** proceeded to deliver **5** with near-perfect maintenance of enantiomeric excess. Tushar Kanti Chakraborty of the Central Drug Research Institute, Lucknow applied (*Tetrahedron Lett.* **2009**, *50*, 3306) the Ti(III) reduction of epoxides to the Sharpless-derived ether **6**, leading to the pyrrolidine **7**. Chun-Jiang Wang of Wuhan University devised (*Chem. Commun.* **2009**, 2905) a silver catalyst that directed the absolute sense of the dipolar addition of **9** to **8** to give **10**.

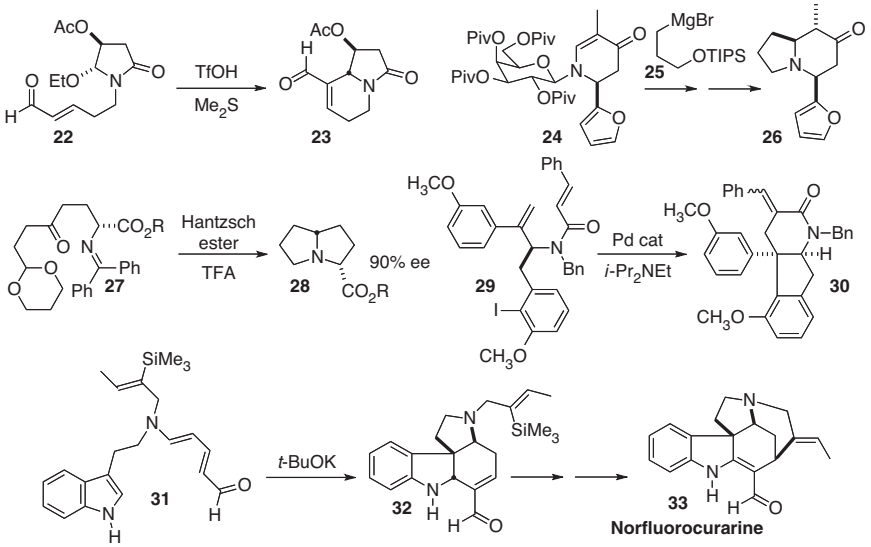


Homoallyic azides such as **11** are readily prepared in high enantiomeric excess from the corresponding alcohol. Bernhard Breit of Albert-Ludwigs-Universität, Freiburg and André Mann of the Faculté de Pharmacie, Illkirch showed (*Organic Lett.* **2009**, *11*, 261) that Rh-mediated hydroformylation could be effected in the presence of the azide. Subsequent reduction delivered the piperidine **12**. Jan-E. Bäckvall of Stockholm University applied (*J. Org. Chem.* **2009**, *74*, 1988) the protocol for dynamic kinetic asymmetric transformation (DYKAT) that he had developed to the cyanodiol **13**. Remarkably, a single enantiomerically-pure diasteromer emerged, which he carried on to **14**. Xiaodong Shi of West Virginia University found (*Organic Lett.* **2009**, *11*, 2333) that the stereogenic center of **17**, even though it ended up outside the ring, directed the absolute configuration of the other centers of **18** as they formed. Jan Vesely of Charles University and Albert Moyano and Ramon Rios of the Universitat de Barcelona established (*Tetrahedron Lett.* **2009**, *50*, 1943) that an organocatayst directed the absolute configuration in the addition of **19** to **20** to give **21**.





Osamu Tamura of Showa Pharmaceutical University effected (*Organic Lett.* **2009**, *11*, 1179) cyclization of the malic acid-derived amide **22** to give **23** with high diastereocontrol. Horst Kunz of Johannes Gutenberg-Universität Mainz demonstrated (*Angew. Chem. Int. Ed.* **2009**, *48*, 2228) that the galactosylamine-derived auxiliary of **24** directed conjugate addition first to prepare **24**, then again in the conversion of **24** to **26**. Keiji Maruoka of Kyoto University used (*Organic Lett.* **2009**, *11*, 2027) an organocatalyst-directed conjugate addition to prepare **27**, that he then carried on to **28**. Hiroyuki Ishibashi of Kanazawa University established (*J. Org. Chem.* **2009**, *74*, 2624) conditions for the cascade cyclization of **29** to **30**.

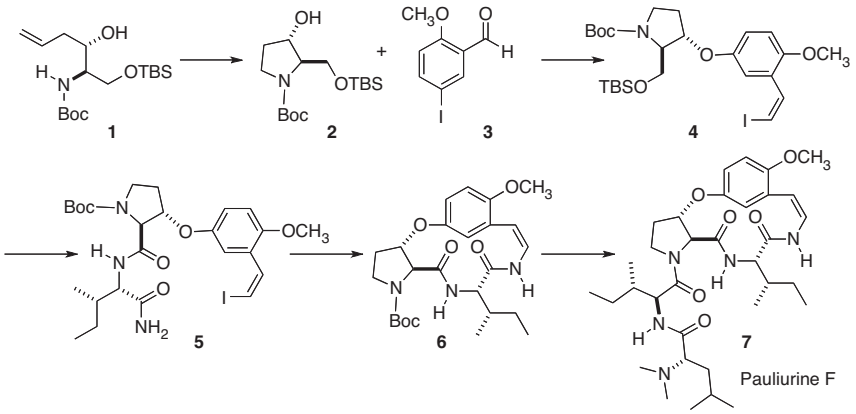


Diels-Alder cyclization of a triene such as **31** would offer rapid access to polycyclic indole alkaloids. Christopher D. Vanderwal of the University of California, Irvine developed (*J. Am. Chem. Soc.* **2009**, *131*, 3472) alkaline conditions for this powerful transformation. He then carried **32** on to the *Strychnos* alkaloid Norfluorocurarine **33**.

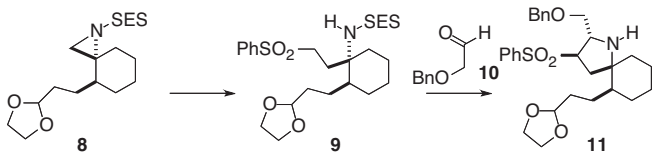
55. Alkaloid Synthesis: Paliurine F, Lepadiformine, and 7-Deoxypancratistatin

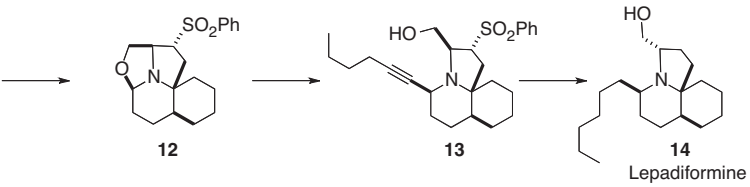
January 14, 2008

The sedative alkaloid paliurine F **7** is a pentapeptide bridged by an arene. Gwilherm Evano of the Université de Versailles took advantage of this in his synthesis (*Angew. Chem. Int. Ed.* **2007**, *46*, 572) of **7**, although it was necessary to prepare, from serine, one of the amino acid derivatives, the protected 3-hydroxyprolinol **2**. The key step in the synthesis was the Cu-catalyzed intramolecular coupling of **5** to give the macrolactam **6**. Deprotection and acylation then gave paliurine F **7**.

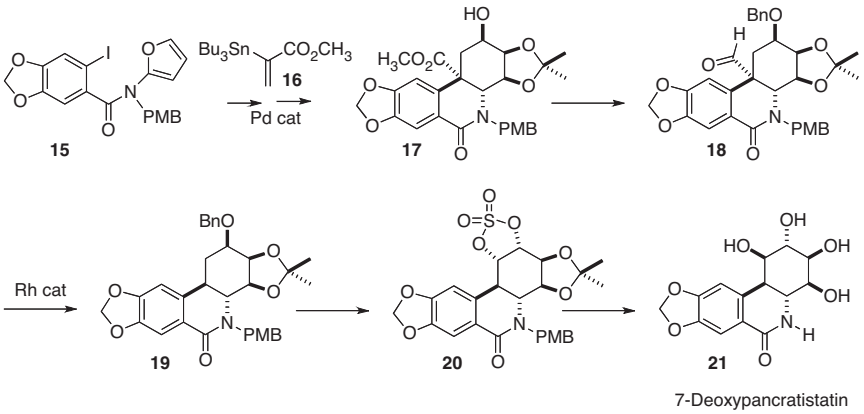


Lepadiformine **14**, isolated from the tunicate *Clavelina lepadiformis*, shows moderate cytotoxicity, and is also a K+ channel blocker. The synthesis of **14** (*Angew. Chem. Int. Ed.* **2007**, *46*, 2631) by Donald Craig of Imperial College started with the aziridine **8**, prepared from the corresponding epoxide. Opening of the protected aziridine with the anion of methyl phenyl sulfone set the stage for condensation of the dianion derived from **9** with the aldehyde **10**, to give, with high diastereocontrol, the amine **11**. Deprotection followed by cyclization then led to the activated ether **12**. While the opening of **12** with an alkyl Grignard reagent proceeded with undesired inversion at the reacting center, opening with the alkynyl Grignard delivered mainly the desired **13**. Reduction followed by oxidation, epimerization and reduction then gave lepadiformine **14**.





The *Amaryllidaceae* alkaloid 7-deoxypancratistatin **21** has potent antiviral activity. A challenge in the assembly of **21** is that the ring fusion is trans, less stable than the corresponding cis diastereomer. The synthesis of **21** (*J. Org. Chem.* **2007**, *72*, 2570) by Albert Padwa of Emory University started with **17**, the preparation of which by the combination **15** and **16** he had previously reported in the course of his synthesis of lycoricidine (*OHL* December 11, 2006). Ester **17** had the desired trans ring fusion, but with an angular ester substituent that had to be removed.



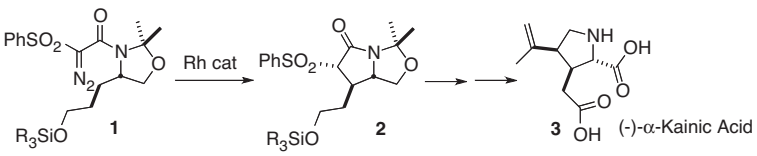
While it would be expected from the mechanism that Rh-mediated decarbonylation of an aldehyde would proceed with retention of absolute configuration, and this had been confirmed experimentally, this reaction had not been applied to such a challenging substrate. In the event, the transformation proceeded smoothly, to give the desired trans **19**. Dehydration and dihydroxylation of **19** led to the cyclic sulfate **20**, selective S_N2 opening of which delivered 7-deoxypancratistatin **21**.

The decarbonylation of **18** was reported on a 2.1 mmol scale, using 3.2 mmol of Wilkinson's catalyst, $(Ph_3P)_3RhCl$. For larger scale reactions, it will be important to make this transformation truly catalytic. It has been reported (*J. Am. Chem. Soc.* **1978**, *100*, 7083; *J. Org. Chem.* **1984**, *49*, 3195) that inclusion of a bridging ligand such as 1,3-bis-diphenylphosphinopropane (dppp) in the decarbonylation can lead to turnover numbers in excess of 100,000.

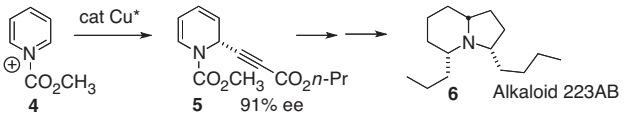
56. Adventures in Alkaloid Synthesis: (+)-α-Kainic Acid (Jung), 223AB (Ma), Pumiliotoxin 251F (Jamison), Spirotryprostatin B (Trost), (-)-Drupacine (Stoltz)

May 12, 2008

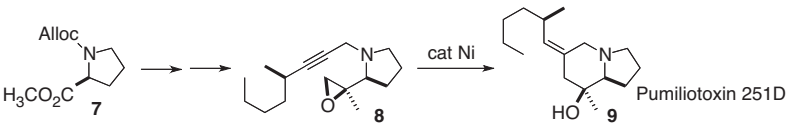
Enantiomerically-pure natural amino acids can serve as starting materials for alkaloid synthesis. In his synthesis (*J. Org. Chem.* **2007**, *72*, 10114) of (-)-α-kainic acid **3**, Kyung Woon Jung of the University of Southern California prepared the diazo sulfone **1** from (L)-glutamic acid. Rh-mediated intramolecular C-H insertion proceeded with the predicted high diastereoselectivity, to give the lactam **2**, containing seven of the ten carbon atoms and two of the three stereogenic centers of (-)-α-kainic acid **3**.



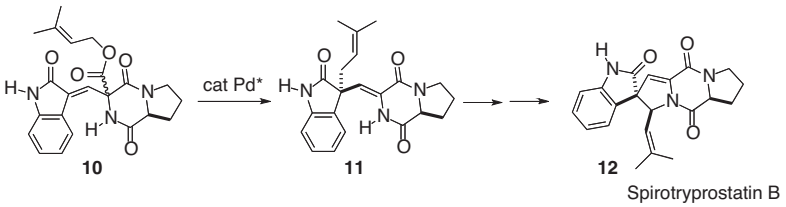
The absolute configuration of the nitrogen ring system(s) can also be established by chiral catalysis. Dawei Ma of the Shanghai Institute of Organic Chemistry has developed (*J. Am. Chem. Soc.* **2007**, *129*, 9300) a chiral Cu catalyst that mediated the addition of alkynyl esters and ketones to the prochiral acylated pyridine **4** in high enantiomeric excess. The dihydropyridines (e.g. **5**) so produced will be versatile starting materials both for alkaloid synthesis, as illustrated by the preparation of the Dendrobatid alkaloid 223AB **6**, and for the production of pharmaceuticals.



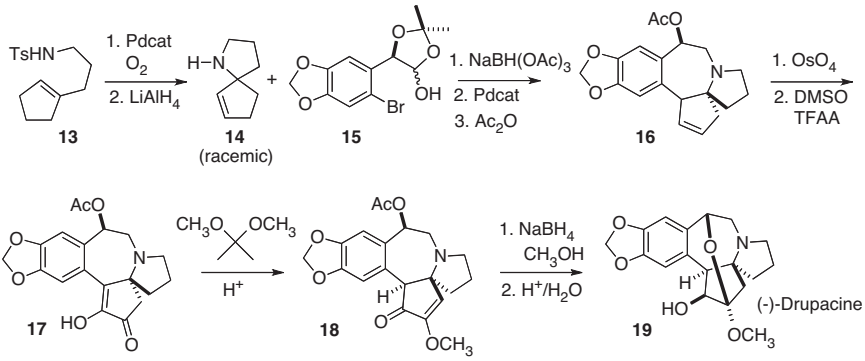
In his synthesis of the Dentrobatid alkaloid pumiliotoxin 251D **9**, Timothy F. Jamison took (*J. Org. Chem.* **2007**, *72*, 7451) as his starting material another amino acid, proline. Ni-mediated cyclization of the epoxide **8** proceeded with high geometric and regiocontrol, to give **9**. The chemistry to convert **7** into **8** with high diastereocontrol and without racemization is a substantial contribution that will have many other applications.



In his synthesis (*Organic Lett.* **2007**, *9*, 2763) of spirotryprostatin B **12**, Barry M. Trost of Stanford University also started with proline, which was readily elaborated to the oxindole **10**. The question was, could the Pd-catalyzed decarboxylation of **10** be induced to provide specifically **11**? Counting geometric isomers of the trisubstituted alkene, and allylic regioisomers, as well as diastereomers, there were sixteen possible products from this prenylation. Using chiral Pd control, the rearrangement proceeded with 14:1 regiocontrol, and 16:1 diasterocontrol. Oxidative cyclization of **11** then delivered spirotryprostatin B **12**.



The *Cephalotaxus* alkaloid (-)-drupacine **19** has five stereogenic centers, including four of the five positions on the cyclopentane ring. Remarkably, Brian M. Stoltz of the California Institute of Technology was able (*J. Org. Chem.* **2007**, *72*, 7352) to prepare enantiomerically-pure **19** by initially controlling just the single stereogenic center of **15**. Reductive amination of **15** with racemic **14** led to a separable 1:1 mixture of diastereomers. Acid-mediated equilibration converted the wrong diastereomer **17** (as well as the correct diastereomer, not shown) to a 2:1 mixture favoring the desired diastereomer **18**.

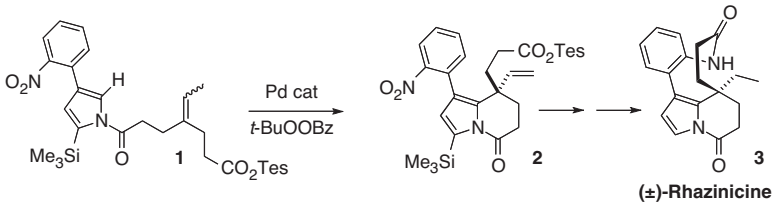


This column is dedicated to the memory of the late John W. Daly, who contributed so much to our knowledge of alkaloid chemistry.

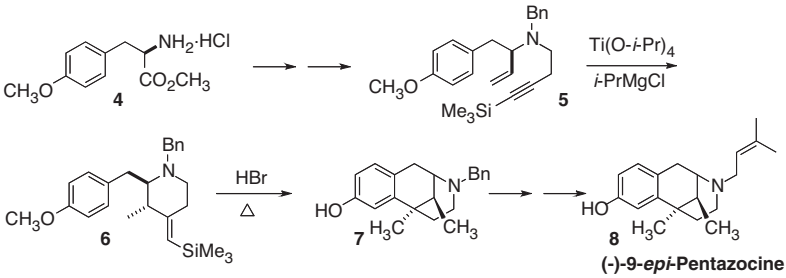
57. Stereocontrolled Alkaloid Construction: Rhazinicine (Gaunt), 9-*epi*-Pentazocine (Zhai and Li), Fawcettidine (Dake), Strychnine (Padwa), and Yohimbine (Jacobsen)

November 24, 2008

The power of catalytic C-H functionalization is illustrated by the elegant synthesis of rhazinicine **3** devised (*Angew. Chem. Int. Ed.* **2008**, *47*, 3004) by Matthew J. Gaunt of the University of Cambridge. The key step in the synthesis was the oxidative cyclization of **1** to **2**. Although **1** has *many* C-H sites, the Pd catalyst selected for the α position of the pyrrole, leading, after intramolecular Heck addition and β-hydride elimination, to the alkene **2**. Reduction and macrolactamization completed the synthesis of **3**.

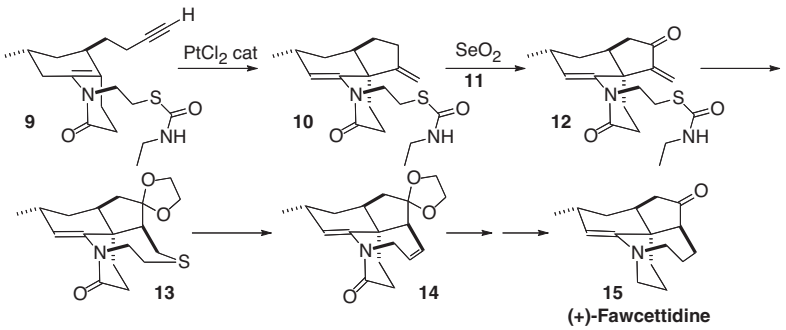


Hongbin Zhai of the Shanghai Institute of Organic Chemistry and Zhong Li of East China University of Science and Technology prepared (*Organic Lett.* **2008**, *10*, 2457) the analgesic (-)-9-*epi*-pentazocine **8** from the amino ester **4**, itself available from D-tyrosine. In the conversion of **5** to **6**, the $(i\text{-PrO})_2$Ti formed a ring, leading to **6** as a single diastereomer and geometric isomer. HBr then effected both deprotection of the methyl ether and cyclization, to give **7**, which was carried on to **8**.

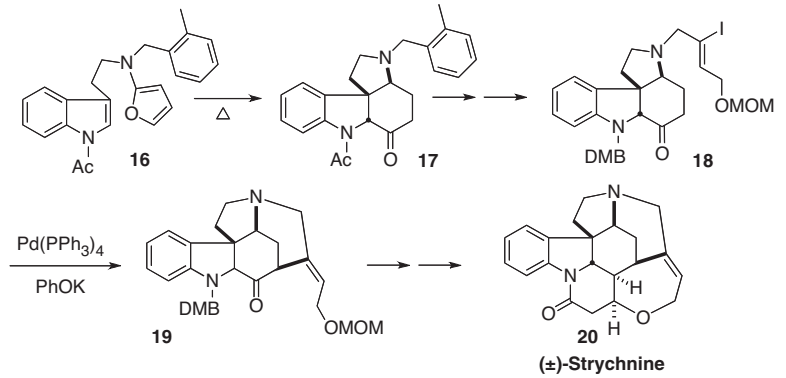


The Pt-catalyzed cyclization of **9** to **10** set the stage for the synthesis of (+)-fawcettidine **15** by Gregory R. Dake of the University of British Columbia (*Angew. Chem. Int. Ed.* **2008**, *47*, 4221). This synthesis also illustrated the power of the Ramberg-Bäcklund reaction for the assembly of medium rings. The thiolate liberated from **12** readily added to the enone, to give **13**.

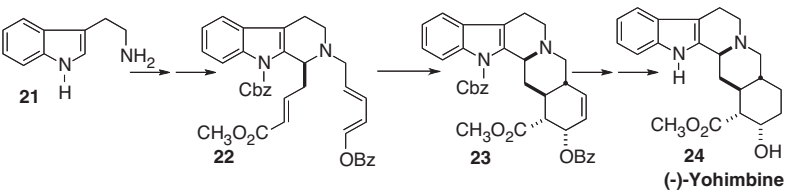
Oxidation to the sulfone followed by the Ramberg-Bäcklund reaction (halogenation, intramolecular displacement, chelotropic elimination of SO_2) then delivered **14**, which was selectively reduced, leading to **15**.



Albert Padwa of Emory University has developed (*J. Org. Chem.* **2008**, *73*, 3539) a general route to the *Strychnos* alkaloids, based on the facile cyclization of the furan **16** to the tetracyclic ketone **17**. This project culminated in the synthesis of the heptacyclic strychnine **20**.



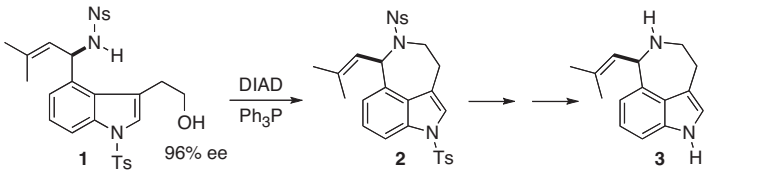
Eric N. Jacobsen of Harvard University has devised a family of catalysts for the enantioselective Pictet-Spengler reaction of tryptamine **21**. He has now (*Organic Lett.* **2008**, *10*, 745) used this approach to prepare the triene **22** in 94% ee. The Diels-Alder cyclization of **22** proceeded with high diastereocontrol to give **23**, the immediate precursor of (-)-yohimbine **24**.



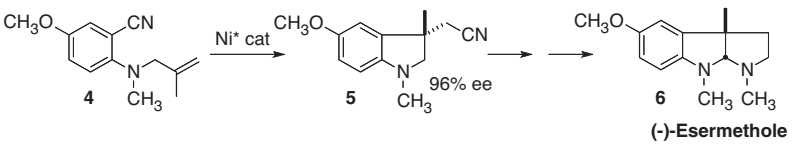
58. Alkaloid Synthesis: (-)-Aurantioclavine (Stoltz), (-)-Esermethole (Nakao/Hiyama/ Ogoshi), (-)-Kainic Acid (Tomooka), Dasycarpidone (Bennasar), (-)-Cephalotaxine (Ishibashi) and Lysergic Acid (Fujii/Ohno)

May 11, 2009

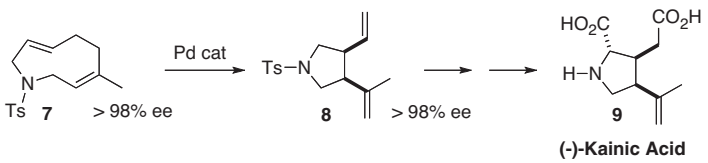
Intriguing strategies have been developed for the stereocontrolled assembly of complex alkaloid structures. Brian M. Stoltz of Caltech prepared (*J. Am. Chem. Soc.* **2008**, *130*, 13745) the enantiomerically-pure alcohol precursor to the secondary amine **1** by enantioselective oxidation of the racemic alcohol. Intramolecular Mitsunobu coupling of **1** then led to (-)-Aurantioclavine **3**.



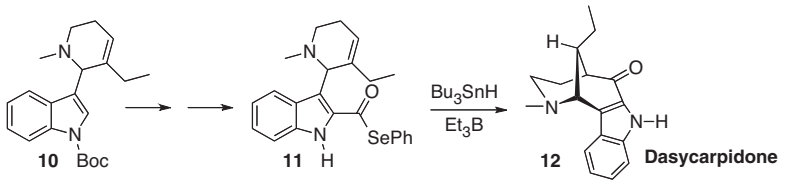
Yoshiaki Nakao and Tamejiro Hiyama of Kyoto University and Sensuke Ogoshi of Osaka University developed (*J. Am. Chem. Soc.* **2008**, *130*, 12874) an enantioselective Ni catalyst for the cyclization of **4** to **5**. Oxidation and cyclization then delivered (-)-Esermethole **6**.



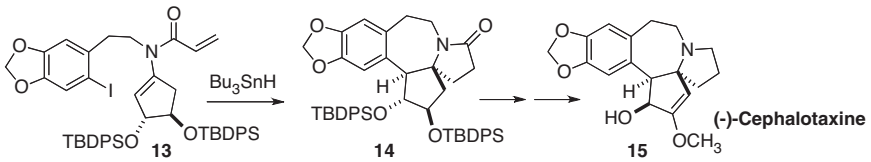
Although the sulfonamide **7** appears to be prochiral, in fact its two most stable conformations are bent, and enantiomers of each other, with a significant barrier for interconversion. Katsuhiko Tomooka of Kyushu University separated (*Tetrahedron Lett.* **2008**, *49*, 6327) the enantiomers of **7**, then carried the enantiomercially-pure **7** on, by Pd-catalyzed Cope rearrangement, to **8** and so to (-)-Kainic Acid **9**.



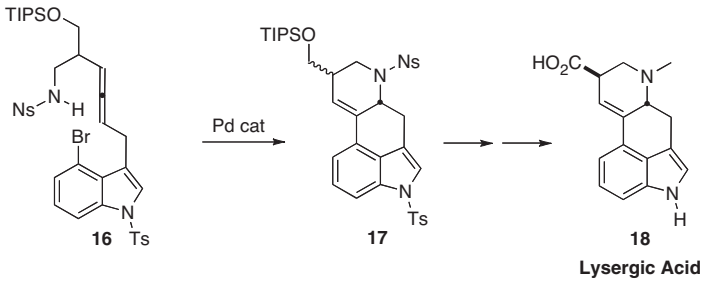
M.-Lluïsa Bennasar of the University of Barcelona prepared (*J. Org. Chem.* **2008**, *73*, 9033) the acyl selenide **11** from the indole **10**. While the radical derived from **11** might have been expected to undergo 5-exo cyclization, in the event the 6-endo mode dominated, to give Dasycarpidone **12** and its diastereomer.



Hiroyuki Ishibashi of Kanazawa University showed (*Organic Lett*. **2008**, *10*, 4129) that the radical cascade cyclization of the enamine **13**, derived from diethyl tartrate, proceeded with remarkable diastereocontrol, to give **14**. The amide **14** was converted to (-)-Cephalotaxine **15**.



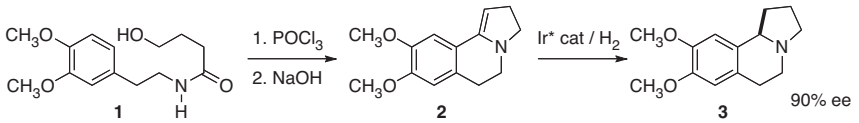
Nobutaka Fujii and Hiroaki Ohno, also of Kyoto University, used (*Organic Lett*. **2008**, *10*, 5239) a Pd catalyst to mediate the cascade cyclization of **16** to **17**. Although **16** has two stereogenic centers, including the allene, it is the aminated stereogenic center of **17** that sets the absolute configuration of the product Lysergic Acid **18**. One intermediate in the conversion of **16** to the tetracyclic **17** is the tricyclic π-allyl Pd complex. If all the material could be channeled through that pathway, there is a good chance that the chiral Trost catalyst could effectively control the absolute configuration of the aminated stereogenic center as it is formed, leading to the enantiomerically enriched product **18**.



59. Alkaloid Synthesis: Crispine A (Zhou), Cermizine C (Zhang), Tangutorine (Poupon), FR901483 (Kerr), Serratezomine A (Johnston)

November 30, 2009

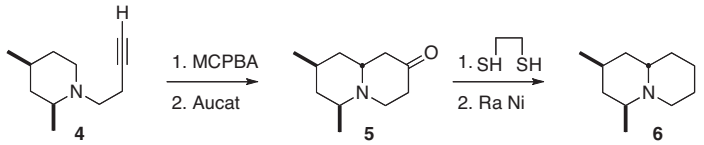
Enantioselective hydrogenation of enamides is a well-established transformation. The corresponding reduction of enamines has been elusive. Qi-Lin Zhou of Nankai University designed (*J. Am. Chem. Soc.* **2009**, *131*, 1366) an Ir catalyst that reduced **2** to the *Carpus* alkaloid Crispine A **3** in high ee.



1 **2** **3**

Crispine A

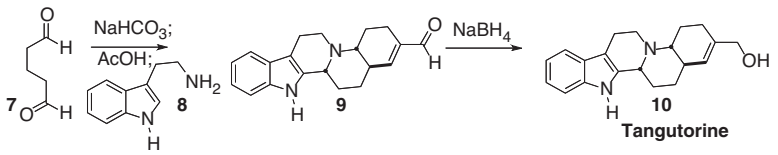
Direct conversion of C-H to C-C bonds is a powerful synthetic transformation. Liming Zhang, now at the University of California, Santa Barbara, observed (*J. Am. Chem. Soc.* **2009**, *131*, 8394) that a gold catalyst converted the N-oxide of **4** into **5**, that was then deoxygenated to give Cermizine C **6**. The gold catalyst and the N-oxide combined to convert the alkyne into an α-keto carbene, in the process reducing the N-oxide back to the amine. The carbene then abstracted a hydride from the carbon adjacent to the amine, generating an intermediate that collapsed to give **5** with high diastereocontrol.



4 **5** **6**

Cermizine C

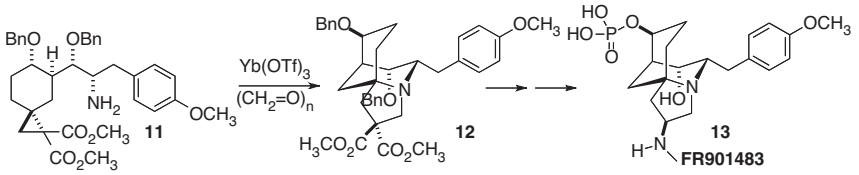
Tangutorine **10**, isolated from the leaves of *Nitraria tangutorum*, affects the morphology of human colon cancer cells. In a biomimetic approach, Erwan Poupon of the Université Paris-Sud stirred (*Organic Lett.* **2009**, *11*, 1891) glutaraldehyde **7** with bicarbonate to give an unstable carbocyclic dimer. Addition of tryptamine in acetic acid delivered the pentacyclic product **9**, that was reduced with borohydride to give the crystalline Tangutorine **10**.



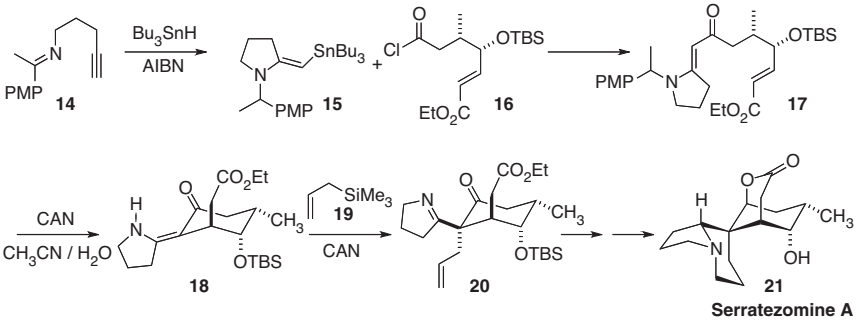
7 **8** **9** **10**

Tangutorine

FR901483, a potent immunosuppressive isolated from a *Cladobotyrum* fermentation broth, presents an challenging array of stereogenic centers in its tricyclic skeleton. Michael A. Kerr of the University of Western Ontario prepared (*Organic Lett*. **2009**, *11*, 777) the activated cyclopropane **11**, then effected intramolecular dipolar opening with an intermediate imine, yielding the tricyclic **12**.



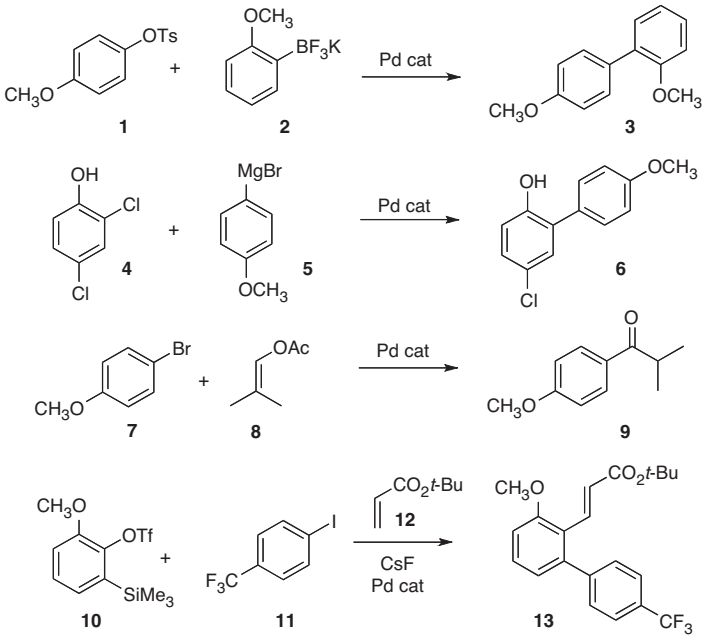
The *Lycopodium* alkaloid Serratezomine A **21** presents a similarly challenging array of stereogenic centers in its tetracyclic structure. Jeffrey N. Johnston of Vanderbilt University constructed (*J. Am. Chem. Soc.* **2009**, *131*, 3470) the pyrrolidine ring of **15** using the imine free radical acceptor that he had previously developed. Having the alkene-Sn bond in place then enabled coupling with the acid chloride **16**. Oxidative deprotection of **17** freed the enamine, that added in a conjugate sense to the unsaturated ester, kinetically setting the axial branch of **18**. A second CAN-mediated step, allylation with **19**, set the quaternary center of Serratezomine A **21**.



60. Synthesis of Substituted Benzenes: The Carter Synthesis of Siamenol

July 14, 2008

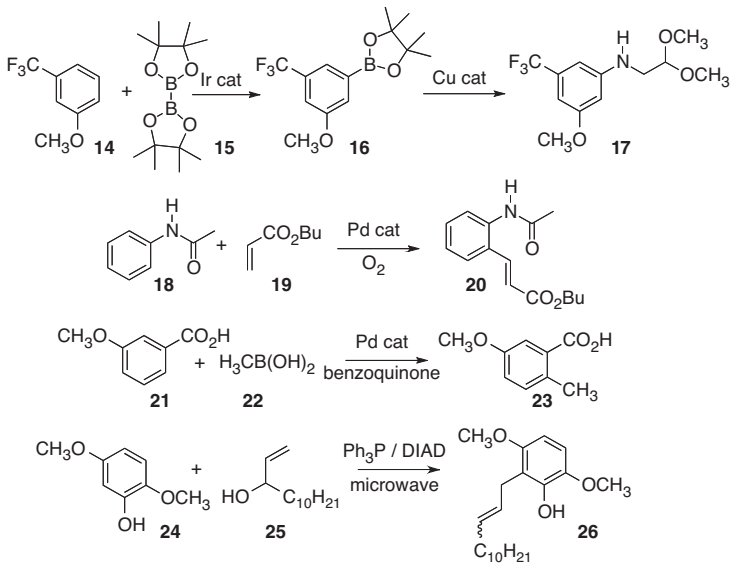
Tosylates are among the least expensive, but also among the least reactive toward Pd(0) oxidative addition, of aryl sulfonates. Jie Wu of Fudan University has now devised conditions (*J. Org. Chem.* **2007**, *72*, 9346) for the Pd-catalyzed coupling of aryl tosylates such as **1** with arene trifluoroborates. Kei Manabe of RIKEN has found (*Organic Lett.* **2007**, *9*, 5593) that an ortho OH activates an adjacent Cl for Pd-mediated coupling, allowing the conversion of **4** to **6**. Philippe Uriac and Pierre van de Weghe of the Université de Rennes I have developed (*Organic Lett.* **2007**, *9*, 3623) conditions for the catalytic acylation of aryl halides with alkenyl acetates such as **8**.



Multi-component coupling lends itself well to diversity-oriented synthesis. As illustrated by the combination of **10** with **11** and **12** to give **13** reported (*Organic Lett.* **2007**, *9*, 5589) by Michael F. Greaney of the University of Edinburgh, benzynes can do double addition with high regiocontrol. For other recent references to unsymmetrical double additions to arynes, see *Angew. Chem. Int. Ed*. **2007**, *46*, 5921; *Chem. Commun*. **2007**, 2405; and *J. Am. Chem. Soc.* **2006**, *128,* 14042.

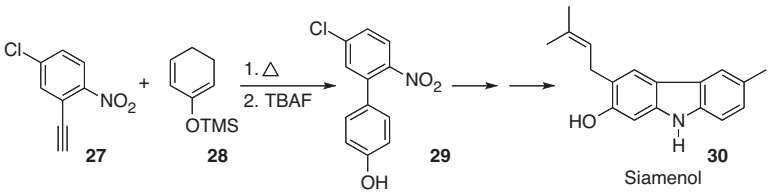
C-H functionalization of arenes is of increasing importance. John F. Hartwig of the University of Illinois has described (*Organic Lett.* **2007**, *9*, 757; 761) improved conditions for Ir-catalyzed meta borylation, and conditions for further coupling of the initial borate **16**

to give amines such as **17**. Lei Liu and Qing-Xiang Guo of the University of Science and Technology, Hefei have found (*Tetrahedron Lett*. **2007**, *48*, 5449) that oxygen can be used as the stoichiometric oxidant in the Pd-catalyzed functionalization of H's ortho to anilides. Two other research groups (*J. Am. Chem. Soc.* **2007**, *129*, 6066; *Angew. Chem. Int. Ed.* **2007**, *46*, 5554; *J. Org. Chem*. **2007**, *72*, 7720) reported advances in this area. In a close competition, Jin-Quan Yu, now at Scripps/La Jolla (*J. Am. Chem. Soc.* **2007**, *129*, 3510) and Olafs Daugulis of the University of Houston (*J. Am. Chem. Soc.* **2007**, *129*, 9879) both reported that a carboxyl group can activate an ortho H for direct functionalization. Note that metalation of **21** would be expected to proceed ortho to the methoxy group.



There are other strategies for directly functionalizing ortho positions. Christopher J. Moody of the University of Nottingham has found (*J. Org. Chem.* **2007**, *72*, 10298) that phenols such as **24** can be coupled with secondary allylic alcohols to give, after Claisen rearrangement, the alkylated product **26**.

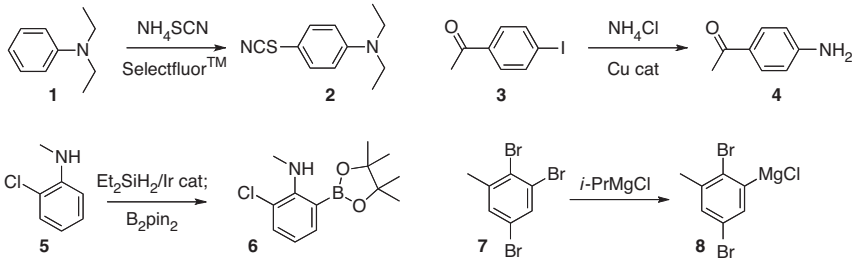
For highly-substituted benzene derivatives, it is sometimes more efficient to build the aromatic ring. Rich G. Carter of Oregon State University, in the course of a synthesis (*J. Org. Chem.* **2007**, *72*, 9857) of siamenol **30**, developed the Diels-Alder addition of aryl alkynes such as **27** to enol derivatives such as **28** to give the biphenyl **29**.



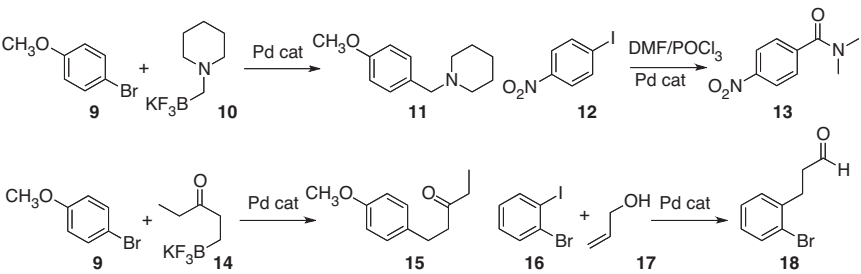
61. Preparation of Benzene Derivatives

October 13, 2008

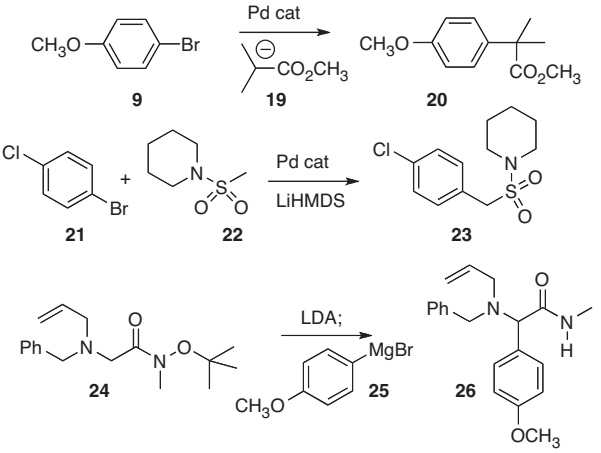
Several new methods have been put forward for the functionalization of benzene derivatives. J. S. Yadav of the Indian Institute of Chemical Technology, Hyderabad has devised (*Chem. Lett*. **2008**, *37*, 652) a procedure for direct thiocyanation, converting **1** into **2**. Sukbok Chang of KAIST has established (*Chem. Commun*. **2008**, 3052) that both NH_4Cl and aqueous NH_3 could be used to directly aminate an aryl iodide such as **3**. John F. Hartwig of the University of Illinois has developed (*J. Am. Chem. Soc.* **2008**, *130*, 7534) a protocol for the directed borylation of anilines such as **5** and of phenols, based on a transient silylation. Karsten Menzel of Merck West Point (*Tetrahedron Lett*. **2008**, *49*, 415) has observed selective exchange of tribromobenzene derivatives such as **7**, with the direction of the selectivity being controlled by the fourth substituent on the benzene.



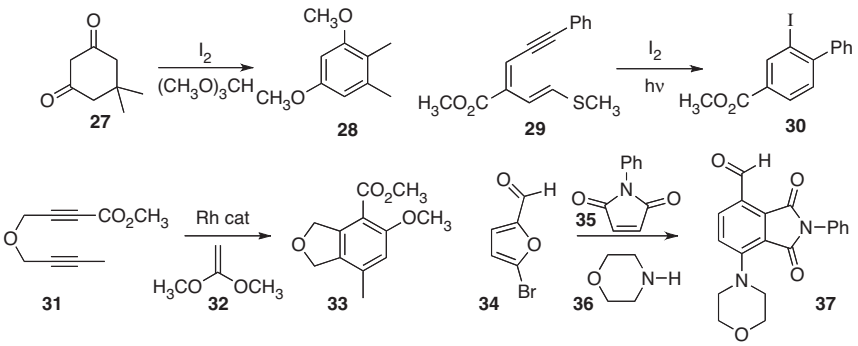
Gary A. Molander of the University of Pennsylvania has extensively developed the stable, readily prepared trifluoroborates, exemplified by **10** (*J. Org. Chem*. **2008**, *73*, 2052) and **14** (*Organic Lett*. **2008**, *10*, 1795) as partners for Suzuki-Miyaura coupling. The conversion of **9** to **10** is complementary to aminocarbonylation, exemplified by the conversion of **12** to **13** reported (*Tetrahedron Lett*. **2008**, *49*, 2221) by Bhalchandra M. Bhanage of the Institute of Chemical Technology, University of Mumbai. The coupling of **9** with **14** is complementary to the long-known Heck coupling of an aryl halide such as **16** with an allylic alcohol, as illustrated by the preparation of **18** described (*Tetrahedron Lett*. **2008**, *49*, 3279) by Martin E. Maier of the Universität Tübingen.



Professor Hartwig has also (*Organic Lett*. **2008**, *10*, 1545, 1549) optimized conditions for the Pd-catalyzed arylation of ester enolates such as **19**. Gang Zhou of Schering-Plough, Kenilworth, NJ has developed (*Organic Lett*. **2008**, *10*, 2517) a related transformation, the arylation of deprotonated sulfonamides. Peter Somfai of the Royal Institute of Technology, Stockholm has established (*Angew. Chem. Int. Ed.* **2008**, *47*, 1907) a complementary procedure, base-mediated elimination of *t*-butoxide from **24**, followed by 1,2-addition of an aryl or heteroaryl Grignard reagent.



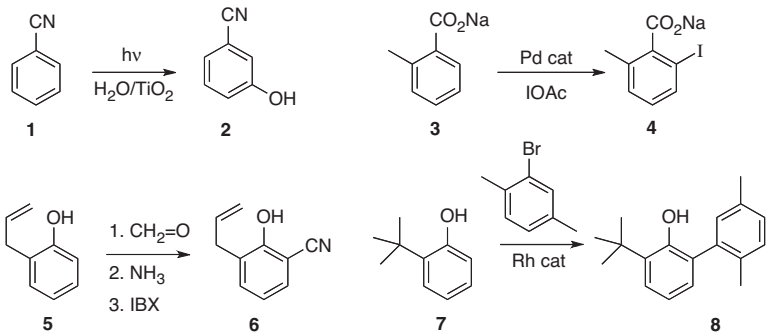
For some substitution patterns, it is more efficient to construct the benzene ring. Professor Yadav observed (*Tetrahedron Lett*. **2008**, *49*, 3810) that **27** was aromatized to **28**. Katsuyuki Ogura of Chiba University showed (*J. Org. Chem.* **2008**, *73*, 1726) that **29** cyclized to **30**. Ken Tanaka of the Tokyo University of Agriculture and Technology established (*Organic Lett*. **2008**, *10*, 2537) that enol ethers or enol acetates could take the place of an alkyne partner in a trimerization reaction, as illustrated by the regioselective cycloaromatization of **31** to **33**. For a related study, see *Tetrahedron Lett*. **2008**, *49*, 445. Sylvain Marque and Damien Prim of the Université de Versailles-Saint-Quentin-en-Yvelines have found (*J. Org. Chem.* **2008**, *73*, 2191) that activation of **34** by condensation with a secondary amine set the stage for Diels-Alder cycloaddition and aromatization, leading to **37**. For related studies, see *Organic Lett*. **2008**, *10*, 233 and *Tetrahedron Lett*. **2008**, *49*, 219.



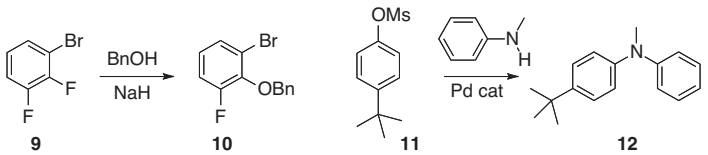
62. Preparation of Benzene Derivatives: The Barrett Syntheses of Dehydroaltenuene B and 15G256β

June 29, 2009

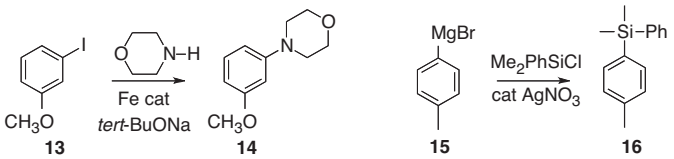
Several new methods for the direct functionalization of Ar-H have appeared. Hisao Yoshida of Nagoya University observed (*Chem. Comm.* **2008**, 4634) that under irradiation, TiO_2 in water effected *meta* hydroxylation of benzonitrile **1** to give the phenol **2**. Anisole showed *ortho* selectivity, while halo and alkyl aromatics gave mixtures. Melanie S. Sanford of the University of Michigan reported (*J. Am. Chem. Soc.* **2008**, *130*, 13285) a complementary study of Pd-catalyzed *ortho* acetoxylation. Jin-Quan Yu of Scripps/La Jolla developed (*Angew. Chem. Int. Ed.* **2008**, *47*, 5215) a Pd-catalyzed protocol for *ortho* halogenation of aromatic carboxylates such as **3**. A related protocol (*J. Am. Chem. Soc.* **2008**, *130*, 17676) led to *ortho* arylation. Trond Vidar Hansen of the University of Oslo devised (*Tetrahedron Lett.* **2008**, *49*, 4443) a one-pot procedure for the net *ortho* cyanation of phenols such as **5** to the salicylnitrile **6**. Robin B. Bedford of the University of Bristol, Andrew J. M. Caffyn of the University of the West Indies and Sanjiv Prashar of the Universidad Rey Juan Carlos established (*Chem. Comm.* **2008**, 990) a Rh-catalyzed protocol for *ortho* arylation of phenols such as **7**.



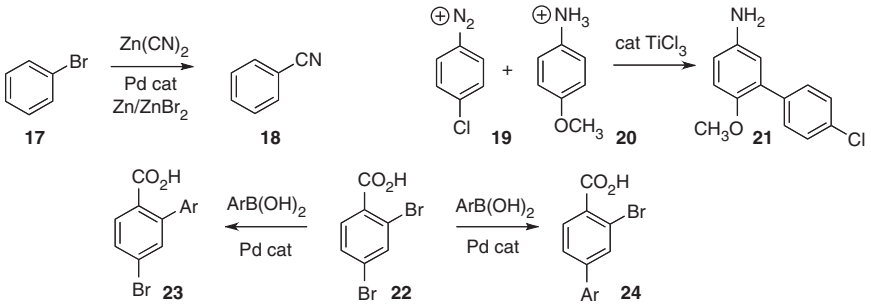
Laurent Désaubry of the Université Louis Pasteur observed (*Tetrahedron Lett.* **2008**, *49*, 4588) regioselective coupling of unsymmetrical difluorobenzenes such as **9** to give the ether **10**. Fuk Yee Kwong of Hong Kong Polytechnic University extended (*Angew. Chem. Int. Ed.* **2008**, *47*, 6402) Pd-mediated amination to the notoriously difficult mesylates, such as **11**. John F. Hartwig of the University of Illinois reported (*J. Am. Chem. Soc.* **2008**, *130*, 13848) a related method for the amination of aryl tosylates.



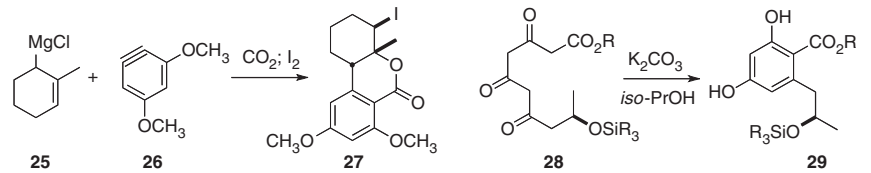
Hong Liu of the Shanghai Institute of Materia Medica found (*Organic Lett.* **2008**, *10*, 4513) that the Fe-catalyzed amination of aryl halides such as **13** sometimes gave mixtures of regioisomers. Hideki Yorimitsu and Koichiro Oshima of Kyoto University effected (*Angew. Chem. Int. Ed.* **2008**, *47*, 5833) Ag-catalyzed Grignard cross coupling with aryl halides, converting **15** into **16**. Note that silyl aromatics such as **16** are readily reduced under dissolving metal conditions to give allyl silanes.



Frederic G. Buono of the Bristol-Myers Squibb chemical process group optimized (*Organic Lett.* **2008**, *10*, 5325) the cyanation of aryl halides, uncovering the valuable co-catalytic role of $ZnBr_2$. Markus R. Heinrich of the Technische Universität München developed (*Angew. Chem. Int. Ed.* **2008**, *47*, 9130) an intriguing Ti(III)-catalyzed radical arylation, converting **23** into **24**. Ioannis N. Houpis of the Johnson and Johnson chemical process group established (*Organic Lett.* **2008**, *10*, 5601) conditions for Pd coupling to selectively convert **19** to either **20** or **21**.



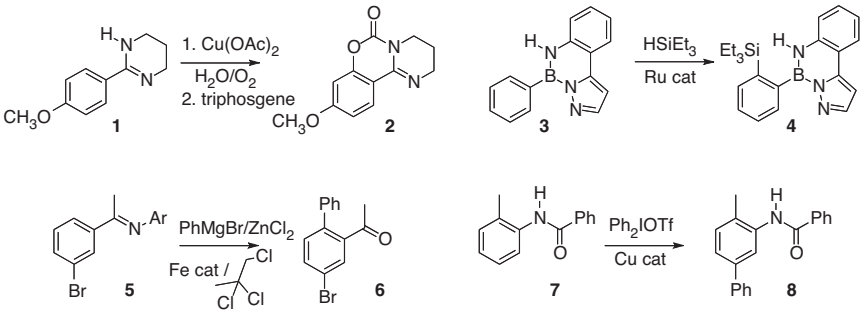
Anthony G. M. Barrett of Imperial College London took advantage (*Organic Lett.* **2008**, *10*, 3833) of regioselective addition the allylic anion **22** to the benzyne **23** to give, after carboxylation, the iodolactone **24**, that he carried on to Dehydroaltenuene B. Following up on the work of Thomas M. Harris, Professor Barrett also demonstrated (*J. Am. Chem. Soc.* **2008**, *130*, 10293) the facile aromatization of the triketone **25** to the arene **26**, that he carried on to the antifungal agent 15G256β.



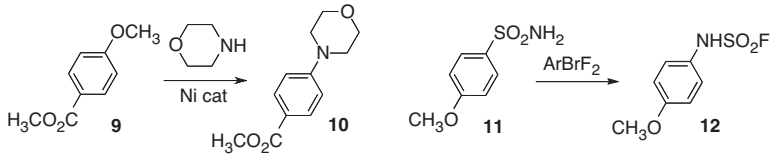
63. Substituted Benzenes: The Alvarez-Manzaneda Synthesis of (-)-Taiwaniquinone G

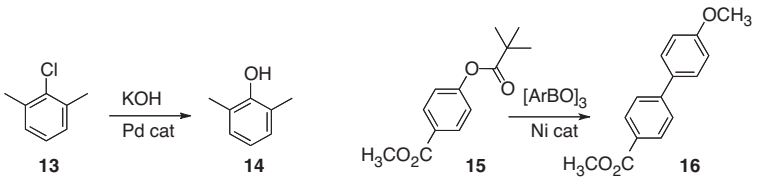
October 12, 2009

Continuing efforts toward the direct functionalization of aromatic C-H bonds, Nobutaka Fujii and Hiroaki Ohno of Kyoto University described (*Chem. Commun.* **2009**, 3413) a Pd-mediated protocol for the *ortho* hydroxylation of aryl tetrahydropyrimidines such as **1**. To use a boronic acid as an activating/directing group, Michinori Suginome, also of Kyoto University, devised (*J. Am. Chem. Soc.* **2009**, *131*, 7502) the pyrazolylpyridyl derivative **3**. The product **4** could be returned to the boronic acid or carried on to the borate ester, in each case with recovery of the directing group. Eiichi Nakamura of the University of Tokyo established (*Angew. Chem. Int. Ed.* **2009**, *49*, 2925) that *ortho* arylation of **5** could be accomplished even in the presence of a reactive aryl halide. In a complementary approach, Matthew J. Gaunt of the University of Cambridge developed (*Science* **2009**, *323*, 1593) a procedure for C-H arylation of anilides such as **7** that showed good *meta* selectivity.



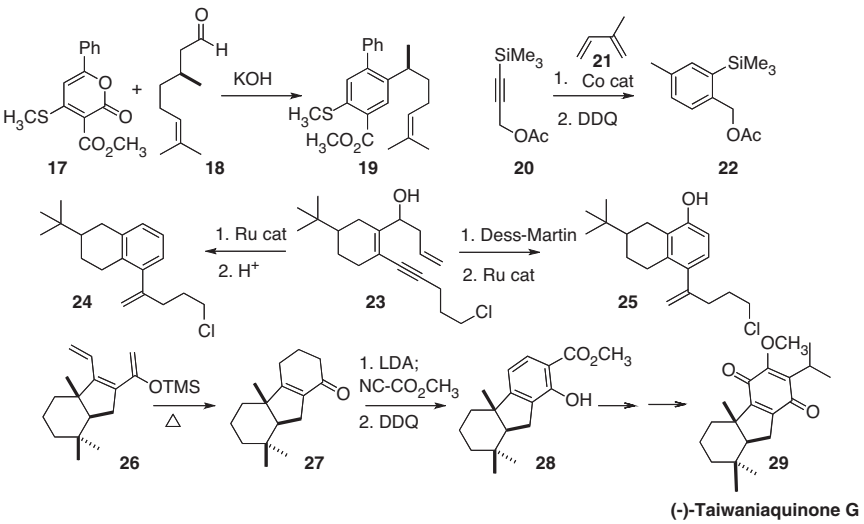
Mamoru Tobisu and Naoto Chatani of Osaka University have found (*Chem. Lett.* **2009**, *38*, 710) for the conversion of aryl ethers such as **9** to the tertiary amine. Masahito Ochiai of the University of Tokushima observed (*J. Am. Chem. Soc.* **2009**, *131*, 8392) the remarkable inversion of an arene sulfonamide such as **11** to the protected aniline **12**. Matthias Beller of the Universität Rostock established (*Angew. Chem. Int. Ed.* **2009**, *49*, 918) a Pd-mediated procedure for the conversion of even a congested aryl halide **13** to the phenol **14**.





The first C-C bond formations with phenols used very reactive, but expensive, leaving groups such as triflates. With improving ligand design, conditions have been found that work well even with inexpensive mesylates. Now, Zhang-Jie Shi of Peking University (*J. Am. Chem. Soc.* **2008**, *130*, 14468) and Neil K. Garg of UCLA (*J. Am. Chem. Soc.* **2008**, *130*, 14422), working independently, developed similar procedures for the Ni-mediated arylation of *esters* such as **15**. Both groups found that pivalates worked particularly well.

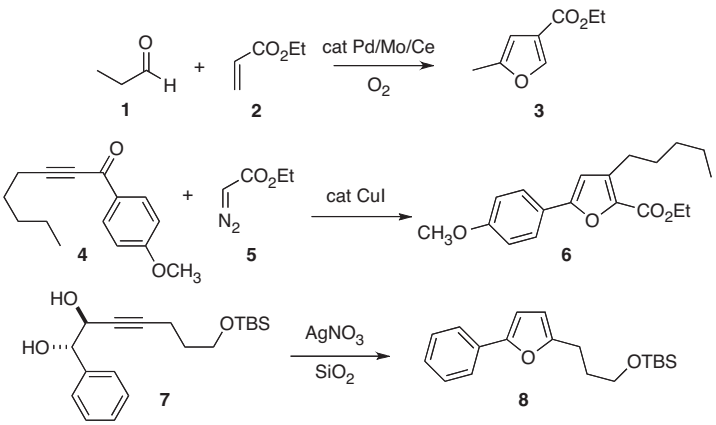
For some highly-substituted benzene derivatives, construction of the aromatic ring can be an economical approach. Atul Goel of the Central Drug Research Institute, Lucknow, found (*Tetrahedron Lett*. **2009**, *50*, 2086) that the direct coupling of a pyrone such as **17** with an aldehyde **18** delivered the aryl ester **22**. Gerhard Hilt of Philipps-Universität Marburg developed (*Organic Lett*. **2009**, *11*, 773) Co catalysts for the Diels-Alder cyclization of **23** with **24**, with subsequent oxidation to the arene **25**. With the proper choice of catalyst, either regioisomer of the Diels-Alder adduct could be made to dominate. Kazuhiro Yoshida and Akira Yanagisawa of Chiba University found (*J. Org. Chem.* **2009**, *74*, 3632) a similar flexibility in a Ru-mediated arene construction. Cyclization of **23** followed by dehydration gave **24**, while oxidation followed by cyclization delivered the phenol **25**. Enrique Alvarez-Manzaneda of the Universidad de Granada, in the course (*Chem. Commun*. **2009**, 592) of a synthesis of (-)-Taiwaniaquinone G **29**, built the aromatic ring by cyclization of **26** to **27**, followed by oxidation to **28**.



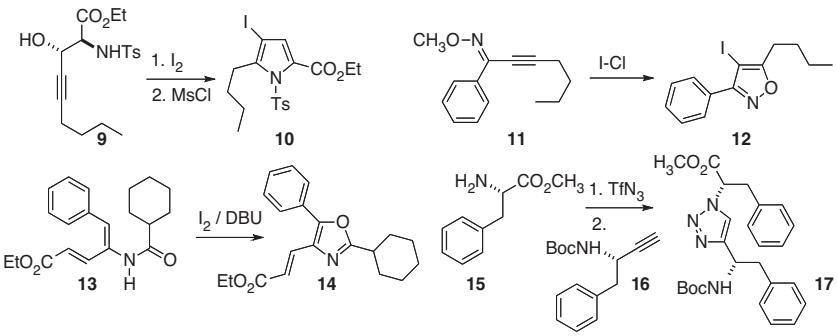
64. Synthesis of Heteroaromatics

July 21, 2008

Yasutaka Ishii of Kansai University has developed (*J. Org. Chem.* **2007**, *72*, 8820) a novel route to furans, using a mixed-metal catalyst to effect condensation of an aldehyde or 1,3 diketone such as **1** with an acceptor such as **2** to give the 3-furoate **3**. In a complementary approach, Yong-Min Liang of Lanzhou University has found (*J. Org. Chem.* **2007**, *72*, 10276) that diazoacetate **5** will condense with an alkynyl ketone to give the 2-furoate **6**. David W. Knight of Cardiff University has shown (*Tetrahedron Lett*. **2007**, *48*, 7709) that an alkynyl diol such as **7**, readily available by dihydroxylation of the corrresponding alkenyl alkyne, cyclized to the furan on exposure to $AgNO_3$ on silica gel.

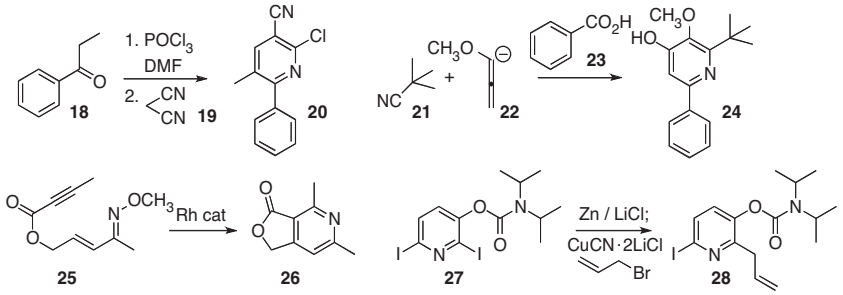


Professor Knight has also (*Tetrahedron Lett*. **2007**, *48*, 7906) established a route to polysubstituted pyrroles **10**, by iodination of alkynyl sulfonamides such as **9**. Similarly, Richard C. Larock of Iowa State University found (*J. Org. Chem.* **2007**, *72*, 9643) that I-Cl cyclized methoximes such as **11** to the corresponding iodo isoxazole **12**, and Stephen L. Buchwald of MIT uncovered (*Organic Lett.* **2007**, *9*, 5521) the cyclization of an enamide such as **13**

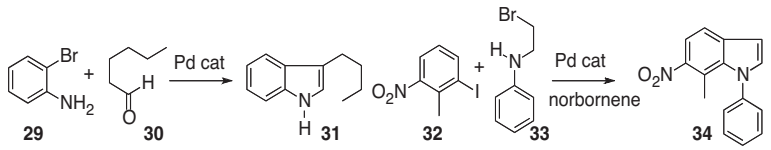


with I_2 to the corresponding oxazole **14**. In developing a more efficient route to a new class of materials that he has named "triazolamers", Paramjit S. Arora of New York University was able (*J. Org. Chem.* **2007**, *72*, 7963) to effect diazo transfer to the amine **15** and subsequent condensation with **16** to give **17**, without isolation of the intermediate azide.

C. V. Asokan and E. R. Anabha of Mahatma Gandhi University have described (*Tetrahedron Lett*. **2007**, *48*, 5641) the activation of a ketone **18** followed by condensation with malononitrile **19** to give the pyridine **20**. Hans-Ulrich Reissig of the Freie Universität Berlin has established (*Organic Lett.* **2007**, *9*, 5541) a complementary three-component coupling of a nitrile **21** with the allenyl anion **22**, followed by a carboxylic acid **23** to deliver the pyridine **24**. Akio Saito and Yuji Hanzawa of the Showa Pharmaceutical University have reported (*Tetrahedron Lett*. **2007**, *48*, 6852) the intramolecular Rh-catalyzed cyclization of a methoxime lactone such as **25** to the pyridine **26**. Paul Knochel of the Ludwig-Maximilians-Universität München has demonstrated (*J. Am. Chem. Soc.* **2007**, *129*, 12358) that halogen exchange can be directed by an adjacent carbamate, enabling homologation of **27** to **28**.



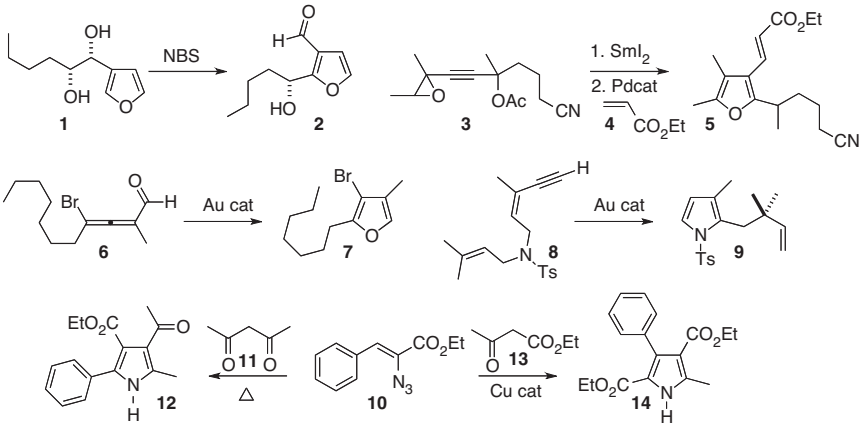
Professor Buchwald has also developed (*Angew. Chem. Int. Ed.* **2007***, 46,* 7236) a protocol for the Pd-mediated α-arylation of aldehydes. This procedure converted an *o*-halo aniline **29** to the indole **31**. In a C-H activation-based approach, Mark Lautens of the University of Toronto demonstrated (*Organic Lett.* **2007**, *9*, 5255) that Pd-catalyzed condensation of **32** with the aniline **33** led to the indole **34**.



65. Preparation of Heteroaromatic Derivatives

October 20, 2008

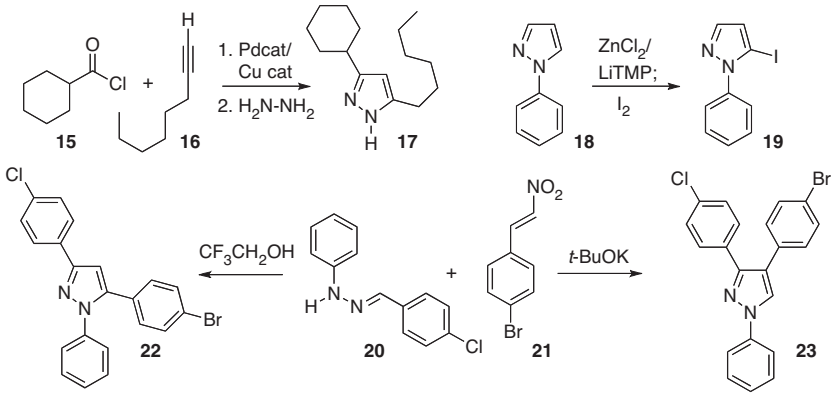
Several new routes to furans and to pyrroles have recently been put forward. Inspired by the Achmatowicz ring expansion, Patrick J. Walsh of the University of Pennsylvania developed (*J. Am. Chem. Soc.* **2008**, *130*, 4097) the oxidative rearrangement of 3-hydroxalkyl furans such as **1** to the 3-aldehyde **2**. José M. Aurrecoechea of the Universidad del País Vasco established (*J. Org. Chem.* **2008**, *73*, 3650) that cumulated alcohols, available by reduction of alkynes such as **3** with SmI_2, rearrange under Pd catalysis, and then add to an acceptor alkene such as **4**, to give the furan **5**. Vladimir Gevorgyan of the University of Illinois at Chicago used (*J. Am. Chem. Soc.* **2008**, *130*, 1440) an Au catalyst to rearrange an allene such as **6** to the bromo furan **7**. Fabien L. Gagosz of the Ecole Polytechnique, Palaiseau, also found (*Organic Lett*. **2007**, *9*, 3181) that an Au catalyst rearranged the eneyne **8** to the pyrrole **9**.



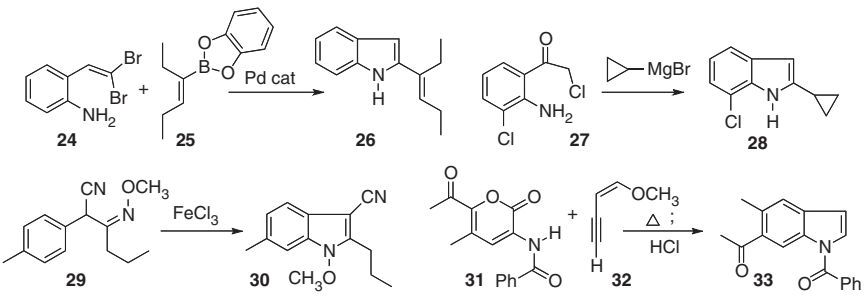
Azido esters such as **10** are readily prepared from the corresponding aldehyde by phosphonate condensation. Shunsuke Chiba and Koichi Narasaka of Nanyang Technology University demonstrated (*Organic Lett*. **2008**, *10*, 313) that thermal condensation of **10** with acetyl acetone **11** gave the pyrrole **12**, while Cu catalyzed condensation with acetoacetate **13** gave the complementary pyrrole **14**.

Huan-Feng Jiang of South China University of Technology observed (*Tetrahedron Lett*. **2008**, *49*, 3805) that condensation of an acid chloride **15** with an alkyne **16**, presumably to give the alkynyl ketone, followed by the addition of hydrazine delivered the pyrazole **17**. Masanobu Uchiyama of RIKEN and Florence Mongin of the Université de Rennes 1 established (*J. Org. Chem.* **2008**, *73*, 177) that a pre-formed pyrazole **18** could be metalated and then iodinated, to give **19**. Xiaohu Deng of Johnson & Johnson, San Diego reported (*Organic Lett*. **2008**, *10*, 1307; *J. Org. Chem.* **2008**, *73*, 2412) complementary routes to pyrazoles,

combining **20** and **21** under acidic conditions to give **22**, and under basic conditions to give **23**.



Mark Lautens of the University of Toronto demonstrated (*J. Org. Chem.* **2008**, *73*, 538) that dibromoalkenes such as **24**, readily available from the corresponding aldehyde, could be condensed with an organoborane such as **25** to give the indole **26**. Tao Pei and Cheng-yi Chen of Merck Process established (*Angew. Chem. Int. Ed*. **2008**, *47*, 4231) that the addition of an organometallic to the ketone **27** drove rearrangement to a homologated ketone, that on acid work-up gave the indole **28**.



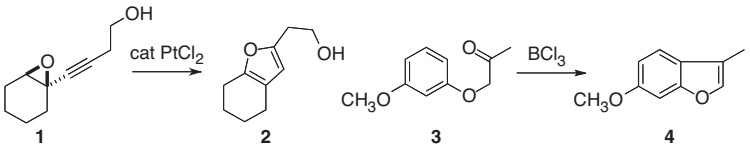
Each of these approaches depended on the availability of the ortho-substituted aniline starting materials. Junbiao Chang and Kang Zhao of Tianjin University devised (*J. Org. Chem.* **2008**, *73*, 2007) a complementary approach, the cyclization of **29** to **30**, in the process directly aminating the benzene ring. Marijan Kocevar of the University of Ljubljana established (*Tetrahedron* **2008**, *64*, 45) an alternative Diels-Alder approach to indoles, combining **31** and **32** to give **33**.

The preparation of pyridines will be covered in the next column on heteroaromatic construction.

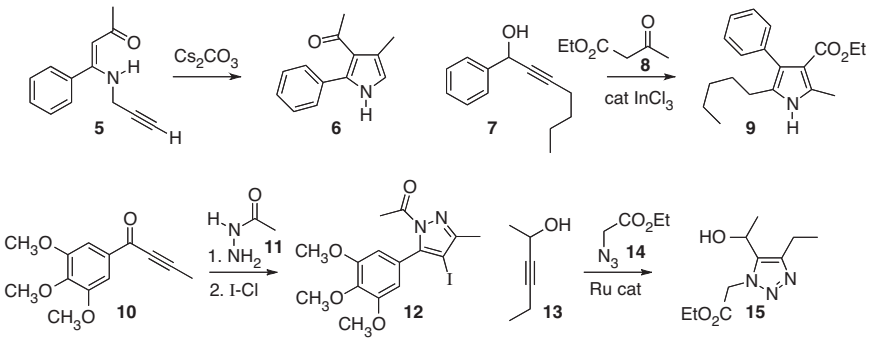
66. Preparation of Heteroaromatics

July 13, 2009

Masahiro Yoshida of the University of Tokushima described (*Tetrahedron Lett.* **2008**, *49*, 5021) the Pt-mediated rearrangement of alkynyl oxiranes such as **1** to the furan **2**. Roman Dembinski of Oakland University reported (*J. Org. Chem.* **2008**, *73*, 5881) a related zinc-mediated rearrangement of propargyl ketones to furans. The cyclization of aryloxy ketones such as **3** to the benzofuran **4** developed (*Tetrahedron Lett.* **2008**, *49*, 6579) by Ikyon Kim of the Korea Research Institute of Chemical Technology is likely proceeding by a Friedel-Crafts mechanism.

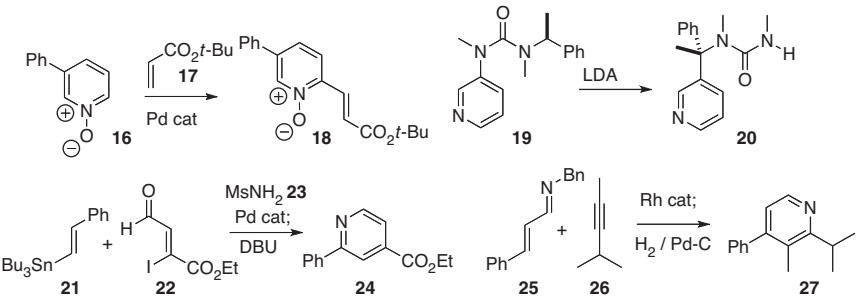


Sandro Cacchi and Giancarlo Fabrizi of Università degli Studi "La Sapienza", Roma, observed (*Organic Lett*. **2008**, *10*, 2629) that base converted the enamine **5** to the pyrrole **6**. Alternatively, oxidation of **5** with CuBr led to a pyridine. Zhuang-ping Zhuan of Xiamen University prepared (*Adv. Synth. Cat.* **2008**, *350*, 2778) pyrroles such as **9** by condensing an alkynyl carbinol **7** with a 1,3-dicarbonyl compound. Richard C. Larock of Iowa State University found (*J. Org. Chem.* **2008**, *73*, 6666) that combination of an alkynyl ketone **10** with **11** followed by oxidation with I-Cl led to the pyrazole **12**.

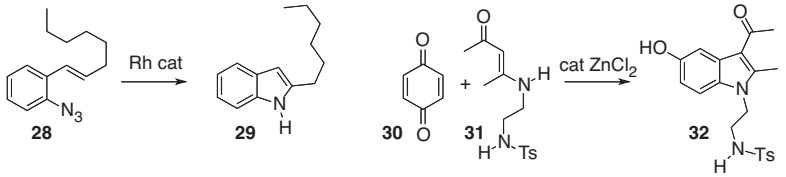


The "click" condensation of azides with alkynes, leading to the 1,4-disubstituted 1,2,3-triazole, has proven to be a powerful tool for combinatorial synthesis. Valery V. Fokin of Scripps/La Jolla and Zhenyang Lin and Guochen Jia of the Hong Kong University of Science and Technology have developed (*J. Am. Chem. Soc.* **2008**, *130*, 8923) a complementary approach, using Ru catalysts to prepare 1,5-disubstituted 1,2,3- triazoles. Remarkably, internal alkynes participate, and, as in the conversion of **13** to **15**, propargylic alcohols direct the regioselectivity of the cycloaddition.

A variety of methods have been put forward for functionalizing pyridines. Sukbok Chang of KAIST described (*J. Am. Chem. Soc.* **2008**, *130*, 9254) the direct oxidative homologation of a pyridine *N*-oxide **16** to give the unsaturated ester **18**. Jonathan Clayden of the University of Manchester observed (*Organic Lett*. **2008**, *10*, 3567) that metalation of **19** gave an anion that rearranged to **20** with complete retention of enantiomeric excess.



Shigeo Katsumura of Kwansei Gakuin University developed (*Tetrahedron Lett.* **2008**, *49*, 4349) an intriguing three-component coupling, combining **21**, **22**, and methanesulonamide **23** to give the pyridine **24**. Robert G. Bergman and Jonathan A. Ellman of the University of California, Berkeley established (*J. Am. Chem. Soc.* **2008**, *130*, 3645) a C-H activation based coupling, combining **25** and **26** to give, after debenzylation/aromatization, the pyridine **27**.

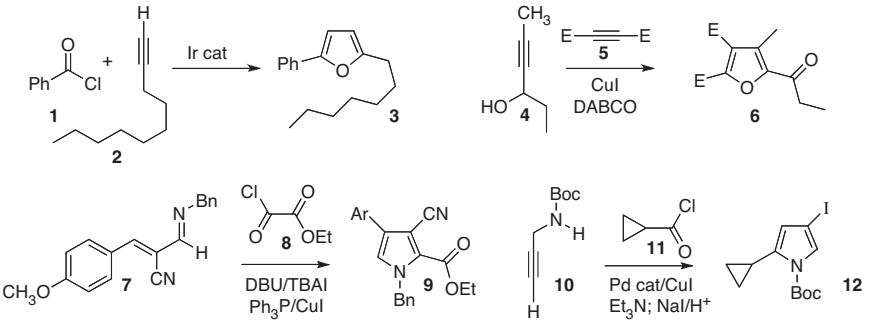


Tom G. Driver of the University of Illinois, Chicago found (*Angew. Chem. Int. Ed.* **2008**, *47*, 5056) that Rh octanoate catalyzed the well-known thermal conversion of an azide such as **28** to the indole **29**. Valeriya S. Velezheva of the A. N. Nesmeyanov Institute of Organoelement Compounds uncovered (*Tetrahedron Lett.* **2008**, *49*, 7106) an improved protocol for the Nenitzescu synthesis, combining **30** and **31** to give **32**. For an overview of the nine types of indole synthesis, see our upcoming review in *Angewandte Chemie*.

67. Heterocycle Construction: The Chang Synthesis of Louisianin C

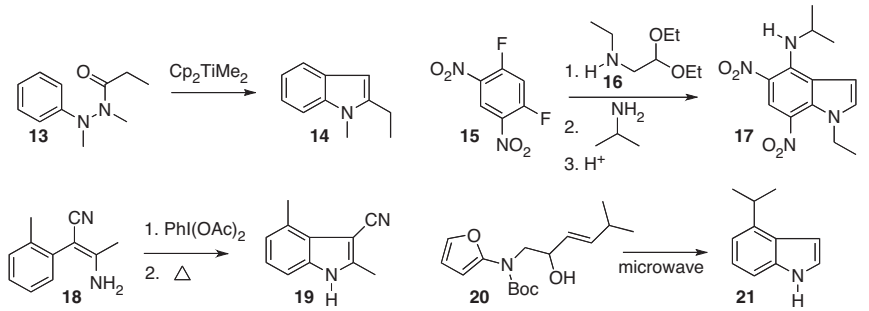
October 19, 2009

It has been known for some time that an acid chloride **1** can be added to an alkyne **2** to give the β-chloro enone. Yasushi Tsuji of Kyoto University found (*J. Am. Chem. Soc.* **2009**, *131*, 6668) that with an Ir catalyst, the condensation of **1** with **2** could be directed to the furan **3**. Huanfeng Jiang of the South China University of Technology described (*Organic Lett*. **2009**, *11*, 1931) a complementary route to furans, Cu-mediated condensation of a propargyl alcohol **4** with the diester **5** to give **6**.



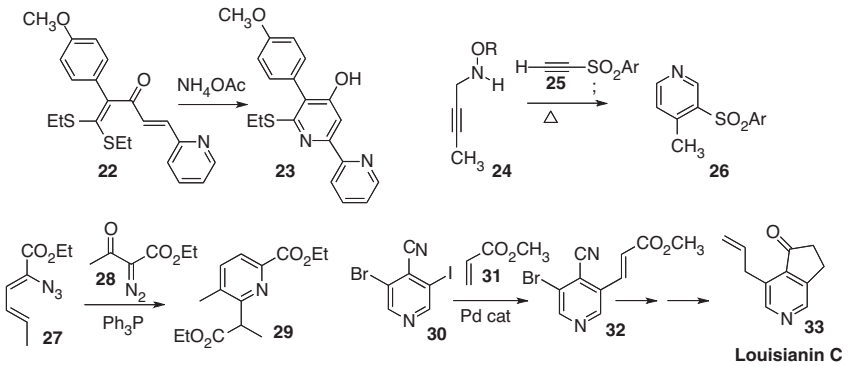
Bruce A. Arndtsen of McGill University developed (*Organic Lett*. **2009**, *11*, 1369) an approach to pyrroles such as **9**, by condensation of an α,β-unsaturated α-cyano imine **7** with the acid chloride **8**. Thomas J. J. Müller of Heinrich-Heine-Universität Düsseldorf observed (*Organic Lett*. **2009**, *11*, 2269) the condensation of an acid chloride **11** with a propargyl amine **10**, leading to the iodo pyrrole **12**.

John A. Murphy of the University of Strathclyde uncovered (*Tetrahedron Lett*. **2009**, *50*, 3290) a new entry to the Fischer indole synthesis, by Petasis homologation of a hydrazide **13**. Dali Yin of Peking Union Medical College took advantage (*Organic Lett*. **2009**, *11*, 637) of the easy sequential displacement of the fluorides of **15**, leading, after acid-catalyzed



cyclization, to the indole **17**. Kang Zhao of Tianjin University extended (*Organic Lett*. **2009**, *11*, 2417; *Organic Lett*. **2009**, *11*, 2643) his studies of oxidation of an enamine **18** to the 2*H*-azirine, that on heating cyclized to the indole **19**. Peter Wipf of the University of Pittsburgh established (*Chem. Commun*. **2009**, 104) a microwave-promoted indole synthesis, illustrated by the intramolecular Diels-Alder cyclization of **20** to **21**. A review delineating all nine types of indole syntheses will appear shortly in *Angewandte Chemie*.

Fushun Liang and Qun Liu of Northeast Normal University demonstrated (*J. Org. Chem*. **2009**, *74*, 899) that the readily-prepared ketene thioacetal **22** condensed with NH_3 to give the pyridine **23**. Sundaresan Prabhakar and Ana M. Lobo of the New University of Lisbon observed (*Tetrahedron Lett*. **2009**, *50*, 3446) that the addition of the alkoxy propargyl amine to the alkyne **25** gave a *Z* alkene, that on warming rearranged to the pyridine **26**. Yan-Guang Wang of Zhejiang University, Hangzhou developed (*J. Org. Chem*. **2009**, *74*, 903) a pyridine synthesis based on the Wolff rearrangement of a diazo ketone such as **28**. The iminophosphorane derived from **27** added to the resulting ketene, leading, after by electrocyclic rearrangement, to the pyridine **29**.

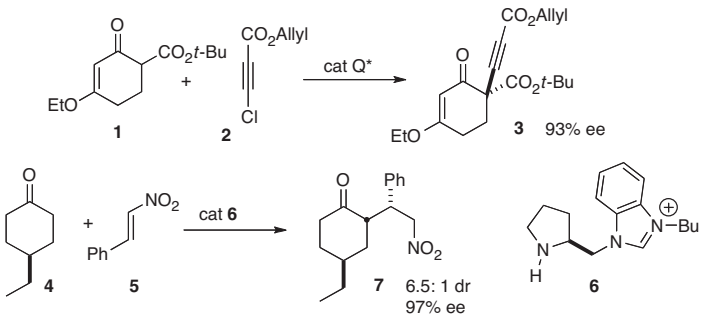


A great deal of work has been done on the selective metalation of pyridines. Ching-Yao Chang of Asia University, Taichung used this (*Tetrahedron* **2009**, *65*, 748; for another report on pyridine metalation, see *Tetrahedron Lett*. **2009**, *50*, 1768) to advantage in developing a synthetic route to the *Streptomyces*-derived Louisianin alkaloids. Lithiation of 4-cyanopyridine was followed by bromination. The product was again lithiated, then iodinated to give **30**. A selective Heck reaction on **30** gave **32**, that was carried on to Louisianin C **33**.

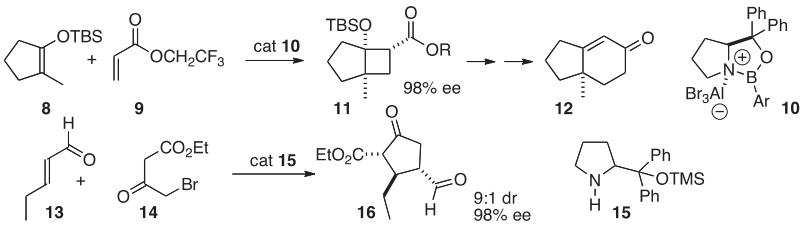
68. Enantioselective Organocatalytic Construction of Carbocycles: The Nicolaou Synthesis of Biyouyanagin A

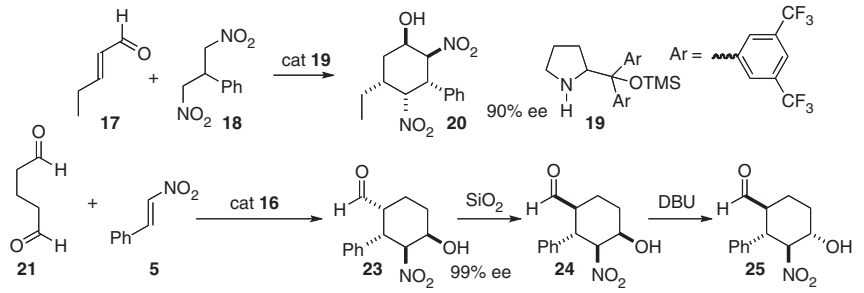
August 11, 2008

One of the more powerful routes to enantiomerically-pure carbocycles is the desymmetrization of a prochiral ring. Karl Anker Jørgensen of Aarhus University has found (*J. Am. Chem. Soc.* **2007**, *129*, 441) that many cyclic β-ketoesters, including the vinylogous carbonate **1**, can be homologated with **2** to the corresponding alkyne **3**, in high ee. Sanzhong Luo of the Chinese Academy of Sciences, Beijing, and Jin-Pei Cheng, of the Chinese Academy of Sciences and Nankai University, have shown (*J. Org. Chem.* **2007**, *72*, 9350) that the catalyst **6** mediated the selective addition of 4-substituted cyclohexanones such as **4** to the nitroalkene **5**, establishing three new stereogenic centers.

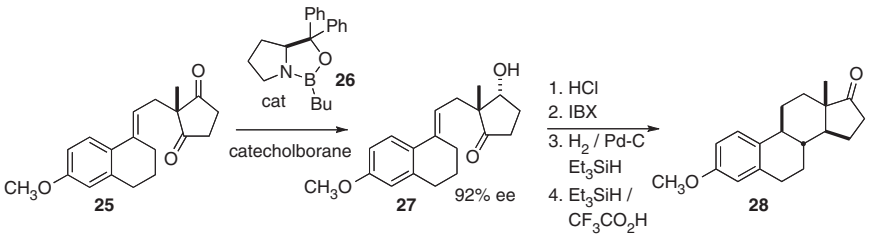


Organocatalysts, alone or complexed with activating metals, have also been used to effect enantioselective ring construction. E. J. Corey of Harvard University has established (*J. Am. Chem. Soc.* **2007**, *129*, 12686) that the proline-derived complex **10** will mediate the 2+2 addition of a cyclic enol ether with an acrylate to give the cyclobutane **11**. Further elaboration led to the cyclohexenone **12**. Armando Córdova of Stockholm University has described (*Tetrahedron Lett.* **2007**, *48*, 5835) a novel route to cyclopentanones such as **16**, via tandem conjugate addition/intramolecular alkylation. Professor Jørgensen has reported (*Angew. Chem. Int. Ed*. **2007**, *46*, 9202) the double addition of **18** to the unsaturated aldehyde **17** to give **20**. Earlier last year, Yujiro Hayashi of the Tokyo University of Science had shown (*Angew. Chem. Int. Ed*. **2007**, *46*, 4922) that the double addition of the inexpensive **21** to **5** could, depending on conditions, be directed selectively to **22**, **23**, or **24**.

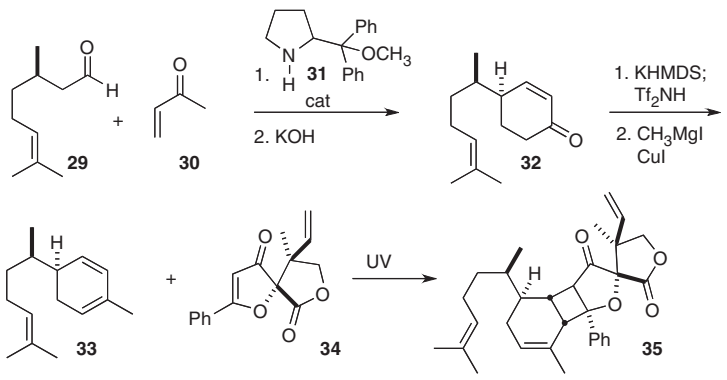




As illustrated by the conversion of **8** to **13**, organocatalysis can be used to effect the enantioselective construction of polycarbocyclic products. The initial ring prepared in enantiomerically-pure form by organocatalysis can also set the chirality of a polycyclic system. Professor Corey has reported (*J. Am. Chem. Soc.* **2007**, *129*, 10346) that Itsuno-Corey reduction of the prochiral diketone **25** led to the ketone **27**. Cyclization followed by oxidation and reduction then delivered estrone methyl ether **28**.



Professor Hayashi, Professor Jørgensen and Samuel H. Gellman of the University of Wisconsin had established (OHL July 24, 2006) that an aldehyde could be added to a vinyl ketone in high ee. Building on these results, K. C. Nicolaou of Scripps/La Jolla has found (*Angew. Chem. Int. Ed.* **2007**, *46*, 4708) that the initial Michael adduct from the condensation of (*R*)-citronellal **29** with methyl vinyl ketone **30** can be converted into the Robinson annulation product **32** without epimerization at the gamma position. This led to **33**, cycloaddition of which with **34** delivered (-)-biyouyanagin **35**.

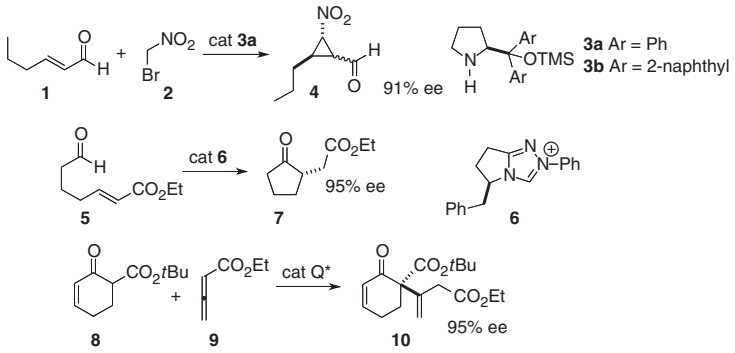


(-)-Biyouyanagin A

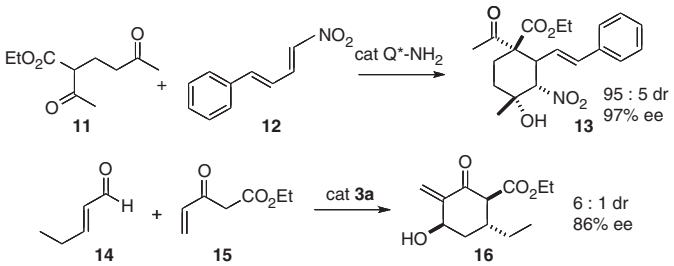
69. Organocatalytic Ring Construction: The Corey Synthesis of Coraxeniolide A

December 8, 2008

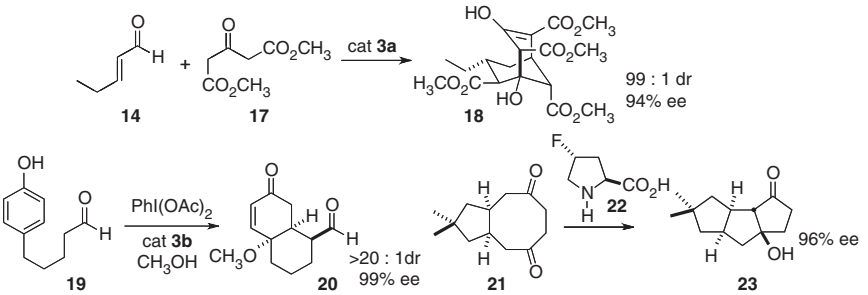
Armando Córdova of Stockholm University has found (*Tetrahedron Lett*. **2008**, *49*, 4209) that the organocatalyst **3a** effected enantioselective conjugate addition of bromonitromethane **2** to the α,β-unsaturated aldehyde **1**, to give the cyclopropane **4** as a ~ 1:1 diastereomeric mixture, both in high ee. Tomislav Rovis of Colorado State University has published (*J. Org. Chem.* **2008**, 73*,* 2033) a detailed account of his development of catalysts such as **6**, that effected enantioselective cyclization of **5** to **7** with excellent ee. Karl Anker Jørgensen of Aarhus University has employed (*J. Am. Chem. Soc.* **2008**, *130*, 4897) chiral quaternary salts derived from quinine that mediated the enantioselective addition of prochiral rings such as **8** to the allenoate ester **9** to give **10** with high ee.



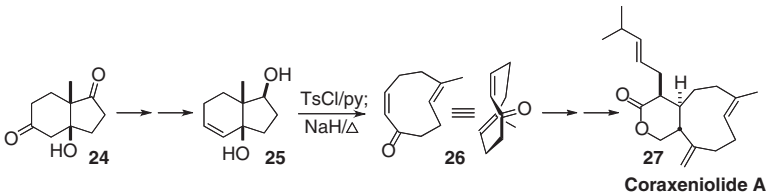
Organocatalysts have also been used to prepare more highly substituted cyclohexane derivatives. Guofu Zhong of Nanyang Technological University used (*Organic Lett.* **2008**, *10*, 2437) a quinine-derived secondary amine to catalyze the Michael addition of **12** to **11** followed by intramolecular aldol (Henry) reaction, to give **13**. When Professor Jørgensen attempted (*Angew. Chem. Int. Ed.* **2008**, *47*, 121) the related addition of **14** and **15** using catalyst **3a**, he did not observe the expected Michael-Michael sequence. Rather, the initial Michael addition was followed by a Morita-Baylis-Hillman condensation, to give **16**. The β-keto ester **16** existed primarily in its enol form.



Organocatalysts can also be used to prepare polycyclic systems. Professor Jørgensen has found (*Chem. Commun*. **2008**, 3016) that condensation of **14** with acetone dicarboxylate **17**, again using catalyst **3a**, gave the bicyclic β-keto ester **18**. Matthew J. Gaunt of the University of Cambridge observed (*J. Am. Chem. Soc.* **2008**, *130*, 404) that for the cyclization of **19**, catalyst **3b** was superior to catalyst **3a**. The power of desymmetrization of prochiral intermediates was illustrated by the report (*J. Am. Chem. Soc.* **2008**, *130*, 6737) from Benjamin List of the Max-Planck-Institute, Mülheim of the cyclization of **21** to **23**.



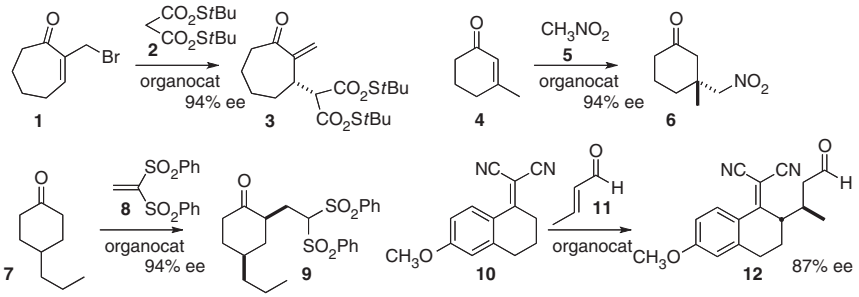
Organocatalysts can also be used to prepare larger rings. The Hajos-Parrish condensation of 2-methyl cyclopentane-1,3-dione with methyl vinyl ketone mediated by proline to give the aldol product **24** in high ee is one of the classic examples of enantioselective bicyclic construction directed by an organocatalyst. E. J. Corey of Harvard (*J. Am. Chem. Soc.* **2008**, *130*, 2954) effected Grob fragmenation on the derived diol **25** to give the cyclononadienone **26**. While **26** might appear to be prochiral, in fact it was formed in the kinetically stable enantiomerically-pure conformation illustrated. With only one face of the enone open, conjugate addition to **26** proceeded with high diastereocontrol, leading to coraxenliolide A **27**.



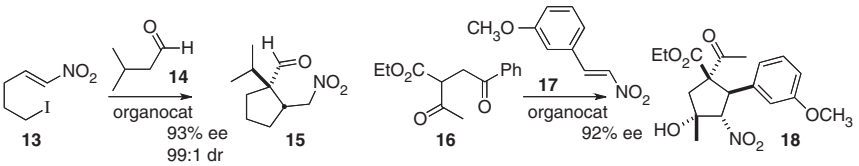
70. Enantioselective Organocatalyzed Construction of Carbocyclic Rings

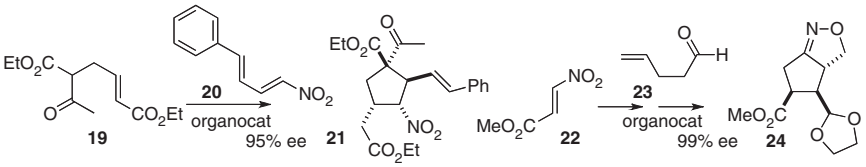
August 10, 2009

One of the most practical ways to construct enantiomerically-enriched carbocyclic systems is to effect asymmetric transformation of preformed prochiral rings. Choon-Hong Tan of the National University of Singapore observed (*Chem. Commun.* **2008**, 5526) that allylic halides such as **1** coupled with malonates such as **2** to give the α-methylene ketone **3** in high ee. Xinmiao Liang of the Dalian Institute of Chemical Physics and Jinxing Ye of the East China University of Science and Technology reported (*Chem. Commun.* **2008**, 3302) that nitromethane **5** could be added to enones such as **4** to construct cyclic quaternary stereogenic centers such as that of **6**. The addition of the cyclohexanone **7** to the acceptor **8** described (*Chem. Commun.* **2008**, 6315) by Yixin Lu, also of the National University of Singapore led to the creation of two new cyclic stereogenic centers. Polycarbocyclic prochiral rings are also of interest. Teck-Peng Loh of Nanyang Technological University devised (*Tetrahedron Lett.* **2008**, *49*, 5389) the steroid AB donor **10**, that added to crotonaldehyde **1** to give the single enantiomerically-pure diastereomer **12**.



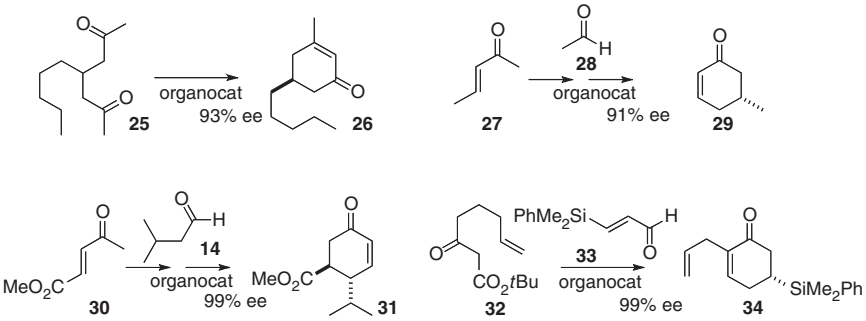
Nitro alkenes are excellent Michael acceptors. Dieter Enders of RWTH Aachen took advantage of this (*Angew. Chem. Int. Ed.* **2008**, *47*, 7539) in developing the addition of aldehydes such as **14** to the nitroalkene **13**. Intramolecular alkylation ensued, to deliver the product **15** as a single diastereomer. Guofu Zhong, also of Nanyang Technological University, established (*Organic Lett.* **2008**, *10*, 3425; *Organic Lett.* **2008**, *10*, 3489) an approach to cyclopentane construction based on the Michael addition of β-ketoesters such as **16** and **19** to nitroalkenes such as **17** and **20**. Intramolecular nitro aldol (Henry) addition led to **18**, while an intramolecular Michael addition delivered **21**.





Damien Bonne and Jean Rodriguez of Aix-Marseille Université employed (*Organic Lett.* **2008**, *10*, 5409) intramolecular dipolar cycloaddition to convert the initial adduct between **22** and **23** to the cyclopentane **24**. They also prepared cyclohexane derivatives using this approach.

The diketone **25** is prochiral. Benjamin List of the Max-Planck Institut, Mülheim devised (*Angew. Chem. Int. Ed.* **2008**, *47*, 7656) an organocatalyst that mediated the intramolecular aldol cyclization of **25** to **26** in high ee. Mark J. Kurth of the University of California, Davis developed (*Angew. Chem. Int. Ed.* **2008**, *47*, 6407) a resin bound organocatalyst that, *inter alia*, combined **27** with **28** to give the Robinson annulation product **29**. Dawei Ma of the Shanghai Institute of Organic Chemistry reported (*Organic Lett.* **2008**, *10*, 5425) a related Robinson annulation, combining **30** and **14** to give **31**.

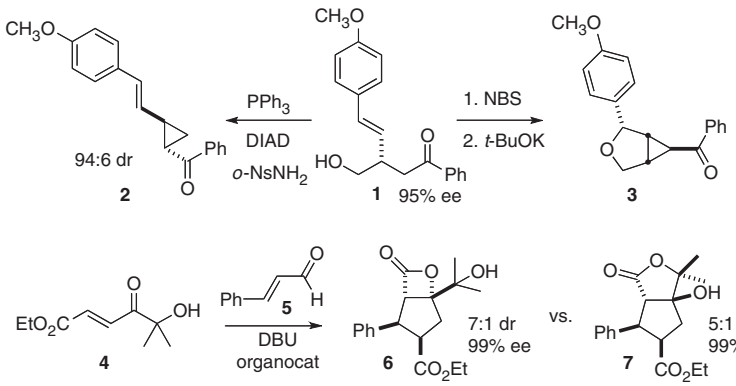


The most powerful such Robinson annulation reported to date was by (*Organic Lett.* **2008**, *10*, 3753) Karl Anker Jørgensen of Aarhus University, Denmark, who showed that α-alkyl acetoacetates such as **32** could be combined with the silyl aldehyde **33** to give the 5-silyl cyclohexenones **34**. Conjugate addition to such cyclohexenones is expected to proceed with high diastereocontrol, leading, for instance, after oxidative desilylation to the 5,6-dialkyl cyclohexenone.

71. Organocatalytic C-C Ring Construction: (+)-Ricciocarpin A (List) and (-)-Aromadendranediol (MacMillan)

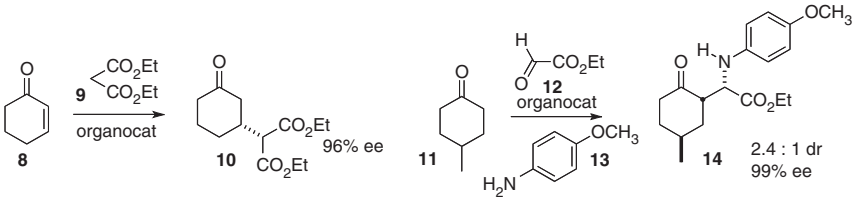
December 14, 2009

Yoshiji Takemoto of Kyoto University designed (*Organic Lett*. **2009**, *11*, 2425) an organocatalyst for the enantioselective conjugate addition of alkene boronic acids to γ-hydroxy enones, leading to **1** in high ee. Attempted Mitsunobu coupling led to the cyclopropane **2**, while bromoetherification followed by intramolecular alkylation delivered the cyclopropane **3**.

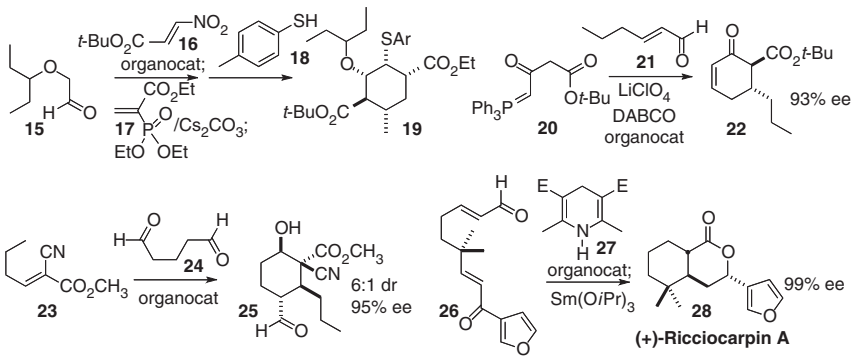


Jeffrey W. Bode of the University of Pennsylvania demonstrated (*Organic Lett*. **2009**, *11*, 677) a remarkable dichotomy in the reactivity of N-heterocyclic carbenes. A triazolium precatalyst combined **4** and **5** to give **6**, whereas an imidazolium precatalyst combined **4** and **5** to give **7**.

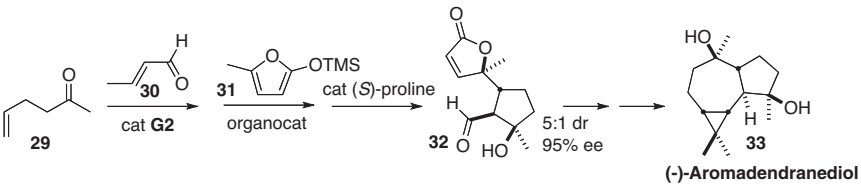
Xinmiao Liang of the Dalian Institute of Chemical Physics and Jinxing Ye of the East China University of Science and Technology devised (*Organic Lett*. **2009**, *11*, 753) a *Cinchona*-derived catalyst that converted the prochiral cyclohexenone **8** into the diester **10** in high ee. Rich G. Carter of Oregon State University found (*J. Org. Chem.* **2009**, *74*, 2246) a simple sulfonamide-based proline catalyst that effected the Mannich condensation of the prochiral ketone with ethyl glyoxalate **12** and the amine **13**, leading to the amine **14**.



In the first pot of a concise, three-pot synthesis of (-)-oseltamivir, Yujiro Hayashi of the Tokyo University of Science combined (*Angew. Chem. Int. Ed.* **2009**, *48*, 1304) **15** and **16** in the presence of a catalytic amount of diphenyl prolinol TMS ether to give an intermediate nitro aldehyde. Addition of the phosphonate **17** led to a cyclohexenecarboxylate, that on the addition of the thiophenol **18** equilibrated to the ester **19**. Ying-Chun Chen of Sichuan University used (*Organic Lett*. **2009**, *11*, 2848) a related diaryl prolinol TMS ether to direct the condensation of the readily-prepared phosphorane **20** with the unsaturated aldehyde **21** to give the cyclohexenone **22**. Armando Córdova of Stockholm University also used (*Tetrahedron Lett*. **2009**, *50*, 3458) diphenyl prolinol TMS ether to mediate the addition of **24** to **23**. The subsequent intramolecular aldol condensation proceeded with high diastereocontrol, leading to **25**.



Benjamin List of the Max-Planck Institut, Mülheim employed (*Nat. Chem.* **2009**, *1*, 225) a MacMillan catalyst for the reductive cyclization of **26**. Subsequent epimerization and Tishchenko hydride transfer then proceeded with high diastereoselectivity, leading directly to the liverwort-derived (+)-Ricciocarpin A **28**.

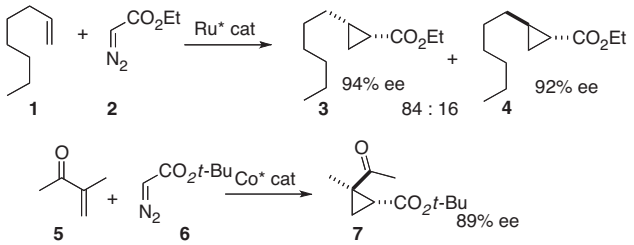


David W. C. MacMillan of Princeton University devised (*Angew. Chem. Int. Ed.* **2009**, *48*, 4349) a remarkable one-pot three-component assembly of the lactone **32**. Cross-metathesis of **29** with **30** gave a keto aldehyde. Direct addition of the furan **31** and an chiral imidazolidinone catalyst effected conjugate addition to the unsaturated aldehyde. A third catalyst, (*S*)-proline, then mediated intramolecular aldol condensation. The crystalline lactone **32** was readily carried on to (-)-Aromadendranediol **33**.

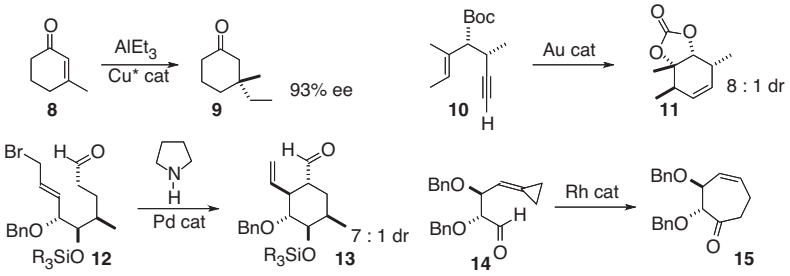
72. Transition Metal-Mediated Construction of Carbocycles: Dimethyl Gloiosiphone A (Takahashi), Pasteurestin A (Mulzer), and Pentalenene (Fox)

August 18, 2008

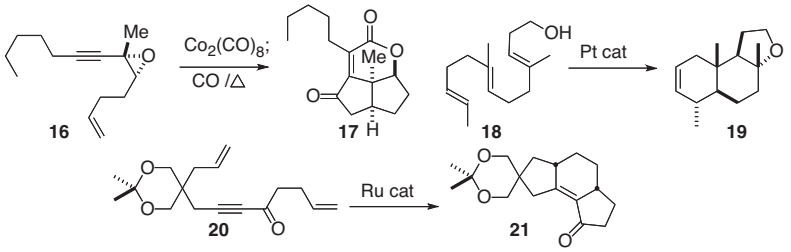
There continue to be new developments in transition metal- and lanthanide-mediated construction of carbocycles. Although a great deal has been published on the asymmetric cyclopropanation of styrene, relatively little had been reported for other classes of alkenes. Tae-Jeong Kim of Kyungpook National University has devised (*Tetrahedron Lett*. **2007**, *48*, 8014) a Ru catalyst for the cyclopropanation of simple α-olefins such as **1**. X. Peter Zhang of the University of South Florida has developed (*J. Am. Chem. Soc.* **2007**, *129*, 12074) a Co catalyst for the cyclopropanation of alkenes such as **5** having electron-withdrawing groups.



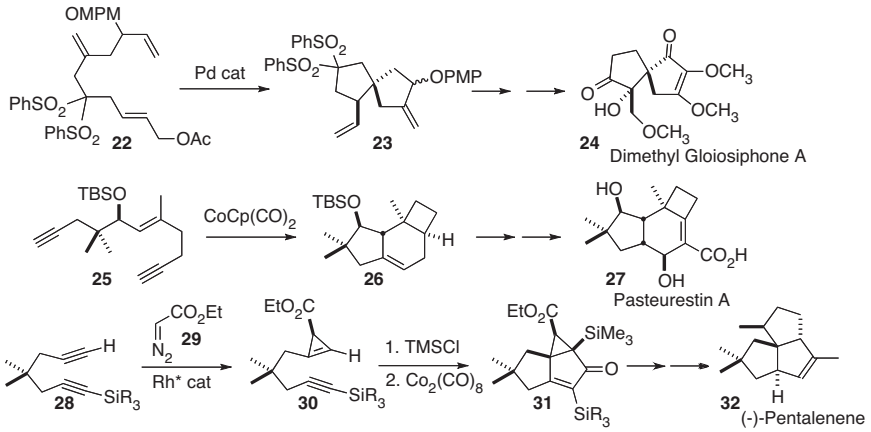
Alexandre Alexakis of the Université de Genève has reported(*Angew. Chem. Int. Ed.* **2007**, *46*, 7462) simple monophosphine ligands that enabled enantioselective conjugate addition to prochiral enones, even difficult substrates such as **8**. Seunghoon Shin of Hanyang University has found (*Organic Lett.* **2007**, *9*, 3539) an Au catalyst that effected the diastereoselective cyclization of **10** to the cyclohexene **11**, and Radomir N. Saicic of the University of Belgrade has carried out (*Organic Lett.* **2007**, *9*, 5063), via transient enamine formation, the diastereoselective cyclization of **12** to the cyclohexane **13**. Alois Fürstner of the Max-Planck-Institut, Mülheim has devised (*J. Am. Chem. Soc.* **2007**, *129*, 14836) a Rh catalyst that cyclized the aldehyde **14** to the cycloheptenone **15**.



Some of the most exciting investigations reported in recent months have been directed toward the direct diastereo- and enantioselective preparation of polycarbocyclic products. Rai-Shung Liu of National Tsing-Hua University has extended (*J. Org. Chem.* **2007**, *72*, 567) the intramolecular Pauson-Khand cyclization to the epoxy enyne **16**, leading to the 5-5 product **17**. Michel R. Gagné of the University of North Carolina has devised (*J. Am. Chem. Soc.* **2007**, *129*, 11880) a Pt catalyst that smoothly cyclized the polyene **18** to the 6-6 product **19**. Yoshihiro Sato of Hokkaido University and Miwako Mori of the Health Science University of Hokkaido have described (*J. Am. Chem. Soc.* **2007**, *129*, 7730) a Ru catalyst for the cyclization of **20** to the 5-6-5 product **21**. Each of these processes proceeded with high diastereocontrol.



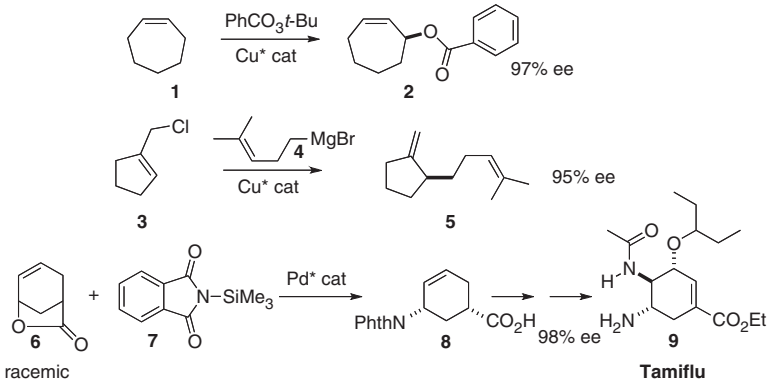
Transition metal-mediated polycarbocyclic construction has also been applied to natural product synthesis. Takashi Takahashi of the Tokyo Institute of Technology has developed (*J. Org. Chem.* **2007**, *72*, 3667) the Pd-mediated spirocyclization of **22** to **23**, leading to a formal synthesis of dimethyl gloiosiphone A **24**. Johann Mulzer of the Universität Wien employed (*Angew. Chem. Int. Ed.* **2007**, *46*, 9320) the Vollhardt cyclization of **25** to **26** in an enantioselective synthesis of pasteurestin A **27**. In a particularly straightforward approach, Joseph M. Fox of the University of Delaware used (*Organic Lett.* **2007**, *9*, 5625) Rh*-mediated enantioselective cyclopropanation of **28** to set the absolute configuration of (-)-pentalenene **32**.



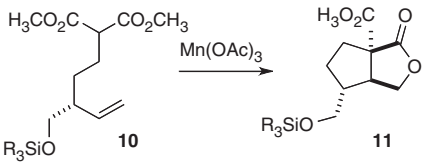
73. Transition Metal-Mediated Ring Construction: The Yu Synthesis of 1-Desoxyhypnophilin

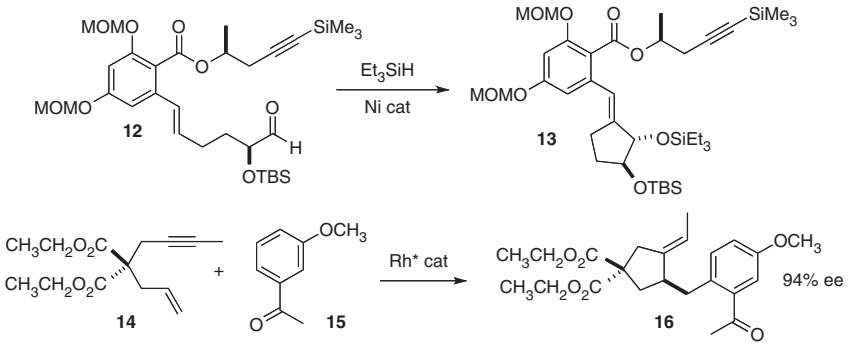
December 15, 2008

Both **1** and **3** are inexpensive prochiral starting materials. Tae-Jong Kim of Kyungpook National University devised (*Organomet.* **2008**, *27*, 1026) a chiral Cu catalyst that efficiently converted **1** (other ring sizes worked as well) to the enantiomerically pure ester **2**. Alexandre Alexakis of the University of Geneva found (*Adv. Synth. Cat.* **2008**, *350*, 1090) a chiral Cu catalyst that mediated the enantioselective coupling of **3** with Grignard reagents such as **4**. The π-allyl Pd complex derived from **6** is also prochiral. Barry M. Trost of Stanford University showed (*Angew. Chem. Int. Ed.* **2008**, *47*, 3759) that with appropriate ligand substitution, coupling with the phthalimide **7** proceeded to give **8**, readily convertible to (-)-oseltamivir (Tamiflu) **9**, in high ee.

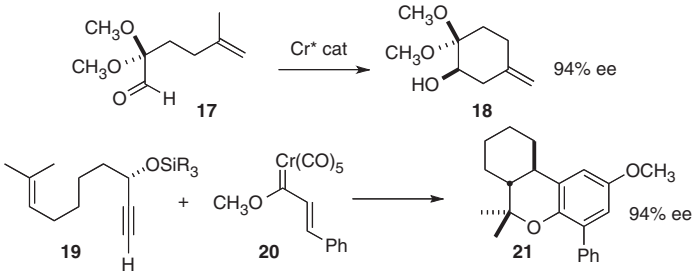


Jonathan W. Burton of the University of Oxford found (*Chem Commun.* **2008**, 2559) that $Mn(OAc)_3$-mediated cyclization of **10** delivered the lactone **12** with high diastereocontrol. John Montgomery of the University of Michigan observed (*Organic Lett.* **2008**, *10*, 811) that the Ni-catalyzed cyclization of **12** also proceeded with high diastereocontrol. Ken Tanaka of the Tokyo University of Agriculture and Technology combined (*Angew. Chem. Int. Ed.* **2008**, *47*, 1312) Rh-catalyzed ene-yne cyclization of **14** with catalytic ortho C-H functionalization, leading to **16** in high ee.

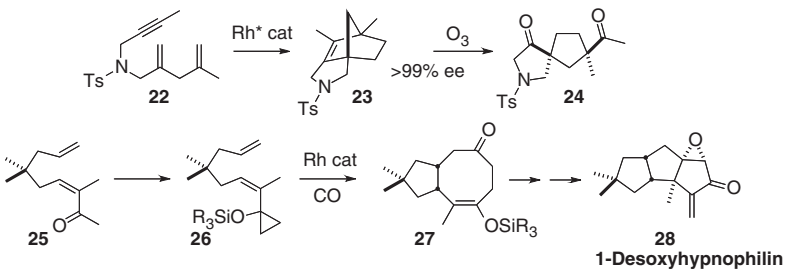




Eric N. Jacobsen of Harvard University designed (*Angew. Chem. Int. Ed.* **2008**, *47*, 1469) a chiral Cr catalyst for the intramolecular carbonyl ene reaction, that converted **17** to **18** in high ee. Using a stoichiometric prochiral Cr carbene complex **20** and the enantiomerically-pure secondary propargylic ether **19**, Willam D. Wulff of Michigan State University prepared (*J. Am. Chem. Soc.* **2008**, *130*, 2898) a facially-selective Cr-complexed *o*-quinone methide intermediate, that cyclized to **21** with high ee.



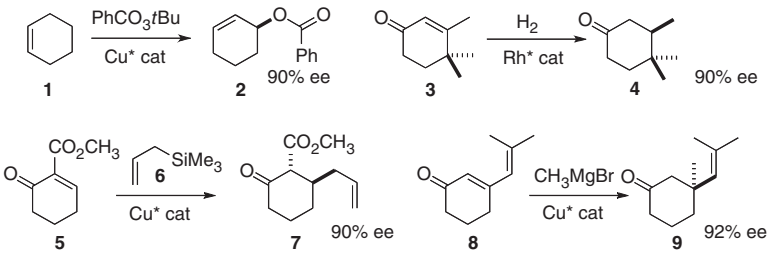
A variety of methods have been put forward for the transition metal-mediated construction of polycarbocyclic systems. One of the more powerful is the enantioselective Rh-catalyzed stitching of the simple substrate **22** into the tricycle **23** devised (*J. Am. Chem. Soc.* **2008**, *130*, 3451) by Takanori Shibata of Waseda University. *Inter alia*, ozonolysis of **23** delivered the cyclopentane **24** containing two all-carbon quaternary centers. Zhi-Xiang Yu of Peking University has devised both carbonylative (*J. Am. Chem. Soc.* **2008**, *130*, 4421), illustrated, and non-carbonylative (*J. Am. Chem. Soc.* **2008**, *130*, 7178) Rh-catalyzed cylization of alkenyl cyclopropanes such as **26**. Intramolecular aldol condensation followed by further functionalization converted **27** into 1-desoxyhypnophilin **28**.



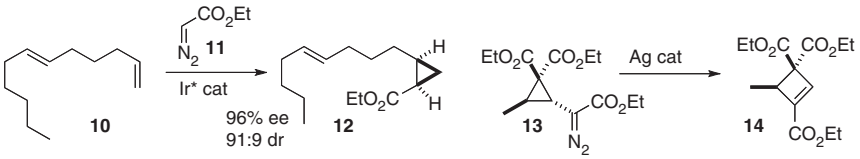
74. Transition Metal Catalyzed Construction of Carbocyclic Rings: (-)-Hamigeran B

August 17, 2009

Several elegant methods for the enantioselective transformation of preformed prochiral rings have been put forward. Derek R. Boyd of Queen's University, Belfast devised (*Chem. Commun*. **2008**, 5535) a Cu catalyst that effected allylic oxidation of cyclic alkenes such as **1** with high ee. Christoph Jaekel of the Ruprecht-Karls-Universität Heidelberg established (*Adv. Synth. Cat.* **2008**, *350*, 2708) conditions for the enantioselective hydrogenation of cyclic enones such as **3**. Marc L. Snapper of Boston College developed (*Angew. Chem. Int. Ed.* **2008**, *47*, 5049) a Cu catalyst for the enantioselective allylation of activated cyclic enones such as **5**. Alexandre Alexakis of the University of Geneva showed (*Angew. Chem. Int. Ed.* **2008**, *47*, 9122) that dienones such as **8** could be induced to undergo 1,4 addition, again with high ee.

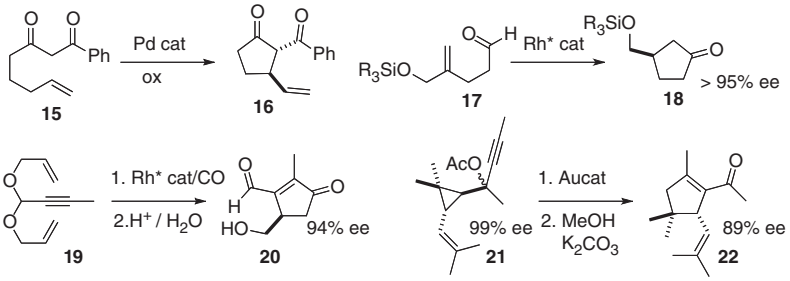


Tsutomu Katsuki of Kyushu University originated (*J. Am. Chem. Soc.* **2008**, *130*, 10327) an Ir catalyst for the addition of diazoacetate **11** to alkenes such as **10** to give the cyclopropane **12** with high chemo-, enantio- and diastereoselectivity. Weiping Tang of the University of Wisconsin found (*Angew. Chem. Int. Ed.* **2008**, *47*, 8933) a silver catalyst that rearranged cyclopropyl diazo esters such as **13** to the cyclobutene **14** with high regioselectivity.

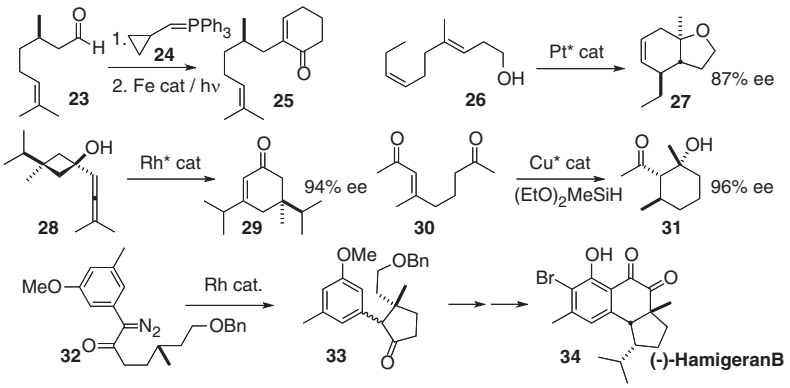


Zhang-Jie Shi of Peking University demonstrated (*J. Am. Chem. Soc.* **2008**, *130*, 12901) that under oxidizing conditions, a Pd catalyst could cyclize **15** to **16**. Sergio Castillón of the Universitat Rovira i Virgili, Tarragona devised (*Organic Lett*. **2008**, *10*, 4735) a Rh catalyst for the enantioselective cyclization of **17** to **18**. Virginie Ratovelomanana-Vidal of the ENSCP Paris and Nakcheol Jeong of Korea University established (*Adv. Synth. Cat.* **2008**, *350*, 2695) conditions for the enantioselective intramolecular Pauson-Khand cyclization of **19** to give, after hydrolysis, the cyclopentenone **20**. Quanrui Wang of Fudan University,

Cristina Nevado of the Universität Zurich and Andreas Goeke of Shanghai Givaudan described (*Angew. Chem. Int. Ed.* **2008**, *47*, 10110) the Au-mediated rearrangement of **21** to give, after hydrolysis, the cyclopentene **22** with minimal racemization. An alternative Au process converted **21** into the corresponding cyclohexenone with high ee.



We developed (*J. Org. Chem.* **2008**, *73*, 8030) a general method for the conversion of an aliphatic aldehyde **23** to the cyclohexenone **25**, condensation with the commercial phosphorane **24** followed by Fe-mediated cyclocarbonylation of the resulting alkenyl cyclopropane. Michel R. Gagné of the University of North Carolina devised (*Angew. Chem. Int. Ed.* **2008**, *47*, 6011) a Pt catalyst for the cyclization of polyalkenes such as **26** in high ee. Nicolai Cramer of ETH Zurich found (*Angew. Chem. Int. Ed.* **2008**, *47*, 9294) that ring expansion of the prochiral **28** to the cyclohexenone **29** could be effected with substantial enantioselectivity. Bruce H. Lipschutz of the University of California, Santa Barbara extended (*J. Am. Chem. Soc.* **2008**, *130*, 14378) his enantioselective conjugate reduction to substrates such as **30**, leading, via aldol condensation, to the cyclohexane **31**.

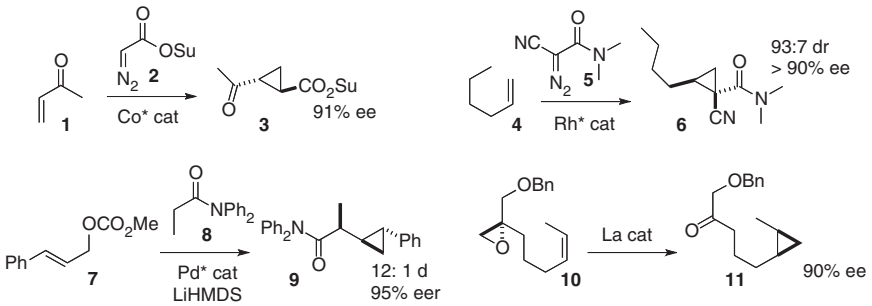


Many methods for transition metal-mediated polycarbocyclic construction have also been reported. We showed (*J. Org. Chem.* **2008**, *73*, 7560) that cyclization of **32** gave **33**, which we carried on to (-)-Hamigeran B **34**.

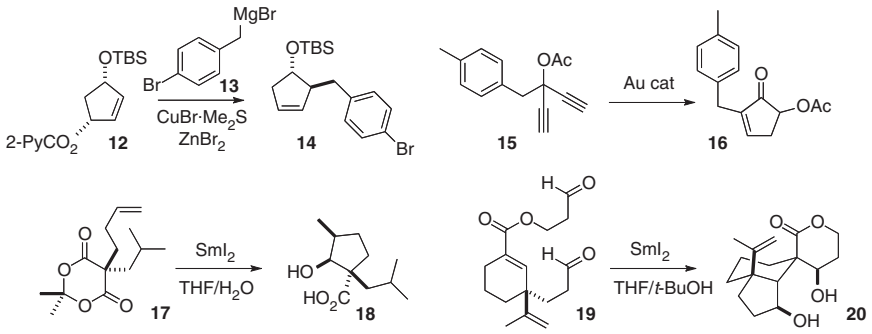
75. Transition Metal-Mediated C-C Ring Construction: The Stoltz Synthesis of (-)-Cyanthiwigin F

December 21, 2009

X. Peter Zhang of the University of South Florida extended (*Organic Lett*. **2009**, *11*, 2273) Co-catalyzed asymmetric cyclopropanation to the activated ester **2**. The product **3** readily coupled with amines. André B. Charette of the Université de Montréal showed (*J. Am. Chem. Soc.* **2009**, *131*, 6970) that even α-olefins such as **4** could be cyclopropanated in high ee with the diazo amide **5**. Xue-Long Hou of the Shanghai Institute of Organic Chemistry established (*J. Am. Chem. Soc.* **2009**, *131*, 8734) conditions for the enantioselective coupling of **7** and **8** to give **9**, in which sidechain chirality was also controlled. Tristan H. Lambert of Columbia University found (*J. Am. Chem. Soc.* **2009**, *131*, 7536) that "methylene" could be transferred in an intramolecular sense from the epoxide of **10** to the alkene, delivering the cyclopropane **11** in high ee.

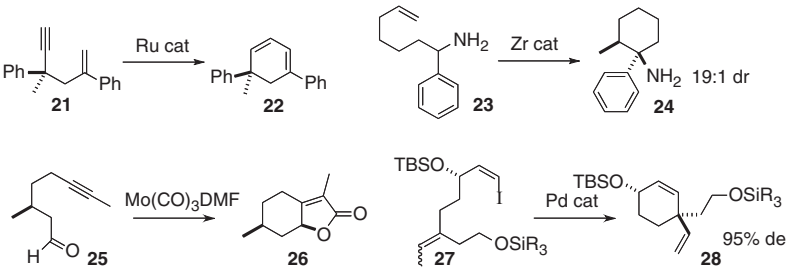


Yuichi Kobayashi of the Tokyo Institute of Technology established (*Organic Lett*. **2009**, *11*, 1103) that the 2-picolinoxy leaving group worked well for the S_N2' coupling with **13** to give **14**. Chang Ho Oh of Hanyang University developed (*J. Org. Chem.* **2009**, *74*, 370) a new route to cyclopentenones such as **16**, by gold-catalyzed cyclization of diynes such as **15**. David J. Procter of the University of Manchester used (*J. Am. Chem. Soc.* **2009**, *131*, 7214;

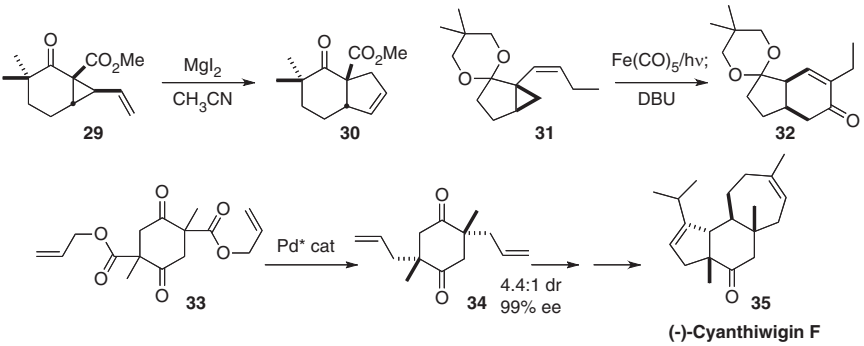


Tetrahedron Lett. **2009**, *50*, 3224) SmI_2 to cyclize **17** to **18** and **19** to **20**, each with high diastereocontrol.

Yoshiaki Nishibayashi of the University of Tokyo devised (*Angew. Chem. Int. Ed.* **2009**, *48*, 2534) Ru catalysts for the cyclization of an enyne such as **21** to the cyclohexadiene **22**. Laurel L. Schafer of the University of British Columbia developed (*J. Am. Chem. Soc.* **2009**, *131*, 2116) a Zr catalyst for the diastereocontrolled cyclization of amino alkenes such as **23**. Hongbin Zhai of the Shangahi Institute of Organic Chemistry showed (*J. Org. Chem.* **2009**, *74*, 2592) that the Mo-mediated cyclization of **25** also proceeded with high diastereocontrol. Even more impressive was the selectivity Kozo Shishido of the University of Tokushima demonstrated (*Tetrahedron Lett*. **2009**, *50*, 1279) for the cyclization of **27**.



Professor Lambert established (*J. Am. Chem. Soc.* **2009**, *131*, 2496) that the rearrangement of the vinyl cyclopropane **29** to the cyclopentene **30**, usually a high temperature process, could be effected with MgI_2. We (*J. Org. Chem.* **2009**, *74*, 2433) found that Fe-mediated cyclocarbonylation of **31** led to the cyclohexenone **32**.

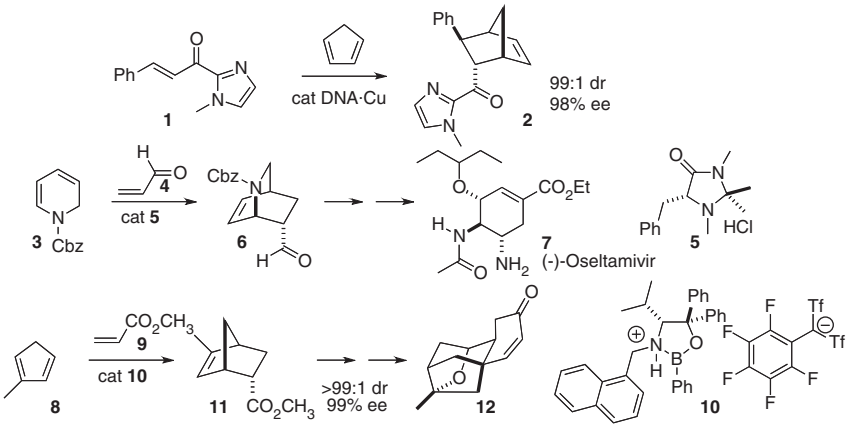


Brian M. Stoltz of Caltech prepared (*Nature* **2008**, *453*, 1228) the diester **33** by dimerization of diallyl succinate followed by methylation. Pd-mediated rearrangement delivered **34**, the central ring of (-)-Cyanthiwigin **35**, in high de and ee.

76. Intermolecular and Intramolecular Diels-Alder Reactions: (-)-Oseltamivir (Fukuyama), Platensimycin (Yamamoto) and 11,12-Diacetoxydrimane (Jacobsen)

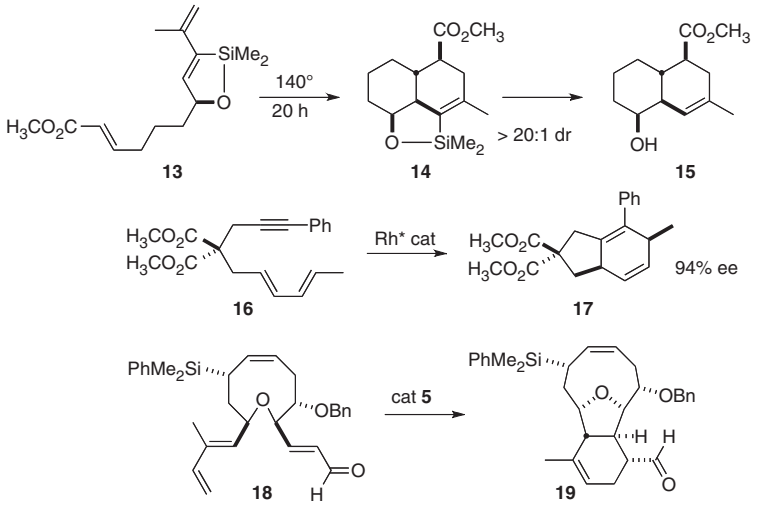
August 25, 2008

Powerful methods for catalytic, enantioselective intermolecular Diels-Alder reactions have been developed. Ben L. Feringa and Gerard Roelfes of the University of Groningen have shown (*Organic Lett*. **2007**, *9*, 3647) that a catalyst prepared by combining salmon testes DNA with a Cu complex directed the absolute sense of the addition of **1** to cyclopentadiene **2**. Mukund P. Sibi of North Dakota State University has reported (*J. Am. Chem. Soc*. **2007**, *129*, 395) related work with achiral pyrazolidinone dienophiles and chiral Cu catalysts. Tohru Fukuyama of the University of Tokyo found (*Angew. Chem. Int. Ed*. **2007**, *46*, 5734) that the MacMillan catalyst **5** was effective at mediating the addition of acrolein **4** to the pyridine-derived diene **3**, enabling an enantioselective synthesis of the prominent antiviral (-)-oseltamivir (tamiflu) **7**. Hisashi Yamamoto of the University of Chicago has demonstrated (*J. Am. Chem. Soc*. **2007**, *129*, 9534 and 9536) that the novel catalyst **10** effected addition of methyl acrylate **9** to the diene **8**, leading to an elegant enantioselective synthesis of the tetracycle **12**, the key intermediate in the Nicolaou synthesis of platensimycin.

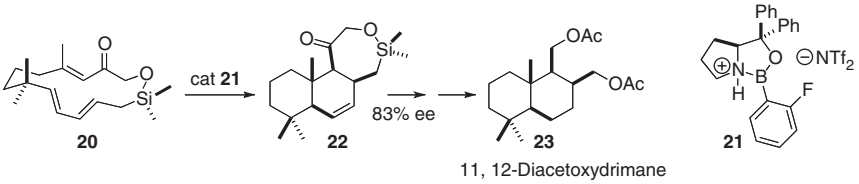


New illustrations of the power of the intramolecular Diels-Alder reaction have been put forward. Demonstrating the influence of a single subsituent on the tether, William R. Roush of Scripps/Florida found (*Organic Lett*. **2007**, *9*, 2243) that cyclization of **13** led to the diastereomer **14**, complementary to the result observed with an acyclic triene. Ryo Shintani and Tamio Hayashi of Kyoto University have extended (*Angew. Chem. Int. Ed*. **2007**, *46*, 7277) their studies of chiral diene-based Rh catalysts to the enantioselective cyclization of alkynyl dienes such as **16**. Jonathan W. Burton of the University of Oxford and Andrew B. Holmes of the University of Melbourne employed (*Chem. Commun*. **2007**, 3954) the

MacMillan catalyst **5** for the cyclization of **18** to **19**. It is impressive that ent-**5** catalyzed the cyclization of **18** cleanly into the diastereomer of **19** in which both of the newly-created stereogenic centers were inverted.



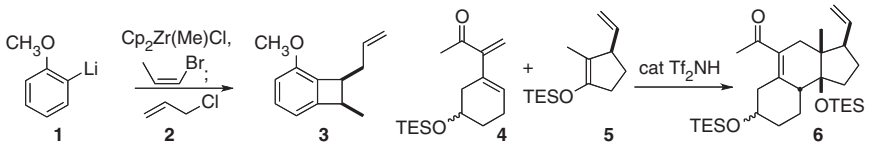
Transannular intramolecular Diels-Alder (TADA) cyclizations have been widely employed. Although a great deal has been learned about relative stereocontrol, little progress had been made on asymmetric catalysis of the cyclization of prochiral trienes such as **20**. Eric N. Jacobsen of Harvard University has now found (*Science* **2007**, *317*, 1736) that the *o*-fluoro complex **21** served effectively. The power of this approach was illustrated by the conversion of the adduct **22** into the natural product 11,12-diacetoxydrimane **23**.



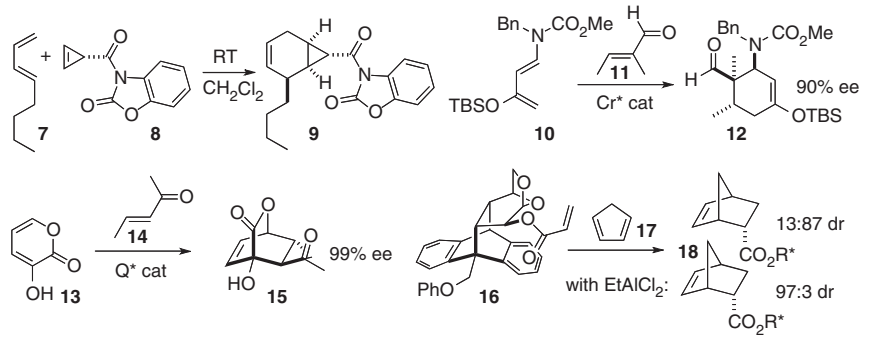
77. Intermolecular and Intramolecular Diels-Alder Reactions: Platencin (Banwell), Platensimycin (Matsuo), (-)-Halenaquinone (Trauner), (+)-Cassaine (Deslongchamps)

August 24, 2009

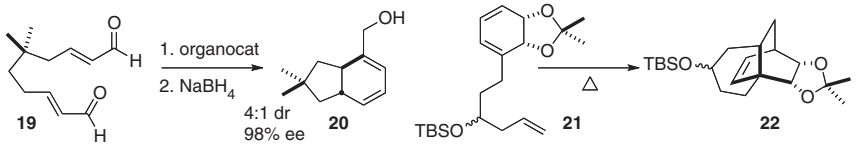
José Barluenga of the Universidad de Oviedo described (*Organic Lett.* **2008**, *10*, 4469) a powerful route from lithiated arenes such as **1** to the benzocyclobutane **3**, the immediate precursor to the powerful *o*-quinone methide Diels-Alder diene. Michael E. Jung of UCLA developed (*Organic Lett.* **2008**, *10*, 3647) a triflimide catalyst for the inverse electron demand coupling of the highly substituted diene **4** with the enol ether **5** to give **6** with high diastereocontrol.



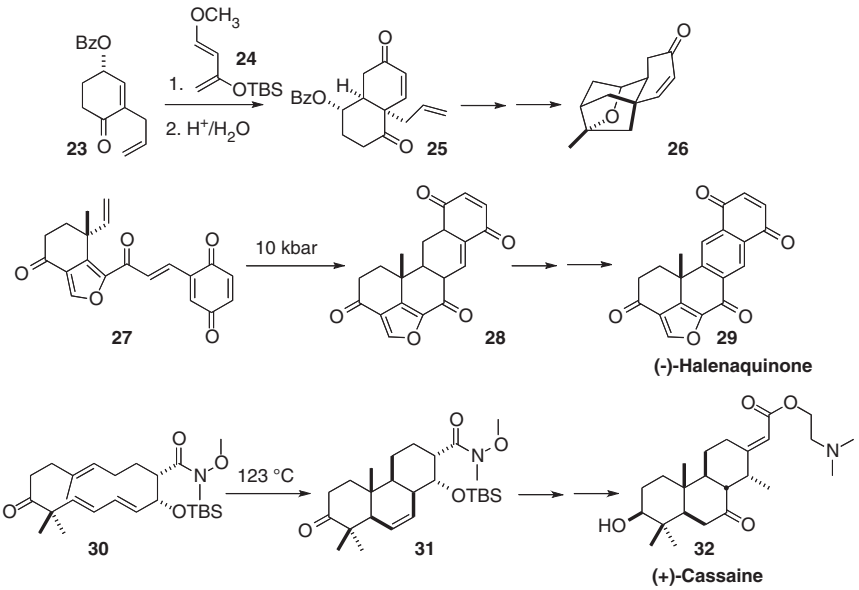
Joseph M. Fox of the University of Delaware showed (*J. Org. Chem.* **2008**, *73*, 4283) that the cyclopropene carboxylate **8** was a powerful and selective dienophile. Richard P. Hsung and Kevin P. Cole of the University of Wisconsin finally (*Adv. Synth. Cat.* **2008**, *350*, 2885) reduced to practice the long-sought enantioselective Diels-Alder cycloaddition of a *trisubstituted* aldehyde, **11**. Li Deng of Brandeis University devised (*J. Am. Chem. Soc.* **2008**, *130*, 2422) a *Cinchona*-derived catalyst for Diels-Alder cycloaddition to the diene **13** with high ee. Miguel Á. Sierra of the Universidad Complutense, Madrid, and Alejandra G. Suárez of the Universidad Nacional de Rosario described (*Organic Lett.* **2008**, *10*, 3389) a clever switchable chiral auxiliary **16** that favored diastereomer *S*-**18** on thermal addition, but *R*-**18** with $EtAlCl_2$.



New approaches to the intramolecular Diels-Alder reaction continue to be introduced. Mathias Christmann, now at the TU Dortmund, showed (*Angew. Chem. Int. Ed.* **2008**, *47*, 1450) that a secondary amine organocatalyst converted the prochiral dialdehyde **19** into the bicyclic diene **20** with high de and ee. Martin G. Banwell of the Australian National University prepared (*Organic Lett.* **2008**, *10*, 4465) the triene **21** in high ee by microbiological oxidation of iodobenzene. On warming, **21** was converted smoothly into **22**, which was carried on in a formal synthesis of platencin.



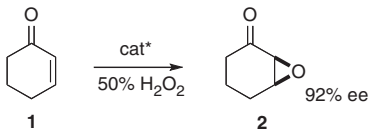
Jun-ichi Matsuo of Kanazawa University was able (*Organic Lett.* **2008**, *10*, 4049) to induce (neat, 180 °C) the intermolecular Diels-Alder cycloaddition of **23** with **24**, delivering the cycloadduct **25** with 11:1 diastereocontrol. This set the two rings and angular substitution of the key platensimycin intermediate **26**. Dirk Trauner, now at the University of Munich, found (*J. Am. Chem. Soc.* **2008**, *130*, 8604) that the intramolecular Diels-Alder cyclization of **27** was most efficient at high pressure. The product **28** was readily tautomerized and then oxidized to give (-)-Halenaquinone **29**. Pierre Deslongchamps of the Université de Sherbrooke extensively investigated (*J. Am. Chem. Soc.* **2008**, *130*, 13989) the transannular Diels-Alder cyclization of **30** and derivatives. The adduct **31** was carried on to (+)-cassaine **32**.



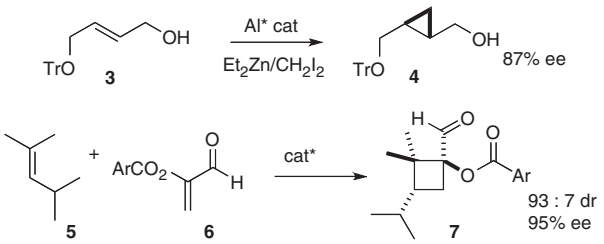
78. Stereocontrolled Carbocyclic Construction: The Trauner Synthesis of the Shimalactones

December 22, 2008

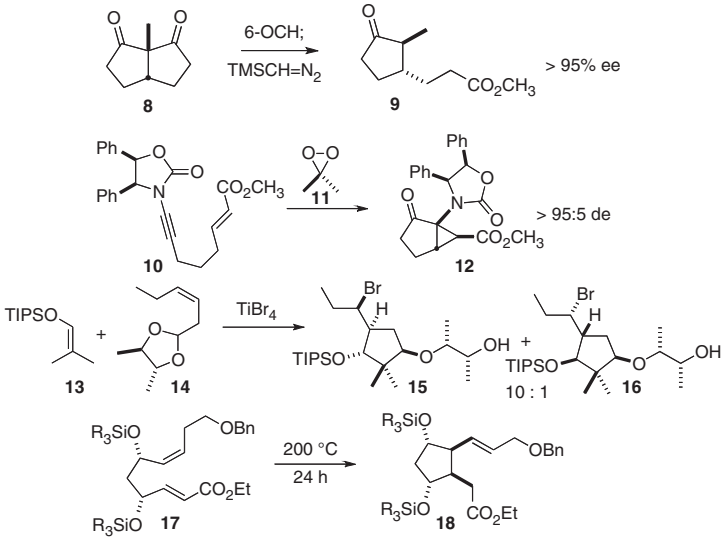
Benjamin List of the Max Planck Institute, Mülheim devised (*J. Am. Chem. Soc.* **2008**, *130*, 6070) a chiral primary amine salt that catalyzed the enantioselective epoxidation of cyclohexenone **1**. Larger ring and alkyl-substituted enones are also epoxidized with high ee.



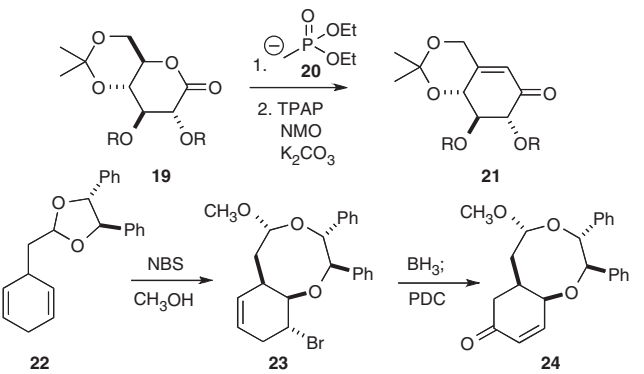
Three- and four-membered rings are versatile intermediates for further transformation. Tsutomu Katsuki of Kyushu University developed (*Angew. Chem. Int. Ed.* **2008**, *47*, 2450) an elegant Al(salalen) catalyst for the enantioselective Simmons-Smith cyclopropanation of allylic alcohols such as **3**. Kazuaki Ishihara of Nagoya University found (*J. Am. Chem. Soc.* **2007**, *129*, 8930) chiral amine salts that effected enantioselective 2+2 cycloaddition of α-acyloxyacroleins such as **5** to alkenes to give the cyclobutane **7** with high enantio- and diastereocontrol.



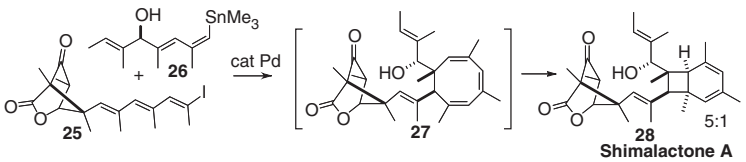
Gideon Grogan of the University of York overexpressed (*Adv. Synth. Cat.* **2008**, *349*, 916) the enzyme 6-oxocamphor hydrolase in *E. coli*. The 6-OCH so prepared converted prochiral diketones such as **8** to the cyclopentane **9** in high ee. Richard P. Hsung of the University of Wisconsin found (*Organic Lett.* **2008**, *10,* 661) that the carbene produced by oxidation of the ynamide **10** cyclized to **11** with high de. Teck-Peng Loh of Nanyang Technological University extended (*J. Am. Chem. Soc.* **2008**, *130*, 7194) butane-2,3-diol directed cyclization to the preparation of the cyclopentane **15**. Note that sidechain relative configuration is also controlled. We established (*J. Org. Chem.* **2008**, *73*, 3467) that the thermal ene reaction of **17** delivered the tetrasubstituted cyclopentane **18** as a single diastereomer.



Tony K. M. Shing of the Chinese University of Hong Kong devised (*J. Org. Chem.* **2007**, *72*, 6610) a simple protocol for the conversion of carbohydrate-derived lactones such as **19** to the highly-substituted, enantiomerically-pure cyclohexenone **21**. Hiromichi Fujioka and Yasuyuki Kita of Osaka University established (*Organic Lett.* **2007**, *9,* 5605) a chiral diol-mediated conversion of the cyclohexadiene **22** to the diastereomerically pure cyclohexenone **24**.



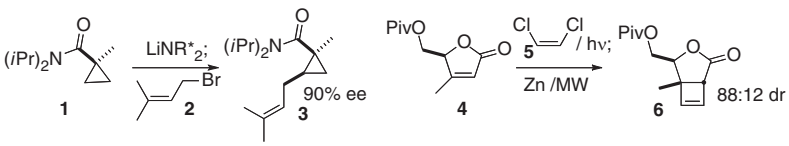
Dirk Trauner, now of the University of Munich, reported (*Organic Lett.* **2008**, *10,* 149) an elegant assembly of the neuritogenic polyketide shimalactone A **28**. As anticipated, the polyene prepared by Stille coupling of the iodide **25** with the stannane **26** underwent 8 π cyclization to **27**, that then spontaneously underwent 8 π cyclization to **28**, with substantial diastereocontrol.



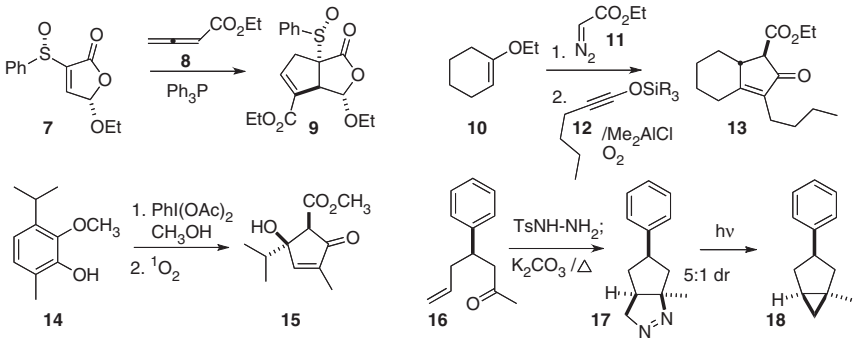
79. Stereocontrolled Carbocyclic Construction: (-)-Mintlactone (Bates), (-)-Gleenol (Kobayashi), (-)-Vibralactone C (Snider)

August 31, 2009

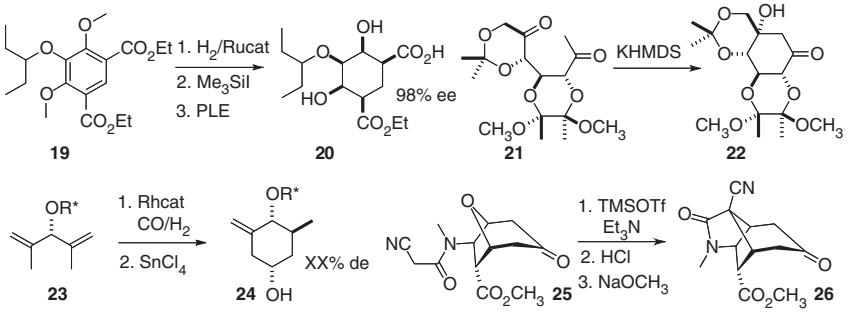
Nigel S. Simpkins, now at the University of Birmingham, found (*Chem. Commun*. **2008**, 5390) that the prochiral cyclopropane amide **1** could be deprotonated to give, after alkylation, the substituted cyclopropane **3** with high enanantio- and diastereocontrol. In the course of a synthesis of (+)-Lineatin, Ramon Alibés of the Universitat Autònoma de Barcelona optimized (*J. Org. Chem.* **2008**, *73*, 5944) the photochemical cycloaddition of **4** and **5** to give, after reductive dechlorination, the cyclobutene **6**.



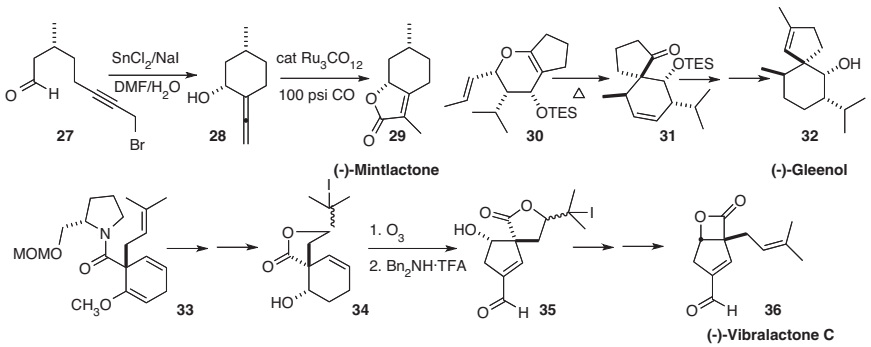
In a related reaction, José L. García Ruano and M. Rosario Martín of the Universidad Autónoma de Madrid observed (*J. Org. Chem.* **2008**, *73*, 9366) that the cycloaddition of **8** to **7** proceeded with high regio- and diastereocontrol, to give the cyclopentene **9**. Joseph M. Ready of UT Southwestern in Dallas developed (*Angew. Chem. Int. Ed.* **2008**, *47*, 7068) a powerful new cyclopentannulation, condensing the cyclopropane derived from the addition of **11** to **10** with the protected ynolate **12** to give **13**, in the presence of a modified Lewis acid catalyst. Chun-Chen Liao of the National Tsing Hua University, Hsinchu described (*Angew. Chem. Int. Ed.* **2008**, *47*, 7325) the oxidative ring contraction of the *o*-alkoxy phenol **14** to the cyclopentenone **15**. Stéphane Quideau of the Université de Bordeaux reported (*Organic Lett.* **2008**, *10*, 5211) a related ring contraction. We uncovered (*J. Org. Chem.* **2008**, *73*, 9479) a simple protocol for the *in situ* conversion of an ω-alkenyl ketone such as **16** to the corresponding diazo compound, leading, via dipolar cycloaddition, to the adduct **17**.



Ulrich Zutter of Roche Basel described (*J. Org. Chem.* **2008**, *73*, 4895), in a synthesis of Tamiflu, the hydrogenation of **19** to give the cyclohexane with all-cis diastereocontrol. Selective removal of the methyl ethers with trimethylsilyl iodide set the stage for enzymatic ester hydrolysis, delivering **20** in high ee. Jonathan Clayden of the University of Manchester developed (*Angew. Chem. Int. Ed.* **2008**, *47*, 5060) a complementary approach for converting benzene precursors to enantiomerically-pure cyclohexenones. In a synthesis of valiolamine, Tony K. M. Shing of the Chinese University of Hong Kong carried out (*Organic Lett.* **2008**, *10*, 4137) the direct aldol cyclization of **21** to **22**. Catalysis with proline gave the alternative diastereomer. Bernhard Breit of Albert-Ludwigs-Universität, Freiburg developed (*Organic Lett.* **2008**, *10*, 5321) a chiral directing group for allylic alcohol hydroformylation. Subsequent carbonyl ene cyclization gave the cyclohexane **24**. In pursuit of the complex polycyclic alkaloid gelsemine, Professor Simpkins reported (*Organic Lett.* **2008**, *10*, 4747) a remarkable double elimination-intramolecular Michael cyclization, converting **25** into the bridged cyclohexanone **26**.



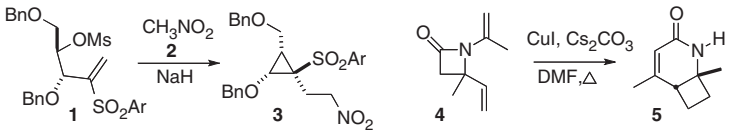
Roderick W. Bates of Nanyang Technological University found (*J. Org. Chem.* **2008**, *73*, 8104), in a synthesis of (-)-Mintlactone **29**, that the diastereocontrolled reductive cyclization of **27** to **28** worked best in wet DMF. Susumu Kobayashi of the Tokyo University of Science showed (*Chemistry Lett*. **2008**, *37*, 770), en route to (-)-Gleenol **32**, that the Claisen rearrangement of **30** delivered the cyclohexene **31** with high diastereocontrol. Barry B. Snider of Brandeis University prepared (*J. Org. Chem.* **2008**, *73*, 8049) (-)-Vibralactone C **36** from **33**, available from *o*-anisic acid by the Schultz protocol.



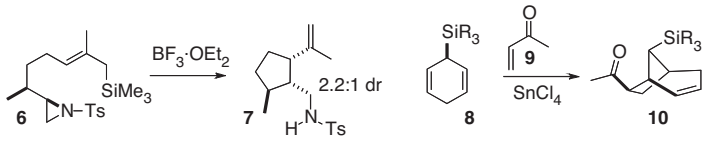
80. Stereocontrolled Carbocyclic Construction: The Mulzer Synthesis of (-)-Penifulvin A

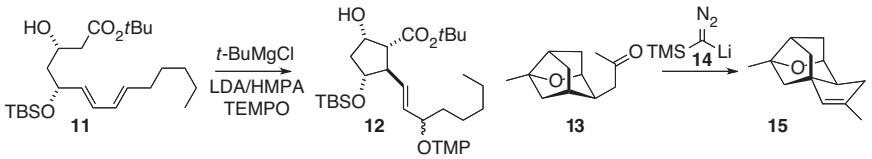
December 28, 2009

Tanmaya Pathak of the Indian Institute of Technology, Kharagpur devised (*J. Org. Chem.* **2009**, *74*, 2710) a preparation of enantiomerically-pure oxygenated cyclopropanes such as **3** from carbohydrate precursors. Andrei K. Yudin of the University of Toronto established (*Organic Lett*. **2009**, *11*, 1281) a route to aminated cyclobutanes such as **5** based on sigmatropic rearrangement of the β-lactam **4**.



Stephen C. Bergmeier of Ohio University reported (*Tetrahedron* **2009**, *65*, 741) a study of the balance between five- and six-membered ring formation in the cyclization of aziridines such as **6**. Professor Bergmeier also described (*Tetrahedron Lett*. **2009**, *50*, 1261) the bridging additions of enones to cyclic allyl silanes such as **8**. This is particularly interesting, as **8** is easily prepared by Birch reduction of the corresponding phenyl silane.

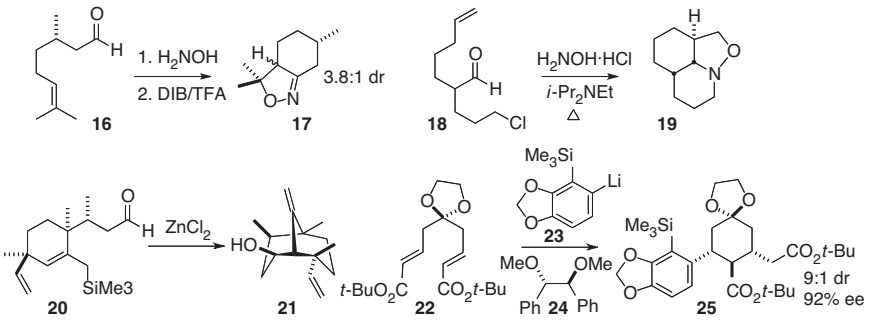




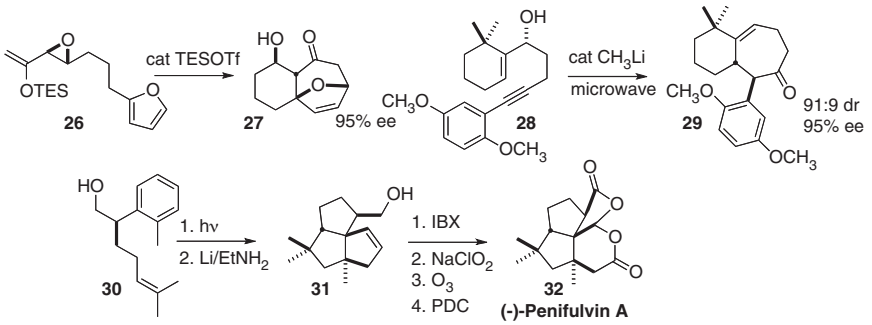
Ullrich Jahn of the Academy of Sciences of the Czech Republic observed (*Chem. Eur. J.* **2009**, *15*, 58) that the free-radical cyclization of **11** proceeded to give mainly the diastereomer **12** (~ 1:1 at the secondary allylic position). Daesung Lee of the University of Illinois at Chicago reasoned (*J. Am. Chem. Soc.* **2009**, *131*, 8413) that the stereochemical relationship between the O and the adjacent C-H of **13** was such that the C-H would be *deactivated*. The cyclization of the alkylidene carbene derived from **13** indeed proceeded to give **14**, setting the stage for the synthesis of platensimycin.

Marco A. Cufolini of the University of British Columbia found (*Organic Lett*. **2009**, *11*, 1539) an easy protocol for the generation of a nitrile oxide and subsequent dipolar cycloaddition, by oxidation of the oxime. In a related investigation, Adam J. M. Burrell and

Iain Coldham of the University of Sheffield cyclized (*Organic Lett*. **2009**, *11*, 1515) the oxime derived from **18**, by way of the intermediate nitrone, to give **19** with high diastereocontrol.



Toshio Honda of Hoshi University established (*J. Org. Chem.* **2009**, *74*, 3424) that the intramolecular Sakurai cyclization of **20** proceeded with high diastereocontrol, to give **21**. Kiyoshi Tomioka of Kyoto University showed (*Organic Lett*. **2009**, *11*, 1631) that the chiral ligand **24** directed the absolute course of the cascade addition of **23** to **22**. The product **25** was carried on to (-)-Lycorine.

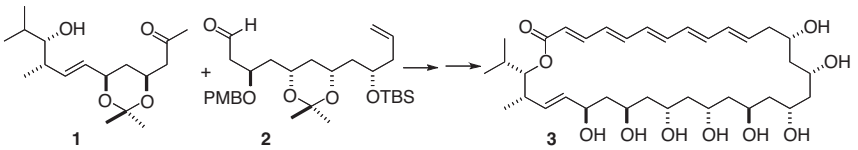


Pauline Chiu of the University of Hong Kong devised (*J. Am. Chem. Soc.* **2009**, *131*, 4556) conditions for the cyclization of the epoxide **26** to **27**, with the enantiomerically-pure epoxide controlling the absolute configuration of the tricyclic ring system. Timo V. Ovaska of Connecticut College set (*Organic Lett*. **2009**, *11*, 2715) the absolute configuration of **28** by Itsuno-Corey reduction of the corresponding ketone. Cascade cyclization then delivered **29**. Tanja Gaich and Johann Mulzer of the University of Vienna designed (*J. Am. Chem. Soc.* **2009**, *131*, 452) a short route to the dioxafenestrane insecticide (-)-Pentifulvin A **32**. Photocyclization converted the alcohol **30** to a ~ 1:1 mixture of regioisomers. Reduction of one of them gave **31**, which was oxidized to **32**.

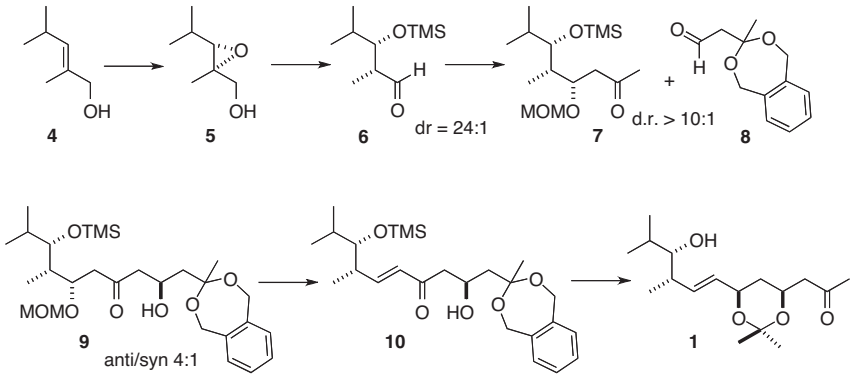
81. The Sammakia Synthesis of the Macrolide RK-397

January 7, 2008

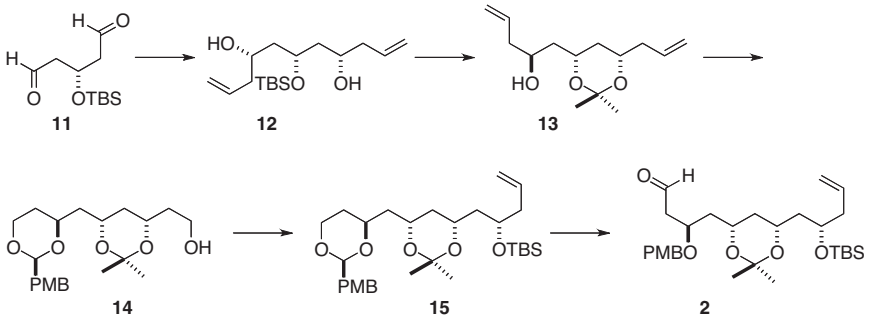
The polyene macrolide RK-397 **3**, isolated from soil bacteria, has antifungal, antibacterial and anti-tumor activity. Tarek Sammakia of the University of Colorado has described (*Angew. Chem. Int. Ed.* **2007**, *46*, 1066) the highly convergent coupling of **1** with **2**, leading to **3**.



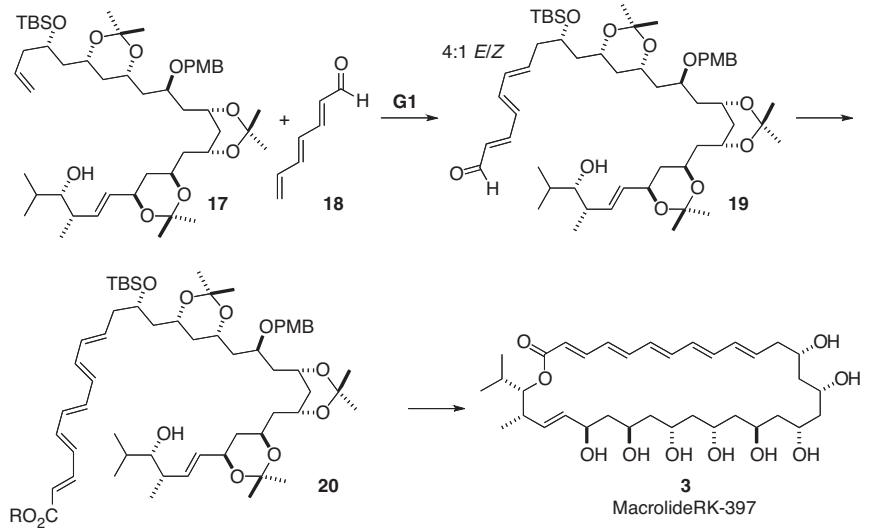
The preparation of **1** depended on the powerful methods that have been developed for acyclic stereocontrol. Beginning with the allylic alcohol **4**, Sharpless asymmetric epoxidation established the absolute configuration of **5**. Following the Jung "non-aldol aldol" protocol, exposure of **5** to TMSOTf delivered the aldehyde **6** in high de. Condensation of **6** with the lithium enolate of acetone also proceeded with high de. The resulting alcohol was protected as the MOM ether, to direct the stereoselectivity of the subsequent aldol condensation with **8**. Selective β-elimination followed by reduction and protecting group exchange then gave **1**.



The preparation of **2** took advantage of the power of Brown asymmetric allylation. Allylation of the symmetrical **11** led to the diol **12**. This was desymmetrized by selective acetonide formation, to give **13**. Ozonolysis, reductive work-up, and protection of the newly-formed 1,3-diol gave **14**, setting the stage for oxidation and asymmetric allylation to give **15**. Reductive deprotection and oxidation then delivered the acetonide **2**.



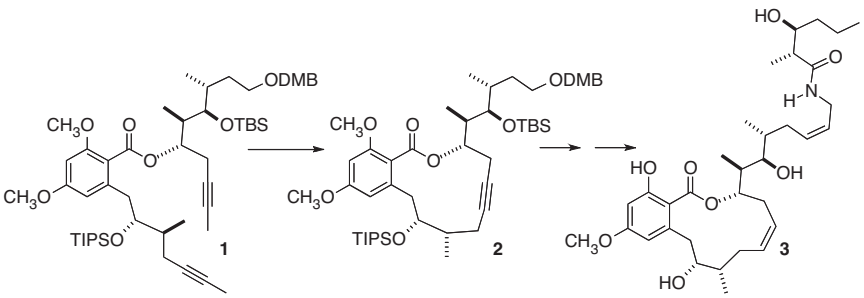
The tris acetonide **16** was assembled by addition of the enolate derived from **1** to the aldehyde **2**, followed by reduction and protection. Kinetically-controlled metathesis with **17** established the triene **18**. Phosphonate-mediated homologation to the pentaene **19** followed by hydrolysis and Yamaguchi macrolactonization then completed the synthesis of the macrolide RK-397 **3**.



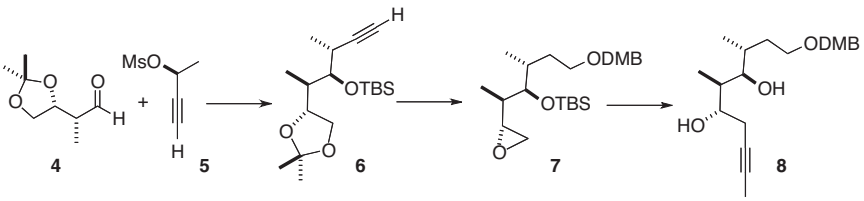
82. The Maier Synthesis of Cruentaren A

February 4, 2008

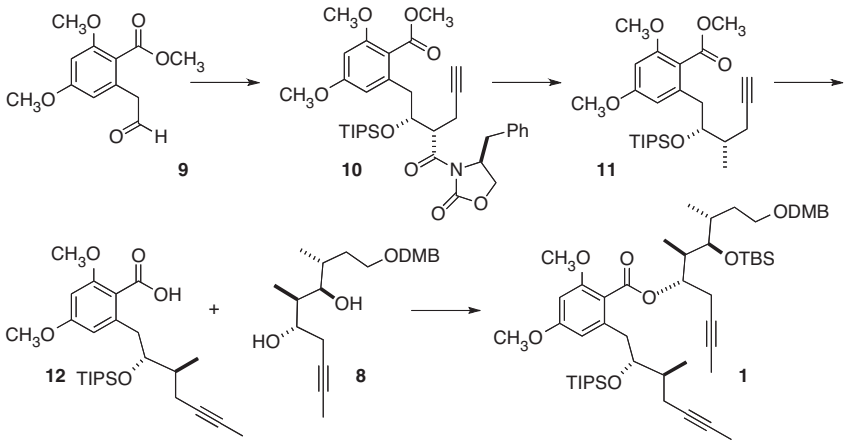
Cruentaren A **3**, isolated from the myxobacterium *Byssovorax cruenta*, is an inhibitor of mitochondrial F-ATPase. The synthesis of **3** (*Organic Lett*. **2007**, *9*, 655; *Angew. Chem. Int. Ed.* **2007**, *46*, 5209) by Martin E. Maier of the Universität Tübingen illustrates the power of alkyne metathesis as a tool for the synthesis of complex natural products. Very recently, Alois Fürstner of the Max-Planck-Institut, Mülheim, reported (*Angew. Chem. Int. Ed.* **2007**, *46*, 9275) an alternative synthesis, also based on alkyne metathesis, of cruentaren A **3**.



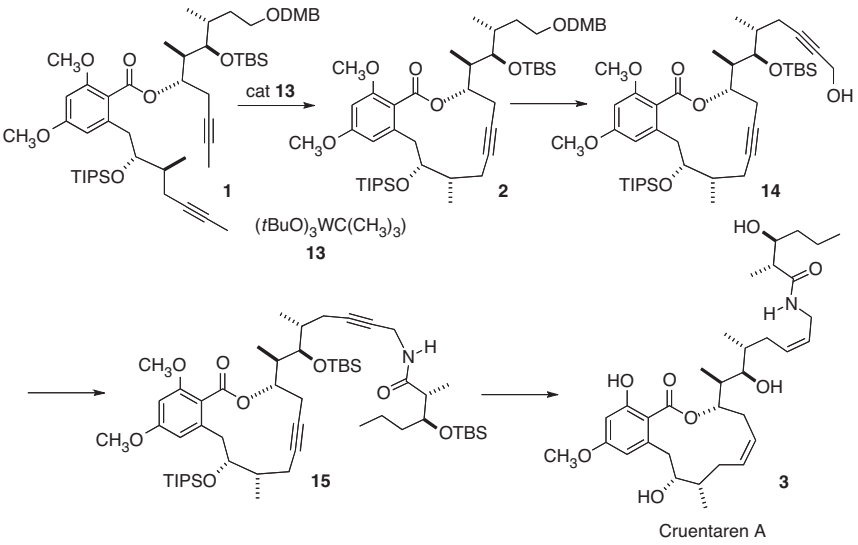
The alcohol portion of **1** was prepared by Marshall homologation of **4** with **5**, leading to **6**. Homologation of the derived epoxide **7** then gave **8**. Note that the homologation of **7** to **8** required three steps. This might have been accomplished more directly with the Li salt of 1-propyne, easily prepared from commercial 1- or 2-bromopropene.



Evans auxiliary-controlled homologation of **9** set the relative and absolute configuration of **10**, which was carried on to **12**. To effect coupling, the acid of **12** was activated with carbonyl diimidazole, then condensed with the bis-alcoholate of **8**. This acylation was highly regioselective, giving **1** as the only observed product.



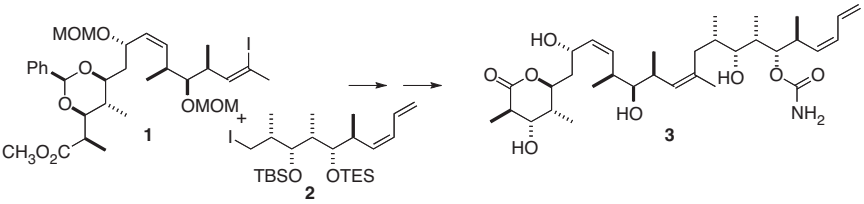
Cruentaren A **3** has two *Z* alkenes, so the authors chose a bis-alkyne strategy, with a partial hydrogenation of both alkynes at the end of the synthesis. To this end, alkyne metathesis was accomplished with the Schrock tungsten carbine catalyst **13**. Homologation to **15** followed by deprotection and hydrogenation then gave enantiomerically pure cruentaren A **3**.



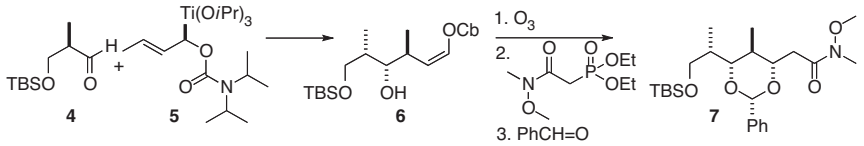
83. The Betzer and Ardisson Synthesis of (+)-Discodermolide

March 3, 2008

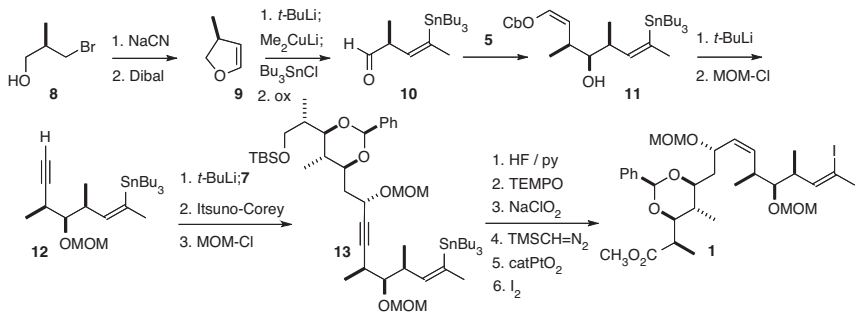
(+)-Discodermolide **3**, a potent anticancer agent that works synergistically with taxol, may yet prove to be clinically effective. For the synthetic material to be affordable, a highly convergent synthesis is required. Jean-François Betzer and Janick Ardisson of the Université de Cergy-Pontoise have described (*Angew. Chem. Int. Ed.* **2007**, *46*, 1917) such a synthesis, coupling **1** and **2**. A central feature of their approach was the repeated application of the inherently chiral secondary organometallic reagent **5**.



The first use of **5** was the addition to the aldehyde **4**. The product **6** was ozonized, and the resulting aldehyde was carried on to the α,β-unsaturated ester. Exposure of the hydroxy ester to benzaldehyde under basic conditions delivered, by intramolecular Michael addition, the acetal **7**.

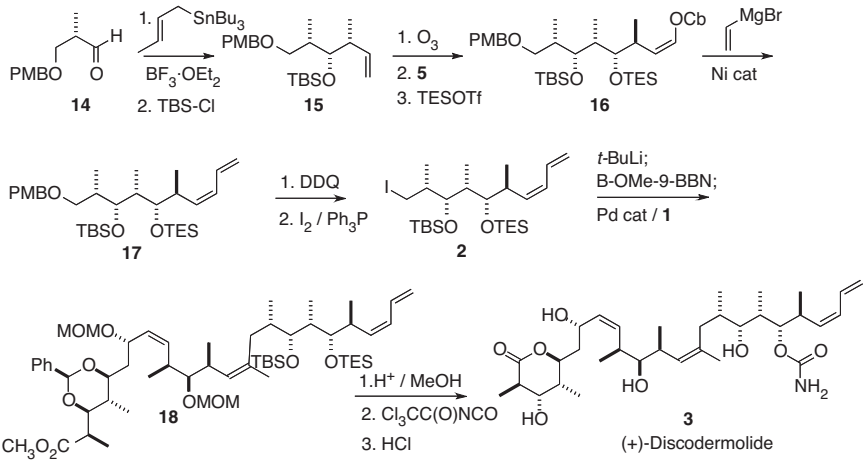


The next addition of the reagent **5** was to the aldehyde **10**. The adduct **11** was deprotonated with *t*-BuLi to effect α-elimination, providing, after protection of the alcohol, the alkyne **12**. Coupling of **12** with the amide **7** gave a ketone, enantioselective reduction of which under Itsuno-Corey conditions led, again after protection of the alcohol, to the alkyne **13**.



Oxidation followed by selective hydrogenation and iodine-tin exchange then completed the assembly of **1**. Note that PtO_2, not typically used for partial hydrogenation, was the catalyst of choice for this congested alkyne.

The third application of the enantiomerically-pure reagent **5** was addition to the aldehyde that had been prepared by ozonolysis of **15**. Advantage was then taken of another property of the alkenyl carbamate, Ni-mediated Grignard coupling, to form the next carbon-carbon bond with high geometric control. Deprotection of the diene **17** so prepared followed by iodination then completed the synthesis of **2**.



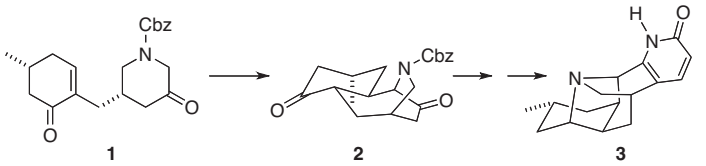
The convergent coupling of **1** with **2** was carried out under Suzuki conditions. Reduction of the iodide of **2** to the corresponding alkyl lithium followed by exchange with B-OMe-9-BBN gave an intermediate organoborane, that smoothly coupled with **1** under Pd catalysis to give **18**. Deprotection and carbamate formation then led to (+)-discodermolide **3**.

This synthesis clearly illustrates the power of **5** as an enantiomerically-defined secondary organometallic reagent, and the synthetic versatility of the product alkenyl carbamates. The ready availability of the three enantiomerically-pure four-carbon fragments **4**, **8**, and **14** was also a key consideration in the design of this synthesis.

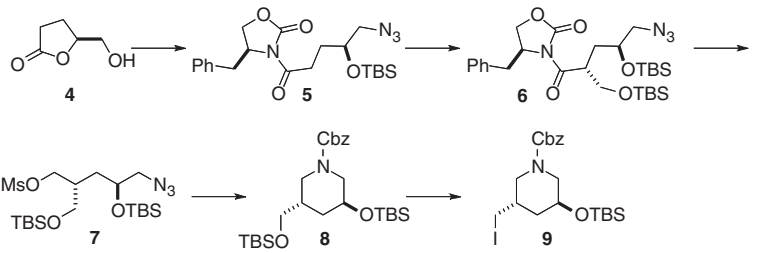
84. The Smith Synthesis of (+)-Lyconadin A

April 7, 2008

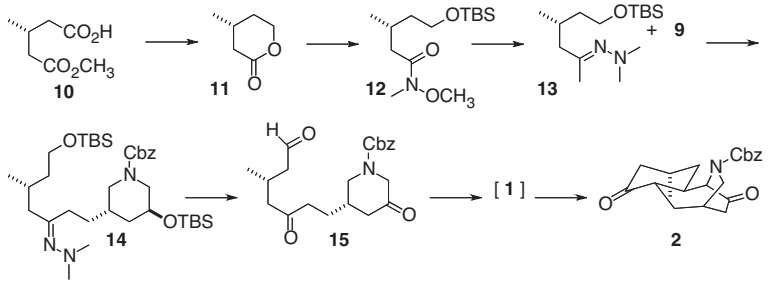
The pentacyclic alkaloid (+)-lyconadin A **3**, isolated from the club moss *Lycopodium complanatum*, showed modest in vitro cytotoxicity. A key step in the first reported (*J. Am. Chem. Soc.* **2007**, *129*, 4148) total synthesis of **3**, by Amos B. Smith III of the University of Pennsylvania, was the cyclization of **1** to **2**.



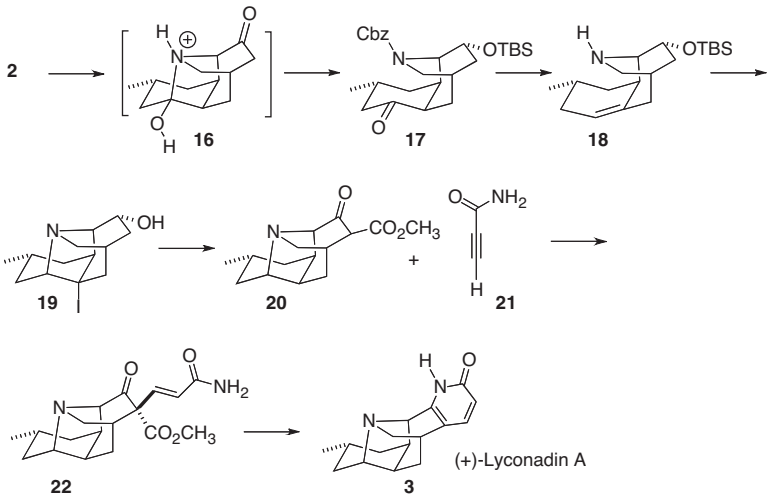
The pentacyclic skeleton of **3** was constructed around a central organizing piperidine ring **9**. This was prepared from the known (and commercial) enantiomerically-pure lactone **4**. The akylated stereogenic center of **9** was assembled by diastereoselective hydroxy methylation of the acyl oxazolidinone **5** with *s*-trioxane, followed by protection. Reduction of the imide to the alcohol led to the mesylate **7**, which on reduction of the azide spontaneously cyclized to give, after protection, the piperidine **8**. Selective desilylation of the primary alcohol then enabled the preparation of **9**.



The plan was to assemble the first carbocyclic ring of **3** by intramolecular aldol condensation of the keto aldehyde **15**. The enantiomerically-pure secondary methyl substituent of **15** derived from the commercial monoester **10**. Activation as the acid fluoride followed by selective reduction led to the volatile lactone **11**. Opening of the lactone with $H_3CONHCH_3{\cdot}HCl$ gave, after protection, the Weinreb amide **12**. Alkylation of the derived hydrazone **13**, selectively on the methyl group, led, after deprotection, to **15**. The intramolecular aldol condensation of **15** did deliver the unstable cyclohexenone **1**. Under the acidic conditions of the aldol condensation, the enol derived from the piperidone added in a Michael sense, from the axial direction on the newly-formed ring, to give the trans-fused bicyclic diketone **2**.



To move forward, it was necessary to epimerize **2** to the cis ring fusion, and also to differentiate the two ketones of **2**. These two problems were solved simultaneously by deprotection and epimerization to the cis-fused hemiaminal **16**.

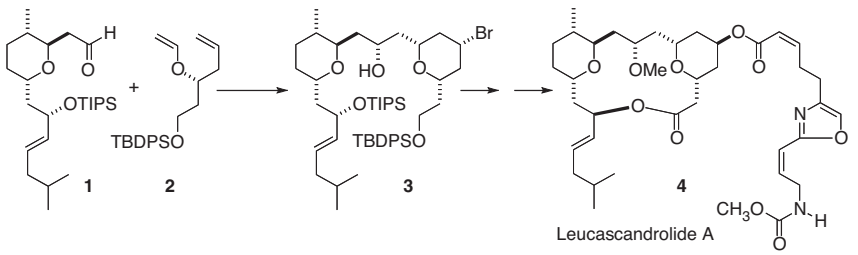


Attempts to deoxygenate the tertiary alcohol of **16** failed, so instead, selective reduction followed by protection delivered **17**. Reduction to the axial alcohol followed by dehydration with the Martin sulfurane then installed the trisubstituted alkene of **18**. The C-N bond was re-established by exposure of **18** to NIS, leading to the crystalline **19**. Activation of the derived ketone with Mander's reagent followed by reductive deiodination (Et_3SiH/Pd) gave **20**, Michael addition of which with **21** led to **3**.

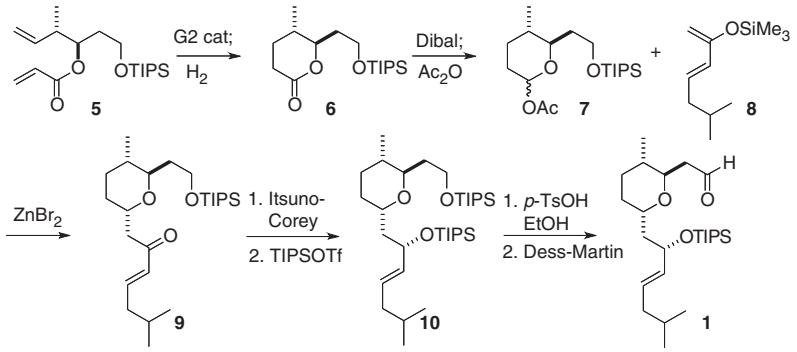
85. The Rychnovsky Synthesis of Leucascandrolide A

May 5, 2008

The macrolactone leucascandrolide A **4**, isolated from the calcareous sponge *L. caveolata*, has both cytotoxic and antifungal activity. The key step in the synthesis of **4** reported (*J. Org. Chem.* **2007**, *72*, 5784) by Scott D. Rychnovsky of the University of California, Irvine, was the stereoselective condensation of the aldehyde **1** with the allyl vinyl ether **2** to give **3**.



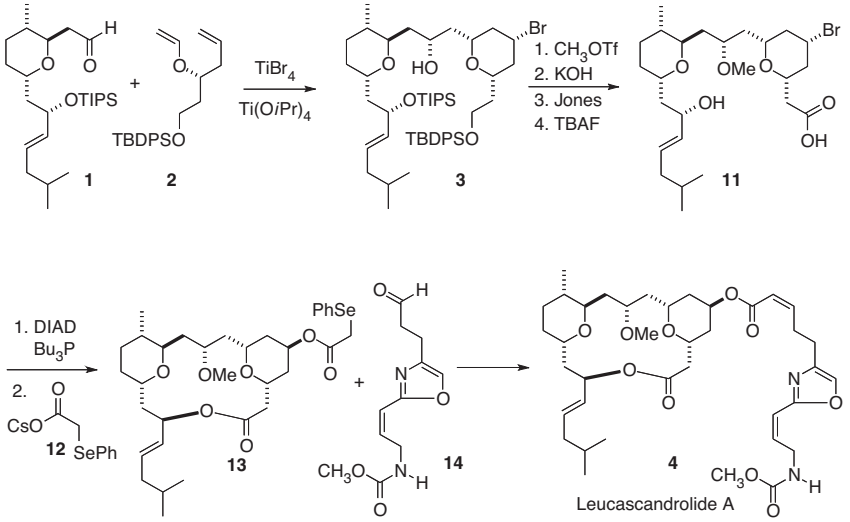
The cyclic ether of **1** was assembled from the crotyl addition product **5**. Tandem Ru-catalyzed metathesis/hydrogenation converted **5** to the lactone **6**. Reduction of **6** to the lactol followed by activation as the acetate gave **7**, axial-selective condensation of which with the enol ether **8** delivered the enone **9**. Diastereoselective Itsuno-Corey reduction of **9** followed by protecting group exchange and oxidation then gave **1**, containing four of the eight stereogenic centers of leucascandrolide A **4**.



The vinyl ether **2** was readily prepared from the corresponding homoallylic alcohol. Condensation of **1** with **2** involved Lewis acid activation of the aldehyde, addition of the resulting carbocation to the vinyl ether, and cyclization with trapping by bromide ion. In this process, the other four of the eight stereogenic centers were assembled. Three of those centers were formed in the course of the reaction. While stereocontrol was not perfect, the

route is pleasingly succinct, so practical quantities of diastereomerically pure **3** could be prepared.

To complete the synthesis, the secondary alcohol of **3** was methylated. Selective desilyation of the primary alcohol followed by oxidation and desilylation then set the stage for the Mitsunobu macrolactonization. The intermediates in the Mitsunobu reaction are such that the lactonization can proceed with either inversion of absolute configuration at the secondary center, or retention. While the usually-employed Ph_3P gave the lactone with retention of absolute configuration, Bu_3P led to clean inversion.

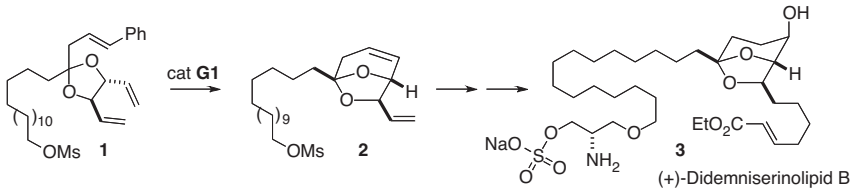


The last challenge was the establishment of the (*Z*) alkene of the side chain. This was accomplished using the Toru protocol. Coupling of the secondary bromide with the Cs salt **12** proceeded with inversion of absolute configuration, to give **13**. The carboxylates of stronger acids were not sufficiently nucleophilic to displace the bromide. Aldol condensation of **13** with the aldehyde **14** gave a mixture of diastereomers, exposure of which to MsCl in pyridine delivered the requisite (*Z*) alkene **4**.

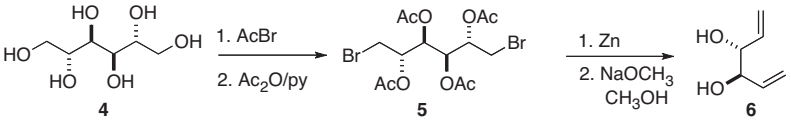
86. The Burke Synthesis of (+)-Didemniserinolipid B

June 2, 2008

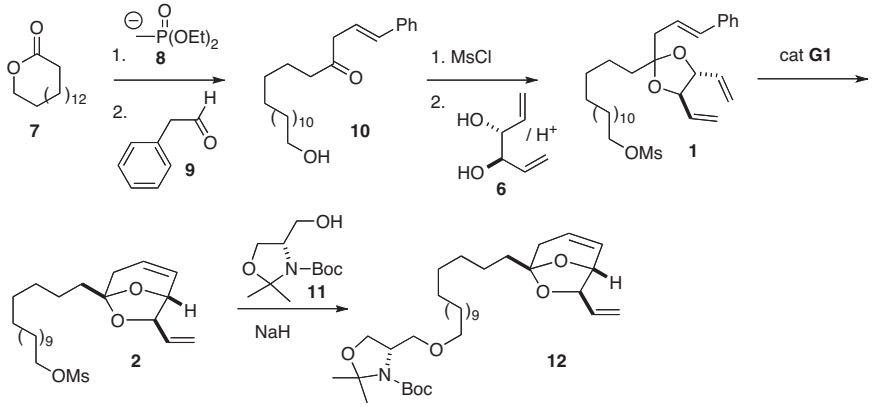
The sulfate (+)-didemniserinolipid B **3**, isolated from the tunicate *Didemnum sp*, has an intriguing spiroether core. A key step in the synthesis of **3** reported (*Organic Lett*. **2007**, *9*, 5357) by Steven D. Burke of the University of Wisconsin was the selective ring-closing metathesis of **1** to **2**.



The diol **6** that was used to prepare the ketal **1** was readily prepared from the inexpensive D-mannitol **4**. Many other applications can be envisioned for the enantiomerically-pure diol **6** and for the monoacetate and bis acetate that are precursors to it.

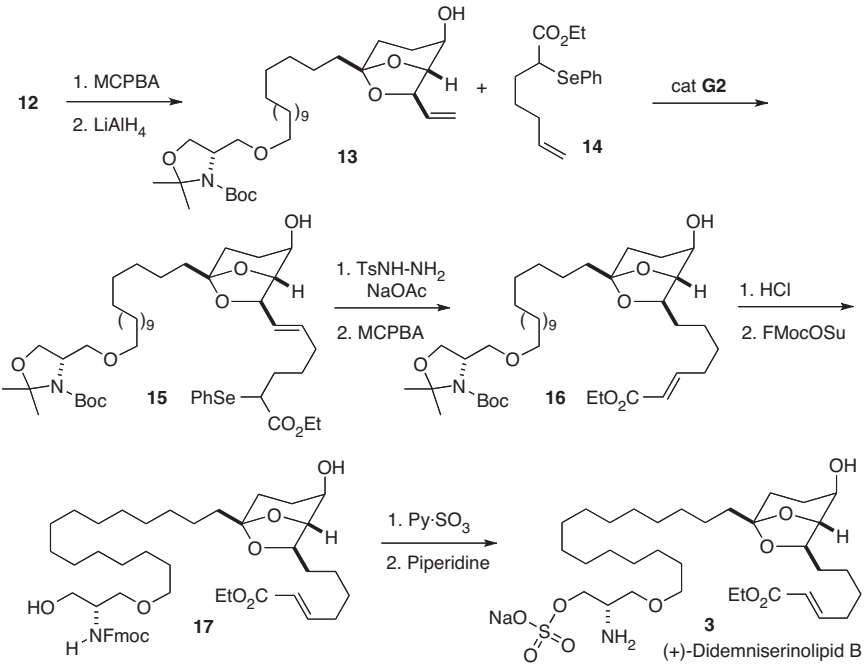


To set up the metathesis, the β,γ-unsaturated ketone **10** was needed. To this end, the keto phosphonate derived from the addition of the phosphonate anion **8** to the lactone **7** was condensed with phenyl acetaldehyde **9**. The derived enone **10** was a 5:1 mixture of β,γ- and α,β- regioisomers.



The diol **6** is C_2-symmetrical, but formation of the ketal **1** dissolved the symmetry, with one terminal vinyl group directed toward the styrene double bond, and the other directed away from it. On exposure to the first generation Grubbs catalyst, ring formation proceeded efficiently, to give **2**. Williamson coupling with the serine-derived alcohol **11** then gave **12**.

To establish the secondary alcohol of **13** and so of **3**, the more electron rich alkene of **12** was selectively epoxidized, from the more open face. Diaxial opening with hydride then gave **13**.

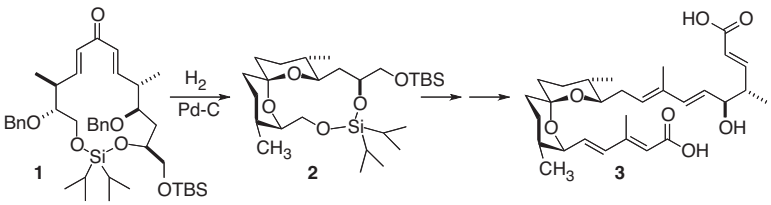


With **13** in hand, another challenge of selectivity emerged. The plan had been to attach the ester-bearing sidechain to **13** using alkene metathesis, then hydrogenate. As the sidechain of **3** contained an additional alkene, this had to be present in masked form. To this end, the α-phenylselenyl ester **14** was prepared. Alkene metathesis with **13** proceeded smoothly, this time using the second generation Grubbs catalyst. The unwanted alkene was then removed by reduction with diimide, and the selenide was oxidized to deliver the α,β-unsaturated ester.

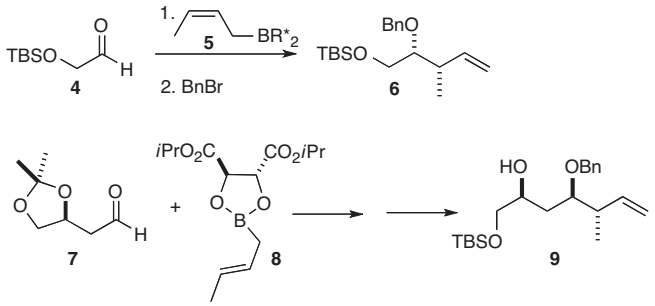
87. The Kozmin Synthesis of Spirofungin A

July 7, 2008

Often, 6,6-spiroketals such as Spirofungin A **3** have a strong anomeric bias. Spirofungin A does not, as the epimer favored by double anomeric stabilization suffers from destabilizing steric interactions. In his synthesis of **3**, Sergey A. Kozmin of the University of Chicago took advantage (*Angew. Chem. Int. Ed*. **2007**, *46*, 8854) of the normally-destablizing spatial proximity of the two alkyl branches of **3**, joining them with a siloxy linker to assure the anomeric preference of the spiroketal. The assembly of **1** showcased the power of asymmetric crotylation, and of Professor Kozmin's linchpin cyclopropenone ketal cross metathesis.

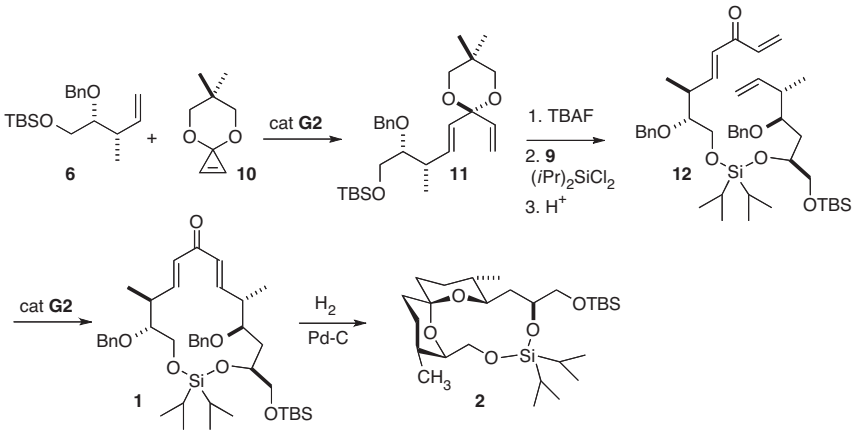


To achieve the syn relative (and absolute) configuration of **6**, commercial cis-2-butene was metalated, then condensed with the Brown (+)-MeOB(Ipc)$_2$ auxiliary. The accompanying Supporting Information, accessible via the online HTML version of the journal article, includes a succinct but detailed procedure for carrying out this homologation. For the anti relative (and absolute) configuration of **9**, it is more convenient to use the tartrate **8** introduced by Roush.

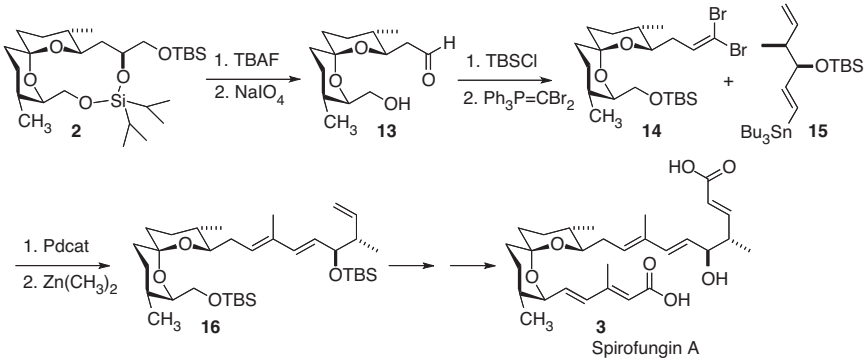


Driven by the release of the ring strain inherent in **10**, ring opening cross metathesis with **6** proceeded to give the 1:1 adduct **11** in near quantitative yield. The derived cross-linked silyl ether **12** underwent smooth ring-closing metathesis to the dienone **1**.

On hydogenation, the now-flexible ring system could fold into the spiro ketal. With the primary and secondary alcohols bridged by the linking silyl ether, only one anomeric form, **2**, of the spiro ketal was energetically accessible.



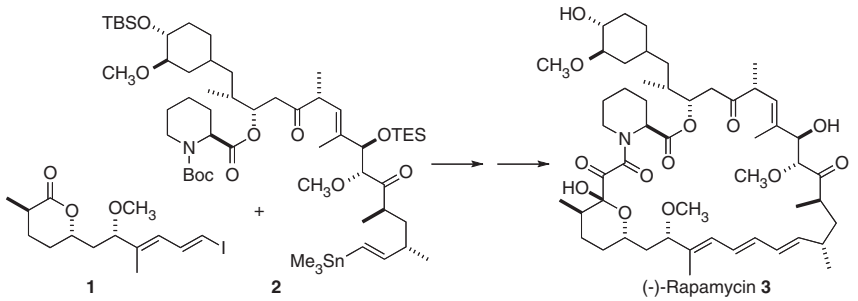
A remaining challenge was the stereocontrolled construction of the trisubstituted alkene. To this end, the aldehyde **13** was homologated to the dibromide **14**. Pd-mediated coupling of the alkenyl stannane **15** with **14** was selective for the*E* bromide. The residual *Z* bromide was then coupled with $Zn(CH_3)_2$ to give **16**. These steps, and the final steps to complete the construction of spirofungin A **3**, could be carried out without exposure to equilibrating acid, so the carefully established spiro ketal configuration was maintained.



88. The Ley Synthesis of Rapamycin

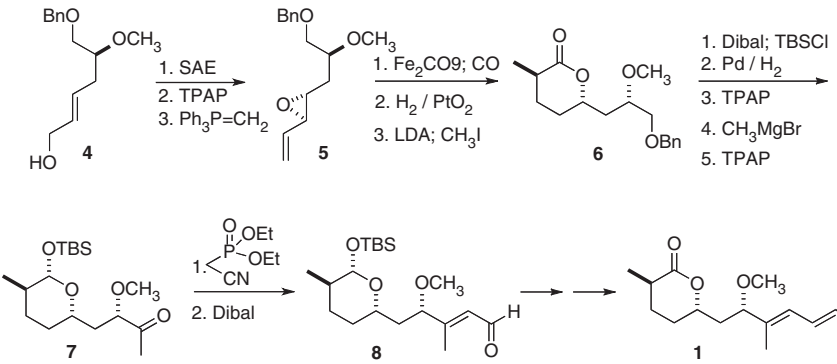
August 4, 2008

Rapamycin **3** is used clinically as an immunosuppressive agent. The synthesis of **3** (*Angew. Chem. Int. Ed.* **2007**, *46*, 591) by Steven V. Ley of the University of Cambridge was based on the assembly and subsequent coupling of the iododiene **1** and the stannyl alkene **2**.



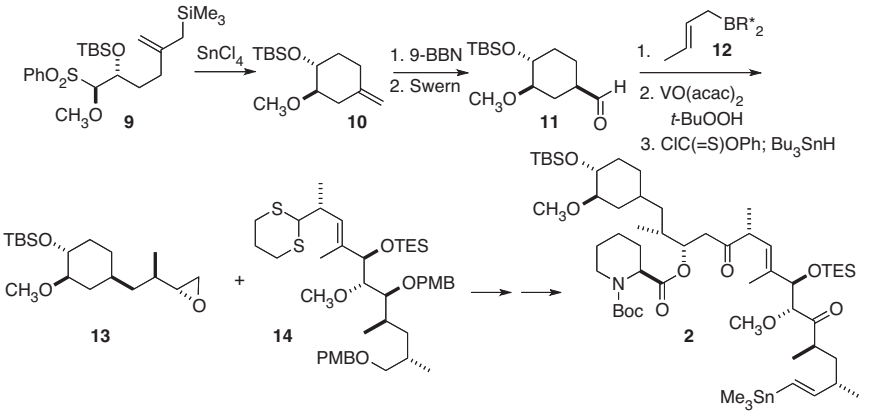
1 2

The lactone of **1** was prepared by Fe-mediated cyclocarbonylation of the alkenyl epoxide **5**, following the protocol developed in the Ley group.

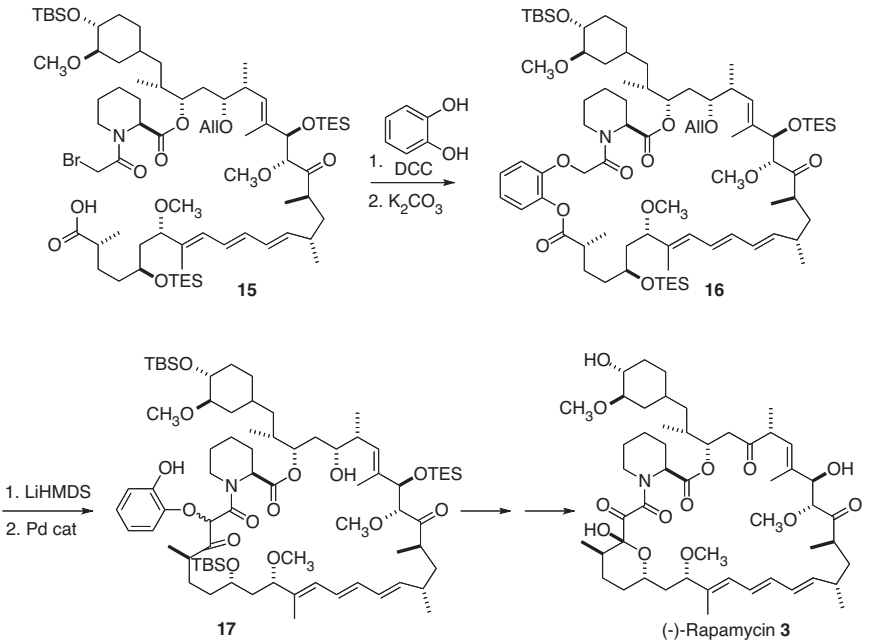


4 5 6 7 8 1

The cyclohexane of **2** was constructed by $SnCl_4$-mediated cyclization of the allyl stannane **9**, again employing a procedure developed in the Ley group. Hydroboration delivered the aldehyde **11**, which was crotylated with **12**, following the H. C. Brown method. The alcohol so produced (not illustrated) was used to direct the diastereoselectivity of epoxidation, then removed, to give **13**. Coupling with **14** then led to **2**.



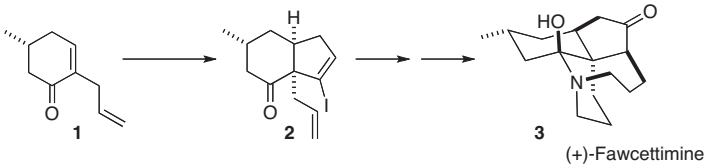
Combination of **1** with **2** led to **15**, which was condensed with catechol to give the macrocycle **16**. Exposure of **16** to base effected Dieckmann cyclization, to deliver the ring-contracted macrolactone **17**, which was carried on to (-)-rapamycin **3**.



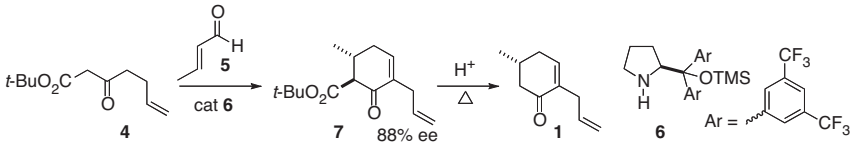
89. The Toste Synthesis of (+)-Fawcettimine

September 1, 2008

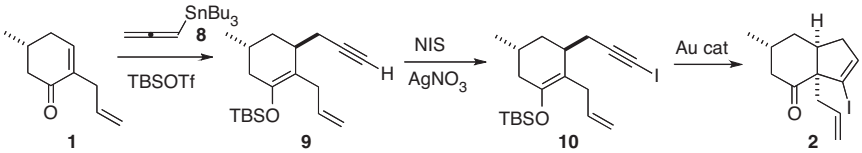
The tetracyclic *Lycopodium* alkaloid fawcettimine **3** and its derivatives are of interest as inhibitors of acetylcholine esterase. F. Dean Toste of the University of California, Berkeley recently reported (*Angew. Chem. Int. Ed.* **2007**, *46*, 7671) the first enantioselective synthesis of **3**. The key to the synthesis was the rapid assembly of the enantiomerically-enriched hydrindane **2**.



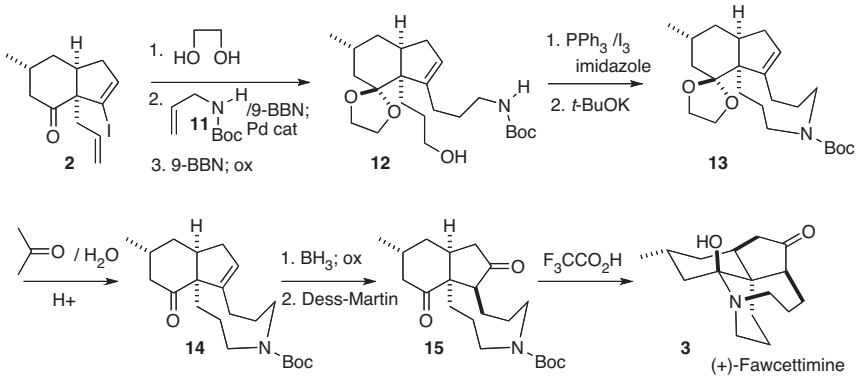
The preparation of **2** began with the enantioselective Robinson annulation of the β-keto ester **4** with crotonaldehyde **5**, mediated by the organocatalyst **6**. In this protocol, originally developed by Karl Anker Jørgensen, the single stereogenic center was established by conjugate addition, presumably to the chiral iminium salt generated by the condensation of **5** with **6**. Subsequent aldol (or more likely Mannich) cyclization followed by elimination gave **7**. Hydrolysis and decarboxylation by heating with *p*-TsOH converted **7** to **1**. This procedure was robust enough to allow preparation of a ten gram batch of **1**. This Jørgensen annulation is the current method of choice for the enantioselective preparation of 2,5-dialkyl cyclohexenones.



Conjugate addition of the propargyl anion equivalent **8** to **1** proceeded with the expected > 95:5 axial diastereoselectivity, to give the silyl enol ether **9**. Exposure of the derived iodide **10** to catalytic $[Ph_3PAu]Cl$ and $AgBF_4$ induced smooth cyclization to the cis hydrindane **2**.



Before constructing the nine-membered ring amine of fawcettimine **3**, it was first necessary to protect the ketone as the ketal. Pd-mediated coupling of the alkenyl iodide with the organoborane derived from **11** then proceeded smoothly, as did the subsequent hydroboration of the terminal alkene.



Neither the mesylate nor the tosylate derived from **12** could be induced to cyclize. In contrast, intramolecular displacement of the iodide proceeded well, to give **13**. Hydroboration followed by oxidation then gave **15**, which on deprotection cyclized to (+)-fawcettimine **3**.

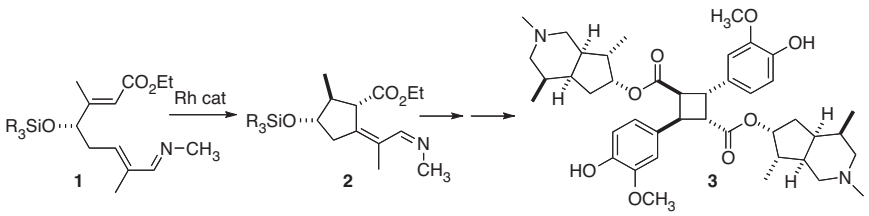
Several aspects of this synthesis are attractive. While the stereochemical outcome of the hydroboration of **14** could not necessarily be predicted with confidence, in fact it did not matter, as the stereogenic center adjacent to the ketone could be epimerized under the trifluoroacetic acid deprotection conditions, and only the desired diastereomer would be able to add in an intramolecular fashion to the cyclohexanone. The construction of **2** from **10** underscores the importance of the Au-catalyzed cyclizations developed by Professor Toste.

The most important news from this synthesis is the validation in a second research group of the enantioselective Robinson annulation previously described by Professor Jørgensen. In the assembly of polycarbocycles, the central challenge is the enantioselective construction of the first ring. The Jørgensen annulation is a powerful solution to that problem.

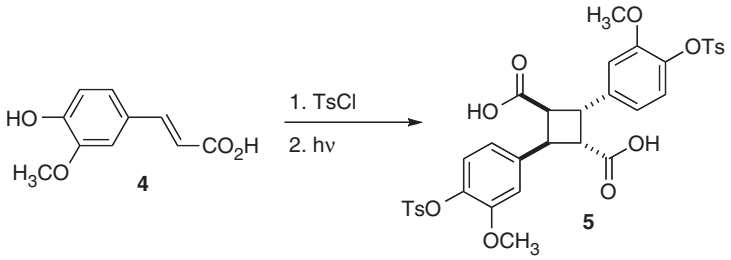
90. The Bergman-Ellman Synthesis of (-)-Incarvillateine

October 6, 2008

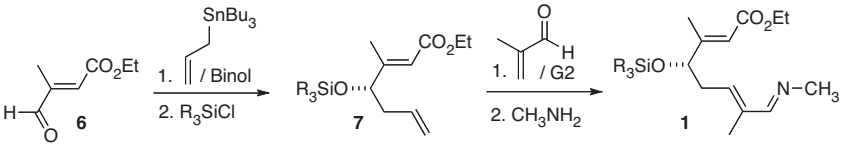
The monoterpene alkaloid (-)-incarvillateine **3** has interesting symmetry properties. The central cyclobutane diacid core is not itself chiral, but the appended alkaloids are. The key step in the total synthesis of **3** recently (*J. Am. Chem. Soc.* **2008**, *130*, 6316) described by Robert G. Bergman and Jonathan A. Ellman of the University of California, Berkeley was the diastereoselective Rh-catalyzed cyclization of **1** to **2**.



The cyclobutane diacid core **5** was assembled from ferulic acid **4** following the procedure of Kibayashi (*J. Am. Chem. Soc.* **2004**, *126*, 16553).

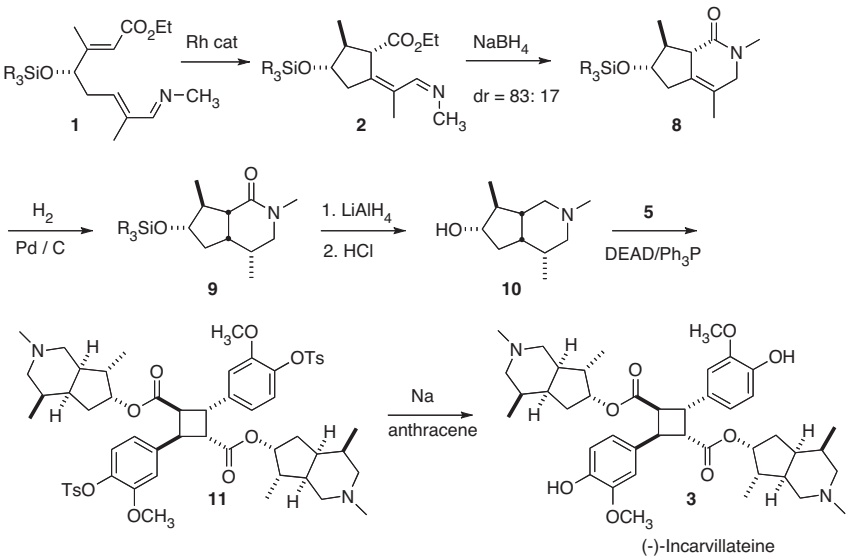


The starting point for the preparation of **1** was the commercial aldehyde **6**. Enantioselective allylation followed by silylation delivered **7**, which on cross metathesis with methacrolein gave the diene aldehyde **8**. Imine formation then completed the construction of **1**.



The cyclization of **1** was effected by warming (45 °C, 6 h) with 2.5 mol % $[RhCl(coe)_2]_2$ and 5.5 mol % (DMAPh)Pet_2 ligand. While eight products were possible from the cyclization (four diastereomers, two geometric isomers of the exo alkene), only two were observed,

with one predominating. Since the product mixture was easily susceptible to tautomerization, it was carried on directly to reduction and cyclization, to form the lactam **8**.



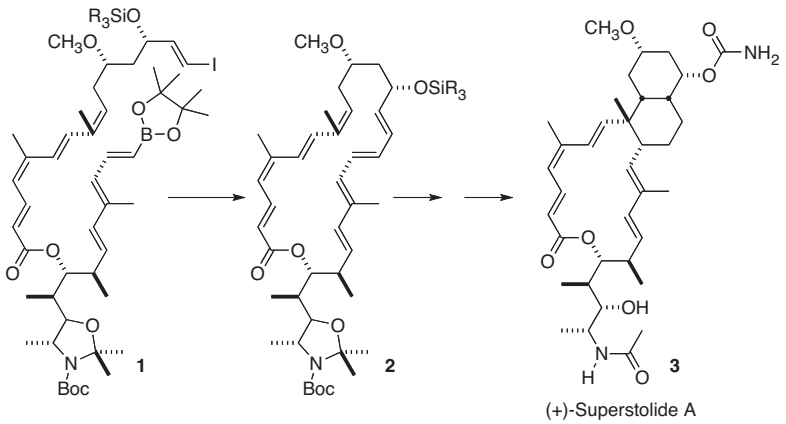
Hydrogenation of **8** to **9** required high temperature and pressure, but delivered **9** as a single diastereomer. Reduction and desilylation then set the stage for Mitsunobu coupling with **5**, to give **11**. Dissolving metal conditions removed the tosyl groups from **5** to give (-)-incarvillateine **3.**

It will be interesting to see how general this Rh catalyzed cyclization will be. It will also be interesting to establish the mechanism. The authors described the cyclization of **1** as proceeding via initial metalation of the alkene C-H bond, followed by insertion of the ester-bearing alkene into the C-Rh bond to form a new C-Rh bond, and finally reductive elimination. Their previous observation of metalation of such an unsaturated imine with maintenance of the alkene geometry suppported this mechanism. The high diastereocontrol also suggested intramolecular C-C bond formation. Whatever the mechanism, the enantiomerically-pure cyclopentane **2**, having four of its five carbons functionalized, is a versatile intermediate for further transformation.

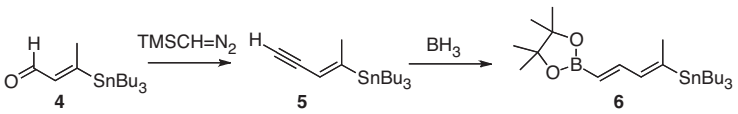
91. The Roush Synthesis of (+)-Superstolide A

November 3, 2008

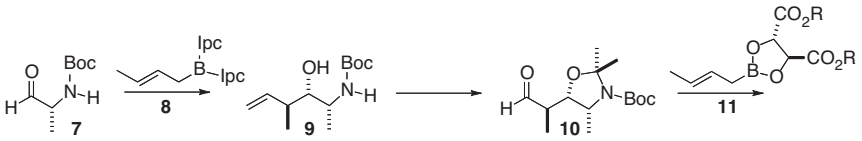
(+)-Superstolide A **3**, isolated from the New Caledonian sponge *Neosiphonia superstes*, shows interesting cytotoxicity against malignant cell lines at ~ 4 ng/mL concentration. The key transformation in the synthesis of **3** described (*J. Am. Chem. Soc.* **2008**, *130*, 2722) by William R. Roush of Scripps Florida was the transannular Diels-Alder cyclization of **2**, which established, in one step with high diastereocontrol, both the cis decalin and the macrolactone of **3**.

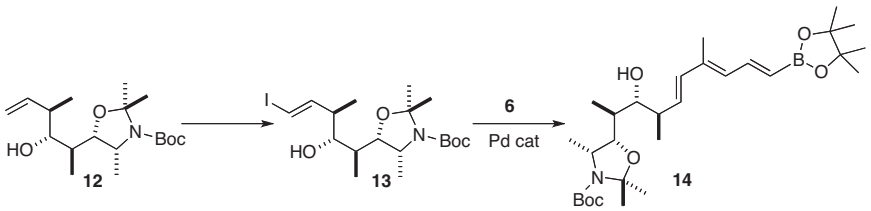


The octaene **1** was assembled from four stereodefined fragments. The first, the linchpin **6**, was prepared from the stannyl aldehyde **4**. Homologation gave the enyne **5**, which on hydroboration and oxidation gave **6**.

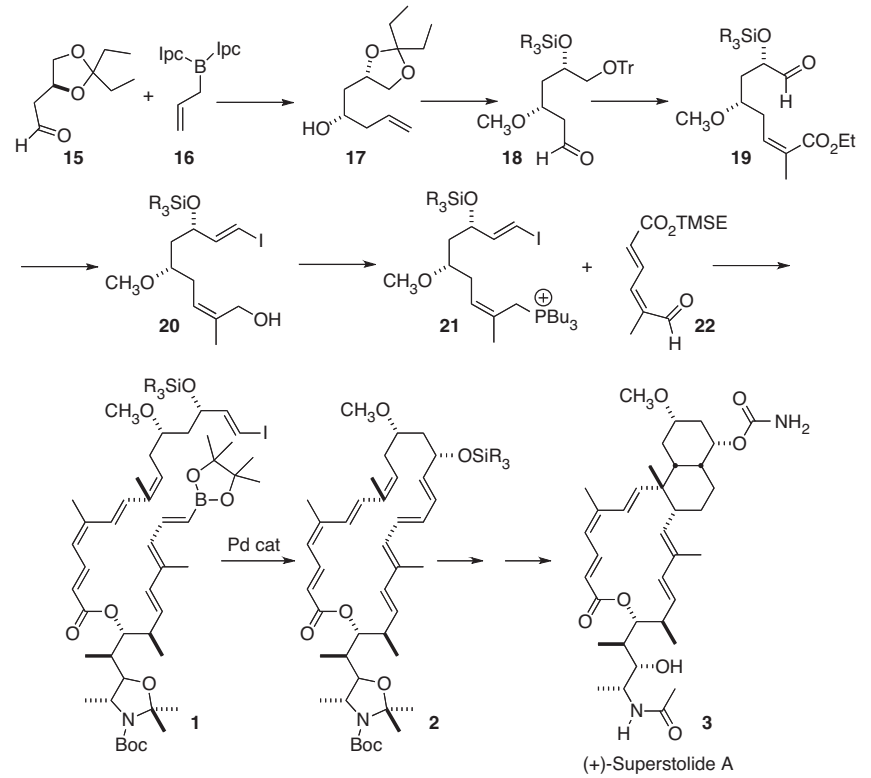


Earlier, Professor Roush had optimized the crotylation of the protected alaninal **7**. In this case, the Brown reagent **8** delivered the desired Felkin product **9**. Protection followed by ozonolysis gave the aldehyde **10**. Crotylation with the Roush-developed tartrate **11** then gave the alkene **12**, setting the stage for conversion to the iodide **13**. Coupling of **13** with **6** completed the preparation of **14**.





The third component of (+)-superstolide A **3**, the phosphonium salt **21**, was assembled by Brown allylation of the aldehyde **15**, to give **17**. Protecting group interchange followed by ozonolysis delivered **18**, which via Still-Gennari homologation was carried on to **21**. Condensation with the fourth component, the aldehyde **22**, and esterification with **14** then gave **1**.

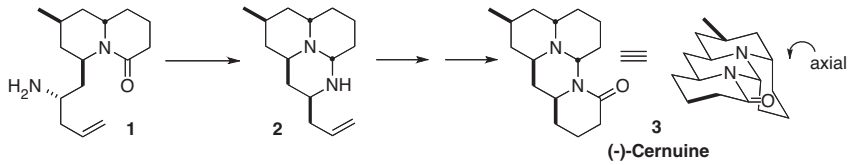


Under high dilution Suzuki conditions **1** was converted to **2**. Storage in $CDCl_3$ for five days, or brief warming, cyclized **2** to a single diastereomer of the transannular Diels-Alder product, that was carried on to (+)-superstolide A **3**. While acyclic trienes comparable to **2** could be induced to cyclize, the *transannular* Diels-Alder reaction proceeded with much higher diastereocontrol.

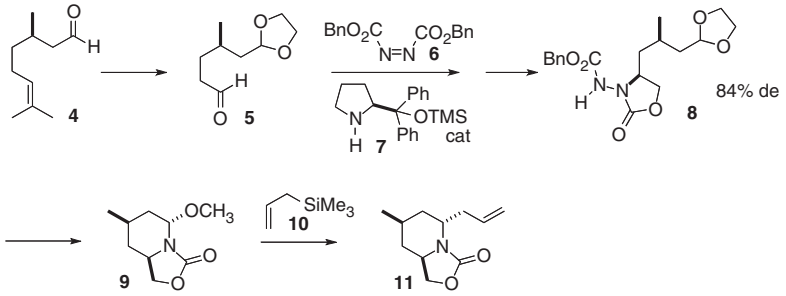
92. The Takayama Synthesis of (-)-Cernuine

December 1, 2008

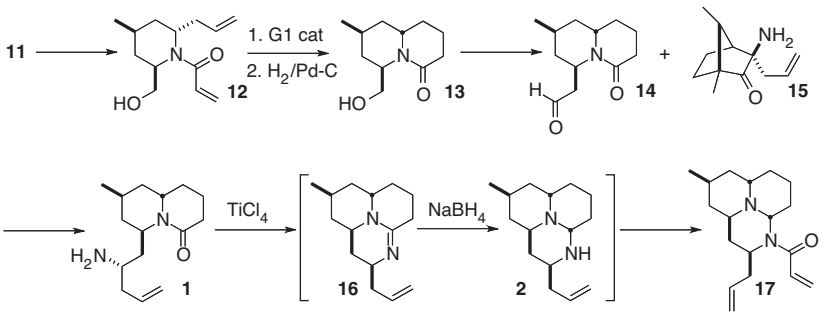
(-)-Cernuine **3** falls in the subset of the *Lycopodium* alkaloids that feature a bicyclic aminal core. There had not been a total synthesis of this class of alkaloids until the recent (*Organic Lett*. **2008**, *10*, 1987) work of Hiromitsu Takayama of Chiba University. The key step in this synthesis was a diastereoselective intramolecular reductive amination, converting **1** to **2**. As is apparent from the 3-D projection, (-)-cernuine **3** has a tricyclic trans-anti-trans aminal core, with an appended six-membered ring, both branches of which are axial on the core. While the branch that is part of the aminal could be expected to equilibrate, the other branch had to be deliberately installed.



The synthesis began with (+)-citronellal **4**, each enantiomer of which is commercially available in bulk. After protection and ozonolysis, the first singly-aminated stereogenic center was installed by enantioselective, and therefore diastereoselective, addition of **5** to the azodicarboxylate **6**, mediated by the organocatalyst **7**. Reductive cleavage of the N-N bond followed by acetal methanolysis converted **8** to **9**. Ionization followed by allyl silane addition then delivered **11**, having the requisite axial alkyl branch.

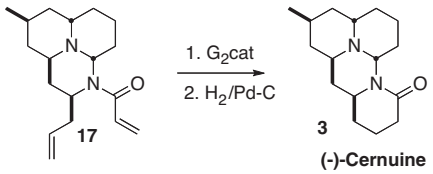


The next two tasks were the assembly of the second of the four rings of **3**, and the construction of the second single-aminated stereogenic center. The ring was assembled by deprotection of **11** followed by acylation with acryloyl chloride, to give **12**. Grubbs cyclization followed by hydrogenation then led to **13**. Homologation of **13** to the aldehyde **14** set the stage for condensation with the camphor-derived tertiary amine **15**, following the protocol developed by Kobayashi. Sequential imine formation, aza-Cope rearrangement, and hydrolysis led to **1** in 94% de.



One could envision reduction of the lactam carbonyl of **1** to an aldehyde equivalent, that would then, under acidic conditions, condense to form the desired aminal **2**. This approach was, however, not successful. As an alternative, conditions were developed to convert **1** to the amidine **16**. Reduction then proceeded with the expected high diastereocontrol, to give the cis 1,3-fused aminal **2**. This was not isolated, but was directly acylated with acryloyl chloride, to **17**.

The synthesis of (-)-cernuine **3** was concluded by Grubbs cyclization of **17** to **3**, followed again by hydrogenation. Note that there was a key difference between this cyclization and the Grubbs cyclization of **12** that led to **13**, in that **17** contained a basic N, while **12** did not. For the cyclization of **12**, the first generation Grubbs catalyst was sufficient, while for the cyclization of **17**, the second generation catalyst was required.

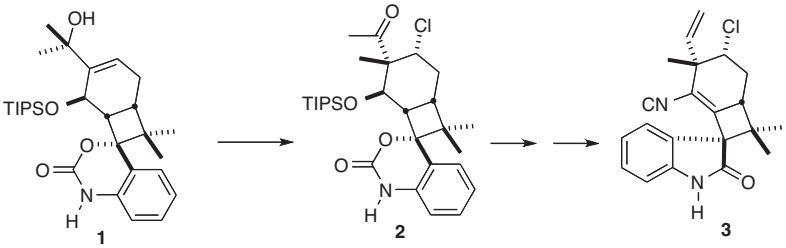


This synthesis illustrates the efficacy of the Grubbs cyclization for polycyclic construction. The approach outlined here also highlights the power of current methods for enantioselective allylation of imines for the construction of enantiomerically pure, and, in the context of this synthesis, diastereomerically pure, aminated secondary stereogenic centers.

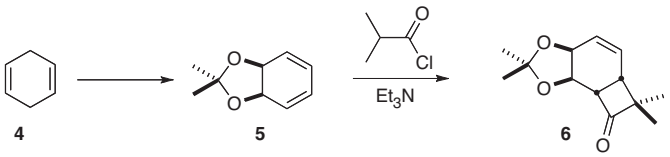
93. The Wood Synthesis of Welwitindolinone A Isonitrile

January 5, 2009

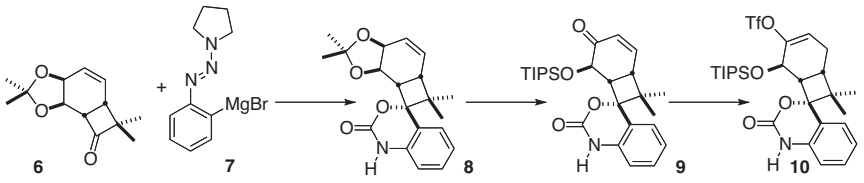
Welwitindolinone A Isonitrile **3** is the first of a family of oxindole natural products isolated from the cyanobacteria *Hapalosiphon welwischii* and *Westiella intricate* on the basis of their activity for reversing multiple drug resistance (MDR). A key transformation in the total synthesis of **3** reported (*J. Am. Chem. Soc.* **2008**, *130*, 2087) by John L. Wood, now at Colorado State University, was the chlorination of **1**, that in one step established both the axial secondary chloro substituent and the flanking chiral quaternary center.

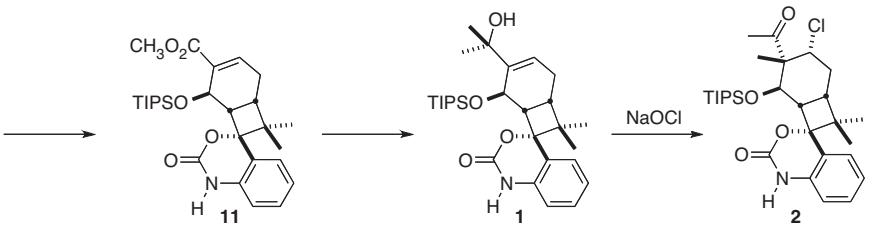


The starting material for the synthesis of **3** was the diene acetonide **5**, readily prepared from the Birch reduction product **4**. Intermolecular ketene cycloaddition proceeded with high regio- and diastereoselectivity, to give the bicyclooctenone **6**.



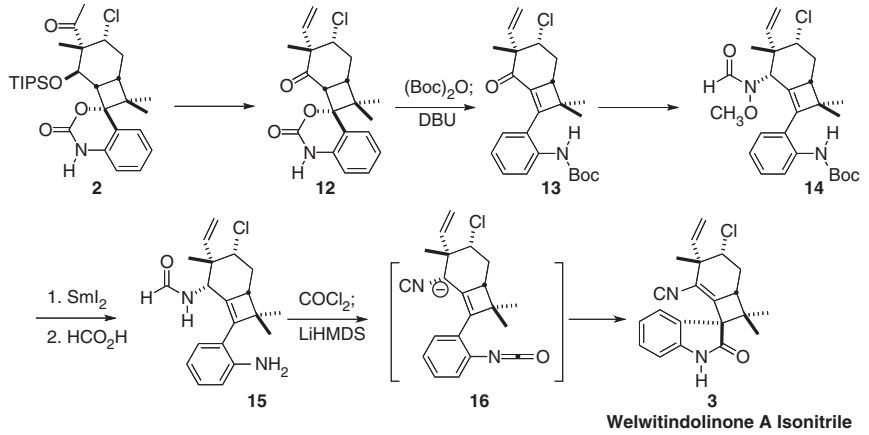
The triazene-bearing Grignard reagent **7** added to the ketone **6** with the anticipated high diastereocontrol, to give, after reduction and protection, the cyclic urethane **8**. Selective oxidation of the diol derived from **8** followed by silylation delivered the enone **9**. Conjugate addition of hydride followed by enolate trapping gave the triflate **10**. Pd-catalyzed methoxycarbonylation established the methyl ester **11**. Addition of CH_3MgBr to **11** gave **1**, setting the stage for the establishment of the two key stereogenic centers of **2** and so of **3**.





The transformation of **1** to **2** was envisioned as being initiated by formation of a bridging chloronium ion. Pinacol-like 1,2-methyl migration then proceeded to form the trans diaxial product, moving the ketone-bearing branch equatorial. In addition to being an elegant solution of the problem of how to establish the axial chloro substituent of **3**, this strategy might have some generality for the stereocontrolled construction of other alkylated cyclic quaternary centers.

Reduction of the ketone **2** and dehydration of the resulting alcohol led, after deprotection and oxidation, to the ketone **12**. Protection followed by β-elimination gave the enone **13**. Direct reductive amination of **13** failed, but reduction of the methoxime was successful, giving, after acylation, the formamide **14**. Reductive N-O bond cleavage followed by deprotection and isonitrile formation then set the stage for the planned intramolecular acylation to complete the synthesis of Welwitindolinone A Isonitrile **3**.

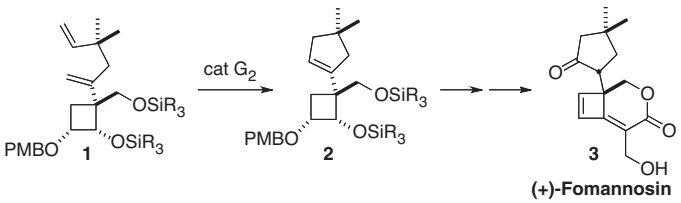


The starting diene **5** used in this synthesis was prochiral, leading to racemic **3**. Now that the route to **3** is established, it would be interesting to devise a method for preparing enantiomerically-enriched **6**. Enantiomerically-pure variants of **5** have been prepared, *inter alia* by fermentation of halogenated aromatics. Alternatively, an enantioselective version of the [2+2] cycloaddition to the prochiral **5** could be developed.

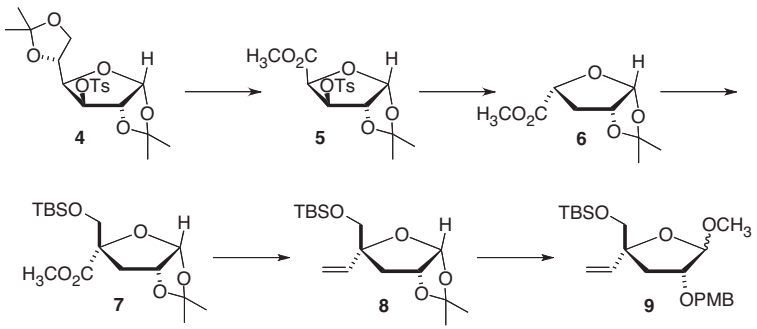
94. The Paquette Synthesis of Fomannosin

February 2, 2009

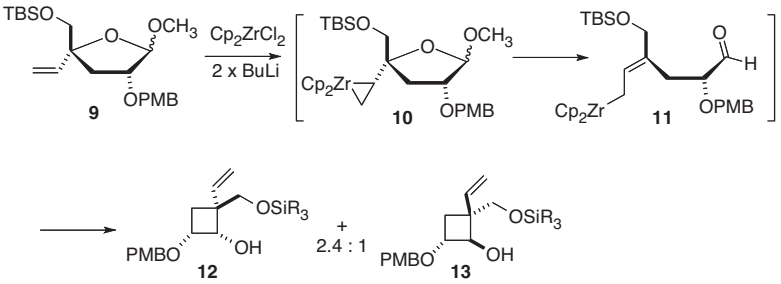
The compact sesquiterpene (+)-fomannosin **3**, isolated from the pathogenic fungus *Fomes annonsus*, presents an interesting set of challenges for the organic synthesis chemist, ranging from the strained cyclobutene to the easily epimerized cyclopentanone. In the synthesis of **3** developed (*J. Org. Chem*. **2008**, *73*, 4548) by Leo A. Paquette of Ohio State University, the cyclopentane was constructed by ring-closing metathesis of **1**. The real challenge of the synthesis was the enantiospecific preparation of **1** from D-glucose.



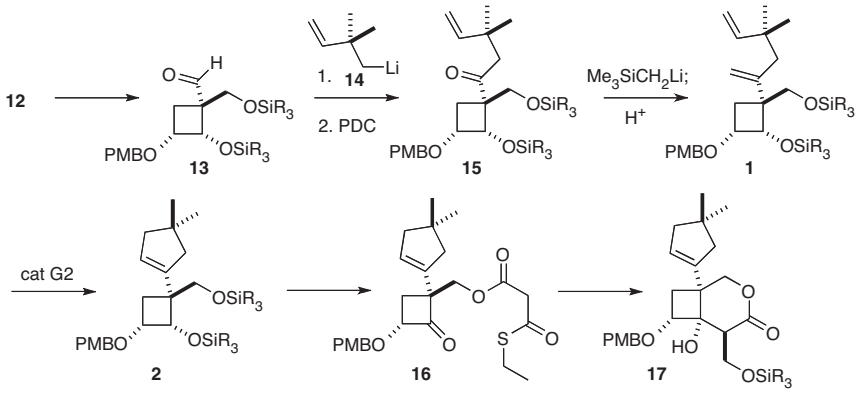
The starting point for the preparation of **1** was the glucose derivative **4**. Selective acetonide hydrolysis followed by oxidative cleavage gave the ester **5**, which on base treatment followed by hydrogenation delivered the endo ester **6**. Condensation of the enolate of **6** with formaldehyde proceeded with high diastereoselectivity, to give, after protection, the ester **7**. Conversion of the ester to the vinyl group, exposure to methanolic acid and ether formation completed the preparation of **9**.



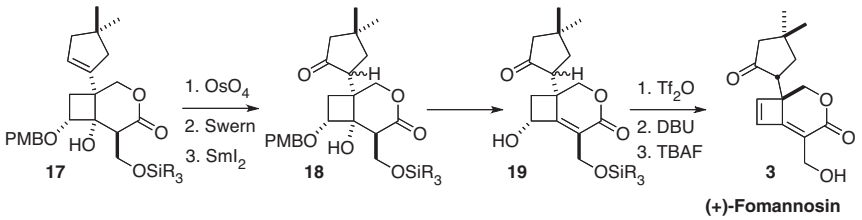
The construction of the cyclobutane of **1** was effected by an interesting application of the Negishi reagent (Cp_2ZrCl_2/2 x BuLi). Complexation of Cp_2Zr with the alkene followed by elimination generated an allylic organometallic **11**, which added to the released aldehyde to give the cyclobutanes **12** and **13** in a 2.4:1 diastereomeric ratio.



Homologation of the aldehyde **13** and subsequent oxidation were straightforward, but subsequent methylenation of the hindered carbonyl was not. At last, it was found that Peterson olefination worked well. Metathesis then delivered the cyclopentene **2**. The last carbons of the skeleton were added by intramolecular aldol cyclization of the thioester **16**.



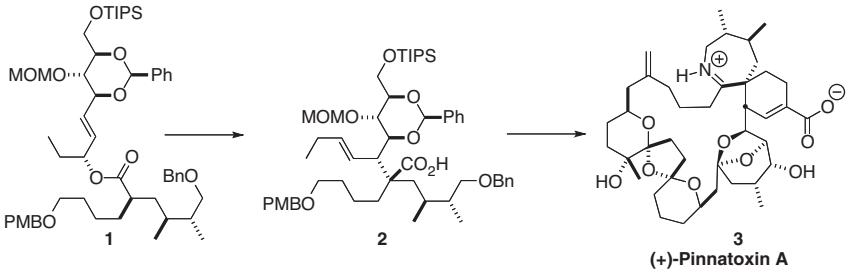
The seemingly simple task of converting the alkene of **17** into a ketone proved challenging. Eventually, dihydroxylation followed by oxidation, and then SmI_2 reduction, completed the transformation. This still left the challenge of controlling the cyclopentane stereogenic center. Remarkably, dehydration and epimerization led to (+)-Fomannosin **3** as a single dominant diastereomer.



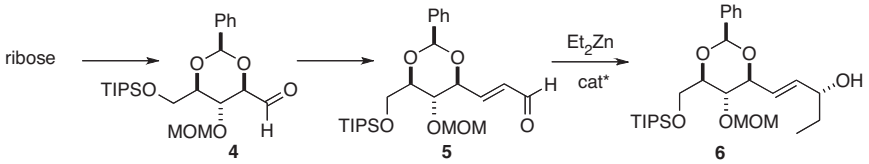
95. The Zakarian Synthesis of (+)-Pinnatoxin A

March 2, 2009

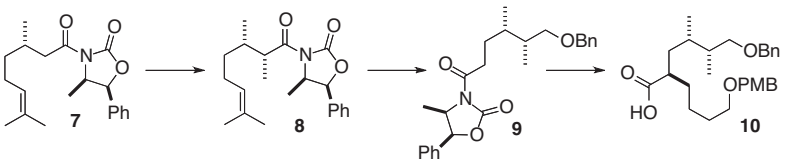
(+)-Pinnatoxin A **3**, isolated from the shellfish *Pinna muricata*, is thought to be a calcium channel activator. A key transformation in the synthesis of **3** reported (*J. Am. Chem. Soc.* **2008**, *130*, 3774) by Armen Zakarian, now at the University of California, Santa Barbara, was the diastereoselective Claisen rearrangement of **1** to **2**.



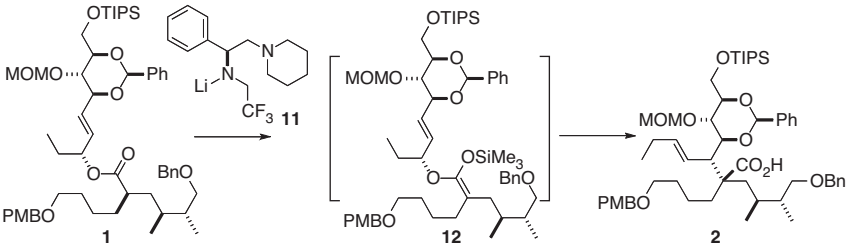
The alcohol portion of ester **1** was derived from the aldehyde **4**, prepared from D-ribose. The absolute configuration of the secondary allylic alcohol was established by chiral amino alcohol catalyzed addition of diethyl zinc to the unsaturated aldehyde **5**.



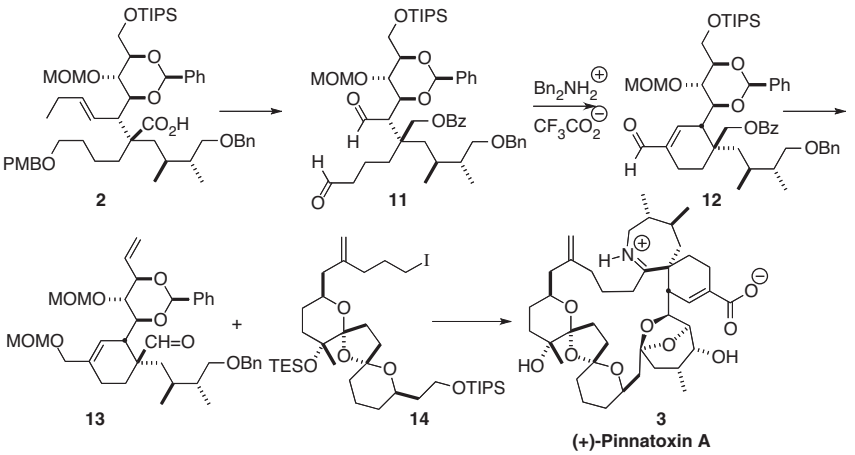
The acid portion of the ester **1** was prepared from (*S*)-citronellic acid, by way of the Evans imide **7**. Methylation proceeded with high diasterocontrol, to give **8**. Functional group manipulation provided the imide **9**. Alkylation then led to **10**, again with high diastereocontrol. In each case, care had to be taken in the further processing of the α-chiral acyl oxazolidinones. Direct $NaBH_4$ reduction of **8** delivered the primary alcohol. To prepare the acid **10**, the alkylated acyl oxazolidinone was hydrolyzed with alkaline hydrogen peroxide.



On exposure of the ester **1** to the enantiomerically-pure base **11**, rearrangement proceeded with high diastereocontrol, to give the acid **2**. This outcome suggests that deprotonation proceeded to give the single geometric form of the enolate, that was then trapped to give specifically the ketene silyl acetal **12**. This elegant approach is dependent on both the ester **1** and the base **11** being enantiomerically pure.



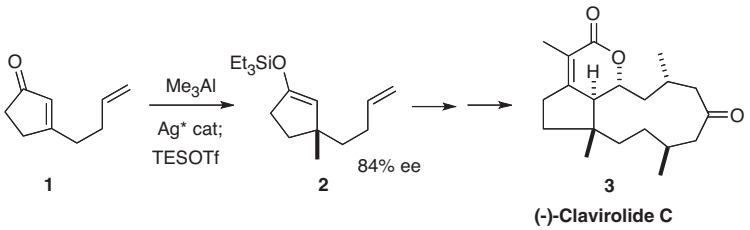
The carbocyclic ring of pinnatoxin A **3** was assembled by intramolecular aldol condensation of the dialdehyde **11**. This outcome was remarkable, in that **11** is readily epimerizable, and might also be susceptible to β-elimination. Note that the while the diol corresponding to **11** could be readily oxidized to **11** under Swern conditions, attempts to oxidize the corresponding hydroxy aldehyde were not fruitful.



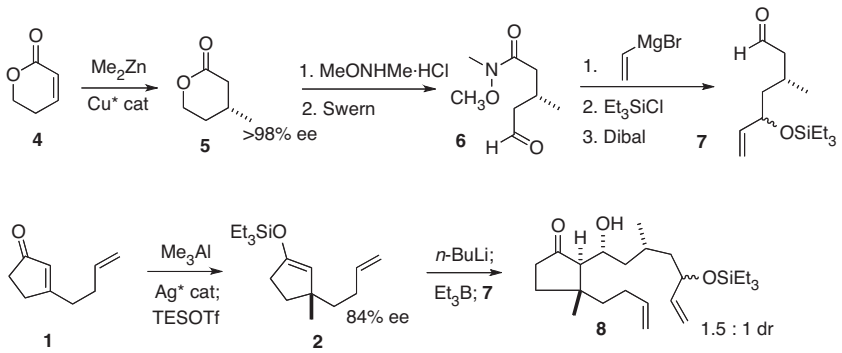
96. The Hoveyda Synthesis of (-)-Clavirolide C

April 6, 2009

Conjugate addition-enolate trapping, a strategy originally developed by Gilbert Stork, has become a powerful method for stereocontrolled ring construction. A key step in the synthesis of (-)-Clavirolide C **3** reported (*J. Am. Chem. Soc.* **2008**, *130*, 12904) by Amir H. Hoveyda of Boston College occurred early on, with the enantioselective conjugate addition of Me_3Al to **1** to give the silyl enol ether **2**. Enantioselective conjugate addition to establish a quaternary center β on a cyclohexanone had been established (OHL August 18, 2008), but not yet on cyclopentanones. Professor Hoveyda found that a modified form of the Ag catalyst that they had published earlier, in combination with the Lewis acidic $AlMe_3$, effected conjugate addition to **1** in 84% ee. Quenching of the reaction mixture led to the enol silyl ether **2**.



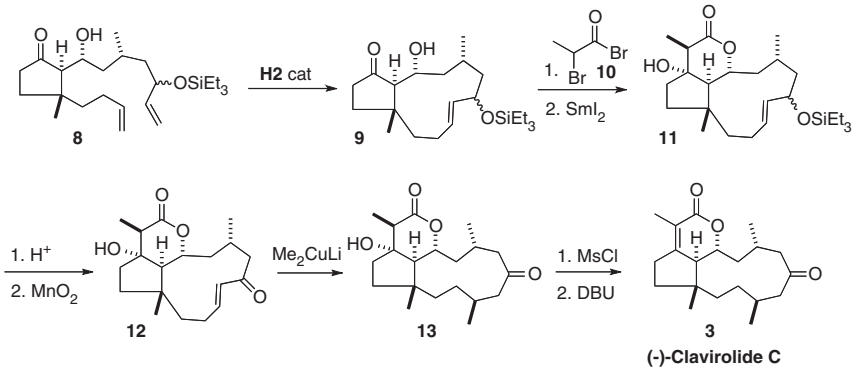
The assembly of the 11-membered ring of **3** also began with an enantioselective conjugate methylation, of the lactone **4** with Me_2Zn, again using a catalyst developed by Professor Hoveyda. Opening of the lactone **5** followed by Swern oxidation gave the Weinreb amide **6**, that was homologated and reduced to give **7**.



Addition of *n*-BuLi to **2** regenerated the enolate. There were two issues in the addition of that enolate to the aldehyde **7**: syn vs. anti stereocontrol, and control of the configuration of the newly formed ternary center on the ring relative to the already-established quaternary center. Inclusion of Et_3B in the reaction mixture assured anti aldol formation, but there was

only a modest preference for the desired bond formation trans to the slightly more bulky butenyl group, to give **8**.

Medium rings are more strained than are larger rings. The diene **8** was reluctant to close with the second generation Grubbs catalyst, but the catalyst developed by Professor Hoveyda worked well. The δ-lactone of **3** was then constructed by acylation of **9** with **10** followed by reductive cyclization with SmI_2. Conjugate addition to the derived enone **12** on the outside face of the medium ring alkene gave the desired **13** (9:1 dr). This reaction may be proceeding via the *s-cis* conformer, as the more stable *s-trans* conformer would have been expected to give the other diastereomer. Dehydration of **13** then delivered (-)-Clavirolide C **3**.

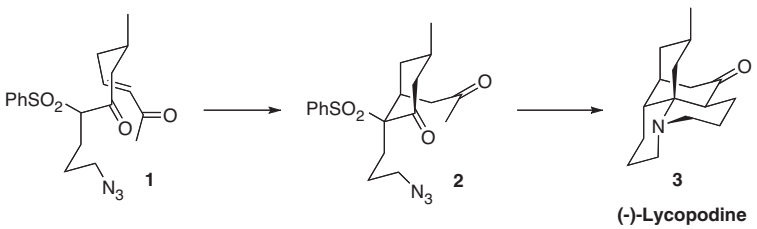


This concise synthesis of the dolabellane **3** showcases the power of the catalytic enantioselective methods for the construction of both ternary and quaternary, including cyclic quaternary, centers that Professor Hoveyda has developed. Clearly, asymmetric transformation of inexpensive prochiral ring precursors such as **1** and **4** will make advanced, high ee intermediates such as **2** and **5** much more readily available than they have been in the past.

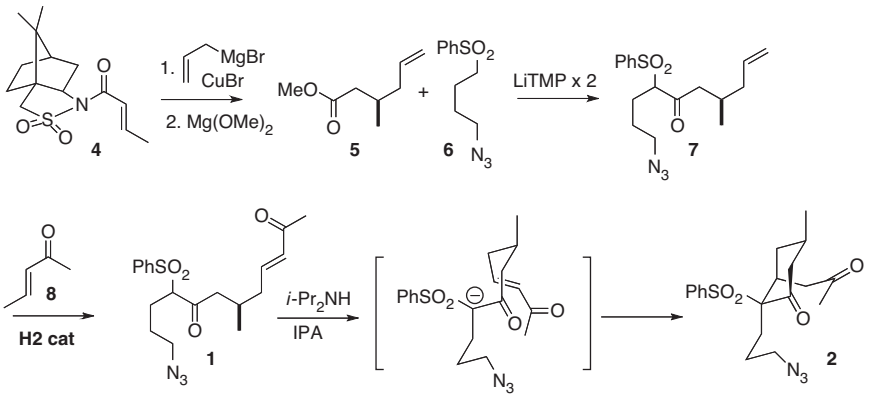
97. The Carter Synthesis of (-)-Lycopodine

May 4, 2009

Rich G. Carter of Oregon State University described (*J. Am. Chem. Soc.* **2008**, *130*, 9238) the first enantioselective synthesis of the *Lycopodium* alkaloid (-)-lyopodine **3**. A key step in the assembly of **3** was the diastereoselective intramolecular Michael addition of the keto sulfone of **1** to the enone, leading to the cyclohexanone **2**.



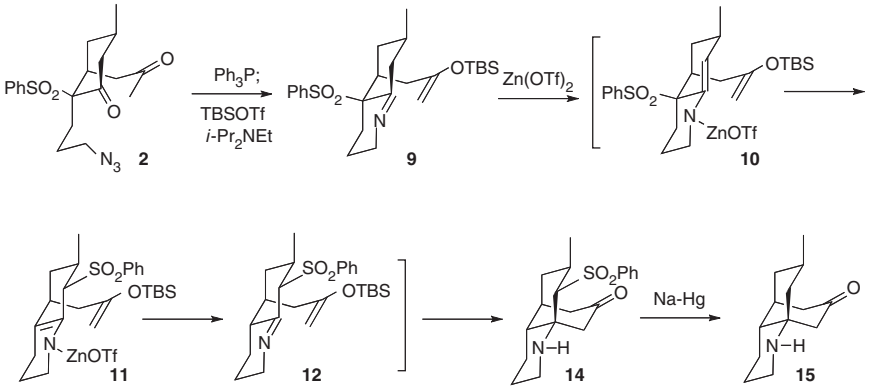
The key cyclization substrate **1** bore a single secondary methyl group. While that could have been derived from a natural product, it was operationally easier to effect chiral auxiliary controlled conjugate addition to the crotonyl amide **4**, leading, after methoxide exchange, to the ester **5**. The authors reported that double deprotonation with LiTMP gave superior results, vs. LDA or BuLi, in the condensation of **6** with **5** to give **7**. Metathesis with pentenone **8** gave the intramolecular Michael substrate **1**.



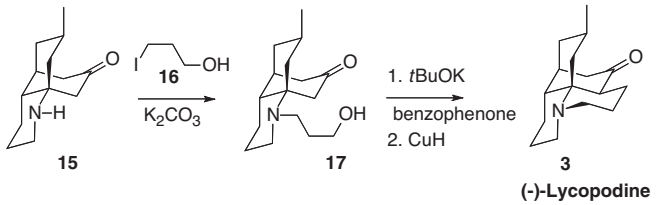
The authors thought that they would need a chiral catalyst to drive the desired stereocontrol in the cyclization of **1** to **2**. As a control, they tried an achiral base first, and were pleased to observe the desired diastereomer crystallize from the reaction mixture in 89% yield. The structure of **2** was confirmed by X-ray crystallography.

To prepare for the intramolecular Mannich condensation, the azide was reduced to give the imine, and the methyl ketone was converted to the silyl enol ether. Under Lewis acid conditions, the sulfonyl group underwent an unanticipated 1,3-migration, to give **11**.

Cyclization of **12** then delivered the crystalline **14**. Reduction converted **14** to the known (in racemic form) ketone **15**.



To complete the synthesis, the amine **15** was alkylated with **16** to give the alcohol **17**. Oppenauer oxidation followed by aldol condensation delivered the cyclized enone, that was reduced with the Stryker reagent to give (-)-Lycopodine **3**.

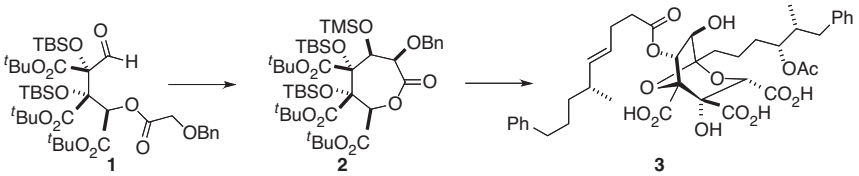


Both the cyclization of **1** to **2** and the cyclization of **9** to **14** are striking. It may be that the steric demand of the phenylsulfonyl group destabilizes the competing transition state for the cyclization of **1**.

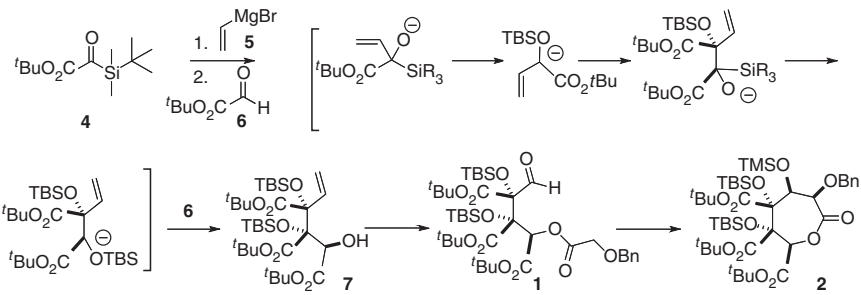
98. The Johnson Synthesis of Zaragozic Acid C

June 1, 2009

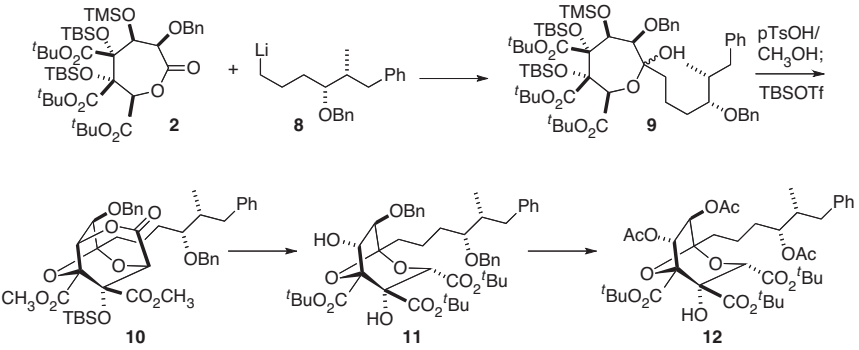
The zaragozic acids, exemplified by Zaragozic Acid C **3**, are picomolar inhibitors of cholesterol biosynthesis. Jeffrey S. Johnson of the University of North Carolina developed (*J. Am. Chem. Soc.* **2008**, *130*, 17281) an audacious silyl glyoxylate cascade approach to the oxygenated backbone fragment **1**. Intramolecular aldol cyclization converted **1** to **2**, setting the stage for the construction of **3**.



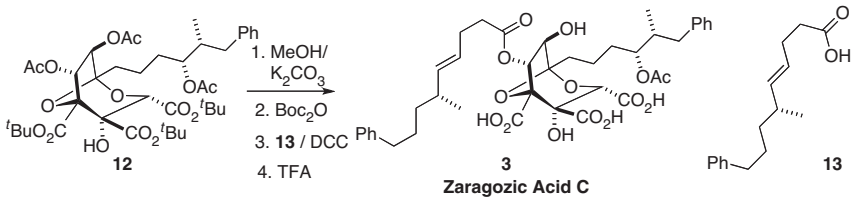
The lactone **2** includes five stereogenic centers, two of which are quaternary. The authors were pleased to observe that exposure of **4** to vinyl magnesium bromide **5** led, via condensation, silyl transfer, condensation, and again silyl transfer, to a species that was trapped with *t*-butyl glyoxylate **6** to give **7** as a *single* diastereomer. This one step assembled three of the stereogenic centers of **2**, including both of the quaternary centers. The alcohol **7** so prepared was racemic, so the wrong enantiomer was separated by selective oxidation. Intramolecular aldol condensation of the derived α-benzyloxy acetate **1** then completed the construction of **2.**



Addition of the alkyl lithium **8**, again as a single enantiomerically-pure diasteromer, to **2** gave the hemiketal **9**. Exposure of **9** to acid initially gave a mixture of products, but this could be induced to converge to the tricyclic ester **10**. To convert **10** to **11**, the diastereomer that was needed for the synthesis, two of the stereogenic centers had to be inverted. This was accomplished by exposure to *t*-BuOK/*t*-amyl alcohol, followed by re-esterification. The inversion of the secondary hydroxyl group was thought to proceed by retro-aldol/re-aldol condensation.



Debenzylation of **11** followed by acetylation delivered **12**, an intermediate in the Carreira synthesis of the zaragozic acids. Following that precedent, the ring acetates of **12** were selectively removed, leaving the acetate on the side chain. Boc protection was selective for the endo ring secondary hydroxyl, leaving the exo ring secondary hydroxyl available for condensation with the enantiomerically-pure acid **13**. Global deprotection then completed the synthesis of Zaragozic Acid C **3**.

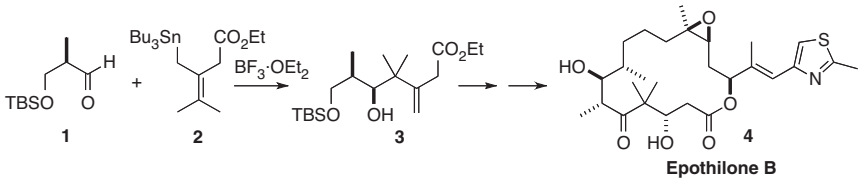


The key to the success of this synthesis of the complex spiroketal **3** was the assembly of **7** in one step as a single diastereomer from the readily-available building blocks **4**, **5**, and **6**. This process, reminiscent of group transfer polymerization, will be a useful complement to the cascade organocatalyzed aldol condensations that have recently been developed.

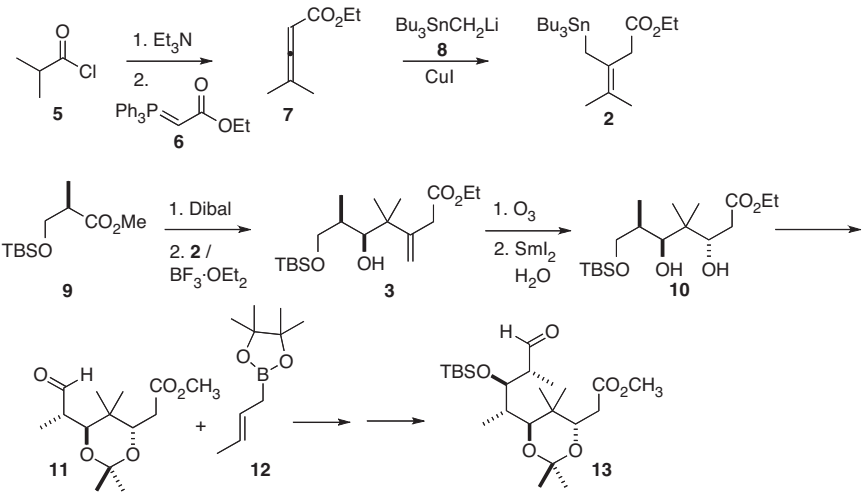
99. The Keck Synthesis of Epothilone B

July 6, 2009

The total synthesis of Epothilone B **4**, the first natural product (with Epothilone A) to show the same microtubule-stabilizing activity as paclitaxel (Taxol®), has attracted a great deal of attention since that activity was first reported in 1995. The total synthesis of **4** devised (*J. Org. Chem.* **2008**, *73*, 9675) by Gary E. Keck of the University of Utah was based in large part on the stereoselective allyl stannane additions (e.g. **1** + **2** → **3**) that his group originated.



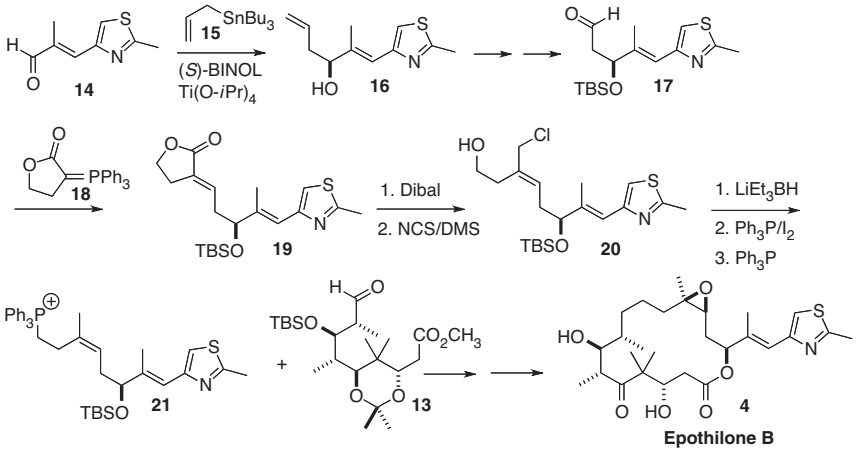
The allyl stannane **2** was prepared from the acid chloride **5**. Exposure of **5** to Et_3N generated the ketene, that was homologated with the phosphorane **6** to give the allene ester **7**. Cu-mediated conjugate addition of the stannylmethyl anion **8** then delivered **2**.



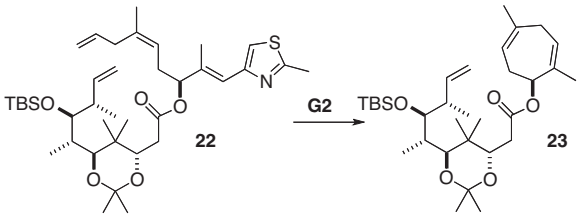
The silyloxy aldehyde **1** was prepared from the ester **9** by reduction with Dibal. Felkin-controlled 1,2-addition of the allyl stannane **2** established the relative configuration of the secondary alcohol of **3**, that was then used to control the relative configuration of the new alcohol in **10**. Addition of the crotyl borane **12** to the derived aldehyde **11** also proceeded with high diastereocontrol.

The other component of **4** was prepared from the aldehyde **14**. Enantioselective allylation, by the method the authors developed, delivered the alcohol **16**. The *Z* trisubstituted

alkene was then assembled by condensing the aldehyde **17** with the phosphorane **18**. Dibal reduction of the product lactone **19** gave a diol, the allylic alcohol of which was selectively converted to the chloride with the Corey-Kim reagent. Hydride reduction then delivered the desired homoallylic alcohol, that was converted to the phosphonium salt **21**. Condensation of **21** with **13** gave the diene, that was carried on to Epothilone B **4**.



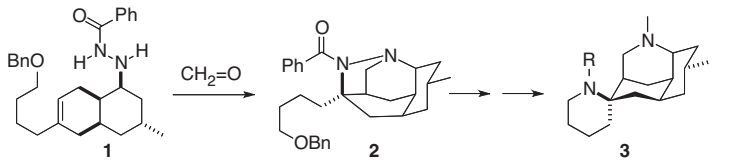
The synthesis of Epothilone B **4** as originally conceived by the authors depended on ring-closing metathesis of the triene **22**. They prepared **22**, but on exposure to the second-generation Grubbs catalyst it was converted only to **23**. The authors concluded that the trans acetonide kept **22** in a conformation that did not allow the desired macrocyclization.



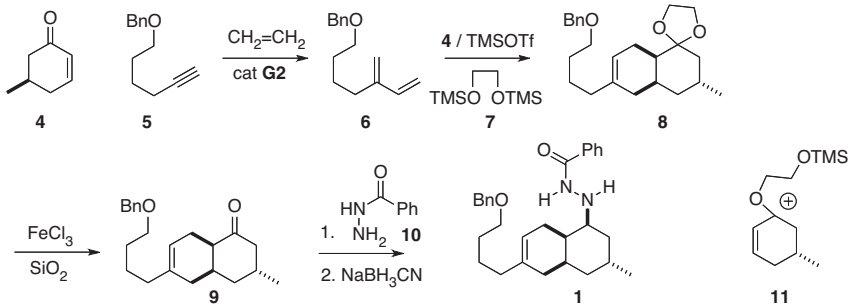
100. The Overman Syntheses of Nankakurines A and B

August 3, 2009

The tetracyclic alkaloids Nankakurine A and Nankakurine B were isolated from the club moss *Lycopodium hamiltonii*. A preliminary study of the biological activity of Nankakurine A suggested that it could induce secretion of neurotrophic factors and promote neuronal differentiation. The key step in the first syntheses of Nankakurine A and of Nankakurine B, reported (*J. Am. Chem. Soc.* **2008**, *130*, 11297) by Larry E. Overman of the University of California, Irvine was the intriguing intramolecular aza-Prins cyclization of **1** to **2**.

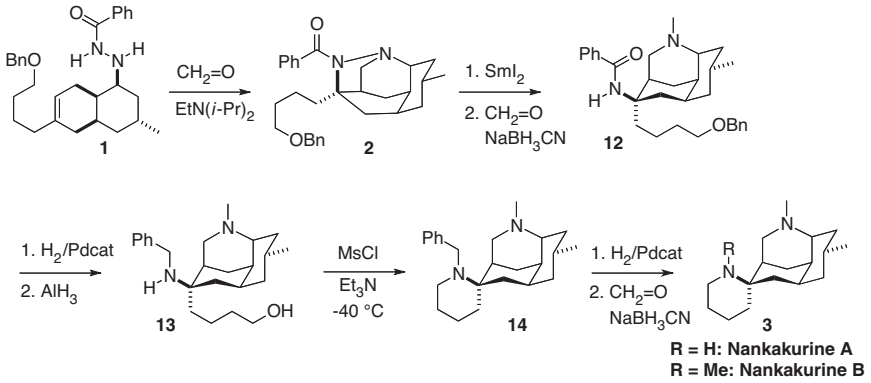


The starting material for the synthesis was 5-methyl cyclohexenone **6**, prepared from (*R*)-pulegone. The diene **5** was prepared from the alkyne **4**, following the procedure developed by Diver. There were two issues in developing the Diels-Alder addition of the enone **4** to the diene **6**. The first was the relative lack of reactivity of **4** as a dienophile. The other issue was the ready epimerization of the product ketone **9**. Both of these problems were solved using the activation method devised by Gassman. Condensation of **4** with **7** in the presence of the bis-silyl ether **7** and the diene **6** at cryogenic temperatures led to the ketal **8**. It is thought that the active dienophile was the cation **11**.



Gentle hydrolysis of the ketal **8** was effected with minimal epimerization. Reductive amination with the hydrazide **10** proceeded with high diastereocontrol, to give the precursor **1**.

The intramolecular aza-Prins cyclization of **1** to **2** proceeded well, though the desired tetracyclic **2** was only observed when base was included in the reaction medium. In the absence of base, tricyclic alkenes dominated.



Reduction of the N-N bond of **2** proceeded smoothly with freshly prepared SmI_2. After reductive methylation, hydrogenation removed the benzyl ether, and AlH_3 converted the benzamide to the benzyl amine. At low temperature, mesylation of the alcohol was apparently faster than mesylation of the secondary amine, enabling cyclization to **14**. Removal of the benzyl protecting group gave Nankakurine A, which was successfully methylated to give Nankakurine B.

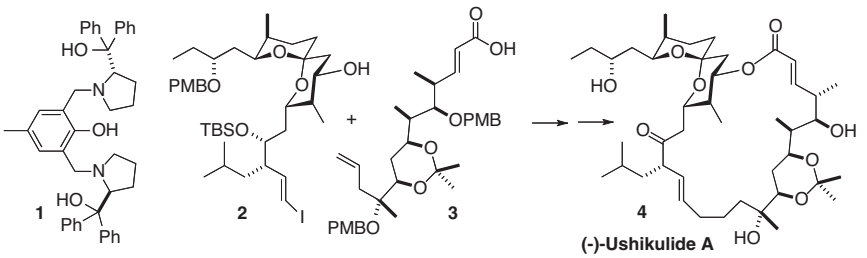
The completion of a total synthesis is an anxious moment, as for the first time it is possible to compare spectra of the synthetic material with those reported for the natural product. There is always a concern as to whether or not the spectra are being acquired under precisely the same conditions employed by those who did the initial isolation. This is particularly true for very polar molecules such as these diamines. In fact, the spectra in CD_3OD did not initially match, but on the addition of small amounts of CF_3CO_2H they were brought into congruence.

Although in this synthesis the starting enantiomerically-pure cyclohexenone **4** was derived from natural sources, one could imagine that enantioselective conjugate methylation of cyclohexenone or a derivative could get one into the same manifold.

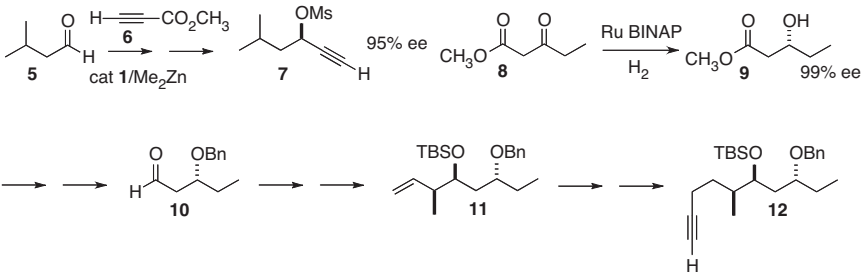
101. The Trost Synthesis of (-)-Ushikulide A

September 7, 2009

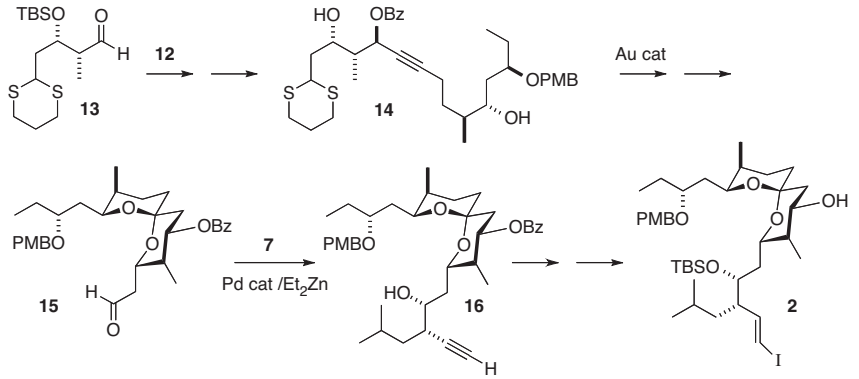
(-)-Ushikolide A **4**, isolated from a culture broth of *Streptomyces* sp. IUK-102, showed powerful activity against murine splenic lymphocyte proliferation (IC_{50}= 70 nM). The most important player in the synthesis of **4** described (*J. Am. Chem. Soc.* **2008**, *130*, 16190) by Barry M. Trost of Stanford University was the ProPhenol ligand **1**.



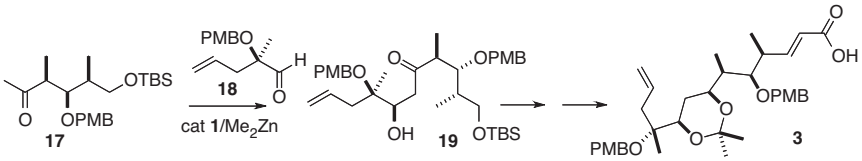
The precursor **2** was prepared by coupling the mesylate **7**, the alkyne **12**, and the aldehyde **13**. The first role of catalyst **1** was in mediating the enantioselective coupling of commercial **5** with **6** to give, after saponification and CuCl decarboxylation, the mesylate **7**. The preparation of **12** began with the Noyori hydrogenation of the ester **8** to the alcohol **9** in the expected high ee. Note that although this transformation was carried out at 1800 psi, such reductions proceed well and in similar ee at 60°C and 60 psi. Brown crotylation of the derived aldehyde **10** delivered **11**, that was homologated to the alkyne **12**.



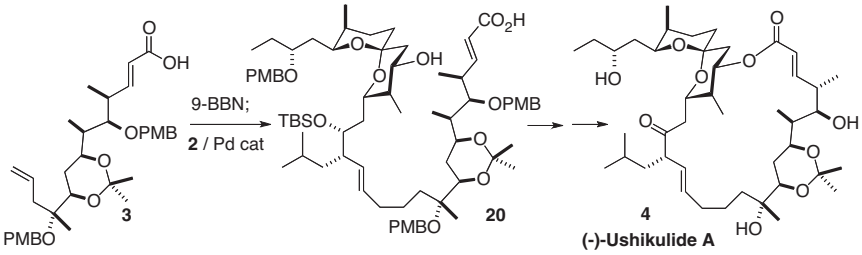
The third fragment **13** was prepared by chiral auxiliary directed aldol condensation. Combination of **12** with **13** was followed by Au-mediated cyclization, converting the internal alkyne of **14** to the spiroketal of **15**. Pd-catalyzed coupling of **15** with **7** then led to **2** with high diastereocontrol.



The aldol addition of the enolate of **17** to **18** proved elusive under the usual conditions, but with 30 mol % of the Zn catalyst **1** the reaction proceeded smoothly, to deliver **19** with high diastereocontrol.



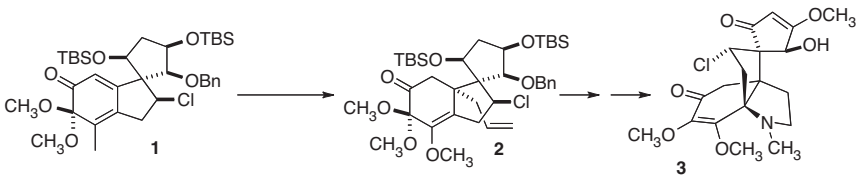
To complete the synthesis, hydroboration with 9-BBN was effected on the free carboxylic acid **3**, and Pd-mediated coupling of the derived borane was carried out with the free iodo alcohol **2**. As a result, the product hydroxy acid **20** could be taken directly to the subsequent macrolactonization.



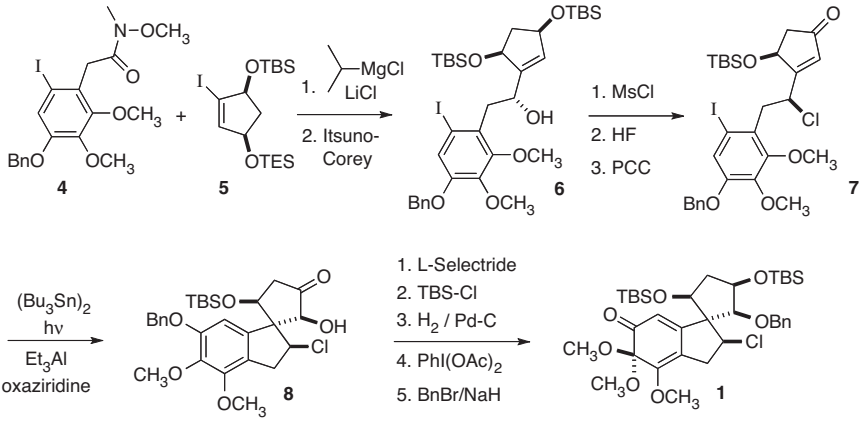
102. The Castle Synthesis of (-)-Acutumine

October 5, 2009

The complex tetracyclic alkaloid (-)-acutumine **3**, isolated from the Asian vine *Menispermum dauricum*, shows selective T-cell toxicity. The two adjacent cyclic all-carbon quaternary centers of **3** offered a particular challenge. Steven L. Castle of Brigham Young University solved (*J. Am. Chem. Soc.* **2009**, *131*, 6674) this problem by effecting net enantioselective conjugate allylation of the enantiomerically pure substrate **1** to give **2** with high diastereocontrol.



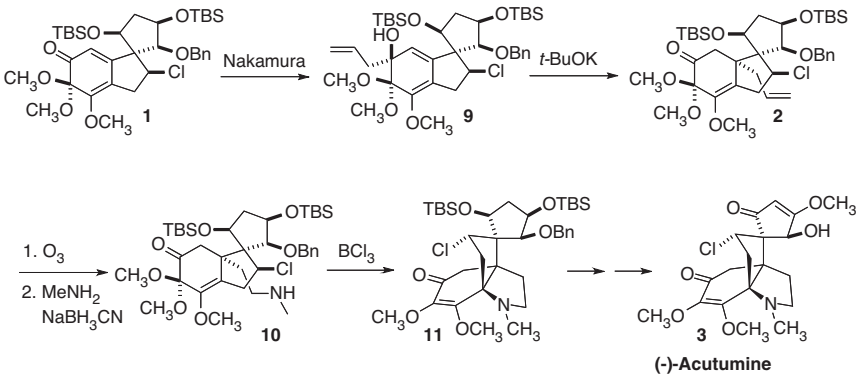
The starting coupling partners (*Organic Lett*. **2006**, *8*, 3757; *Organic Lett*. **2007**, *9*, 4033) for the synthesis were the Weinreb amide **4**, prepared over several steps from 2,3-dimethoxyphenol, and the diastereomerically- and enantiomerically-pure cyclopentenyl iodide **5**, prepared by singlet oxygenation of cyclopentadiene followed by enzymatic hydrolysis. Transmetalation of **5** by the Knochel protocol, addition of the resulting organometallic to **4** and enantioselective (and therefore diastereoselective) reduction of the resulting ketone delivered the alcohol **6**. Methods for installing cyclic halogenated stereogenic centers are not well developed. Exposure of the allylic alcohol to mesyl chloride gave the chloride **7** with inversion of absolute configuration. Remarkably, this chlorinated center was carried through the rest of the synthesis without being disturbed.



A central step in the synthesis of **3** was the spirocyclization of **7** to **8**. Initially, iodine atom abstraction generated the aryl radical. The diastereoselectivity of the radical addition to the

cyclopentene was set by the adjacent silyloxy group. The α-keto radical so generated reacted with the Et_3Al to give a species that was oxidized by the oxaziridine to the α-keto alcohol, again with remarkable diastereocontrol.

Conjugate addition to the cyclohexenone **1** failed, so an alternative strategy was developed, diastereoselective 1,2-allylation of the ketone followed by oxy-Cope rearrangement. The stereogenic centers of **1** are remote from the cyclohexenone carbonyl, so could not be used to control the facial selectivity of the addition. Fortunately, the stoichiometric enantiomerically-pure Nakamura reagent delivered the allyl group preferentially to one face of the ketone **1**, to give **9**. The subsequent sigmatropic rearrangement to establish the very congested second quaternary center of **2** then proceeded with remarkable facility, at 0°C for one hour.



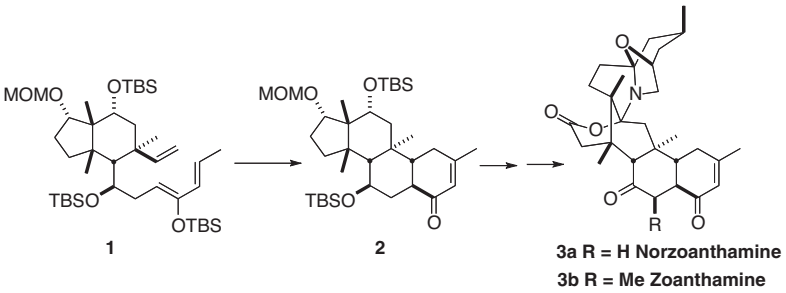
Oxidative cleavage to the aldehyde followed by reductive amination gave **10**, that looks as though it could be poised for intramolecular displacement of the secondary chloride. Nonetheless, Lewis acid mediated ionization followed by cyclization proceeded smoothly, to establish the fourth ring of the natural product. Oxidation state adjustment then completed the synthesis of (-)-Acutumine **3**.

The face selective enone allylation followed by oxy-Cope rearrangement (**1** → **2**), a highlight of the approach presented here, will have many applications in target-directed synthesis.

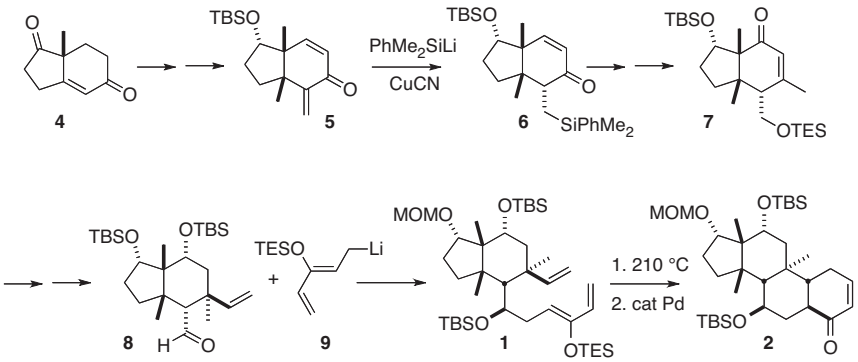
103. The Kobayashi Synthesis of (-)-Norzoanthamine

November 2, 2009

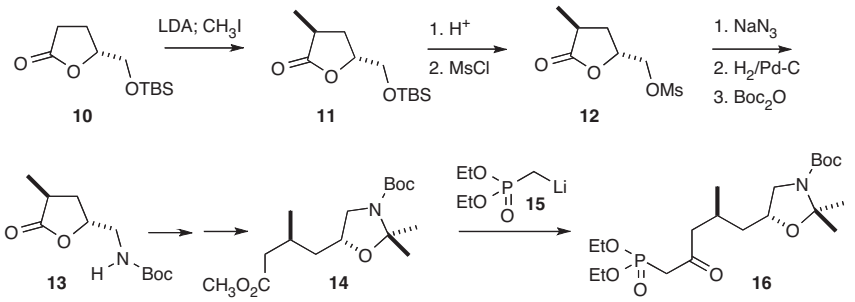
The *Zoanthus* alkaloids, exemplified by (-)-norzoanthamine **3a** and zoanthamine **3b**, show promising activity against osteoporosis. Susumu Kobayashi of the Tokyo University of Science assembled (*Angew. Chem. Int. Ed.* **2009**, *48*, 1400; *Angew. Chem. Int. Ed.* **2009**, *48*, 1404) the challenging tricyclic core of **3a** employing the intramolecular Diels-Alder cyclization of **1** to **2**. The cyclopentane of **1** served as useful scaffolding, even though it was cleaved en route to **3a**.



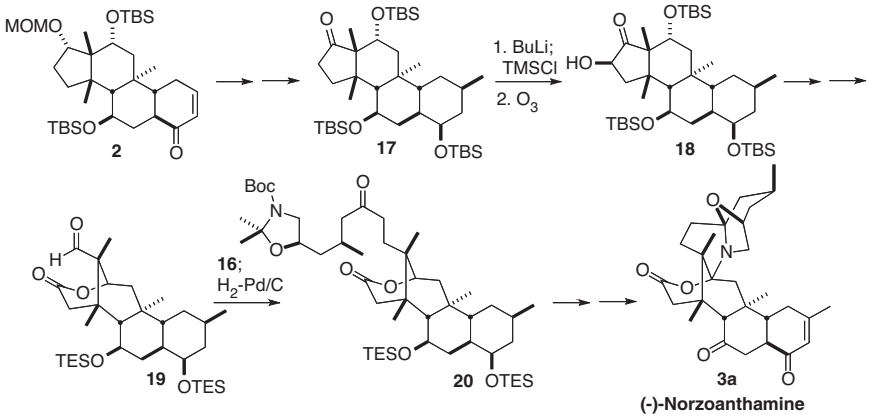
The cyclohexane ring of **1** has five of its six positions substituted, including three that are alkylated quaternary centers. The starting point for the preparation of **1** was the enantiomerically-pure Hajos-Parrish ketone **4**, containing the first of the those quaternary centers. Conjugate addition of MeLi established the second quaternary center. The less stable endo alkyl branch of **1** was installed by conjugate addition to the more reactive α-methylene ketone of the cross-conjugated **5**, followed by kinetic quench. Addition of vinyl cuprate across the open face of the enone **7** then established the final quaternary center, setting the stage for the intramolecular Diels-Alder reaction. The silyl enol ether from the cyclization of **1** was not stable, so it was directly oxidized to the enone **2**.



The keto phosphonate **16** for the last two rings of **3a** was prepared from the previously-reported crystalline glutamic acid-derived mesylate **12**. Reduction and homologation delivered the ester **14**, that was condensed with the phosphonate anion **15** to give **16**.



The congested cyclopentanone **17**, derived from **2**, was most efficiently deprotonated with *n*-BuLi. Exposure of the resulting silyl enol ether to ozone led to the α-hydroxylated product **18**. Unexpectedly but happily, oxidative cleavage of **18** delivered, after deprotection and reprotection, the more congested aldehyde **19**. This cleavage may be proceeding by tautomerization of **18** to the regioisomeric keto alcohol. The aldehyde **19** was condensed with the keto phosphonate **16**, to give, after hydrogenation, the keto lactone **20**. A series of oxidation state adjustments then completed the synthesis of (-)-norzoanthamine **3a**.

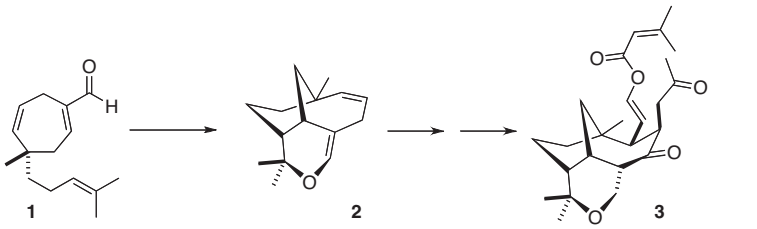


The preparation of **3a** outlined here underlines the importance of developing new methods for concise stereocontrolled carbocyclic construction. The utility of an enantiomerically-pure bicyclic scaffold such as **4** for subsequent relative stereocontrol is particularly apparent.

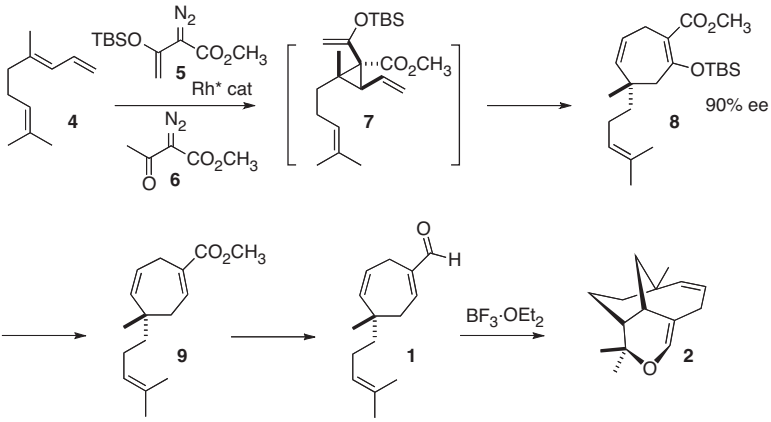
104. The Davies/Williams Synthesis of (-)-5-*epi*-Vibsanin E

December 7, 2009

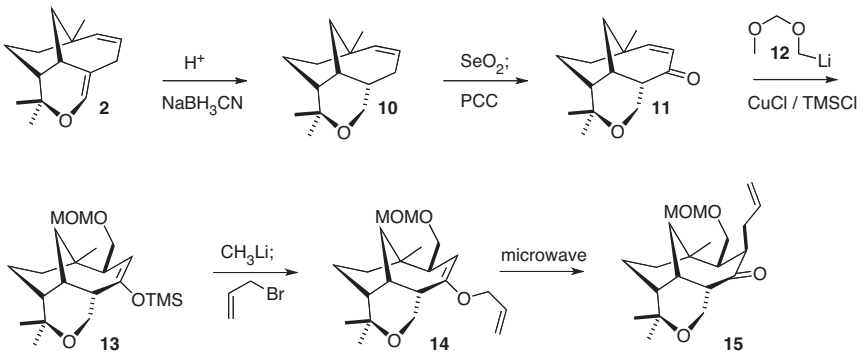
There are currently 61 known vibsane-type diterpenes, as exemplified by (-)-5-*epi*-Vibsanin E **3**. The first synthesis of **3**, described (*J. Am. Chem. Soc.* **2009**, *131*, 8329) by Huw M. L. Davies of Emory University and Craig M. Williams of the University of Queensland, was based on the enantioselective seven-membered ring construction developed by the Davies group and the end game established by the Williams group. A key step in the synthesis was the intramolecular hetero Diels-Alder cyclization of **1** to **2**.



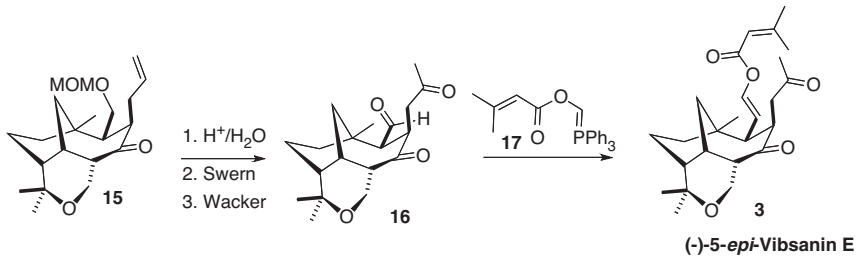
The absolute configuration of **1** was set by the Rh-mediated cyclopropanation of **4** with the diazo ester **5**. Though closely related to the α-diazo β-keto ester **6**, the alkene of **5** *donates* electron density to the intermediate Rh carbene, making it more susceptible to the influence of the chiral ligands. The alkene of the enol ether then participated in the Cope rearrangement, delivering **8**. Routine functional group transformation then converted **8** to **1**, that cyclized smoothly to **2**.



The enol ether of **2** was reduced with high diastereocontrol to give **10**. The ketone was installed by allylic oxidation, setting the stage for attachment of the two pendant sidechains of **3** by conjugate addition followed by enolate trapping. Cu-catalyzed addition of the α-oxygenated organolithium **12** proceeded well in the presence of TMS-Cl, to establish the silyl enol ether **13**. Allylation of the regenerated enolate proceeded at oxygen, but the enol ether **14** so prepared rearranged to the desired C-alkylated product **15** on microwave heating.



The synthesis endgame was based on an unusual transformation, the addition to the keto aldehyde **16** of the phosphonium salt **17**, developed (*Tetrahedron* **2008**, *64*, 6482) by the Williams group. This allowed the introduction of the complete vinyl ester array of (-)-5-*epi*-Vibsanin E **3**.



(-)-5-*epi*-Vibsanin E

This synthesis illustrates the power of the elegant enantioselective seven-membered ring construction developed by the Davies group. The Williams phosphonium salt will also have general applicability. In a simpler manifestation, conversion of an aldehyde to, e.g., the enol benzoate, followed by exposure to dilute methoxide, will allow the conversion of an aldehyde to the aldehyde one carbon longer, without the acidic hydrolysis usually required for such a transformation.

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Reaction Index