Titanium and Zirconium in Organic Synthesis. Edited by Ilan Marek

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Editor:

Prof. Ilan Marek
Department of Chemistry
Technion – Israel Institute of Technology
Haifa 32000
Israel

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Foreword

The time is apt for synthetic chemists to fully enter the world of organozirconium and organotitanium chemistry. While Pd, Cu, and Ni catalyzed reactions have been embraced by synthetic practitioners and the long-standing hydrogenation catalysts, Rh and Ru, are being increasingly accepted for other uses, Zr and Ti reagents, with, of course, the notable exceptions of the polymerization catalysts, have not broken the barrier to widespread application for small molecule synthesis, especially in industry. Aside from reagent availability and sensitivity, perhaps part of the explanation lies in the inability of the chemist trained in the Corey retrosynthetic analysis mold to adapt their thinking to what are, compared to more classical paths, the less rational dissection based on organozirconium and organotitanium reactions. This volume, edited with dedication to content and care in presentation by Ilan Marek and encompassing forefront topics by the most active researchers in the field will, with reading and revisit, provide persuasion to irreversibly change this perspective and to traverse the borders to new exciting synthetic chemistry.

In a masterly introductory chapter, Negishi and Huo set the stage for zirconocene chemistry, providing historical aspects which chronologically attribute the various discoveries by numerous chemists in this field, including the major contributions from the Negishi laboratories and the systematic studies of hydrozirconation by Schwartz and his students, since the first report in 1954 of the structure of Cp_2ZrCl_2 by Wilkinson. In a innovative series of tabulated highlights, Negishi and Huo teach the generalizations and reactivity patterns of Zr(IV) and Zr(II), the most synthetically useful species, and provide X-ray structural and mechanistic insight wherever available. They also delineate what is currently feasible with Zr reagents (e. g. transmetallation) and where additional work may lead to new synthetic value (e. g. radical and photochemical reactions). The defined subsections (e. g. π-Complexation, Carbonylation, σ-Bond Metathesis) allow the reader, both expert and novice, to quickly focus on given areas and easily pursue the relevant chapter for details. The discussion is concise, mechanistically friendly to the synthetic organic chemist, and, whenever appropriate, comparative (e.g effect of Li, Mg, Zn, and Al in Zr-catalyzed cyclic carbometallation) thus providing a most useful overview of the topics in this volume.

Takahashi and Li (Chapter 2) focus on the preparation and reactions of zirconacyclopentadienes which, for a quarter of a century since their discovery in 1974 by

Watt and Drummond, were considered to be inert for C-C bond forming reactions. However, by the expedient of transmetallation to Cu, Ni, Zn, Li, and Al, methodologies for the stereoselective synthesis of olefins and dienes, as well as unusual heterocycles, aromatics and their ring-annulated products are now available which are beginning to make impact on material science, e. g. synthesis of pentacenes and polyphenylenes. Takahashi and Li provide evidence that, with further developments in transmetallation and handling the zirconacycles outside of the Schlenk tube techniques, synthetic utility will increase and new catalytic reactions will be developed.

In a fascinating chapter (Chapter 3) with considerable promise for synthetic chemists, Dixon and Whitby describe the insertion of carbenoids (α-halo-α-lithio species) into organozirconocenes. Setting the appropriate background of the mechanistically analogous rapid insertion of the isoelectronic carbon monoxide and alkylisonitrile (which complements the Pauson-Khand reaction), the authors systematically review the status of various halocarbenoids from which result synthetic methods for functionalized olefins, dienes, dienynes, among other organic molecules. The focus on the most extensively studied insertion of allyl carbenoids into zirconacycles leads to illustrations of tandem processes with initial demonstration of application to natural product synthesis. Appropriate mechanistic speculation on very new processes suggests that this area offers a promising future for synthesis.

Lipshutz, Pfeiffer, Noson, and Tomioka (Chapter 4) assume the formidable task of providing a seven-year update of the advances in the hydrozirconation–transmetallation sequence in organic synthesis. At the outset, as expected from an experimental organic group, a discussion of practical aspects of the commercial CpZr(H)Cl (Schwartz reagent) are presented and, similarly graciously, the difficulties of control of its reactions in appropriate air- and moisture-free atmosphere are stressed. Similarly expected is the emphasis on synthetic utility of the reactions, which involve acyl- and allylzirconocenes and, most prominently, the cross-coupling reactions following transmetallation to Cu, Zn, B, and Ni. This survey invites the chemist to view anew various processes which were learned retrosynthetically by more traditional pathways, e. g. carbocyclization, equivalency of acylzirconocenes as acyl anions and demonstrates in instructive schemes the impact that not only zirconium chemistry but other transition metal-catalyzed reactions have made on bioactive molecule and natural product synthesis. More specialized systems, e. g. vinyl tellurides, selenides, and phosphonates, are also effectively prepared. Recent reports (e. g. reduction of tertiary amide to aldehyde using the Schwartz reagent) and the promise of catalytic hydrozirconation will continue to fuel this area in the future.

In useful and minor overlap with Chapters 3 and 4, the review (Chapter 5) on progress in acylzirconocene chemistry by Hanzawa points to the extensive mechanistic investigation of this class of Zr reagents but lack of synthetic application. Following discussion of the stability and ease of handling of the $RCOZr(Cl)Cp_2$ reagent, its umpolung reactivity is delineated in general synthetic procedures for α-ketols, α-aminoketones (including Bronsted acid catalysis), selective 1,2-addition

products of enones (including the first results of demonstration of enantioselectivity). The closing sections on Pd- and Cu- catalyzed reactions of acylzirconocenes to give ketones appear to promise scope and the use of unsaturated acylzirconocenes as ketone α,β-dianion equivalents offer stimulus that the promise of this area may be imminent.

With Chapter 6 by Hoveyda concerned with a critical review of chiral Zr catalysts in enantioselective synthesis, synthetic utility goes into high gear. A plethora of successful or highly promising asymmetric reactions (*inter alia*, inter- and intramolecular alkylations, kinetic resolution of unsaturated exocyclic allylic ethers, hydrocyanation, Strecker, aldol, Mannich, and cycloaddition reactions) attest to the excitement in this young area of research. Synthetic applications abound already from simple functionalized chiral pieces to heterocycles and complex macrocyclic natural products. Connections to other modern protocols, e. g. ring-closing metathesis, provide additional innovative synthetic value. In a unique feature of this chapter, Hoveyda makes the admirable effort to delineate, for each topic, comparison with catalytic asymmetric reactions, which are promoted by non-Zr catalysis. Thus the preparation of optically pure acyclic allylic (Sharpless epoxidation) and homoallylic (Yamamoto, Keck, Tagliavini protocols) alcohols are contrasted and compared. A provocative section on Zr-catalyzed enantioselective C-H bond formation closes this review of a field for which more practical and rapid developments are anticipated.

gem-Metallozirconocenes, a field that sprung forth from the discovery of the Tebbe reagent and was fueled by the bimetallic Al – Zr (Schwartz) and Zn – Zr (Knochel) contributions is reviewed (Chapter 7) by Dembitsky and Srebnik with the major concentration being given to the chemistry of bimetallic Al, B, Li, Ga, Ge, Sn, Zn, and Zr species. An early section on the preparation of stable planar tetracoordinate carbon Zr/Al compounds sets the tone for this review in which availability of structural information of Zr derivatives rather than as yet synthetic application is recognized. In the latter aspect, the use of *gem*-**bora**zirconocene species for the construction of dienes, trienes, and allenes appears to be in a developed state and incorporates a useful method for α-aminoboronic ester synthesis. In addition, their application to the preparation of simple natural products and heterocycles invites further study to achieve a more general status. Other *gem*-bimetallic species, e. g. Ga-Zr, lead to structurally interesting but unusual systems while the application of Zn-Zr derivatives provide simple organic molecules, which may be readily obtained by more standard methods. This statement is not meant to detract from undertaking further studies of scope and limitations in this evolving area.

Cationic zirconocenes, especially as they find significant value in glycoside bond formation, are reviewed (Chapter 8) by Suzuki, Hintermann, and Yamanoi. With an acknowledgement to the value of the rich mechanistic background of this area due to cationic zirconocene polymerization catalysis, the authors focus on the Cp_2ZrCl_2/AgX combination as reagent, intermediate, and catalyst. In turn, glycosylations of simple sugars, terpenes, and nucleosides, are discussed, culminating in a major section dealing with the construction of highly complex glycosylphosphatidylinositols, constituting plasma membrane anchors on the cell walls of

parasitic protozoa which effect parasite survival and infectivity. A useful section on the generation, modification, and tuning of the Cp_2ZrCl_2/AgX reagent is included. Simpler cationic Zr- mediated reactions, *inter alia*, addition to aldehydes and epoxides, the generation of *ortho*-quinodimethides, Diels-Alder, Mukaiyama, and an intriguing dioxolenium ion alkylation and epoxy ester to orthoester rearrangement are presented which augers well for the future of this promising area.

Sato and Urabe introduce their chapter (Chapter 9) on the use of Ti(II) alkoxides in synthetic chemistry by a useful table of available reagents and a classification of the reactions of the combination Ti($OiPr_2$)-*i*PrMgX into four categories. Utility is evidenced in the synthesis (some stereoselective) of tetrasubstituted alkenes, allenyl alcohols, β-alkylidenecycloalkylamines, allylic and homoallylic alcohols and amines, aromatics (metallative Reppe reaction), among other functionalized organics. Particularly unique appears to be the intramolecular nucleophilic acyl substitution mediated by Ti($OiPr_2$)-*i*PrMgX which leads to bicyclo[3.1.0]hexane systems, furans, and fused heterocycles, including an alkaloid total synthesis. Another, equally intriguing reaction which can be equated with Pauson-Khand and the stoichiometric metallo-ene process is the intramolecular alkene–acetylene coupling, a reaction which also has found application in natural product synthesis. The development of the inexpensive and easily operational Ti(O*i*Pr_2)-*i*PrMgX reagent in many interesting selective reactions which cannot be carried out with conventional metallocene reagents suggests that new transformations of synthetic value will be forthcoming.

In Chapter 10, Rosenthal and Burlakov summarize recent work on the specific reactions of titanocenes and zirconocenes with bis(TMS)acetylene. Similar to the classes of Zr derivatives reviewed by Dembitsky and Srebnik (Chapter 7), the potential of the derived complexes in organic synthesis is at an early stage of development. Thus the reagents, of the type $Cp_2M(L)(\eta_2\text{-}TMSC_2TMS)$, prepared with Schlenk tube techniques, undergo reactions with acetylenes, alkenes, diacetylenes, conjugated and unconjugated dienes, carbonyl compounds, imines, among others to give metallocyclopentadiene and other, structurally intriguing, complexes. The main synthetic organic application appears to be in polymerization reactions and the synthesis of unusual poly-enes, -ynes, and diyne thiophenes. The advantages of $Cp_2M(L)(\eta_2\text{-}TMSC_2TMS)$ over the widely used Cp_2ZrCl_2/*n*-BuLi system should stimulate further research on the reactions of the former type reagents.

The discovery in 1989 by Kulinkovich of the reaction of *in situ* generated alkenetitanium complexes with esters leading, by a two carbon-carbon bond forming process, to cyclopropanols has spawned a new area of low-valent titanium chemistry which is summarized in Chapter 11 for the active synthetic chemist by de Meijere, Kozhushkov, and Savchenko. Using extensive tabular surveys, the review begins with the scope and limitations of the cyclopropanol synthesis from esters, diesters, and lactones, the authors emphasize the significance of ligand exchange of the initially derived alkenetitanium complex to derive different substitution on the cyclopropane ring, selective cyclopropanations of dienes and trienes, enantioselective synthesis of bicyclo[3.1.0]hexane systems, and applications in the context of heterocycles. The discovery in the de Meijere laboratories of the low-valent Ti amide to

cyclopropylamine variant is elaborated in the other main section of this chapter, showing scope in terms of cyclopropane ring substitution, enantioenrichment using Ti bis(TADDOLate) reagents, and other reactions some of which parallel the ester to cyclopropanol conversion. Variation by replacement of Grignard by organoZn reagent, and addition of metal alkoxides gave rise a promising variant. The review closes with sections on applications to natural product and materials synthesis and useful transformations of the synthetized cyclopropanols and cyclopropylamines. Although stoichiometric or semi-catalytic in $Ti(OiPr)_4$ (5-10 mol%), these reactions appear to be operationally simple, use low-cost reagents, proceed in good yields and with high chemo- and stereo-selectivity, and therefore appear primed for new synthetic applications.

As reviewed in Chapter 12 by Gansäuer and Rinker, the general context of the emerging area of reagent-controlled radical reactions, titanocene complexes are most promising systems for epoxide opening processes. Originating with the work of Nugent and RajanBabu who demonstrated the concept of electron-transfer opening the strained epoxide reductively with stoichiometric amounts of low-valent metal complexes, this field is evolving to provide new methods for deoxygenation, reductive opening to alcohols, and 3-*exo* and 5-*exo* carbocyclizations. In recent work, especially in the authors' laboratories, a protocol has been devised involving protonation of Ti-O and Ti-C bonds allowing reasonable catalytic turnover. This leads to the development of preparative chemistry for tandem epoxide-opening–α,β-unsaturated carbonyl trapping, including intramolecular versions, to give initial indications of diastereo- and enantio–selective control of these radical processes. This work clearly constitutes the beginning of another new area of titanocene chemistry.

In Chapter 13, Szymoniak and Moise summarize the progress in the area of allyltitanium reagents in organic synthesis, an area pioneered by the work of Seebach and Reetz. This review delineates, following the historic and convenient grouping for allyltitaniums into three classes according to ligands (with two Cps; with one Cp, and without Cps), achievements of the last 10-15 years. As a highlight in the first category, while the addition to η^3-allyltitanocenes to aldehydes and ketones to give homoallylic alcohols in excellent yields and (for aldehydes) with high *anti* stereoselectivity is now well appreciated, other reactions such as intramolecular reactions to cyclobutanes and carboxy alkylation and amidation of cycloheptatriene appear to be of unique synthetic value. Furthermore, combinations of allylTi and Mukaiyama-aldol or aldol-Tishchenko reactions constitute new diastereoselective routes to polypropionates. The contrast between the useful η^3-allylTi derivatives, the corresponding η^1-species, although readily available, have not enjoyed wide application nor are their enantioselective reactions known. In the one Cp ligand group, the work of Hafner and Duthaler of highly enantioselective and practical asymmetric allyltitanation using tartrate-derived (TADDOL) ligands and their application to prepare useful chiral building blocks and natural products is summarized. AllylTi reagents without Cp ligands, in spite of being very reactive, are chemo- and highly diastereoselective in reactions with aldehydes and ketones allowing the development of diastereo- and enantio-selective homoaldol additions.

Based on the Kulinkovich reagent ($Ti(OiPr)_4/iPrMgCl$), a new route to allyltitaniums has been devised by Sato and coworkers and this has allowed the synthesis of chiral allylTi reagents which, by reaction with aldehydes and imines provide diverse polyfunctional chiral building blocks. Thus, while a number of versatile and dependable Ti-based allyl-transfer reagents are now available, the development and employment of chiral allyltitaniums appears to be poised for new application.

Perhaps appropriately in view of the current high profile of Grubbs metathesis chemistry, the topic of titanium-based olefin metathesis by Takeda constitutes the last chapter (Chapter 14) for the volume. The report in 1979 by Tebbe of the first olefin metathesis between titanocene-methylidene and simple olefins was, in retrospect, less significant for synthetic chemists than its reaction with esters. Nevertheless, early tandem carbonyl olefination-olefin metathesis sequences in complex molecule synthesis appeared, as documented by Takeda. Following discussion of limitations due to steric effects and unavailability of higher homologues of titanocene-methylidene, potentially useful reactions of thioacetals with $Cp_2Ti[P(OEt)_3]_2$ and subsequent metathesis (apparently via titanacyclobutane intermediates) to carbo- and hetero-cyclic products are described and tabulated. Possibly related reactions (e. g. reaction of 6,6-dihalo-1-alkenes with Ti(II) species to afford bicyclo[3.1.0]hexanes offer new grounds for exploration while carbonyl, especially ester, thioesters, and lactone, olefination constitutes an established synthetic method. Ti-based reagents generated by reduction of *gem*-dihalides with low-valent metals for alkylidenation of carbonyl compounds (a half-McMurry reaction), also noted as a general methodology has, as judged from the synthetic literature, reached full potential. Similarly, reactions with alkynes and nitriles offer early indications of new routes to dienes and pyridine and diimines, respectively. Perhaps with further definition of conditions, new synthetic tools from Ti-based olefin metathesis chemistry will be developed.

Sixty years ago, organic chemists were struggling with the preparation and observation of properties of organolithiums; today, metallation chemistry is routinely executed on gram and multi-ton scale. Since chemists are recognized for their intense level of curiosity and pride in experimental achievement, the real or apparent intricacies associated with the preparation and use of Zr and Ti reagents that appear to be bizarre, unavailable, and/or relegated to the Schlenk tube will be overcome. May this volume be a hallmark in this quest.

Victor Snieckus
Queen's University
Kingston, ON, Canada

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Preface

Although more than a century has passed since the first preparation of titanium and zirconium species, modern organic synthesis continues to benefit from the unique versatility of these organometallic derivatives.

This special feature arises from the combination of the transition metal behavior such as the coordination of a carbon-carbon multiple bond, oxidative addition, reductive elimination, β-hydride elimination, addition reactions and the behavior of classical σ-carbanion towards electrophiles.

My primary purpose in editing this book was to bring together, in a single volume, the remarkable recent achievements of organo- titanium and zirconium derivatives and to give a unique overview on the many possibilities of these two organometallic compounds such as reagents and catalysts, which are characteristic for their enduring versatility as intermediates over the years.

In this multi-authored monograph, fourteen experts and leaders in the field bring the reader up to date in these various areas of research. A special emphasis was placed on the practical value of this book by the inclusion of key synthetic protocols.

I gratefully acknowledge the work done by all authors in presenting their recent and well-referenced contributions. Without their effort, this volume would not have been possible. It is their expertise that will familiarize the reader with the essence of the topic. Finally, I express my great gratitude to my wife, Cecile, whose persistence, encouragement and comprehension made possible the editing of this book.

Technion-Israel Institute of Technology *Ilan Marek*
April 2002

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List of Contributors

Dr. Vladimir V. Burlakov
Institut für Organische
Katalyseforschung
Universität Rostock
Buchbinderstraße 5–6
18055 Rostock
Germany

Dr. Valery M. Dembitsky
Department of Medicinal Chemistry
and Natural Products
School of Pharmacy
P. O. Box 12065
The Hebrew University of Jerusalem
Jerusalem 91120
Israel

Dr. Sally Dixon
Department of Chemistry
University of Southampton
Hants SO17 1BJ
United Kingdom

Prof. Andreas Gansäuer
Kekulé-Institut für Organische Chemie
und Biochemie
Gerhard-Domagk-Straße 1
53121 Bonn
Germany

Prof. Yuji Hanzawa
School of Pharmacy
Tokyo University
1432-1 Horinouchi
Hachioji
Tokyo 192-0392
Japan

Dr. Lukas Hintermann
Department of Chemistry
Tokyo Institute of Technology
O-okayama
Meguro-Ku
Tokyo 152-8551
Japan

Prof. Amir H. Hoveyda
Department of Chemistry
Merkert Chemistry Center
Boston College
Chestnut Hill
Massachusetts 02467
USA

Dr. Shouquan Huo
Department of Chemistry
Purdue University
West Lafayette
Indiana 47907-1393
USA

Dr. Sergei I. Kozhushkov
Institut für Organische Chemie
Georg-August-Universität
Tammannstraße 2
37077 Göttingen
Germany

Dr. Yanzhong Li
Catalysis Research Centre
and Graduate School
of Pharmaceutical Sciences
Hokkaido University and CREST
Sapporo 060 811
Japan

Prof. Bruce H. Lipshutz
Department of Chemistry
and Biochemistry
University of California Santa Barbara
California 93106-9510
USA

Prof. Armin de Meijere
Institut für Organische Chemie
Georg-August-Universität
Tammannstraße 2
37077 Göttingen
Germany

Prof. Claude Moïse
Laboratoire de Synthèse et
d'Electrosynthèse Organométalliques
associe au CNRS
Faculté des Sciences
6, Bd Gabriel
21000 Dijon
France

Prof. Ei-ichi Negishi
Department of Chemistry
Purdue University
West Lafayette
Indiana 47907-1393
USA

Dr. Kevin Noson
Department of Chemistry
and Biochemistry
University of California Santa Barbara
California 93106-9510
USA

Dr. Steven S. Pfeiffer
Department of Chemistry
and Biochemistry
University of California Santa Barbara
California 93106-9510
USA

Dr. Björn Rinker
Kekulé-Institut für Organische Chemie
und Biochemie
Gerhard-Domagk-Straße 1
53121 Bonn
Germany

Prof. Uwe Rosenthal
Institut für Organische
Katalyseforschung
Universität Rostock
Buchbinderstraße 5–6
18055 Rostock
Germany

Prof. Fumie Sato
Department
of Biomolecular Engineering
Tokyo Institute of Technology
4259 Nagatsuta-cho, Midori-ku
Yokohama
Kanagawa 226-8501
Japan

Dr. Andrei I. Savchenko
Institut für Organische Chemie
Georg-August-Universität
Tammannstraße 2
37077 Göttingen
Germany

Prof. Morris Srebnik
Department of Medicinal Chemistry
and Natural Products
School of Pharmacy,
P. O. Box 12065
The Hebrew University of Jerusalem
Jerusalem 91120
Israel

Prof. Keisuke Suzuki
Department of Chemistry
Tokyo Institute of Technology
O-okayama
Meguro-ku
Tokyo 152-8551
Japan

Prof. Jan Szymoniak
Universitè de Reims
CNRS UMR 6519
Groupe Synthèse par voie
Organométallique
B.P. 1039 Reims Cedex 2
France

Prof. Tamotsu Takahashi
Catalysis Research Center
and Graduate School
of Pharmaceutical Sciences
Hokkaido University and CREST
Kita-ku
Sapporo 060 811
Japan

Prof. Takeshi Takeda
Department of Chemistry
Tokyo University of Agriculture
and Technology
Koganei
Tokyo 184-8588
Japan

Dr. Takashi Tomioka
Department of Chemistry
and Biochemistry
University of California Santa Barbara
California 93106-9510
USA

Dr. Hirokazu Urabe
Department
of Biomolecular Engineering
Tokyo Institute of Technology
4259 Nagatsuta-cho, Midori-ku
Yokohama
Kanagawa 226-8501
Japan

Prof. Richard J. Whitby
Department of Chemistry
University of Southampton
Hants SO17 1BJ
United Kingdom

Dr. Shigeo Yamanoi
Department of Chemistry
Tokyo Institute of Technology
O-okayama
Meguro-Ku
Tokyo 152-8551
Japan

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1
Synthesis and Reactivity of Zirconocene Derivatives

Ei-ichi Negishi and Shouquan Huo

1.1
Introduction and Historical Background

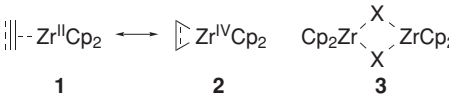
Zirconium (Zr) occurs in the lithosphere to the extent of 0.022 % [1]. Although it is much less abundant than Ti (0.63 %), it is roughly as abundant as C. Despite some technical difficulties in the production of pure Zr compounds, requiring separation of Hf-containing contaminants, it is one of the least expensive transition metals. Some of its fundamental properties are listed in Table 1.1

The most common oxidation state for zirconium compounds is +4, as suggested by the electronic configuration of Zr. There are, however, a significant number of Zr(II) compounds, such as $Cp_2Zr(CO)_2$ and $Cp_2Zr(PMe_3)_2$ [2], where Cp = η^5-C_5H_5. Alkene- and alkyne-$ZrCp_2$ complexes are often viewed as Zr(II) complexes, although they can also be considered as zirconacyclopropanes and zirconacyclopropenes, respectively, in which Zr is in the +4 oxidation state. *It appears best to view them as resonance hybrids of* ***1*** *and* ***2*** *and to use* ***1*** *and* ***2*** *interchangeably, as deemed desirable* (**Generalization 1**).

Atomic Number	40
Atomic Weight	91.22
Electronic Configuration	$[Kr]4d^25s^2$
Isotopic Composition	^{90}Zr (51.46 %), ^{91}Zr (11.23 %), ^{92}Zr (17.11 %)
	^{94}Zr (17.40 %), ^{96}Zr (2.8 %)
Magnetic Property	^{91}Zr ($I = 5/2$) The others are magnetically inactive.
Electronegativity	1.4 (Pauling[a]), 1.22 (Sanderson[b])

[a] Pauling, L., *The Nature of the Chemical Bond*, 3rd Ed., Cornell University Press, Ithaca, N.Y., **1960**, p. 93.
[b] Sanderson, R.T., *Inorganic Chemistry*, Van Nostrand-Reinhold, New York, **1967**, p. 72.

Table 1.1. Some fundamental properties of Zr



1 2 3

Scheme 1.1. Alkene- and alkyne-$ZrCp_2$ complexes (**1** and **2**), and **3** as an example of a Cp_2Zr(III) complex.

There have been relatively few Zr(III) compounds, and Zr(I) compounds are fewer still [2]. The dimer of Cp_2ZrCl (**3**) [2] is an example of a Zr(III) complex. Although very interesting from the viewpoint of structural chemistry, it has displayed few synthetically useful transformations. It even appears that its formation is something to be avoided in the use of Cp_2Zr derivatives for organic synthesis. In fact, *few Zr(III) compounds and reactions thereof have been shown to be synthetically useful. Thus, synthetically useful Zr compounds have been almost exclusively Zr(IV) and Zr(II) compounds* (**Generalization 2**).

Although there are many different types of Zr(IV) and Zr(II) compounds, *roughly 75–80%* of the *currently known well-characterized organozirconium compounds are zirconocene derivatives* [2]. *They are even more dominant in the application of Zr to organic synthesis* (**Generalization 3**). For this reason, essentially all the Zr compounds discussed in this chapter are $ZrCp_2$ derivatives.

Zirconocene derivatives are usually derived from Cp_2ZrCl_2, first reported by Wilkinson [3] in 1954, and analogues thereof. Zirconocene dichloride was one of the first organozirconium compounds to be reported in the literature, and so organozirconium chemistry is almost half a century old. Some zirconocene and other Zr compounds may have been used as catalysts in the Friedel–Crafts reaction or Ziegler–Natta-type polymerization before the discovery of hydrozirconation in the 1970–1971 period by Wailes and Weigold [4,5]. However, it was the development and systematic investigation of hydrozirconation by Schwartz [6–9] in the mid-1970s that marked the birth of the application of organozirconium chemistry to organic synthesis. Aside from the synthesis of alkyl- and alkenylzirconocene chlorides by hydrozirconation and subsequent protonolysis, halogenolysis, and oxidation, however, only a very limited range of C–C bond-forming reactions, such as carbonylation, were initially known [6–9].

The discoveries of the Ni- or Pd-catalyzed cross-coupling with alkenylzirconocene chlorides [10–12] and the Zr-catalyzed alkyne carboalumination [13] in the 1977–1978 period by Negishi, along with Schwartz's conjugate addition [14–17] and acylation [18] promoted or catalyzed by Cu, Ni, Al, etc., in the late 1970s significantly expanded the scope of organozirconium chemistry in organic synthesis. The Zr-catalyzed carboalumination, often referred to as the Negishi carboalumination, is particularly noteworthy since Zr is used as a component of catalysts. In all of the other reactions mentioned above, Zr is used stoichiometrically. Together with the concurrent but seemingly independent development of the zirconocene-based alkene polymerization, mainly by Kaminsky [19–21], the Zr-catalyzed carboalumination established the synthetic value of Zr as a catalyst component.

Systematic and extensive explorations of "Cp_2Zr(II)" chemistry in the 1980s by Negishi [22–33], Takahashi [34,35], Buchwald [36–44], and others substantially expanded the scope of synthetic organozirconium chemistry. Related investigations by many others, including some pioneering works of Bercaw [45,46], Erker [47–49], and others, are also noteworthy. Although the foundation of "Cp_2Zr(II)" chemistry was firmly established in the 1980s, it is still a rapidly growing area, as eloquently demonstrated by var-

ious chapters in this book. The use of Zr in organic synthesis nevertheless lags far behind that of Pd at present. Even so, it may already rank among the most widely used transition metals along with Cu, Ni, Rh, Ru, and Ti.

1.2 Fundamental Patterns of Transformations of Zirconocene Derivatives

Scheme 1.2. Some structural parameters and the available coordination sites of Cp_2ZrCl_2.

Zirconocene dichloride (Cp_2ZrCl_2) and its derivatives represented by the general formula Cp_2ZrXY are 16-electron d^0 Zr(IV) complexes with one valence-shell empty orbital available for coordination. *They are therefore fundamentally Lewis acidic* (**Generalization 4**). The absence of a valence-shell filled nonbonding orbital suggests that *their intrinsic nucleophilicity or Lewis basicity might be relatively low* (**Generalization 5**), and the currently available data indeed support this generalization. It is not unreasonable to state that most of the reactions of 16-electron zirconocene derivatives are triggered by interaction of the empty Zr orbital with electron donors.

Just like any other valence-shell empty orbital, the empty Zr orbital may interact with any proximal electrons, including (i) nonbonding electron pair donors, abbreviated here as *n-donors* or *n-electron pair* for simplicity, (ii) *π-bonds* or *π-electrons*, or (iii) *σ-bonds* or *σ-electrons*. Such interactions may be intermolecular or intramolecular. Some of the significant examples are listed in a generalized manner in Scheme 1.3.

Although some other two-electron processes may exist and may be found in the future, the 15 **Patterns** shown in Scheme 1.3 should cover most of the known two-electron processes. The following additional discussions of these patterns might be useful in dealing with them.

First, the 15 **Patterns** in Scheme 1.3 represent 15 elementary processes showing primarily the relationships between the starting and ending species. These elementary processes may or may not be the same as experimentally observable reactions that may bear the same technical terms of transformation. For example, the Zr-catalyzed ethylmagnesation of 1-alkenes with EtMgBr [50] (Scheme 1.4) might be considered as an example of **Pattern 7**. A mechanistic investigation has established a three-step catalytic cycle consisting of (i) decomposition of Cp_2ZrEt_2 to give ethylenezirconocene by β-H abstraction (**Pattern 13**), (ii) carbometallative ring-expansion (**Pattern 7′**) and (iii) transmetallation (**Pattern 13**), and (iv) second β-H abstraction (**Pattern 13**) [51,52].

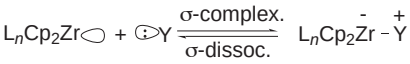
Second, π-complexation (**Pattern 3**) is best interpreted in terms of the Dewar–Chatt–Duncanson synergistic bonding model (Scheme 1.5). The π-compound and Cp_2Zr must provide two electrons each. This process is therefore not available to d^0 Cp_2Zr(IV) complexes. These d^0 Cp_2Zr(IV) complexes can nevertheless participate in similar synergistic interactions involving σ-bonds between Zr and H (**Pattern 5**) or C (**Pattern 7**) (Scheme 1.5). Since the parent d^2 Cp_2Zr(II) is not readily accessible, π-com-

Patterns **Comments**

I. Interactions with *n*-Donors

Patterns 1 and 2 (σ-Complexation and σ-Dissociation)

Intermolecular



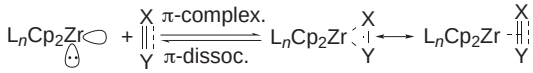
Ex. $Cp_2ZrCl_2 \xrightarrow{Na\text{-}Hg}$ "Cp_2Zr" $\xrightarrow{2\ PMe_3}$ $Cp_2Zr(PMe_3)_2$

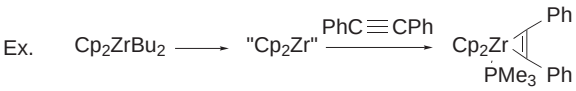
1. σ-interaction with *n*-donors
2. non-redox process
3. generation of Zr^- (ate complexation)
4. σ-dissociation generally unfavorable
5. similar intramolecular processes possible

II. Interactions with π-Bonds

Patterns 3 and 4 (π-Complexation and π-Dissociation)

Intermolecular

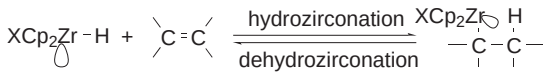


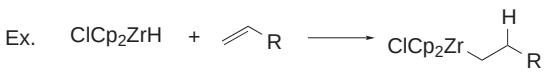


1. not an option for d^0 complexes
2. π-dissociation generally unfavorable
3. similar intramolecular processes possible

Patterns 5 and 6 (Hydrozirconation and Dehydrozirconation)

Intermolecular

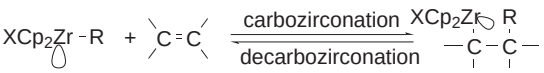




1. both processes kinetically favorable
2. similar intramolecular processes possible
3. similar reactions of alkynes as well as heteroatom-containing X=Y and X≡Y possible

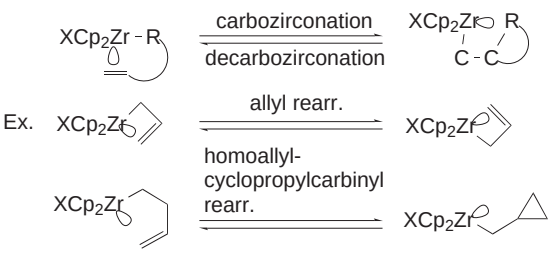
Patterns 7 and 8 (Carbozirconation and Decarbozirconation)

Intermolecular



Ex.

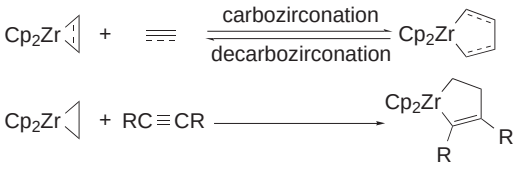
Intramolecular



1. carbozirconation generally more favorable than decarbozirconation
2. either bimetallic activation or "strained" zirconacycles generally needed (*cf*. Patterns 7' and 8')
3. allyl rearr. and homoallyl-cyclopropylcarbinyl rearr. ....examples of intramolecular carbozirconation
4. similar reactions of alkynes as well as heteroatom-containing X=Y and X≡Y possible

Scheme 1.3. Basic patterns of interaction of the empty orbital of Cp_2Zr derivatives with various electron donors.

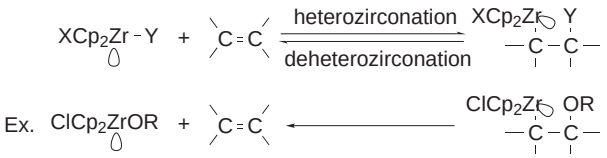
Patterns 7' and 8'



1. both forward and reverse processes favorable
2. corresponding processes with $Cp_2Zr{=}CR_2$ possible but few known examples
3. similar reactions of heteroatom-containing X=Y and X≡Y possible

Patterns 9 and 10 (Heterozirconation and Deheterozirconation)

Intermolecular

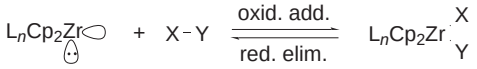


1. with electronegative groups, forward process unfavorable and reverse process favorable
2. metallozirconation possible, but few known examples
3. similar reactions of alkynes as well as heteroatom-containing X=Y and X≡Y possible

III. Interactions with σ-Bonds

Patterns 11 and 12 (Oxidative Addition and Reductive Elimination)

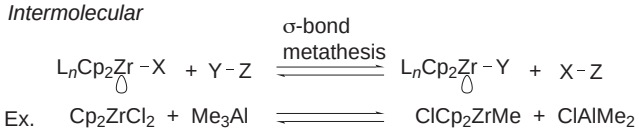
Intermolecular



1. oxid. add. not an option for d^0 complexes
2. few authentic examples of intermolecular processes

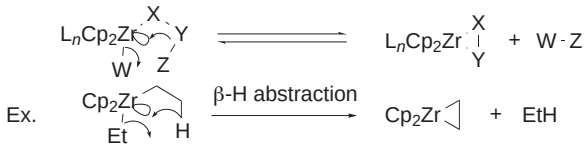
Patterns 13 (σ-Bond Metathesis Including Transmetallation)

Intermolecular



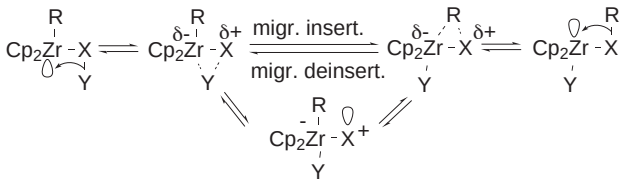
1. both directions can be favorable
2. transmetallation if Y or Z is a metal

Intramolecular



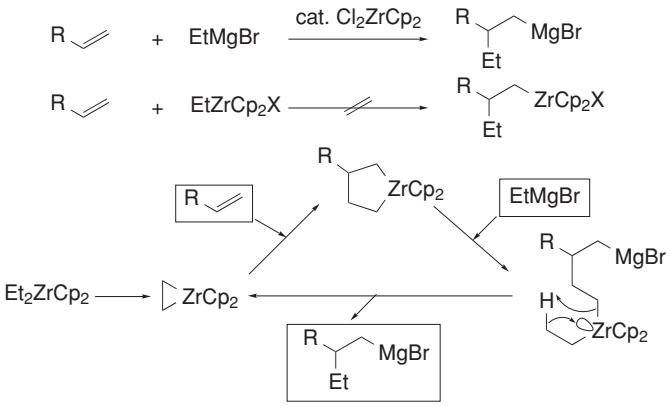
Patterns 14 and 15 (Migratory Insertion and Migratory Deinsertion)

Intramolecular

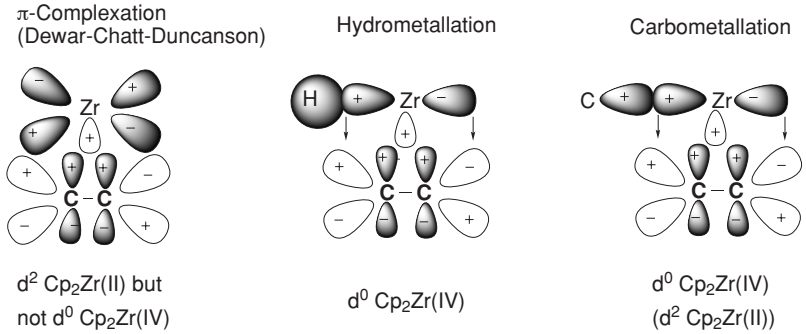


1. Intramolecular process only
2. preceded by complexation
3. X=Y and X≡Y can react similarly

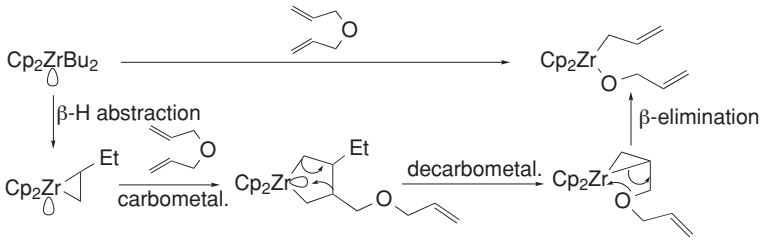
Scheme 1.3. (continued)



Scheme 1.4. Mechanism of the Zr-catalyzed ethylmagnesation of alkenes.



Scheme 1.5. Frontier orbital interactions in π-complexation, hydrometallation, and carbometallation.



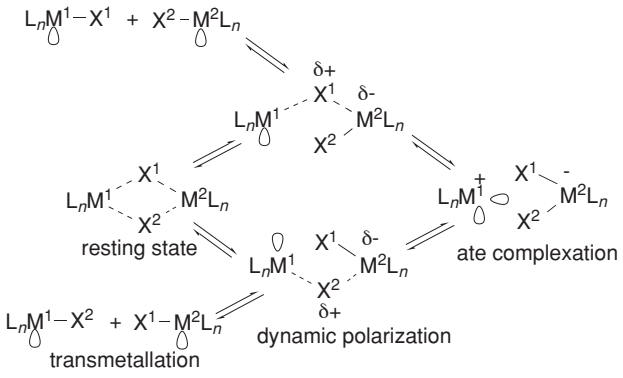
Scheme 1.6. Four-step mechanism for oxidative addition of allyl ethers to Cp_2Zr complexes.

plexation represented by **Pattern 3** is not readily observable, and the formation of π-complexes of zirconocene must be more involved than shown in **Pattern 3** [53].

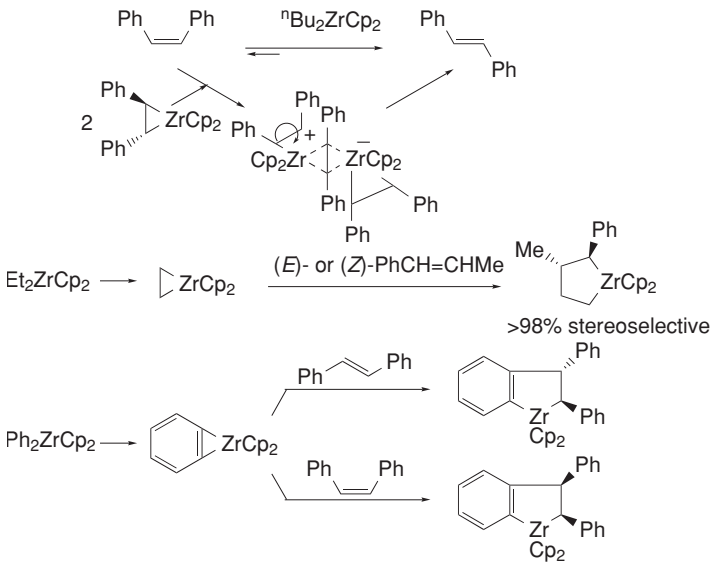
Third, in analogy with the discussion presented above, oxidative addition represented by **Pattern 11** may not be readily observable, and oxidative addition must also proceed mostly through more complex processes, such as that shown in Scheme 1.6 [31]. More readily observable are various types of σ-bond metathesis reactions of d^0 $Cp_2Zr(IV)$ species (**Pattern 13**).

Fourth, interactions between two coordinatively unsaturated metal compounds, including 16- and 14-electron transition metal complexes as well as 6-electron main group metal compounds, deserve special comments. They display a strong tendency to produce both homo- and cross-dimers and oligomers through two three-center bonds in an effort to generate coordinatively saturated stable species. There are some synthetically interesting consequences of such interactions, three of which are shown in Scheme 1.7 [54]. If ligand exchange through σ-bond metathesis (**Pattern 13**) leads to a thermodynamically more favorable pair, then the formation of these will be observed (transmetallation). If, on the other hand, one metal is significantly more electronegative than the other, ate complexation may result. More dynamic interactions (dynamic polarization), in which one or more three-center bonds are formed and cleaved, are also interesting. In a singly-bridged form, one metal center is more Lewis acidic or electrophilic than in its original form, while the other is more Lewis basic or nucleophilic than in its original form. This has provided an intricate but very significant mode of activation of the C−Zr bond, and *intermolecular acyclic carbozirconation appears to require this bimetallic activation* [55−58] (**Generalization 6**). As is clear from Scheme 1.7, ate complexation represents the extreme form of polarization and activation mentioned above. If M^1L_n corresponds to $ZrCp_2R$, the $^+M^1L_n$ moiety in the ate complex in Scheme 1.7 would be a 14-electron d^0 $^+ZrCp_2R$ species. This has indeed been proposed as an active species in alkene polymerization [59] and in some reactions with carbon electrophiles, such as aldehydes [60,61] and epoxides [62−64]. However, it appears likely that these species largely exist as further loosely ligated 16-electron $ZrCp_2$ derivatives.

Fifth, the polarization discussed above provides an entry into non-concerted polar reactions of zirconocene derivatives. One of the early examples of non-concerted polar organozirconium reactions was provided by a Cp_2Zr-catalyzed stilbene stereoisomerization [28]. A later study revealed a stereoselective but non-stereospecific formation of zirconacycles [65], which was in sharp contrast with a closely related but strictly stereospecific cyclization [49] (Scheme 1.8). The non-stereospecific processes were shown to involve dipolar zirconate species [65]. *While the majority of the currently known reactions of $ZrCp_2$ derivatives appear to be concerted, one should nevertheless be aware of these non-concerted ionic processes involving either $^+ZrCp_2$ or $ZrCp_2$ species* (**Generalization 7**). The radical and photochemical reaction of organylzirconocene derivatives is still very much underdeveloped at present.



Scheme 1.7. Chemical consequences of interactions between two coordinatively unsaturated metal complexes.



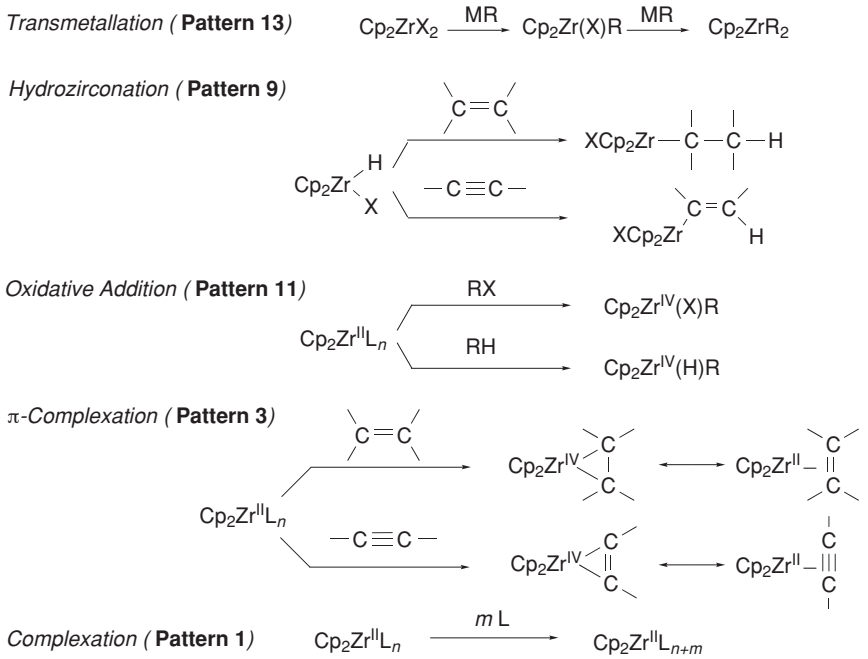
Scheme 1.8. Polar stepwise *vs.* concerted interactions of Cp_2Zr complexes with π-bonds.

1.3
Synthesis of Organic Derivatives of $ZrCp_2$

In this section, attention is mainly focused on the conversion of $ZrCp_2$ derivatives without any additional carbon substituents into those containing one or more carbon substituents besides Cp. Carbozirconation (**Pattern 7**), for example, is viewed as an organozirconium interconversion reaction and is discussed later. In cases where the originally present carbon groups mainly serve as ligands to be displaced, however, the transformations are discussed here. Of the 15 **Patterns** shown in Scheme 1.3, σ-complexation (**Pattern 1**), π-complexation (**Pattern 3**), hydrozirconation (**Pattern 5**), oxidative addition (**Pattern 11**), transmetallation and other σ-bond metathesis reactions (**Pattern 13**) are available and have been used for the synthesis of organic derivatives of $ZrCp_2$ (Scheme 1.9). It is clear from Scheme 1.3 that their reverse processes can provide routes for the decomposition of organic derivatives of $ZrCp_2$. In principle, heterozirconation (**Pattern 9**) can also generate organic derivatives of $ZrCp_2$, but few examples are known and so it is omitted here. It should nonetheless be kept in mind that its reversal (**Pattern 10**) is readily observable and is useful as a method of decomposition.

1.3.1
Transmetallation

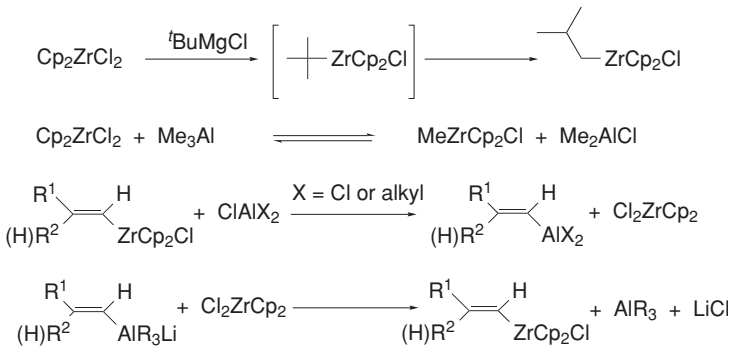
Transmetallation represents the most widely applicable method for the preparation of $ZrCp_2$ derivatives. In view of the relatively low electronegativity (EN hereafter) of Zr (EN 1.2–1.4), however, transmetallation as shown in Scheme 1.9 may be expected to be favorable only with organometals containing highly electropositive metals, such as Li (EN 1.0) and Mg (EN 1.20). Indeed, facile and complete dialkylation of Cp_2ZrCl_2 may be readily observed with these metals. With organolithiums, however, the reaction



Scheme 1.9. Several fundamental patterns for the formation of C–Zr bonds.

can proceed past dialkylation to produce trialkylated derivative, which may be accompanied by the replacement of one Cp group [66]. With some sterically hindered Grignard reagents, clean monoalkylation is possible, as in the synthesis of *i*BuZrCp$_2$Cl in 94–95 % yield [67,68] (Scheme 1.10).

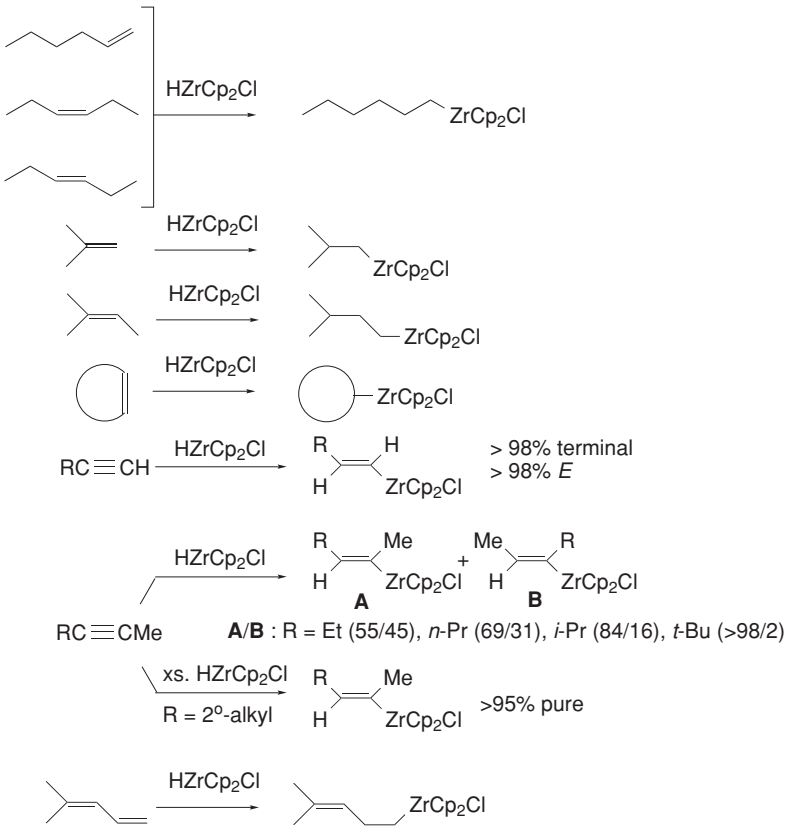
With Al (EN 1.5), only monoalkylation of Cp$_2$ZrCl$_2$, which may be complete or partial, has been observed [55,56]. No dialkylation of Cp$_2$ZrCl$_2$ has been observed. Depending on the ligands and other reaction conditions, one carbon group can be transferred either from Zr to Al or from Al to Zr [69] (Scheme 1.10).



Scheme 1.10. Some examples of the synthesis of monoorganylzirconocene chlorides by transmetallation.

1.3.2
Hydrozirconation

Hydrozirconation converts alkenes and alkynes into alkyl- and alkenylzirconium derivatives, respectively [6–9]. The most widely used reagent is $HZrCp_2Cl$, which can be prepared by the treatment of Cp_2ZrCl_2 with various aluminum hydrides, such as $LiAlH_4$ [4], $LiAlH(OtBu)_3$ [4], and $NaAlH_2(OCH_2CH_2OCH_3)_2$ [18], as well as by the treatment of iBuZrCp$_2$Cl with aluminum chlorides followed by trapping of the Al-containing by-product [70]. The low solubility of $HZrCp_2Cl$ in common organic solvents provides a simple, if tedious, means of its purification by filtration under an inert atmosphere. In less demanding cases, in situ generation of $HZrCp_2Cl$ and its equivalents by the treatment of Cp_2ZrCl_2 with $LiAlH_4$ [71,72], $NaAlH_2(OCH_2CH_2OCH_3)_2$ [71], $LiBEt_3H$ [71,73], and tBuMgCl [67,68,71] provides convenient alternatives. However, these alternative procedures may be associated with various difficulties, and solutions to some of these difficulties have also been provided. Among such attempts are conversion of Cp_2ZrH_2 formed as an unwanted by-product into $HZrCp_2Cl$ by washing with CH_2Cl_2 [72] and promotion of the H-transfer hydrozirconation with iBuZrCp$_2$Cl with various metal compounds [68]. Despite these efforts, further refinements of the alternative procedures are desirable.



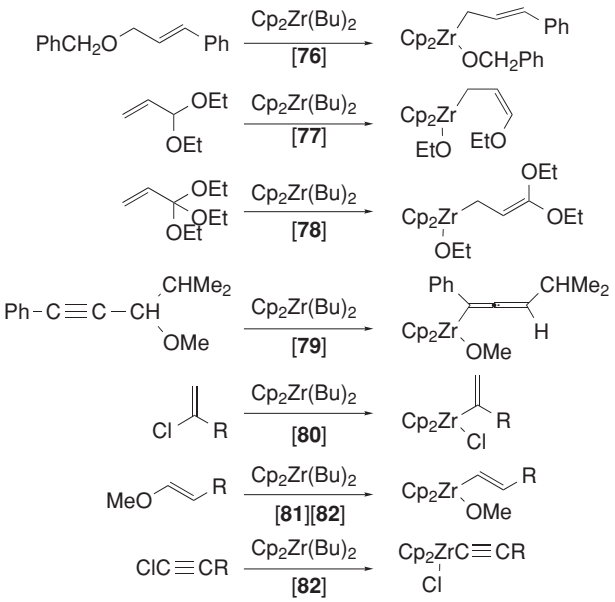
Scheme 1.11. Synthesis of monoorganylzirconocene chlorides by hydrozirconation.

Hydrozirconation with $HZrCp_2Cl$ is thought to involve a concerted four-center process, as shown in Scheme 1.5. It involves a clean *syn* addition, placing Zr at the least substituted carbon atom. This may involve migration of Zr along an alkyl chain (Scheme 1.11). Migration of Zr in alkenylzirconocene chlorides is confined to the two-carbon alkenyl moiety [7]. The use of an excess of $HZrCp_2Cl$ permits generation of >95 % regioisomerically pure (*E*)-2-alkenylzirconocene chlorides [74] (Scheme 1.11).

Monosubstituted alkenes and certain alkynes can undergo hydroalumination with iBu_3Al in the presence of a catalytic amount of Cp_2ZrCl_2, providing a convenient alternative to hydrozirconation [75].

1.3.3 Oxidative Addition

Oxidative addition and reductive elimination in the manner observed with late transition metals, such as Ni and Pd (**Patterns 11** and **12**), have rarely been observed with Zr, even though some such claims may have been made (*cf.* **Generalization 7**). In the first place, generation of genuine 14-electron $Cp_2Zr(II)$ has rarely been clearly established. Even if it were to be generated as a transient species, it is not clear whether it would be capable of undergoing intermolecular oxidative addition in preference to intramolecular C–H activation and other possible side reactions. It is much more likely that effective "oxidative addition" occurs through some indirect processes involving 16-electron species. One of the earliest examples, if not the earliest, of such indirect oxidative addition equivalents is shown in Scheme 1.6 [30]. The reaction has since been developed into a preferred method for the preparation of allyl- [76–78], allenyl- [79], alkenyl- [80–82], and alkynylzirconocene [82] derivatives (Scheme 1.12). As discussed above, these reactions may not qualify as genuine oxidative addition processes. However, conversion of organic halides

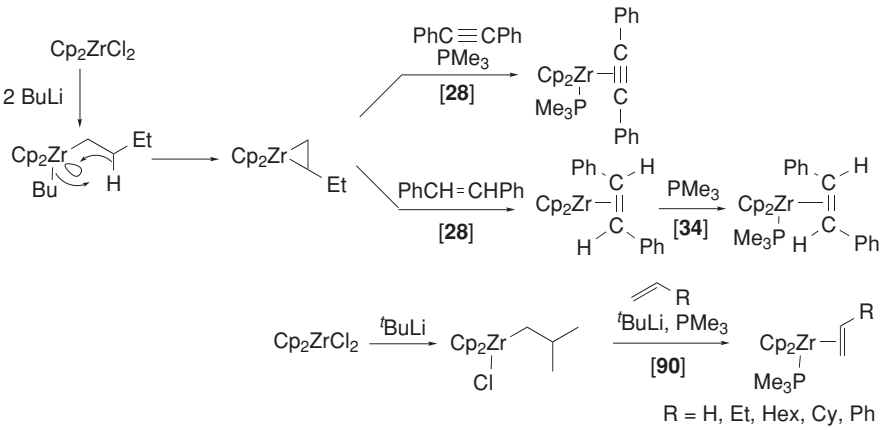


Scheme 1.12. Synthesis of monoorganylzirconocene derivatives by oxidative addition.

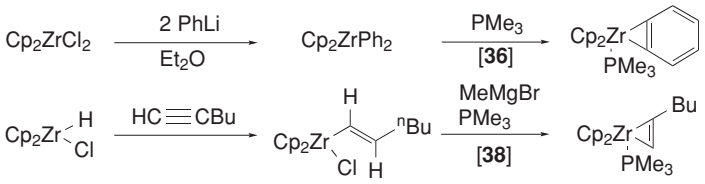
and related electrophiles into the corresponding organozirconium derivatives must involve two-electron reduction of the organic electrophiles. In this sense, the use of this term appears to be appropriate.

1.3.4
π-Complexation (Oxidative π-Complexation)

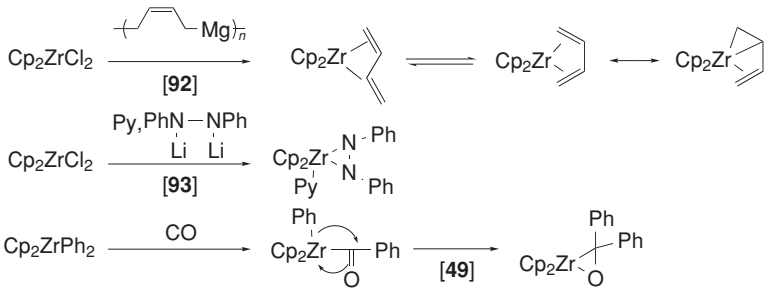
π-Complexation (**Pattern 3**) may also be termed oxidative complexation. If the products are viewed as zirconacyclopropanes, the latter is particularly appropriate. In the conversion of alkenes into the corresponding zirconacyclopropanes, the alkenes must undergo two-electron reduction, and Zr must consequently undergo two-electron oxidation. The required $Cp_2Zr(II)$ species were initially generated by reducing Cp_2ZrCl_2 and related $Cp_2Zr(IV)$ derivatives with Na/naphthalene [83], Mg/$HgCl_2$ [84], and Na/Hg [85]. However, in situ treatment of Cp_2ZrCl_2 with two equivalents of *n*BuLi was shown to generate (1-butene)$ZrCp_2$, which effectively served as a "Cp_2Zr" equivalent [24,29]. This reagent has been widely used for a variety of purposes, including the oxidative addition reactions shown in Schemes 1.6 and 1.12, and has often been called the Negishi reagent. Together with a few other related derivatives, including $Cp_2Zr(CO)_2$ [84] and $Cp_2Zr(i\text{Bu})(t\text{Bu})$ [86], the reagent has provided a very convenient method (Negishi–Takahashi protocol) for the generation of "Cp_2Zr" equivalents as well as zirconacycles and other zirconocene derivatives that can be derived from them [87–89]. *Conversion of dialkylzirconocenes into the corresponding zirconacyclopropanes has been shown to be a non-dissociative concerted process* [53,90]. *Consequently, free Cp_2Zr is not generated at any time* (**Generalization 8**). Another potentially useful "Cp_2Zr" equivalent is $(Me_3SiC{\equiv}CSiMe_3)ZrCp_2$ [91], which has been shown to be superior to (1-butene)$ZrCp_2$ in some cases.



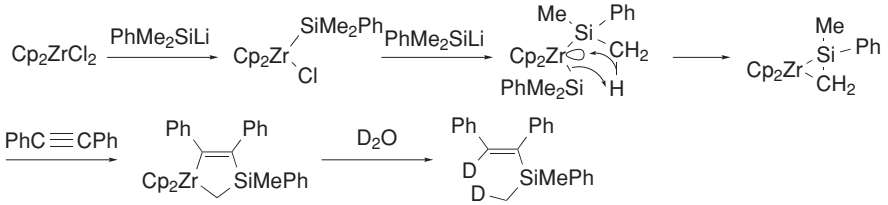
Scheme 1.13. Synthesis of alkene- and alkyne-$ZrCp_2$ complexes by β-H abstraction of dialkylzirconocenes in the presence of π-compounds (Negishi–Takahashi protocol).



Scheme 1.14. Alkyne- and Benzyne-$ZrCp_2$ complexes by β-H abstraction of diorganylzirconocenes in the absence of π-compounds (Erker–Buchwald protocol).



Scheme 1.15. Synthesis of other three-membered zirconacycles.



Scheme 1.16. Synthesis of zirconasilacycles by β-H abstraction.

Another major protocol for the generation of three-membered zirconacycles was initially devised by Erker [47–49] and was extensively developed by Buchwald [36–44] (Erker–Buchwald protocol) (Scheme 1.14). No alkenes or alkynes are used as temporary ligands in this protocol. Unless hydrozirconation is used to generate the initial organylzirconocene derivatives, even final alkene or alkyne ligands are not usually derived from the corresponding π-compounds. Thus, the synthetic values of the two representative protocols are quite different and often complementary to each other.

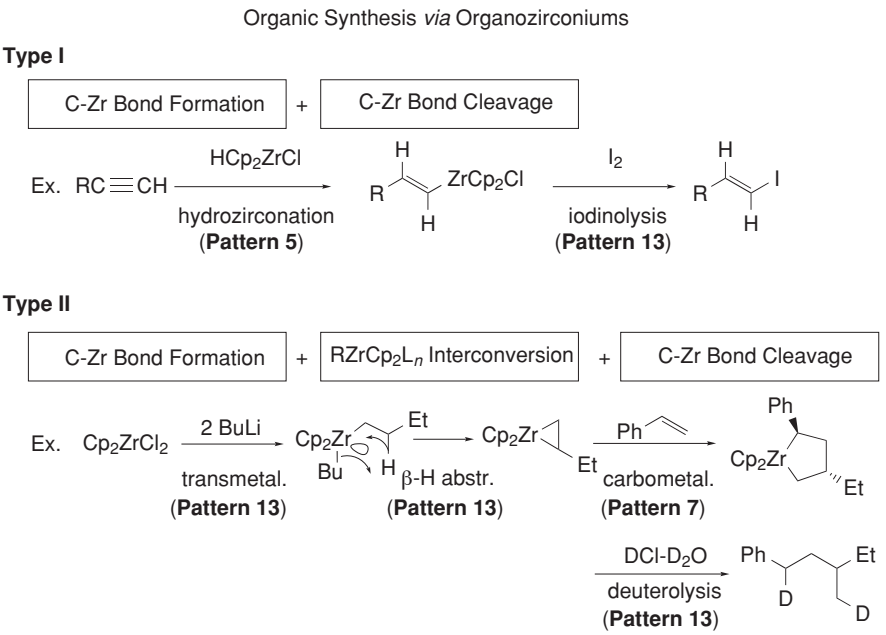
In addition to the methods discussed above, transmetallation and migratory insertion also provide useful routes to three-membered zirconacycles (Scheme 1.15).

One interesting recent addition is a silene–zirconocene complex proposed in the reaction shown in Scheme 1.16 [94].

Although 16-electron three-membered zirconacycles are generally unsuitable for X-ray analysis, their complexes with phosphines, such as PMe_3, or some ethers, such as THF, have often yielded crystalline compounds suitable for X-ray analysis. Thus, their existence and identity have been firmly established.

1.4
Reactivity of Organylzirconocene Compounds

In the preceding section, several synthetically important methods for the formation of C−Zr bonds that can be used for the preparation of organylzirconocene compounds were discussed. Since essentially all organic compounds are Zr-free, Zr must now be removed in a productive manner through C−Zr bond cleavage in order to complete organic synthesis with organylzirconocene compounds. Thus, C−Zr bond formation and C−Zr bond cleavage are two minimally required components in the use of organozirconium compounds in organic synthesis. Conversion of 1-alkynes into the corresponding (*E*)-l-iodo-l-alkenes by hydrozirconation and iodinolysis is a typical and synthetically useful example of such two-component processes. More often than not, some organozirconium interconversion processes are inserted between the formation and cleavage of the C−Zr bonds. Of the various elementary processes shown in Scheme 1.3, carbozirconation (**Pattern 7**) and decarbozirconation (**Pattern 8**) invariably involve interconversion of organozirconium compounds. σ-Bond metathesis or transmetallation (**Pattern 13**) would be an interconversion process if X and Y are carbon groups, and migratory insertion (**Pattern 14**) and migratory deinsertion (**Pattern 15**) would also be interconversion processes in cases where X is C. It should be noted that any of the other transformations in Scheme 1.3 may also participate in organozirconium interconversion processes by virtue of one or more carbon groups being bonded to Zr besides Cp. For example, hydrozirconation of an alkene with $HZrCp_2Me$ may be viewed as an organozirconium interconversion process. *It is various different combinations and permutations of a relatively limited number of different types of elementary processes shown in Scheme 1.3 that give rise to a large number of organozirconium reactions of synthetic use, but they all can be classified into the following two types (Scheme 1.17)* (**Generalization 9**).



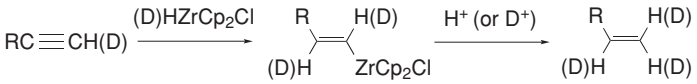
Scheme 1.17. Two types of organic synthesis by organozirconium derivatives.

1.4.1 Formation of Carbon–Hydrogen and Carbon–Heteroatom Bonds

The Zr atom of the C–Zr bond has been replaced with H, D, and several non-metallic heteroatoms, such as Cl, Br, I, and O. Although some reactions of $RZrCp_2Cl$, where R is an alkyl or alkenyl group, with SO_2 and NO [95,96] are known, very little is known beyond them about the formation of C–S, C–N, C–P, and other C–heteroatom bonds containing Group 15 and 16 atoms.

1.4.1.1 Protonolysis and deuterolysis

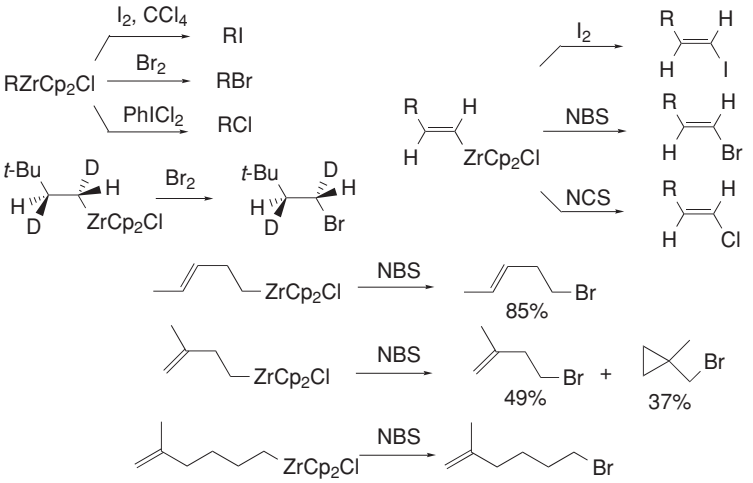
Cleavage of Zr–C σ bonds occurs readily on treatment with H_2O or dilute acids, while the Zr–Cp bond usually survives mild protonolysis conditions. The use of D_2O or DCl/D_2O permits the replacement of Zr with D. Deuterolysis provides a generally reliable method for establishing the presence of Zr–C bonds. Protonolysis or deuterolysis of $Zr-C_{sp^2}$ bonds proceeds with retention of configuration [97]. In the hydrozirconation of terminal alkynes, deuterium can be introduced at any of the three positions in the vinyl group in a completely regio- and stereoselective manner, as shown in Scheme 1.18. Although relatively little is known about the mechanistic details, the experimental results appear to be consistent with concerted σ-bond metathesis (**Pattern 13**) between C–Zr and H–X bonds.



Scheme 1.18. Synthesis of non-deuterated, partially deuterated, and fully deuterated vinyl derivatives *via* hydrozirconation of terminal alkynes.

1.4.1.2 Halogenolysis

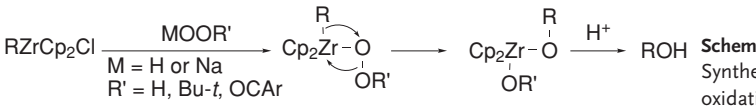
Cleavage of alkyl–Zr bonds has been achieved with I_2, Br_2, and $PhICl_2$ to produce the corresponding alkyl iodides, bromides, and chlorides, respectively [6–9]. In cases where alkenyl groups are present, NBS and NCS are preferred reagents for brominolysis and chlorinolysis, respectively. Iodinolysis and brominolysis of both $Zr-C_{sp^3}$ and $Zr-C_{sp^2}$ bonds have been found to proceed with retention of configuration. Halogenolysis of some homoallyl derivatives is hampered by skeletal rearrangement [6–9]. These results are summarized in Scheme 1.19. These reactions can also proceed by concerted σ-bond metathesis (**Pattern 13**).



Scheme 1.19. Synthesis of alkyl and alkenyl halides *via* halogenolysis.

1.4.1.3 **Oxidation**

Alkylzirconocene derivatives can be converted to alcohols with H_2O_2/NaOH, *t*BuOOH, or *m*-chloroperbenzoic acid (*m*-CPBA) [98]. These reactions appear to involve migratory insertion processes (**Pattern 14**) similar to those observed with organoboranes (Scheme 1.20). On the other hand, oxidation with O_2 may be a radical process.



Scheme 1.20. Synthesis of alcohols by oxidation of $RZrCp_2Cl$.

1.4.2
Formation of Carbon–Metal Bonds by Transmetallation

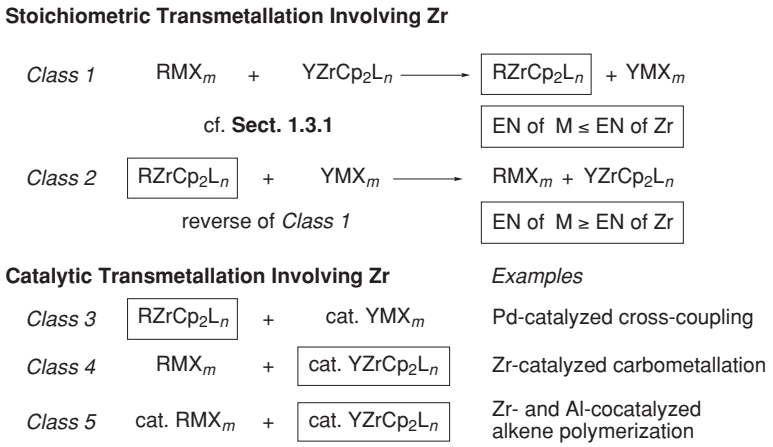
Stoichiometric transmetallation of organolithiums and Grignard reagents with halozirconium compounds, as discussed in Section 1.3.1, laid the foundation of organozirconium chemistry. In addition, transmetallation has also provided a powerful means of substantially expanding the scope, synthetic or otherwise, of organozirconium chemistry. Some of the earliest studies along these lines were carried out by Schwartz, which dealt with stoichiometric transmetallation reactions of $RZrCp_2Cl$ generated by hydrozirconation with halometal compounds containing relatively electronegative metals (**Class 2** in Scheme 1.21). Those metals that have been used in this reaction include Cu [14], Hg [99], B [100], Al [70,75], and Sn [101]. After discrete transmetallation, the newly formed organometals display their own reactivities, as exemplified by conjugate addition of organocoppers (Section 1.4.3.1.2) and acylation of organoaluminums (Section 1.4.3.1.3).

More intricate and potentially more attractive are catalytic transmetallation processes involving Zr, which may be classified into three categories shown as **Classes 3–5** in Scheme 1.21. This area was mainly initiated and developed by Negishi in the 1970s. The initial discovery of the Ni-catalyzed cross-coupling [10] was soon followed by that of the Pd-cat-

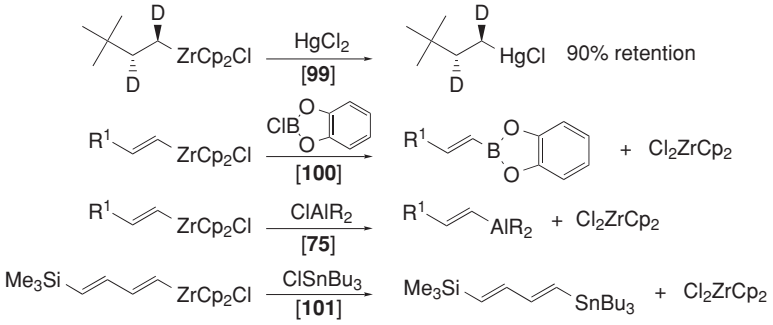
alyzed cross-coupling by Negishi himself [11] and of the Ni-catalyzed conjugate addition by Schwartz [14–17]. Another breakthrough was the discovery of the Zr-catalyzed carboalumination [13]. Interestingly, it has become increasingly clear, albeit only in recent years, that the essentially concurrent but independent chemistry of the Zr- and Al-cocatalyzed alkene polymerization of Kaminsky [19–21] and the Zr-catalyzed carboalumination share some key features.

Under catalytic conditions, discrete and complete transmetallation in one direction or other, i. e. M→Zr or Zr→M, is not a critical requirement. Thus, the thermodynamics of the transformation is relatively insignificant. Far more critical is the kinetics of the transformation (**Generalization 10**). This is particularly true in dynamic bimetallic systems (Scheme 1.7), where essentially thermoneutral transmetallation between C–Zr and other C–M bonds is involved. In such cases, the electronegativity (EN) of M is relatively insignificant, and metals of widely different electronegativities ranging from Mg (EN 1.2) or possibly even Li (EN 1.0) to B (EN 2.0) can participate in catalytic reactions with Zr, even though metals of intermediate electronegativity, such as Al (EN 1.5), appear to be of maximum synthetic utility.

A few examples of the discrete formation of organometals from organozirconiums (**Class 2**) are shown in Scheme 1.22, but many other examples of various classes of transformation are discussed throughout this chapter.



Scheme 1.21. Stoichiometric and catalytic transmetallation involving Zr.



Scheme 1.22. Conversion of organylzirconocene chlorides into organometals containing electropositive metals *via* transmetallation.

1.4.3 Formation of Carbon–Carbon Bonds

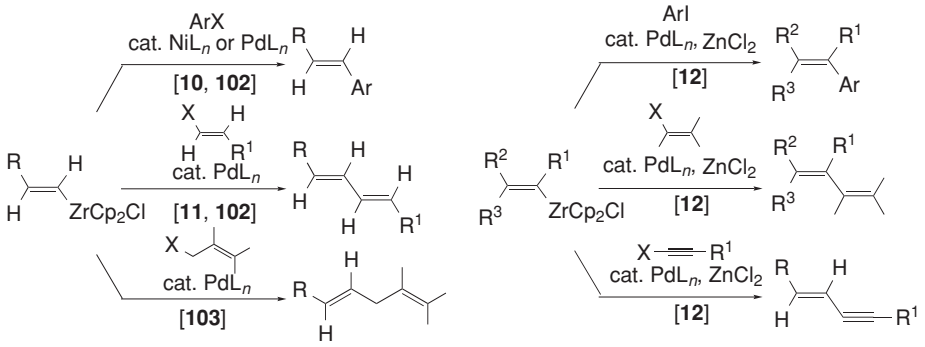
Of the 15 ***Patterns*** *of transformation of organylzirconocene derivatives shown in Scheme 1.3, only carbozirconation (**Pattern 7**), reductive elimination (**Pattern 12**), and migratory insertion (**Pattern 14**) can, in principle, permit C–C bond formation. Moreover, reductive elimination of d^0 diorganylzirconocene derivatives is neither well-documented nor promising. Thus, chemists are currently left only with carbozirconation and migratory insertion of organylzirconocene derivatives as tools for C–C bond formation* (**Generalization 11**). This, of course, is a stiflingly severe restriction, which must nevertheless be dealt with by synthetic chemists. On the one hand, each of these patterns must be duly respected and maximally utilized. On the other hand, other synthetic possibilities with Zr not involving these two patterns need to be explored. In reality, however, a search for new patterns permitting C–C bond formation may prove to be challenging and difficult, if not impossible. A much more realistic strategy has been to resort to transmetallation (**Pattern 13**), as discussed above, and this has very significantly expanded the scope of organozirconium chemistry in organic synthesis. Yet another strategy is to structurally modify organylzirconocene derivatives to generate more electrophilic, e. g. $R^+ZrCp_2^-X$, or more nucleophilic, e. g. $^+MR^-ZrCp_2L_n$, species. Use of the former has been quite successful in recent years. Although still very limited, radical, photochemical, and electrochemical reactions of organozirconium compounds may prove to be fruitful. The development of organozirconium chemistry not involving organylzirconocene derivatives would also be desirable.

Despite many limitations, the various alternative strategies mentioned above that do not involve either carbozirconation or migratory insertion of organozirconiums have made more conventional patterns of organometallic C–C bond formation, such as cross-coupling, carbonyl addition, and conjugate addition via organozirconium derivatives very useful, as discussed below. As the C–C bond-forming reactions must be the main subjects of most of the subsequent chapters, only a very brief discussion outlining their use is presented in this section, with a considerable bias towards the author's own contribution.

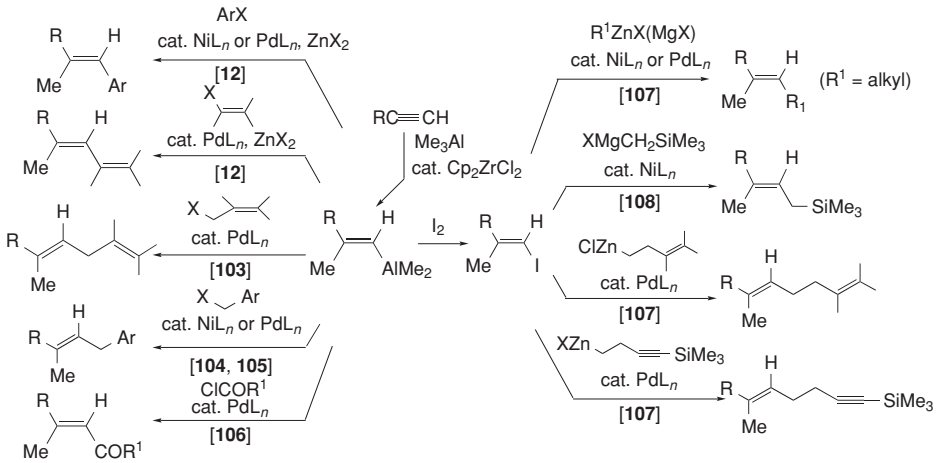
1.4.3.1 Polar carbon–carbon bond-forming reactions

1.4.3.1.1 Cross coupling

Monoorganylzirconocene derivatives, i. e. $RZrCp_2Cl$, rarely react with organic halides and related electrophiles in the manner of RLi or RMgX, although their reaction with acyl halides is an exception (**Generalization 12**). In this respect, the discovery and development of the Zr version of the Negishi coupling [10–12] in the 1970s was a significant turning point. Although catalysis with Ni is effective in many cases, Pd catalysts have been shown to be more widely applicable and often superior to Ni catalysts. Another significant finding, first reported in 1978 [12], is the Zn effect. Thus, the addition of a catalytic amount of a Zn salt significantly accelerates some of the otherwise sluggish Pd- or Ni-catalyzed cross-coupling reactions. Some of the seminal results are summarized in Scheme 1.23. Together with the Al and Zn versions of the Negishi coupling summarized in Scheme 1.24, these cross-coupling reactions have provided the most generally applicable and reliable method for the stereo-, regio-, and chemoselective synthesis



Scheme 1.23. Pd- or Ni-catalyzed cross-coupling reactions of alkenylzirconium derivatives by Zr-to-Pd (or Ni) transmetallation.

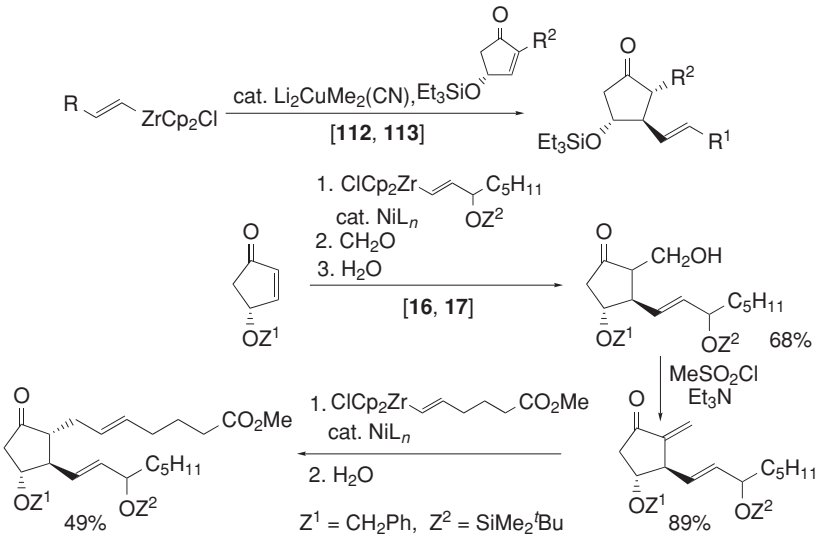


Scheme 1.24. Synthesis of alkenylalanes by Zr-catalyzed carboalumination of alkynes followed by Pd- or Ni-catalyzed cross–coupling.

of a wide variety of alkene-containing compounds. It should be noted that the alkenylalanes in Scheme 1.23 are usually generated by the Zr-catalyzed carboalumination of alkynes, as discussed in Section 1.4.3.3.2. For further details, the references cited in these schemes and reviews [109–111] may be consulted.

1.4.3.1.2 **Conjugate addition**

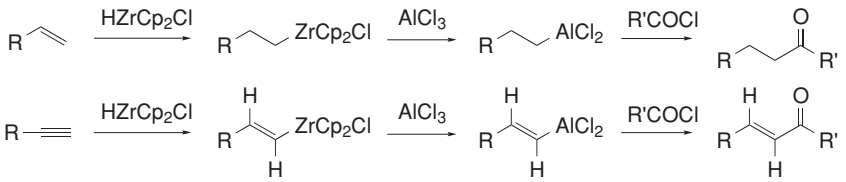
Organylzirconocene derivatives do not show any useful reactivity toward α,β-unsaturated carbonyl compounds, but the reaction can be promoted by the addition of CuOTf [14]. The initial version was stoichiometric in Cu [14], but a Cu-catalyzed version was subsequently developed [112,113]. Adaptation of the Ni salt + DIBAH catalysts for cross-coupling [10] to conjugate addition led to the Ni-catalyzed conjugate addition of alkenylzirconocene chlorides [16,17] (Scheme 1.25).



Scheme 1.25. Cu- or Ni-catalyzed conjugate addition reactions of alkenylzirconocene derivatives by Zr-to-Cu (or Ni) transmetallation.

1.4.3.1.3 **Acylation with acyl chlorides**

Alkylzirconocene derivatives react with CH_3COCl to give the corresponding ketones, but alkenylzirconocene derivatives fail to produce ketones [18]. Both alkyl- and alkenylzirconocene derivatives can be readily converted to the corresponding monoorganylaluminum dichlorides by transmetallation with $AlCl_3$, and the resultant organoalanes can react satisfactorily with acyl chlorides to give ketones [18].



Scheme 1.26. Acylation of organoalanes generated *in situ* by Zr-to-Al transmetallation.

1.4.3.1.4 **Carbonyl addition reactions**

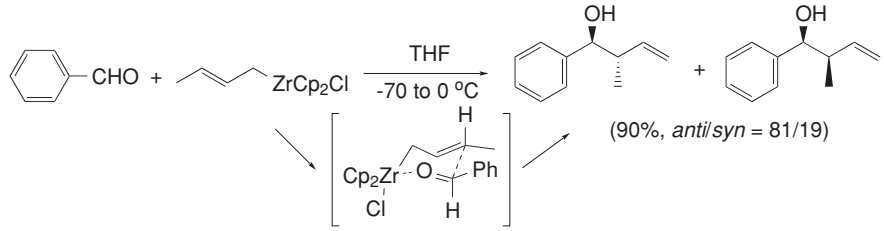
Although some organozirconium compounds, such as $MeZr(OBu)_3$ [114], are known to react with ketones, organylzirconocene derivatives are generally unsatisfactory nucleophiles in carbonyl addition reactions. There are, however, a few classes of organylzirconocene derivatives that react readily with aldehydes and ketones, including those containing (i) allyl and (ii) α-metalloalkenyl groups.

Allylzirconocene derivatives are reactive toward aldehydes, presumably because of the availability of six-centered transition states permitting an *anti*-selective synthesis of homoallyl alcohols (Scheme 1.27) [115].

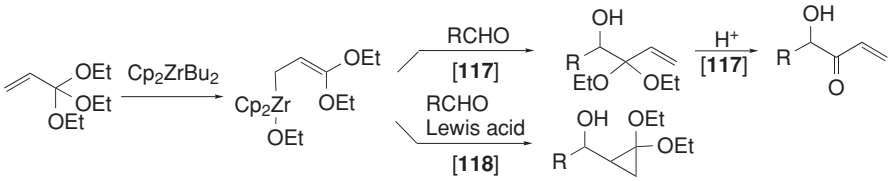
The development of a new route to allylzirconocene derivatives has prompted further investigations in this area [76–79]. Its elegant application to the synthesis of (−)-macronecine is noteworthy [116]. More recent investigations have led to an assortment of interesting transformations, as shown in Scheme 1.28 [117,118].

Closely related to the reaction of allylzirconocene derivatives with aldehydes are various carbonyl addition reactions of 1,3-dienezirconocene complexes [119], including additions to even ketones, esters, and nitriles (Scheme 1.29).

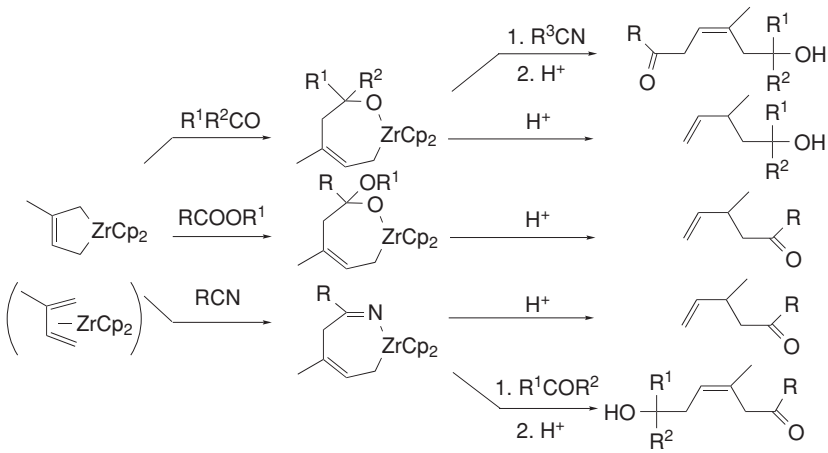
Another class of organylzirconocene derivatives capable of reacting with ketones are 1,1-dimetalloalkanes and -alkenes containing Zr and Al, as well as their Ti and Zn analogues [120,121] (Scheme 1.30). These serve as Zr- or Ti-carbene complex equivalents, but mechanistic details are not clear.



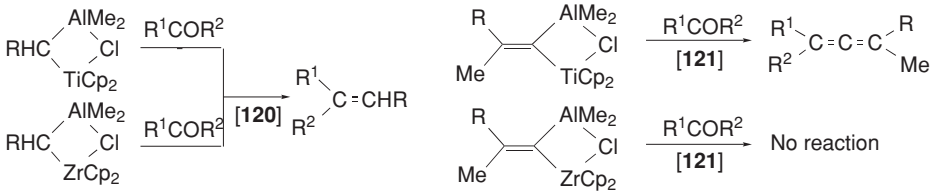
Scheme 1.27. Addition of allylzirconocene derivatives to aldehydes.



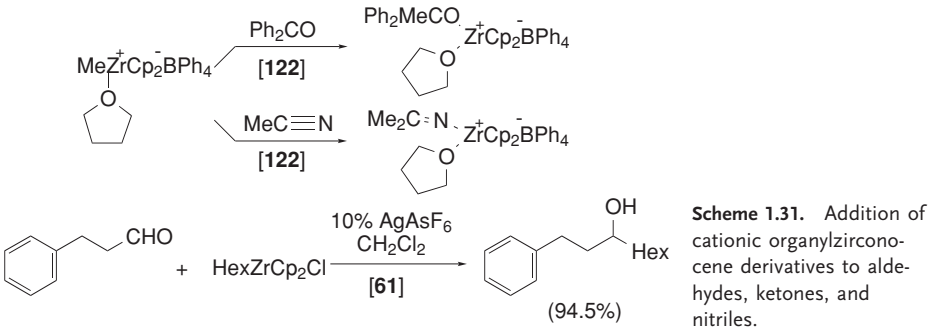
Scheme 1.28. Addition of γ,γ-bis(ethoxy)allylzirconocene derivatives to aldehydes.



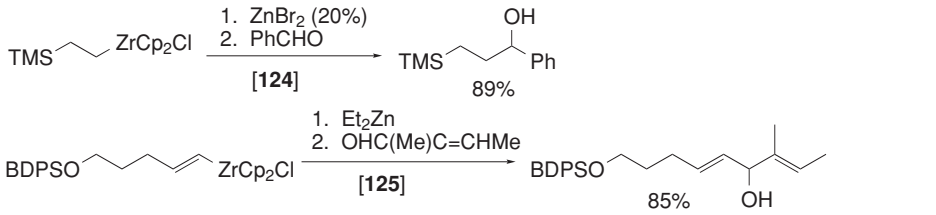
Scheme 1.29. Addition of 1,3-dienezirconocene complexes to carbonyl compounds and nitriles.



Scheme 1.30. Reactions of α-titana- or α-zirconaorganoalanes with carbonyl compounds.



Scheme 1.31. Addition of cationic organylzirconocene derivatives to aldehydes, ketones, and nitriles.



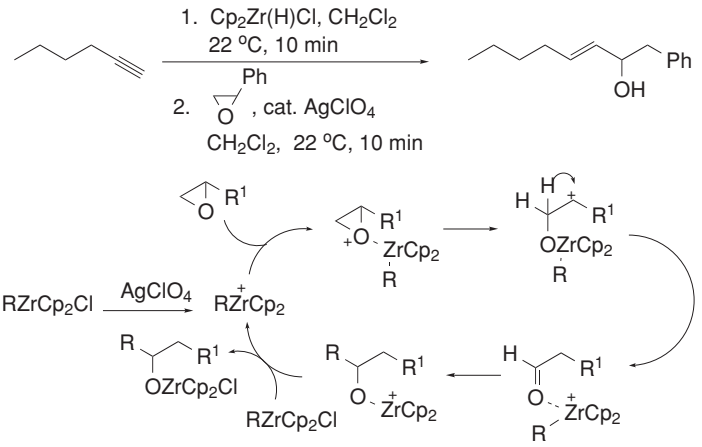
Scheme 1.32. Addition of organylzirconocene derivatives to aldehydes promoted or catalyzed by Zn compounds.

More recently, two promising methods for promoting carbonyl addition reactions of organylzirconocenes containing "ordinary" organic groups have been devised. One is to generate and use highly electrophilic $R^+ZrCp_2^-X$, presumably exploiting their high affinity towards the nucleophilic O end of the carbonyl group [60,61,122] (Scheme 1.31).

The other is to convert organylzirconocene derivatives to the corresponding zinc derivatives in situ and to carry out their addition to aldehydes [123–125] (Scheme 1.32).

1.4.3.1.5 Reactions with epoxides

Activation of C–Zr bonds as electrophiles with Ag salts has also been applied to the reaction with epoxides (Scheme 1.33) [62–64]. In fact, the reaction has been shown to involve isomerization of epoxides to aldehydes and is therefore very closely related to that shown in Scheme 1.31.

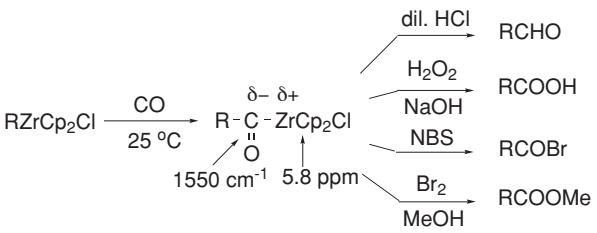


Scheme 1.33. Reaction of cationic organylzirconocene derivatives with epoxides and its mechanism.

1.4.3.2 **Carbonylation and other migratory insertion reactions**

Aside from two-center (**Patterns 1** and **2**) and three-center (**Patterns 3**, **4**, **11**, and **12**) processes, most of the processes shown in Scheme 1.3 are four-center processes involving either addition (**Patterns 5**–**10**) or σ-bond metathesis (**Pattern 13**). In this context, it should be noted that addition is simply a four-center metathesis in which one molecule happens to be multiply-bonded. In addition to these metathetical processes, there is yet another fundamentally important four-center metathetical process termed migratory insertion and deinsertion (**Patterns 14** and **15**). It should be clear from **Patterns 14** and **15** shown in Scheme 1.3 that distinction between insertion and deinsertion is only a relative and semantic issue. In the current discussion, a process involving cleavage of the C–Zr bond is termed migratory insertion, while the reverse process is termed migratory deinsertion.

The fundamental significance of migratory insertion as a process permitting C–C bond formation was discussed earlier. Despite its potential significance, however, the current scope of organozirconium migratory insertion chemistry is surprisingly limited. Nevertheless, the author is inclined to believe that the area is still in its infancy and that its growth potential is very high. At the time of publication of the first monograph on organozirconium chemistry [1] in 1974, the only migratory insertion of organylzirconocene derivatives was evidently that of Cp_2ZrMe_2 with CO to produce $Cp_2ZrMe(COMe)$, which was carried out by Wailes et al. but had remained unpublished. Following the discovery of the carbonylation of organozirconium compounds, a more systematic developmental study was carried out by Schwartz [97,126] in the mid-1970s (Scheme 1.34). It should be clearly noted

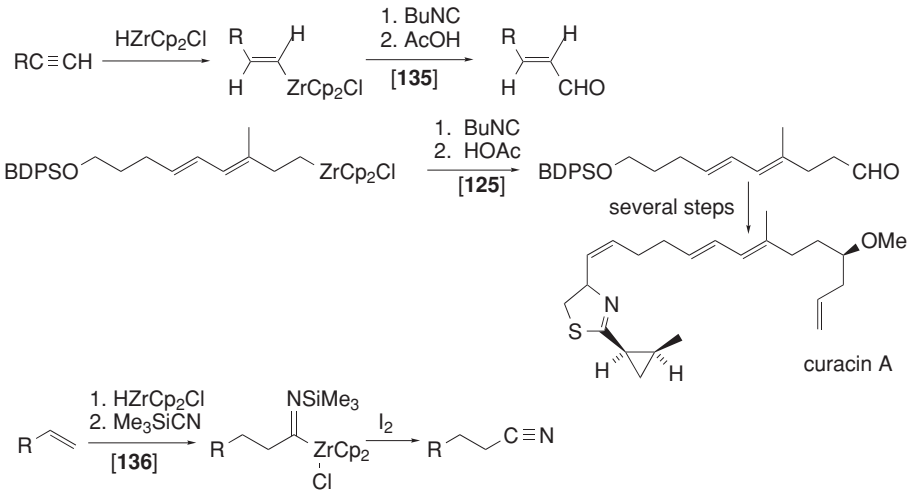


Scheme 1.34. Formation of acylzirconocene derivatives by carbonylation and their conversion into aldehydes, carboxylic acids, and derivatives thereof.

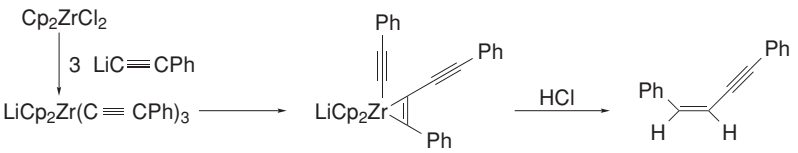
that *the acyl group generated by migratory insertion acts as an acyl anion equivalent, as indicated by the formation of aldehydes upon protonolysis. This is precisely opposite to the protonolysis of acylmetal derivatives containing Pd or other late transition metals, which gives carboxylic acid derivatives and metal hydrides* (**Generalization 13**). Detailed studies on the carbonylation of η^5-$(Me_5C_5)_2ZrH_2$ [127,128], Cp_2ZrMe_2 [129,130], and some zirconacycles [45,48] by Bercaw and Erker during the 1976–1980 period clarified many specific aspects of the reaction.

The synthetic utility of the carbonylation of zirconacycles was further enhanced by the development of a pair of selective procedures producing either ketones or alcohols [30] and has been extensively applied to the synthesis of cyclic ketones and alcohols, most extensively by Negishi [22–27,29–33,65,87,131–134], as detailed below in Section 1.4.3.3.4. The preparation of α,β-unsaturated aldehydes by carbonylation with CO is not very satisfactory. The use of isonitriles in place of CO, however, has provided a useful alternative [135], and this has been applied to the synthesis of curacin A [125]. Another interesting variation is the cyanation of alkenes [136]. Further developments and a critical comparison with carbonylation using CO will be necessary before the isonitrile reaction can become widely useful. The relevant results are shown in Scheme 1.35.

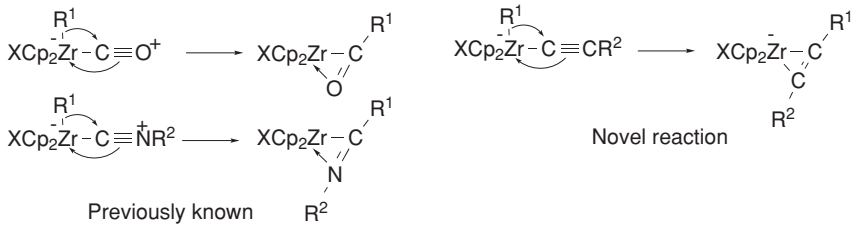
The recent discovery of the reaction shown in Scheme 1.36 [137] has nicely rounded off Scheme 1.37 by providing one previously missing equation. The structure of the zirconate product proposed to account for the observed results has recently been confirmed by X-ray analysis [138]. The synthetic utility of the reaction has been significantly enhanced by the



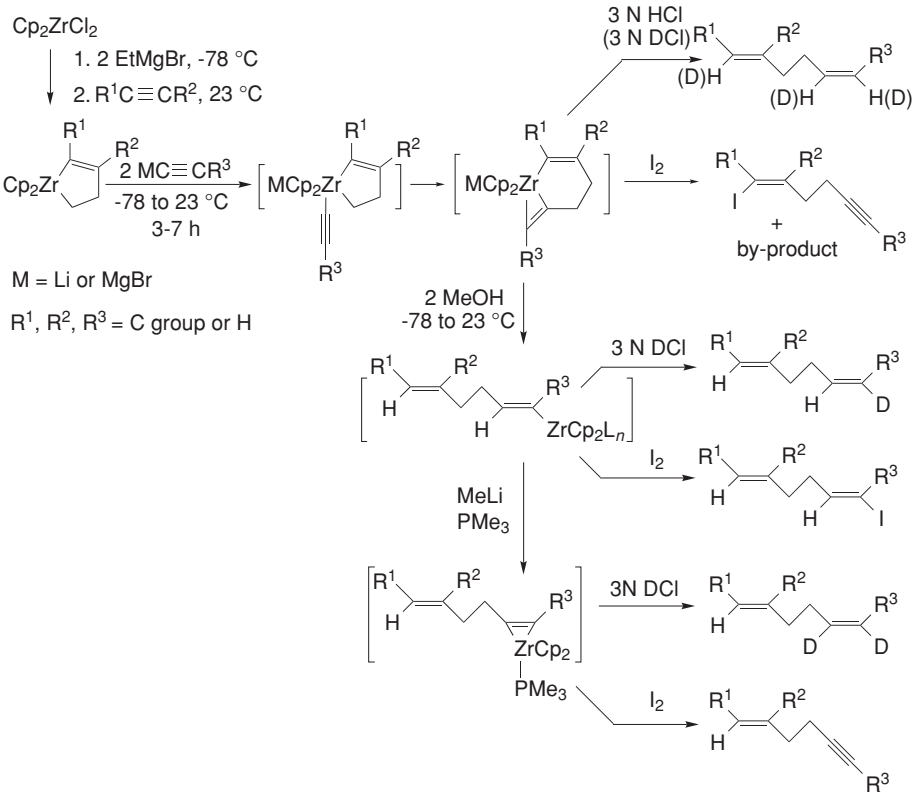
Scheme 1.35. Reactions of organylzirconocene derivatives with isonitriles to give aldehydes and nitriles.



Scheme 1.36. Formation of tris(alkynyl)zirconates and their migratory insertion reaction to give zirconacyclopropene-containing zirconates. Synthesis of *Z*-conjugated enynes.



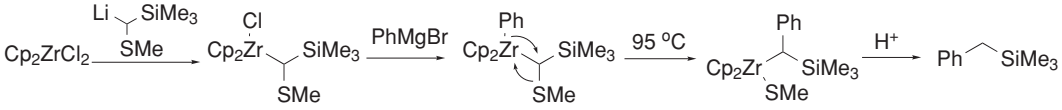
Scheme 1.37. Common patterns in the migratory insertion of zirconocene complexes with CO, isonitriles, and metal alkynylates.



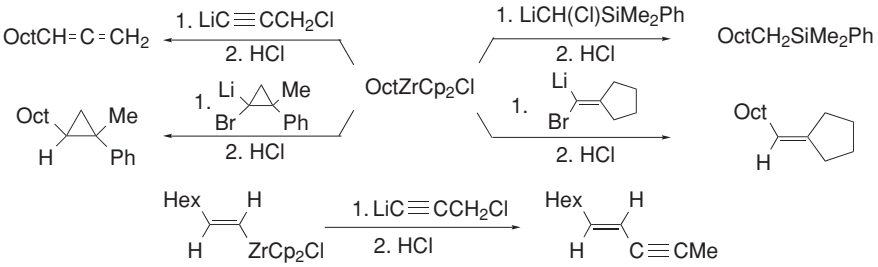
Scheme 1.38. Migratory insertion reaction of alkynylzirconacyclopentene derivatives.

reactions shown in Scheme 1.38, which can produce various 1,5-dienes and 1,5-enynes in a regio- and stereocontrolled manner [139].

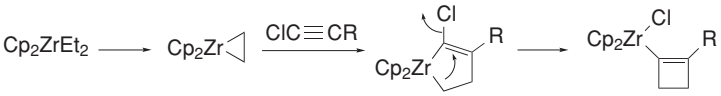
In view of the plethora of migratory insertion reactions that organoboranes undergo [140], it was of interest to see whether organozirconium compounds would also undergo similar migratory insertion reactions. Aside from the carbonylation reaction discussed above, there was just one such reaction of somewhat questionable synthetic potential as of 1985 [141] (Scheme 1.39). The use of α- and γ-haloorganolithiums led to several migratory insertion reactions of potential synthetic utility [142] (Scheme 1.40).



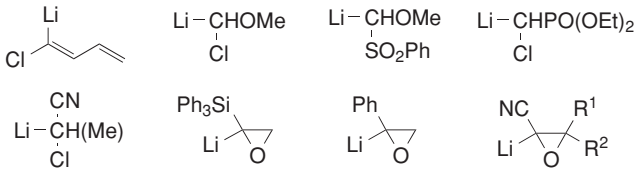
Scheme 1.39. Migratory insertion reaction of α-silyl-α-thiomethylzirconocene derivatives.



Scheme 1.40. Migratory insertion reactions of organylzirconocene derivatives with α- or γ-haloorganolithiums.



Scheme 1.41. Synthesis of cyclobutenylzirconocene derivatives by the reaction of zirconacyclopropane derivatives with 1-chloroalkynes.



Scheme 1.42. Additional examples of α-hetero-substituted organolithiums used in migratory insertion reactions of organylzirconocene derivatives.

The use of haloalkynes for generating α-haloorganylzirconocene derivatives provides an interesting variation [143] (Scheme 1.41). Many additional reagents containing α- and/or γ-halogens and related heteroatom groups may be used to devise related migratory insertion reactions, as indicated by the recent examples shown in Scheme 1.42 [144–148].

1.4.3.3 Carbozirconation and related carbometallation reactions

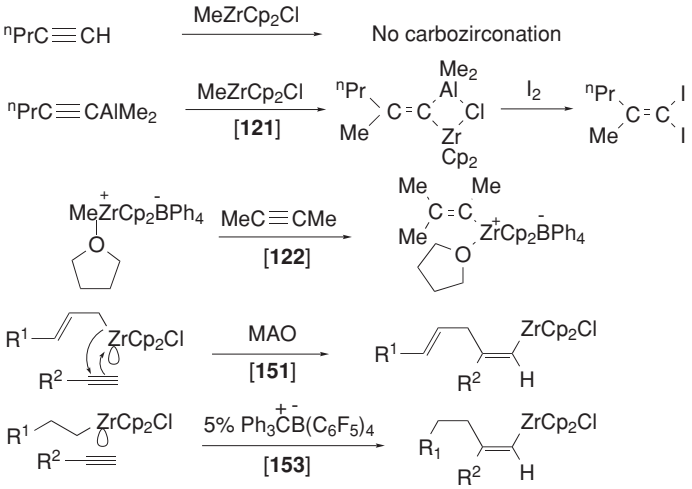
As genuine examples of reductive elimination of diorganylzirconocene derivatives in the manner of those of diorganylpalladiums and similar complexes containing late transition metals might be considered to be rare, among those **Patterns** shown in Scheme 1.3, carbozirconation (**Pattern 7**) and migratory insertion (**Pattern 14**) would represent those **Patterns** of concerted C–C bond formation in which C–Zr bonds participate directly. Moreover, the synthetic scope of migratory insertion of organozirconium compounds is still rather limited with the exception of that of carbonylation. The other protocols will have to be extensively further developed for widespread use among synthetic chemists. In con-

trast, various types of both stoichiometric and catalytic carbozirconation reactions have been extensively developed, and some, such as the Zr-catalyzed carboalumination, have already been accepted as standard synthetic methods.

It has recently been established that *carbozirconation with organylzirconocene derivatives evidently requires dipolar (and mostly bimetallic) activation and/or small-ring zirconacycles, especially three-membered ones, that can undergo cyclic carbozirconation* (**Generalization 6′**) [149]. One of the recent examples has been shown to involve both bimetallic and cyclic organozirconium species [150]. These reactions can be either stoichiometric or catalytic in Zr.

1.4.3.3.1 Stoichiometric acyclic carbozirconation

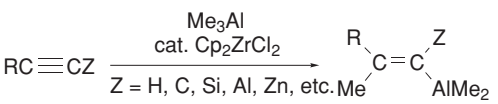
Virtually all known acyclic carbozirconation reactions involve activation through dynamic polarization or ate complexation as shown in Scheme 1.7. Some of the representative examples are shown in Scheme 1.43. The reaction of allylzirconocene derivatives [151] shares similar regiochemical features with the Zr-catalyzed allylalumination [22,152] and appears to be mechanistically closely related.



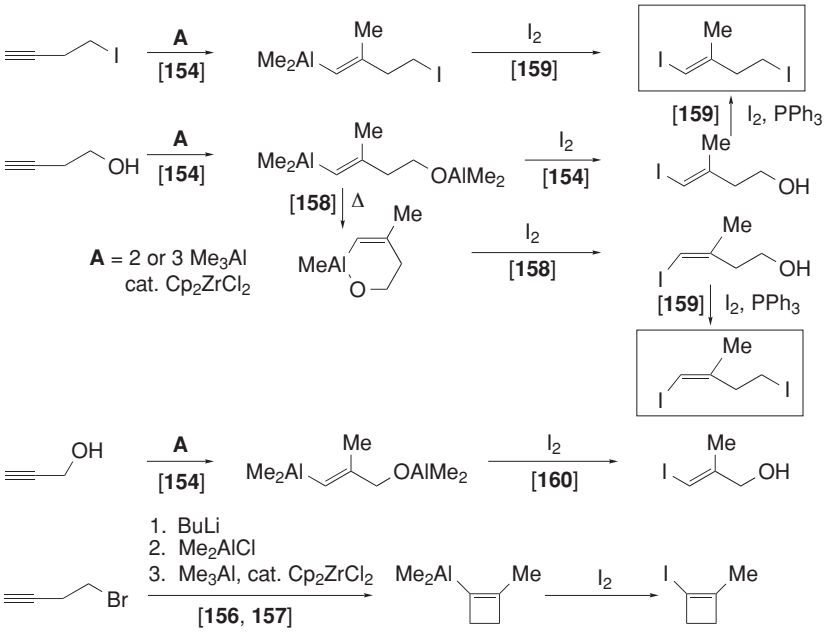
Scheme 1.43. Examples of stoichiometric carbozirconation.

1.4.3.3.2 Zr-catalyzed carboalumination of alkynes

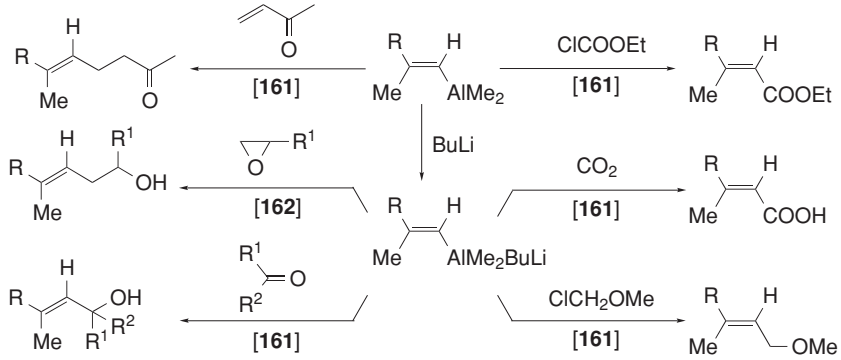
As mentioned earlier, the Zr-catalyzed carboalumination of alkynes [13,56] (Scheme 1.44) most probably represents the first example of Zr-catalyzed synthetic reactions suitable for controlled and selective synthesis of natural products and other organic compounds of low structural symmetry. *The reaction is characterized by (a) generally high yields, (b) essentially 100% syn-stereoselectivity, (c) about 95% regioselectivity for the methylalumination of 1-alkynes, (d) compatibility with heterofunctional groups, such as halogens, alcohols, and amines* (**Generalization 14**) [154]. In some cases, however, heterofunctional groups can lead to side reactions, including synthetically useful cyclobutenation [155–157] and *anti*-carbometallation [158] (Scheme 1.45). Once alkenylalanes are generated, they can be subjected to a



Scheme 1.44. Zr-catalyzed carboalumination of alkynes.



Scheme 1.45. Stereoisomerization and skeletal rearrangement of alkenylalanes formed *via* Zr-catalyzed carboalumination.

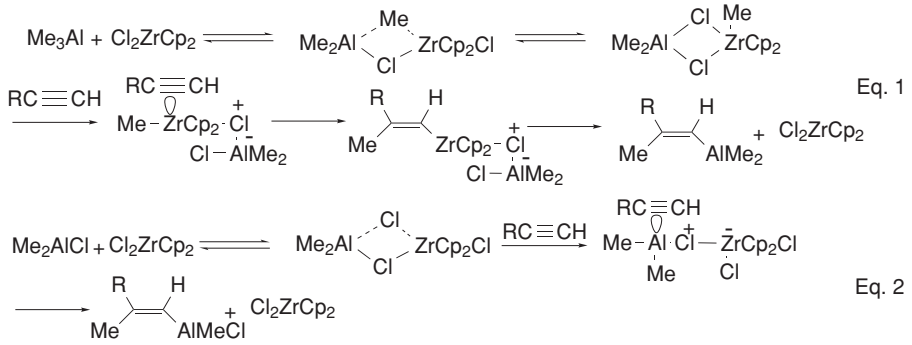


Scheme 1.46. Reactions of alkenylalanes and alkenylaluminates obtained *via* Zr-catalyzed carboalumination with carbon electrophiles.

wide variety of known reactions of organoaluminum compounds, including the Pd- or Ni-catalyzed cross-coupling (Scheme 1.24). Some of the more conventional C–C bond-forming reactions of alkenylalanes are shown in Scheme 1.46.

Many dozen complex natural products have been synthesized in a highly selective manner by the use of Zr-catalyzed carboalumination of alkynes. Although most of them are not mentioned here due to space limitation, those that have been reported by the author's group over the past few years alone include freelingyne [160], coenzyme Q_{10} [159], and β- and γ-carotenes [163], which were synthesized with unprecedented efficiency and selectivity.

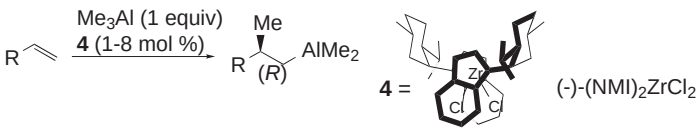
The available data clearly indicate that *the Zr-catalyzed carboalumination is multi-mechanistic and that the mechanism is strongly dependent on a number of parameters, such as R of R_3Al, the number and nature of other substituents including Cl, and the solvent used* (**Generalization 15**). For methylalumination with Me_3Al and Cp_2ZrCl_2, an acyclic, bimetallic, and Zr-centered four-centered concerted process (Eq. 1 in Scheme 1.47) is the most plausible one [56]. However, use of the Me_2AlCl/Cp_2ZrCl_2 reagent system appears to proceed by an Al-centered reaction (Eq. 2 in Scheme 1.47) [55,56]. Moreover, it has recently been shown that the reaction with Et_3Al and Cp_2ZrCl_2 proceeds via cyclic intermediates and produces cyclic products as discussed later, whereas that with Et_2AlCl and Cp_2ZrCl_2 must be an acyclic process similar to that shown in Eq. 2 in Scheme 1.47 [150].



Scheme 1.47. Dichotomous mechanisms of Zr-catalyzed methylalumination.

1.4.3.3.3 Zr-catalyzed asymmetric carboalumination of alkenes

Since the discovery of the Zr-catalyzed carboalumination of alkynes in 1978 [13], several attempts have been made to achieve a related carboalumination of alkenes with Me_3Al and Cp_2ZrCl_2, but all have resulted in disappointingly low yields of the desired products. A recent investigation has revealed that the desired reaction does take place with high conversion, but that the products are depleted through their competitive dehydrometallation to give 1,1-dialkyl-1-alkenes [164]. Unexpectedly, *the use of bulky chiral zirconocene derivatives, in particular (−)-bis(neomenthylindenyl)zirconocene dichloride, (−)-$(NMI)_2ZrCl_2$* (**4**) [165], *facilitated the desired carboalumination, giving not only good yields, typically 70–90%, but also respectable enantioselectivities, typically 70–80% ee* [164] (**Generalization 16**) (Scheme 1.48 and Table 1.2). This reaction represents an as yet very rare example of a catalytic C–C bond-forming reaction involving one-point binding that leads to reasonably high *ee* values. Although its mechanistic details are still largely unclear, it is thought to involve an acyclic concerted four-centered C–Zr bond addition to alkenes, in which bimetallic polarization [54,57,58,150] is important.

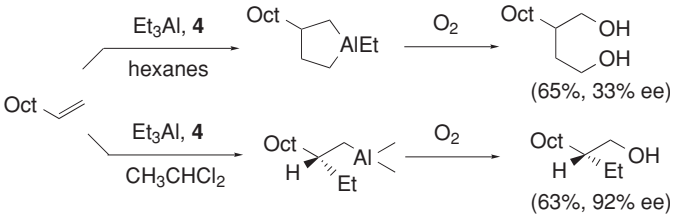


Scheme 1.48. Zr-catalyzed enantioselective methylalumination of alkenes.

Table 1.2. 2-Alkyl-substituted 1-alkanols via Zr-catalyzed alkylalumination–oxidation

Substrate	Me_3Al Yield, %	Me_3Al % *ee*	Et_3Al Yield, %	Et_3Al % *ee*
$RCH{=}CH_2$ (R = *n*-alkyl)	88	72	63–75	90–93
i-$BuCH{=}CH_2$	92	74	77	90
$PhCH_2CH{=}CH_2$	77	70	69	93
c-$HexCH{=}CH_2$	80	65	–	–
$HO(CH_2)_4CH{=}CH_2$	79	75	88 (protonolysis)	90
$Et_2N(CH_2)_3CH{=}CH_2$	68	71	56	95

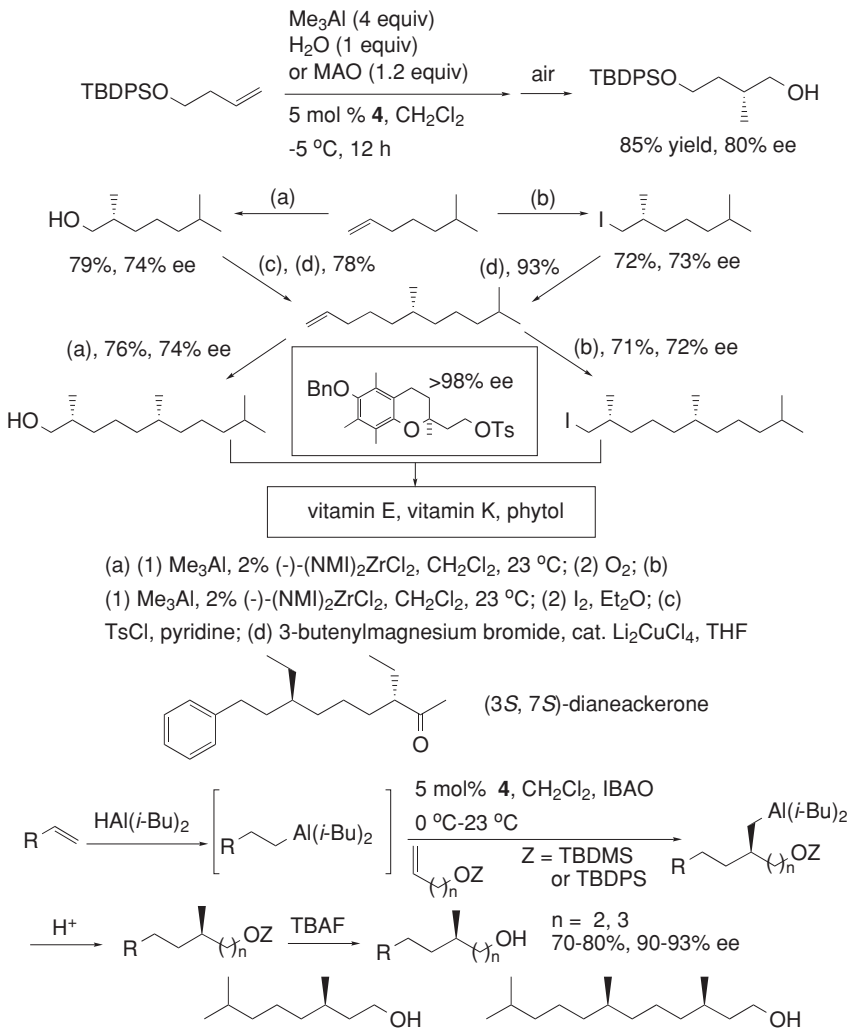
The corresponding reaction of Et_3Al and other higher alkylalanes in non-polar solvents was shown to be a cyclic process producing aluminacyclopentanes with low ee, but a complete mechanistic switch from cyclic to acyclic was observed by changing from non-polar solvents to chlorinated alkanes, such as CH_2Cl_2, $ClCH_2CH_2Cl$, and CH_3CHCl_2. Although the chemical yields might be somewhat lower than for methylalumination, ee values of 90–95% have been observed [166] (Scheme 1.49 and Table 1.2). *This reaction is also thought to proceed by an acyclic concerted process* (**Generalization 16′**).



Scheme 1.49. Zr-catalyzed cyclic and acyclic asymmetric ethylalumination of alkenes.

It has recently been shown that *some of the sluggish reactions, such as those with styrene and ω-alkenol derivatives, can be significantly accelerated by the addition of H_2O, MAO (methylaluminoxane)* [167], *and IBAO (isobutylaluminoxane)* [168], *and that the ee values can be improved by several %* (**Generalization 17**). Some of the earlier results discussed above have also been reviewed recently [169,170].

Although the application of carboalumination to the synthesis of natural products is still in its infancy, a few preliminary results shown in Scheme 1.50 [167,168,171,172] suggest that it promises to become a major asymmetric synthetic reaction, provided that (i) the singularly important case of methylalumination can be made to proceed with ≥90% *ee*, and (ii) satisfactory and convenient methods for enantiomeric and diastereomeric separation/purification can be developed. In this context, significant increases in *ee* in the synthesis of methyl-substituted alkanols from around 75% to 90–93% achieved through some strategic modifications are noteworthy (Scheme 1.50) [168]. Shortly before the discovery of the Zr-catalyzed enantioselective carboalumination, a fundamentally discrete Zr-catalyzed asymmetric reaction of allylically heterosubstituted alkenes proceeding via cyclic carbozirconation was reported, as discussed later in this section.



Scheme 1.50. Asymmetric synthesis of natural products by Zr-catalyzed asymmetric alkylalumination of alkenes.

1.4.3.3.4 **Stoichiometric bicyclization of enynes, diynes, and dienes by cyclic carbozirconation**

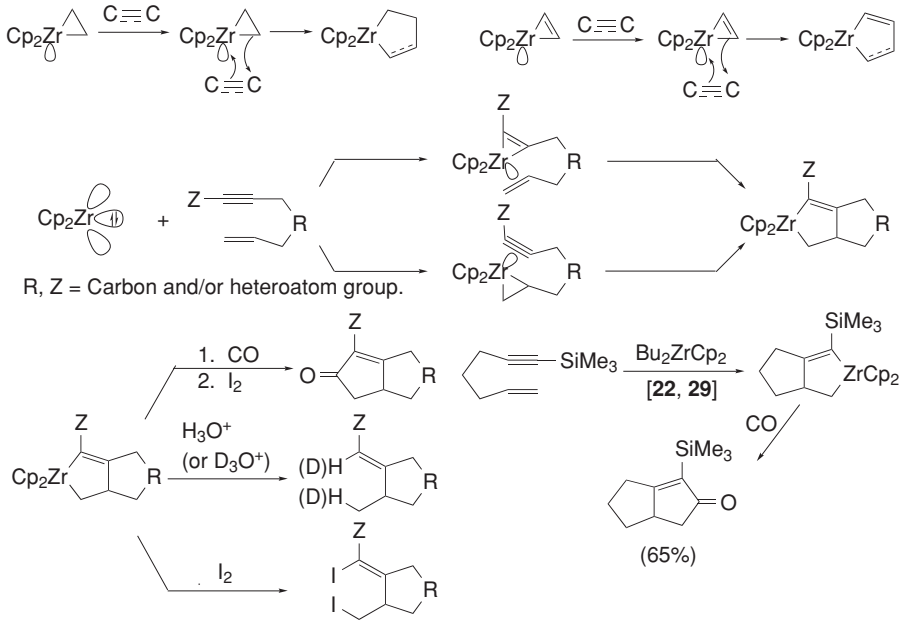
Simple molecular orbital considerations suggested that zirconacyclopropanes and zirconacyclopropenes could, in principle, undergo ring-expansion through cyclic carbozirconation, as shown in Scheme 1.51. The reaction of the putative benzyne-$ZrCp_2$ with stilbenes, as shown in Scheme 1.8 [49], may well represent one of the earliest examples, if not the earliest, of such reactions. Another major breakthrough was the development of the enyne bicyclization–carbonylation tandem process, which could proceed in a "pair"-selective and regioselective manner to give a single desired product in high yields [22,29], whereas the corresponding intermolecular reaction could, in principle, produce a mixture of up to ten products. The subsequent development of $n Bu_2ZrCp_2$, commonly referred to as the Negishi reagent, as a "$ZrCp_2$" equivalent [24] has further promoted the development of

the "$Cp_2Zr(II)$" chemistry discussed below. In view of the enormous current scope of this area and the fact that some later chapters also discuss this area, only a very brief discussion is presented here. The enyne bicyclization–carbonylation tandem reaction has been applied to the synthesis of some complex natural products, including pentalenic acid [131]. The following discussion may also be supplementary to some of the author's reviews on the topic [23,27,33,87–89].

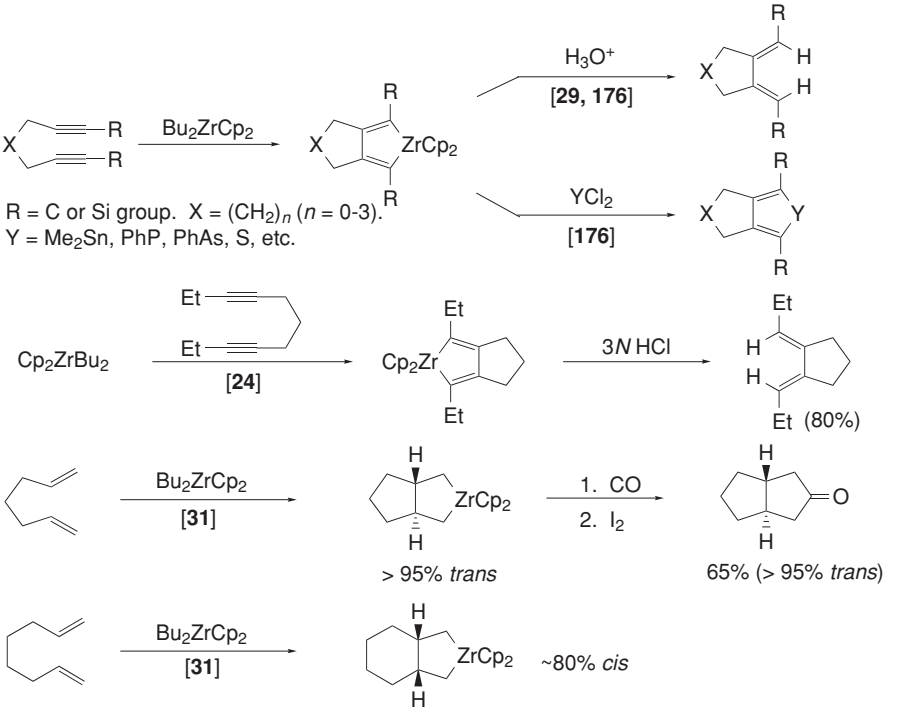
The enyne bicyclization–carbonylation tandem reaction has often been compared with the Pauson–Khand reaction involving Co [173] and other related reactions of late transition metals, some of which have become catalytic and even enantioselective [174]. On the other hand, the Zr-promoted enyne bicyclization–carbonylation tandem reaction has largely remained stoichiometric in Zr and racemic, although some promising results on its catalytic version have also been reported [175]. These are two major deficiencies that need to be rectified. It should not be overlooked, however, that the Zr reaction offers many advantageous features not readily shared by the Pauson–Khand and related reactions of late transition metals. Thus, *the Zr reaction is not only readily adaptable to the bicyclization of diynes* [24,29,176], *dienes* [31,177,178], *and related heteroatom analogues* [179], *but can also be readily stopped at the stage of zirconabicycles, from which many different types of organic compounds may be derived* (**Generalization 18**). This is exemplified by the syntheses of cyclic conjugated dienes [24,29,176], including a series of oligocyclic and polymeric conjugated dienes reported by Tilley [180–184], and stereodefined exocyclic alkenes [22,29,185], including key intermediates for the syntheses of phorbol [186], iridomyrmecin [132], and 7-*epi*-β-bulnesene [187]. The synthesis of dendrobine [188] through diene bicyclization–carbonylation is another example that cannot be readily achieved with the Pauson–Khand reaction. Conversion of 1,6-heptadiene into a highly unexpected *trans*-fused 3-zirconabicyclo[3.3.0]octane [31,65] is also noteworthy in this context.

1.4.3.3.5 Stoichiometric intermolecular cyclic carbozirconation of three-membered zirconacycles

In the preceding section, at least three critical assumptions were initially made in the development of the reactions shown in Scheme 1.51. The first was the generation of hypothetical 14-electron $Cp_2Zr(II)$. Subsequent studies have shown that, *in essentially all cases, such a 14-electron species has most probably never been directly observed and that all "$Cp_2Zr(II)$" equivalents, including 1-butene-$ZrCp_2$* [24,29] *are 16- or even 18-electron species* (**Generalization 19**). The second assumption was the formation of three-membered zirconacycles as intermediates by the reaction of "$Cp_2Zr(II)$" equivalents with alkenes, alkynes, and other π-compounds. This has proved to be correct, as already discussed in some detail in Section 1.3.4. Although there are several different protocols, the Negishi–Takahashi protocol involving the reaction of in situ generated dialkylzirconocenes with π-compounds as a route to various three-membered zirconacycles [89], and the Erker–Buchwald protocol, in which the desired three-membered zirconacycles are generated directly by β-H abstraction without the use of π-compounds [189], have emerged as two convenient routes. A variant of the former involving the use of bis(trimethylsilyl)acetylene as a temporary π-ligand is also promising and has been shown to be advantageous in some cases [183,184]. The third assumption was the carbometallative ring-expansion leading to the formation of five-membered zirconacycles. In the reactions of enynes, diynes, and dienes, this was merely assumed [22,23,46]. The availability of structurally well-defined three-membered zirconacycles since the mid-1980s [25,36–38] permitted detailed studies of their reactions



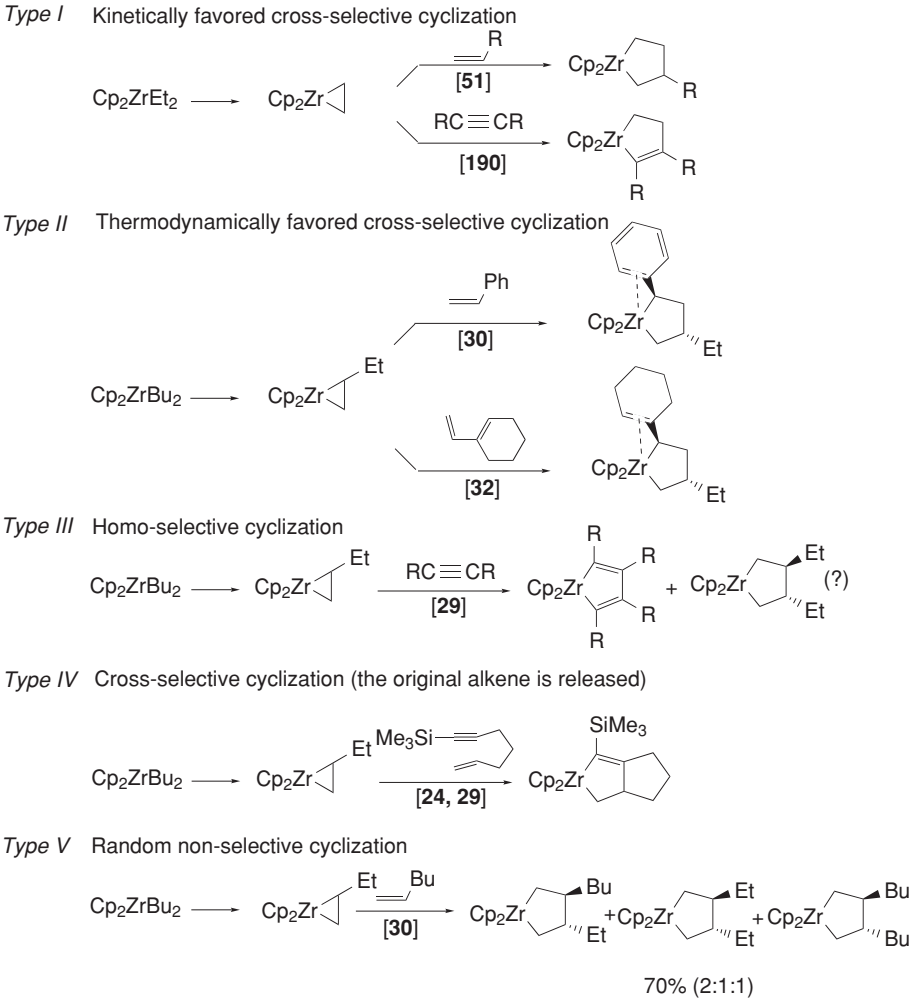
Scheme 1.51. General patterns and hypothetical mechanisms of cyclic carbozirconation of three-membered zirconacycles.



Scheme 1.52. Cyclic carbozirconation of three-membered zirconacycles with alkenes and alkynes.

with various π-compounds, including such aspects as "pair"-selectivity and regioselectivity, which were largely avoided in the preceding section.

As mentioned earlier, a random and statistical cyclization with two different and regiodefined π-compounds would produce a synthetically unattractive mixture of ten different zirconacycles. In reality, however, there are a few factors that can be exploited to produce a single desired zirconacycle. A systematic investigation has revealed that *there are several discrete types of five-membered zirconacycle formation, as shown in* Scheme 1.53 [88,89] (**Generalization 20**). In the Type I reaction, the cross-selective cyclization is kinetically favored. Presumably, little ethylene is displaced during the reaction. Type I reactions cannot be readily observed with $ZrCp_2$ complexes with 1-butene. In contrast, Type II cyclization must be thermodynamically controlled, as 1-butene is readily displaced by a number of "better" π-ligands. It is predicted, however, that the cross-combination of the two π-com-

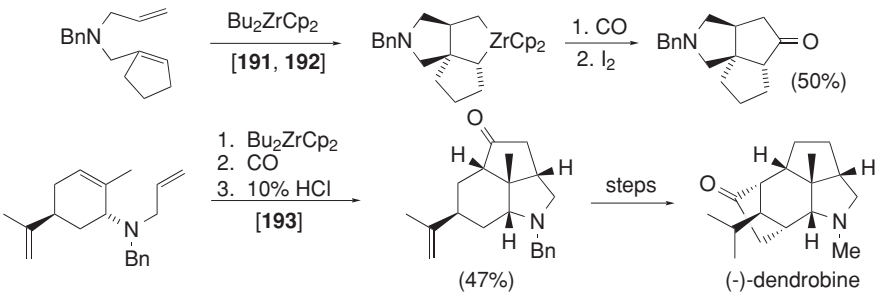


Scheme 1.53. Types of cyclic carbozirconation of three-membered zirconacycles with alkenes and alkynes.

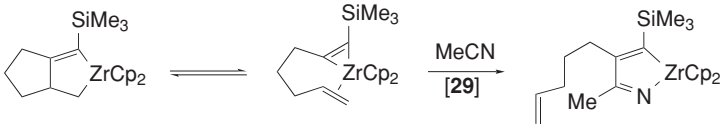
pounds may, in many cases, be thermodynamically favored when the two π-compounds and "$ZrCp_2$" are present in a 1:1:1 molar ratio. In the two cases shown in Scheme 1.53, two factors may contribute to high levels of cross-selection. The zirconacycle containing two 1-butene molecules must be thermodynamically disfavored, as it cannot participate in the Zr-alkene π-stabilization. That containing two styrene molecules or the conjugated diene may be at least as stable or perhaps more stable than those shown. However, their formation must necessarily be accompanied by the formation of the aforementioned unfavorable product, as long as the reactant ratio is restricted to 1:1:1. Under such constraints, the best compromise may be the observed cross-selective cyclization under thermodynamically controlled conditions. If the formation of one of the homodimeric products becomes overwhelmingly favorable, however, homo-selective cyclization may occur (Type III cyclization). Thus, intramolecularity and favorable tether length must indeed be responsible for the observed high cross-selectivity in the enyne bicyclization (Type IV cyclization). Finally, if two π-compounds are similar in chemical properties, non-selective cyclization should be expected under thermodynamically controlled conditions. Some other types of cyclization may also be observed.

High regioselectivity and stereoselectivity have been observed in many of those cases in which the products are regio- and/or stereodefined. In the absence of overriding factors, alkyl substituents prefer to be β to Zr, whereas aryl and alkenyl substituents, in particular, prefer to be α to Zr (**Generalization 21**). In cases where there are two carbon-bound substituents, they usually prefer to be *trans* to one another, presumably to minimize steric interactions. This must be an overriding factor favoring the *trans* fusion shown in Scheme 1.52. The observed *cis* fusion for the bicyclo[4.3.0]nonane system has been shown to represent a kinetic preference [178]. However, there is no myth associated with *trans* fusion, and the preferred stereochemistry is only a reflection of a thermodynamic preference, as is nicely demonstrated by the predominant *cis* fusion in some zirconatricycles [191–193] (Scheme 1.54).

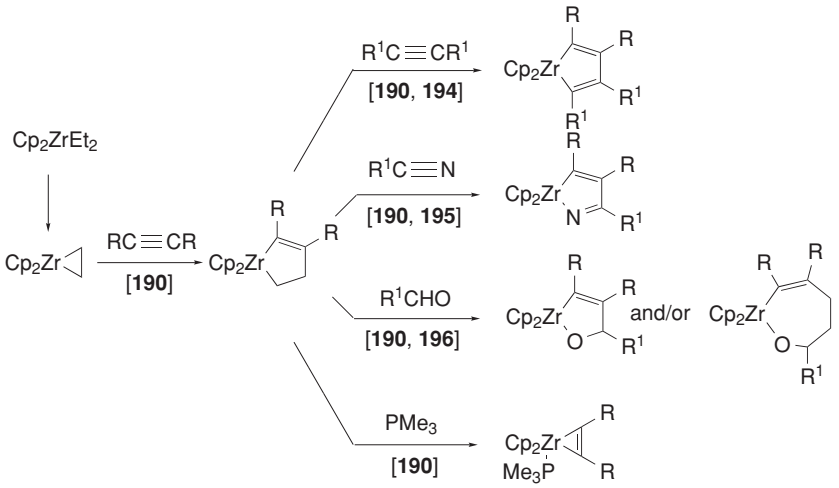
One important aspect of the Cp_2Zr-promoted cyclization that has slowly emerged through a number of experimental observations is its ready reversibility through decarbozirconation (**Pattern 8′**), *presumably involving an interaction between the empty Zr orbital and the C_β–$C_{\beta'}$ bond of the five-membered zirconacycle* (**Generalization 22**). The unexpected transformation shown in Scheme 1.55 [29] was one of the earliest eye-opening results that led to the development of a very convenient and satisfactory general protocol for "pair"-selective syntheses of various types of five-membered zirconacycles without the use of expensive and potentially toxic phosphines (Scheme 1.56) [190,194,195].



Scheme 1.54. *Syn* fusion in Zr-promoted bicyclization of diallylamines.



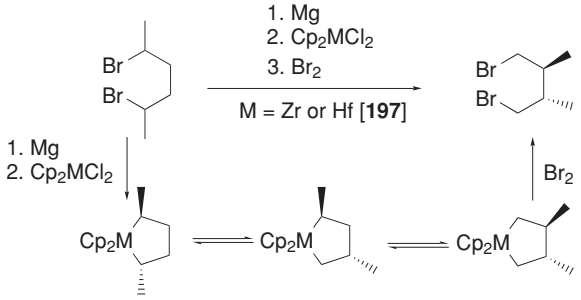
Scheme 1.55. First observation of reversible cyclic carbozirconation of three-membered zirconacycles.



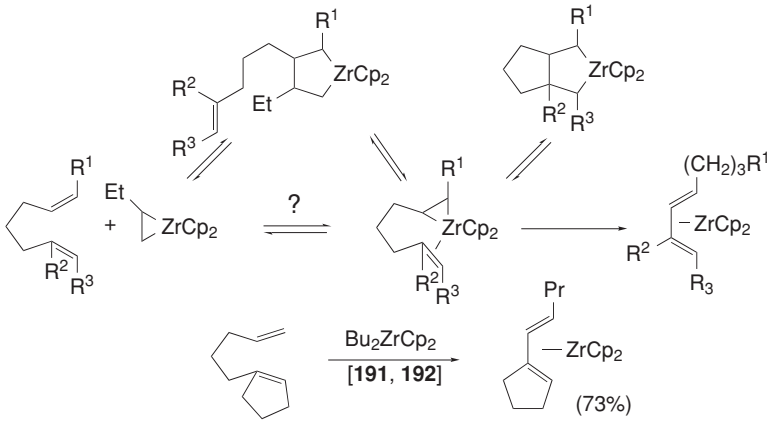
Scheme 1.56. Displacement of ethylene from zirconacyclopentenes by π-compounds.

A few other interesting and potentially important consequences of the reversible formation of five-membered zirconacycles include stereo- and regioselective skeletal rearrangement, as exemplified by Scheme 1.57 [197], *and 1,3-C=C bond and Zr migration* (Scheme 1.58) [191,192], *supporting the associative mechanism for alkene displacement* (**Generalization 22′**).

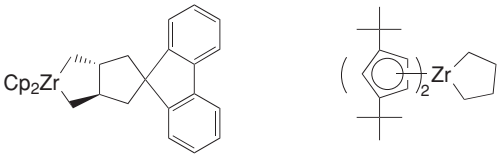
Until recently, the structures of the five-membered zirconacycles had been proposed on the basis of NMR data and identification of the final organic compounds, especially the products of deuterolysis, iodinolysis, and carbonylation. Determination of their structures by X-ray analysis proved to be more difficult than that of three-membered zirconacycles, largely because attempts to obtain their stable 18-electron derivatives led to ring-contraction to give three-membered zirconacycles, as in the last example in Scheme 1.56. This difficulty was overcome by the use of bulky Cp derivatives that permitted the formation of stable, crystalline, 16-electron, five-membered zirconacycles such as **5** [198] and $(t\mathrm{Bu}_2\mathrm{C}_5\mathrm{H}_3)_2\mathrm{Zr}(\mathrm{CH}_2)_4$ (**6**) [199] (Scheme 1.59).



Scheme 1.57. Skeletal rearrangement of α,α′-dialkylzirconacyclopentanes.



Scheme 1.58. Zirconium and alkene migration of diene-zirconocene complexes.

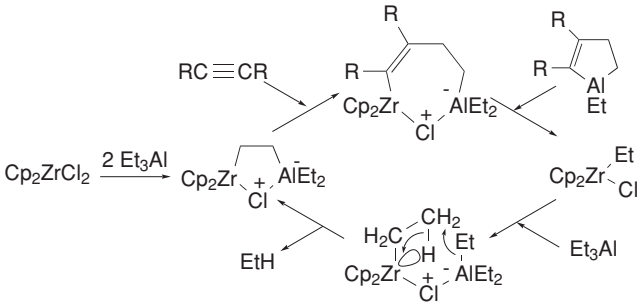


Scheme 1.59. Zirconacyclopentanes characterized by X-ray analysis.

1.4.3.3.6 **Zr-catalyzed C–C bond formation by cyclic carbozirconation and σ-bond metathesis of zirconacycles**

Most probably, Zr-catalyzed C–C bond formation by cyclic carbozirconation was first observed in 1978, when the Zr-catalyzed reaction of alkynes with Et_3Al was reported [13,56]. An acyclic carbozirconation mechanism similar to that of methylalumination was initially considered [56].

A recent study has, however, unraveled a most intricate four-step catalytic cycle involving a bimetallic cyclic carbozirconation (Scheme 1.60) [150]. The stoichiometric conversion of $EtZrCp_2Cl$ and Et_3Al into the five-membered bimetallic complex and its subsequent stoichiometric reaction with an alkyne to give an aluminacyclopentene and $EtZrCp_2Cl$ were the two key experimental findings.

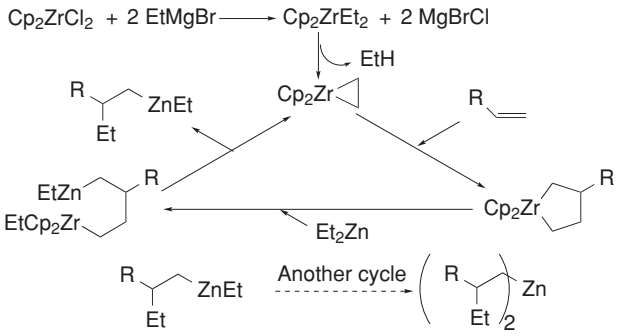


Scheme 1.60. Mechanism of Zr-catalyzed ethylalumination of alkynes.

On the one hand, this mechanistic study represents the culmination of many preceding studies. On the other hand, this, together with several other recent developments, represents a new generation of organozirconium chemistry characterized by (i) Zr catalysis, (ii) bimetallic and multimetallic systems, in which bi- and multimetallic interplay is significant, and (iii) significant roles of various σ-bond metatheses.

An earlier breakthrough along these lines was the clarification in 1991 of the three-step catalytic cycle shown in Scheme 1.4 [51] for the Dzhemilev ethylmagnesation of alkenes [50], which also initially appeared to be a straightforward acyclic carbometallation reaction. Unlike Grignard reagents, alkyllithiums do not induce a similar catalysis, even though they are capable of producing zirconacyclopropanes, which can then produce zirconacyclopentanes. Some insights into a possible catalyst poisoning have recently been provided [66]. Ethylzinc derivatives alone cannot participate in the Zr-catalyzed ethylmetallation, but the desired ethylzincation takes place smoothly once the initial catalytic amount of Et_2ZrCp_2 is generated by the reaction of EtMgBr and Cl_2ZrCp_2 (Scheme 1.61) [200]. Presumably, EtMgBr does not participate in the catalytic cycle of the reaction.

The differences in catalytic reactivity between Li, Mg, Zn, and Al are summarized in Table 1.3 (**Generalization 23**), and the trend indicated in the table is readily understandable on the basis of the current knowledge of Cp_2Zr chemistry.



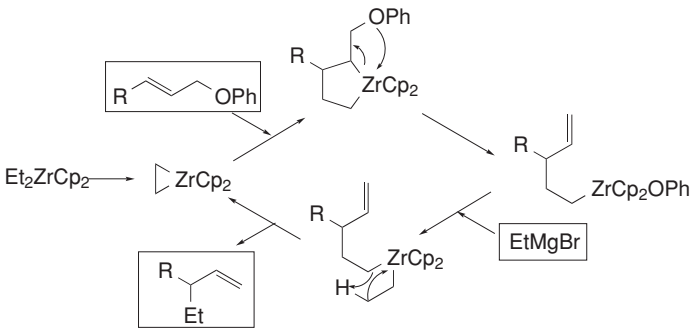
Scheme 1.61. Ethylzincation of alkenes catalyzed by Cp_2ZrCl_2-2EtMgBr.

Table 1.3. Comparison of Li, Mg, Zn, and Al in the Zr-catalyzed cyclic carbometallation

Metal	*Catalytic process observable or not*	*Possible explanation and other comments*
Li	Catalysis not induced	Cp displacement and ate complexation
Mg	Monometallic cyclic carbozirconation occurs	*cf.* Monometallic cyclic carbozirconation mechanism in Scheme 1.4.
Zn	Monometallic cyclic carbozirconation occurs; EtMgBr needed as catalyst	Et_2Zn is capable of sustaining the catalytic cycle shown in Scheme 1.61 but incapable of generating Et_2ZrCp_2
Al	Bimetallic cyclic carbozirconation	Only monoethylation of Cl_2ZrCp_2 occurs, but a novel monoalkylative and bimetallic activation of β-CH bond possible (Scheme 1.60).

As is clear from the mechanisms, these reactions cannot occur with methylmetals. Their extensions beyond ethylmetallation are possible, but are prone to various side reactions [201,202]. In contrast to the widely observable Zr-catalyzed carboalumination of alkynes discussed earlier, the alkyne version of the Zr-catalyzed ethylmagnesation has not been widely observable, the only successful examples being those of conjugated diynes [203]. In this context, further investigation of the Zr-catalyzed carbozincation of alkynes reported as early as 1983 [204,205] appears to be very desirable.

In the Zr-catalyzed cyclic carbometallation discussed above, a tandem process consisting of (i) transmetallation and (ii) β-H abstraction provides the "missing link" in the catalytic cycle. In a series of recent examples reported by Takahashi [206–208] and Hoveyda [209–214], the "missing link" has been provided by a process consisting of (i) β-elimination or deheterometallation (**Pattern 10**), (ii) transmetallation, and (iii) β-H abstraction (Scheme 1.62). Some of these reactions have been developed into enantioselective C–C bond-forming processes, as discussed below.

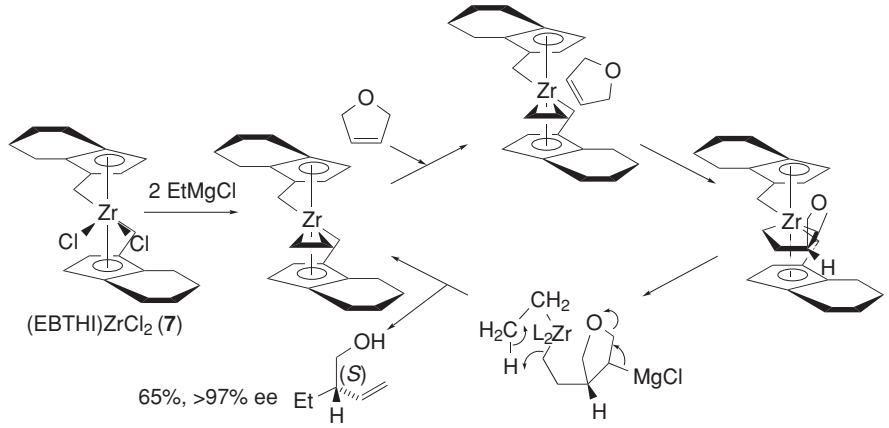


Scheme 1.62.
Mechanism of the Zr-catalyzed γ-ethylation of allyl ethers.

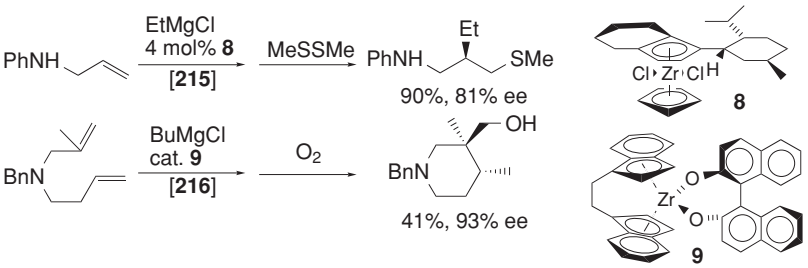
1.4.3.3.7 **Zr-catalyzed asymmetric C–C bond formation by cyclic carbozirconation**

The Zr-catalyzed enantioselective carbomagnesation of ordinary terminal alkenes does not appear to have been reported. In a related Zr-catalyzed cyclic carboalumination, low *ee* values of ≤40% were observed (Scheme 1.49) [166]. On the other hand, *allylically heterosubstituted alkenes, such as allyl ethers, allyl alcohols, and allylamines, have been converted to allylically ethylated terminal alkenes, most probably through cyclic carbozirconation, as shown in* Scheme 1.63 [209–211]. *With 10 mol% of (EBTHI)*$ZrCl_2$*, (7) [EBTHI = ethylenebis(tetrahydroindenyl)], the desired products were obtained in 65–75% yields with ≥90% ee by using EtMgCl* (**Generalization 24**). The corresponding reactions of higher alkylmagnesium derivatives give the desired products in only 35–40% yield, and no methylation is possible unless a mechanistic switch similar to that shown in Scheme 1.49 can be induced. As attractive as the favorable results are, the current scope is practically limited to allylic ethylation of allylically heterosubstituted alkenes. Kinetic resolution of allyl ethers also proceeds with high *ee* [212–214].

Some related studies by Whitby [215] and Mori [216] are also promising, but all favorable results have so far been obtained with allylically heterosubstituted alkenes (Scheme 1.64).



Scheme 1.63. Zr-catalyzed enantioselective γ-ethylation of allyl ethers.

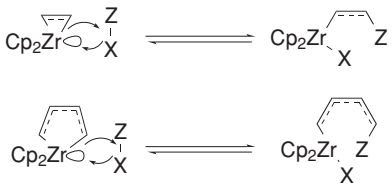


Scheme 1.64. Zr-catalyzed enantioselective carbomagnesation of allylamines.

1.4.4
σ-Bond Metathesis of Zirconacycles

In some of the preceding sections, the significance of interactions between three-membered zirconacycles with π-bonds (**Pattern 7′** in Scheme 1.3 and Scheme 1.51) has been amply demonstrated. More recently, their σ-bond analogues (**Pattern 13**) and variants involving five-membered zirconacycles, as shown in Scheme 1.65, have been recognized as important fundamental processes in organozirconium chemistry.

In general, *σ-bond metathesis itself does not lead to C–C bond formation. However, it can provide kinetically favorable paths for generating and interconverting organozirconium compounds, which can then be used for the formation of C–C and other types of bonds* (**Generalization 25**). Indeed, it is rapidly growing into an important new branch of organozirconium chemistry. The significance of transmetallation as a method for C–Zr bond forma-

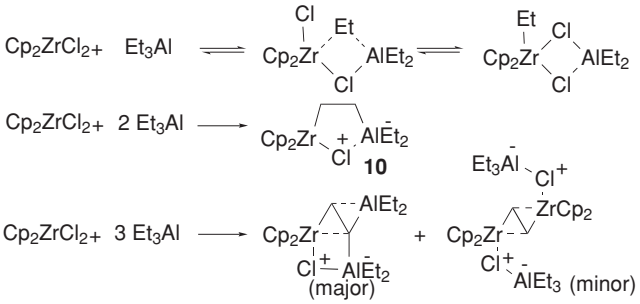


Scheme 1.65. σ-bond metathesis of zirconacycles.

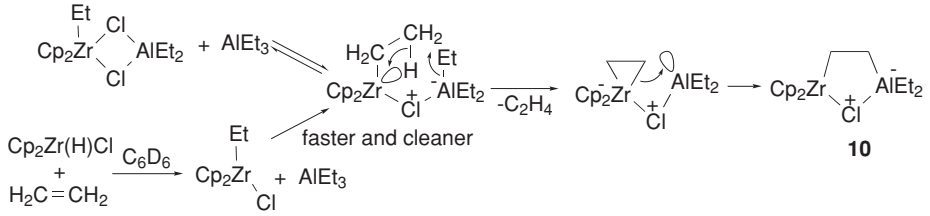
tion and for the formation of other carbon–metal bonds was discussed in Sections 1.3.1 and 1.3.2, respectively. Conversion of C–Zr bonds into other carbon–heteroatom bonds appears in many cases to proceed through σ-bond metathesis, even though mechanistic details are often unclear. In this section, attention is focused on the transformations involving zirconacycles depicted in Scheme 1.65. Such transformations may be either stoichiometric or catalytic in Zr.

The reaction of Et_3Al with Cp_2ZrCl_2 was studied by Sinn as early as the mid-1960s [217]. Depending on the reactant ratio, three to four different products were obtained (Scheme 1.66). One of the bimetallic and pseudocyclic compounds (**10**) has recently been shown to serve as an active intermediate in the Zr-catalyzed carboalumination of alkynes (Scheme 1.60) [150]. The same investigation has further clarified the mechanism of the formation of **10**, which involves σ-bond metathesis of ethylene-zirconocene with $ClAlEt_2$, as shown in Scheme 1.67 [150]. Thus, the formation of **10** from Et_3Al and Cp_2ZrCl_2 reported by Sinn in 1966 [217] may well represent the first example of a transformation proceeding via σ-bond metathesis of three-membered zirconacycles. The formation of **11** from PhC≡CPh and H_2ZrCp_2 reported in 1972 [218] can also be interpreted in terms of a mechanism involving σ-bond metathesis of a five-membered zirconacycle (Scheme 1.68) [23].

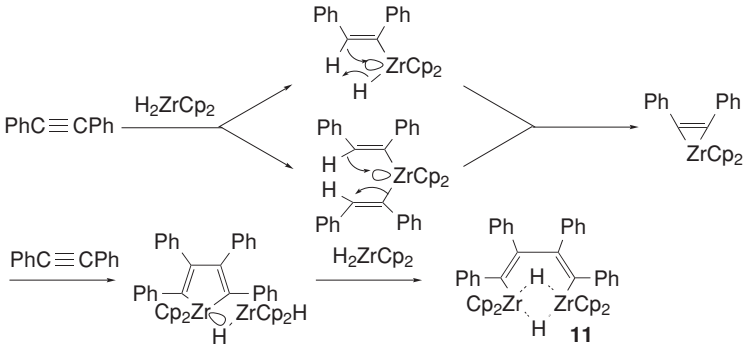
In these early studies, however, the concept of σ-bond metathesis most probably did not exist, and the results were presented just as observed facts. Mainly in the 1990s, a wide variety of σ-bond metathesis reactions of both three- and five-membered zirconacycles were reported. In Scheme 1.4, the reaction of the five-membered zirconacycle with EtMgBr via σ-bond metathesis followed by another σ-bond metathesis (β-H abstraction) produces the ethylmagnesation product along with ethylene-zirconocene [51]. Some representative examples of σ-bond metathesis reactions of three-membered zirconacycles are shown in Scheme 1.69. These are examples of stoichiometric σ-bond metathesis reactions from which the products have been identified.



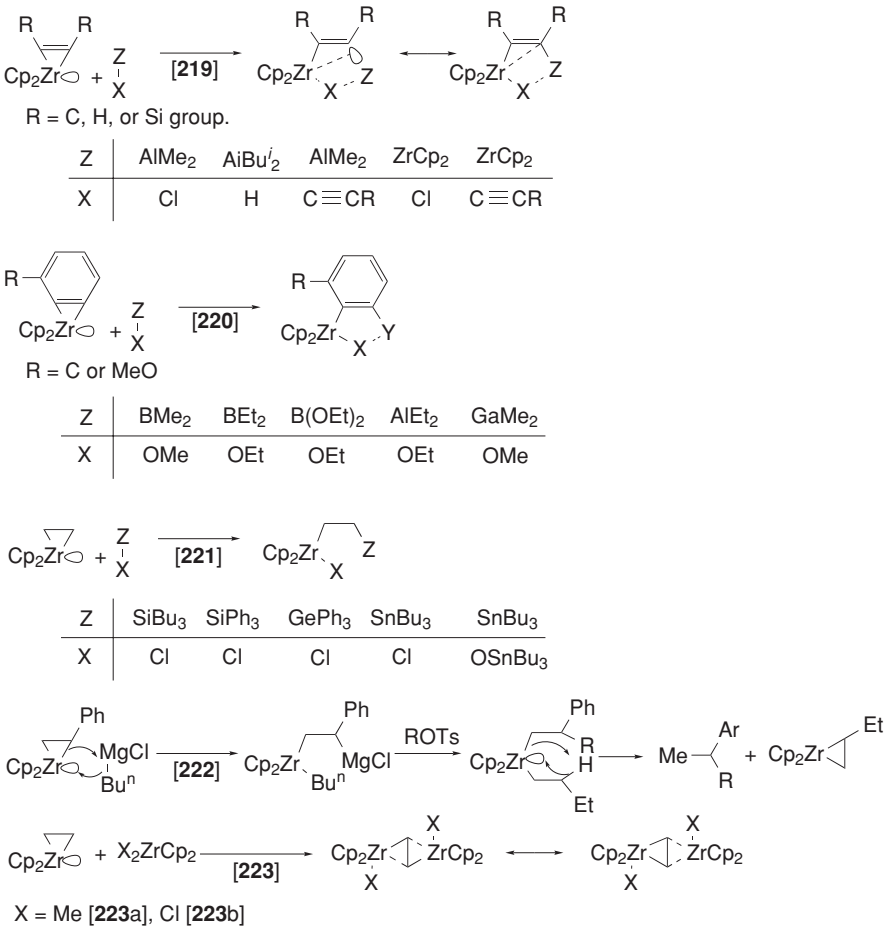
Scheme 1.66. Reaction of Cp_2ZrCl_2 with Et_3Al.



Scheme 1.67. Mechanism of the formation of chloroaluminazirconacyclopentane **10** by the reaction of Cp_2ZrCl_2 or $EtZrCp_2Cl$ with Et_3Al.



Scheme 1.68. A suggested mechanism for the formation of **11** through σ-bond metathesis of zirconacyclopentadienes with H_2ZrCp_2.

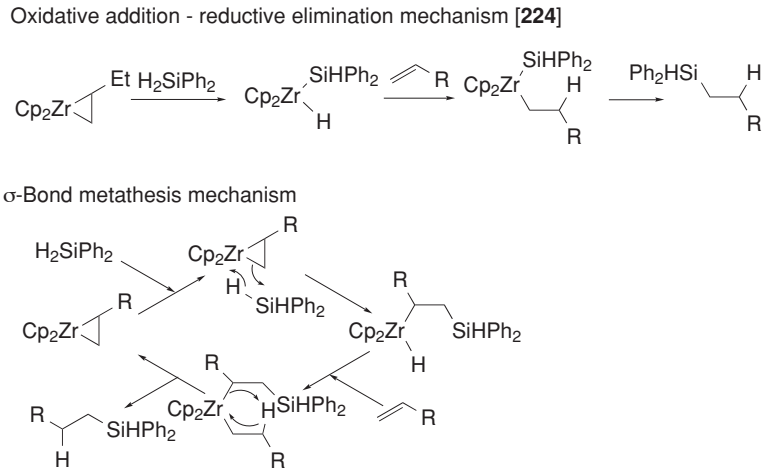


Scheme 1.69. Various examples of σ-bond metathesis reactions of three-membered zirconacycles.

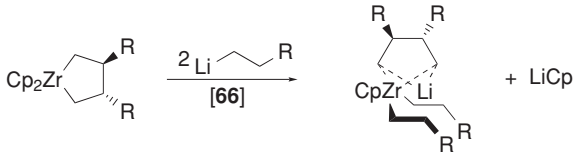
It is anticipated that many of the catalytic "$Cp_2Zr(II)$" reactions that might have been considered to proceed via oxidative addition and reductive elimination, such as hydrosilation [224] and hydrogenation [225], may actually proceed via a couple of σ-bond metatheses, i. e. transmetallation and β-H abstraction, as exemplified by the two contrasting mechanisms for the hydrosilation of alkenes (Scheme 1.70).

Although σ-bond metathesis of five-membered zirconacycles with EtMgBr [51] (Scheme 1.4) and H_2ZrCp_2 (Scheme 1.68) has been implicated, there are as yet very few well-established examples. The reaction of zirconacyclopentanes with alkyllithiums is interesting since it involves (i) the displacement of one of the two Cp groups, and (ii) the generation of a bimetallic species, the NMR spectroscopic data of which are consistent only with a fluxional structure as shown in Scheme 1.71 [66].

In many other reactions of zirconacycles catalyzed by transition metal complexes containing Cu, Ni, Pd, etc., σ-bond metathesis (transmetallation) must undoubtedly be involved, but such products have not generally been identified. Partly for this reason, they are not discussed here. Readers are referred to the chapter by T. Takahashi.



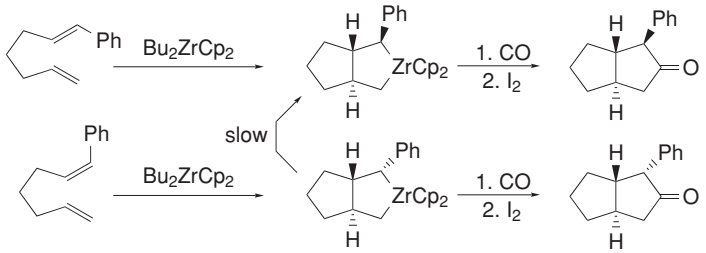
Scheme 1.70. Dichotomous mechanisms suggested for Zr-catalyzed hydrosilation of alkenes.



Scheme 1.71. σ-Bond metathesis reaction of zirconacyclopentanes with alkyllithiums.

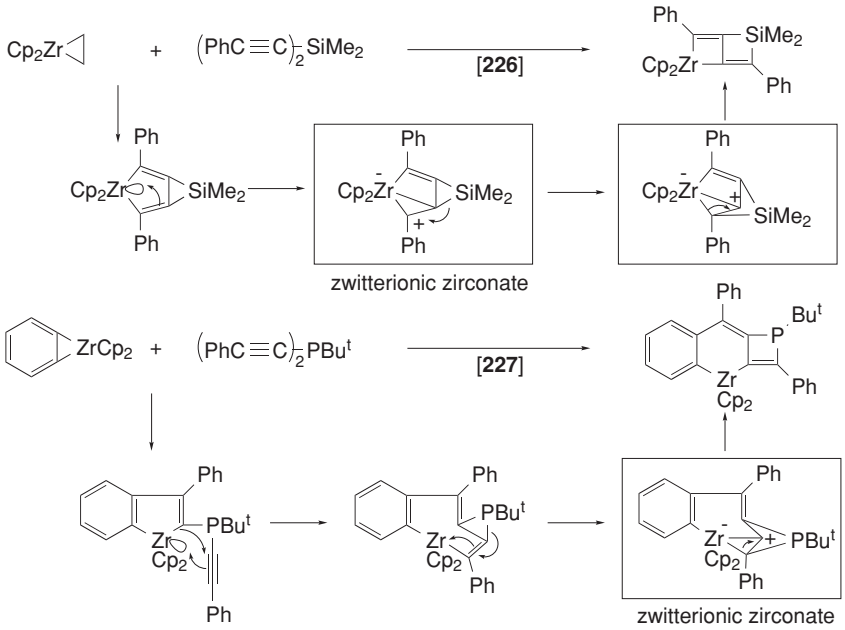
1.4.5
Ionic Reactions of Organozirconates

The great majority of the reactions discussed so far are considered to proceed through concerted processes, in which an empty valence-shell orbital of Zr plays a major role. In some cases, however, cationic zirconocene derivatives have been implicated as intermediates (Sections 1.4.3.1.4 and 1.4.3.1.5). More recently, *some reactions that are best interpreted by invoking zwitterionic zirconate intermediates have been observed* (**Generalization 26**). Electron transfer from an organic ligand to a 16-electron Zr permits generation of a carbocationic center, which can then undergo those reactions that are characteristic of carbocations, such as isomerization and rearrangement. One of the earliest indications along these lines was observed in the reaction of stilbene with *n*-Bu_2ZrCp_2, which did not produce the desired zirconacyclopentane derivative presumably because the steric hindrance was excessive. Instead, the *Z*-to-*E* isomerization of stilbene was observed, which was clearly catalyzed by zirconocene derivatives [28]. Some non-concerted process must have taken place, but the reaction was neither radical nor photochemical. Subsequent studies have shown that stereoisomerization can take place even in the formation of zirconacyclopentanes [65] (Schemes 1.8 and 1.72). These results are in contrast with the related but stereospecific transformations shown in Scheme 1.8 [49]. In the formation of a monocyclic zirconacyclopentane derivative, the rate of *Z*-to-*E* isomerization is so high that the *E*-isomer is the only observable product. In the transformations shown in Scheme 1.72, the initial stereospecificity is ≥90 %, but the more stable isomer dominated to an extent of about 90 % in both cases after 48 h at 23 °C. A detailed mechanistic study has pointed to an intricate ionic mechanism involving a zwitterionic zirconate containing a β-carbocation (Scheme 1.8).



Scheme 1.72. Stereoisomerization observed in the Zr-promoted bicyclization of dienes.

It has since become increasingly clear that zwitterionic zirconates may be generated in many other reactions and may lead to unexpected and interesting chemical consequences, as suggested by the results and interpretations shown in Scheme 1.73. It should be noted that the empty orbital and electrophilicity of Zr must lead to zwitterionic species containing zirconates and carbocationic centers. Further systematic investigations in this area appear to be desirable.



Scheme 1.73. Skeletal rearrangement of zirconacycles *via* dipolar zirconates.

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2
Zirconacyclopentadienes in Organic Synthesis

Tamotsu Takahashi and Yanzhong Li

2.1
Introduction

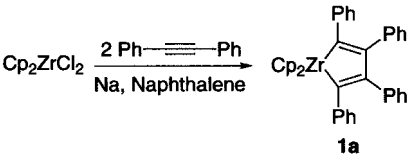
Five-membered metallacycles are mainly prepared by coupling a low-valent metal complex and two molecules of unsaturated compounds, such as alkenes, alkynes, ketones, aldehydes, imines, nitriles, and so on [1,2]. Since the resulting metallacycle contains two reactive bonds, various interesting transformations can be performed. Metallacycles of early transition metals such as Zr, Ti, and Hf show similar reaction patterns, but with some different limitations and scope. In this chapter, we focus on the reactions of zirconacyclopentadienes and related compounds. The first zirconacyclopentadiene was prepared in 1970 [3]. Since then, many groups have reported the formation of zirconacyclopentadienes, which have mainly been prepared from diphenylacetylene [3,4]. It is interesting to note that no systematic carbon–carbon bond-forming reactions of zirconacyclopentadienes were developed for more than 20 years. Only one report appeared in 1983, which was presented as an insertion reaction of an alkyne [5]. Therefore, zirconacyclopentadiene was considered as being inert with regard to carbon–carbon bond-forming reactions. However, in 1994, transmetalation of zirconacyclopentadienes to copper opened up a new area in carbon–carbon bond formation [6]. Numerous transmetalations of zirconacyclopentadienes to Cu [7], Ni [8], Zn [9], Li [10], and Al [11] have since been developed and various further transformations in organic synthesis have been reported.

2.2
Preparation and Reaction of Zirconacyclopentadienes

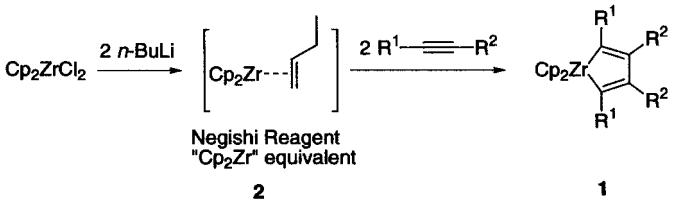
2.2.1
Preparation of Zirconacyclopentadienes

The first reported zirconacyclopentadiene was 2,3,4,5-tetraphenyl-1-zirconacyclopentadiene (**1a**), prepared from two molecules of diphenylacetylene and a low-valent zirconocene [3]. The low-valent zirconocene species was produced by the reaction of Cp_2ZrCl_2 with sodium/naphthalene (Eq. 2.1).

Eq. 2.1. Preparation of tetraphenylzirconacyclopentadiene using Cp_2ZrCl_2 and Na/naphthalene.

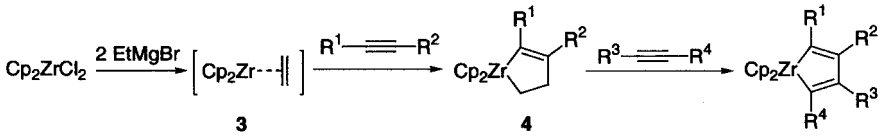


There are several methods for generating low-valent zirconocene species in situ. Although the conventional method has been the reduction of Cp_2ZrCl_2 with Na/Hg or Mg/Hg, more convenient methods have since been developed for the preparation of symmetrical zirconacyclopentadienes such as Cp_2ZrBu_2 **2** [the so-called Negishi reagent (Eq. 2.2)] [12].



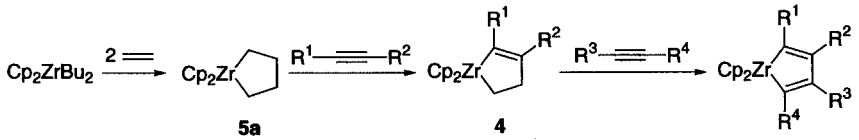
Eq. 2.2. Preparation of zirconacyclopentadienes using the Negishi reagent.

For unsymmetrical zirconacyclopentadienes, Cp_2ZrEt_2, which we developed as an equivalent to the zirconocene–ethene complex (**3**), is a very useful reagent [13]. Two different alkynes couple selectively via zirconacyclopentenes (**4**) (Eq. 2.3).



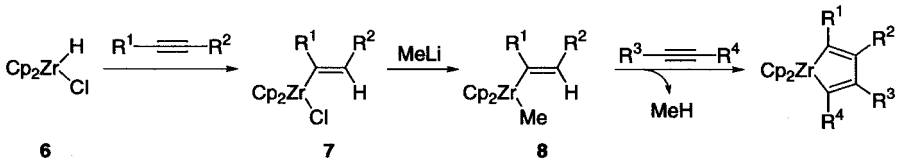
Eq. 2.3. Preparation of unsymmetrical zirconacyclopentadienes using Cp_2ZrEt_2.

In order to prepare very clean unsymmetrical zirconacyclopentadienes, the use of ethene is a prerequisite [14] (Eq. 2.4). An excess of ethene stabilizes the intermediates such as zirconacyclopentane **5a** and zirconacyclopentene **4**. Such a transformation from a metallacyclopentane to a metallacyclopentene was first demonstrated by Erker in the case of the hafnium analogues [15].



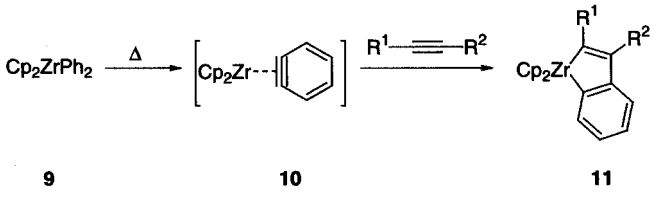
Eq. 2.4. Preparation of unsymmetrical zirconacyclopentadienes using ethene.

Hydrozirconation of alkynes with the Schwartz reagent, $Cp_2Zr(H)Cl$ (**6**), and subsequent methylation is also a general method (Eq. 2.5) [16].



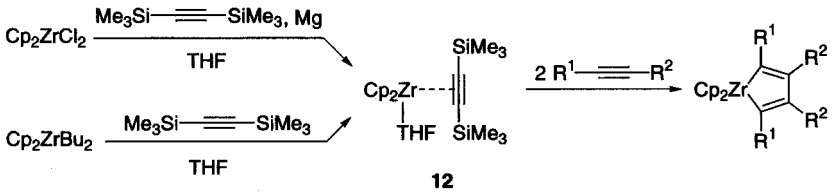
Eq. 2.5. Preparation of zirconacyclopentadienes using the Schwartz reagent.

Thermolysis of diphenylzirconocene (**9**) affords the zirconocene–benzyne complex (**10**), which can provide zirconaindene complexes (**11**) (Eq. 2.6) [17].



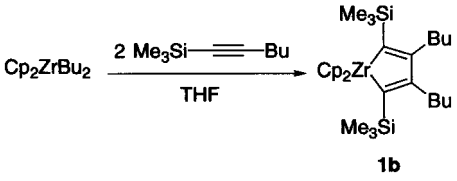
Eq. 2.6. Preparation of zirconaindene complexes.

Rosenthal's reagent, $Cp_2Zr(Me_3SiCCSiMe_3)$ (**12**), which can be prepared from bis(trimethylsilyl)acetylene and either Cp_2ZrCl_2/Mg [18] or Cp_2ZrBu_2 [19], has also proved useful (Eq. 2.7).



Eq. 2.7. Preparation of zirconacyclopentadienes using Rosenthal's reagent.

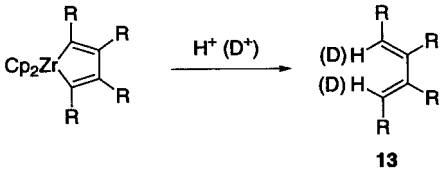
The regiochemistry can be controlled by the nature of the substituents. With a trimethylsilyl-substituted acetylene, the trimethylsilyl groups are placed in α positions of zirconacyclopentadienes with excellent selectivity (Eq. 2.8) [20]. With a phenyl-substituted alkyne, regioselective reactions are usually observed, although in some cases a mixture of two isomers may be formed.



Eq. 2.8. Regioselective formation of a zirconacyclopentadiene using a trimethylsilyl-substituted acetylene.

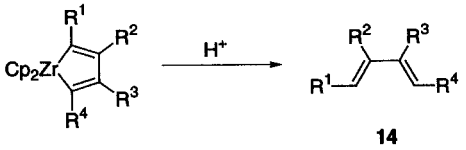
2.2.2 Hydrolysis

The simplest reaction of zirconacyclopentadienes is their hydrolysis. It is characteristic for organo-early transition metal compounds; the metal–carbon bond is easily hydrolyzed with acids to give free organic compounds. Similarly, deuterolysis of zirconacyclopentadienes, rather than protonolysis, affords deuterated compounds as expected (Eq. 2.9). The position of the deuterium is indicative of the position of the metal–carbon bond in the organozirconium compound.



Eq. 2.9. Hydrolysis or deuterolysis of zirconacyclopentadienes.

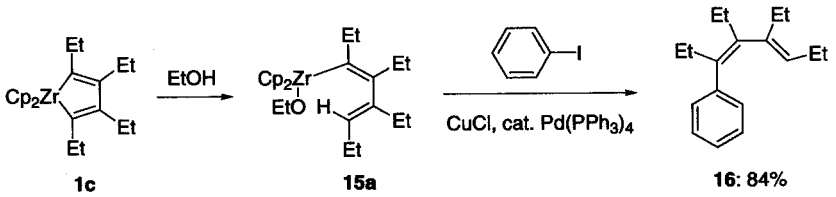
Hydrolysis of zirconacyclopentadienes provides, in a stereocontrolled manner, 1,2,3,4-tetrasubstituted dienes **13**. In particular, unsymmetrical diene derivatives **14** can be prepared by this method (Eq. 2.10) [14].



Eq. 2.10. Hydrolysis of unsymmetrical zirconacyclopentadienes.

Table 2.1 shows several examples of the coupling of two different alkynes on zirconocene and the resulting hydrolysis products using ethene gas according to Eq. 2.4.

Protonolysis with weak acids such as ethanol gives mono-protonated dienylzirconocene compounds **15a** (Eq. 2.11), which can be converted into substituted diene derivatives **16** [21].



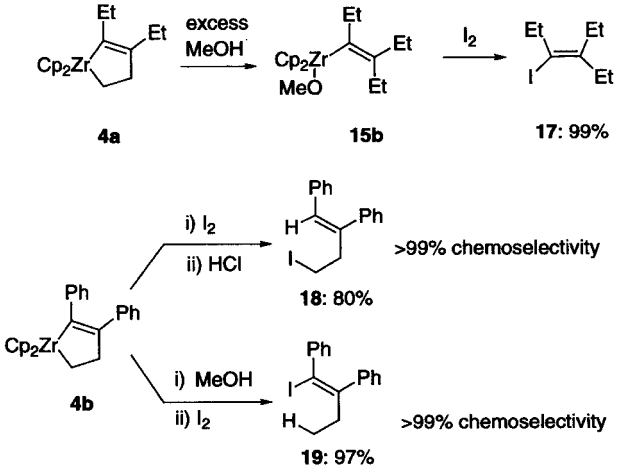
Eq. 2.11. Protonolysis of a zirconacyclopentadiene with ethanol.

Table 2.1. Cross-coupling reactions of alkynes on zirconocene

1st alkyne R^1—≡—R^2	*2nd alkyne* R^3—≡—R^4	*Yield (%)*[a]	*% dimer of 1st alkyne*[b]	*% dimer of 2nd alkyne*[b]
Pr—≡—Pr	Et—≡—Et	97	0	<1
Pr—≡—Pr	Bu—≡—Bu	94	<1	0
Pr—≡—Pr	Ph—≡—Ph	83	2	0
Ph—≡—Ph	Pr—≡—Pr	90	0	1
Pr—≡—Pr	Ph—≡—H	77[c]	0	0
Me_3Si—≡—Bu	Ph—≡—Ph	88	3	0
Ph—≡—Ph	Me_3Si—≡—Bu	92	1	0
Me_3Si—≡—Me	Ph—≡—Ph	96	<1	0
Ph—≡—Ph	Me_3Si—≡—Me	95	Trace	0
Ph—≡—Ph	Ph—≡—H	93[d]	0	Trace
Ph—≡—H	Ph—≡—Ph	71[d]	0	0

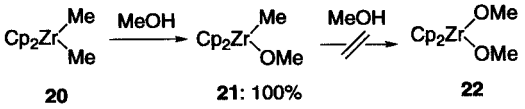
[a] Yields were determined by gas chromatography after hydrolysis of the reaction mixture.
[b] Maximum yield of dimer is 50%.
[c] Two isomers in a 20:1 ratio.
[d] Two isomers in a 18:1 ratio.

As the second protonation of zirconacycles with weak acids such as methanol is much slower than the first, selective reactions can easily be performed (e.g. protonation with methanol, followed by iodination of the corresponding vinyl zirconium derivative with complete control of the selectivity; see Eq. 2.12) [22].



Eq. 2.12. Chemoselective reaction of zirconacyclopentenes with MeOH and I_2.

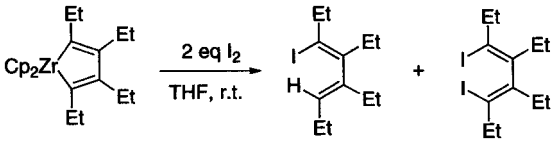
The first protonation occurs much more rapidly at the sp^3 carbon attached to zirconium than at the sp^2 carbon. Reaction at the sp^2 carbon attached to the zirconium in the zirconacyclopentene is very slow with methanol. As regards the second protonation of the organozirconocene, even the sp^3 carbon does not react with MeOH (Eq. 2.13) [23].



Eq. 2.13. Protonation of an organozirconocene containing two sp^3 carbons with MeOH.

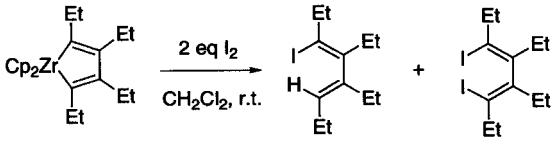
2.2.3 Halogenolysis

Halogenolysis of zirconacyclopentadienes affords 1,4-dihalodienes (Eq. 2.14) [20]. Solvent effects on halogenolysis are remarkable. Indeed, whereas the iodination of zirconacyclopentadienes in THF with 2 equivalents of I_2 affords mainly the monoiodinated diene, the diiododiene can be the major product in CH_2Cl_2. For example, 2,3,4,5-tetraethylzirconacyclopentadiene reacts with 2 equivalents of I_2 in THF at room temperature to give the monoiodinated 3-iodo-4,5-diethylocta-3,5-diene **23** in 70 % yield along with only an 18 % yield of 3,6-diiodo-4,5-diethylocta-3,5-diene **24** (Eq. 2.14).



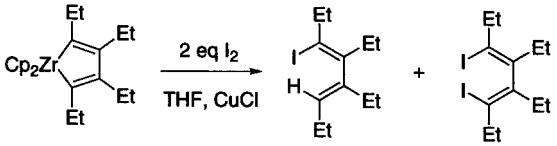
Eq. 2.14. Reaction of a zirconacyclopentadiene with I_2 in THF.

When the same iodination reaction is carried out in CH_2Cl_2 at room temperature, the diiodination product **24** is obtained in 73 % yield as the major product, accompanied by an 18 % yield of the monoiodination product **23** (Eq. 2.15) [20].



Eq. 2.15. Reaction of a zirconacyclopentadiene with I_2 in CH_2Cl_2.

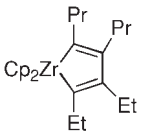
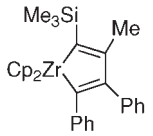
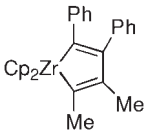
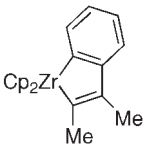
Transmetalation of zirconacyclopentadienes to copper will be discussed later. However, it is noteworthy here that when the iodination is carried out in THF in the presence of 2 equivalents of CuCl, the product of diiodination (**24**) is obtained in 95 % yield without any trace of the monoiodinated adduct **23** (Eq. 2.16) [24].



Eq. 2.16. Selective formation of the diiodination product from a zirconacyclopentadiene using CuCl.

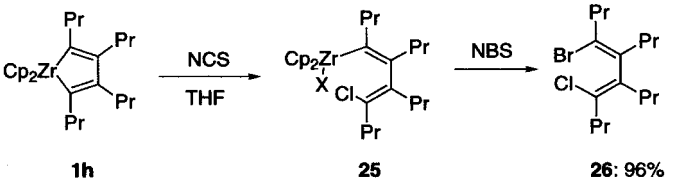
This transmetalation of zirconacyclopentadienes to copper is very effective. Table 2.2 shows several examples of diiodination reactions of zirconacyclopentadienes performed in the presence of CuCl.

Table 2.2. Diiodination of zirconacyclopentadienes using CuCl[a]

Zirconacyclopentadienes	*CuCl (n eq.)*	*I_2*	*Monoiodide (%)*	*Diiodide (%)*
 **1d**	1	2	0	79
 **1e**	1	2	0	66
 **1f**	1	2	0	94
 **1g**[b]	1	2	0	76

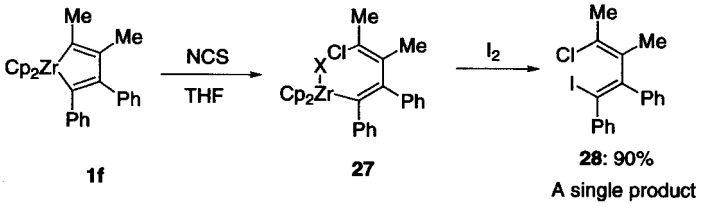
[a] All the reactions were performed at room temperature.
[b] When the zirconaindene complex was prepared in benzene, the diiodide was cleanly formed without CuCl.

Selective mixed halogenation of zirconacyclopentadienes is attractive from a synthetic point of view. Indeed, the successive treatment of zirconacyclopentadienes with *N*-chlorosuccinimide (NCS) followed by iodine, *N*-bromosuccinimide (NBS)/I_2, or NCS/NBS selectively affords chloroiododienes, bromoiododienes, and chlorobromodienes, respectively (Eq. 2.17) [25].



Eq. 2.17. Selective mixed halogenation of a zirconacyclopentadiene.

Iodine cannot be used as the first halogenating agent for this tandem halogenation reaction since halogen exchange occurs to give diiodides rather than mixed halogenated dienes. It is interesting to note that with unsymmetrical zirconacyclopentadienes such as 2,3-diphenyl-4,5-dimethylzirconacyclopentadienes (**1f**), the initial chlorination with NCS occurs selectively at the methyl-substituted carbon attached to zirconium. The subsequent iodination with I_2 occurs at the other carbon, i. e. that bearing a phenyl substituent. However, such excellent selective halogenation is substituent-dependent (Eq. 2.18) [25].

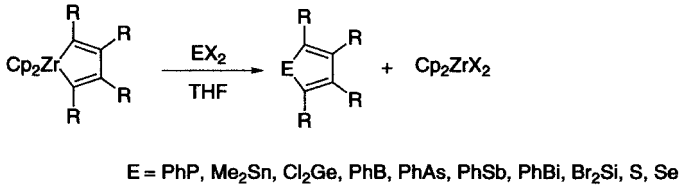


Eq. 2.18. Selective mixed halogenation of an unsymmetrical zirconacyclopentadiene.

2.2.4

Formation of Heterocycles by Substitution Reactions

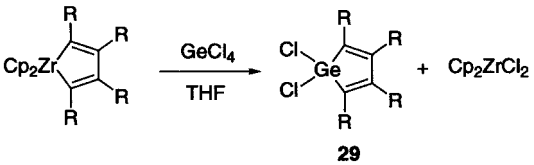
An important area of progress in zirconacyclopentadiene chemistry has been the heteroatom transfer developed by Fagan and Nugent, leading to five-membered heterocycles (Eq. 2.19) [26].



Eq. 2.19. Heterocycle formation from zirconacyclopentadienes by heteroatom transfer.

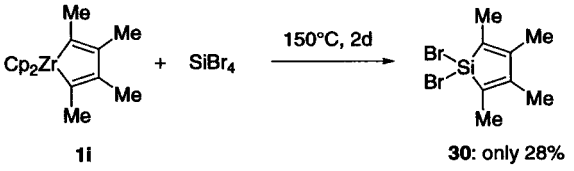
Heteroatom transfer in metallacyclopentadienes was first developed in the context of cobalt chemistry in the mid-1970s [27]. Cobaltacyclopentadienes were converted into various five-membered heterocyclic compounds such as pyrrole and thiophene, and into six-membered heterocyclic compounds such as pyridine and pyridone derivatives. In the case of zirconacyclopentadienes, the heteroatom compound must bear at least two halide substituents, since the "Cp_2Zr" moiety is re-converted to the stable Cp_2ZrX_2. Indeed, this is the driving force behind the heteroatom transfer of zirconacyclopentadienes.

The reaction of zirconacyclopentadienes with Group 14 compounds such as Me_2SiCl_2, Me_2GeCl_2, and Me_2SnCl_2 should be discussed here. $GeCl_4$ readily reacts with both monocyclic and bicyclic zirconacyclopentadienes (Eq. 2.20) [26].



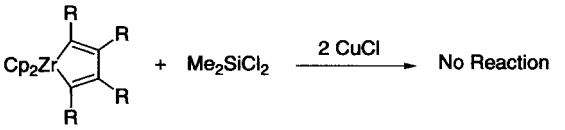
Eq. 2.20. Reaction of zirconacyclopentadienes with $GeCl_4$.

Neat $SiBr_4$ was found to react with 2,3,4,5-tetramethylzirconacyclopentadiene (**1i**) at 150 °C, but only 28 % of the silol **30** was obtained (Eq. 2.21) [26].



Eq. 2.21. Reaction of tetramethylzirconacyclopentadiene with $SiBr_4$.

Me_2SiCl_2 does not react with either monocyclic or bicyclic zirconacyclopentadienes (Eq. 2.22) [7g,7h].

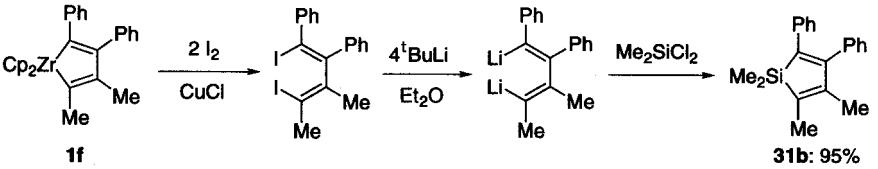


Eq. 2.22. No reaction between zirconacyclopentadienes and Me_2SiCl_2

Steric constraints and size-mismatching of Me_2SiCl_2 with zirconacyclopentadienes are the main reasons for the lack of reactivity. When the steric factor is reduced, in other words, when $MeHSiCl_2$ is used as a silyl electrophile, the reaction proceeds at room temperature to give 88 % of the corresponding silols after 24 h. Moreover, the reaction of H_2SiCl_2 with 2,3,4,5-tetraethylzirconacyclopentadiene (**1c**) generates the corresponding silol **31a** in 92 % yield within 5 min. (Eq. 2.23) [28]. This result clearly shows the importance of the steric factor in this heteroatom transfer.

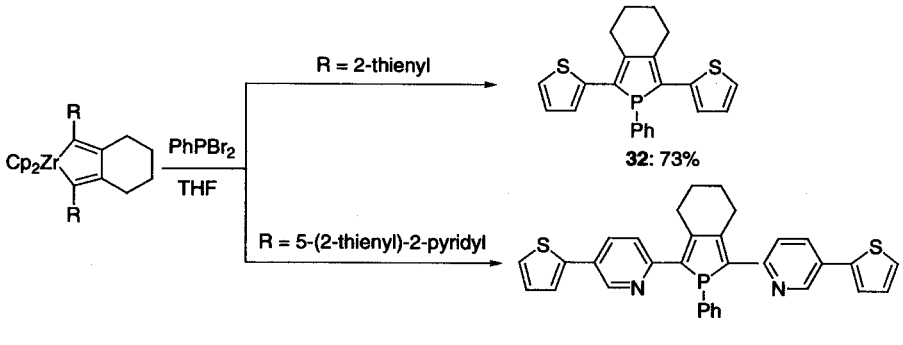
Eq. 2.23. Reaction of a zirconacyclopentadiene with H_2SiCl_2.

For the preparation of substituted silols such as **31b**, it can be circumvented by using dilithiated dienes obtained from diiododienes prepared as described above. As various kinds of diiododienes are available in high yields (*vide supra*), this method should be very useful (Eq. 2.24) [24].



Eq. 2.24. Preparation of a silol from a zirconacyclopentadiene via a diiododiene.

Phosphole formation from zirconacyclopentadienes is useful for preparing novel organic materials. As shown in Eq. 2.25, this method can provide monomers (**32** and **33**) or oligomers for electropolymerization reactions [29].



Eq. 2.25. Preparation of phospholes from zirconacyclopentadienes.

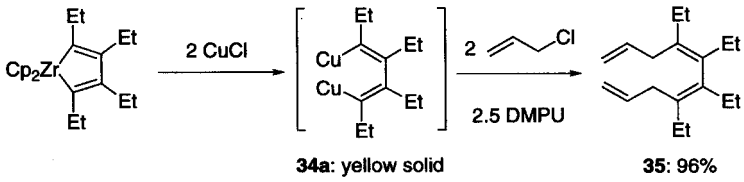
2.3 Carbon–Carbon Bond Formation

2.3.1 Transmetalation

As mentioned above, for more than 20 years after the first preparation of zirconacyclopentadiene, no systematic carbon–carbon bond-forming reactions were investigated. The major reason was the low nucleophilicity of the zirconacyclopentadienes. Indeed, such was the reputation of zirconacyclopentadienes in the 1980s that they were referred to as "dead-end compounds". This statement clearly emphasizes the assumption that zirconacyclopentadienes were completely inert with regard to the creation of carbon–carbon bonds. In this context, transmetalation of zirconacyclopentadienes to copper and subsequent carbon–carbon bond formation represents a milestone in zirconacyclopentadiene chemistry.

2.3.1.1 Transmetalation to Copper

Addition of CuCl to a solution of a 2,3,4,5-tetraethylzirconacyclopentadiene in THF at room temperature leads to the precipitation of a yellow solid (**34a**) (Eq. 2.26) [6].



Eq. 2.26. Transmetalation of a zirconacyclopentadiene to Cu.

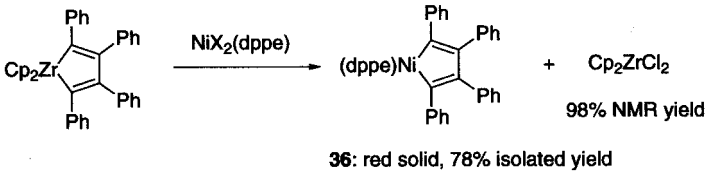
Although not completely characterized, this yellow solid was assumed to be a dicopper diene derivative. In order to dissolve the yellow precipitate, DMPU (dimethylpropylene urea) was required. The dicopper diene species **34a** is unstable in solution and gradually decomposes to undefined compounds. Therefore, all reactions involving transmetalation to copper are performed in situ in a one-pot or one-step process.

As described above, when CuCl is regenerated in the reaction, the process can be catalytic in copper. In other cases, a stoichiometric amount (2 equiv.) of CuCl is used. Although CuCN shows similar reactivity, CuBr and CuI are not so effective as compared to CuCl. Allylation; benzene, naphthalene, and anthracene formation, as well as acylation are representative examples, which are described below.

2.3.1.2 Transmetalation to nickel

The aforementioned dienyl dicopper derivatives show the characteristic reactivity of organocopper compounds. However, one limitation to the use of copper is that an electron-withdrawing group is usually required for reaction with alkynes. In order to develop an insertion protocol for alkynes bearing electron-donating groups, transmetalation of zirconacyclopentadienes to nickel was investigated.

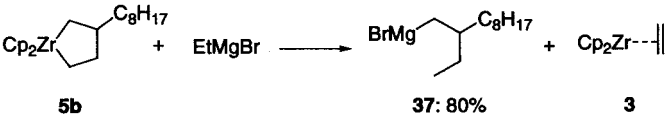
When 2,3,4,5-tetraphenylzirconacyclopentadiene was treated with $NiCl_2$(dppe) under reflux, the 2,3,4,5-tetraphenylnickelacyclopentadiene-dppe complex **36** was obtained as a red solid in 78 % isolated yield, along with Cp_2ZrCl_2 (98 % yield by NMR) (Eq. 2.27) [8a]. This complex was the same as that prepared from $NiCl_2$(dppe) and 1,4-dilithio-1,2,3,4-tetraphenyl-1,3-diene [30]. In the case of $NiCl_2(PPh_3)_2$, a similar transmetalation can proceed. Using this method, benzene and pyridine formation and CO insertion have been developed [8a,8b,46].



Eq. 2.27. Transmetalation of a zirconacyclopentadiene to Ni.

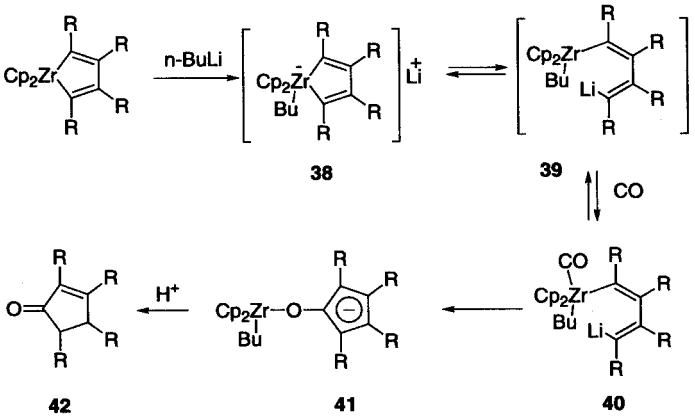
2.3.1.3 Transmetalation to lithium

As the electronegativity of zirconium is greater than that of lithium according to Pauling, the transmetalation of zirconacyclopentadienes to lithium sounds strange. Indeed, an organic moiety on lithium is usually transmetalated to zirconium. However, as reported in the transmetalation of zirconacyclopentane (**5b**) to magnesium, if there is some compensation of the energy and if the step is in equilibrium, such transmetalation in the opposite direction can occur (Eq. 2.28) [31].



Eq. 2.28. Transmetalation of a zirconacyclopentane to Mg.

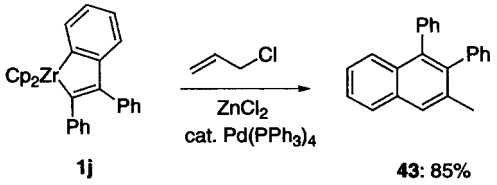
Actually, while zirconacyclopentadienes alone do not react with CO at −78 °C, the addition of BuLi allows the reaction to proceed, thereby leading to cyclopentenones **42** (Eq. 2.29) [10]. A similar transmetalation to Li has been proposed for zirconacyclopentanes.



Eq.2.29. Transmetalation of zirconacyclopentadienes to Li.

2.3.1.4 **Transmetalation to zinc**

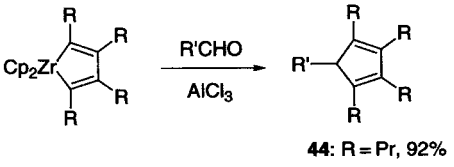
It is well known that alkenylzirconocenes are transmetalated to zinc and conveniently undergo further palladium-catalyzed cross-coupling reactions [7k,8a,32]. Although the transmetalation of zirconacyclopentadienes to zinc is not yet well developed, some interesting reactions that take place in the presence of $ZnCl_2$ have already been described (Eq. 2.30) [9].



Eq. 2.30. Transmetalation of a zirconacyclopentadiene to Zn.

2.3.1.5 **Transmetalation to aluminum**

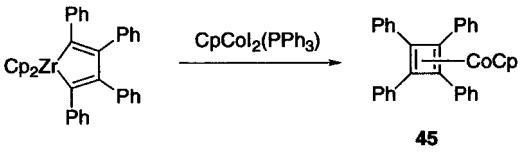
As yet, there are not many examples of this. As a representative example, the reaction of zirconacyclopentadienes with aldehydes in the presence of $AlCl_3$ affords cyclopentadiene derivatives. In this case, the aluminum abstracts the oxygen atom from the aldehyde moiety (Eq. 2.31) [11]. Aluminacyclopentadiene might be the intermediate in this reaction.



Eq. 2.31. Transmetalation of zirconacyclopentadienes to Al.

2.3.1.6 Transmetalation to other metals

Transmetalations of zirconacyclopentadienes to other metals have to be found and the products can be expected to show some characteristic carbon–carbon bond formation. For example, evidence for the transmetalation of zirconacyclopentadienes to Co has been described (Eq. 2.32) [33]. The most attractive feature of the transmetalation of zirconacyclopentadienes is the formation of dimetallo-diene species, the reactivities of which are completely dependent on the metal.

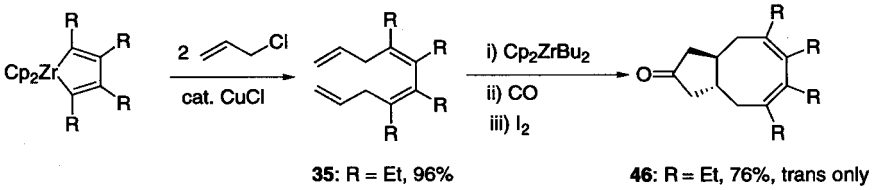


Eq. 2.32. Transmetalation of a zirconacyclopentadiene to Co.

2.3.2 Coupling Reactions

2.3.2.1 Coupling with allyl halides

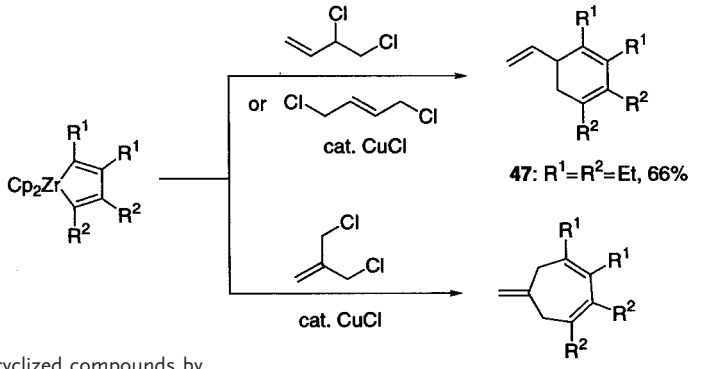
The first carbon–carbon bond-forming reaction of zirconacyclopentadienes involving a copper transmetalation was the double allylation reaction shown in Eq. 2.33 [6].



Eq. 2.33. Double allylation of zirconacyclopentadienes catalyzed by CuCl.

Here, both carbons attached to the zirconium react with allyl chloride in the presence of a catalytic amount of CuCl. In a subsequent step, the formed tetraenes (**35**) cyclize with Cp_2ZrBu_2 to give the corresponding zirconacyclopentanes, which, by a carbonylation reaction at low temperature and subsequent treatment with iodine, afford the 8-5 fused-ring ketones (**46**) in good yields. In this case, the six carbons C3–C8 are fixed in a plane and hence the two terminal double bonds can coordinate simultaneously to the zirconocene and lead to the zirconacyclopentane compounds. This cyclization to an eight-membered ring can be attributed to the system of two conjugated dienes within the tetraenes. It is noteworthy that 1,9-dodecadiene is not cyclized with Cp_2ZrBu_2 to produce an eight-membered ring compound.

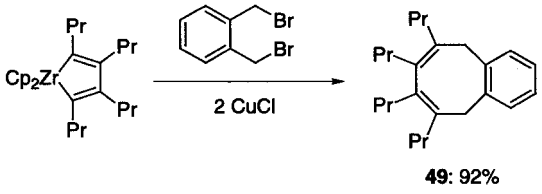
When the electrophile contains two allyl halide moieties, two carbon–carbon bonds are formed, resulting in cyclized compounds **47** and **48**, as shown in Eq. 2.34 [7f].



Eq. 2.34. Preparation of cyclized compounds by double allylation of zirconacyclopentadienes.

2.3.2.2 **Coupling with benzyl halides**

In a similar way to allyl chloride, benzyl halides also react smoothly with zirconacyclopentadienes in the presence of CuCl. An interesting reaction is shown in Eq. 2.35, whereby the benzo-type eight-membered ring compound **49** can be prepared [7j].



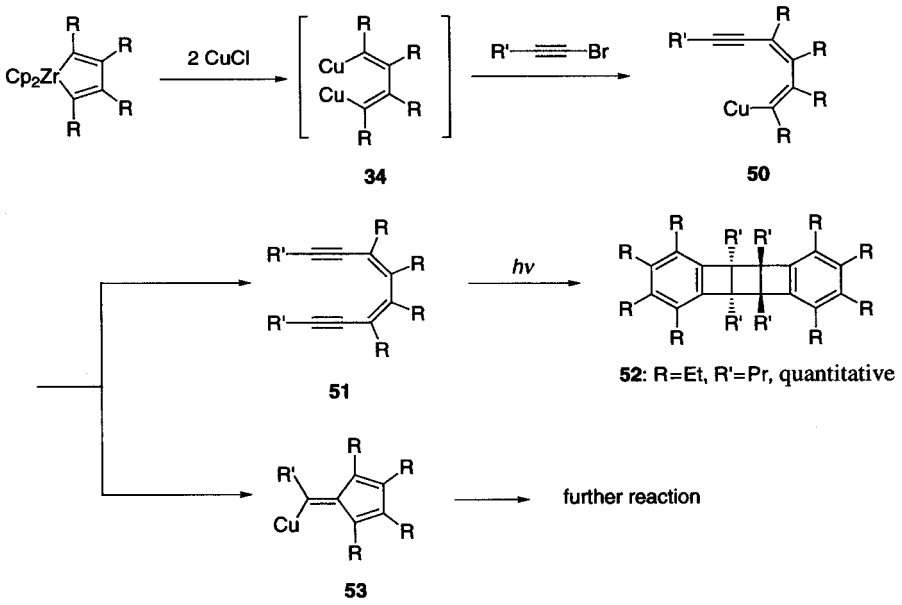
Eq. 2.35. Preparation of an eight-membered ring by the reaction of a zirconacyclopentadiene with bis(bromomethyl)benzene.

2.3.2.3 **Coupling with alkynyl halides**

Yields of the coupling products with alkynyl bromides are relatively low as compared with those obtained with allyl chloride or benzyl chloride. One reason for this is the instability of the product. The dienediynes **51** are slowly cyclized under the influence of light to give pentacyclic dimers **52** (Eq. 2.36), one of which has been characterized by X-ray analysis.

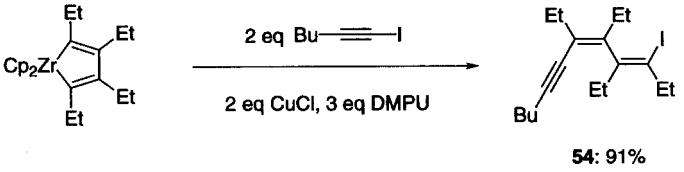
The second reason for the lower yields is the high reactivity of the intermediate. Two molecules of the alkynyl bromide react in a stepwise manner with the zirconacyclopentadiene. When one alkynyl halide molecule couples with the zirconacyclopentadiene, the intermediate bears a metalladienyne moiety (as in **50**), as shown in Eq. 2.36 [34].

The remaining alkenyl copper moiety in **50** can react intramolecularly with the carbon–carbon triple bond to give metallofulvene derivatives **53**. However, the coupling of the intermediate with the second molecule of alkynyl halide would seem to be faster than the cyclization reaction. Therefore, the dienediyne is obtained as the major product.



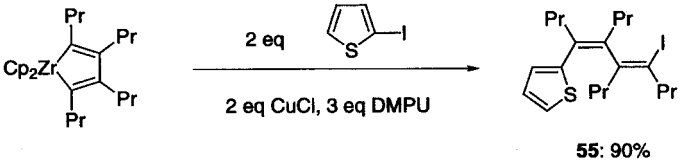
Eq. 2.36. Coupling reaction of zirconacyclopentadienes with alkynyl bromides.

The coupling with alkynyl iodides in the presence of CuCl and DMPU proceeds quite differently from that with alkynyl bromides. Although the first step of the coupling is the same, the subsequent Cu/I exchange reaction of the intermediate is different. As the final product, iododienyne **54** is obtained in high yields, as shown in Eq. 2.37 [35]. In the case of alkynyl bromides, Cu/Br exchange does not proceed. Therefore, the alkenyl copper moiety couples with the second alkynyl bromide molecule.



Eq. 2.37. Coupling reaction of a zirconacyclopentadiene with an alkynyl iodide.

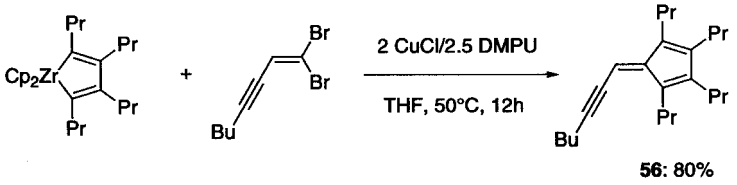
Similar coupling and iodination reactions are observed with thienyl iodide, as shown in Eq. 2.38 [35]. Thus, carbon–carbon bond formation occurs with the first molecule of thienyl iodide, and subsequent Cu/I exchange occurs with the second molecule.



Eq. 2.38. Coupling reaction of a zirconacyclopentadiene with thienyl iodide.

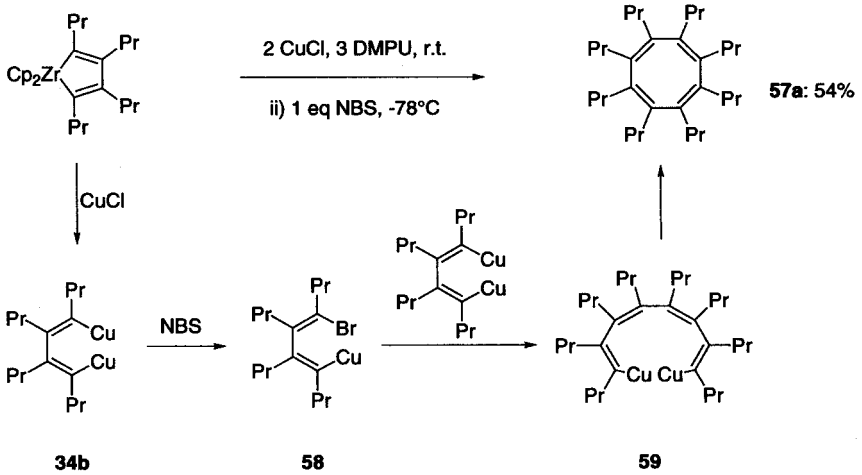
2.3.2.4 Coupling with alkenyl halides

As shown in Eq. 2.39, 1,1-dihaloalkenes react with zirconacyclopentadienes to afford fulvene compounds (**56**) [7p].



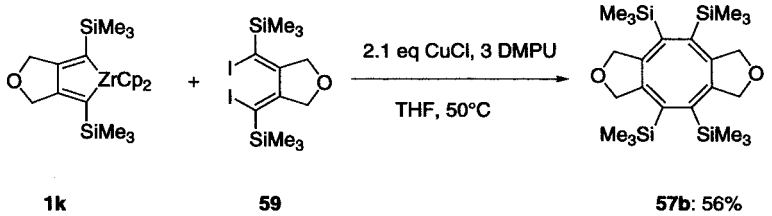
Eq. 2.39. Coupling reaction of a zirconacyclopentadiene with a 1,1-dibromoalkene.

After treatment of zirconacyclopentadienes with 2 equivalents of CuCl at room temperature, the addition of a halogenating agent such as NBS at −78 °C leads to the formation of octatetraenes **57a** [7m]. This reaction involves slow bromination of the diene-dicopper compounds and coupling with the alkenyl bromide moiety (Eq. 2.40).



Eq. 2.40. Preparation of a cyclooctatetraene from a zirconacyclopentadiene.

A more direct coupling affording an eight-membered ring is that of bicyclic zirconacyclopentadienes with diiododienes. As shown in Eq. 2.41 [36a], in the presence of the standard 2.1 equivalents of CuCl and 3 equivalents of DMPU, bicyclic zirconacyclopentadienes react with bicyclic diiododienes to produce similar eight-membered ring compounds. This

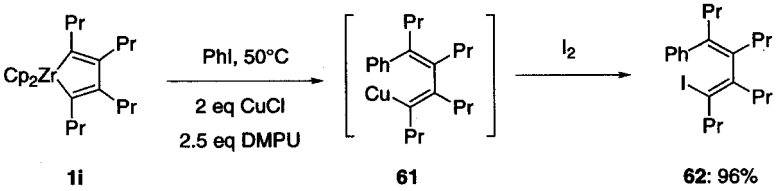


Eq. 2.41. Preparation of a tricyclic cyclooctatetraene from a bicyclic zirconacyclopentadiene and a diiododiene.

reaction is dependent on the size of the side ring of the bicyclic zirconacyclopentadiene. Simple zirconacyclopentadienes do not afford the desired eight-membered ring compounds. Even bicyclic zirconacyclopentadienes with a six-membered side ring do not react. This is due to the direction of the C–Cu bonds in the dienyldicopper compound and its matching with the direction of the C–I bonds in the diiododienes. Bicyclic zirconacyclopentadienes with a four-membered ring also afford cyclooctatetraenes [36b].

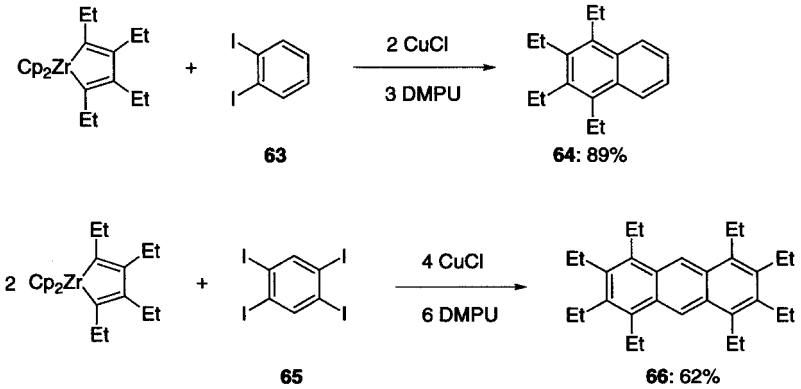
2.3.2.5 Coupling with aryl halides

In the presence of CuCl and DMPU, zirconacyclopentadienes react with iodobenzene to give phenyldienes or diphenyldienes in high yields (Eq. 2.42) [35].



Eq. 2.42. Reaction of a zirconacyclopentadiene with iodobenzene.

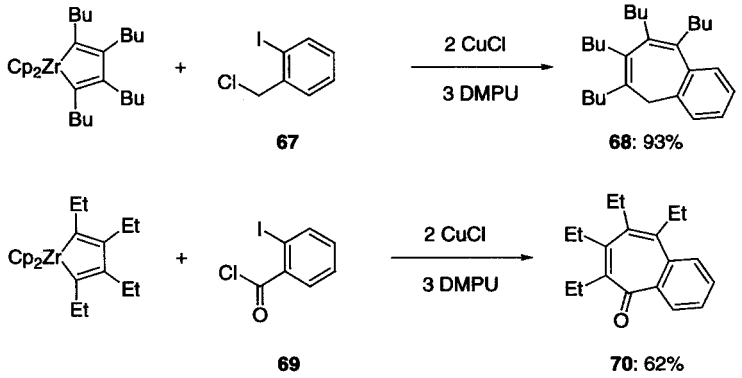
An application of this reaction to aromatic ring extension is noteworthy. As shown in Eq. 2.43, zirconacyclopentadienes couple with diiodobenzene (**63**) to afford naphthalenes **64**. When tetraiodobenzene (**65**) is used, octasubstituted anthracene derivatives **66** are obtained [7c].



Eq. 2.43. Reactions of a zirconacyclopentadiene with diiodobenzene and with tetraiodobenzene.

2.3.2.6 Combination of coupling reactions

As described above, the coupling of zirconacyclopentadienes with diiodobenzene affords six-membered aromatic rings (Eq. 2.43), while coupling with bis(bromomethyl)benzene gives eight-membered rings (Eq. 2.35). A combination of the aryl coupling and benzyl coupling, in other words the coupling of zirconacyclopentadienes with *o*-iodo(chloromethyl)-benzene, produces benzo-type seven-membered ring compounds (**68**). Benzoyl halide moieties also show a similar type of reactivity, as shown in Eq. 2.44 [7o].



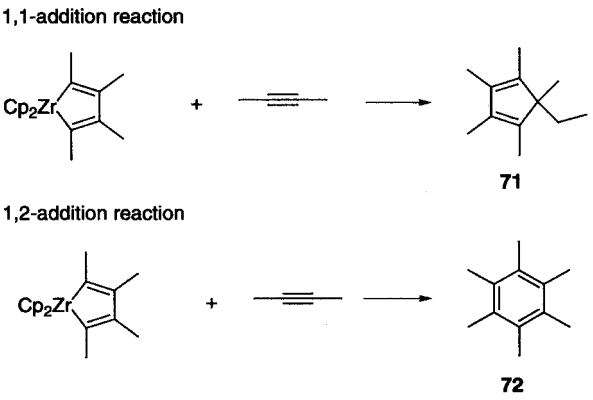
Eq. 2.44. Formation of seven-membered rings from zirconacyclopentadienes and *o*-iodo(chloromethyl)-benzenes.

2.3.3

Addition Reactions to Carbon–Carbon Triple Bonds

Addition reactions depend on the metal used for the transmetalation of the zirconacyclopentadiene. After transmetalation to copper, an addition reaction occurs to the carbon–carbon double bond or to a carbon–carbon triple bond bearing electron-withdrawing groups (Michael addition reactions). On the other hand, transmetalation to Ni allows the use of carbon–carbon triple bonds bearing electron-donating groups.

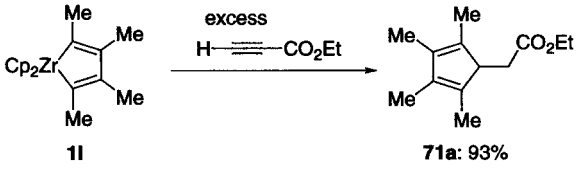
The addition reactions of zirconacyclopentadienes to carbon–carbon triple bonds can be classified into two types: (a) 1,1-addition reactions, and (b) 1,2-addition reactions, which furnish benzene derivatives as shown in Eq. 2.45.



Eq. 2.45. 1,1-Addition and 1,2-addition of zirconacyclopentadienes to alkynes.

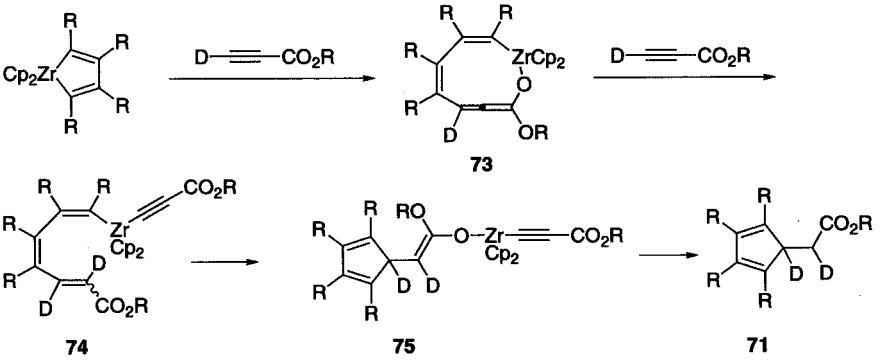
2.3.3.1 1,1-Addition to carbon–carbon triple bonds

1,1-Additions of metallacyclopentadienes to carbon–carbon triple bonds are rare, and only a few examples are known (Eq. 2.45) [37]. The 1,1-addition of zirconacyclopentadienes is quite different from other carbon–carbon bond-forming reactions described in this chapter. This reaction does not require transmetalation of zirconacyclopentadienes to other metals. Thus, in the absence of any added metal halide, zirconacyclopentadienes react with propynoates to give cyclopentadiene derivatives. This reaction requires the use of at least 2 equivalents of the propynoate (Eq. 2.46).



Eq. 2.46. 1,1-Addition of a zirconacyclopentadiene to a propynoate.

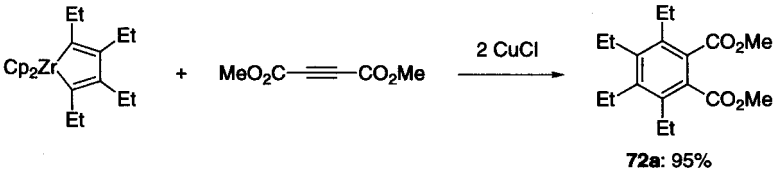
The first propynoate molecule undergoes a carbon–carbon bond-forming reaction with the zirconacyclopentadiene. The second molecule of the propynoate then donates a proton to the zirconacycle to open the ring. Further intermolecular Michael addition to the resulting carbon–carbon double bond produces the cyclopentadiene compounds. Investigations using deuterated propynoate were clearly indicative of the reaction mechanism shown in Eq. 2.47.



Eq. 2.47. Reaction pathway of 1,1-addition of zirconacyclopentadienes to propynoates.

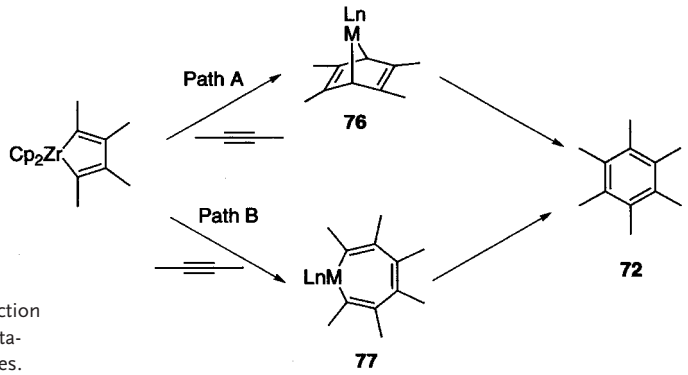
2.3.3.2 1,2-Addition to carbon–carbon triple bonds: Formation of benzene derivatives

Reactions of zirconacyclopentadienes with dimethyl acetylenedicarboxylate (DMAD) proceed to give benzene derivatives in high yields, as shown in Eq. 2.48 [7b,7k].



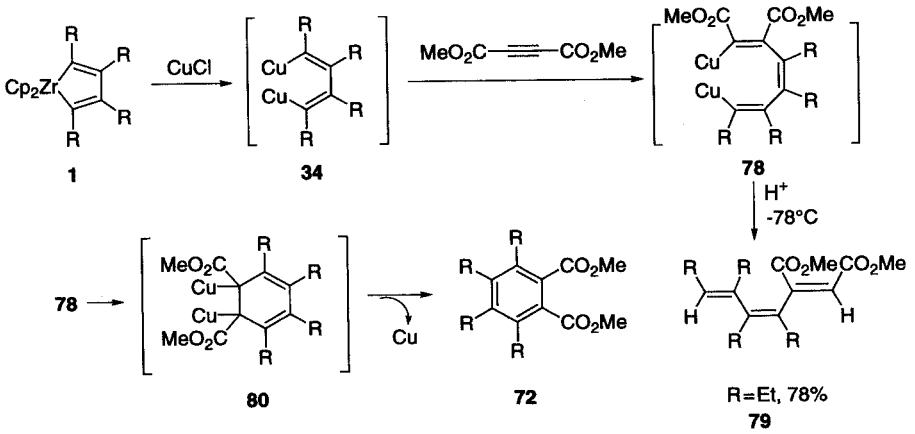
Eq. 2.48. 1,2-Addition of a zirconacyclopentadiene to DMAD.

Generally speaking, two mechanisms may be considered for the formation of benzene derivatives from metallacyclopentadienes. These are the concerted mechanism (Path A) and the insertion (addition) mechanism (Path B), as shown in Eq. 2.49.



Eq. 2.49. Two possible reaction paths from zirconacyclopentadienes to benzene derivatives.

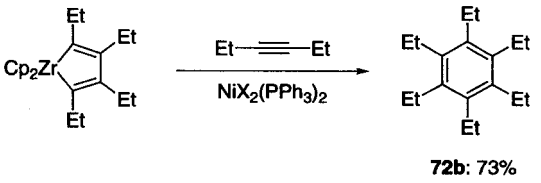
There are several examples of the concerted mechanism. However, no report of an insertion of a carbon–carbon triple bond into a metallacyclopentadiene had appeared prior to discovery of this reaction. At low temperatures, during the reaction of zirconacyclopentadienes with DMAD, the formation of trienes (**79**) is observed upon hydrolysis. This clearly indicates that the benzene formation involves the insertion (addition) reaction of DMAD. As shown in Eq. 2.50, the alkenyl copper moiety adds to the carbon–carbon triple bond of DMAD and elimination of Cu metal leads to the benzene derivatives **72**. Indeed, a copper mirror is observed on the wall of the reaction vessel.



Eq. 2.50. Reaction mechanism of benzene formation from zirconacyclopentadienes and DMAD in the presence of CuCl.

It is interesting to note that benzene derivatives are also obtained in the presence of only a catalytic amount of CuCl. In this case, copper metal deposition is obviously not observed. This means that there must be more than two routes from zirconacyclopentadienes to benzenes.

As for the third alkyne, at least one electron-withdrawing group is needed for the formation of benzene derivatives. The main path of this reaction is the addition of the alkenyl copper moiety to the carbon–carbon triple bond. Therefore, with copper chloride, alkynes bearing electron-donating groups cannot be used. This is a critical problem in benzene formation using CuCl. This problem can be solved by using $NiX_2(PPh_3)_2$. Alkyl-substituted alkynes such as 3-hexyne and 4-octyne react with zirconacyclopentadienes in the presence of $NiX_2(PPh_3)_2$ to give benzene derivatives **72b**, as shown in Eq. 2.51 [8a].



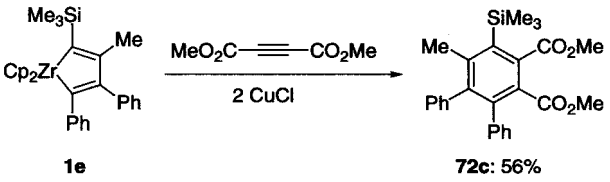
72b: 73%

Eq. 2.51. Preparation of a benzene derivative from a zirconacyclopentadiene in the presence of $NiX_2(PPh_3)_2$.

With $NiX_2(PPh_3)_2$, alkynes bearing either electron-donating or electron-withdrawing groups can be used for the formation of benzenes. The mechanism of the reaction in the presence of $NiX_2(PPh_3)_2$ is not yet clear. A study using $NiCl_2$(dppe) showed the formation of nickelacyclopentadienes, as described in Section 2.3.1.2. After the formation of nickelacyclopentadienes, both the concerted and insertion mechanisms are possible.

2.3.3.3 Benzene formation from three different alkynes

Transition metal mediated or catalyzed benzene formation reactions have been reported using various metals. However, the use of three different alkynes is difficult [38]. In many cases, a mixture of several benzene derivatives is obtained. In 1974, Wakatsuki and Yamazaki used three different alkynes with Co complexes [27b], but isomers were formed and a tedious chromatographic separation was necessary. The first selective coupling of three different alkynes in high yields was reported in 1995 using a combination of unsymmetrical zirconacyclopentadienes and CuCl, as shown in Eq. 2.52 [7k].



1e

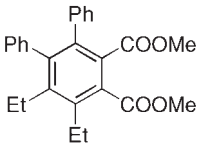
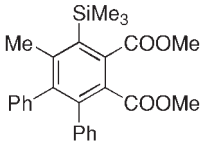
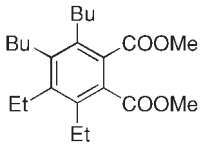
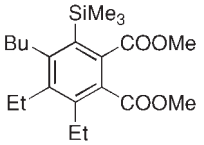
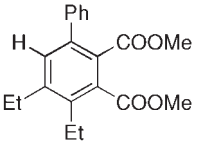
72c: 56%

Eq. 2.52. Benzene formation from three different alkynes using CuCl via a zirconacyclopentadiene.

The zirconacyclopentadiene prepared from unsymmetrical trimethylsilylpropyne and diphenylacetylene reacts with DMAD in the presence of 2 equivalents of CuCl and 3 equivalents of DMPU to give the corresponding benzene derivative **72c** in 56 % yield as a single product in a one-pot reaction. Some other examples are shown in Table 2.3.

In transition metal mediated or catalyzed reactions, high selectivity can be achieved, in many cases through the assistance of some functional groups. The selective coupling of three different alkynes bearing similar substituents is a difficult goal to achieve. In other words, selective coupling of three alkyl-substituted alkynes, such as 2-butyne, 3-hexyne, and 4-octyne, presents a considerable challenge. To this end, benzene formation from

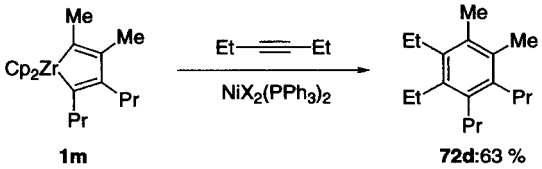
Table 2.3. Benzene formation from three different alkynes

1st Alkyne	*2nd Alkyne*	*Product*	*Yield (%)[a]*
Et—≡—Et	Ph—≡—Ph		95(63)
Me_3Si—≡—Me	Ph—≡—Ph		(56)
Bu—≡—Bu	Et—≡—Et		90(71)
Et—≡—Et	Me_3Si—≡—Bu		83(74)
Et—≡—Et	Ph—≡—H		85(66)

[a] GC yields. Isolated yields are given in parentheses.

three different alkynes via zirconacyclopentadienes in the presence of Ni complexes has proved valuable.

Unsymmetrical zirconacyclopentadiene **1m**, prepared from 2-butyne and 4-octyne, reacts with 3-hexyne in the presence of $NiCl_2(PPh_3)_2$ to give a single product (**72d**), as shown in Eq. 2.53 [8a].

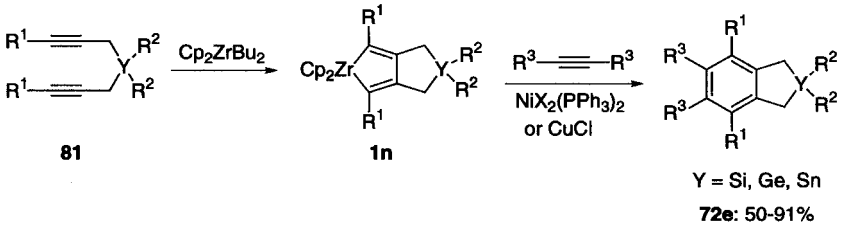


Eq. 2.53. Benzene formation from three different alkynes using $NiX_2(PPh_3)_2$ via a zirconacyclopentadiene.

This result clearly shows that the positions of three alkyl groups such as Me, Et, and Pr can be completely controlled in this reaction.

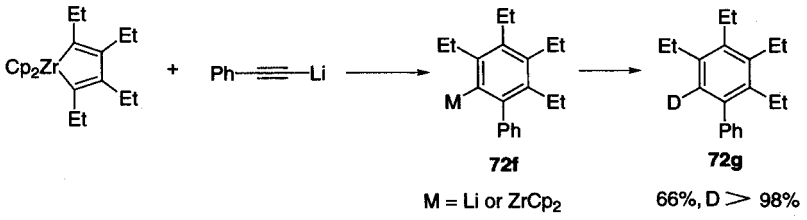
2.3.3.4 Applications of benzene formation

Benzo-type heterocyclic compounds can be prepared by this method. There have been many examples of this type of reaction using various metals, as shown in Eq. 2.54 [7q].



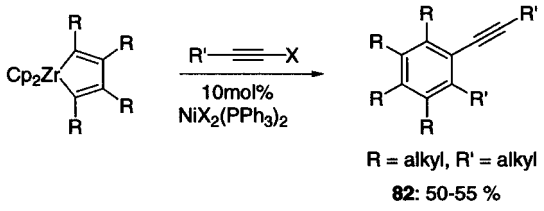
Eq. 2.54. Benzo-type heterocycle formation from zirconacyclopentadienes.

Metalated benzene derivatives can also be prepared by the reaction of alkynyl lithium reagents with zirconacyclopentadienes (Eq. 2.55) [39].



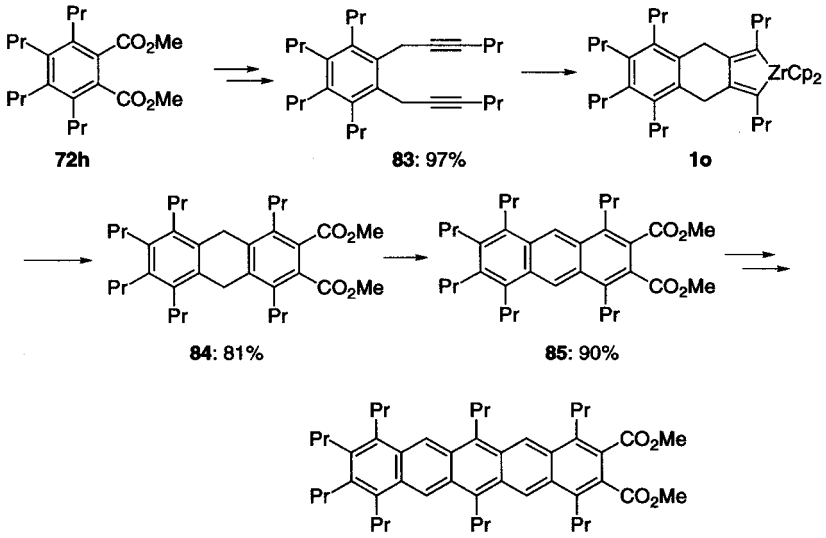
Eq. 2.55. Metalated benzene formation from a zirconacyclopentadiene.

Further carbon–carbon bond formation on the benzene ring is possible and the reaction can be catalytic when an Ni metal oxidation step is introduced, as shown in Eq. 2.56 [40].



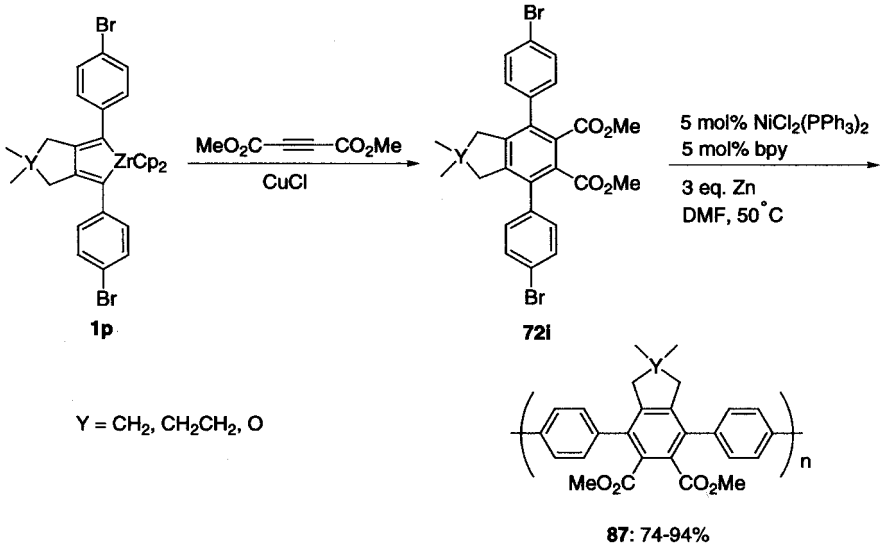
Eq. 2.56. Benzene formation from zirconacyclopentadienes catalyzed by Ni.

Pentacene is a useful compound in materials science, in particular for use in solar batteries, superconductors, and laser emission materials, etc. Unfortunately, however, pentacene is not soluble in organic solvents. As shown in Eq. 2.57, a combination of the aforementioned benzene formation reaction and alkynylation of phthalate leads to alkyl-substituted pentacenes, which are very soluble in various organic solvents [41].



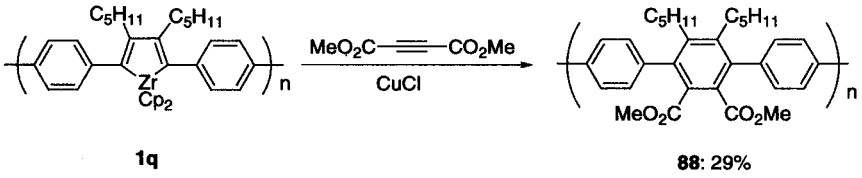
Eq. 2.57. Formation of a substituted pentacene.

Dibromoterphenyl compounds (**72i**) can be prepared from zirconacyclopentadienes. They polymerize in the presence of a Ni catalyst to afford polyphenylene derivatives **87**, as shown in Eq. 2.58 [42].



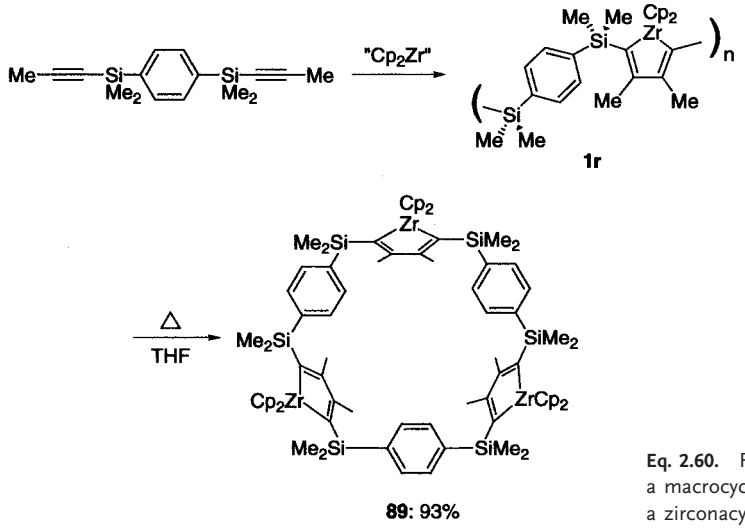
Eq. 2.58. Polyphenylene formation from zirconacyclopentadiene-containing precursors.

As shown in Eq. 2.59, zirconacyclopentadienes can be inserted into such a polymer chain (**1q**) from the beginning. The polymer can then be converted into polyphenylenes **88** in good yields [43]. Silyl-bridged diynes react with Cp_2ZrBu_2 to afford a macrocyclic trimer (**89**), as shown in Eq. 2.60 [43].



1q **88**: 29%

Eq. 2.59. Reaction of a zirconacyclopentadiene in a polymer chain with DMAD.

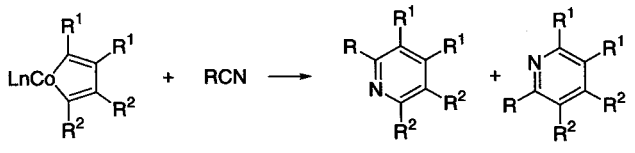


89: 93%

Eq. 2.60. Formation of a macrocyclic trimer from a zirconacyclopentadiene.

2.3.3.5 Addition of azazirconacyclopentadienes to carbon–carbon triple bonds. Formation of pyridine derivatives

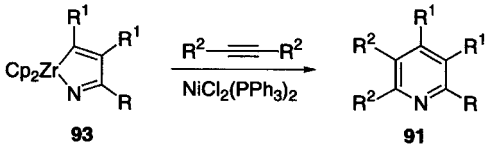
Pyridine formation, by the reaction of a metallacyclopentadiene with a nitrile, has been extensively investigated in the case of cobalt [1f]. When pyridine derivatives are prepared from two different alkynes and a nitrile, specific substituents are needed for the selective coupling reactions. In most cases, a mixture of two isomers (**91** and **92**) is obtained, the formation of which can be rationalized as shown in Eq. 2.61 [1f,27a,44].



90 **91** **92**

Eq. 2.61. Reaction of cobaltacyclopentadienes with nitriles.

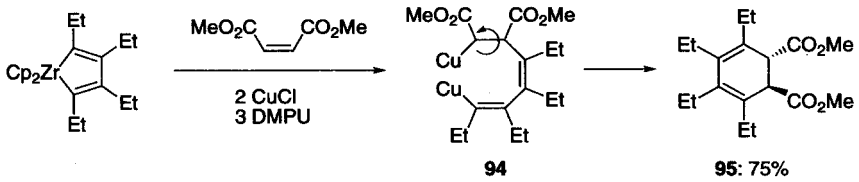
This selectivity can only be achieved with the assistance of functional groups on the alkynes. Thus, if an alternative selective procedure that was independent of the nature of the alkyne substituents were to be available, it would be synthetically very useful. In order to develop such a new procedure for the formation of pyridine derivatives, azazirconacyclopentadienes, prepared from an alkyne and a nitrile, are important. As shown in Eq. 2.62, treatment of an azazirconacyclopentadiene with an alkyne in the presence of $NiCl_2(PPh_3)_2$ gives a pyridine derivative as a single product [8b]. Preparative methods for azazirconacyclopentadiene derivatives will be discussed below.



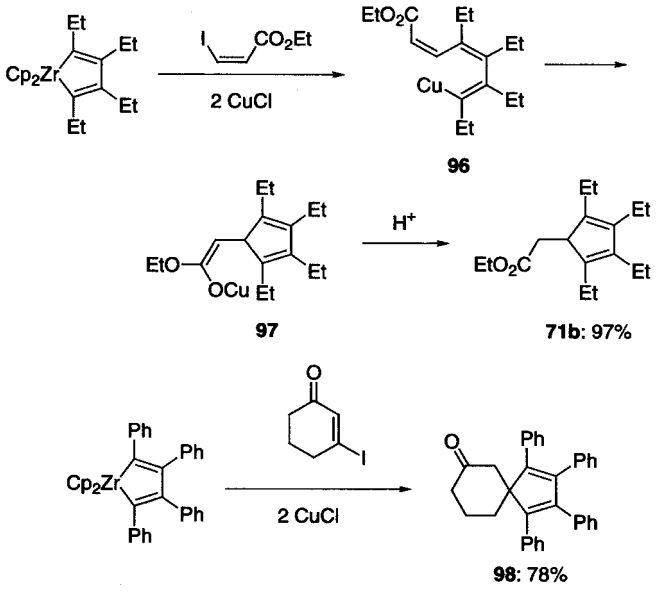
Eq. 2.62. Reaction of azazirconacyclopentadienes with nitriles.

2.3.3.6 **Addition to carbon–carbon double bonds**

In a similar way to the addition of zirconacyclopentadienes to DMAD, their addition to methyl maleate gives cyclohexadiene derivatives. It is noteworthy that the two COOMe groups are *cis* in the starting material and *trans* to one another in the product, as shown in Eq. 2.63 [7k].



Eq. 2.63. Addition of a zirconacyclopentadiene to an alkene.



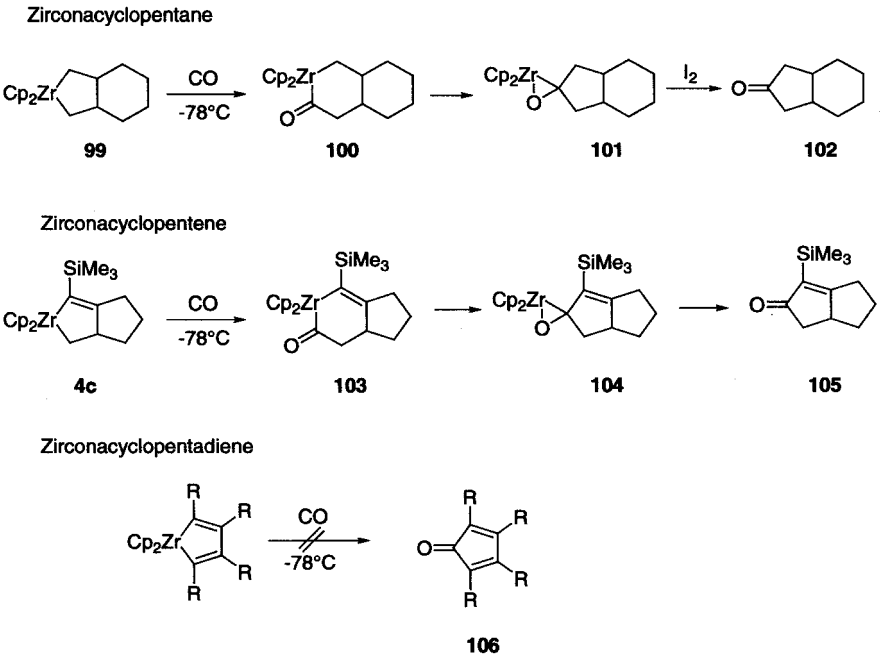
Eq. 2.64. Reactions of zirconacyclopentadienes with alkenyl iodides.

This result reveals that the reaction proceeds in a stepwise manner with rotation about the C–C single bond in the intermediate to produce the more stable product.

A combination of addition to an activated carbon–carbon double bond and the coupling reaction with alkenyl iodides produces cyclopentadienes or spiro-anellated cyclopentadiene derivatives **98**, as shown in Eq. 2.64 [7i,7n].

2.3.4 Insertion Reactions of Carbon Monoxide and Isonitriles

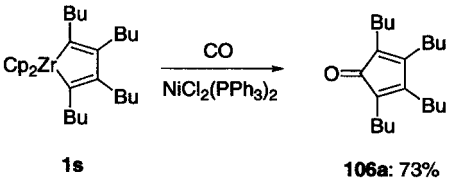
Zirconacyclopentadiene shows a different reactivity towards CO as compared with zirconacyclopentane and zirconacyclopentene. Zirconacyclopentane and zirconacyclopentene readily react with CO at low temperature to give cyclopentanone and cyclopentenone, respectively. The different reactivity of zirconacyclopentadienes can be explained by comparing the reactivity of the $Zr-C_{sp2}$ bond with that of the $Zr-C_{sp3}$ bond. Insertion of CO into the $Zr-C_{sp3}$ bond proceeds readily at low temperature and therefore zirconacyclopentane and zirconacyclopentene, which contain $Zr-C_{sp3}$ bonds, react directly with CO as shown in Eq. 2.65 [45]. Zirconacyclopentadienes, on the other hand, do not.



Eq. 2.65. Different reactivities of zirconacycles towards CO.

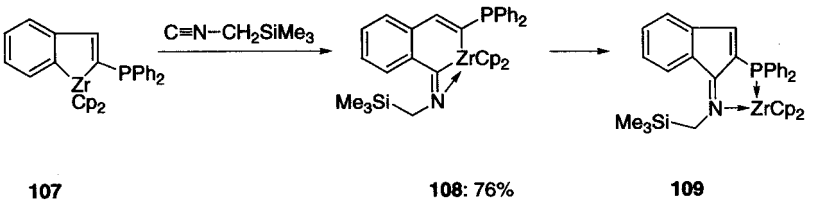
The first successful reaction of zirconacyclopentadienes with CO is shown in Eq. 2.29. However, this reaction gives cyclopentenones rather than cyclopentadienones. In order to form cyclopentadienones from zirconacyclopentadienes by CO insertion, transmetalation to Ni is very effective. Thus, in the presence of $NiCl_2(PPh_3)_2$, zirconacyclopentadienes react with CO to afford cyclopentadienones, as shown in Eq. 2.66 [46].

Eq. 2.66. Formation of a cyclopentadienone from a zirconacyclopentadiene.



1s **106a: 73%**

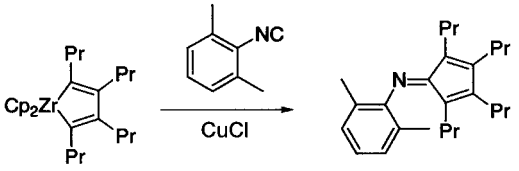
Usually, an isonitrile can be inserted without transmetalation. As shown in Eq. 2.67, Majoral et al. have isolated and characterized by X-ray analysis the intermediate involved in isonitrile insertion into zirconaindene complexes [47].



107 **108: 76%** **109**

Eq. 2.67. Reaction of a zirconaindene with an isonitrile.

In particular cases, such as with sterically hindered substituents in the α-positions of the zirconacyclopentadiene, the addition of CuCl is effective (Eq. 2.68) [46].



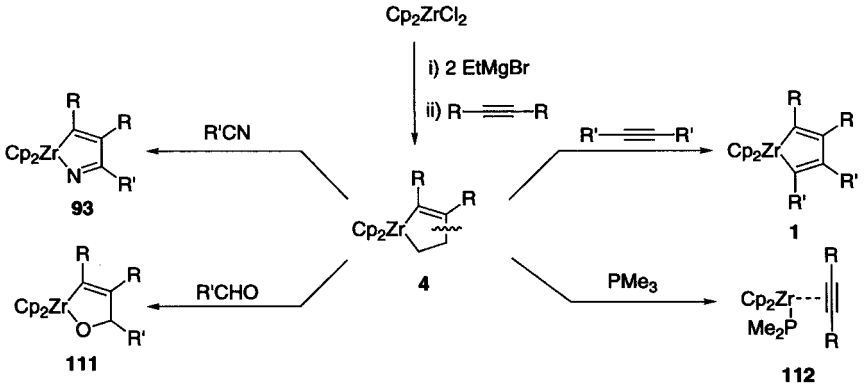
Eq. 2.68. Reaction of a zirconacyclopentadiene with an isonitrile.

1h **110: 63%**

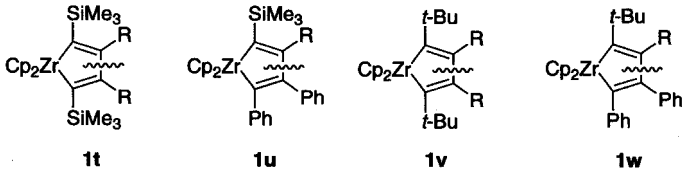
2.3.5
Carbon–Carbon Bond Cleavage Reactions

Cleavage of the β,β-carbon–carbon bonds of zirconacyclopentanes and zirconacyclopentenes is very often observed. This cleavage reaction is useful for the preparation of various zirconacycles. As examples, various transformations of zirconacyclopentenes involving β,β-carbon–carbon bond cleavage are shown in Eq. 2.69 [13,48].

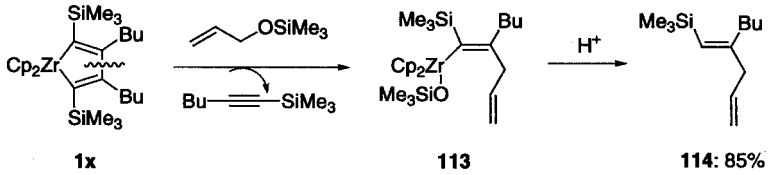
Reactions of zirconacyclopentenes with nitriles involving carbon–carbon bond cleavage offer an effective preparative method for azazirconacyclopentadienes [48], which, in turn, are of key importance in the selective preparation of pyridine derivatives from two different alkynes and a nitrile (*vide supra*). Zirconacyclopentadienes are more stable than zirconacyclopentanes or zirconacyclopentenes. In fact, 2,3,4,5-tetraethylzirconacyclopentadiene does not undergo the β,β-carbon–carbon bond-cleavage reaction. Only with zirconacyclopentadienes bearing sterically bulky groups, as shown in Eq. 2.70 [49], is the β,β-carbon–carbon bond cleavage observed, thereby replacing the unsaturated system (Eq. 2.71) [50].



Eq. 2.69. Reactions of zirconacyclopentenes involving β,β-C–C bond cleavage.

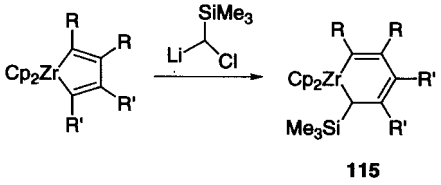


Eq. 2.70. Zirconacyclopentadienes which undergo the β,β-C–C bond-cleavage reaction.



Eq. 2.71. β,β-C–C bond-cleavage reaction of a zirconacyclopentadiene.

The migration of organic groups on metals to α-halogenated groups has been developed by Negishi and used by Whitby in zirconium chemistry [51]. A similar type of migration in the case of zirconacyclopentadienes is also possible, as shown in Eq. 2.72, which affords zirconacyclohexadiene derivatives [52].



Eq. 2.72. Migration reaction of zirconacyclopentadienes.

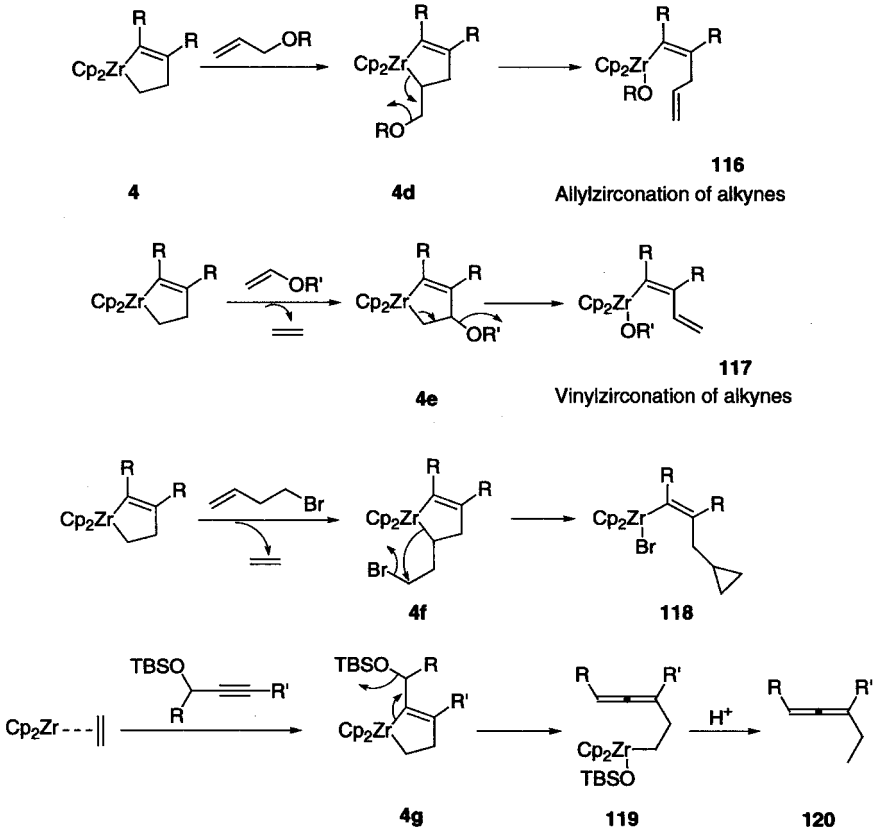
2.3.6 Elimination Reactions

In this section, two types of elimination are discussed:

- Eliminations of functional groups from zirconacycles with the zirconium metal still attached to the organic molecule.
- Elimination of the zirconium itself from the product.

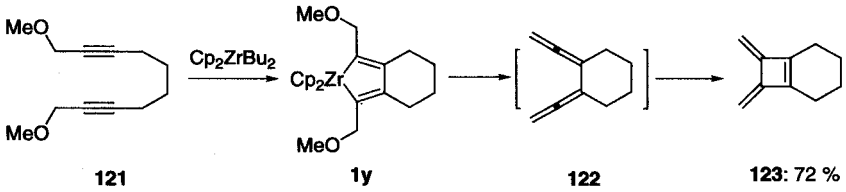
2.3.6.1 Elimination of an alkoxy group or halogen

Elimination of an alkoxy group or of a halogen in the case of zirconacyclopentenes has been investigated in combination with the β,β-carbon–carbon bond-cleavage reaction. As shown in Eq. 2.73, an OR group or a halogen at a β-position is eliminated and trapped by the zirconium metal center [53].



Eq. 2.73. Elimination of OR or halogen from zirconacyclopentenes.

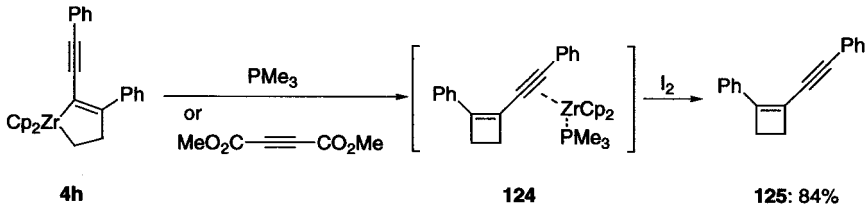
In the case of zirconacyclopentadienes, there have not been many examples, but a similar elimination can proceed, as shown in Eq. 2.74 [53c].



Eq. 2.74. Elimination of OR from a zirconacyclopentadiene.

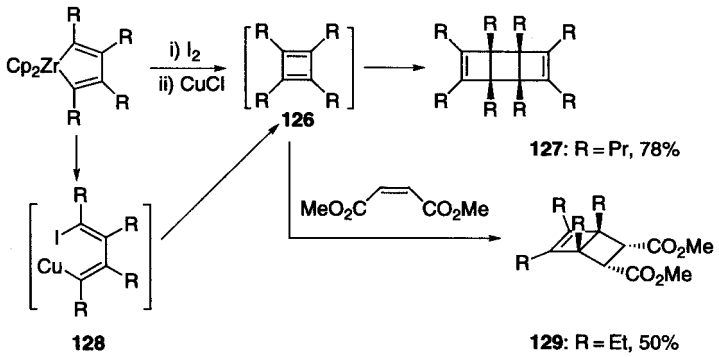
2.3.6.2 **Reductive elimination**

Reductive elimination of a zirconacycle to give a four-membered ring is very rare. Only one example has been reported in the case of α-alkynylated zirconacyclopentenes, as shown in Eq. 2.75 [54].



Eq. 2.75. Reductive elimination of an α-alkynylated zirconacyclopentene.

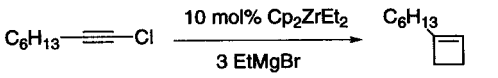
The formation of cyclobutadiene derivatives from zirconacyclopentadienes can be accomplished as follows (Eq. 2.76) [55].



Eq. 2.76. Formation of cyclobutadienes from zirconacyclopentadienes.

Monoiodination of a zirconacyclopentadiene with one equivalent of iodine followed by the addition of one equivalent of CuCl gives the dimer of the cyclobutadiene and the Diels–Alder product in the presence of methyl maleate. This indicates the formation of a 1-iodo-1,3-dienyl copper compound and the subsequent elimination of CuI to give a cyclobutadiene equivalent. Direct reductive elimination of zirconacyclopentadienes affording cyclobutadienes has not yet been observed.

Cyclobutene formation via zirconacyclopentenes can be catalytic, as shown in Eq. 2.77 [56].

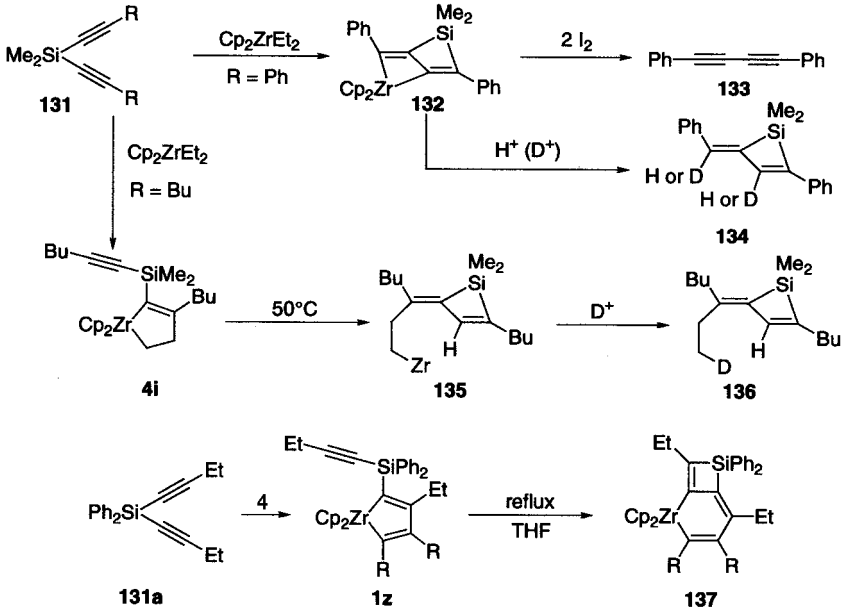


130: 61%

Eq. 2.77. Formation of a cyclobutene catalyzed by Zr.

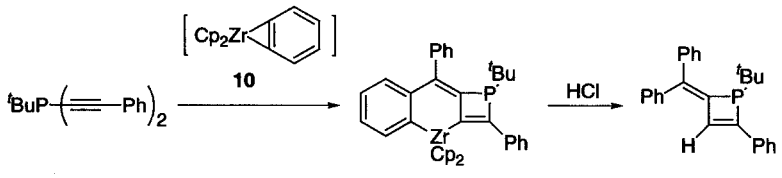
2.3.7 Rearrangement

When an alkynylsilyl group is present at the α-position of zirconacycles such as zirconacyclopropene, zirconacyclopentene, or zirconacyclopentadiene, an unusual rearrangement proceeds to give zirconacyclosilacyclobutene derivatives **132**, as shown in Eq. 2.78 [57]. The zirconacyclosilacyclobutene fused complex **132** and the zirconacyclohexadiene silacyclobutene fused complex **137** have been characterized by X-ray analysis.



Eq. 2.78. Rearrangement reactions of zirconacycles bearing an alkynylsilyl group.

In line with the known similarity between the chemistry of Si and P, alkynyl phosphorus species undergo a similar rearrangement (Eq. 2.79) [58].



138 139: 65% 140

Eq. 2.79. Rearrangement reaction of zirconacycles containing an alkynyl phosphorus group.

2.4 Conclusion

For a long time, zirconacyclopentadiene was considered to be inert towards carbon–carbon bond formation. However, through transmetalation to Cu, Ni, Zn, Li, and Al, various kinds of carbon–carbon bond-formation methodologies have been widely developed. One major advantage of this chemistry is that zirconacyclopentadienes can be conveniently prepared in situ, in high yields and with excellent selectivities, from two different alkynes. Combination of the selective formation of zirconacyclopentadienes and the chemistry of Cu, Ni, Zn, Li, or Al provides useful tools in organic synthesis. In the near future, it can be expected that more metals will be used for the transmetalation reactions of zirconacycle derivatives and some catalytic reactions will hopefully be developed.

Typical Experimental Procedures

Synthesis of (3*E*,5*E*)-4-Ethyl-5-propyl-3,5-nonadiene (see Eq. 2.10, representative procedure for preparation of zirconacyclopentadienes) Under dry nitrogen, a 50 mL Schlenk tube was charged with Cp_2ZrCl_2 (6 mmol, 1.75 g) and THF (30 mL). The mixture was cooled to −78 °C (dry-ice/methanol bath), whereupon *n*BuLi (1.7 M in THF, 12 mmol, 7.1 mL) was added dropwise by means of a syringe. The reaction mixture was stirred at −78 °C for 1 h under nitrogen and then ethene gas was introduced for 1 h. Thereafter, the reaction mixture was allowed to gradually warm to room temperature. 4-Octyne (5.0 mmol, 0.74 mL) was added, and the resulting mixture was stirred for 1 h at room temperature under a positive pressure of ethene gas. 3-Hexyne (5.0 mmol, 0.57 mL) was then added to the solution. The mixture was heated at 50 °C under an atmosphere of dry N_2 instead of ethene gas, and was stirred for 1 h. The cross-coupling intermediate, 1,1-bis(cyclopentadienyl)-2,3-diethyl-4,5-dipropylzirconacyclopentadiene, was formed in 98 % yield (by NMR). The reaction mixture was quenched with 3 N HCl and extracted with diethyl ether (3 × 70 mL). The combined extracts were washed sequentially with water, aq. $NaHCO_3$ solution, brine, and water, and then dried over $MgSO_4$. The solvent was evaporated in vacuo to leave a light-brown liquid. Distillation provided (3*E*,5*E*)-4-ethyl-5-propyl-3,5-nonadiene as a colorless liquid (0.80 g, 82 %).

General Procedure for the Formation of Benzene Derivatives (see Eq. 2.48) At 0 °C, dimethyl acetylenedicarboxylate (284 mg, 2 mmol) and CuCl (198 mg, 2 mmol) were added to a solution of zirconacyclopentadiene (1 mmol) in THF, prepared in situ according to the known procedure [12]. The reaction mixture was then allowed to warm to room temperature and was stirred for 1 h. After hydrolysis with 3 N HCl, the mixture was extracted with diethyl ether. The combined extracts were washed sequentially with water, aq. $NaHCO_3$ solution, brine, and water, and then dried over $MgSO_4$. Concentration in vacuo followed by flash-chromatography eluting with a mixture of hexane and diethyl ether (10 %) afforded benzene derivatives.

Typical Procedure for the Preparation of Benzene Derivatives from Three Different Alkynes using $NiCl_2(PPh_3)_2$ (see Eq. 2.53) To a solution of a zirconacyclopentadiene (1.0 mmol) [4] prepared from two different alkynes in THF (20 mL), the third alkyne (1.5 mmol)

and $NiCl_2(PPh_3)_2$ (0.74 g, 1.0 mmol) were added at room temperature. The mixture was stirred for 1 h, then quenched with 3 N HCl and extracted with hexane. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Column chromatography on silica gel (hexane) afforded the desired products.

Typical Procedure for the Preparation of Silacyclobutene Derivatives (see Eq. 2.78) To a solution of Cp_2ZrCl_2 (1.25 mmol, 0.365 g) in THF (10 mL) at −78 °C (dry-ice/methanol bath) in a 20 mL Schlenk tube, EtMgBr (2.5 mmol, 0.90 M solution in THF, 2.78 mL) was added dropwise by means of a syringe. After the addition was complete, the reaction mixture was stirred at −78 °C for 1 h. Bis(phenylethynyl)dimethylsilane (1 mmol) was then added and the mixture was allowed to gradually warm to room temperature. After the reaction mixture had been stirred at room temperature for 1 h, it was quenched with 3 N HCl, and the resulting mixture was extracted with diethyl ether (3 × 70 mL). The combined extracts were washed with water and brine, and then dried over $MgSO_4$. Evaporation of the solvent in vacuo gave the desired products.

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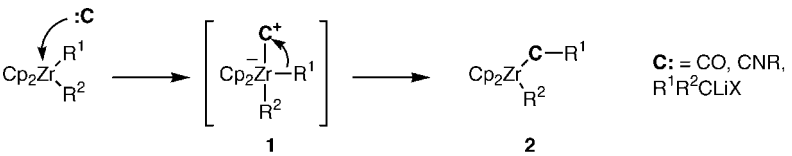
3
Elaboration of Organozirconium Species by Insertion of Carbenoids

Sally Dixon and Richard J. Whitby

3.1
Introduction

The use of stoichiometric zirconium chemistry for the synthesis of organic compounds has developed rapidly over the past 15 years. The starting points for most synthetic applications of zirconium chemistry are hydrozirconation of alkenes or alkynes with Cp_2ZrHCl [1] to give organozirconocene chlorides, and co-cyclization of alkenes and/or alkynes with a zirconocene equivalent ("Cp_2Zr") to afford five-membered zirconacycles [2,3]. Further elaboration of these intermediates through carbon–carbon bond-forming reactions is important, but they are rather unreactive towards conventional electrophiles [4]. In marked contrast, carbon monoxide is observed to insert rapidly into Cp_2ZrMe_2 at −130 °C [5]. In order to understand the exceptional reactivity of carbon monoxide, we note that a key characteristic of organozirconocene complexes is the generally preferred 16-electron configuration of the metal. In reactions with carbenes (such as CO), the remaining empty orbital on zirconium is able to accept an electron pair to form an 18-electron 'zirconate' species **1**, which may undergo a 1,2-rearrangement to form a new carbon–carbon bond as in **2** (Scheme 3.1). The product of insertion of the carbene retains a carbon–zirconium bond, making the reaction ideally suited to iterative methods. The close analogy to more familiar organoboron chemistry is worth noting [6].



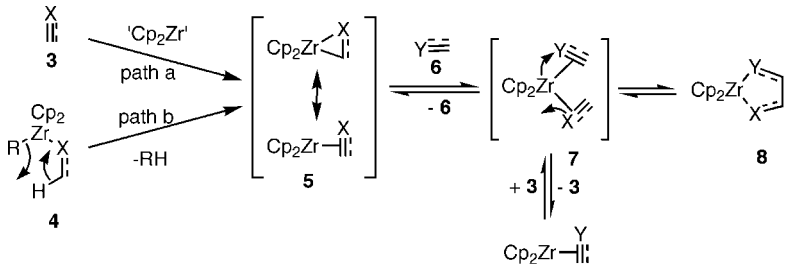
1 **2**

Scheme 3.1. Carbene insertion into organozirconocenes.

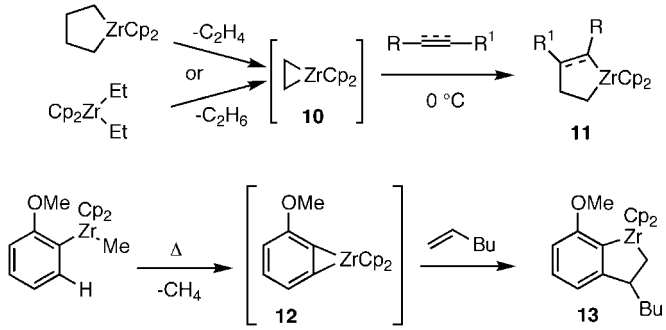
In this chapter, we provide the necessary background concerning the formation of zirconacycles, then briefly review the insertion of carbon monoxide and isoelectronic isonitriles into organozirconocenes. We then describe in more detail the insertion of α-halo-α-lithium species (R^1R^2CLiX, 'carbenoids'[7]), which may be viewed as taking place according to a conceptually similar mechanism.

3.1.1 Formation of Zirconacycles

A wide variety of five-membered zirconacycles **8** may be formed by the formal co-cyclization of two π-components (**3** and **6**; alkene, alkyne, allene, imine, carbonyl, nitrile) on zirconocene ('Cp_2Zr') (Scheme 3.2) [2,3,8]. The co-cyclization takes place via the η^2-complex **5** of one of the components, which is usually formed by complexation of **3** with a zirconocene equivalent (path a) ('Cp_2Zr' itself is probably too unstable to be a true intermediate) or by oxidation on the metal (cyclometallation/β-hydrogen elimination) (path b). Two additional routes to zirconocene η^2-complexes are by the reverse of the co-cyclization reaction (i. e. **8** reverting to **5** or **9** via **7**), and by rearrangement of iminoacyl complexes (see Section 3.2.2 below). The "direct complexation" method (path a) is generally only useful for intramolecular co-cyclizations (see below), or when the two π-components are the same, or when dimerization of one component is unfavorable. Co-cyclization of the intermediate **7** is generally slow relative to the loss of one of the π-components (to revert to **5** or **9**) and so, even when the starting η^2-complex **5** is formed by a path that avoids self-condensation, exchange to form **9** with the liberation of **3** takes place and, consequently, mixtures of the desired zirconacycle **8** and zirconacycles resulting from the dimerization of **3** or **6** are formed. Intermolecular co-cyclizations may be successful when cycloreversion of **7** invariably gives **5** and not **9**. This may be because the η^2-complex **5** is much more stable than **9** (e. g. zirconocene η^2-imine complexes, zirconocene ethylene, some zirconocene alkyne complexes), or because the π-component **3** is very unstable (e. g., when **3** would be a benzyne). Examples are the formation of zirconacyclopentenes or -pentanes **11** from zirconocene ethylene **10** (Scheme 3.3), and of zirconaindanes **13** via a zirconocene benzyne complex **12** [9–11].

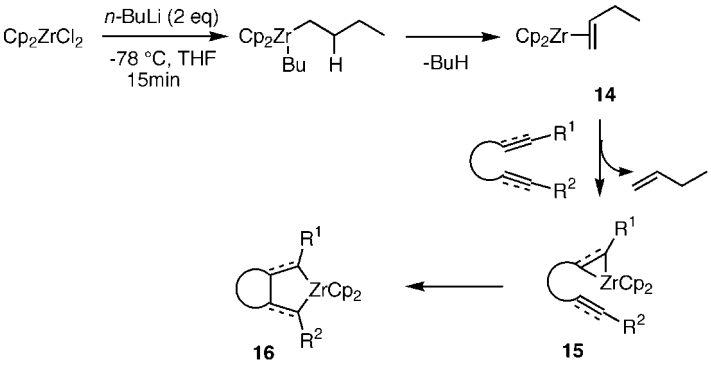


Scheme 3.2. Formation of zirconacycles.



Scheme 3.3. Formation of monocyclic zirconacycles.

Various sources of the zirconocene fragment have been used for intramolecular co-cyclization, of which the most popular is zirconocene(1-butene) **14**, generated in situ by reduction of zirconocene dichloride (Cp_2ZrCl_2) with two equivalents of *n*-butyllithium (Scheme 3.4) [12]. The procedure is applicable to the formation of a wide range of carbocyclic and heterocyclic systems **16** [2,3,13,14]. As regards the intramolecular co-cyclization of dienes, only the formation of five- and six-membered rings works well, although larger rings may be formed when the chain contains a nitrogen or when there are steric constraints. Co-cyclizations of substrates containing multiply-substituted alkenes (tri- or tetra-substituted) are generally not successful. Enyne co-cyclization readily leads to five- to seven-membered rings, while diyne co-cyclization is amenable to the formation of four-membered to large rings. Ether or alkoxide substituents are compatible, except when β to a carbon–zirconium bond in the intermediate **15**. Carbonyl groups are usually not compatible with the cyclization although, when remote from the metal, amide groups survive. The use of zirconocene ethylene or zirconocene dichloride reduced in situ with magnesium metal (with or without $HgCl_2$ as an activator) sometimes has advantages, particularly for the use of substrates containing terminal alkyne or allylic or propargylic ether functionalities [15,16].



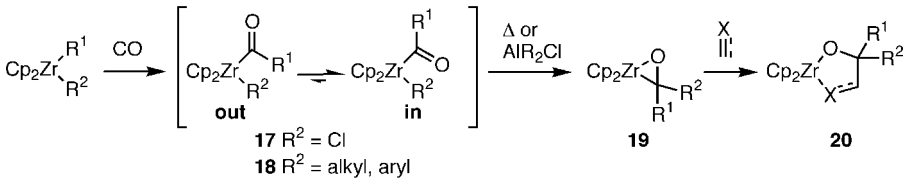
Scheme 3.4. Co-cyclizations using Negishi's reagent.

3.2 Carbonylation and Isonitrile Insertion

3.2.1 Acyclic Organozirconocenes

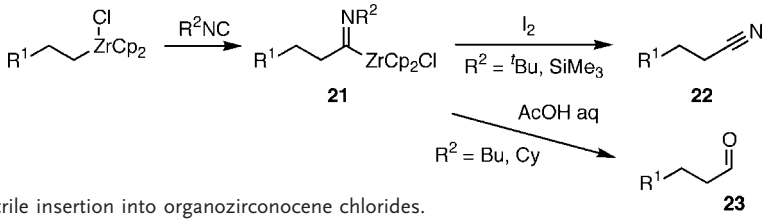
Carbon monoxide rapidly inserts into the carbon–zirconium bond of alkyl- and alkenylzirconocene chlorides at low temperature with retention of configuration at carbon to give acylzirconocene chlorides **17** (Scheme 3.5). Acylzirconocene chlorides have found utility in synthesis, as described elsewhere in this volume [17]. Lewis acid catalyzed additions to enones, aldehydes, and imines, yielding α-keto allylic alcohols, α-hydroxy ketones, and α-amino ketones, respectively [18], and palladium-catalyzed addition to alkyl/aryl halides and α,β-ynones [19] are examples. The acyl complex **18** formed by the insertion of carbon monoxide into dialkyl, alkylaryl, or diaryl zirconocenes may rearrange to a η^2-ketone complex **19** either thermally (particularly when $R^1 = R^2 = Ph$) or on addition of a Lewis acid [5,20,21]. The rearrangement proceeds through the less stable

18-out isomer. The η^2-ketone complexes **19** undergo insertion of π-components to form zirconacycles **20** [20,21].



Scheme 3.5. Carbonylation of organozirconocenes.

The synthesis of analogous iminoacyl complexes by isonitrile insertion into linear alkylzirconocene chlorides is also known. In an overall regiospecific hydrocyanation of alkenes, iminoacyls **21** derived from *t*BuNC or Me_3SiCN (as the Me_3SiNC isomer) may be treated with I_2 to rapidly generate an imidoyl iodide and subsequently the nitrile **22** (Scheme 3.6) [22]. Less hindered iminoacyl complexes (e.g. R = Bu, Cy) may be hydrolyzed to afford aldehydes **23** [23].

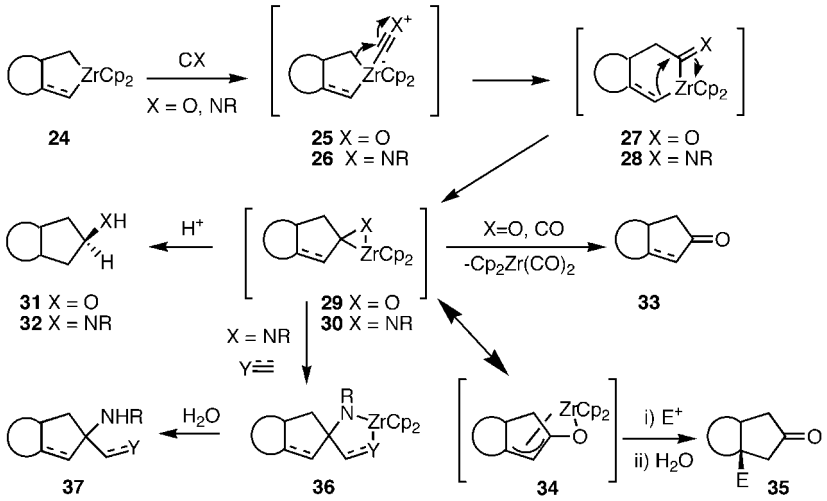


Scheme 3.6. Isonitrile insertion into organozirconocene chlorides.

3.2.2 Zirconacycles

In the carbonylation of zirconacycles **24** [24], the initially formed η^2-acyl complex **27** rapidly rearranges to the η^2-ketone complex **29**, presumably because **27** is locked in the acyl-out form (*cf.* **18** in Scheme 3.5). In the case of carbonylation of saturated zirconacycles, the η^2-ketone complex **29** is rather stable and protonation soon gives the alcohol **31** (Scheme 3.7). Prolonged exposure to CO affords the saturated ketone **33**, probably through displacement of the η^2-ketone ligand by CO. Higher yields of the saturated ketone **33** are generally obtained by work-up of **29** with iodine [25]. Carbonylation of zirconacyclopentenes **24** (1 atm CO, 20 °C, 16 h) generally gives cyclopentenones **33** in high yield [2,3]. It has been observed with certain zirconacyclopentene substrates that carbonylation for a short time followed by work-up with electrophiles affords the saturated ketones **35**, implying the intermediate formation of the allyl-zirconocene tautomer **34** of **29** [26,27]. The generality of this process is not yet clear.

Isonitrile insertion into zirconacycles to afford iminoacyl complexes **28** is fast, but rearrangement to η^2-imine complexes **30** is slow. In the case of *t*BuNC, the rearrangement does not occur. Amines **32** are formed on protonolysis of the η^2-imine complex. The η^2-imine complexes **30** readily undergo insertion of π-components (alkenes, alkynes, ketones, aldehydes, imines, isocyanates) to provide a wide variety of products **37** via zirconacycles **36**. The overall sequence gives a nice demonstration of how a number of compo-

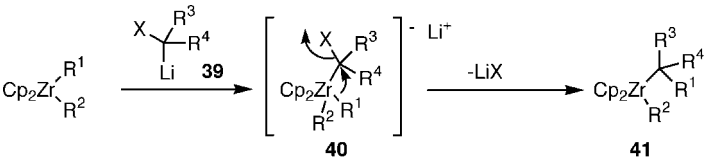


Scheme 3.7. Carbonylation and isonitrile insertion into zirconacycles.

nents may be assembled sequentially on a zirconocene template. A variety of isonitriles (R = Ph, Bu, Cy, Me_3Si) may be used, the most useful of which is trimethylsilyl cyanide; insertion of the latter as its isocyanide isomer gives primary amines [28–31].

3.3
Insertion of 1-Halo-1-lithio Species into Organozirconocenes

The success of the described carbonylation and isonitrile insertion reactions for exploitation of organozirconium species in carbon–carbon bond formation is attributed to the carbenic character of carbon monoxide and isonitriles, which facilitates initial donation of an electron pair to the 16-electron zirconium atom. Compounds containing a lithium atom and a nucleofugal group on the same carbon (R^3R^4CLiX, **39**), for which we use the term "carbenoid" introduced by Köbrich, can be expected to show similar reactivity [7,32–35]. Initial attack on the 16-electron zirconium atom to form an 18-electron metallate complex **40** may be followed by a 1,2-rearrangement [36] with loss of halogen to give a new organozirconocene **41** (Scheme 3.8). The mechanism predicts clean inversion of configuration at the carbenoid carbon.

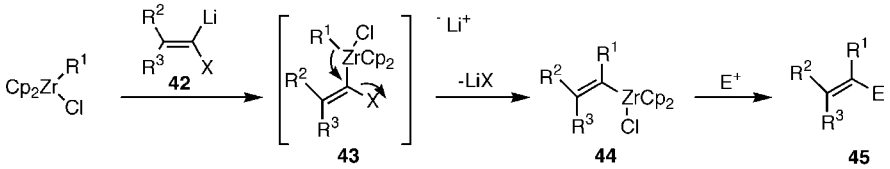


Scheme 3.8. Insertion of a carbenoid into a carbon–zirconium bond.

In an important communication of 1989, Negishi reported [37] the first insertions of α- and γ-haloorganolithium reagents into acyclic zirconocene chlorides. Recently, this work has been extended to a wide variety of carbenoids and organozirconium species, including zirconacycles, to provide a variety of new synthetic methods. These are described below.

3.3.1 Insertion of 1-Halo-1-lithioalkenes into Acyclic Organozirconocene Chlorides

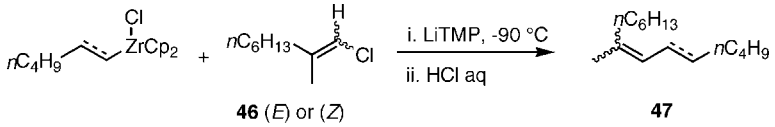
Scheme 3.9 illustrates the potential for synthesis of highly functionalized, stereodefined alkenes **45** from insertion of 1-halo-1-lithioalkenes **42** into organozirconocene chlorides. Alkenyl carbenoids **42** may be generated by halogen/lithium exchange at low temperature or by deprotonation of alkenyl halides. The latter process may be carried out with in situ trapping by the organozirconocene, thereby reducing the need for very low temperatures.



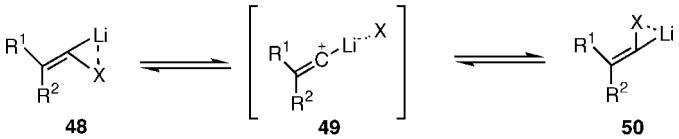
Scheme 3.9. Insertion of an alkenyl carbenoid into an organozirconocene chloride.

3.3.1.1 Insertion of 1-chloro-1-lithio-2,2-disubstituted alkenes

Insertion of 2,2-disubstituted alkenyl carbenoids into alkyl- or alkenyl-zirconocene chlorides occurs in high yields [37,38]. Insertion of the carbenoids arising from in situ deprotonation of the stereodefined (*E*)- or (*Z*)-1-chloro-2-methyl-1-octenes **46** into alkyl- or alkenylzirconocene chlorides gives mixtures of isomeric products **47** showing between 86 % inversion and 26 % retention of configuration at the alkenyl carbenoid center (Scheme 3.10) [38]. The poor stereocontrol appears to contradict the clean inversion of configuration at the carbenoid carbon required by concerted 1,2-rearrangement of the intermediate **43** (Scheme 3.9). However, mechanistic studies established that interconversion of the (*E*)- and (*Z*)-alkenyl carbenoids occurs at a rate comparable with that of insertion into the organozirconocene chloride, and hence that this is responsible for the loss of stereochemistry. A similar loss of stereochemical integrity of 2,2-disubstituted-1-halo-1-lithioalkenes, generated by deprotonation of the corresponding alkenyl halides, has been described and was attributed to "metal-assisted ionization" [39–41] (Scheme 3.11). Theoretical calculations show that the ground-state structure of alkenyl carbenoids is best represented as **48**, and that isomerization to **50** through the intermediate **49** has a relatively low activation energy. β-Alkyl substituents should favor formation of the intermediate **49**, both by inductive electron donation and by the relief of steric strain. As described below, β-monosubstituted alkenyl carbenoids do not isomerize at a significant rate relative to that of trapping by organozirconocenes.



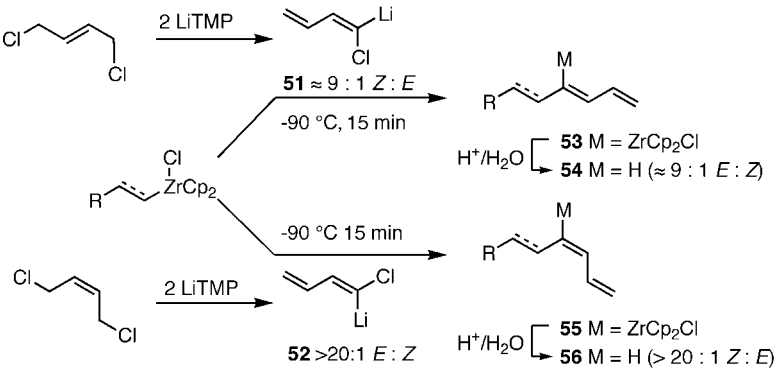
Scheme 3.10. Insertion of 2,2-disubstituted alkenyl carbenoids into organozirconocene chlorides.



Scheme 3.11. Metal-assisted ionization.

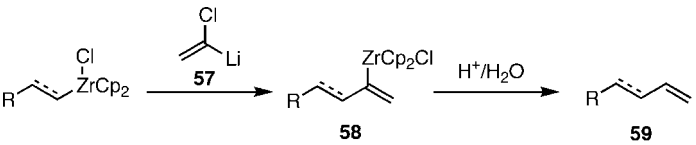
3.3.1.2 Insertion of 1-chloro-1-lithio-2-monosubstituted alkenes

Unlike the insertion of 2,2-disubstituted alkenyl carbenoids, the insertion of 2-monosubstituted alkenyl carbenoids is found to be stereospecific in accordance with Scheme 3.9 (R^2 or R^3 = H) [38]. The carbenoids (*Z*)- or (*E*)-1-chloro-1-lithio-1,3-butadiene (**51** and **52**) may be generated in situ from (*E*)- or (*Z*)-1,4-dichloro-2-butene, respectively, by elimination of hydrogen chloride followed by α-deprotonation of the thus formed alkenyl halide using two equivalents of lithium 2,2,6,6-tetramethylpiperidide (LiTMP) (Scheme 3.12). Inversion of configuration at the carbenoid carbon during 1,2-metallate rearrangement stereospecifically yields the organozirconocenes **53** and **55** [42]. Protonation affords terminal conjugated (*E*)- or (*Z*)-dienes or (*E*,*E*)- and (*E*,*Z*)-trienes **54** and **56** in a single pot from terminal alkenes or alkynes, respectively. The carbenoid-derived double bond is formed in ≈ 9:1 *E*:*Z* and >20:1 *Z*:*E* isomeric mixtures, respectively, these ratios being determined by the initial elimination of hydrogen chloride from the starting (*E*)- or (*Z*)-1,4-dichloro-2-butenes.



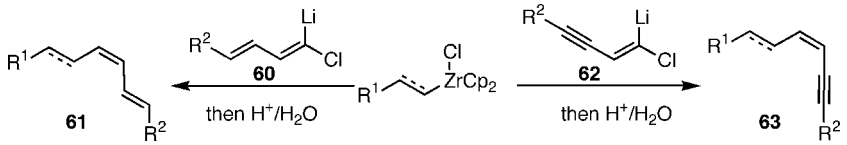
Scheme 3.12. Stereospecific insertion of 1,3-butadienyl carbenoids.

The only other alkenyl carbenoid with a proton *trans* to the halide that can readily be generated by deprotonation is the parent 1-lithio-1-chloroethene **57** [43] (Scheme 3.13). Insertion into organozirconocenes arising from hydrozirconation of alkenes and alkynes, followed by protonation, affords terminal alkenes and (*E*)-dienes **59**, respectively [38]. The latter provides a useful complement to the synthesis of **54** in Scheme 3.12 since the stereocontrol is >99 %.



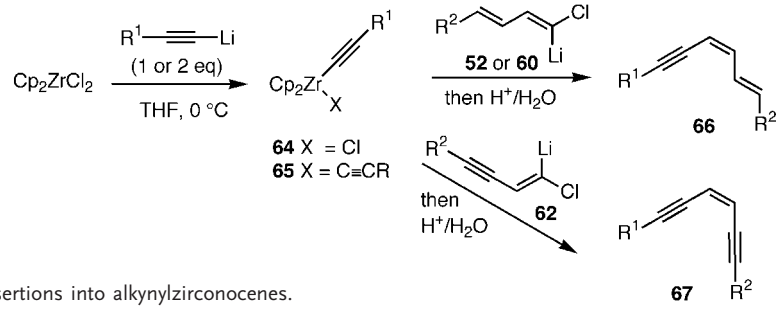
Scheme 3.13. Insertion of vinyl carbenoid.

Access to non-terminal (*E*,*Z*)-dienes and (*E*,*Z*,*E*)-trienes **61** is provided analogously through deprotonation of (*E*,*E*)-4-alkyl-1-chloro-1,3-butadienes followed by insertion of the resultant carbenoid **60** into alkyl- and alkenyl-zirconocene chlorides (Scheme 3.14) [38]. The corresponding internal (*Z*,*Z*)-dienes and (*Z*,Z,*E*)-trienes are also readily obtained by insertion of β-alkynyl carbenoids **62** [44] into alkyl- and alkenylzirconocene chlorides, respectively (Scheme 3.14). Reduction of the triple-bond moiety in the products **63** to afford the *cis*-alkenes is well known [45–47].



Scheme 3.14. Insertion of 1,3-dienyl- and 1-en-3-ynyl-carbenoids.

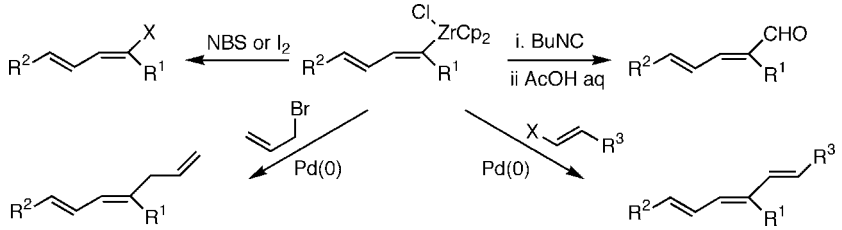
To complete the range of geometric isomers of terminal and non-terminal dienes and trienes available, systems nominally derived from inaccessible (*Z*)-alkenylzirconocenes are desirable. Fortunately, insertion of the various carbenoids discussed above into mono- or bis(alkynyl) zirconocenes **64** and **65** affords dienyne products **66** [38], which are readily reduced to the desired (*E,Z,Z*)-trienes (Scheme 3.15) [45–47]. Insertion of the β-alkynyl carbenoid **62** allows a convenient access to (*Z*)-enediynes **67**.



Scheme 3.15. Insertions into alkynylzirconocenes.

3.3.1.3 Further elaboration of carbenoid insertion products

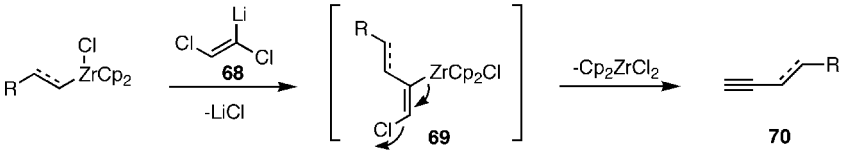
A key feature of the elaboration of organozirconocenes by insertion of a carbenoid is that the product retains the carbon–zirconium bond functionality of the substrate. Several useful elaborations are shown in Scheme 3.16 for the case of the organozirconium product of the insertion of alkenyl carbenoids **52** or **60** [38].



Scheme 3.16. Further elaboration of alkenylzirconocene chlorides.

3.3.1.4 Insertion of 1-lithio-1,2-dihaloalkenes into acyclic organozirconocene chlorides

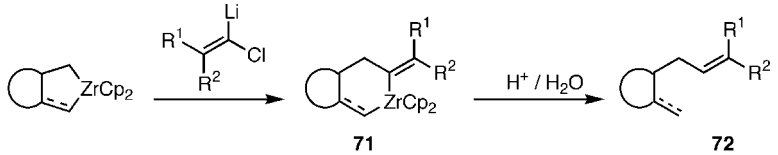
A useful synthesis of alkynes and particularly of terminal (*E*)-enynes results from the insertion of the readily formed (*E*)-1,2-dichloro-1-lithioethene (**68**) into organozirconocene chlorides (Scheme 3.17). An intermediate (*E*)-2-chloroalkenyl zirconium species **69** undergoes *anti*-elimination of zirconocene dichloride to yield terminal alkynes **70** [38].



Scheme 3.17. Insertion/elimination of (*E*)-1,2-dichloro-1-lithioethene.

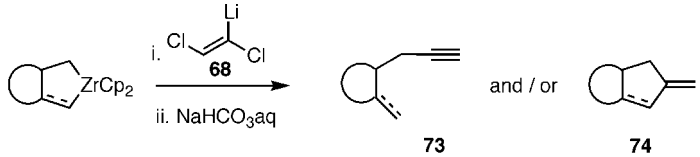
3.3.1.5 Insertion of 1-halo-1-lithioalkenes into zirconacycles

Symmetrical 2,2-disubstituted-1-lithio-1-chloroalkenes mono-insert cleanly into zirconacycles to give trisubstituted olefin products in high yield following protic work-up of the ring-expanded six-membered zirconacycle (Scheme 3.18; $R^1 = R^2 =$ alkyl) [48]. The insertion of non-symmetrical 2,2-disubstituted alkenyl carbenoids has not yet been reported. A wide range of 2-monosubstituted alkenyl carbenoids (**51**, **52**, **60**, **62**) arising from in situ deprotonation of alkenyl chlorides can be successfully inserted into zirconacyclopentanes and -pentenes with the expected inversion of configuration at the carbenoid carbon [49,50].



Scheme 3.18. Insertion of alkenyl carbenoids into zirconacycles.

Insertion of (*E*)-1-lithio-1,2-dichloroethene (**68**) into zirconacycles is followed by elimination of Cp_2ZrCl to afford a terminal alkyne **73** and/or the product **74** of further cyclization (Scheme 3.19) [51]. The alkyne **73** is the sole product with saturated zirconacycles, whereas unsaturated zirconacycles give mostly **74**.



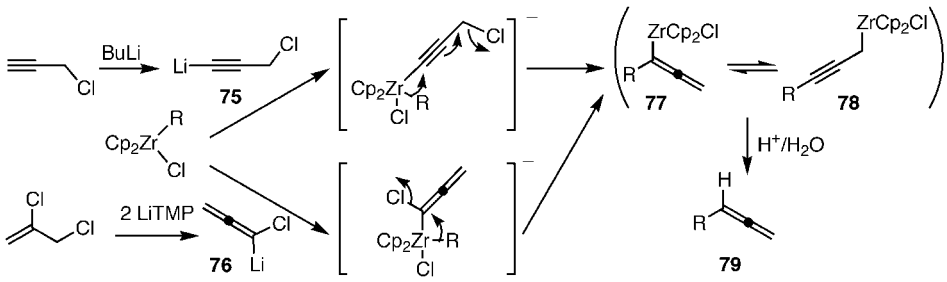
Scheme 3.19. Insertion of (*E*)-1,2-dichloro-1-lithioethene into zirconacycles.

3.3.2 Insertion of Allenyl Carbenoids

3.3.2.1 Insertions into acyclic organozirconocene chlorides

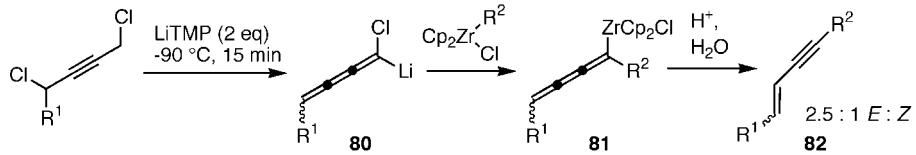
Negishi first observed the insertion of the γ-halolithium species **75** obtained by deprotonation of propargyl chloride into octylzirconocene chloride; protonation of the product afforded the allene **79** (Scheme 3.20) [37]. The overall effect is insertion of an allenyl carbenoid. The α-halolithium equivalent **76** is conveniently generated by addition of two equivalents of base to 2-chloroallyl chloride [52] and affords the same products. The organometallic product **77** of allenyl carbenoid insertion is either in equilibrium with the propargyl

form **78** or exists as a η^3-allenyl/propargyl species, of which **77** and **78** are extreme representations. We would expect **77**/**78** to be reactive towards carbonyl compounds, but this has not yet been reported.



Scheme 3.20. Insertion of allenyl carbenoids into organozirconocene chlorides.

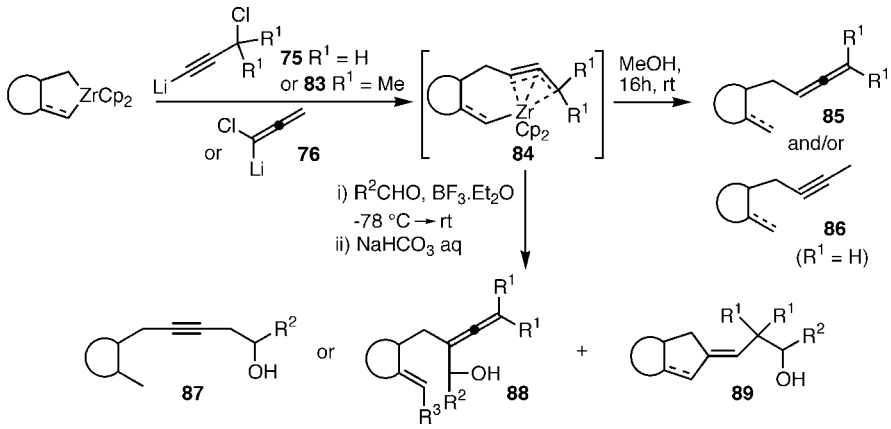
A more complex cumulenyl carbenoid **80** may be generated in situ from 1,4-dihalobut-2-ynes and two equivalents of base (Scheme 3.21). Insertion into organozirconocene chlorides gives allenyl zirconium species **81**, which are regioselectively protonated to afford enyne products **82** [38]. The stereochemistry of the alkene in **82** stems from the initial elimination of hydrogen chloride to form **80**.



Scheme 3.21. Insertion of 1,2,3-butatrienyl carbenoids into organozirconocene chlorides.

3.3.2.2 **Insertions into zirconacycles**

1-Lithio-3-chloro-1-propyne (**75**), 1-lithio-1-chloroallene (**76**), and 1-lithio-3-methyl-3-chlorobut-1-yne (**83**) insert efficiently into zirconacycles to afford η^3-propargyl/allenyl complexes **84** (Scheme 3.22) [53,54]. Protonation affords the allenes **85** and/or alkynes



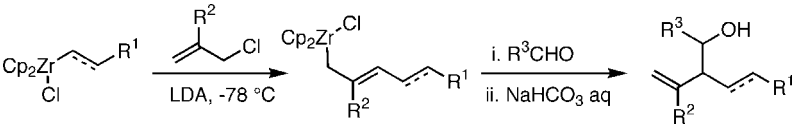
Scheme 3.22. Tandem insertion of allenyl carbenoids and electrophiles into zirconacycles.

86, the former being obtained exclusively with saturated zirconacycles or when $R^1 = Me$. Lewis acid induced addition of aldehydes occurs to give either **87** from saturated zirconacycles or **88** from unsaturated zirconacycles, but in many cases the cyclized compound **89** is formed as the major or exclusive product [54].

3.3.3 Insertion of Allyl Carbenoids into Organozirconium Species

3.3.3.1 Insertion into acyclic organozirconocene chlorides

Allyl chlorides are readily deprotonated α to the halide by strong bases to give allyl carbenoids, which insert into organozirconocene chlorides to afford allyl- or pentadienyl-zirconocene chlorides (Scheme 3.23). These allylmetallic species are reactive towards carbonyl compounds, and so an efficient three-component coupling results [50].



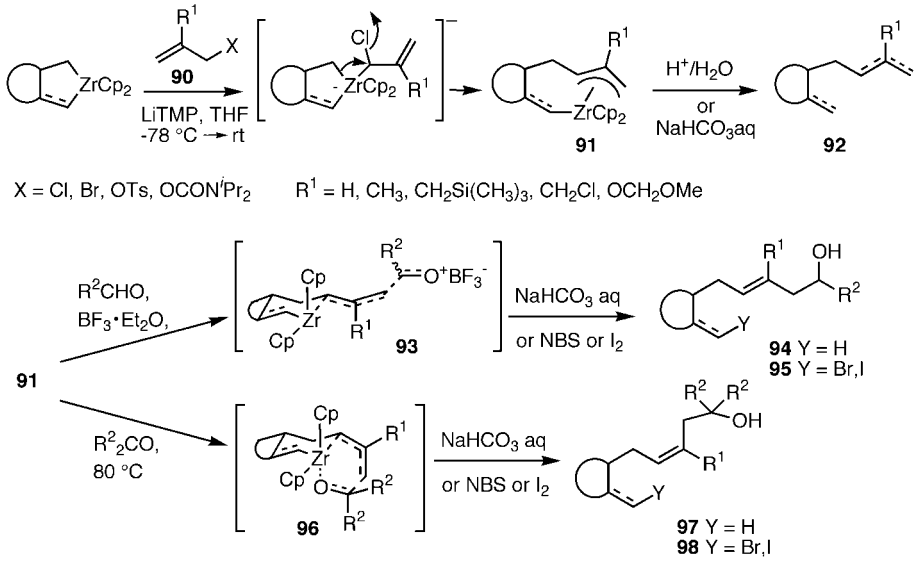
Scheme 3.23. Tandem insertion of allyl carbenoids and aldehydes into organozirconocene chlorides.

3.3.3.2 Insertions into zirconacycles

The most extensively studied application of carbenoid insertion into organozirconocene species is the insertion of allyl carbenoids into zirconacycles and subsequent elaboration of the thus formed allylzirconocenes with electrophiles (Schemes 3.24–3.26) [48,53,55–60].

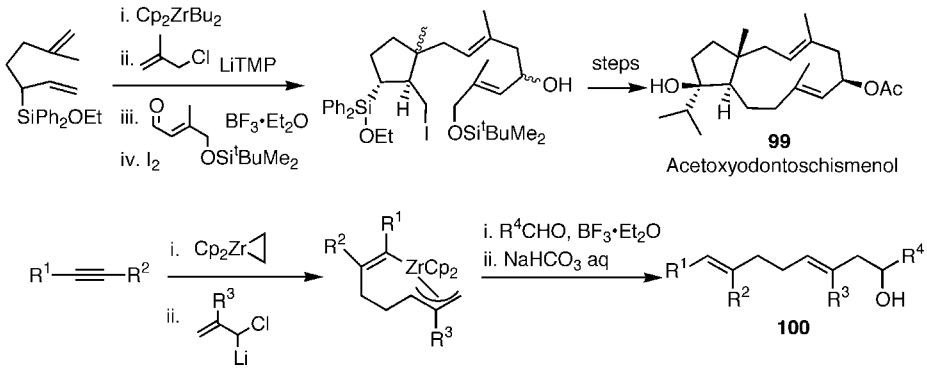
Deprotonation of a variety of allylic systems **90** in the presence of zirconacyclopentanes and -pentenes affords η^3-allyl zirconacycles **91** in quantitative yield (Scheme 3.24) [53]. The leaving group (X) on the allyl fragment may be halide, tosylate, or carbamate, whereas phenoxide or alkoxide give low yields (<25 %). When the group X substantially stabilizes the carbanion (X = SPh, SO_2Ph, P^+Ph_3), insertion does not occur. The allyl fragment tolerates a variety of substituents at the 2-position (Me, CH_2SiMe_3, CH_2Cl, OCH_2OMe) (Scheme 3.24) [55]. Protonation affords products **92** as the terminal, internal, or a mixture of both alkene regioisomers, depending on the substrate and conditions. Allylzirconium species **91** are reactive towards carbonyl compounds and give homoallylic alcohol products **94** and **97** with aldehydes and ketones, respectively, in very high overall yield for a four-component coupling (Scheme 3.24). The carbon–zirconium bond remaining after addition of the carbonyl component may be halogenated to give **95** and **98**. The addition of aldehydes requires a Lewis acid ($BF_3 \cdot Et_2O$ normally works best, but $TiCl_4$ and $SnCl_4$ are also effective). Addition of ketones fails in the presence of $BF_3 \cdot Et_2O$. The remarkable switch in stereochemistry of the alkene formed between addition of aldehyde/$BF_3 \cdot Et_2O$ and ketone/Δ may be rationalized in terms of the transition states **93** and **96**. The Lewis acid mediated addition of aldehydes takes place through an open transition state **93**, in which the stereochemistry of the η^3-allyl moiety in **91** is retained in the product alkene. The observed lack of remote diastereocontrol (<3:1) between the ring-junction stereocenters and the introduced hydroxy group is also accounted for. The geometry about the double bond in **97** results from allylzirconocene reaction with ketones via a postulated

cis-decalin-type transition state **96**. It is significant that *cis*-decalins become more stable than *trans*-decalins when the bonds to a bridgehead atom become long [61].



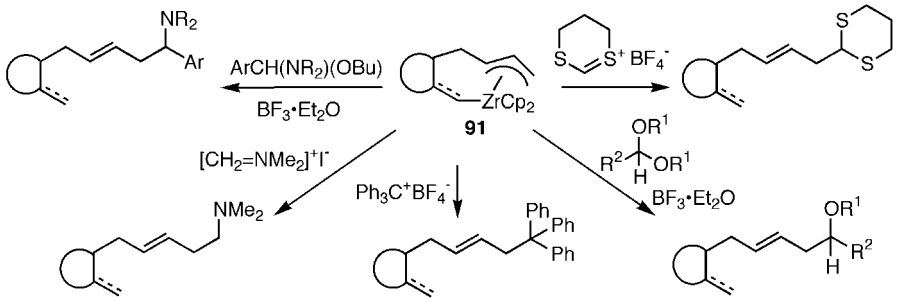
Scheme 3.24. Tandem insertion of allyl carbenoids and electrophiles into zirconacycles.

The tandem zirconocene-induced co-cyclization of dienes or enynes/insertion of allyl carbenoid/addition of electrophile is a powerful method for assembling organic structures. Two illustrations of its application are the synthesis of the dollabelane natural product acetoxyodontoschismenol **99** [57,62,63] and the one-pot construction of linear terpenoids **100** (Scheme 3.25) [59,64].



Scheme 3.25. Synthesis of acetoxyodontoschismenol and terpenoids.

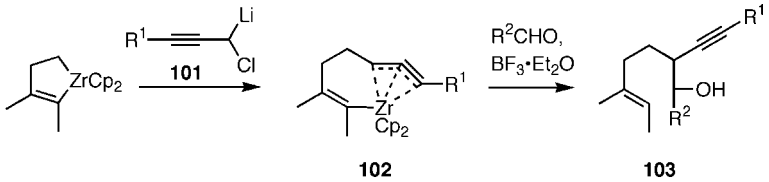
A variety of other powerful electrophiles add to the allylzirconium species **91**, as shown in Scheme 3.26. Such reactions include the Lewis acid catalyzed addition of aryl, alkyl, or alkenyl acetals, derived from aldehydes, but not from ketones, and the addition of iminium species that lack β-hydrogens [56,58].



Scheme 3.26. Insertions of electrophiles into cyclic allylzirconocenes.

3.3.4
Insertion of Propargyl Carbenoids into Zirconacycles

Closely related to both allyl carbenoids and the allenyl carbenoids discussed above, propargyl carbenoids **101** are readily generated in situ and insert into zirconacycles to afford species **102** (Scheme 3.27), which are closely related to species **84** derived from allenyl carbenoids [65]. Protonation affords a mixture of allene and alkyne products, but the Lewis acid assisted addition of aldehydes is regioselective and affords the homopropargylic alcohol products **103** in high yield. Bicyclic zirconacyclopentenes react similarly, but there is little diastereocontrol from the ring junction to the newly formed stereocenters. The η^3-propargyl complexes derived from saturated zirconacycles are inert towards aldehyde addition.



102 **103**

Scheme 3.27. Insertion of propargyl carbenoids into zirconacycles.

3.3.5
Insertion of α-Substituted Alkyl Carbenoids

A wide variety of alkyl carbenoids, for example **104**–**112** (Fig. 3.1) may be generated by deprotonation using a strong base. In the absence of an activating/stabilizing group, bromine–lithium exchange at low temperatures provides access, for example, to **113** or the more stable special case **114**. Most of these carbenoids insert into both organozirconocene chlorides, obtained by hydrozirconation of alkenes or alkynes, and zirconacycles. The chemistry has not yet been investigated in depth and the account below focuses on the most synthetically useful transformations developed to date.

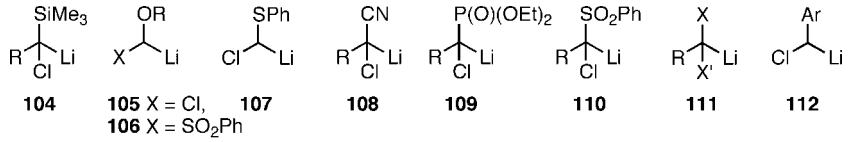
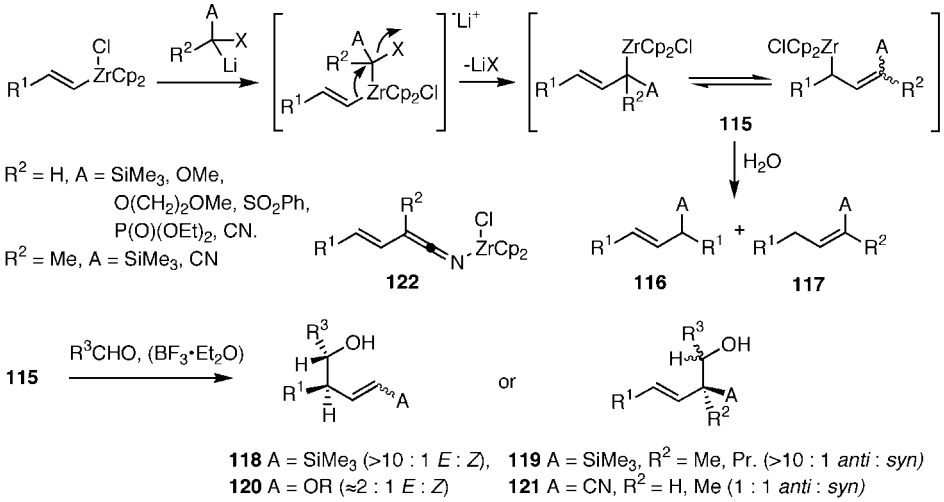


Figure 3.1. Alkyl carbenoids.

3.3.5.1 Insertions into acyclic alkenylzirconocene chlorides. A convergent route to functionalized allylzirconocenes

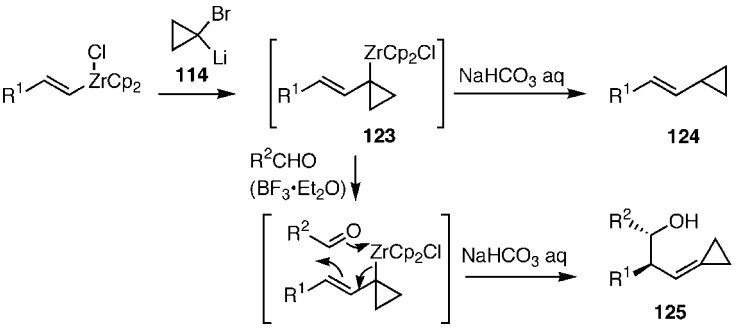
The high reactivity of allylzirconium species towards electrophiles has been described for cyclic complexes (Section 3.3.3.2). A versatile convergent route to allylzirconocene reagents **115** has been demonstrated by the insertion of alkyl carbenoids **104**–**106** and **108**–**110** into alkenylzirconocenes (Scheme 3.28) [50,66,67]. The allylzirconocene **115** possesses some η^3 character, or at least the two η^1-forms are expected to rapidly interconvert. Consequently, the ends of the allyl moiety (R^1 *cf.* R^2 and A) need to be sufficiently different such that good regioselectivity of electrophile addition may be realized. Hydrolysis yields >95 % **116** (*cf.* **117**) as the (*E*)-alkene, the only exception being the case where A = $SiMe_3$ and R^2 = H, which gives an approximately 1:1 *E*:*Z* mixture along with 11 % of the alkenyl silane product **117**. Addition of aldehydes to allylzirconocenes **115** derived from OR-, $SiMe_3$- and CN-substituted carbenoids (**104**–**106** and **108**) gives the adducts **118**–**121**. In the case where A = $SiMe_3$ and R^2 = H, the γ-regioisomer **118** is formed with excellent (*E*)-*anti*-selectivity, particularly in the presence of $BF_3 \cdot Et_2O$. When A = $SiMe_3$ and R^2 = Me or Pr, the α-adduct **119** is formed, again with excellent (*E*)-*anti*-stereocontrol. When A = OR, the *anti*-γ-adduct **120** is formed, but with only around 2:1 *E*:*Z* control of the alkene geometry. Surprisingly, the addition of $BF_3 \cdot Et_2O$ switches the stereochemistry in



Scheme 3.28. Convergent synthesis and elaboration of functionalized allylzirconocenes.

favor of the (*E*)-*syn* form. With A = CN, R^1 = H or Me, the (*E*)-α-adduct **121** is formed, but with no *anti*:*syn* control. The lack of *anti*:*syn* control, and the exclusive formation of α-adducts may be due to the nitrile-substituted allylzirconocene existing in the nitrogen-bound form **122**. The sulfonate- and phosphonate-substituted allyl zirconocenes **115** (A = SO_2Ph, $P(O)(OEt)_2$) do not react cleanly with aldehydes.

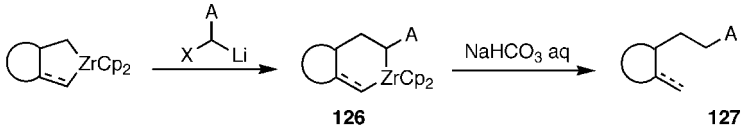
Insertion of alkyl carbenoids into alkenylzirconocenes is not a generally useful route to allylzirconocenes because the two ends of the allyl fragment are not sufficiently differentiated to give good regiocontrol upon reaction with electrophiles. An exception is the insertion of the cyclopropyl carbenoids **114**, where zirconium is localized on the cyclopropyl carbon in the allylzirconocene **123** produced (Scheme 3.29). Protonation provides a useful route to alkenylcyclopropanes **124**, and reaction with aldehydes affords alkylidenecyclopropanes **125** [50]. Alkenylcyclopropanes and alkylidenecyclopropanes are valuable intermediates in organic synthesis.



Scheme 3.29. Synthesis of alkenyl- and alkylidiene-cyclopropanes.

3.3.5.2 **Insertions into zirconacycles**

Many alkyl carbenoids insert into saturated and unsaturated zirconacycles to afford zirconacyclohexanes and -hexenes **126**, which give the expected products **127** upon hydrolysis (Scheme 3.30) [48,50,68]. There should be comparable scope for further elaboration of the six-membered zirconacycles, as has already been established for the five-membered analogues. Yields are generally high, one exception being the insertion of lithiated chloroacetonitrile into saturated zirconacycles, where double insertion predominates [50].

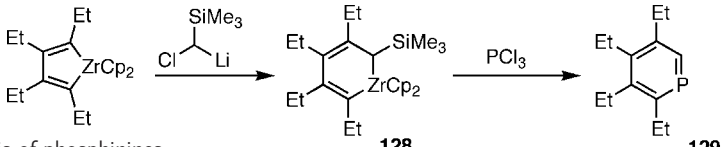


X = Cl, A = H, Ar, $SiMe_3$, $SiMe_2Ph$, SPh, OEt, CN, $PO(OEt)_2$
X = $OC(O)N^iPr_2$, A = H, Me, Ph
X = Br, A = alkyl

Scheme 3.30. Ring-expansion of zirconacycles with alkyl carbenoids.

Lithiated chloromethyltrimethylsilane is a remarkably stable carbenoid [69] and shows exceptional reactivity in insertions into the alkenyl–zirconium bonds of unsaturated zirconacycles. It is the only known carbenoid that will insert into zirconacyclopentadienes

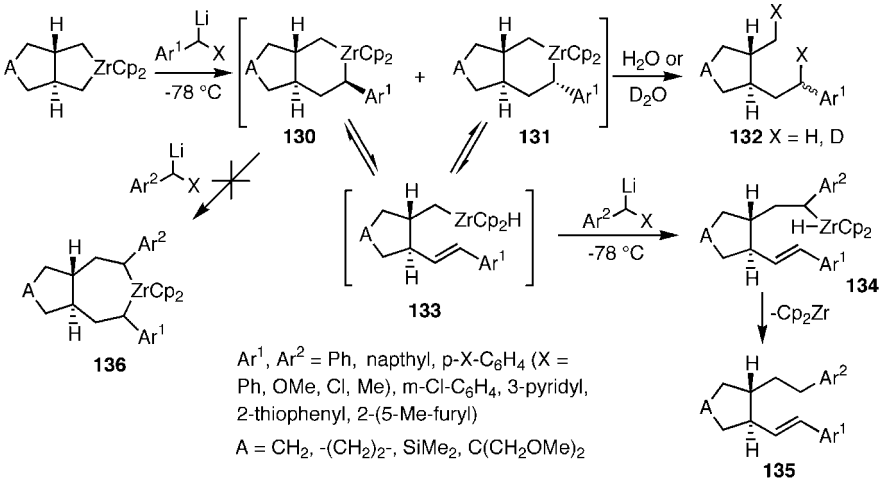
that are substituted α to the zirconium (Scheme 3.31) [70,71]. The thus formed zirconacyclohexadienes **128** are valuable precursors of heteroaromatic compounds such as phosphinines (phosphabenzenes) **129** [71].



Scheme 3.31. Synthesis of phosphinines.

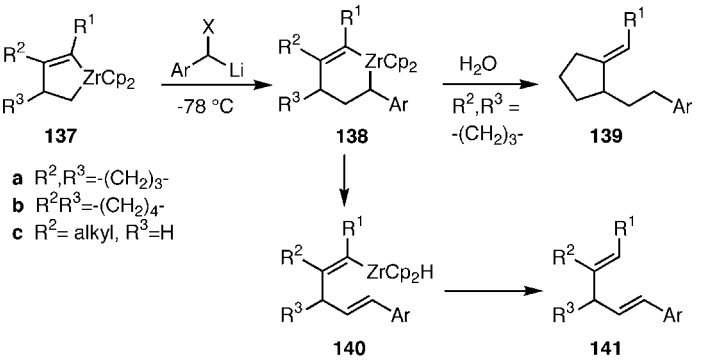
3.3.5.3 Insertion of benzyl carbenoids into zirconacycles

A wide range of benzyl chlorides can readily be metalated using lithium diisopropylamide (LDA) [72–75] and insertion of the thus formed carbenoids into zirconacycles is mechanistically interesting [68]. Insertion into saturated bicyclic zirconacycles gives initially a 1:1 mixture of the diastereoisomeric zirconacyclohexanes **130** and **131**, as would be expected for the stereospecific insertion of a racemic carbenoid into a racemic zirconacycle (Scheme 3.32). However, after several hours at room temperature or a few minutes at 60 °C, complete isomerization to the more stable diastereoisomer **130** is observed. Quenching with water or D_2O gives the expected products **132**. Yields are high and a wide range of aromatic and heteroaromatic groups are tolerated, an exception being electron-poor systems, such as in *p*-nitrobenzyl chloride. A possible mechanism for the isomerization of **131** into **130** proceeds via the zirconium hydride **133** formed by a reversible β-hydrogen transfer to the metal. Strong evidence for the intermediacy of **133** comes from the insertion of a second benzyl carbenoid to afford **135**, in which the regiochemistry of the alkene is defined. If the second insertion occurred via the zirconacycloheptane **136**, a mixture of regioisomeric alkenes would be expected. Presumably, the zirconium center in **133** is sufficiently less sterically hindered than that in **130**/**131** that it is selectively trapped by the carbenoid despite its low concentration (below the detection limits of NMR). It is notable that aqueous work-up is unnecessary in the formation of **135**, and indeed work-up with deuterium oxide gives no deuterium incorporation.



Scheme 3.32. Mono- and bis-insertion of benzyl carbenoids into saturated zirconacycles.

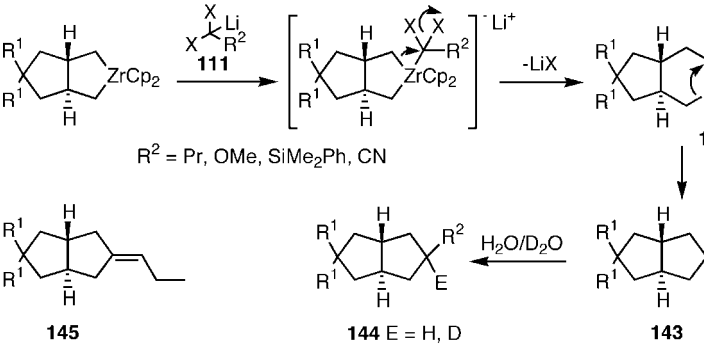
Insertion of benzyl carbenoids into zirconacyclopentenes follows a different, but mechanistically related path (Scheme 3.33). When the zirconacyclopentene is fused to a five-membered ring (**137a**), zirconacyclohexenes **138** are formed as a 1:1 mixture of diastereoisomers. The ratio of the diastereoisomers does not change upon prolonged storage or on heating, implying that there is no equilibrium with the zirconocene hydride species **140**. Hydrolysis gives the expected product **139** in high yield. In comparison, monocyclic zirconacyclopentenes **137c** and those fused to a six-membered ring (**137b**) directly form the products **141** of β-hydride transfer/α-elimination in high yield, presumably via **140**. Possibly, the constraint of the fused five-membered ring in **138a** prevents the β-hydride transfer.



Scheme 3.33. Insertion of benzyl carbenoids into unsaturated zirconacycles.

3.3.5.4 Insertion of halo-substituted carbenoids into zirconacycles

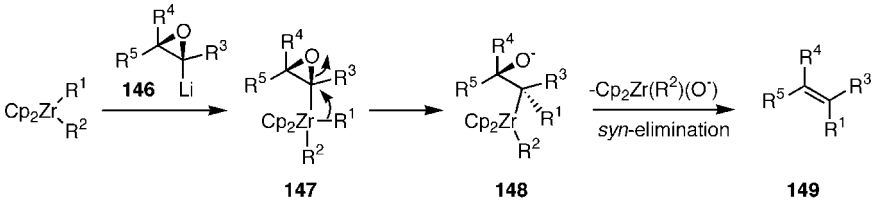
α,α-Dihalolithium species **111** are readily formed by in situ deprotonation of 1,1-dihalides with LDA and insert efficiently into zirconacycles, but the initially formed zirconacyclohexanes **142** further rearrange to form cyclopentanes **143** (Scheme 3.34). The rearrangement of **142** to **143** is analogous to the rearrangement of **27** to **29** during carbonylation (Scheme 3.7). Quenching **143** with water or deuterium oxide affords the expected products **144** [76]. When the carbenoid substituent R^2 bears protons β to zirconium in **143**, warming to room temperature prior to quenching affords an alkylidenecyclopentane (e. g. **145**) in high yield. Insertion of α,α-dihalolithium species **111** into zirconacyclopentenes occurs similarly, but the intermediate analogous to **143** is an allylzirconium and quenches with little regioselectivity.



Scheme 3.34. Insertion/cyclization of halocarbenoids into zirconacycles; R^1,R^1 = -($CH_2OCMe_2OCH_2$)-.

3.3.6 Insertion of Metalated Epoxides into Organozirconium Species

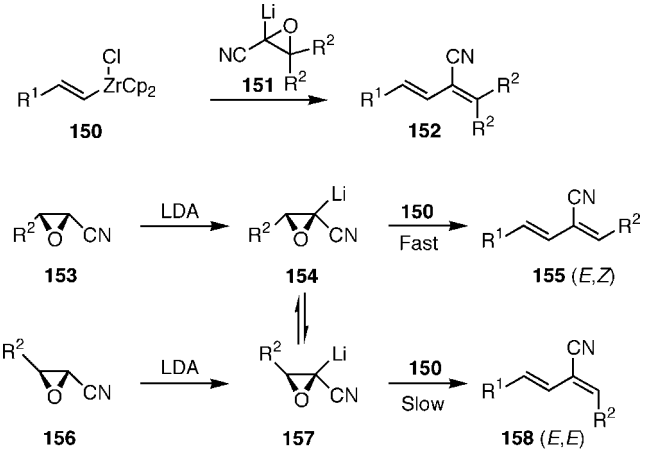
Metalated epoxides **146** [77,78] have been used as nucleophiles, but more commonly are implied intermediates in the formation of carbenes. A stabilizing aryl, alkenyl, alkynyl, nitrile, or silyl group R^3 (Scheme 3.35) is required for their formation by deprotonation [79–83], although unstabilized systems may be generated by tin/lithium exchange [84]. Insertion of metalated epoxides into organozirconocenes by 1,2-rearrangement of an "ate" complex **147** should give the β-alkoxyzirconocene species **148**, which may then undergo stereospecific *syn*-elimination to afford an alkene **149**. The overall process is complementary to the insertion of alkenyl carbenoids described in Section 3.1.



Scheme 3.35. Insertion of metalated epoxides into organozirconocenes.

3.3.6.1 Insertion of 1-nitrile-1-lithio epoxides into acyclic organozirconocene chlorides

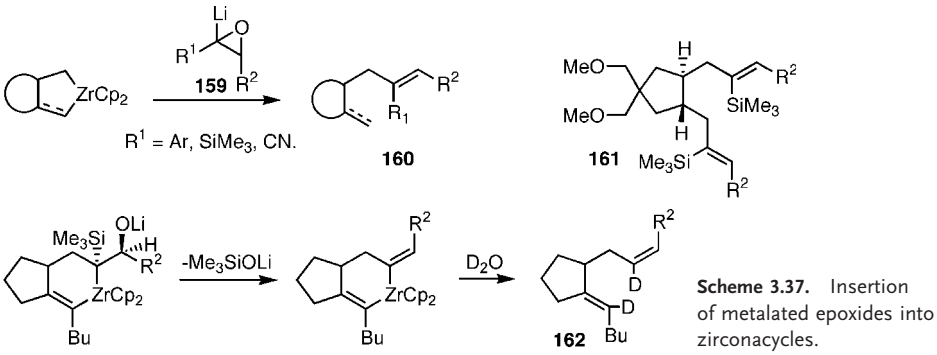
Although various metalated epoxides efficiently insert into acyclic organozirconocenes, only the insertion of lithiated epoxynitriles into alkenylzirconocenes has been properly investigated [85]. Single products **152** are formed from symmetrically β,β-disubstituted lithiated epoxynitriles **151** (Scheme 3.36). Insertion of the lithiated epoxides formed by deprotonation of stereodefined (*E*)- and (*Z*)-mono-β-substituted epoxynitriles **153** and **156** is not stereospecific. The (*Z*)-epoxides **153** give an approximately 9:1 mixture of **155** and **158**, whereas the (*E*)-epoxides **156** give approximately 1:1 mixtures. In the case of **156** (R^2 = Ph), an approximately 8:1 mixture of **155** and **158** is produced. The lack of stereospecificity is due to configurational instability of the lithiated epoxynitriles combined with preferential trapping of the (*Z*)-lithio epoxide **154** [85].



Scheme 3.36. Insertion and isomerization of lithiated epoxynitriles.

3.3.6.2 Insertion of 1-silyl-, 1-nitrile, and 1-aryl-1-lithio epoxides into zirconacycles

Insertion of phenyl, trimethylsilyl, and nitrile-stabilized metalated epoxides into zirconacycles gives the product **160**, generally in good yield (Scheme 3.37). With trimethylsilyl-substituted epoxides, the insertion/elimination has been shown to be stereospecific, whereas with nitrile-substituted epoxides it is not, presumably due to isomerization of the lithiated epoxide prior to insertion [86]. With lithiated trimethylsilyl-substituted epoxides, up to 25 % of a double insertion product, e. g. **161**, is formed in the reaction with zirconacyclopentanes. Surprisingly, the ratio of mono- to bis-inserted products is little affected by the quantity of the carbenoid used. In the case of insertion of trimethylsilyl-substituted epoxides into zirconacyclopentenes, no double insertion product is formed, but product **162**, derived from elimination of Me_3SiO^-, is formed to an extent of up to 26 %.



Scheme 3.37. Insertion of metalated epoxides into zirconacycles.

3.3.7 Regiochemistry of Carbenoid Insertion into Zirconacycles

For application in organic synthesis, the regiochemistry of insertion of carbenoids into unsymmetrical zirconacycles needs to be predictable. In the case of insertion into mono- and bicyclic zirconacyclopentenes where there is an α-substituent on the alkenyl but not on the alkyl side, we have already seen that a wide variety of metal carbenoids insert selectively into the zirconium–alkyl bond [48,59,86]. For more complex systems, the regiocontrol has only been studied for the insertion of lithium chloroallylides (as in Section 3.3.2) [60]. Representative examples of regiocontrol relating to the insertion of lithium chloroallylide are shown in Fig. 3.2.

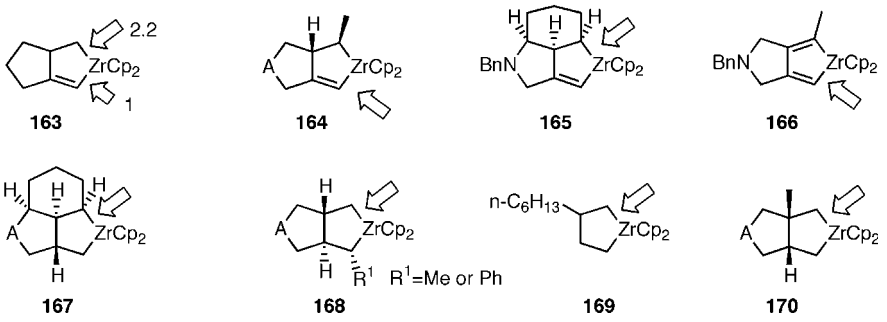


Figure 3.2. Regiochemistry of allyl carbenoid insertion.

It is observed that insertion into a zirconacyclopentene **163**, which is not α-substituted on either the alkyl and alkenyl side of the zirconium, shows only a 2.2:1 selectivity in favor of the alkyl side. Further steric hindrance of approach to the alkyl side by the use of a terminally substituted *trans*-alkene in the co-cyclization to form **164** leads to complete selectivity in favor of insertion into the alkenyl side. However, insertion into the zirconacycle **165** derived from a cyclic alkene surprisingly gives complete selectivity in favor of insertion into the alkyl side. In the proposed mechanism of insertion, attack of a carbenoid on the zirconium atom to form an "ate" complex must occur in the same plane as the C−Zr−C atoms (lateral attack; **171**; Fig. 3.3) [87,88]. It is not surprising that an α-alkenyl substituent, which lies precisely in that plane, has such a pronounced effect. The difference between **164** and **165** may also have a steric basis (Fig. 3.3). The alkyl substituent in **164** lies in the "lateral attack" plane (as illustrated by **172**), whereas in **165** it lies well out of the plane (as illustrated by **173**). However, the difference between **165** and **163** cannot be attributed to steric factors; **165** is more hindered on the alkyl side. A similar pattern is observed for insertion into zirconacyclopentanes **167** and **168**, where insertion into the more hindered side is observed for the former. In the zirconacycles **169** and **170**, where the extra substituent is β to the zirconium, insertion is remarkably selective in favor of the somewhat more hindered side.

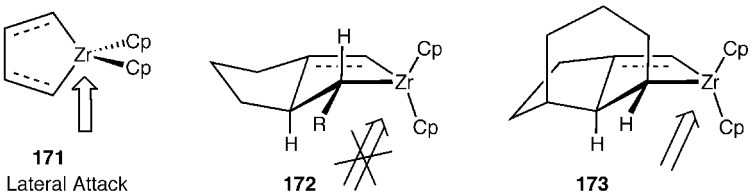
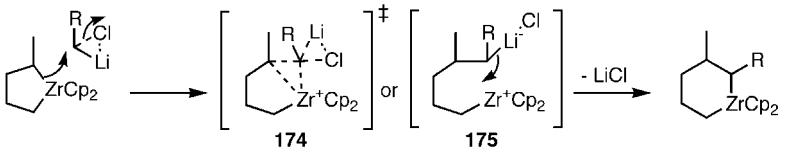


Figure 3.3. Direction of carbenoid attack on zirconacycles.

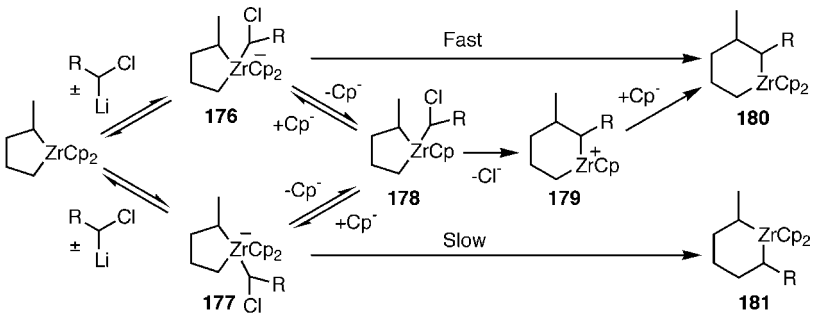
For the regiochemical results that cannot be explained using steric arguments (**165**, **167**, **169**, **170**), the observed selectivity correlates with the largest coefficient of the Highest Occupied Molecular Orbital of the zirconacycle, rather than of the Lowest Unoccupied Molecule Orbital, suggesting that the carbenoid may be attacking as an electrophile. As discussed in Section 3.1.1 and Scheme 3.11, α-lithio-α-halo species behave as electrophilic carbenoids or even as powerful electrophiles [35]. Reaction pathways proceeding through concerted insertion into the carbon−zirconium bonds and transition state **174**, or electrophilic attack on the carbon−zirconium bond and intermediate **175**, are reasonable (Scheme 3.38).



Scheme 3.38. Alternative mechanisms for carbenoid insertion into organozirconocenes.

An alternative explanation is that the regioselectivity of insertion (**180** *vs.* **181**) is determined by the rate of 1,2-metallate rearrangement, the formation of the regioisomeric "ate" complexes **176** and **177** being fast and reversible (Scheme 3.39). Interconversion of **176**

and **177** could take place by loss/re-addition of the carbenoid, but more likely is due to reversible loss of cyclopentadienide anion [89] to afford the common tetrahedral intermediate **178**. It is also possible that **178** rearranges directly to afford **179**, which adds cyclopentadienide to afford the product **180**.



Scheme 3.39. Alternative explanation for the regiochemistry of carbenoid insertion.

3.4 Conclusion

The insertion of carbenoids into metal–carbon bonds to form new organometallic reagents is a little explored but potentially extremely valuable transformation. It may be viewed as both an ideal component for the development of tandem reaction sequences, particularly using zirconacycles, and a convergent route to versatile organometallic reagents (e. g. alkenyl- and allylmetallics). In this chapter, we have described the area in which it is best developed, i. e. zirconium chemistry. Although the field is young, and only the first exploratory steps have been taken, we believe that the results already achieved promise much for the future.

Acknowledgements

We thank the students and postdoctoral fellows whose efforts and enthusiasm led to the work from our group described herein. We also thank the organizations that generously support our work in this area (EPSRC, Pfizer, GlaxoWelcome (now GSK), and Zeneca (now AstraZeneca)).

Typical Experimental Procedures

Insertion of an alkenylcarbenoid into an alkenylzirconocene chloride. Preparation of (3*Z*,5*E*)-1,3,5-dodecatriene (as in Scheme 3.12) To a stirred suspension of $Cp_2Zr(H)Cl$ (0.260 g, 1.00 mmol) in THF (12.0 mL) was added 1-octyne (0.091 g, 0.83 mmol). The mixture was stirred at 20 °C for 1 h to give a clear yellow solution of the alkenylzirconium compound. After cooling to −90 °C, (*Z*)-1,4-dichloro-2-butene (0.135 g, 1.08 mmol) was added followed by a solution of lithium 2,2,6,6-tetramethylpiperidide [LiTMP, preformed from

2,2,6,6-tetramethylpiperidine (TMP, 0.305 g, 2.16 mmol) and BuLi (0.86 mL, 2.5 M in hexane, 2.16 mmol) in THF (2.0 mL)]. The reaction mixture was stirred at −90 °C for 15 min., then hydrolyzed by the addition of 2 M aq. HCl (8.0 mL). After extraction with diethyl ether (12 mL), the organic layer was washed with 2 M aq. HCl (2 ×x 10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (silica; 40−60 petroleum ether) to afford (3*Z*,5*E*)-1,3,5-dodecatriene (0.104 g, 76 % yield) [38].

Tandem zirconacycle formation, allyl carbenoid insertion, and aldehyde addition. Synthesis of 5-[(1*R*,2*S*)-2-methylcyclopentyl]-1-phenylpent-3-en-1-ol (as in Scheme 3.24) To a stirred solution of zirconocene dichloride (0.293 g, 1 mmol) in THF (5 mL) under argon at −78 °C was added dropwise *n*-BuLi (0.8 mL of a 2.5 M soln. in hexanes, 2 mmol). After 20 min., a solution of 1,6-heptadiene (0.096 g, 1 mmol) in THF (3 mL) was added and the reaction mixture was allowed to warm to room temperature over a period of 2 h. After cooling to −78 °C, allyl chloride (0.084 g, 1.1 mmol) followed by LiTMP [1.1 mmol, generated from TMP and BuLi in THF (2 mL) at 0 °C] were added dropwise, and after 15 min. the reaction mixture was allowed to warm to room temperature. After cooling to −78 °C once more, benzaldehyde (0.12 g, 1.1 mmol) and $BF_3 \cdot Et_2O$ (0.16 g, 0.14 mL, 1.1 mmol) were added and the solution was allowed to warm to room temperature over a period of 1.5 h. The reaction was quenched by the addition of methanol (3 mL) and aq. $NaHCO_3$ solution (15 mL) and the resulting mixture was stirred at room temperature for 15 h. Extractive work-up and chromatography (silica; 10−15 % diethyl ether in 40−60 petroleum ether) gave the title alcohol as a colorless oil (0.220 g, 90 %) [90].

Convergent formation and reaction of an allylzirconocene. Synthesis of 1-phenyl-2-hexyl-4-methoxy-3-buten-1-ol (as in Scheme 3.28) 1-Octyne (94 mg, 0.85 mmol) was added to a suspension of $Cp_2Zr(H)Cl$ (253 mg, 0.98 mmol) in THF (3.5 mL) and the mixture was stirred at 20 °C for 1 h. It was then cooled to −100 °C, whereupon a solution of methoxymethyl phenyl sulfone (206 mg, 1.11 mmol) in THF (4.0 mL) was added. This was followed by the slow addition of a solution of LiTMP [preformed from TMP (157 mg, 1.11 mmol) and BuLi (0.44 mL, 2.5 M in hexanes, 1.11 mmol) in THF (2.5 mL) at 0 °C]. After warming to −60 °C over a period of 1 h, benzaldehyde (180 mg, 1.70 mmol) was added and the resulting mixture was allowed to warm to room temperature, stirred for 3 h, and hydrolyzed with satd. aq. $NaHCO_3$ solution (10 mL). The products were extracted into diethyl ether (3 × 6 mL), and the combined organic layers were washed with brine (2 × 10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel; 20 % ethyl acetate in 40−60 petroleum ether) to afford 1-phenyl-2-hexyl-4-methoxy-3-buten-1-ol (156 mg, 70 % yield) as a mixture of three stereoisomers [66].

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4
Hydrozirconation and Further Transmetalation Reactions

Bruce H. Lipshutz, Steven S. Pfeiffer, Kevin Noson, and Takashi Tomioka

4.1
Introduction

Hydrometalation reactions, which take place across carbon–carbon double and, especially, triple bonds provide extremely versatile and extensively utilized routes to valuable organometallic intermediates for synthetic purposes. While *syn* additions of alanes [1] and, in particular, of boranes [2] have a rich tradition of continuing service in this regard, there are processes (most notably cross-coupling reactions) that are best conducted via related transition metal derivatives. Moreover, depending on the nature of the substrate, tolerance to functionality present in the educt may not allow the use of more electron-rich metal hydrides. Given the widespread occurrence of zirconium in Nature, along with the ready availability of the "Schwartz reagent", $Cp_2Zr(H)Cl$ [3], it is perhaps not surprising that there has been extensive usage of this species, which effects hydrozirconations of C–C multiple bonds. Although this 16-electron neutral hydride had been known since 1970 [4], it was a series of papers by Schwartz [5] a few years later which triggered an avalanche of subsequent reports based on the facility with which $Cp_2Zr(H)Cl$ adds to most alkenes and alkynes. The reagent $Cp_2Zr(H)Cl$ can be obtained commercially from several vendors [6], although the quality can vary substantially, often as a function of time spent on the shelf and the care with which it is handled and stored. The best results can be expected when it is stored and weighed out in a dry-box environment. Larger amounts of material are best divided into smaller batches for individual usage over time.

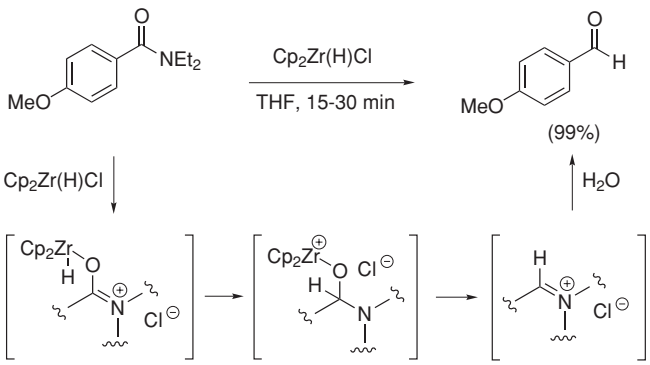
Several alternative procedures now exist for the *in situ* preparation of "$Cp_2Zr(H)Cl$", which, owing to the nature of the respective starting materials, must necessarily contain salts as by-products [3,7]. While such seemingly innocuous materials can on occasion have a deleterious effect on the desired hydrozirconation [8], in many situations an *in situ* protocol can help to avoid the vagaries of quality control for this air- and moisture-sensitive reagent. In contrast to hydrogen-transfer hydrozirconation of alkynes with *i*BuZrCp_2Cl, which normally proceeds well, the corresponding reaction with monosubstituted alkenes is sluggish [9]. Recently, reactions involving this class of substrates have shown promise when conducted in the presence of catalytic amounts of a Lewis acid (e. g., $AlCl_3$, Me_3SiI, $PdCl_2(Ph_3P)_2$) [10] (Procedure 1, p. 139).

Patterns for addition of the Schwartz reagent to multiple C–C bonds in terms of regio- and stereochemistry are well-established for most substituents, as is the fundamental chemistry of the newly formed C_{sp^2}–Zr and C_{sp^3}–Zr bonds. Conversion to halides and

alcohols are among the most useful processes involving such derivatives [11]. Nonetheless, many new transformations of carbon–zirconium bond containing intermediates have recently emerged, several of which are discussed herein.

Although the chemistry of in situ generated C–Zr bonds is useful in several contexts, the facility with which such bonds undergo transmetalations to other organometallics has greatly expanded their popularity within the synthetic community. Among the most important of these processes is the observation that once a C–Zr bond has been established by an initial hydrozirconation across an alkene or alkyne, the resulting intermediate alkyl or vinyl zirconocene readily participates in, for example, group 10 (Pd or Ni)-catalyzed coupling reactions with a host of substrates. Likewise, ligand-exchange phenomena, leading, for example, to organocopper complexes or organozinc intermediates, have opened additional avenues for applying hydrozirconation to synthetic targets.

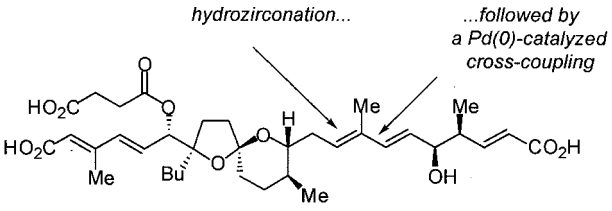
Because of the level of activity associated with *organo*zirconium chemistry, where the accent is firmly on the increase of molecular complexity at carbon, many reviews have been written on this subject [12]. The practical aspects of existing methodology, along with several detailed procedures, have recently been compiled by Negishi and are soon to appear [13]. An outstanding overview of hydrozirconation, as well as subsequent transmetalation processes, up until ca. 1995 by Wipf highlights much of the progress made since the disclosures of Schwartz two decades earlier [14]. In this contribution, we report on developments that have taken place since the Wipf review, focusing on new technologies and/or applications that are initiated by hydrozirconation of an alkene or alkyne. On occasion, however, the addition of H–Zr across a site of unsaturation involving a *heteroatom* can lead to a synthetically worthwhile development. Such was the case in the recent, atypical reactivity pattern observed with $Cp_2Zr(H)Cl$ in its net conversion of a tertiary amide to an aldehyde (Scheme 4.1) [15]. Although both aldehydes and ketones are readily reduced by the Schwartz reagent, esters are usually inert and hence amides would be expected to be even less prone to hydride addition. Since over-reduction to the corresponding alcohol is not observed, the likely pathway involves reduction of an iminium ion intermediate followed by hydrolysis to the aldehydic product. This sequence is further supported by the fact that on quenching a reaction mixture with $H_2{}^{18}O$, significant incorporation of the labeled oxygen into the aldehyde carbonyl is observed (Procedure 2, p. 140).



Scheme 4.1. Reduction of a tertiary amide with the Schwartz reagent.

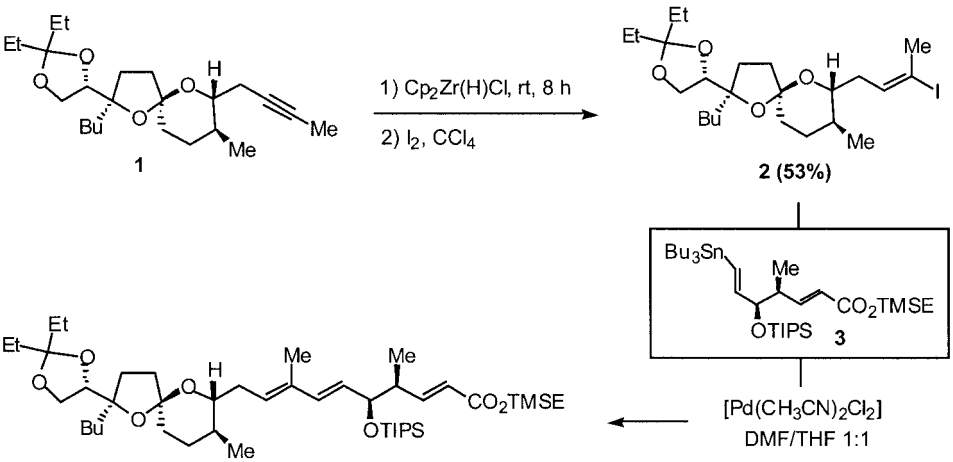
4.2
Hydrozirconation/Quenching

The *cis*-addition of the Schwartz reagent across an alkyne remains as one of the most frequently used routes to functionalized alkenes. Both terminal and, as has been established more recently, differentially substituted alkynes, ultimately give rise to more highly functionalized products. The regiochemistry of addition to disubstituted acetylenes, in particular when heteroatoms are attached to one of the acetylenic carbons, is an especially interesting and important question. Several recent studies have addressed the issue of selectivity in this context. Addition across an alkyne bearing a methyl moiety, which has been known for years to favor placement of zirconium at the least hindered site [5b], still provides an extremely valuable access to fragments of natural products having such a substitution pattern. The synthesis of reveromycin B is one case in point (Figure 4.1). Here, Theodorakis and Drouet converted spirocycle **1** to (*E*)-vinyl iodide **2**, which could then be used in a Stille coupling with vinyl stannane **3** (Scheme 4.2) [16].



reveromycin B

Figure 4.1. Retrosynthetic analysis of reveromycin B.



(52%) TMSE = $Me_3SiCH_2CH_2$-

Scheme 4.2. Hydrozirconation–I_2 quenching en route to reveromycin B.

In the highly competitive arena surrounding the Pfizer compounds CP-263,114 and CP-225,917 (Figure 4.2), Nicolaou and co-workers employed a hydrozirconation–iodination sequence to produce vinyl iodide **4** [17]. Lithium–halogen exchange and subsequent conversion to enone **5** sets the stage for a Lewis acid assisted intramolecular Diels–Alder reaction affording polycyclic **6** as the major diastereomer (Scheme 4.3).

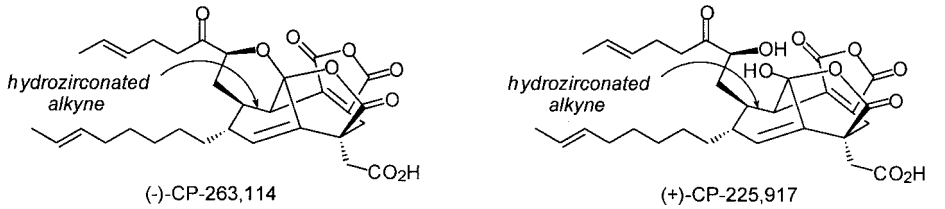
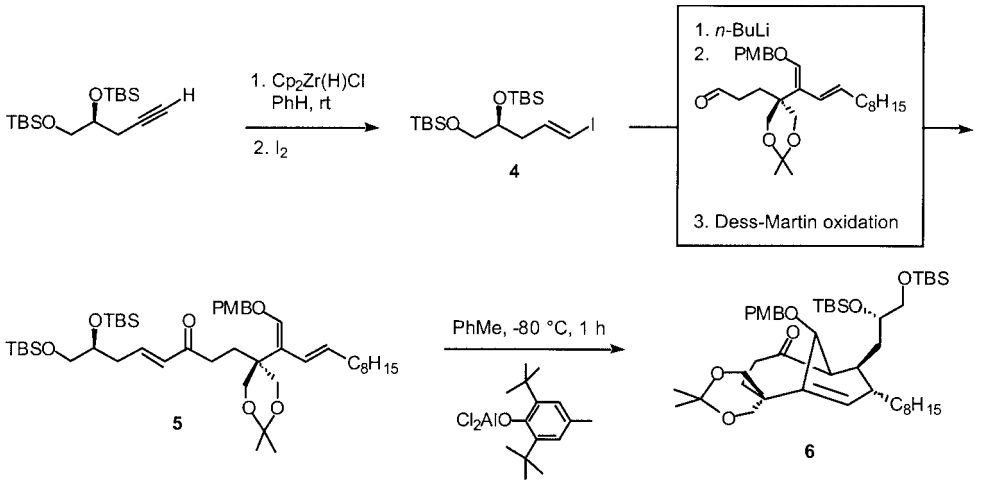
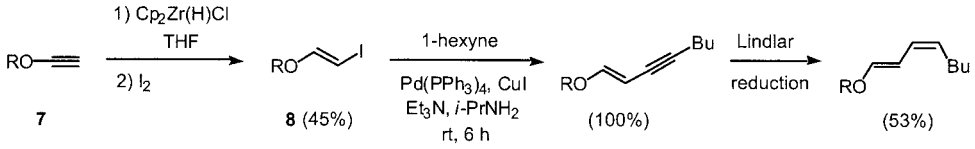


Figure 4.2. Structures of (−)-CP-263,114 and (+)-CP-225,917.



Scheme 4.3. Formation of vinyl iodide **4** en route to polycyclic enone **6**.

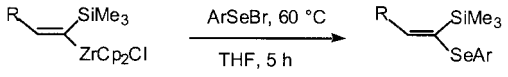
Acetylenic ethers **7** can be hydrozirconated, and subsequent iododezirconation leads to (*E*)-iodo enol ethers **8** (Scheme 4.4) [18]. These species undergo efficient Sonogashira couplings to give (*E*)-enynes, which are ultimately converted to stereodefined dienol ethers. These dienes have proven useful in studies of diastereoselective cycloaddition reactions with singlet oxygen, where R in **8** is a nonracemic auxiliary (e. g., menthyl) (Procedure 3, p. 140).



Scheme 4.4. Hydrozirconation of alkynyl ethers **7**.

In a series of papers, Huang et al. have reported the conversion of intermediate vinyl zirconocenes to an array of functionalized (*E*)-olefins [19−35]. Quenching in THF at room temperature with an arylselenenyl bromide leads to high yields of vinyl selenides, which may be further manipulated to give chain-elongated materials. An analogous conversion can be effected with TMS-substituted alkynes, although more vigorous conditions are required to replace the C−Zr bond with selenium (Scheme 4.5). Yields remain comparable, nonetheless. The regiochemistry associated with this addition is such that zircon-

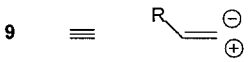
ium adds to the carbon bearing the silyl group, an observation initially made by Erker [36]. Products of general structure **9** are formed readily, with both the selenide and the silane being amenable to replacement (e. g., the aryl selenide by copper-catalyzed couplings with Grignard reagents, and the silicon by displacement with electrophiles; *vide infra*). This makes **9** tantamount to synthon **10** (Figure 4.3) [21] (Procedure 4, p. 140).



R = *n*-C_6H_{13}, CH_2OMe, Ph
Ar = Ph, *p*-$CH_3C_6H_4$, *m*-$CH_3C_6H_4$

9 (81-90%)

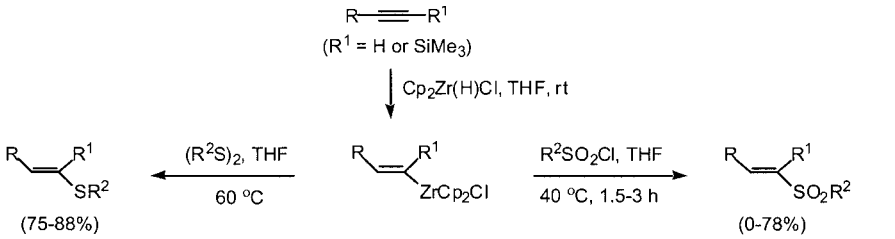
Scheme 4.5. Trapping of a vinyl zirconocene with an aryl selenenyl halide.



10

Figure 4.3. Synthetic equivalent of 1,1-dimetallo reagent **9**.

From the same zirconocene intermediates, Huang and co-workers have prepared vinyl sulfides [24,35] and sulfones [26] through use of the appropriate quenching agents (Scheme 4.6). Treatment of vinyl zirconocenes with an equivalent of a disulfide in THF at 60 °C affords, after work-up and purification, (*E*)-vinyl sulfides in good isolated yields. Vinyl sulfones, which as a class are generally useful as Michael acceptors and Diels–Alder dienophiles, are obtained in about two hours upon treatment of (*E*)-vinyl zirconocenes with various sulfonyl chlorides in THF at 40 °C.

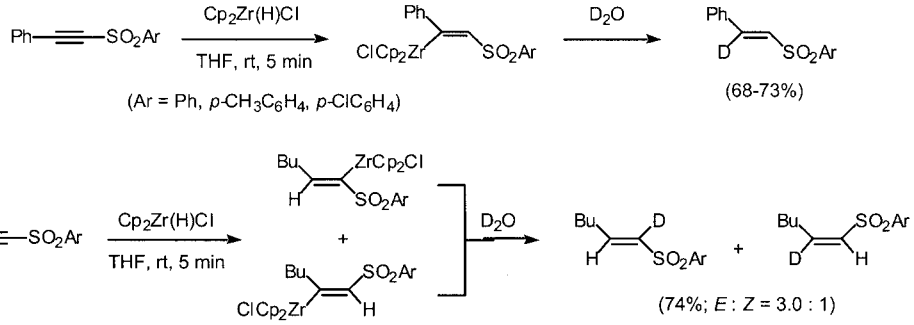


(75-88%)
R = CH_2OMe, Ph, *n*-Bu
R^1 = H
R^2 = Ph or Bn

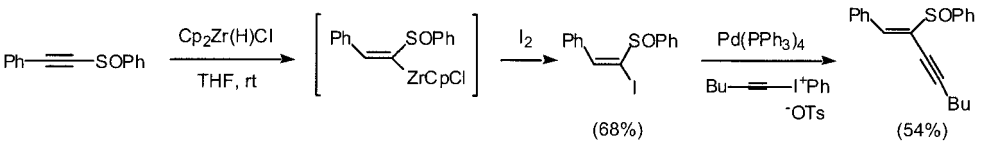
(0-78%)
R = Ph, *n*-Bu, $MeOCH_2$, $TMSCH_2$, $HOCH_2$, $BrCH_2$
R^1 = H
R^2 = Ph, *p*-Tol, Me

Scheme 4.6. Formation of vinyl sulfides and sulfones.

When the sulfone moiety is part of an aryl acetylene, the Schwartz reagent adds quickly and regiospecifically at ambient temperatures, placing the Cp_2ZrCl residue in the β-position (Scheme 4.7) [31]. Most curious is the overall *trans* addition of $Cp_2Zr(H)Cl$, which may reflect double hydrozirconation followed by elimination to give the thermodynamically favored adduct. When the aryl group in the educt is replaced by an alkyl group, a mixture of regioisomers is formed initially, from which the (*E*)- and (*Z*)-vinyl sulfones are obtained in a ca. 3:1 ratio. With aryl acetylenic sulfoxides, in contrast to the situation with the analogous sulfones, the Schwartz reagent adds exclusively in a *cis* fashion, with zirconium being placed in the α-position (Scheme 4.8). Alkyl aryl sulfoxides give mixtures of regioisomers with no apparent selectivity (40–44 % Zr α and 56–60 % Zr β) (Procedure 5, p. 140).



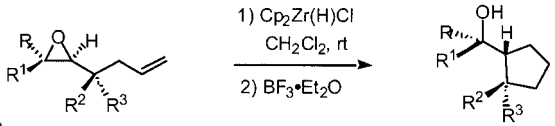
Scheme 4.7. Variations in the regiochemistry of the hydrozirconation of alkynyl sulfones.



Scheme 4.8. Hydrozirconation and electrophilic quenching of alkynyl sulfoxides.

4.3
Hydrozirconation: Ring-Forming and Ring-Opening Reactions

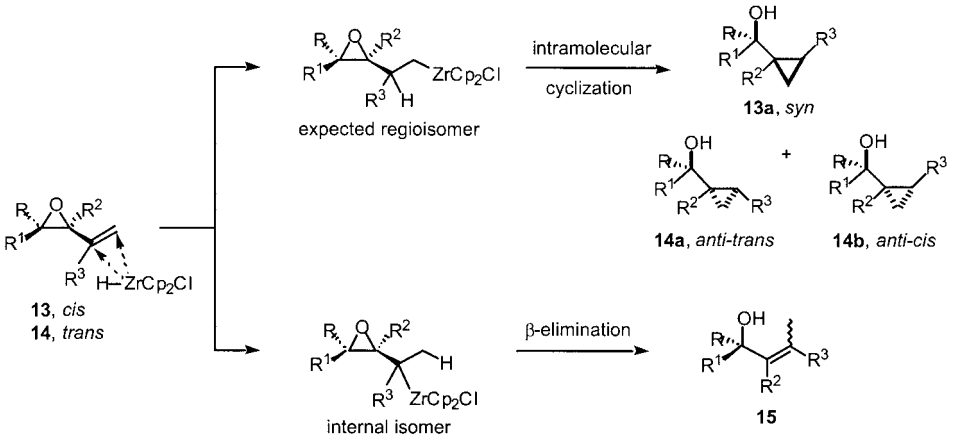
Having established that hydrozirconation of a terminal alkene occurs far faster than reduction of an epoxide by $Cp_2Zr(H)Cl$, Taguchi, Hanzawa, and co-workers [37] were able to exploit these features to construct rings from substrates possessing both oxirane and alkene functionalities. Epoxy olefins of general structure **11** (Scheme 4.9) react to give terminal zirconocenes, which, in the presence of a stoichiometric amount of $BF_3 \cdot OEt_2$, afford cyclopentane methanols **12**. Based on extensive NMR analyses of products and their derivatives, the stereochemical course of the reaction could be conclusively delineated as proceeding by clean inversion at the reacting oxirane center. No reaction took place in the absence of the Lewis acid, and only the 5-*exo* mode of opening was observed.



Scheme 4.9. Lewis acid-assisted intramolecular trapping of an alkylzirconium chloride.

11 **12** (50-77%)

The analogous process involving allylic epoxides is more complex, as issues such as the stereochemistry of substituents on the ring and on the alkene play major roles in determining the course of the reaction [38]. Addition of the Schwartz reagent to the alkene only occurs when an unsubstituted vinyl moiety is present and, in the absence of a Lewis acid, intramolecular attack in an *anti* fashion leads to cyclopropane formation as the major pathway (Scheme 4.10). *cis*-Epoxides **13** afford *cis*-cyclopropyl carbinols, while *trans*-oxiranes **14** give mixtures of *anti-trans* and *anti-cis* isomers. The product of β-elimi-

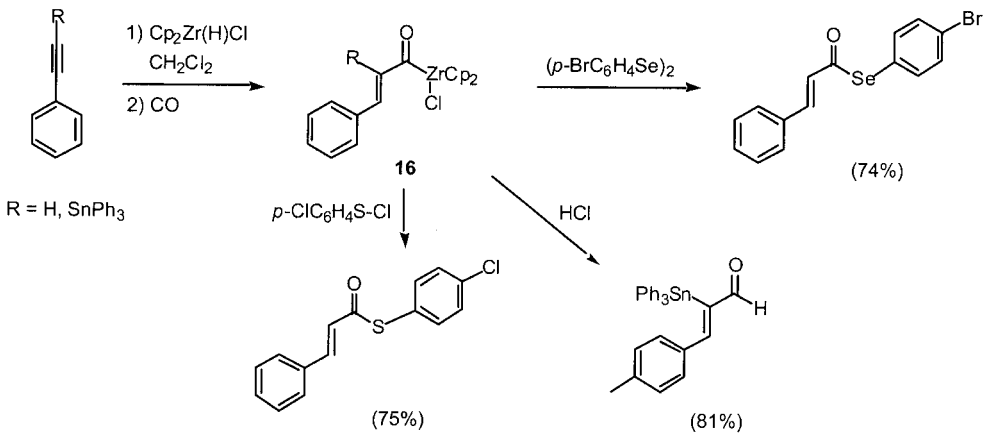


Scheme 4.10. Intramolecular cyclization or β-elimination of hydrozirconated allylic epoxides.

nation, **15**, is observed in all cases and results from the regioisomeric addition of $Cp_2Zr(H)Cl$ to the vinyl moiety. Mixtures of (*E*)- and (*Z*)-isomers associated with minor products **15** are to be expected.

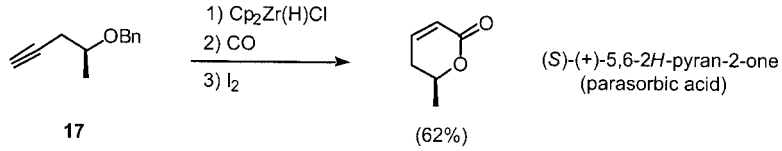
4.4
Acyl Zirconocenes

Insertion of carbon monoxide into C_{sp^2}–Zr bonds occurs readily at ambient temperatures or below to produce α,β-unsaturated, reactive acyl zirconocene derivatives [27–29]. Early work by Schwartz demonstrated the potential of such intermediates in synthesis [5d], as they are highly susceptible to further conversions to a variety of carbonyl compounds depending upon manipulation. More recently, Huang has shown that HCl converts **16** to an enal, that addition of a diaryl diselenide leads to selenoesters, and that exposure to a sulfenyl chloride gives thioesters (Scheme 4.11) [27,28]. All are obtained with (*E*)-stereochemistry, indicative of CO insertion with the expected retention of alkene geometry.



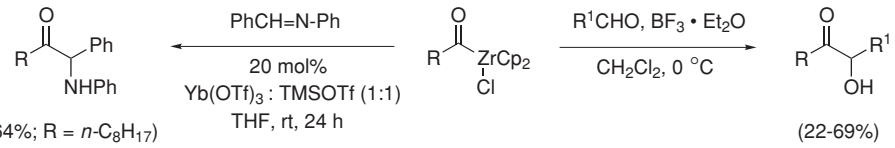
Scheme 4.11. Formation and reactions of acyl zirconocene **16**.

In the case of nonracemic homopropargylic ether **17**, hydrozirconation/carbonylation was followed by exposure of the intermediate to molecular iodine (Scheme 4.12) [39]. The (*E*)- and (*Z*)-forms of the acyl iodide presumed to be formed *in situ* were seemingly in equilibrium under the reaction conditions and intramolecular attack followed by dealkylation afforded (*S*)-(+)-parasorbic acid.



Scheme 4.12. Facile synthesis of parasorbic acid.

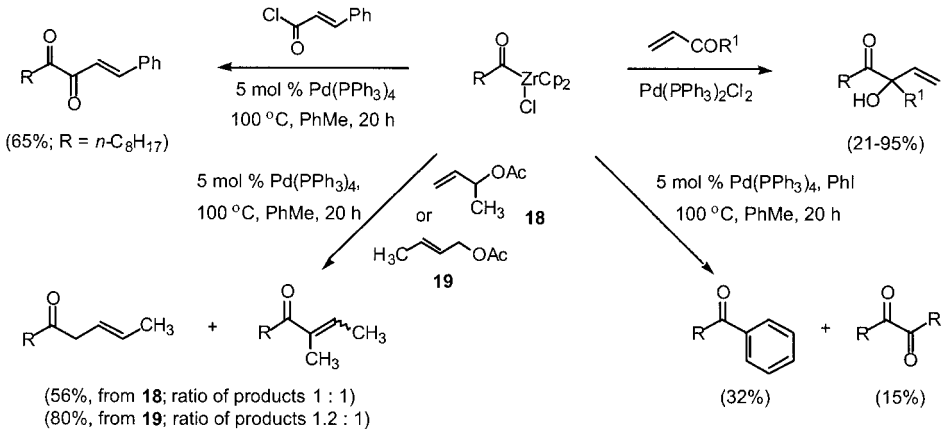
Extensive studies by Taguchi and Hanzawa have extended the utility of acyl zirconocenes through the discovery of a myriad of new reactions [40–45]. These "unmasked" acyl anions add directly to aldehydes to afford acyloins in the presence of a Lewis acid (Scheme 4.13). Of several Lewis acids studied (e. g., $ZnCl_2$, $AgBF_4$, $TiCl_4$, etc.), a stoichiometric amount of $BF_3 \cdot OEt_2$ in CH_2Cl_2 at 0 °C proved to be the most effective. Hindered aldehydes (e. g., pivaldehyde), ketones, and acid chlorides are not reactive under these conditions. Whether the process proceeds via a Lewis acid activated aldehyde or acyl zirconocene, or by 1,2-addition of the acyl anion in transmetalated form, has yet to be determined. Related reactions with imines generate α-amino ketones [41], although with these educts $BF_3 \cdot OEt_2$ proved unsuccessful as an activating Lewis acid, as did $AlCl_3$ and TMSOTf. Success was realized using $Yb(OTf)_3$ in conjunction with either TMSCl or TMSOTf (1:1). Use of THF as solvent (rather than CH_2Cl_2, CH_3CN, DMF, or DME) is crucial for the success of these reactions with imines (Procedures 6, 7, p. 141).



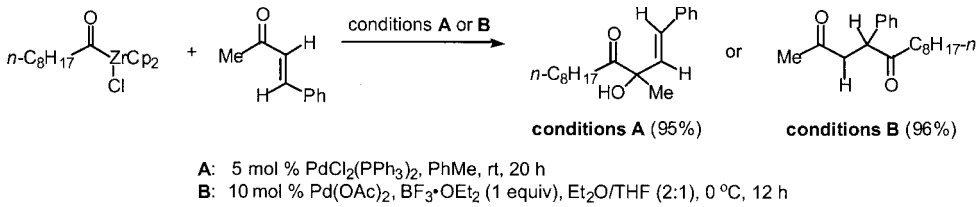
Scheme 4.13. Conversion of an acyl zirconocene to α-hydroxy and α-amino ketones.

Several palladium-catalyzed processes have also been developed for carbon–carbon bond formation based on acyl zirconocenes. Both alkylations and acylations take place using aryl, benzylic, and allylic halides, thereby producing ketones as products [40,43,44]. Yields are highly variable, with the best results being obtained with allylic acetates as coupling partners (Scheme 4.14). Homocoupling in the case of an aryl iodide or benzylic bromide is a significant side reaction, and alkyl halides cannot be used as electrophiles. Traditional π-allylpalladium complexes are likely intermediates, as the product ratio resulting from either isomer **18** or **19** is essentially the same.

The selection of the palladium catalyst is a major factor in reactions of acyl zirconocenes with α,β-unsaturated ketones [43]. Interestingly, the use of $Pd(OAc)_2$ (10 mol%) and a stoichiometric amount of $BF_3 \cdot OEt_2$ in Et_2O/THF favors Michael addition of the acyl zirconocene, thereby leading to 1,4-diketones (Scheme 4.15). Switching to a catalytic amount of $PdCl_2(PPh_3)_2$ in toluene at room temperature promotes the 1,2-addition mode, leading to allylic alcohols. Multiple substituents at the β-site (i. e., β,β-disubstituted enones) not only prevent conjugate addition, but even inhibit 1,2-addition of the acyl zirconocene (i. e., no



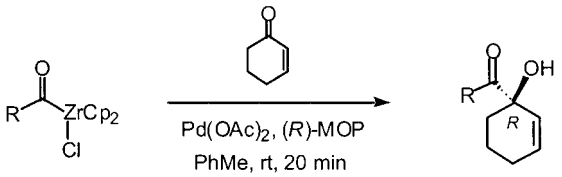
Scheme 4.14. Palladium-catalyzed couplings of acyl zirconocenes.



Scheme 4.15. Pd catalyst-dependent chemoselectivity of an acyl zirconocene.

reaction takes place). Unsaturated esters (e. g., methyl cinnamate) are inert to these reagents.

A procedure for effecting 1,2-additions of acyl zirconocenes with control of asymmetry at the newly formed tertiary alcohol has been reported by the Hanzawa and Taguchi school [42]. Rather than triphenylphosphane, Hayashi's MOP ligand [46] was employed together with 5 mol% of either $PdCl_2(PPh_3)_2$ or $Pd(OAc)_2$ in toluene. The (*R*)-configuration of the monodentate binaphthyl ligand favors the (*R*)-configuration in the product alcohol (Scheme 4.16). Cyclic enones gave *ee* values in the range 38–67 %, while acyclic enones led to significantly lower levels of enantiocontrol. A π-allylpalladium complex (Figure 4.4) has been postulated as the species responsible for the observed induction.



Scheme 4.16. Asymmetric 1,2-addition of acyl zirconocenes to cyclohexenone.

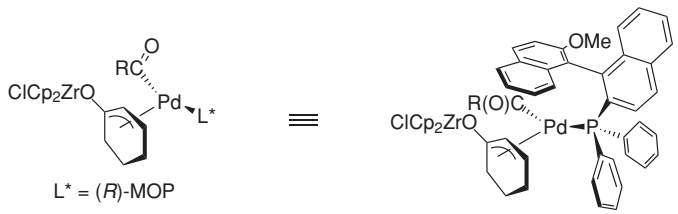
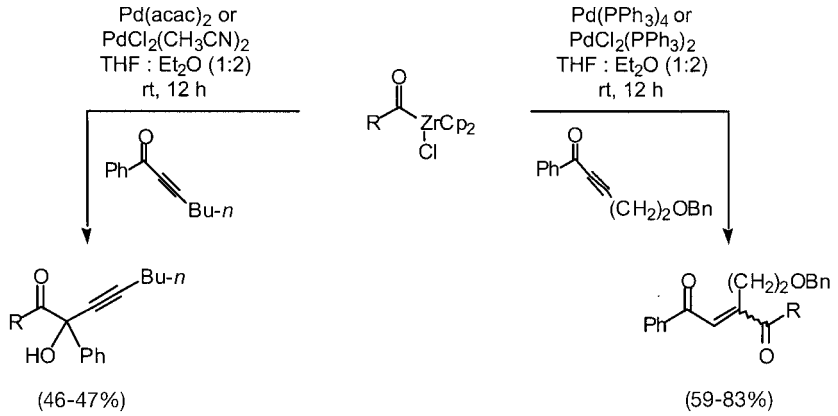


Figure 4.4. Proposed intermediate in Pd-catalyzed asymmetric 1,2-additions of acyl zirconocenes.

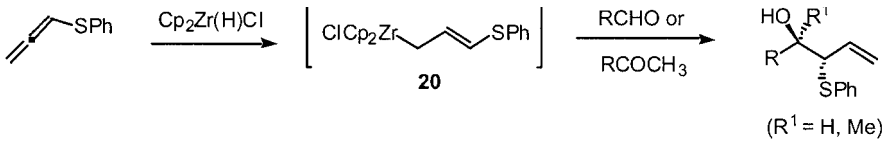


Scheme 4.17. Catalyst-dependent reactions of acyl zirconocenes with ynones.

Ynones represent yet another substrate class with which acyl zirconocenes react under the influence of a palladium catalyst. Here, enediones are formed in good yields, although mixtures of (*Z*)- and (*E*)-isomers are to be expected (Scheme 4.17) [40]. The favored geometrical form is *Z*, although ratios only of the order of 2:1 to 5:1 are common. Either $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$ can be used as the catalyst at a 5 mol% level. Remarkably, alternative sources of palladium, such as $Pd(acac)_2$ and $PdCl_2(CH_3CN)_2$, redirect the course of the reaction in favor of the 1,2-addition mode (yields 46–47%). Apparently, PPh_3 must be present in the catalyst to bring about the favored 1,4-addition. Other PPh_3-free catalysts, such as $PdCl_2 \cdot$dppe and $(dba)_3Pd_2 \cdot CHCl_3$ were ineffective, as were $Ni(COD)_2$, $Ni(acac)_2$, and $Ni(PPh_3)_4$. The alkyne must be fully substituted for the process to occur. An electron-transfer mechanism has been proposed, which proceeds via an allenyl zirconium enolate, although in what capacity the PPh_3 directs this course remains obscure.

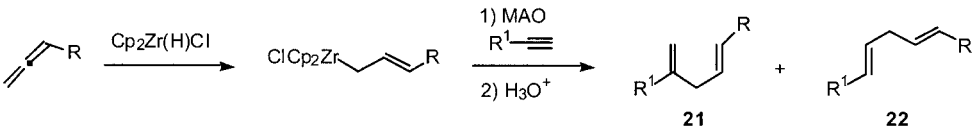
4.5
Allylic Zirconocenes

Hydrozirconation of allenic systems preferentially leads to allylic zirconocenes, which are highly reactive and thus very useful organometallic reagents. Allenic sulfides react in the expected fashion to give the (*E*)-γ-thiophenylallylzirconocene chloride **20** (Scheme 4.18) [47]. These intermediates, upon introduction of an aldehyde or methyl ketone, give predominantly the *anti* isomer (ratios from 82:18 to > 97:3). Exclusive 1,2-addition was observed by Suzuki et al. in the case of an α,β-unsaturated aldehyde. As long as the steric demands of the two substituents attached to the ketone carbonyl are significantly different, synthetically useful levels of selectivity can be achieved.

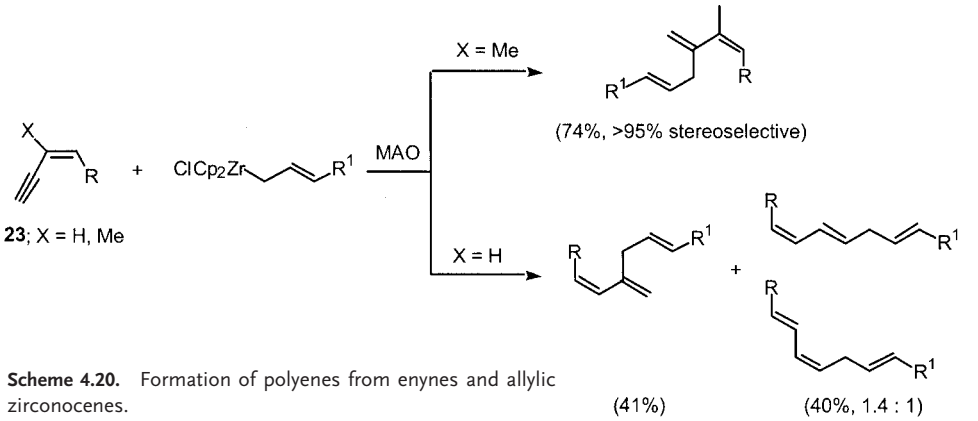


Scheme 4.18. Hydrozirconation/1,2-additions of allenyl sulfides.

Intermediate allylic zirconocenes react with terminal alkynes when activated by methylaluminoxane (MAO) to regioselectively afford 1,4-dienes [48]. Enynes also participate and, as with the former substrates, lead mainly to branched rather than linear arrays. With simple acetylenes, the extent of this preference was determined to be based on the nature of the group attached to the alkyne. Both aromatic and secondary alkyl residues give > 20:1 selectivities of **21** to **22**, while a primary alkyl moiety leads to only 4:1 branched to linear product ratios (Scheme 4.19). With enynes, the presence of a substituent X in **23** greatly affects the regiochemistry of addition, although the (*E*) or (*Z*) nature of the starting enyne is completely retained throughout the sequence (Scheme 4.20). When X = Me, the regioselectivity is very highly in favor of internal addition of the allylic fragment to the allene (>95 % isometric purity). With X = H, however, mixtures of both regioisomers (1:1) and stereoisomers (i. e., (*E*) and (*Z*), from either an initially all-(*E*)- or all-(*Z*)-enyne) are formed, the latter observation indicating a serious loss of stereointegrity.

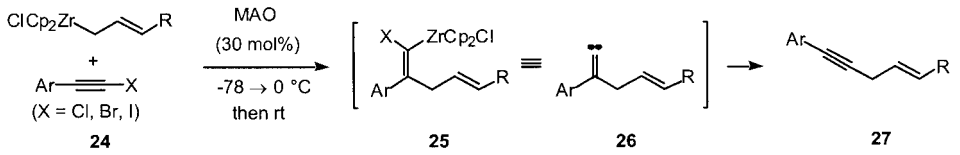


Scheme 4.19. MAO-catalyzed allylmetalations of alkynes with allylzirconocenes.



Scheme 4.20. Formation of polyenes from enynes and allylic zirconocenes.

When applied to halo-alkynes **24**, the same MAO-catalyzed process leads to excellent yields of the linear 1,4- or "skipped" enyne product **27** (Scheme 4.21), again depending upon substituents R [49]. When **24** bears an iodo substituent, the reaction is faster than with the corresponding bromide or chloride. α-Elimination to give the carbene **26**, via carbenoid **25**, would then encourage migration of the aryl substituent (R), ultimately leading to the observed product. ^{13}C labeling experiments strongly support this pathway. By contrast, alkyl iodoalkynes appear to be converted to products without any positional change of the alkyl groups. Thus, to account for these observations, either a 1,2-shift of the allyl moiety or addition of the allylic zirconocene across the alkyne in the opposite sense must occur, thereby leading to an eventual β-elimination.



Scheme 4.21. Synthesis of "skipped" enynes.

4.6 Cross-Coupling Reactions

Constructions of polyenic natural products have benefited considerably from initially formed vinylic zirconocenes, whether used directly as nucleophiles in couplings with vinylic halides, or following conversion to halides for subsequent use as electrophilic partners (*vide supra*). The antibiotic lissoclinolide represents an excellent example where hydrozirconation–Pd-catalyzed couplings have been used to great advantage [50]. The strategy followed by Negishi and co-workers is outlined retrosynthetically in Figure 4.5. Subunits **28** and **29** were both prepared from propargyl alcohol and were incorporated as three-carbon fragments in the product (Scheme 4.22). Vinyl iodide **29** underwent a Sonogashira coupling with propargyl alcohol, the product from which was converted into the next partner, dibromide **30**. Zirconocene **28** selectively coupled with the *trans*-bromide to afford **31**, thus setting the stage for carboxylation and silver ion induced lactonization. The key *trans*-selective (>98 %) coupling of **28** with dihalide **30** is the first such example of the use of a zirconium reagent for this purpose.

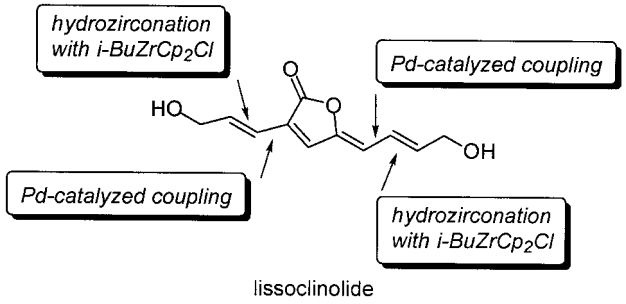
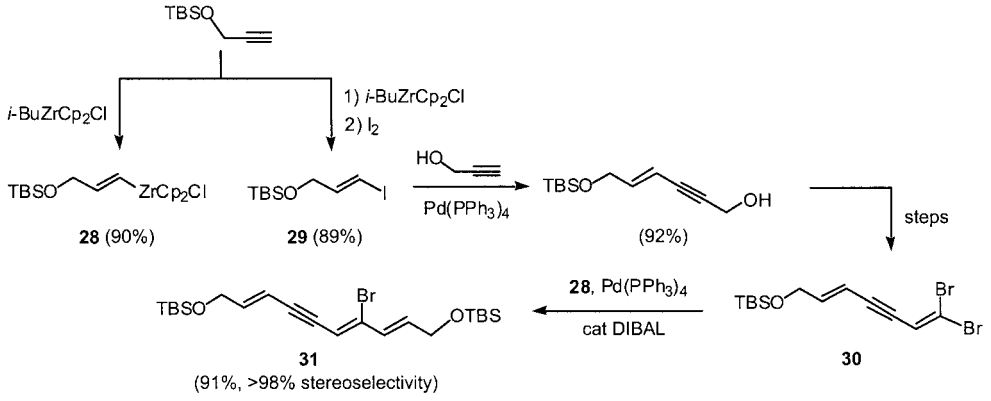
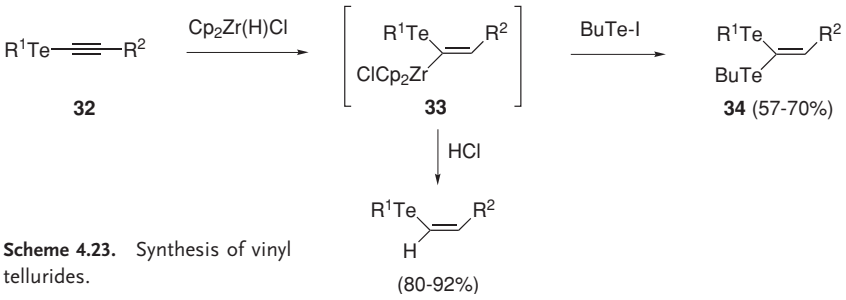


Figure 4.5. Retrosynthetic disconnections for lissoclinolide.



Scheme 4.22. Use of hydrozirconation en route to lissoclinolide.

Vinyl zirconocenes have figured prominently as nucleophiles in the cross-coupling reactions of 1,1- and 1,2-dimetallo reagents. Interestingly, acetylenic tellurides react with Schwartz's reagent in THF at ambient temperatures with completely *opposite* regiocontrol to that observed with alkoxy alkynes (*vide supra*) [51–55]. Oh and co-workers [53,54] showed that no loss of alkene geometry occurred when $R^1 \neq R^2$ in **32**, suggesting complete retention in the newly formed C–Te bond (Scheme 4.23). Intermediate 1,1-dimetallo derivatives **33** can readily be quenched with protons or deuterons to give (*Z*)-vinyl tellurides. Introduction of a tellurenyl iodide as an alkyltellurating agent affords the corresponding mixed ketene telluroacetals (**34**), which are otherwise difficult to prepare. Products **34** are isolable and readily handled, but decompose in solution over a period of days.

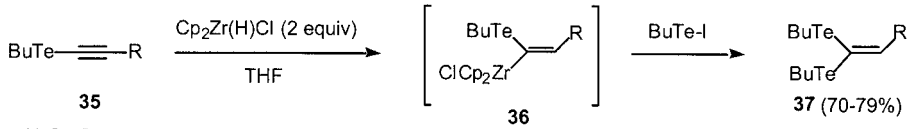


32 **33** **34** (57-70%)

(80-92%)

Scheme 4.23. Synthesis of vinyl tellurides.

A more extensive and detailed study of these reactions (i. e. **32** to **33**) was carried out by Dabdoub et al., who found that two equivalents of $Cp_2Zr(H)Cl$ are needed for complete consumption of acetylenic tellurides **35** (Scheme 4.24) [51]. Solubilization of $Cp_2Zr(H)Cl$ in the reaction medium (THF) is apparently not a sufficient indication of educt consumption when only 1.1 equivalents are employed (e. g., following a proton quench, 58 % of the product **37** and 41 % of the acetylenic telluride **35** were recovered). Furthermore, care must be taken to avoid Cp_2ZrH_2, potentially present following the Buchwald route [3] to $Cp_2Zr(H)Cl$, since C_{sp}–Te bond reduction can occur to a significant extent in the presence of this dihydride or of residual LAH.

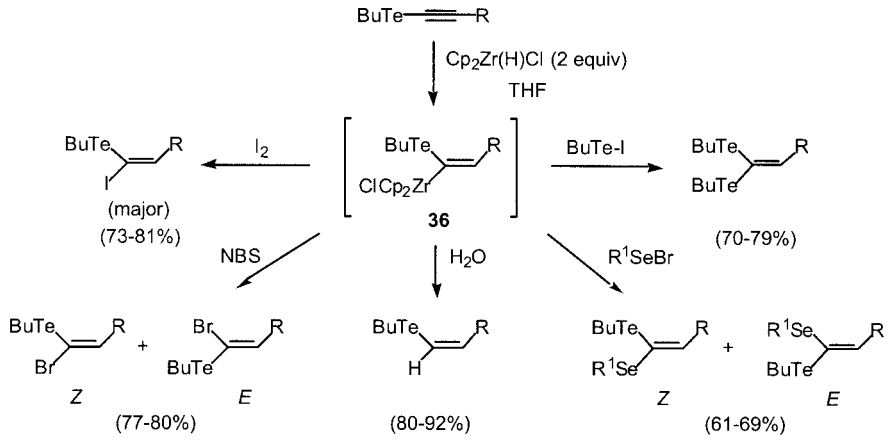


35 **36** **37** (70-79%)

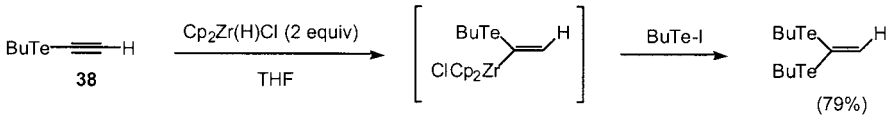
(R = H, Pr, Bu, Ph, etc.)

Scheme 4.24. Preparation of 1,1-vinyl ditellurides.

While intermediates of type **36** maintain olefin integrity upon quenching with protons and alkyltelluro halides, reactions with selenenyl halides produce mixtures of (*E*)- and (*Z*)-1,1-dimetallo products which are inseparable by chromatography (Scheme 4.25) [51]. On quenching with I_2, however, the alkene geometry is retained in the major product. Bromination, akin to selenenylation, unfortunately affords geometrical isomers, typically in a ratio of 55:45. When unsubstituted acetylenic telluride **38** is used, the regiochemistry of hydrozirconation is still such that a 1,1-dimetallo species is generated (Scheme 4.26) [51,52].

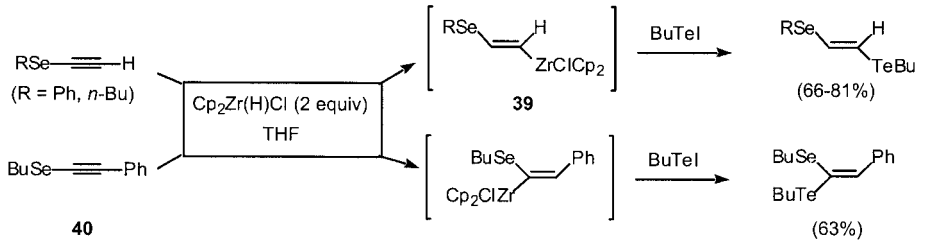


Scheme 4.25. Reactions of 1,1-dimetallo species **36**.



Scheme 4.26. Hydrozirconation of an unsubstituted acetylenic telluride.

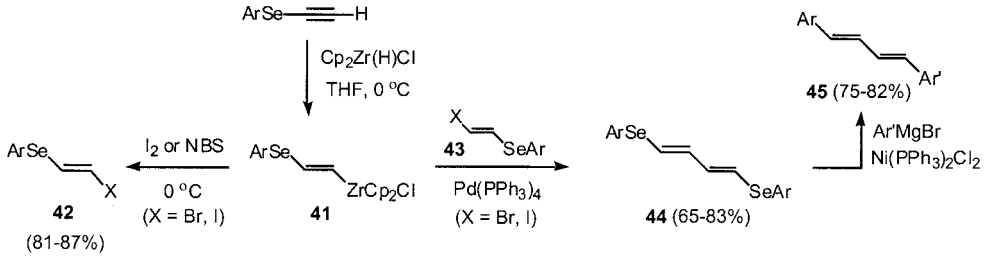
Hydrozirconation of unsubstituted (arylseleno)- or (alkylseleno)ethynes has also been extensively investigated, initially by Huang [22,23,30,33] and more recently by the same Brazilian school [51]. In general, acetylenic tellurides add $Cp_2Zr(H)Cl$ more rapidly than do the corresponding selenides. Both groups have found the 1,2-dimetallo intermediate **39** to be the initial, sole product of hydrozirconation when R is bulky. Again, two equivalents of the Schwartz reagent are critical for complete conversion. The only other regiospecific case, although proceeding with *opposite* regiochemistry, has been that of the aryl-substituted acetylenic derivative **40**. Thus, all alkyl-substituted alkynyl selenides, while favoring the 1,1-dimetallo configuration, give mixtures of olefinic products. Nonetheless, simple proton quenching produces (*Z*)-vinyl selenides in good yields, species that are of considerable value in synthesis (Procedures 8–11, p. 141 f.).



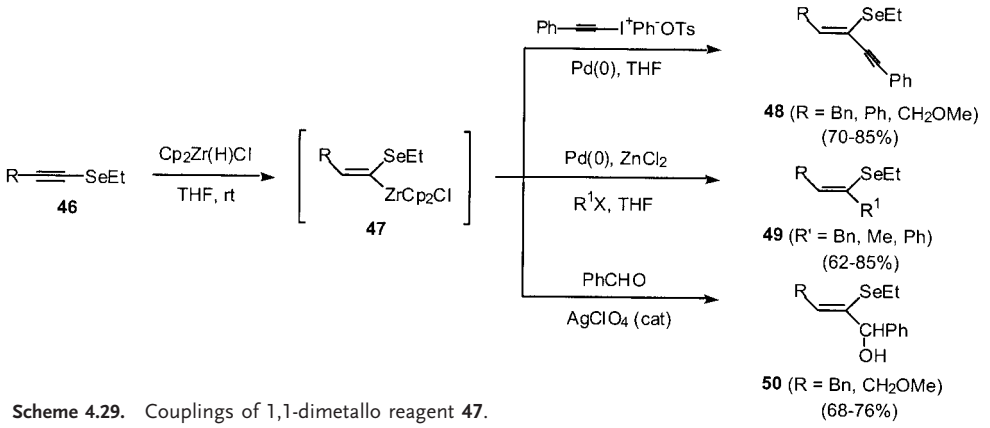
Scheme 4.27. Synthesis of 1,1- and 1,2-dimetallo vinyl chalcogenides.

Cross-coupling reactions of vinyl zirconocenes of general structure **41**, mainly using group 10 metal catalysts, can be smoothly effected to give a variety of vinyl selenide-containing materials, which are amenable to further elaboration through nickel-catalyzed

Grignard displacements (Scheme 4.28). The 1,2-dimetallo reagent **41** can be halogenated to give the (*E*)-β-halovinyl selenides **42**, while Negishi coupling of a vinyl zirconocene with **43** leads to (*E,E*)-derivatives **44**, and ultimately to arylated butadienes **45** [22,30]. With alkyl-substituted selenoalkynes (e. g., **46**; Scheme 4.29), Pd(0)-catalyzed couplings of intermediate **47** provide entry to stereodefined enynes **48** and α-alkylated vinyl selenides **49**, while $AgClO_4$-catalyzed 1,2-additions lead to allylic alcohol derivatives **50**.



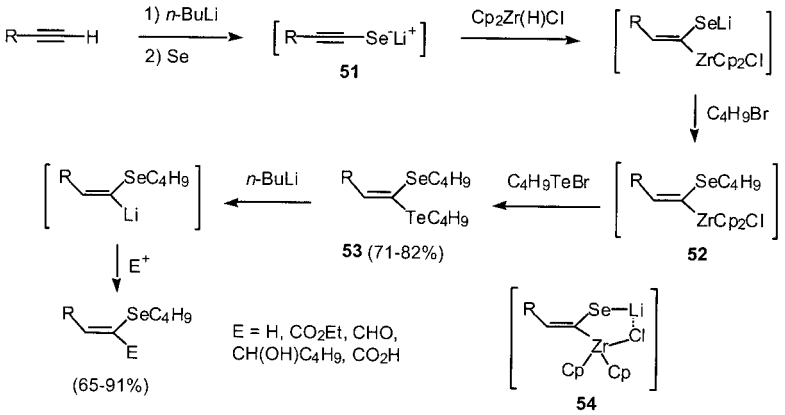
Scheme 4.28. Reactions of selenenylated vinyl zirconocenes **41**.



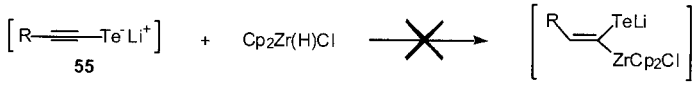
Scheme 4.29. Couplings of 1,1-dimetallo reagent **47**.

As an alternative to hydrozirconation of acetylenic tellurides or selenides, Dabdoub and co-workers have more recently described the first additions of the Schwartz reagent (one equivalent) to acetylenic selenide salts **51** (Scheme 4.30) [52]. Subsequent alkylation at selenium produces 1,1-dimetallo intermediates **52**, which are cleanly converted in a one-pot process to stereodefined products **53**. It is noteworthy that ketene derivatives **52** are of (*E*)-geometry, the opposite regiochemistry to that which results from hydrozirconation of acetylenic tellurides (*vide supra*). This new route also avoids the mixtures of regioisomers observed when seleno ethers are used as educts. The explanation for the stoichiometric use of $Cp_2Zr(H)Cl$ in these reactions, in contrast to the requirement for two equivalents with seleno ethers, may be based on cyclic intermediates **54**, in which Li—Cl coordination provides an additional driving force. Curiously, attempted hydrozirconation of the corresponding telluride salt **55** under similar conditions was unsuccessful (Scheme 4.31) (Procedure 12, p. 143).

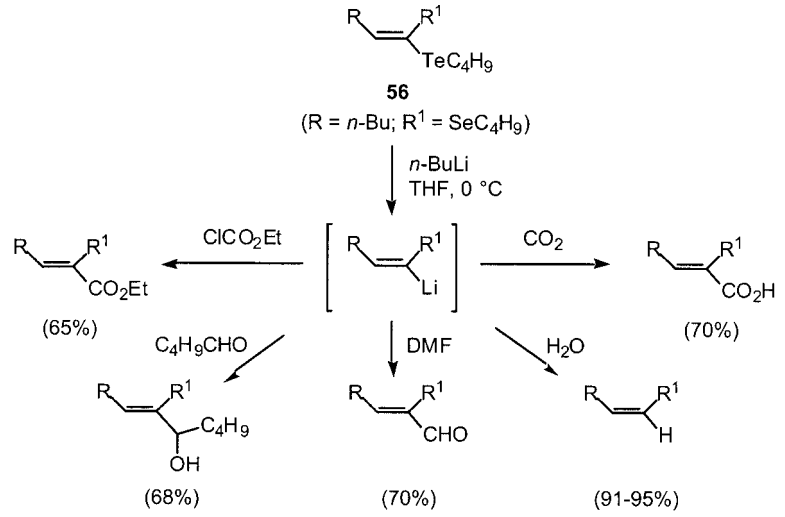
In terms of their synthetic use, (*E*)-vinyl tellurides **56** easily undergo Li/Te exchange upon treatment with *n*BuLi at −78 °C (Scheme 4.32). The resulting vinyllithium has con-



Scheme 4.30. Hydrozirconation of a lithium alkynylselenolate anion **51**.



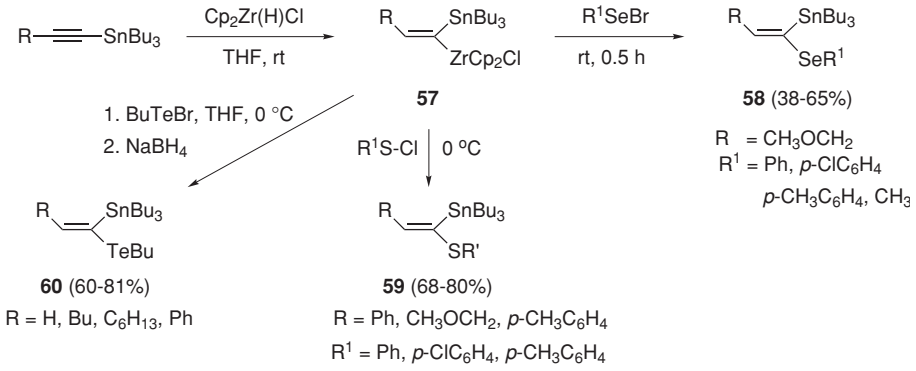
Scheme 4.31. Unsuccessful hydrozirconation of lithium alkynyltellurolate anions **55**.



Scheme 4.32. Transformations of stereodefined vinyl tellurides **56**.

siderable potential for many C–C bond-forming reactions, all of which occur with strict retention of regio- and stereochemical integrity [52,56].

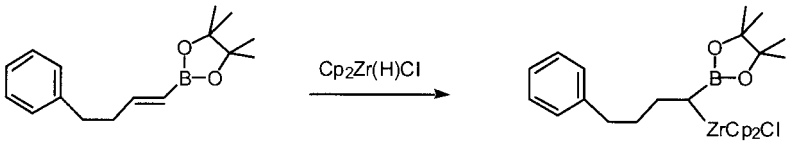
Acetylenic stannanes, which were first shown to undergo regioselective hydrozirconation to afford 1,1-dimetallo reagents **57** in 1992 [7a], have been converted to the derived selenides, sulfides, and tellurides, **58**, **59**, and **60**, respectively [57]. Simply exposing **57** to either a selenenyl bromide or sulfenyl chloride is sufficient to induce coupling with the more reactive vinyl zirconocene component, thereby allowing for subsequent Stille couplings of the intact vinyl stannane unit (Scheme 4.33). Moreover, as noted previously



Scheme 4.33. Formation and reactions of 1,1-dimetallo species **57**.

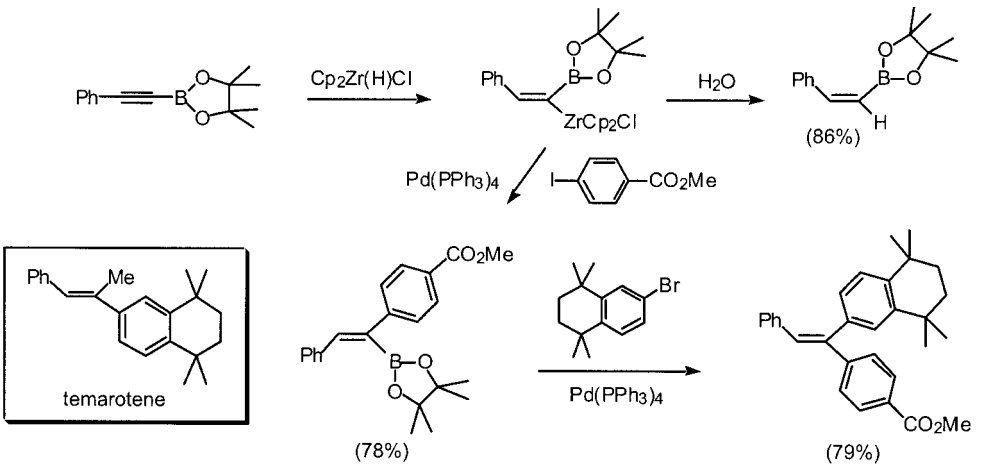
[24,25], vinyl sulfides can be further elaborated using RMgX under Ni(0) catalysis. Huang and co-workers have also shown that quenching the same intermediate **57** with an aryl sulfinyl chloride leads to α,β-unsaturated sulfoxides bearing a triaryl- or trimethylstannyl moiety at the α-site [58] (Procedure 13, p. 143).

Hydrozirconations of both vinyl and acetylenic boranes by Srebnik et al. led to 1,1-dimetallo reagents, which offer the benefits as coupling partners of alkyl- and vinylboranes, respectively [59–62]. Initial trials were conducted with *B*-alkenylborabicyclo[3.3.1]nonanes, but these led to unstable dimetallics. Replacement of the 9-BBN fragment with the pinacolborane-derived analogue produced stable dioxaborolanes **61** (Scheme 4.34).



Scheme 4.34. Generation of the *gem*-borazirconocene **61**. **61**

Addition of the Schwartz reagent across alkynyl boranes also occurs at room temperature [59,60,62]. The more reactive C–Zr bond, perhaps a reflection of the greater electropositivity of zirconium compared to boron, selectively participates in palladium-catalyzed couplings, with the vinylborane fragment remaining untouched (Scheme 4.35). Temarotene, a synthetic retinoid of interest, could be prepared in a very straightforward manner based on two successive Pd(0)-initiated couplings [60].

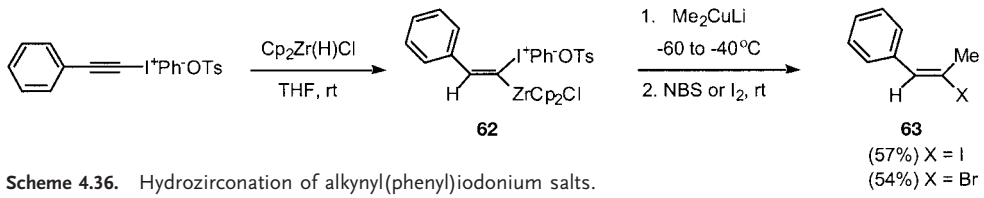


Scheme 4.35. Sequential couplings of a gem-borazirconocene.

4.7
Zirconium to Copper

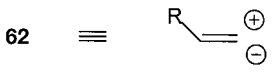
Since the original report by Schwartz in 1977 in which a vinyl zirconocene was shown to deliver a vinyl ligand in a 1,4-sense to an enone in the presence of a Cu(I) salt [63], many modified procedures have been reported based on this type of transmetalation. Several of these appeared in the early to mid-1990s, as discussed in reviews by Wipf [14], and involved the use of either stoichiometric or catalytic quantities of copper to effect both alkylations and conjugate additions of initially formed alkyl and vinyl zirconocenes. In general, ligand-exchange phenomena between zirconocenes and cuprates tend to be far more facile than metathesis events involving copper salts. Moreover, the resulting cuprates generated by this exchange are usually more reactive than their corresponding organocopper (RCu) analogues, a feature often manifested in the temperatures required for a given type of reaction. Most recently developed reactions, however, rely predominately on the catalytic use of Cu(I) salts, mainly due to expediency and to avoid build-up of transition metal containing waste materials.

Gilman cuprates (R_2CuLi) were found by Huang et al. to be effective in couplings with alkenyl(phenyl)iodonium salts [64], as reported earlier by Ochiai (Scheme 4.36) [65]. In this case, however, the precursor alkynyl(phenyl)iodonium salts, popularized by Stang [66], could be initially hydrozirconated to give intermediates **62**, treatment of which with R_2CuLi (R = Me, Et, *n*Bu) followed by quenching with a halogen source afforded stereodefined olefinic products **63**. The fact that the cuprate selectively displaces the iodonium species rather than effecting transmetalation of the vinyl zirconocene is a most in-



Scheme 4.36. Hydrozirconation of alkynyl(phenyl)iodonium salts.

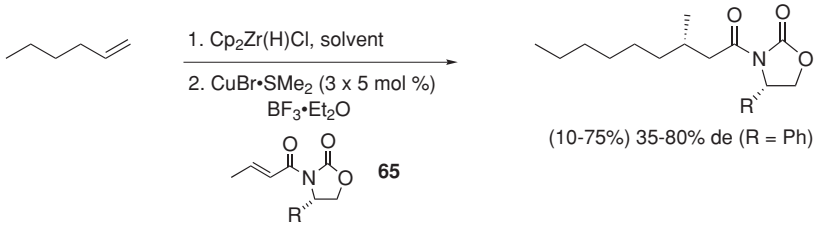
teresting result, although precedents for such cuprate-based transmetalations are usually associated with higher-order cyanocuprates rather than lower-order reagents [67]. The overall utility of the process lies in the synthetic equivalence of intermediates **62** to the idealized 1,1-difunctional reagent **64** (Figure 4.6) (Procedure 14, p. 143).

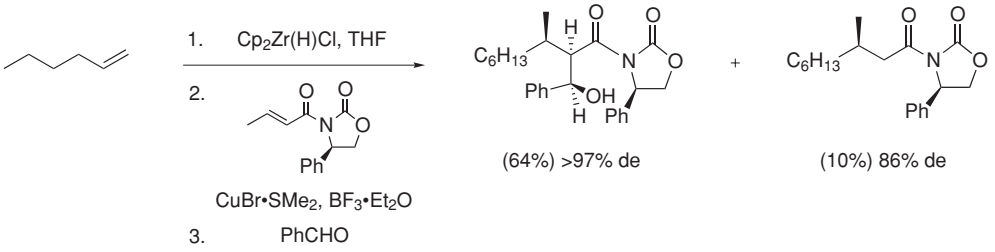


64

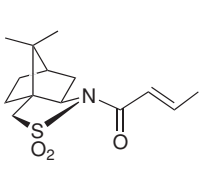
Figure 4.6. Synthetic equivalent of 1,1-dimetallo reagent **62**.

Conjugate additions of alkyl zirconocenes to unsaturated oxazolidinones **65** take place, according to Wipf and co-workers, in the presence of 15 mol% $CuBr \cdot SMe_2$ (Scheme 4.37) [68]. In reactions with the phenylglycine-derived auxiliary (R = Ph), the highest diastereoselectivities were obtained when the reactions were performed in THF, although only in the presence of one equivalent of $BF_3 \cdot OEt_2$. Alternative nonracemic auxiliaries, such as Oppolzer's sultam (**66**; Figure 4.7) [69] dramatically reduced the *de*. The initially formed enolate, postulated as existing in its (*Z*)-configuration as zirconium chelate **67** (Figure 4.7), reacts with benzaldehyde through a six-membered cyclic transition state to give exclusively the *syn* product. The role of the Lewis acid was postulated to be one of assistance in the formation of chelate **67** by (reversible) abstraction of chloride, which is followed by rapid 1,4-addition, predominately from the side opposite to the phenyl substituent.

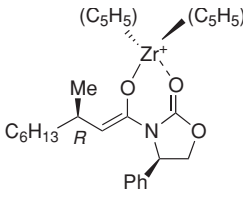




Scheme 4.37. Diastereoselective aldol reactions of an alkyl zirconocene.



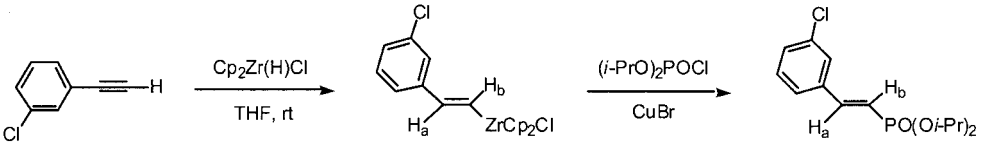
65



66

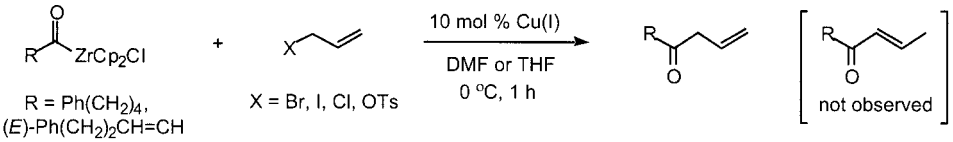
Figure 4.7. Acylated Oppolzer's sultam **66** and proposed Zr-chelate intermediate **67**.

The addition of any one of several dialkyl chlorophosphates to an *aryl*alkyne-derived vinyl zirconocene in the presence of catalytic amounts of CuBr in THF leads to the corresponding vinyl phosphonate in high yields (78–92 %; see, for example, Scheme 4.38) [25]. Here, *alkyl*-substituted acetylenic starting materials do not react beyond the initial hydrozirconation stage. Vinyl phosphonates may be readily converted to acyloins by oxidation to the diol followed by base-induced cleavage.

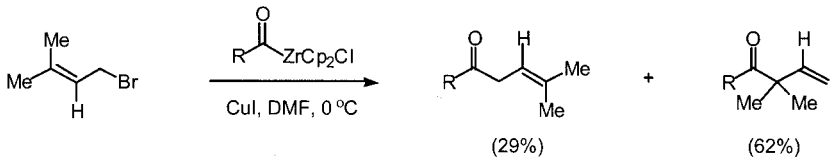


Scheme 4.38. Generation of a vinyl phosphonate via an initial hydrozirconation. (91%)

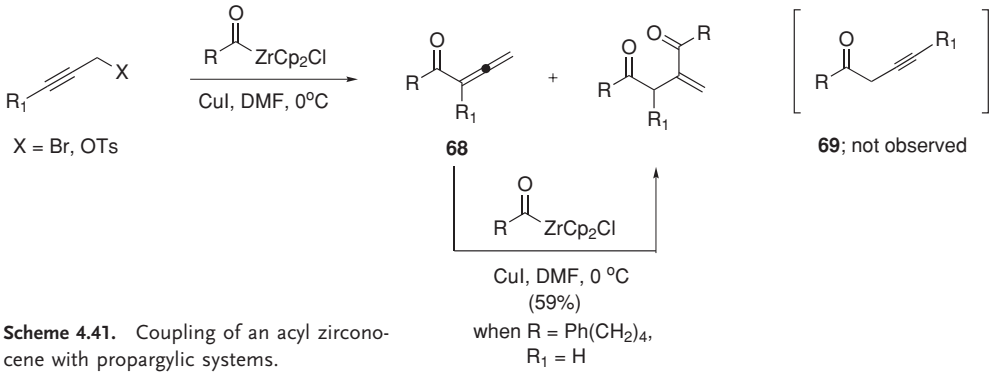
As described by Hanzawa, Narita, and Taguchi, cross-coupling reactions of acyl zirconocenes with allylic halides mediated by 10 mol% of a copper(I) salt occur smoothly at 0 °C (Scheme 4.39) [70]. While CuX (X = Cl, Br, I, CN) are all satisfactory catalysts, $CuBr \cdot SMe_2$ surprisingly proved ineffective. Either THF or DMF can be used as the solvent for these reactions. Allylic systems, including halides and pseudohalides, participate, although allyl chloride was found to be the least efficient substrate (44 %). In no case were products of double-bond migration observed, which highlights the mildness of these reaction conditions relative to those reported previously for the reaction involving Pd(0) catalysis [42]. Substituted allylic bromides led to mixtures resulting from attack at the α- and γ-sites, the latter prevailing (Scheme 4.40). Propargylic bromides reacted in a similar mode, affording exclusively allenic ketones **68** (i. e., **69** was not observed), further testament to the general synthetic utility of acyl zirconocenes as unmasked acyl anions (Scheme 4.41) (Procedure 15, p. 143).



Scheme 4.39. Copper-catalyzed alkylations of acyl zirconocenes.

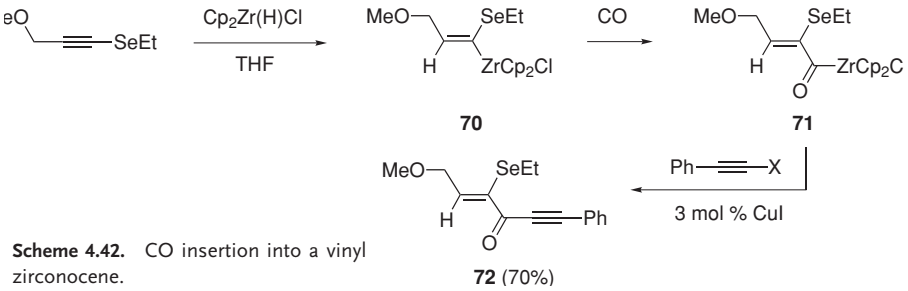


Scheme 4.40. Regiochemistry associated with the prenylation of an acyl zirconocene.



Scheme 4.41. Coupling of an acyl zirconocene with propargylic systems.

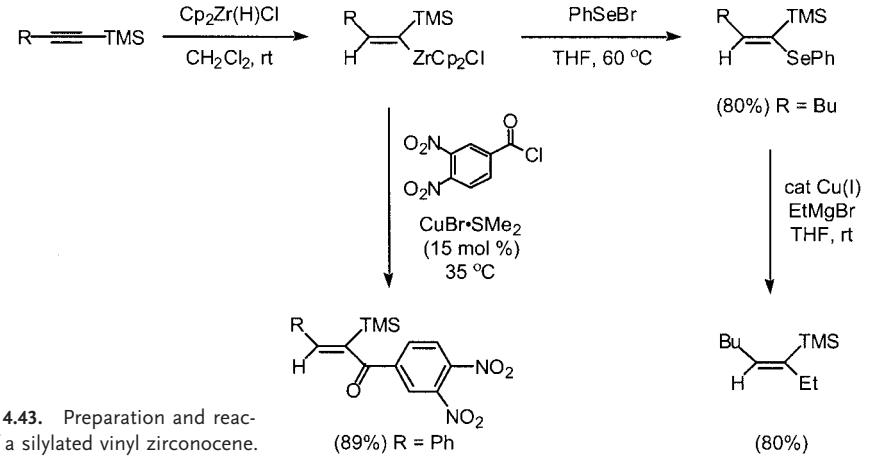
Hydrozirconation of an acetylenic selenide forms a 1,1-dimetallo reagent **70**, which can undergo insertion of carbon monoxide into the C–Zr bond (Scheme 4.42). Huang and Sun have used CuI to catalyze couplings between the acyl zirconocenes **71** thus obtained and acetylenic halides, leading ultimately to vinyl alkynyl ketones **72** bearing a seleno ether moiety on the olefinic α-carbon [71]. Unlike most routes to such compounds, which tend to require high temperatures and high CO pressures [72], these couplings occur at room temperature and atmospheric pressure on the order of 30 minutes (at 0.20 M) in THF. Overall yields are good (58–72 %).



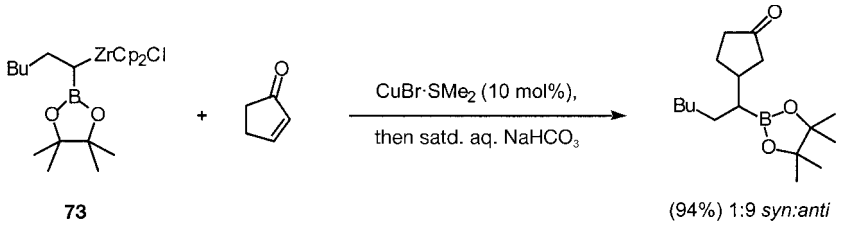
Scheme 4.42. CO insertion into a vinyl zirconocene.

Vinyl zirconocenes, obtained by hydrozirconation of acetylenic silanes, can be quenched with an arylselenium bromide to give a 1,1-dimetallo intermediate that is amenable to further elaboration (Scheme 4.43) [73]. Copper-catalyzed couplings with Grignard reagents displace the selenide, while acylation of the vinyl zirconocene forms enones under the influence of $CuBr \cdot SMe_2$ [21]. α-Silyl-α,β-unsaturated ketones with isomeric purities of >97 % can be realized in high yields using a variety of acid chlorides. Further acylation chemistry involving the vinylsilane can also be effected on these initial products by using an equivalent of $AlCl_3$ in CH_2Cl_2 at low temperatures.

gem-Borazirconocene alkanes [61] (Scheme 4.34) are valued Michael donors toward unhindered unsaturated ketones, esters, and nitrites in the presence of 10 mol % $CuBr \cdot SMe_2$ [74,75]. For example, the 1,1-dimetallo species **73** adds to cyclopentenone to give a 9:1 ratio of *anti* to *syn* isomers in high yield (Scheme 4.44). The possibility of converting the resulting alkylborane to the derived secondary alcohol with basic peroxide renders **73** an equivalent of the alcohol α-anion **74** (Figure 4.8).



Scheme 4.43. Preparation and reactions of a silylated vinyl zirconocene.



Scheme 4.44. Copper-catalyzed 1,4-addition of a *gem*-borazirconocene.

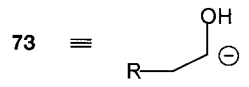
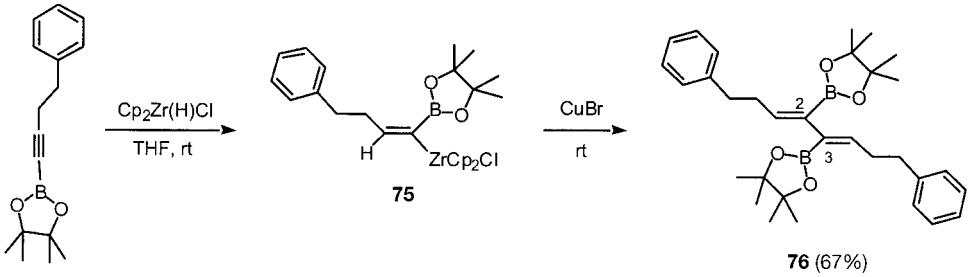
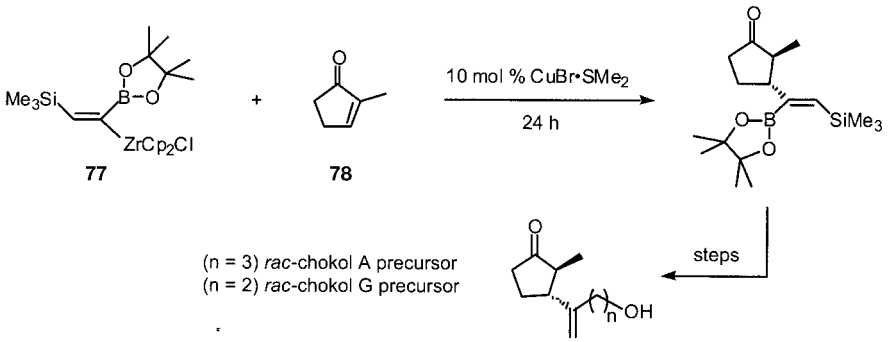


Figure 4.8. 1,1-Dimetallo reagent **73** as a synthetic equivalent of **74**.

Copper bromide has been used by Srebnik and co-workers to homocouple vinyl zirconocenes **75**, thereby providing access to 2,3-dibora-1,3-butadienes (e. g., **76**; Scheme 4.45), which retain their original geometrical relationships [76]. These dimerizations readily take place at room temperature; the products are stable to both air and moisture and can be purified by column chromatography on silica gel. Prolonged heating of the product at 150 °C was found not to lead to decomposition or even isomerization. Similarly, precur-



Scheme 4.45. Generation of 2,3-dibora-1,3-butadienes by homocoupling of vinyl zirconocenes.

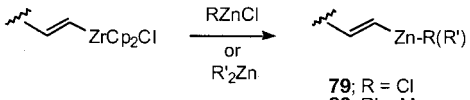


Scheme 4.46. Conjugate additions of 1,1-borazircono alkenes en route to chokol A and G precursors.

sors to both racemic chokols A and G could be fashioned by an initial 1,4-addition of trimetallic **77** to cyclopentenone **78** followed by Suzuki couplings with alkylating agents, the products from which could readily be converted to the target structures (Scheme 4.46) [77].

4.8 Zirconium to Zinc

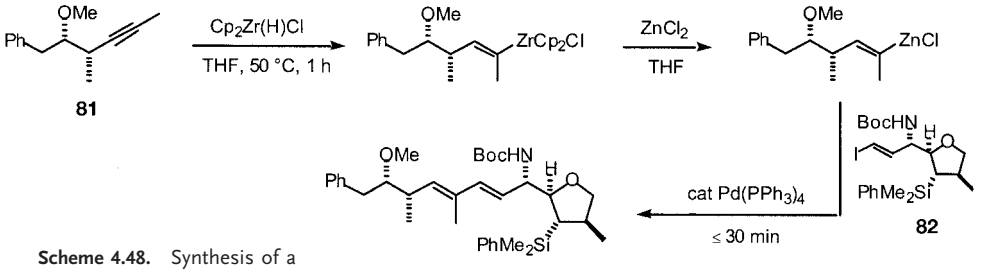
Since the early disclosure by Negishi that zinc halide salts accelerate Pd(0)-catalyzed cross-couplings between vinyl zirconocenes and various halides [78], several methods have been developed that extend the utility of this metathesis process from a zirconium chloride to a zinc chloride (**79**; Scheme 4.47). Alternatively, routes to more reactive diorganozinc intermediates, e. g., using Me_2Zn, convert readily available zinc derivatives to mixed species **80**, which selectively couple with various electrophiles [14].



79; R = Cl
80; R' = Me

Scheme 4.47. Transmetalation of a vinyl zirconocene to a vinyl zinc reagent.

Panek and Hu examined the generation and subsequent Negishi couplings of substituted vinyl zinc chlorides with both (*E*)- and (*Z*)-vinyl iodides [79–81]. Addition of the Schwartz reagent to an internal alkyne (e. g. **81**) could be achieved in THF or benzene, although mild heating was required (Scheme 4.48). Moreover, two equivalents of $Cp_2Zr(H)Cl$ were needed to achieve 100 % conversion as well as regiospecificity in favor of the least hindered site. Addition of anhydrous $ZnCl_2$ (3 equivalents) in THF, followed by the iodide and a source of Pd(0), led to excellent yields of either (*E,E*)- or (*E,Z*)-dienic products. Couplings with (*E*)-vinyl iodides (e. g., **82**) were found to be best conducted using $Pd(PPh_3)_4$ (5 mol%), while those with the (*Z*)-isomers proved most effective using Pd(0) generated *in situ* from $PdCl_2(PPh_3)_2$/DIBAL. Heteroatoms were found to be readily accommodated in these schemes (e. g., as in **83**). The versatility of this approach toward dienic portions of natural products has been further demonstrated in Jacobsen's recent synthesis of the antitumor agent FR901464 (Figure 4.9) [82].



Scheme 4.48. Synthesis of a functionalized (*E*,*E*)-diene.

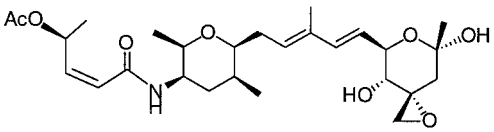
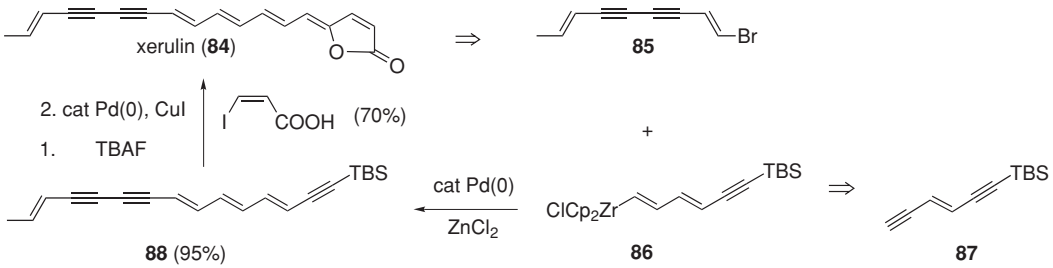


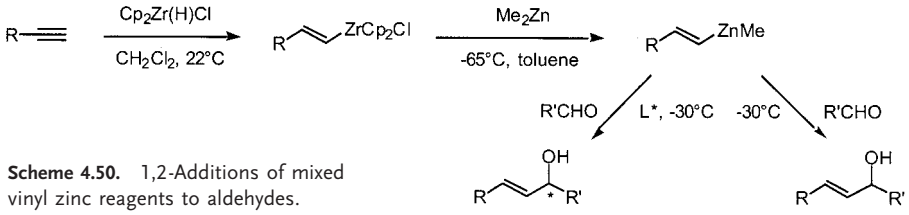
Figure 4.9. Structure of FR901464.

A synthesis of the hexaenediyne xerulin **84**, a naturally occurring inhibitor of cholesterol biosynthesis, has been accomplished by Negishi and co-workers [83]. One key disconnection in **84** was envisaged as corresponding to a Pd(0)-catalyzed coupling of the precursor vinylic bromide **85** and the highly unsaturated zinc reagent derived from vinylic zirconocene **86** (Scheme 4.49). Hydrozirconation of enediyne **87** gave the required intermediate **86**, which indeed underwent transmetalation with $ZnCl_2$ (0.6 equivalents) and coupling to afford **88** in outstanding yield. A final Sonogashira reaction–lactonization sequence developed earlier by this group [84] completed the scheme.

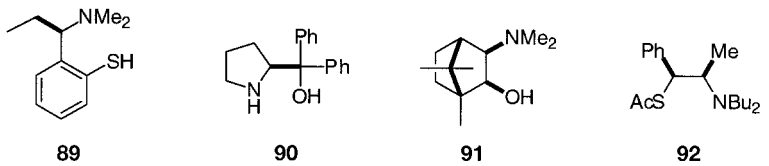


Scheme 4.49. A cross-coupling strategy toward xerulin.

Once hydrozirconation–transmetalation of terminal alkynes has been effected using Me_2Zn at low temperatures in toluene [85,86], the resulting mixed zinc species react with aldehydes to give racemic allylic alcohols (Scheme 4.50). The normally unreactive disubstituted zinc intermediates are able to participate in such 1,2-additions by virtue of the presence of the Lewis acidic zirconocene by-products of the transmetalation. A nonracemic version of this reaction has been developed by Wipf and Ribe [87], in which a more hindered version (**89**) of van Koten's thiol ligand [88] (10 mol%) imparts excellent levels of enantioselectivity (64–99 % *ee*). Wide variation in the alkyne is tolerated, although superior *ee* values are to be expected with aryl as opposed to aliphatic aldehydes. Other likely choices for ligands on zinc, such as amino alcohols (**90** [89] and **91** [90]; Figure 4.10), and thioacetate **92** [91], led to mixed results. Curiously, kinetic studies established that



Scheme 4.50. 1,2-Additions of mixed vinyl zinc reagents to aldehydes.



89 90 91 92

Figure 4.10. Non-racemic ligands screened in 1,2-additions of vinyl zirconocenes to aldehydes.

the enantioselectivities are not simply based on an acceleration of the addition of a zinc reagent ligated by **89**. The presence of both zirconium and zinc in the reaction, however, unfortunately precludes any meaningful interpretation of such data (Procedure 16, p. 144).

The side chains in the antibiotics asukamycin and manumycin A (Figure 4.11) have been fashioned utilizing a 1,2-addition–dehydration sequence involving vinylic zinc intermediates. By transmetalating a vinyl zirconocene to give its mixed zinc analogue **93**, Wipf and Coish carried out 1,2-additions with aldehydes at 0 °C to afford divinyl alcohols **94** and **95**, respectively (Scheme 4.51) [92]. Activation with $(CF_3CO)_2O$ followed by 1,4-elimination in each case led to the all-(*E*)-conjugated trienes suitable for future incorporation into the targeted natural products (Procedure 17, p. 144).

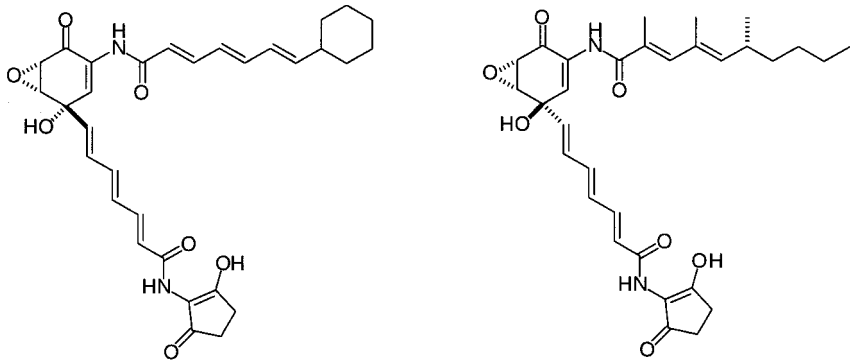
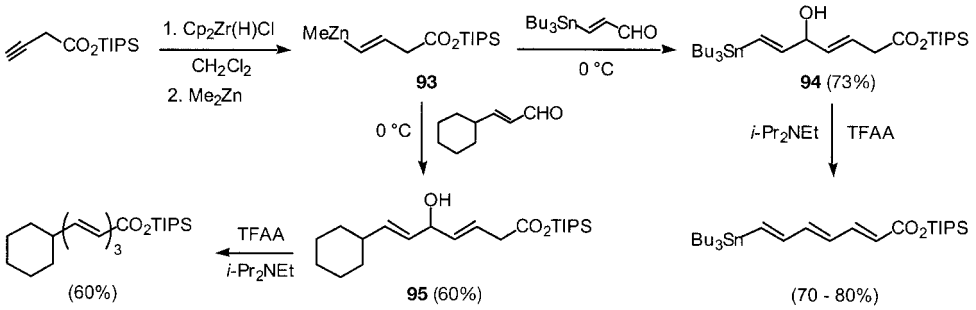
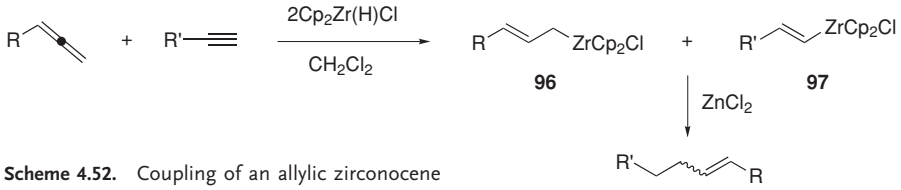


Figure 4.11. Structures of asukamycin and manumycin A.

Suzuki and co-workers have described a novel reductive coupling of allenes and alkynes, starting with hydrozirconations to give allylic and vinylic zirconocenes **96** and **97**, respectively [93]. Following transmetalation of these to give the derived zinc chlorides, a zinca-Claisen rearrangement of **98** ensues upon gradual warming to ambient temperatures (Scheme 4.52). The sole product in most cases is the α-adduct, otherwise unattainable in a selective manner, which is generated as a mixture of (*E*)- and (*Z*)-isomers via the se-

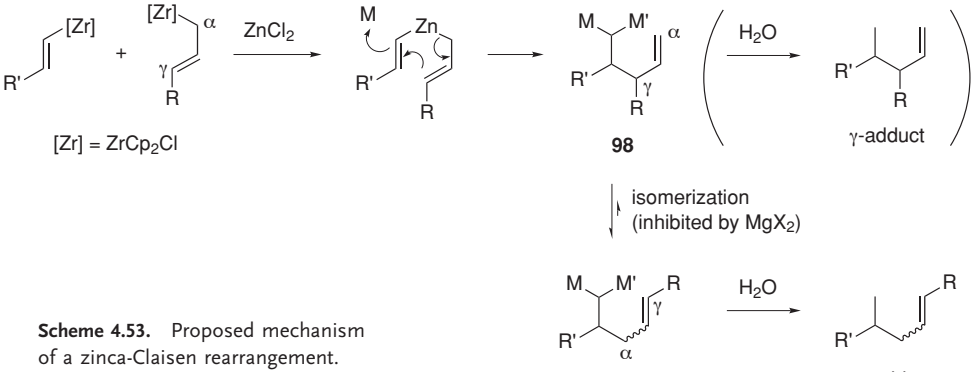


Scheme 4.51. Synthesis of trienes related to asukamycin and manumycin A side chains.

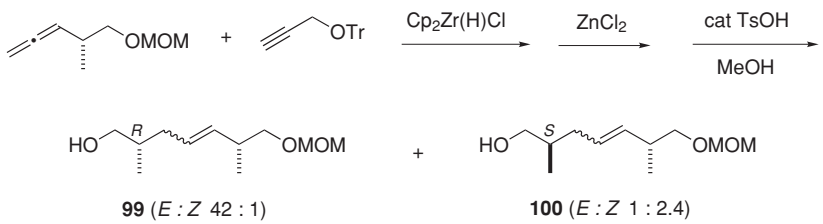


Scheme 4.52. Coupling of an allylic zirconocene with a vinylic zirconocene.

quence shown in Scheme 4.53. Isomerization from the kinetically formed intermediate is unusually rapid and complete, unlike in the cases of the corresponding organolithium or Grignard species [94]. Apparently, the presence of MgX_2 inhibits the γ to α interconversion. An application to the side chain of vitamin E has been reported, in which the stereochemistry of the newly formed alkene in **99** is of no consequence, while that at the sp^3 center is created with remarkable selectivity (93:7, **99***R*:**100***S*; Scheme 4.54) (Procedure 18, p. 144).

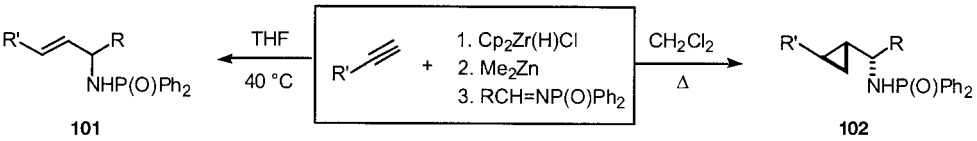


Scheme 4.53. Proposed mechanism of a zinca-Claisen rearrangement.

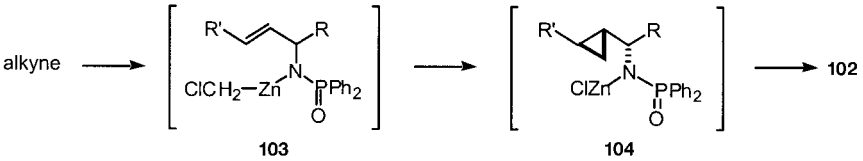


Scheme 4.54. Stereoselective synthesis of vitamin E precursor **99**.

Hydrozirconation–transmetalation to zinc, when carried out in THF, can be used to prepare allylic amines **101** (in *N*-protected form) by straightforward 1,2-additions to aldimines (Scheme 4.55) [95–98]. When carried out in dichloromethane, however, a different reaction pathway is followed, as reported by Wipf et al. [99]. Over time (ca. 16 h), the initial 1,2-adduct (Scheme 4.56), necessarily in anionic form, reacts with the solvent at reflux temperature to give a chloromethylated zinc derivative **103**, which serves in a Simmons-Smith-like capacity to cyclopropanate the alkene to give **104**. The products **102** (44–84 % overall yields) could be formed more rapidly by the inclusion of CH_2I_2 (5 equivalents) in the same reaction medium, and show an *anti* relationship in all cases. The stereochemical outcome is unexpected in view of the usual tendency for a heteroatom to direct cyclopropanation in a *syn*-selective manner [100]. Considerable functional group tolerance is a noteworthy feature, and even internal alkynes participate, thereby leading to trisubstituted amino cyclopropanes. *N*-Phosphinoylimines were used in all examples given the ease with which they can be hydrolyzed with acid (1 N HCl/MeOH).

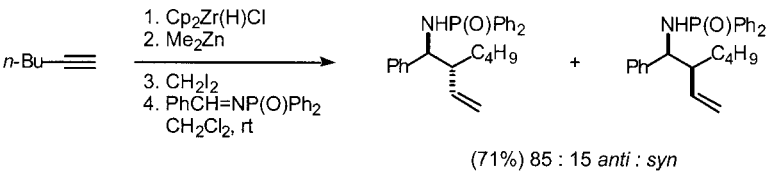


Scheme 4.55. Solvent dependence in reactions of vinyl zinc reagents with aldimines.



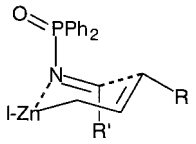
Scheme 4.56. Proposed intermediates leading to cyclopropylamines **102**.

By altering the order in which the above reagents are introduced, Wipf and Kendall discovered that homoallylic amines could be diastereoselectively produced instead of the expected aminocyclopropanes (Scheme 4.57) [101a]. Thus, after alkyne hydrozirconation–Me_2Zn-mediated transmetalation, addition of CH_2I_2 prior to the imine followed by stirring at room temperature led to good yields of the protected amines with a preference for the *anti* isomers. A chair-like transition state **105** (Figure 4.12), following insertion of the methylene group, can account for the observed stereochemical preference. Aryl imines afford lower *anti* selectivities than do aliphatic imines [101b]. This trend is consistent with the closed transition state **105**, as bulkier pseudoaxially oriented aryl substituents on the phosphinoylimine carbon would be expected to decrease the diastereoselectivity (Procedure 19, p. 145).



Scheme 4.57. Homoallylic amine formation resulting from a change in the mode of addition of reagents.

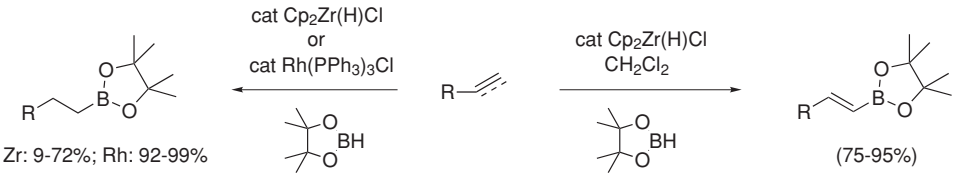
Figure 4.12. A chair-like transition state favoring *anti*-homoallylic amines.



105

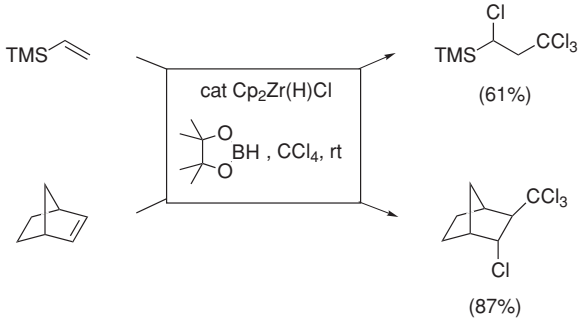
4.9 Zirconium to Boron

As discussed earlier in Wipf's review [14], Cole and co-workers have developed procedures by which alkyl and vinyl zirconocenes react with monohalo- or dihaloboranes to give the corresponding transmetalated boranes [102]. More recently, Srebnik and co-workers have described hydroborations of alkynes catalyzed by the Schwartz reagent (5 mol %) using pinacolborane, which adds cleanly with excellent regio- and stereoselectivity (98:2 (*E*):(*Z*)-vinyl boranes as products; Scheme 4.58) [103]. With alkenes, hydroboration can likewise occur under similar conditions, although $Rh(PPh_3)_3Cl$ (1 mol %) has proven superior to $Cp_2Zr(H)Cl$ as catalyst.



Scheme 4.58. Zirconium- and rhodium-catalyzed hydroborations of alkenes and alkynes with pinacolborane.

An unexpected change in the course of the above reaction was noted on going from CH_2Cl_2 to CCl_4 as solvent. Instead of the anticipated hydroboration of an alkene, a polyhalogenated alkane was obtained (Scheme 4.59) [104]. This Kharasch-like reaction [105], which normally requires elevated temperatures, proceeds in the presence of $Cp_2Zr(H)Cl$ (5 mol%) and pinacolborane (22–25 mol%) at room temperature. In general, the CCl_3 residue is attached at the terminal carbon of the alkene. Yields in most cases are modest (41–87 %). Internal alkenes react to give mixtures of diastereomers. A free radical mechanism, if involved, does not concern the starting alkene, as neither galvinoxyl nor BHT were found to inhibit the reaction. Hydrides of both zirconium and boron are required, as has been established by several control experiments. On completion of the

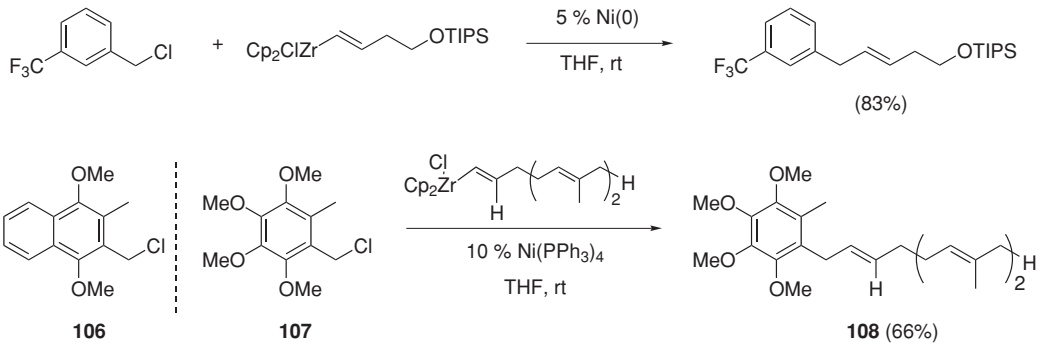


Scheme 4.59. Unusual addition of CCl_4 to alkenes catalyzed by both Zr and B.

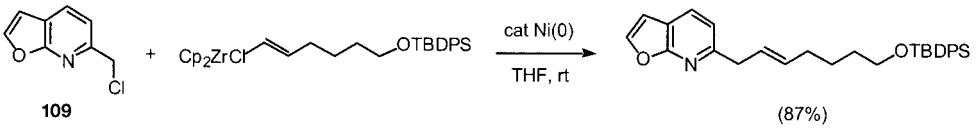
reaction, the boron-containing species was identified as *B*-chloropinacolborane by comparison of its ^{11}B NMR spectrum with that of an authentic sample. Zirconium was found to exist as Cp_2ZrCl_2 (Procedure 20, p. 145).

4.10
Zirconium to Nickel

Previous methodologies involving nickel-catalyzed 1,4-additions of vinyl zirconocenes, first described by Schwartz in 1977 [106] and improved to the level of an *Organic Synthesis* procedure in 1993 [107], have been viewed in particular with an eye towards prostaglandin synthesis. According to Negishi [108], an alternative coupling with aryl halides works well using catalytic amounts of $Ni(PPh_3)_4$, and this is amenable to vinyl zirconocenes derived from ethoxyacetylene, which give β-alkoxystyrenes. Until recently, missing from the repertoire of electrophilic partners were adducts containing sp^3-based leaving groups. Recently, Lipshutz and co-workers have used benzylic chlorides as substrates for couplings with numerous *in situ* formed vinyl zirconocenes under the influence of Ni(0) (Scheme 4.60) [109]. Aromatic rings with varying degrees of substitution appear to exert no influence on the efficiency of these reactions, which take place at room temperature. Pd(0) can be used in place of Ni(0), although heating to 50 °C for the same duration was needed under otherwise identical reaction conditions. In especially electron-rich cases, typified by the vitamin K and ubiquinone [110] subunits **106** and **107**, respectively, significant homocoupling of these moieties was observed. Thus, the standard protocol involving Ni(0) generation by *n*BuLi reduction [111] of $Ni(PPh_3)_2Cl_2$/$2PPh_3$ was supplanted by the use of the combination $Ni(COD)_2/2PPh_3$. On changing the Ni(0) source, the yield increased from 31 % to 66 % in the case of the desmethyl CoQ_3 precursor **108**. Similar couplings can be anticipated between vinyl zirconocenes and heteroaromatic systems that also bear a chloromethyl substituent (e. g. **109**) [112], thereby furnishing allylated aromatic and heteroaromatic rings in a highly stereocontrolled fashion (Scheme 4.61) (Procedure 21, p. 145).

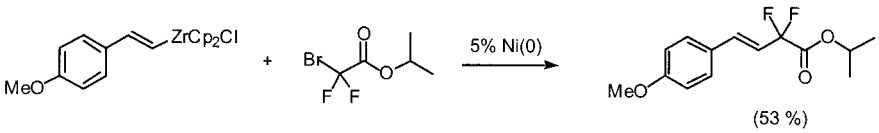


Scheme 4.60. Ni(0)-catalyzed couplings of vinyl zirconocenes with benzylic chlorides.



Scheme 4.61. Ni(0)-catalyzed coupling of a vinyl zirconocene with a chloromethylated heteroaromatic.

By means of nickel-catalyzed couplings of vinyl zirconocenes, Schwaebe et al. succeeded in obtaining fluorinated materials using α-bromo esters as electrophiles (Scheme 4.62) [113]. The yields achieved, albeit modest (24–65 %), were far better using Ni(0) than those obtained in experiments based on several palladium(0) sources (no product observed). Isopropyl esters appear to be crucial, as competing 1,2-addition occurs with both ethyl and *n*-butyl analogues. Curiously, *t*-butyl esters were found to completely inhibit both modes of reaction of the zirconocene.



Scheme 4.62. Ni(0)-catalyzed coupling of a vinyl zirconocene with an α-bromo-α,α-difluoro ester.

4.11 Summary and Outlook

The chemistry discussed herein, a "progress report" of sorts, provides additional testimony to the already well-recognized value that the Schwartz reagent brings to the art of organic synthesis. So long as Nature continues to supply a wealth of alkene and polyene-containing molecules that possess biopotencies of interest to medicine, it is likely that chemists worldwide will continue to refine existing methods and devise novel technologies for realizing such structural motifs. Hydrozirconation, based mainly on $Cp_2Zr(H)Cl$, can clearly play a pivotal role in this planning, owing to the stereo- and regiocontrol elements offered by this mild metal hydride. Whether based on intermediates that contain a carbon–zirconium bond, or alternative organometallics derived from zirconocenes via transmetalation, the sheer breadth of possible products emanating from an initial hydrozirconation is impressive by any yardstick. It is also interesting to note that much of the recent chemistry concerning the Schwartz reagent brings the (organo)chalcogens (S, Se, and Te) into focus, as each atom adds yet another option for furthering molecular complexity.

Future reports in the area of hydrozirconation chemistry may include as yet undiscovered ways whereby zirconium–heteroatom bonds can be used to good advantage, in which $Cp_2Zr(H)Cl$ may serve as a selective reductant for various functionalities. Practical procedures yielding more reactive reagents equivalent to $Cp_2Zr(H)Cl$ (e. g., $Cp_2Zr(H)OTf$) [114] would be welcomed for sterically hindered substrates that are otherwise reluctant to react with the parent reagent, and as a means of altering the normally observed reaction patterns [115]. Additional advances including general methods for effecting catalytic hydrozirconation transmetalations involving other metals would also be most useful.

Typical Experimental Procedures

1. Hydrozirconation of 1-decene with *i*BuZrCp$_2$Cl in the presence of 2 mol% AlCl$_3$ [10] The solvent was removed from an ethereal solution of *t*BuMgCl (2 M, 1.1 mL, 2.2 mmol) under reduced pressure at room temperature. To the residue were added benzene (5 mL) and Cp_2ZrCl_2 (642 mg, 2.2 mmol), and the reaction mixture was heated for 1 h at 50 °C.

The formation of *i*BuZrCp$_2$Cl in 94 % yield was observed by ^{1}H NMR spectroscopy. To this were added AlCl$_3$ (5.5 mg, 0.04 mmol) and 1-decene (0.38 mL, 2.0 mmol) and the resulting mixture was stirred at 50 °C for 3 h. Analysis by ^{1}H NMR spectroscopy indicated the formation of *n*-C$_{10}$H$_{21}$ZrCp$_2$Cl ($\delta = 5.80$ for Cp) in 87 % yield, along with 5 % of Cp$_2$ZrCl$_2$ ($\delta = 5.91$). Treatment of the product with iodine (1.14 g, 4.5 mmol) in THF (10 mL) at 0 to 23 °C, followed by standard extractive work-up and bulb-to-bulb distillation (0.5 mmHg, 70–75 °C) afforded 451 mg (84 %) of 1-iododecane.

2. General procedure for reduction of tertiary amides to aldehydes using the Schwartz reagent [15] The substrate is taken up in anhydrous THF (5 mL) under argon. This solution is then added to 1.5–2.0 equiv. of Cp$_2$Zr(H)Cl at room temperature under argon, which elicits the desired conversion within 15–30 min. Subsequent work-up of the concentrated mixture by short-path silica gel chromatography (hexanes/ethyl acetate) affords the desired aldehydes in near quantitative yields.

3. Hydrozirconation/halogenation of an acetylenic ether; (1*R*,2*S*,5*R*)-(*E*)-2-iodoethenyl 2-isopropyl-5-methylcyclohexyl ether [18] In a flame-dried flask under nitrogen and protected from light were placed Cp$_2$ZrCl$_2$ (4.96 g, 17.0 mmol), THF (68 mL), and SuperHydride^{TM} (LiEt$_3$BH, 16.0 mL, 1.0 M in THF). The mixture was stirred for 1 h, whereupon (1*R*,2*S*,5*R*)-ethynyl 2-isopropyl-5-methylcyclohexyl ether, a menthol-derived alkynyl ether (1.53 g, 8.49 mmol) was added. After 15 min., iodine (2.37 g, 9.34 mmol) was added and the reaction mixture was stirred for 10 min. under protection from light. It was then diluted with ethyl acetate/hexane (~50 mL), the organic phase was washed with saturated aqueous NaHCO$_3$ solution (2 × 30 mL), and the combined aqueous layers were extracted with ethyl acetate/hexane. The combined organic layers were washed with 10 % aqueous Na$_2$SO$_3$ solution and saturated aqueous NaCl solution, dried over anhydrous sodium sulfate, and concentrated in vacuo, and the residue was purified by flash chromatography (pentane; Et$_3$N-pretreated silica) to afford a clear colorless oil (1.17 g, 45 %); $R_f = 0.45$ (hexane); $[\alpha]_D = -27$ ($c = 0.3$, CDCl$_3$).

4. Hydrozirconation/selenenylation; (*E*)-[(2-phenylethenyl)seleno]benzene [20] A mixture of Cp$_2$Zr(H)Cl (0.8 mmol) and phenylacetylene (0.8 mmol) in THF (4 mL) was stirred at room temperature for 20 min. A solution of PhSeBr (0.8 mmol) in THF (3 mL) (prepared in situ) was then added by means of a syringe and the mixture was stirred at room temperature for 10 min. It was then diluted with light petroleum and stirred for a further 5 min., after which the supernatant was filtered through a short plug of silica gel. After evaporation of the solvent from the filtrate, the residue was purified by preparative TLC on silica gel using light petroleum or diethyl ether/light petroleum as eluent to yield the product (84 %).

5. {[(1*Z*)-1-(Phenylmethylene)-2-heptynyl]sulfinyl}benzene [32] To a freshly prepared suspension of Cp$_2$Zr(H)Cl (1.5 mmol) in THF (6 mL) at room temperature under nitrogen, a solution of [(phenylethynyl)sulfinyl]benzene (1.36 mmol) in THF (0.5 mL) was added by means of a syringe. The reaction mixture was then stirred for about 30 min. until the precipitate completely dissolved. To the resulting clear green solution were added Pd(PPh$_3$)$_4$ (0.07 mmol) and 1-hexynyl(phenyl)iodonium tosylate (1.36 mmol), and the mixture was stirred for 2 h at ambient temperature. It was then washed with saturated aqueous

NH_4Cl solution (8 mL) and the product was extracted into diethyl ether. The combined extracts were dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by preparative TLC (silica gel; hexane/AcOEt, 10:1) to give the product (54 %).

6. Standard procedure for the reaction of acyl zirconocenes with benzaldehyde [45] To a suspension of $Cp_2Zr(H)Cl$ (507 mg, 2.0 mmol) in CH_2Cl_2 (8 mL) was added 1-octene (0.62 mL, 4.0 mmol), and the resulting mixture was stirred for 30 min at ambient temperature. After the mixture had been stirred under an atmosphere of CO for 2 h, benzaldehyde (0.10 mL, 1.0 mmol) and $BF_3 \cdot OEt_2$ (0.24 mL, 2.0 mmol) were added at −20 °C and the resulting mixture was stirred at 0 °C for 1 h. It was subsequently treated with aqueous $NaHCO_3$ solution and extracted with diethyl ether (3 × 15 mL). The combined ethereal extracts were washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give a crude oil, which was purified by flash column chromatography (silica gel; hexane/ethyl acetate, 20:1 → 15:1 → 10:1) to give 1-hydroxy-1-phenyl-2-decanone (193 mg, 79 %).

7. Experimental procedure for acyl zirconocene generation and addition to imines [41] A suspension of $Cp_2Zr(H)Cl$ (1.3 equiv.) in CH_2Cl_2 (4 mL) containing 1-octene (2.6 equiv.) was stirred at ambient temperature for 0.5 h and then the mixture was treated with carbon monoxide for 2 h (a CO balloon). The CH_2Cl_2 was subsequently evaporated in vacuo, and THF (6 mL) was added to the residue. To this solution was added a solution of *N*-phenylbenzenamine (1 equiv.), $Yb(OTf)_3$ (20 mol %), and TMSOTf (20 mol %) in THF (3 mL) at 0 °C and the resulting mixture was stirred at ambient temperature for 24 h. The reaction mixture was subsequently treated with saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. After standard work-up, the product was purified by column chromatography on silica gel (hexanes/ethyl acetate, 80:1) to give 1-phenyl-1-(phenylamino)-2-decanone in 64 % yield.

8. General procedure for the synthesis of telluroselenoethenes from acetylenic selenides [51] To a suspension of $Cp_2Zr(H)Cl$ (0.51 g, 2.0 mmol) in THF (6.0 mL) under nitrogen, a solution of the appropriate butylselenoacetylene (1.0 mmol) in THF (2.0 mL) was added by means of a syringe. The reaction mixture was stirred at room temperature for 20 min. to 3 h, depending on the substrate, until complete transformation of the starting material was indicated by TLC monitoring of the reaction on SiO_2 using hexane as eluent. The clear yellow solution obtained was cooled to 0 °C, whereupon a solution of butyltellurenyl bromide (2.0 mmol; prepared separately) was added by means of a syringe. Stirring was continued for an additional 15 min., and then the mixture was transferred to an Erlenmeyer flask and diluted with ethyl acetate (10 mL), 95 % ethanol (5 mL), and water (10 mL). Butyl bromide (0.32 mL, 3.0 mmol) followed by $NaBH_4$ (0.09 g, 3.0 mmol) were added to transform the dibutylditelluride to the corresponding telluride, which is more easily removed by distillation. After this treatment, the product was extracted with ethyl acetate (5 × 20 mL). The combined extracts were washed with water (5 × 20 mL) and dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The dibutyltelluride was removed by distillation of the crude product in a kugelrohr apparatus. The residue was purified by flash chromatography using hexane as eluent to furnish the telluroselenoethene as a yellow liquid.

9. General procedure for the synthesis of (*Z*)-vinylchalcogenides from acetylenic chalcogenides [51] To a suspension of $Cp_2Zr(H)Cl$ (0.51 g, 2.0 mmol) in THF (6.0 mL) under nitrogen, a solution of the appropriate acetylenic chalcogenide (1.0 mmol) in THF (2.0 mL) was added by means of a syringe. The reaction mixture was stirred at room temperature for 20 min. to 3 h (for selenides) or 10 to 30 min. (for tellurides), depending on the substrate. Complete consumption of the starting material was confirmed by monitoring the reaction by TLC on SiO_2 using hexane as eluent. The reaction mixture was subsequently treated with water (2.0 mL), diluted with ethyl acetate (150 mL), and washed with a saturated solution of ammonium chloride (3 × 50 mL). The organic phase was dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. After purification by flash chromatography using hexane as eluent, the products were obtained as yellow oils.

10. General procedure for the synthesis of telluroselenoethenes from acetylenic tellurides [51] To a suspension of $Cp_2Zr(H)Cl$ (0.51 g, 2.0 mmol) in THF (6.0 mL) under nitrogen, a solution of the appropriate butyltelluroacetylene (1.0 mmol) in THF (2.0 mL) was added by means of a syringe. The reaction mixture was stirred at room temperature for 20 min. to 3 h, depending on the substrate. Complete consumption of the starting material was confirmed by monitoring the reaction by TLC on SiO_2 using hexane as eluent. The dark-red solution obtained was cooled to 0 °C, whereupon a solution of butylselenenyl bromide (2.0 mmol; prepared separately) was added by means of a syringe. Stirring was continued for an additional 15 min., and then the mixture transferred to an Erlenmeyer flask and diluted with ethyl acetate (10 mL), 95 % ethanol (5 mL), and water (10 mL). Butyl bromide (0.32 mL, 3.0 mmol) followed by $NaBH_4$ (0.09 g, 3.0 mmol) were added to transform the dibutyldiselenide to the corresponding selenide, which is more easily removed by distillation. After this treatment, the product was extracted with ethyl acetate (5 × 20 mL). The combined extracts were washed with water (5 × 20 mL) and dried over anhydrous $MgSO_4$, and the solvent was evaporated in vacuo. The dibutylselenide was removed by distillation of the crude product in a kugelrohr apparatus (70 °C/0.6 mmHg). The ketene telluroseleno acetal was purified by flash chromatography using hexane as eluent to give a yellow liquid.

11. Representative procedure for the synthesis of (*E*)-vinylic tellurides [52] A 50 mL two-necked, round-bottomed flask equipped with a stirrer bar was charged with $Cp_2Zr(H)Cl$ (0.5 g, 2.0 mmol), and then evacuated and purged with nitrogen. Dry THF (8.0 mL) was injected and 1-pentyne (2.0 mmol) was added. The mixture was stirred for 20 min. to yield a clear yellow solution, which was then cooled to −78 °C. In parallel, dibutyl ditelluride (0.369 g, 1.0 mmol) was placed in a round-bottomed flask containing a stirrer bar. The flask was evacuated and purged with nitrogen and THF (10 mL) was introduced by means of a syringe. The resulting solution was cooled to 0 °C, whereupon a solution of bromine (0.16 g, 1.0 mmol) in benzene (ca. 10 mL) was added. The dark-red solution was stirred for 10 min. and then transferred dropwise by means of a syringe to the aforementioned solution of the vinyl zirconocene, which had been pre-cooled to −78 °C. After stirring for 1 h at −78 °C, the resulting mixture was placed in a separating funnel, diluted with ethyl acetate (150 mL), and washed with water (3 × 70 mL). After drying the organic phase over anhydrous $MgSO_4$, the solvents were evaporated in vacuo and the residue was purified by distillation in a kugelrohr apparatus (60 °C/0.4 mmHg) to yield (*E*)-1-(butyltelluro)-1-pentene (86 %).

12. General procedure for the synthesis of ketene telluro(seleno) acetals via alkynylselenolate anions [56] To a solution of the requisite freshly distilled terminal alkyne (1.0 mmol) in THF (5.0 mL) under a nitrogen atmosphere, butyllithium (1.0 mmol, 0.5 mL, 2.0 M in hexanes) was added at 0 °C and the solution was stirred for 15 min. The mixture was then allowed to warm to room temperature, whereupon elemental selenium (0.079 g, 1.0 mmol) was added. After complete consumption of the selenium, solid $Cp_2Zr(H)Cl$ (0.257 g, 1.0 mmol) was quickly added. The resulting mixture was stirred for 15 to 30 min., depending on the substrate, butyl bromide (0.21 mL, 2.0 mmol) was then added, and the reaction mixture was stirred at room temperature for an additional 1 h. Thereafter, a solution of butyltellurenyl bromide (1.0 mmol), prepared separately, was added by means of a syringe. Stirring was continued for an additional 30 min., and then the mixture was transferred to an Erlenmeyer flask and diluted with ethyl acetate (10 mL), 95 % ethanol (15 mL), and water (100 mL). Butyl bromide (1 mL) was added, followed by $NaBH_4$ (until the solution turned pale yellow), to transform dibutyl ditelluride to the corresponding telluride, which is more easily removed by distillation. After this treatment, the product was extracted with ethyl acetate, the organic phase was washed with water and dried over anhydrous $MgSO_4$, and the solvent was evaporated in vacuo. Dibutyl telluride was removed by distillation of the crude product in a kugelrohr apparatus. The residue contained the ketene telluro(seleno) acetal, which was obtained as a yellow liquid after purification by flash chromatography using hexane as the eluent.

13. Representative procedure for the synthesis of (*Z*)-α-selenenylvinylstannanes [34] A mixture of $Cp_2Zr(H)Cl$ (1.1 mmol) and (3-methoxy-1-propynyl)tributylstannane (1.0 mmol) in THF (5 mL) was stirred at room temperature for 20 min. A solution of PhSeBr (1.0 mmol) in THF (4 mL) (prepared in situ) was then injected into the resulting solution and the mixture was stirred at room temperature for 30 min. It was then diluted with light petroleum and stirred for a further 5 min., after which the supernatant was filtered through a short plug of silica gel. After evaporation of the solvent from the filtrate, the residue was purified by preparative TLC on silica gel to yield (1*Z*)-tributyl-[3-methoxy-1-(phenylseleno)-1-propenyl]stannane (60 %).

14. Representative procedure for the coupling of an alkenyliodonium tosylate with a Gilman cuprate; (*E*)-(2-bromoprop-1-enyl)benzene [64] To a stirred suspension of $Cp_2Zr(H)Cl$ (0.360 g, 1.4 mmol) in THF (6 mL) was added phenyl(phenylethynyl)iodonium tosylate (0.476 g, 1 mmol). Following the addition, the mixture gradually turned into a clear solution at room temperature. Using a syringe, this solution was added dropwise to a stirred solution of Me_2CuLi (2 mmol) in THF (4 mL) at −60 °C, and the reaction mixture was subsequently kept at −40 °C for 8 h. NBS (1.068 g, 6 mmol) was then added portionwise and the reaction mixture was allowed to warm to room temperature. It was stirred for 2 h, and was then quenched with water and extracted with diethyl ether (4 × 15 mL). The combined extracts were filtered and concentrated, and the residue was purified by preparative TLC (light petroleum as the eluent), to give the product (0.107 g, 54 %) as a yellowish oil.

15. General experimental procedure for the copper-catalyzed alkylation of an acylzirconocene [70] A solution of the acylzirconocene (1.5 mmol) in DMF or THF (10 mL) was first prepared by a sequence of reaction of 4-phenyl-1-butene (1.5 mmol) with $Cp_2Zr(H)Cl$

(1.5 mmol) in CH_2Cl_2 (5 mL) at ambient temperature for 0.5 h, insertion of CO by stirring at ambient temperature for 2 h using a CO balloon, concentration of the solution to dryness in vacuo and redissolution of the residue in THF or DMF. To the solution of the acylzirconocene chloride thus obtained was added a solution of the requisite allylic or propargylic halide (1 mmol) in THF or DMF (2 mL) at 0 °C. After the addition of Cu(I) (10 mol%) at 0 °C, the mixture was stirred for 1–10 h at the same temperature. The reaction mixture was then filtered through a short dry silica gel pad and the filtrate was concentrated to dryness to give a crude oil. Purification by column chromatography on silica gel (hexane/ethyl acetate) gave the pure product.

16. (*S*)-1-(4-Chlorophenyl)hept-2-en-1-ol [87] A suspension of $Cp_2Zr(H)Cl$ (0.21 g, 0.81 mmol) in dry CH_2Cl_2 (2 mL) under N_2 was treated with 1-hexyne (94 μL, 0.81 mmol) at room temperature. The mixture was stirred for 5 min., and then all volatiles were removed in vacuo. The resulting light-yellow solid was dissolved in dry toluene (2 mL), the solution was cooled to −65 °C, and then treated with Me_2Zn (2.0 M in toluene, 0.41 mL, 0.82 mmol). To this mixture was added the ligand 2-[(1*R*)-1-(dimethylamino)propyl]benzenethiol (16.6 mg, 0.085 mmol). After a period of 1 h, during which the mixture was slowly warmed to −30 °C, a solution of 4-chlorobenzaldehyde (115 mg, 0.81 mmol) in dry toluene (2 mL) was added. The reaction mixture was stirred overnight (12 h) before being quenched with saturated aqueous $NaHCO_3$ solution. The solution was extracted with EtOAc (3×), and the combined extracts were washed with brine, dried (anhydrous $MgSO_4$), and filtered through a pad of SiO_2. After concentration of the filtrate, the residue was chromatographed on SiO_2 (hexanes/EtOAc, 9:1) to yield 151 mg (83 %) of the product as a colorless oil.

17. (3*E*,6*E*)-Tris(1-methylethyl)silyl 5-hydroxy-7-(tributylstannyl)-3,6-heptadienoate [92] To a suspension of $Cp_2Zr(H)Cl$ (1.56 g, 6.05 mmol) in dry, degassed CH_2Cl_2 (37 mL) at 0 °C was added a solution of freshly distilled triisopropylsilyl 3-butynoate (1.60 g, 6.66 mmol) in CH_2Cl_2 (24 mL). The mixture was allowed to warm to room temperature over a period of 20 min., during which it became homogeneous and orange. This solution was then cooled to −78 °C, whereupon a solution of Me_2Zn (2.0 M in toluene, 6.03 mmol) was added. After 5 min., the −78 °C bath was replaced with a 0 °C bath and the reaction mixture was stirred for an additional 30 min. A solution of 3-tributylstannyl-2-propenal (1.89 g, 5.48 mmol) in CH_2Cl_2 (27 mL) was then added and the mixture was stirred at 0 °C for 3 h. Saturated aqueous NH_4Cl solution (1 mL) was added and the mixture was allowed to warm to room temp. over a period of 15 min. Na_2SO_4 (~2 g) was then added to the resulting suspension and the mixture was stirred for 10 min. and then filtered through Celite (~5 g) with CH_2Cl_2 (ca. 150 mL). Concentration of the filtrate in vacuo followed by dilution with hexanes (~20 mL) gave a suspension, which was filtered through Celite (~5 g; elution with 250 mL of hexanes/ethyl acetate, 80:20). Concentration of the filtrate, followed by flash chromatography (100 g of silica gel; hexanes/ethyl acetate, 93:7) of the crude product afforded 2.35 g (73 %) of the dienyl alcohol as an oil.

18. (*Z*)-1,1',1''-({[7-(Methoxymethoxy)-2-methyl-4-heptenyl]oxy}methylidyne)tris(benzene) [93] A suspension of the Schwartz reagent was prepared by adding CH_2Cl_2 (1.0 mL) to $Cp_2Zr(H)Cl$ (603 mg, 2.34 mmol) at −78 °C. A mixture of 3-(trityloxy)-1-propyne (193 mg, 0.648 mmol) and 5-(methoxymethoxy)-1,2-pentadiene (116 mg, 0.906 mmol) in CH_2Cl_2

(2.5 mL) was then added. After gradual warming to 25 °C, the resulting red solution was chilled to 0 °C, and to this was added $ZnCl_2$ (0.69 M in diethyl ether, 1.3 mL). After 2 h at 25 °C, the mixture was diluted with diethyl ether and poured into cooled, saturated aqueous $NaHCO_3$ solution. The biphasic mixture was extracted with EtOAc (3×) and the combined organic extracts were washed with saturated aqueous Na_2SO_4 solution, dried over anhydrous Na_2SO_4, and filtered through a Celite pad. Evaporation of the volatiles and purification of the residue by preparative TLC (hexane/EtOAc, 9:1) gave the product (231 mg, 83 %).

19. *N*-(2-Ethenyl-1-phenylhexyl)-*P*,*P*-diphenylphosphinic amide [101] A suspension of $Cp_2Zr(H)Cl$ (195 mg, 0.756 mmol) in CH_2Cl_2 (2 mL) was treated at room temperature with 1-hexyne (95.0 μL, 0.827 mmol). After 2 min., the yellow solution was cooled to −78 °C and treated with Me_2Zn (2.0 M solution in toluene, 375 μL, 0.750 mmol). The mixture was allowed to warm to room temperature over a period of 5 min. CH_2I_2 (100 μL, 1.24 mmol) was then added and the mixture was stirred for 2 min. and then treated with a solution of *N*-(diphenylphosphanyl)benzaldimine (76.0 mg, 0.249 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred at room temperature for 12 h, and then quenched with saturated aqueous NH_4Cl solution, diluted with EtOAc and saturated aqueous $NaHCO_3$ solution, and filtered through Celite. The organic phase was washed with H_2O and brine, dried over anhydrous $MgSO_4$, filtered through a pad of Florisil, and concentrated in vacuo. The residue was chromatographed on deactivated SiO_2 (hexanes/EtOAc, 1:9, containing 1 % Et_3N) to yield 71 mg (71 %) of the *anti* and *syn* products as an 85:15 (separable) mixture of diastereomers.

20. General procedure for the addition of CCl_4 to alkenes catalyzed by $Cp_2Zr(H)Cl$ and pinacolborane [104] The alkene (1.0 mmol) was dissolved in CCl_4 (0.5 mL) at 25 °C and pinacolborane (28.2 mg, 0.22 mmol) was added dropwise. The solution was stirred for 3 min. and then transferred via a cannula to a flask containing $Cp_2Zr(H)Cl$ (12.9 mg, 0.05 mmol). The reaction mixture was stirred for 24 h at 25 °C and then quenched with wet diethyl ether (2 mL) to obtain the corresponding addition products. The resulting mixture was washed with water (3 × 5 mL), and dried with anhydrous Na_2SO_4 (1.0 g). The products were isolated by column chromatography on silica gel eluting with hexanes/diethyl ether (95:5).

21. General procedure for the preparation and Ni(0)-catalyzed couplings of vinyl zirconocenes [109] A suspension of the alkyne (0.75 mmol) and $Cp_2Zr(H)Cl$ (0.75 mmol) in THF (2 mL) was stirred under argon in the dark until a clear solution was obtained (ca. 30 min.). In a separate flask, the benzylic chloride (0.60 mmol) was slowly added to a solution of $Ni(PPh_3)_4$ (0.030 mmol) in dry THF. After stirring for 5−10 min., this mixture was added to the vinyl zirconocene solution via a cannula. The resulting mixture was stirred at room temperature for 1.5 h, after which GC analysis showed that the benzylic chloride had been completely consumed. Hydrogen peroxide (0.09 mL of a 30 % solution in water) was then added, and the mixture was stirred for 10 min. and then filtered. The filtrate was quenched with 5 % aqueous HCl and extracted with EtOAc (4×). The combined organic layers were washed successively with water and brine, dried (anhydrous $MgSO_4$), and concentrated in vacuo. Column chromatography of the residue on silica gel afforded the desired (*E*)-allylated aromatic.

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5
Acylzirconocenes in Organic Synthesis

Yuji Hanzawa

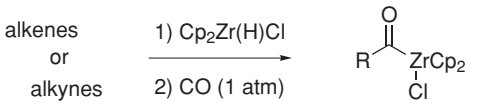
5.1
Introduction

Over the past two decades, a variety of reactions using organozirconocene complexes as catalysts or as stoichiometric reagents have been developed for the purpose of creating carbon–carbon bonds. The frequent use of such organometallics has established their reliability as reagents or as catalysts, not only in polymer chemistry but also in fine organic chemistry. However, among the organozirconocene complexes, use of acylzirconocene complexes in organic synthesis has been infrequent despite their ready availability from organozirconocene compounds. Although there have been extensive mechanistic studies on the formation and reactivity of acylzirconocene complexes related to carbon monoxide reduction, very little synthetic application of the complexes to carbon–carbon bond formation has been reported. This chapter deals with the synthetic use of acylzirconocene compounds (mainly acylzirconocene chloride complexes) in carbon–carbon bond formation. Therefore, for detailed discussions on the mechanistic studies of the formation of acylzirconocene complexes and their structural or spectral properties, the reader is referred to other pertinent review articles [1].

5.2
Synthesis and Stability of Acylzirconocene Complexes

Acylzirconocene chloride derivatives are easily accessible in a one-pot procedure through the hydrozirconation of alkene or alkyne derivatives with zirconocene chloride hydride (Schwartz reagent) [$Cp_2Zr(H)Cl$, Cp = cyclopentadienyl] and subsequent insertion of carbon monoxide (CO) into the alkyl– or alkenyl–zirconium bond under atmospheric pressure (Scheme 5.1) [2].

Although this migratory insertion of CO into a carbon–zirconium bond accounts for the majority of acylzirconocene complexes that have been reported, the CO insertion

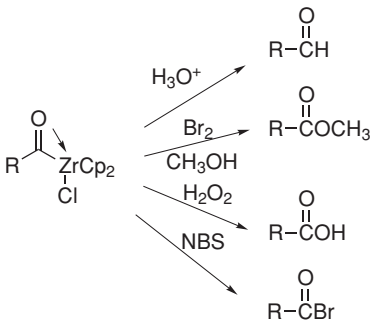


Scheme 5.1. Formation of acylzirconocene chlorides.

into the carbon–zirconium bond and the stability of the generated acylzirconocene complex are dependent on the organoligand of the zirconocene derivative [3]. Thus, a dimethylzirconocene complex [$Cp_2Zr(CH_3)_2$], for example, reacts with CO under high pressure (20 °C, 40–80 atm) to give the unstable species $Cp_2Zr(COCH_3)(CH_3)$, which rapidly loses CO at 1 atm [3]. It has been reported that insertions of CO into *n*-alkyl– and alkenyl–zirconium bonds can be achieved with almost equal efficiency and rate, and that the insertion of CO into a cyclohexyl–zirconium bond is even faster [4]. The stability of the acylzirconocene chlorides at ambient temperature is remarkable, preserving their integrity and retaining CO even under reduced pressure. This stability should provide new possibilities; in other words, the easy handling and preparation of the complexes should render them a new type of reagent for organic synthesis.

5.3
Reactions of Acylzirconocene Complexes

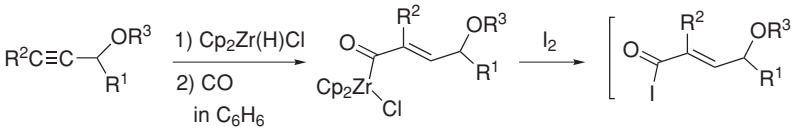
5.3.1
Historical Background

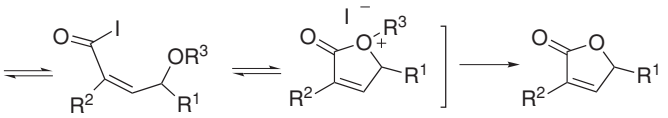


Scheme 5.2. Conversion to carboxylic acid derivatives.

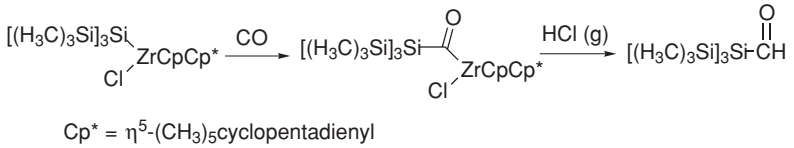
A pioneering study on the reactions of acylzirconocene chlorides by Schwartz et al. revealed that the acyl group of the acylzirconocene chloride can be converted, depending on subsequent procedures, into aldehydes, carboxylic acids, esters, or acyl halides (Scheme 5.2) [2]. Acid hydrolysis of the acylzirconocene chloride produces an aldehyde, while the acyl bromide can be obtained by treatment with *N*-bromosuccinimide (NBS). Oxidative work-up, such as treatment with aqueous H_2O_2 followed by acidification or treatment with bromine in methanol gives carboxylic acids or methyl esters, respectively. These conversions were the first practical applications of acylzirconocene chlorides to organic synthesis. Subsequently, these acylzirconocene chloride based transformations have been applied to an efficient preparation of optically active butenolides from propargyl alcohols (Scheme 5.3) [5] and to the preparation of silaaldehyde (Scheme 5.4), which is difficult to prepare through other means [6].

Transfer of the acyl group from the acylzirconocene chloride to aluminum (transmetalation) by treatment with aluminum chloride has been reported to give an acylaluminum species in situ, and the possibility of the acylaluminum acting as an acyl anion donor has been suggested (Scheme 5.5) [7]. However, the acyl anion chemistry through this transmetalation procedure appears to be limited since only protonolysis to the aldehyde proceeds in good yield, which could be achieved by direct hydrolysis of the acylzirconocene chloride.

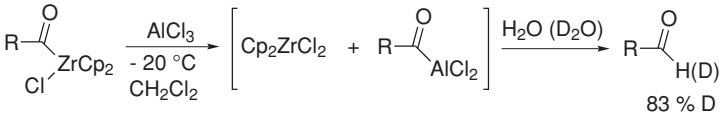




Scheme 5.3. Preparation of butenolides.



Scheme 5.4. Preparation of silaaldehyde.



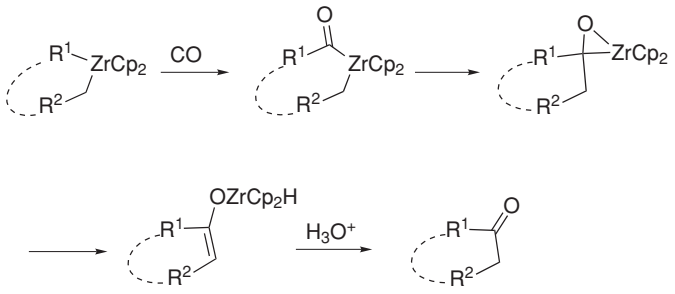
Scheme 5.5. Formation of acylaluminum.

5.3.2

Conversion to Ketone– and Ketene–Zirconocene Complexes and Reactions Thereof

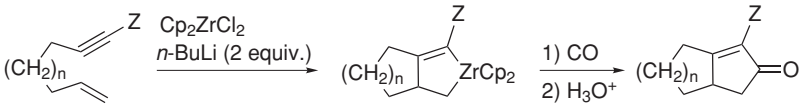
5.3.2.1 Ketone–zirconocene complexes

The sequential double migratory insertion of CO into acyclic and cyclic diorganozirconocene complexes through acylzirconocene and ketone–zirconocene species provides a convenient procedure for preparing acyclic and cyclic ketones (Scheme 5.6) [8]. Thus, the bicyclic enones from enynes can be obtained through CO insertion into zirconacyclopentenes followed by a subsequent rearrangement (Scheme 5.7). The scope and limitations of this procedure have been described in detail elsewhere [8d]. This procedure provides a complementary version of the well-known Pauson–Khand reaction [9].



Scheme 5.6. Double migratory insertion.

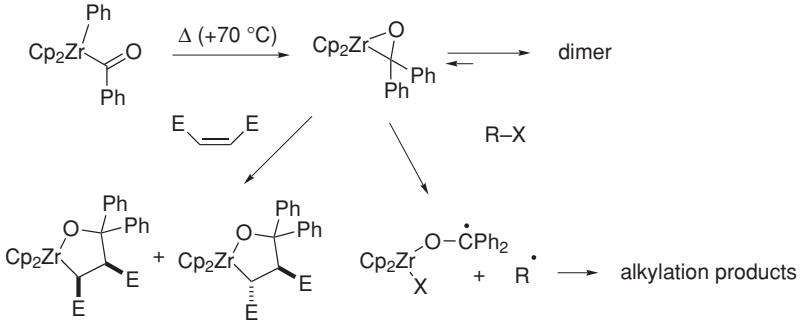
The migratory insertion of CO into a carbon–zirconium bond forming a ketone–zirconocene complex has been studied in detail using diphenylzirconocene (Cp_2ZrPh_2) [8c]. Upon heating of the initially formed (benzoyl)phenylzirconocene complex [$Cp_2Zr(COPh)(Ph)$] at +70 °C, intramolecular migration of the remaining phenyl



n = 1 or 2
Z = C, Si, Ge or Sn group

Scheme 5.7. Preparation of bicyclic enones.

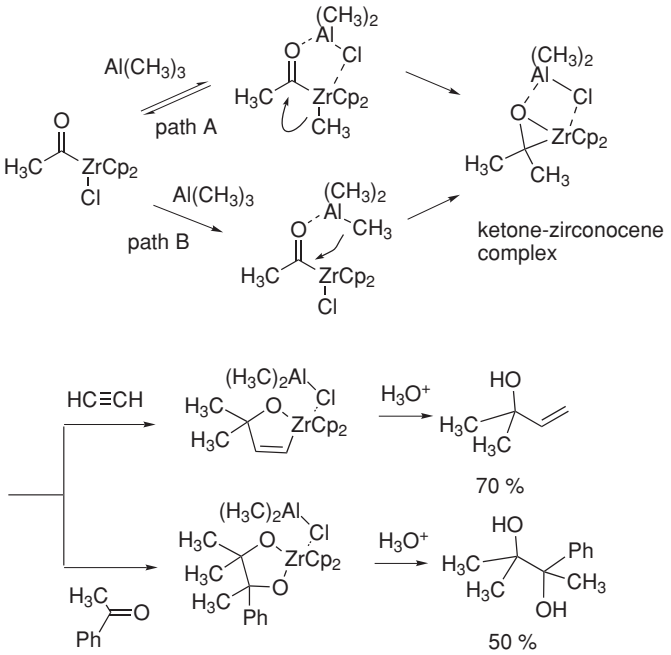
group to the benzoyl carbon yields a benzophenone–zirconocene complex (Scheme 5.8). The reaction of the benzophenone–zirconocene complex with dimethyl maleate proceeds with partial loss of the stereochemistry to give a mixture of stereoisomers of the oxazirconacyclopentane complex [10], while reaction with alkyl halides yields the alkylation products through a radical mechanism [11]. These transformations point to the possible use of the acylzirconocene complex in carbon–carbon bond-forming reactions.



E = $COOCH_3$

Scheme 5.8. Formation and reactions of benzophenone–zirconocene complex.

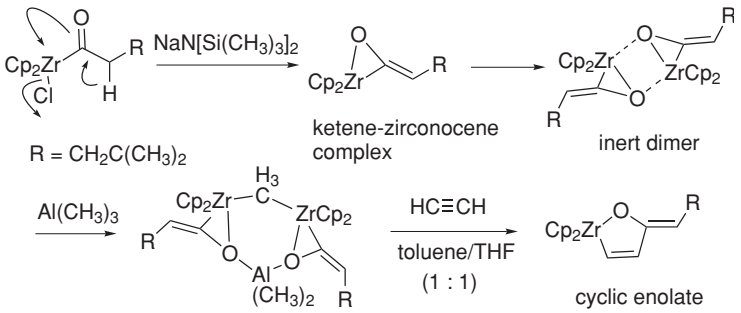
Acylzirconocene chlorides react with organoaluminum reagents to produce aluminum-stabilized ketone–zirconocene complexes in 60–90% yields (Scheme 5.9) [12]. The formation of the complexes has been suggested to proceed by a stepwise mechanism (path A) involving initial transmetalation followed by Lewis acid promoted intramolecular migration of an alkyl group to the acyl ligand. However, the possibility of a direct reductive alkylation of the acyl ligand in the acylzirconocene chloride (path B) could not be strictly ruled out by a labeling experiment. The coordination of the ketone complexes to the dialkylaluminum chloride ligand prevents dimerization. The aluminum-coordinated ketone complexes react with acetylenes to regioselectively afford oxymetallacyclopentenes, and with ethylene to give oxymetallacyclopentanes. Treating the ketone complexes with ketones such as PhCOMe yields diolates, which can be hydrolyzed to give a 1,2-diol (Scheme 5.9).



Scheme 5.9. $(CH_3)_3Al$-mediated formation of a ketone–zirconocene complex and reactions.

5.3.2.2 **Ketene–zirconocene complexes**

Clear formation of ketene–zirconocene complexes upon treatment of acylzirconocene chlorides with a hindered amide base indicates that the carbonyl group of the acylzirconocene chloride possesses usual carbonyl polarization (Scheme 5.10). However, these zirconocene–ketene complexes are exceptionally inert due to the formation of strongly bound dimers [13a]. Conversion of the dimer to zirconocene–ketene–alkylaluminum complexes by treating with alkylaluminum and reaction with excess acetylene in toluene at 25 °C has been reported to give a cyclic enolate in quantitative yield. Although the ketene–zirconocene–alkylaluminum complex reacts cleanly with acetylene, it does not react with ethylene or substituted acetylenes [13b]. Thus, the complex has met with limited success as a reagent in organic synthesis.



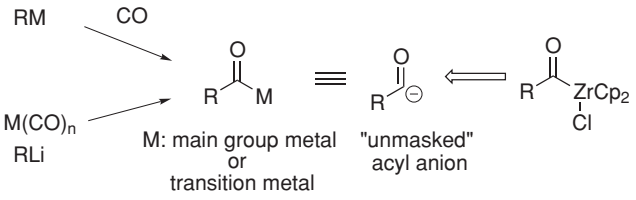
Scheme 5.10. Generation and reaction of a ketene–zirconocene complex.

Although the chemistry described in Sections 5.3.2.1 and 5.3.2.2 indicates an attractive feature of the acylzirconocene chloride complex for carbon–carbon bond formation, application to the synthesis of metal-free organic molecules has not been extensively studied.

5.4
Reactions of Acylzirconocene Chlorides as "Unmasked" Acyl Group Donors

5.4.1
Introductory Remarks

The acyl-metal [RC(O)M, M = metal] species as a donor of an "unmasked" acyl group is an important reactive intermediate [14] since the direct introduction of an acyl group in a nucleophilic manner can be carried out without using the so-called "umpolung" procedure [15]. Thus, extensive research has been conducted concerning the generation and reaction of acyl-metal compounds. In particular, acyl-metal species involving main group metals (M = Li, Zn, etc.) have been studied by many research groups, and an attractive feature of the reactivity of these species has been established (Scheme 5.11) [16]. However, their use as "unmasked" acyl anion donors in organic synthesis is hampered by their limited stability and/or the extreme reaction conditions required. Thus, the generation and reactions of the acyl-lithium species, for example, have been carried out *in the presence of* electrophiles under very low temperature conditions (−110 to −130 °C). As well as the acyl-main group metal species, acyl-transition metal complexes have also long attracted our attention in organic synthesis because of their intrinsic usefulness as "unmasked" acyl anion equivalents (Scheme 5.11). In this context, acylate complexes of nickel, iron, and cobalt have been reported to be efficient "unmasked" acyl anion donors [17]. However, there is a serious drawback to their use as reagents due to the severe toxicity of the starting metal carbonyl required for the generation of the acyl-transition metal species, and hence only a limited number of synthetic applications has been reported. In addition to the acyl-transition metals complexes described, acyl-samarium, -chromium, and -tin compounds show attractive reactivity as acyl group donors [18].

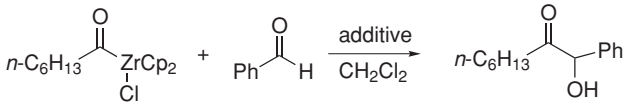


Scheme 5.11. Acylmetal as an "unmasked" acyl anion donor.

To replace the aforementioned acyl-main group and acyl-transition metal complexes, the natural course of events was to search for a stable and easy-to-handle acyl-metal complex that reacts as an "unmasked" acyl anion donor. Thus, the salient features of acylzirconocene chlorides as "unmasked" acyl anion donors remained to be explored. In the following, mostly carbon–carbon bond-forming reactions with carbon electrophiles using acylzirconocene chlorides as acyl group donors are described.

5.4.2
Reaction with Aldehydes

Synthetic routes to α-ketol through the reactions of an "unmasked" acyl anion with carbonyl compounds are not numerous. The first practical application of an acylzirconocene chloride as an "unmasked" acyl anion donor was reported in the reaction with aldehydes in 1998 (Scheme 5.12 and Table 5.1) [19].

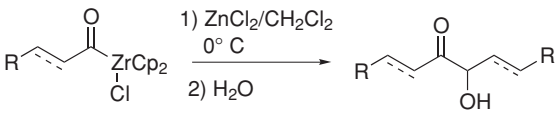


Ag salt	yield (%)	Lewis acid	yield
$AgBF_4$	22	$BF_3 \cdot OEt_2$	79
$AgAsF_6$	34	$ZnCl_2$	58
		$TiCl_4$	60
		$TiCl_2(O\textit{i}\text{-}Pr)_2$	25
		$AlCl_3$	9

Scheme 5.12. Formation of α-ketol.

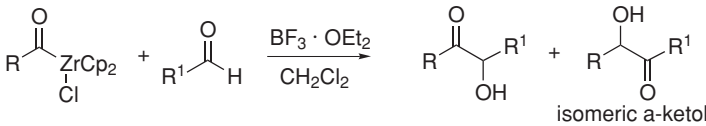
The reactivity of acylzirconocene chlorides towards carbon electrophiles is very low, and no reaction takes place with aldehydes at ambient temperature. In the reaction described in Scheme 5.12, addition of a silver salt gave the expected product, albeit in low yield (22–34 %). The yield was improved to 79 % by the use of a stoichiometric amount of boron trifluoride etherate ($BF_3 \cdot OEt_2$) (1 equivalent with respect to the acylzirconocene chloride) at 0 °C. Other Lewis acids, such as chlorotitanium derivatives, zinc chloride, aluminum trichloride, etc., are less efficient. Neither ketones nor acid chlorides react with acylzirconocene chlorides. In Table 5.1, $BF_3 \cdot OEt_2$-mediated reactions of acylzirconocene chlorides with aldehydes in CH_2Cl_2 are listed.

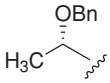
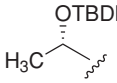
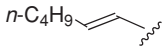
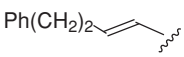
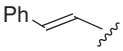
The steric bulk of the alkyl group of the aldehyde severely impedes the reaction, and no reaction takes place with pivaldehyde. Isomeric α-ketol is occasionally isolated as a side product (entries 1, 2) or as a major product (entries 3, 7), while the reactions of α,β-unsaturated acylzirconocene chlorides do not give the isomeric α-ketol products (entries 8–12). Although the precise mechanism for the formation of the isomeric α-ketol is not clear, it has also been reported in the reaction of acylsamarium with aldehydes [18c]. Reactions of α-alkoxy aldehydes with acylzirconocene chlorides preferentially give the 1,2-*syn* product (*syn/anti* ratio ranging from 3.5 to 5.4) (entries 4, 5). Treatment of acylzirconocene chlorides with $ZnCl_2$ at 0 °C without adding an aldehyde affords the α-ketol derived from the acylzirconocene chloride (Scheme 5.13). This might suggest that transmetalation with $ZnCl_2$ giving an acylzinc derivative is partly involved. The facile isomerization of acylzinc to an oxy-carbene intermediate and formation of the α-ketol product through self-coupling have been suggested [16q].



Scheme 5.13. $ZnCl_2$-mediated reaction.

Table 5.1. α-Ketol formations.



Entry	R	Conditions a	R^1	Yields (%) b	isomer
1	*n*-C_6H_{13}	A	$Ph(CH_2)_2$	49 c	29 c
2	"	A	*p*-$MeOC_6H_4$	62 c	18 c
3	"	A	(*E*)-PhCH=CH	—	59 c
4	"	A		53 c, d	—
5	"	A		77 c, e	—
6	$BnO(CH_2)_4$	B	Ph	74 f	—
7		B	(*E*)-CH_3CH=CH	22 f	53 f
8		B	Ph	69 f	—
9		B	Ph	43 f	—
10		B	Et	48 f	—
11		B	Ph	65 f	—
12		B	$Ph(CH_2)_2$	60 f	—

a A ; Alkene or alkyne : Cp_2ZrHCl : R^1CHO : additive = 4 : 2 : 1 : 2. B; Alkene or alkyne : Cp_2ZrHCl : R^1CHO : additive = 1 : 1.5 : 2 : 2.

b Isolated yield.

c Based on aldehyde.

d *syn/anti* = 5.4.

e *syn/anti* = 3.5.

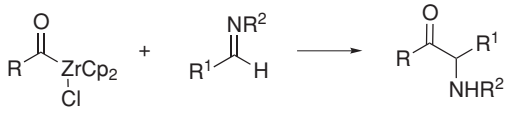
f Based on alkene or alkyne.

Thus, the involvement of one of the following three possible mechanisms has been suggested: (i) nucleophilic addition of the acylzirconocene chloride to the Lewis acid activated aldehyde, (ii) nucleophilic addition of the cationic species of the acylzirconocene chloride formed by an Ag(I) salt or a Lewis acid, or (iii) transmetalation of the acylzirconocene chloride with the Lewis acid and subsequent nucleophilic addition.

5.4.3 Reactions with Imines

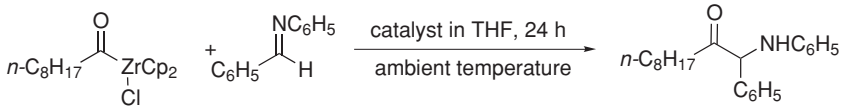
5.4.3.1 $Yb(OTf)_3$/TMSOTf-catalyzed reactions

An extension of the strategy described for the reaction with aldehydes (Section 5.4.2) to imine derivatives might be expected to yield α-amino ketone compounds (Scheme 5.14), which are the constituents of a variety of biologically important molecules.



Scheme 5.14. Formation of α-amino ketones.

However, the use of a stoichiometric amount of a Lewis acid, such as $BF_3 \cdot OEt_2$, $TiCl_4$, TMSOTf, or $AlCl_3$, in the reaction of *N*-benzylideneaniline with an acylzirconocene chloride fails to yield an α-amino ketone (Scheme 5.15). Lanthanide Lewis acids, which have been reported to be efficient in the Mannich-type reaction of imine derivatives with ketene silyl acetal [20], are efficient catalysts for the intended reaction [21]. In the presence of $Yb(OTf)_3$ (20 mol%), the reaction proceeds slowly at ambient temperature in THF (72 h) to give the α-amino ketone in 23 % yield (Scheme 5.15). At higher temperature (50 °C), the α-amino ketone is obtained in 53 % yield in a short period (8 h). However, under the heating conditions, a longer reaction period (> 8 h) tends to yield a contaminated reaction mixture. Using the catalytic system (20 mol%, $Yb(OTf)_3$/TMSOTf, 1:1), which has been reported to be an efficient catalyst for ene reactions of imine derivatives [22], the reaction proceeds at ambient temperature in 24 h to give the α-amino ketone in 64 % yield. A higher ratio of TMSOTf to $Yb(OTf)_3$ (5:1) is less efficient, while the use of TMSCl as a substitute for TMSOTf gives the product in a comparable yield (63 %). The use of scandium triflate [$Sc(OTf)_3$] (20 mol%) in place of $Yb(OTf)_3$ leads to similar efficiency. In the $Yb(OTf)_3$/TMSOTf-catalyzed reactions, use of THF as the solvent is crucial since the

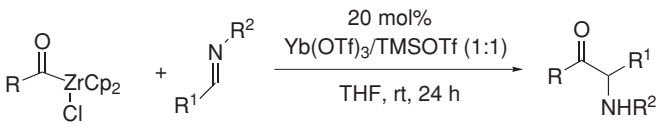


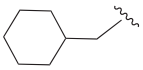
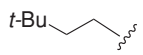
20 mol % catalyst	yield (%)
$BF_3 \cdot OEt_2$[a]	—
$TiCl_4$	—
$AlCl_3$	—
$Sc(OTf)_3$	23
$Yb(OTf)_3$	23[b](53)[c]
$Yb(OTf)_3$/TMSOTf (1 : 1)	64
$Yb(OTf)_3$/TMSOTf (1 : 5)	51
$Yb(OTf)_3$/TMSCl (1 : 1)	63

[a] Stoichiometric amount. [b] Ambient temperature, 72 h
[c] 50 °C, 8 h.

Scheme 5.15. Lewis acid-catalyzed formation of an α-amino ketone.

Table 5.2. $Yb(OTf)_3$/TMSOTf (20 mol%, 1:1)-catalyzed reactions of acylzirconocene chlorides with imines.



Entry	R	R^1	R^2	Yield (%) a
1	*n*-C_8H_{17}	C_6H_5	C_6H_5	64
2	"	*p*-$CF_3C_6H_4$	C_6H_5	54
3	"	*p*-$CH_3OC_6H_4$	C_6H_5	65
4	"	*o*-$CH_3OC_6H_4$	C_6H_5	37
5	"	1-Naphthyl	C_6H_5	41
6	"	C_6H_5	*p*-$CF_3C_6H_4$	51
7	"	C_6H_5	*p*-CF_6H_4	55
8	"	*cy*-C_6H_{11}	C_6H_5	< 10
9	"	*t*-Bu	C_6H_5	—
10		C_6H_5	C_6H_5	59
11		"	"	41

a Isolated yield.

use of a different solvent either retards the reaction (CH_2Cl_2, CH_3CN) or renders it complex (DMF, DME). Thus, $Yb(OTf)_3$/TMSOTf (20 mol%, 1:1) in THF is the catalyst system of choice for the reactions.Results of the $Yb(OTf)_3$/TMSOTf (20 mol%, 1:1)-catalyzed reactions of imine derivatives with acylzirconocene chlorides in THF are listed in Table 5.2. The reaction of the acylzirconocene chlorides is restricted to derivatives of *N*-benzylideneaniline. Indeed, imine derivatives derived from cyclohexanecarbaldehyde or pivaldehyde with aniline give products in yields of less than 10 % (entries 8 and 9, Table 5.2).

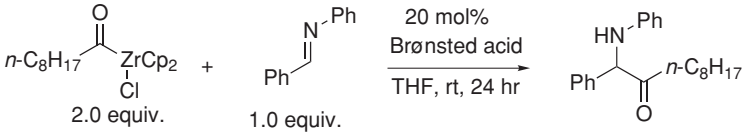
Although the reactivity of acylzirconocene chlorides towards imine derivatives under $Yb(OTf)_3$/TMSOTf (20 mol%, 1:1)-catalyzed conditions is not necessarily very high, the direct access to α-amino ketone derivatives indicates the usefulness of acylzirconocene chlorides as "unmasked" acyl anion donors.

5.4.3.2 **Brønsted acid-catalyzed reactions with imines**

The reactions of acylzirconocene chlorides with imines also proceed under Brønsted acid-catalyzed conditions, even with aqueous acids (Table 5.3) [23].

In the reactions of *N*-benzylideneaniline with acylzirconocene chlorides catalyzed by phenol derivatives, the yield of the α-amino ketone increases markedly with increasing acidity of the phenol derivative (entries 1–3). Addition of a catalytic amount of a Brønsted acid besides the phenol derivative, such as CF_3SO_3H, HCl (g), 35 % aq. HCl, or 50 % aq. $HClO_4$, gives the product α-amino ketone in good yield (entries 5–8). These rather surprising results open a new application of acylzirconocene chlorides, since the ease of their hydrolysis to aldehydes in aqueous acidic media is well known [2]. An *N*-phenyl group is necessary to perform the reaction. Under 20 mol% HCl/THF (0.5 M solution)-catalyzed conditions (Table 5.4), the imine derived from cyclohexane carboxaldehyde and aniline gives the α-amino ketone in 57 % yield (entry 4), which could not be obtained

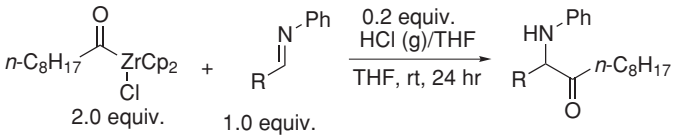
Table 5.3. Brønsted acid-catalyzed reactions.



Entry	Brønsted acid	pK_a	Yield (%) a	Entry	Brønsted acid	pK_a	Yield (%) a
1	PhOH b	10.0	9	5	aq. HCl (36%)	–7	70
2	*p*-NO_2PhOH	7.2	17	6	CF_3SO_3H	–16	72
3	2,4-$(NO_2)_2$-PhOH	4.0	62	7	aq. $HClO_4$ (60%)	–10	55
4	picric acid	0.3	24	8	HCl (gas)		80

a Isolated yield based on imine.
b 1.0 equiv.

Table 5.4. 0.2 equiv. HCl(g)/THF (0.5 M)-catalyzed reaction.

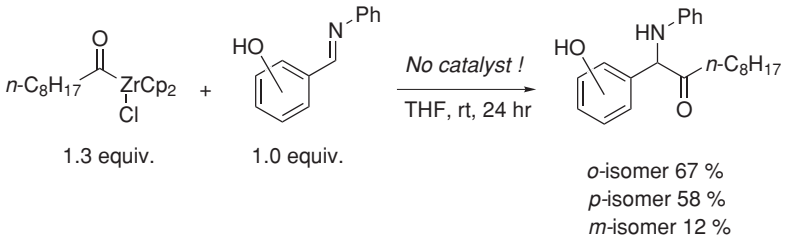


Entry	R	Yield (%) a
1	Ph	80
2	*p*-CH_3OPh	80
3	*p*-NO_2Ph	49
4	*c*-C_6H_{11}	57

a Isolated yield based on imine.

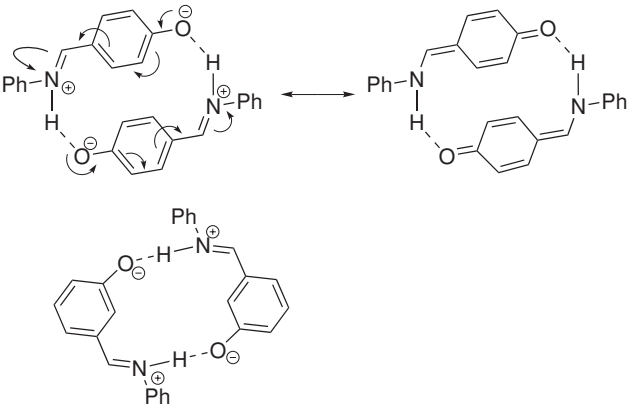
by means of the $Yb(OTf)_3$/TMSOTf-catalyzed reaction. This observation suggests that the protonation of imine derivatives has a significant effect on the reaction.

It is interesting to note that the reaction of *N*-salicylideneaniline, which possesses a free phenolic hydroxyl group at the *ortho* position in the benzylidene portion, with the acylzirconocene chloride gives the α-amino ketone in 67 % yield *in the absence of any additive* (Scheme 5.16) [23]. Similarly, *N*-(*p*-hydroxybenzylidene)aniline reacts with the acylzirconocene chloride to give the α-amino ketone in 58 % yield. The reaction of *N*-(*m*-hydroxybenzylidene)aniline, however, gives the α-amino ketone in just 12 % yield. Neither *N*-(*o*-MeO-benzylidene)aniline nor *N*-(*p*-MeO-benzylidene)aniline gives an appreciable amount of product *in the absence of additive*.



Scheme 5.16. Reactions of hydroxylated benzylideneanilines.

These results also indicate that the protonation of the imine group is important for the reaction. In the *o*-OH and *p*-OH isomers, resonance between the protonated imine and quinoido species would contribute in facilitating the protonation of the imine portion (Scheme 5.17). In the *m*-OH isomer, however, no such resonance contribution is possible. Thus, the poor additive effect of phenol in the reaction of *N*-benzylideneaniline with the acylzirconocene chloride (entry 1, Table 5.3) might imply less efficient protonation of the imine, as in the case of the *m*-OH isomer (Scheme 5.16).

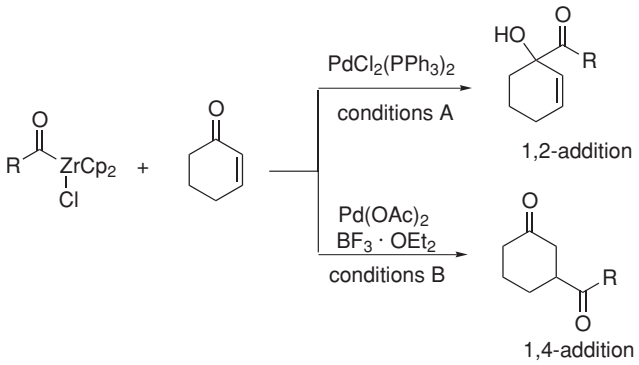


Scheme 5.17. Intermolecular protonation of *p*- and *m*-isomers.

5.4.4 Reactions with α,β-Unsaturated Ketones

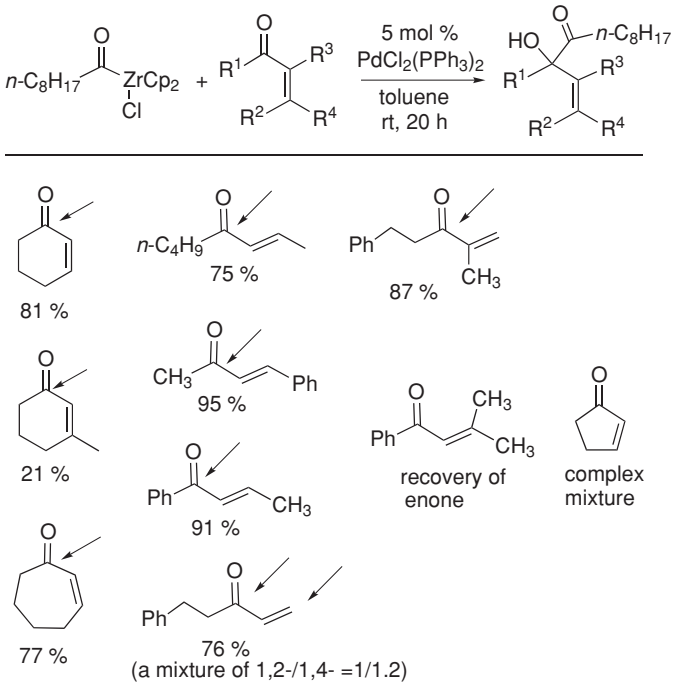
5.4.4.1 1,2- and 1,4-Selective additions to α,β-enone derivatives

Michael-type reaction of an "unmasked" acyl anion by utilizing acyl-metals is a practical procedure for the preparation of 1,4-dicarbonyl compounds and many acyl-metals have been examined for this purpose [17]. The reactions of acylzirconocene chlorides with cyclohexenone in the presence of a palladium catalyst proceed efficiently to give acylated products (Scheme 5.18). Importantly, *the regioselectivity (1,2- or 1,4-selectivity) can be efficiently controlled by the choice of the catalytic system*. The triphenylphosphane ligand tends to selectively afford a 1,2-addition product [$PdCl_2(PPh_3)_2$ (5 mol%) in toluene at ambient temperature (conditions A)], while the presence of an equivalent amount of a Lewis acid [$Pd(OAc)_2$ (10 mol%)/$BF_3 \cdot OEt_2$ in Et_2O/THF (2:1) at 0 °C (conditions B)] yields a 1,4-addition product (Michael-type product) [24]. Other Lewis acids, such as $ZnCl_2$, $MgBr_2$, and $EtAlCl_2$, can also efficiently promote the 1,4-addition. The bidentate bis(phosphane) ligand gives less satisfactory yields and regioselectivities. Among nickel complexes, $Ni(acac)_2$ shows a similar efficiency to $Pd(OAc)_2$. Other Ni complexes [$NiCl_2$(dppf), $NiCl_2(PPh_3)_2$, and $Ni(PPh_3)_4$] are ineffective. Cu(I) is also a catalyst of choice for the 1,4-selective addition of acylzirconocene chlorides to α,β-enones, although a higher temperature (40 °C) is required [25].

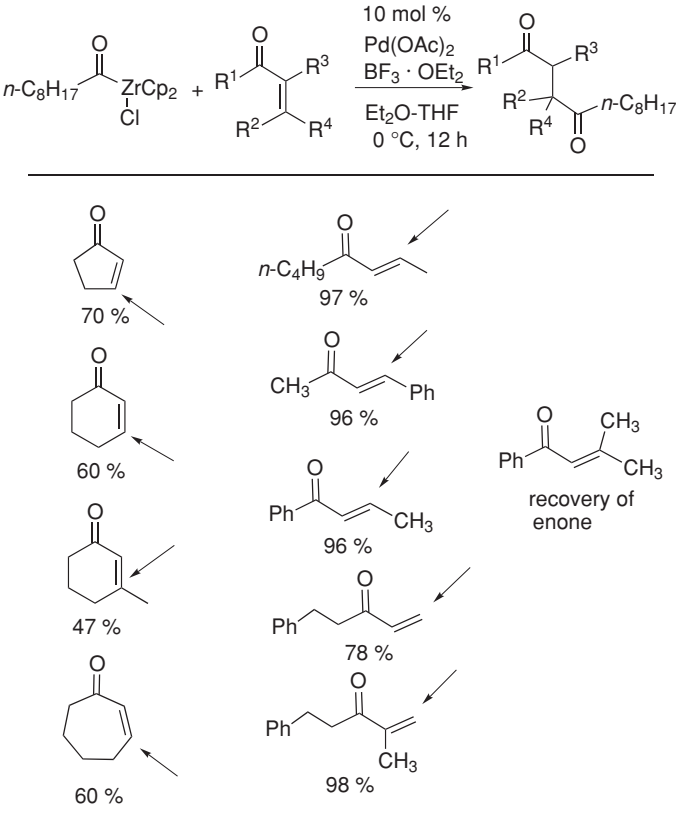


Scheme 5.18. Regioselective nucleophilic acylation.

The Pd-catalyzed regioselective reactions of acylzirconocene chlorides with α,β-enone compounds are quite general, and most products are obtained with good to excellent regioselectivities and in high yields (Schemes 5.19 and 5.20). The reaction of cyclopentenone gives a complex mixture under conditions A (Scheme 5.19), while the 1,4-product is obtained in good yield under conditions B (Scheme 5.20). β,β-Disubstitution of α,β-unsaturated ketones retards the formation of not only the 1,4-adduct but also the 1,2-adduct. Concomitant formation of a small amount (< 5 %) of diketone derived from coupling of the acylzirconocene chloride under both reaction conditions (A and B) and the fact that $Pd(PPh_3)_4$ can be used as a catalyst indicate the participation of the Pd(0) complex in the catalytic cycle (Scheme 5.21). The unreactivity of α,β-unsaturated esters, γ,δ-unsaturated ketones, and saturated ketones indicates that an α,β-unsaturated ketone skeleton is essential.

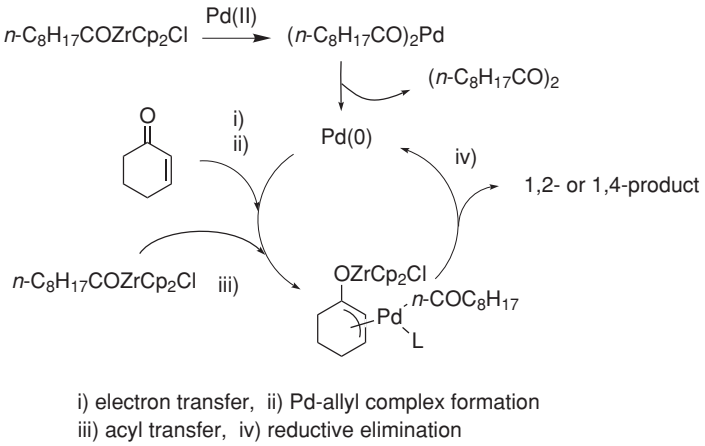


Scheme 5.19. $PdCl_2(PPh_3)_2$-catalyzed 1,2-selective acylation (Conditions A).

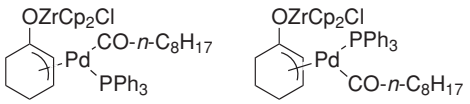


Scheme 5.20. $Pd(OAc)_2$/$BF_3 \cdot OEt_2$-catalyzed 1,4-selective acylation (Conditions B).

Thus, (i) electron transfer from Pd(0) to cyclohexenone, for example, (ii) Pd–allyl complex formation, (iii) transmetalation forming an acylpalladium complex, and (iv) reductive elimination of Pd(0), would give either a 1,2- or a 1,4-acylation product [26] (Scheme 5.21). The role of the triphenylphosphane ligand in the regioselective formation of a 1,2-acylation product may be explained by the preferred formation of a stereochemically less crowded intermediate complex **A** (Scheme 5.22) and subsequent reductive elimination of Pd(0).



Scheme 5.21. Catalytic cycle for the regioselective acylation.



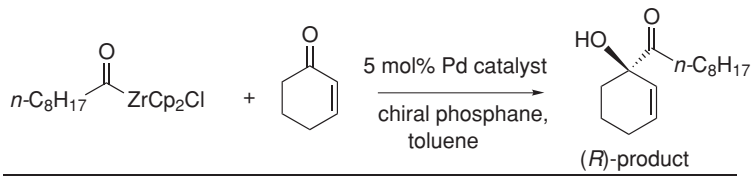
Scheme 5.22. Isomeric complexes.

Although the mechanism responsible for the alteration in the regioselectivity on changing the palladium catalyst from $PdCl_2(PPh_3)_2$ to $Pd(OAc)_2/BF_3 \cdot OEt_2$ remains to be clarified, $BF_3 \cdot OEt_2$ might exert an electronic or a steric effect by coordinating to the assumed acyl π-allyl complex intermediate.

5.4.4.2 **Enantioselective 1,2-selective addition to α,β-enone derivatives**

In the reactions of acylzirconocene chlorides with α,β-enone derivatives described in Section 5.4.4.1, the triphenylphosphane ligand exerts a significant influence on regioselectivity, favoring 1,2-selectivity. This leads to an enantioselective version of the 1,2-acylation through the use of a chiral phosphane ligand [27]. In this way, the first enantioselective additions of an "unmasked" acyl anion to carbonyl compounds have been achieved, and the results of Pd(II)-catalyzed reactions of an acylzirconocene chloride with cyclohexenone in the presence of chiral phosphane ligands are shown in Table 5.5. All these reactions were carried out by utilizing 5 mol% of palladium catalyst and a chiral phosphane ligand (Pd:P = 1:2).

Table 5.5. Enantioselective formation of an (*R*)-1,2-product.

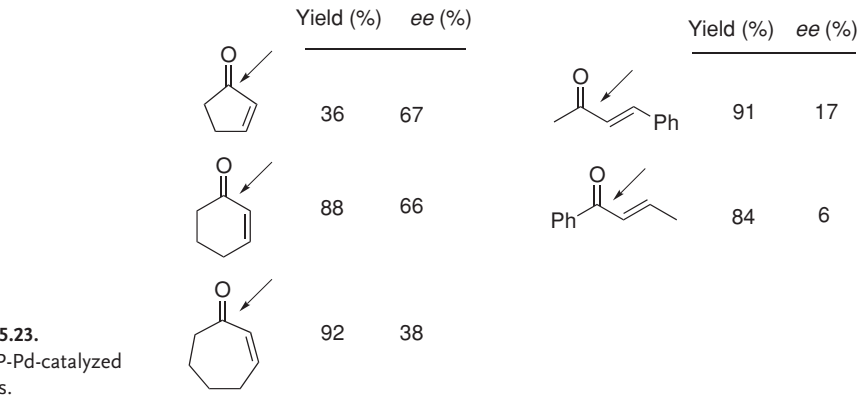


Pd catalyst	Phosphane a	Yield (%) b	ee (%) c
$PdCl_2$[(*R*)-BINAP]	—	19	—
$Pd(OAc)_2$	(*R,R*)-CHIRAPHOS	14	—
$Pd(OAc)_2$	(+)-NMDPP	81	—
$Pd(OAc)_2$	(*R*)-MOP	88	66
$PdCl_2(PPh_3)_2$	(*R*)-MOP	90	12
$PdCl_2(CH_3CN)_2$	(*R*)-MOP	86	64
$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	(*R*)-MOP	48	56
$Pd_2(dba)_3 \cdot CHCl_3$	(*R*)-MOP	70	64

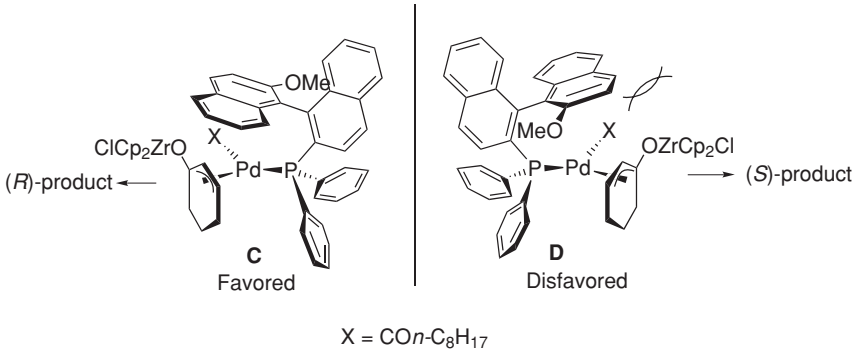
a Pd/P=1/2.
b Isolated yield.
c Determined by HPLC using Chiralcel AD column after derivatization to benzoyl ester.

As can be deduced from the results described in Section 5.4.4.1, chiral bidentate bis(phosphane) ligands such as (*R*)-2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl [(*R*)-BINAP] [28] and (2*R*,3*R*)-bis(diphenylphosphanyl)butane [(*R,R*)-CHIRAPHOS] [29], are ineffective in the reaction. A chiral monodentate phosphane ligand, (*R*)-2-(diphenylphosphanyl)-2′-methoxy-1,1′-binaphthyl [(*R*)-MOP] [30], shows considerable efficiency in chiral induction to give the (*R*)-product (66 % *ee*, 88 % yield). No significant differences between (*R*)-MOP and its derivatives (BnO-, *i*PrO-, or TBDMSO-(*R*)-MOP) [30] were observed in the chiral induction. Interestingly, utilization of the (*R*)-MOP ligand significantly increases the yields of the products and the reaction rate compared to those achieved using the triphenylphosphane ligand. This ligand effect of (*R*)-MOP enables isolation of a 1,2-acylation product (67 % *ee*, 36 % yield) from cyclopentenone (Scheme 5.23), which gives a complex mixture under the $Pd(OAc)_2/PPh_3$ conditions (Scheme 5.19). The use of acyclic α,β-unsaturated ketones is ineffective in the chiral induction, although excellent chemical yields and regioselectivities are obtained (Scheme 5.23).

Based on the discussed acylpalladium π-allylic complex (Scheme 5.22) and the reported X-ray structure of the (*R*)-MOP−Pd π-allylic complex [31], the acylpalladium−(*R*)-MOP π-allylic complex **C** (Scheme 5.24) is proposed for the formation of the (*R*)-product. Complex **D**, which would give the (*S*)-product, suffers from steric compression between the MeO-naphthyl ring and the acyl group, while there is no such steric interaction in complex **C**. Thus, reductive elimination of Pd(0) from **C** would preferentially yield the



Scheme 5.23. (*R*)-MOP-Pd-catalyzed reactions.

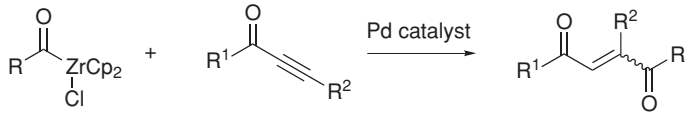


Scheme 5.24. Complexation of (*R*)-MOP ligand.

(*R*)-product. Although there is still room for further improvement of the enantioselectivity, this first example of an enantioselective reaction with α,β-unsaturated ketones reveals the potential of acylzirconocene chlorides as "unmasked" acyl anion donors.

5.4.4.3 1,4-Selective addition to α,β-ynone derivatives

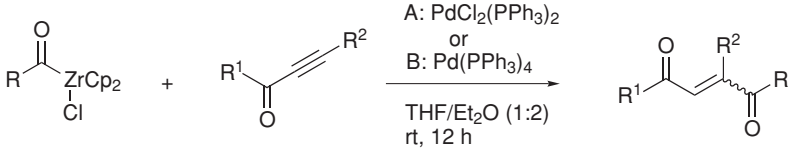
α,β-Ynones also act as good Michael acceptors with acylzirconocene chlorides. The Pd-catalyzed reactions lead to 1,4-selective acylation and offer a facile access to cyclopentenone derivatives (Schemes 5.25 and 5.28) [32].

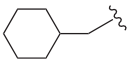
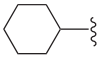
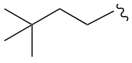


Scheme 5.25. Pd-catalyzed reactions of α,β-ynones.

The $PdCl_2(PPh_3)_2$-catalyzed (5 mol%) reaction of *n*-nonanoylzirconocene chloride with 1-phenylhept-2-yn-1-one leads to selective formation of the 1,4-acylation product in 85 % yield with a slight preference for the *Z*-isomer ($E/Z = 1/2.4$). A trace amount

Table 5.6. Pd-catalyzed reactions of α,β-ynones with saturated acylzirconocene chlorides.

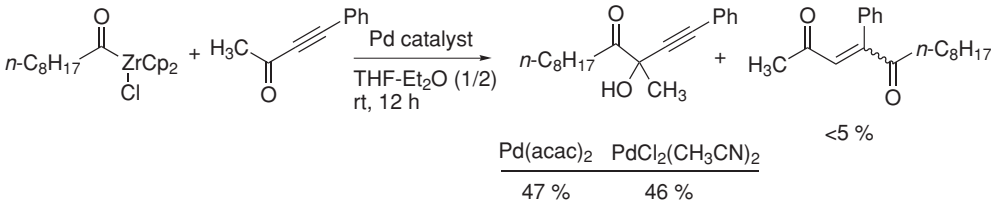


Entry	R	R^1	R^2	Pd catalyst	Yield (%) a	(*E*/*Z*) b
1	*n*-C_8H_{17}	Ph	*n*-Bu	A	85	(1/2.4)
				B	68	(1/2.4)
2	"	CH_3	*t*-Bu	A	71	(1/3)
				B	77	(1/2)
3	"	CH_3	Ph	A	64	(1/5)
				B	45	(1/3)
4	"	Ph	$BnO(CH_2)_2$	A	59	(1/2)
				B	83	(1/1)
5	"	Ph	*t*-Bu	A	82	(1/1)
				B	95	(1/2.5)
6	"	*t*-Bu	*n*-Bu	A	73	(1/3.5)
				B	73	(1/3)
7		Ph	*n*-Bu	A	70	(1/3)
				B	51	(1/3)
8		"	"	A	54	(1/2.8)
				B	40	(1/4)
9		"	"	A	78	(1/3.6)
				B	71	(1/3)

a Isolated yield based on ynone.
b Determined by ^{1}HNMR.

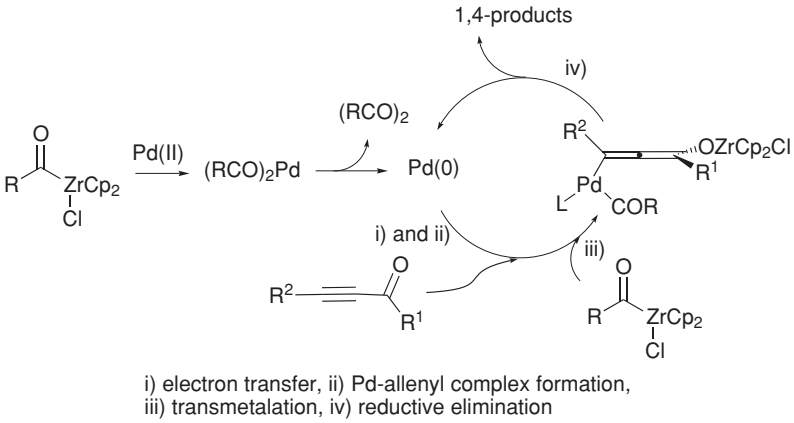
(< 5%) of the diketone generated by homocoupling of the acylzirconocene chloride (entry 1, Table 5.6) is also present. $Pd(PPh_3)_4$ is also an efficient catalyst for this transformation.

In all cases, low *Z*-stereoselectivity of the product and a quite general 1,4-regioselectivity are realized. It is notable that the regioselectivity is unaffected even in the reactions of α,β-ynones that possess a bulky substituent at the β-sp carbon (entries 2 and 5). Use of $Pd(acac)_2$ or $PdCl_2(CH_3CN)_2$ as a catalyst retards the reaction, and the 1,2-adduct is obtained in 40–47% yield together with a small amount (5–15%) of the 1,4-adduct (Scheme 5.26). Attempts to use other catalysts [$PdCl_2$DPPE, $(dba)_3Pd_2\cdot CHCl_3$, $NiCl_2(PPh_3)_2$, $Ni(PPh_3)_4$, $Ni(acac)_2$, and $Ni(COD)_2$] have resulted either in recovery of the starting material or in the formation of a complex mixture.



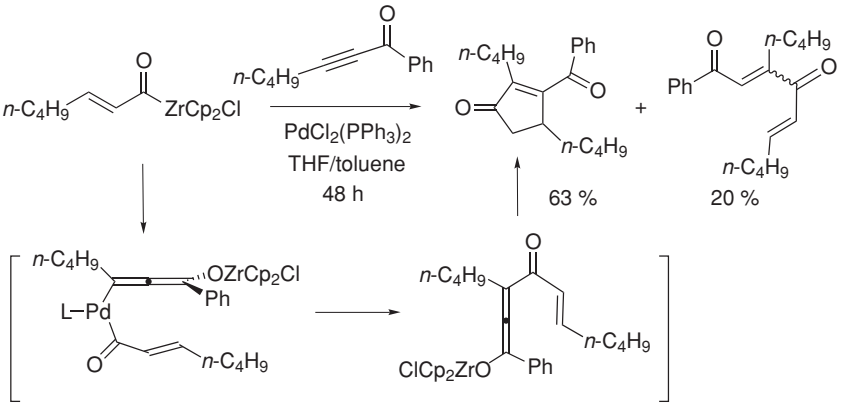
Scheme 5.26. 1,2-Selective reaction of an α,β-ynone.

The regioselectivity seen with α,β-ynones is in remarkable contrast to that observed in the reactions of α,β-*enone* derivatives, for which excellent 1,2-regioselectivity has been achieved by the use of $PdCl_2(PPh_3)_2$ as a catalyst (Section 5.4.4.1) [24]. Ethyl phenylpropiolate and oct-4-yne do not react with acylzirconocene chlorides, while 1-phenylpropynone, a terminal acetylene derivative, gives a complex mixture. Activation of the triple bond by an electron-withdrawing ketone carbonyl group and the absence of an alkynyl hydrogen are prerequisites for the reaction to proceed. In accordance with the facts that $PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$ can be used as efficient catalysts, and that a trace amount of diketone is generated through homocoupling of the acylzirconocene chloride in the $PdCl_2(PPh_3)_2$-catalyzed reaction, a mechanism analogous to that of the Pd-catalyzed reactions of α,β-unsaturated enones with acylzirconocene chlorides (Scheme 5.21) can be assumed, as shown in Scheme 5.27. However, the role of the triphenylphosphane ligand in inducing the 1,4-selectivity is not clear in the present case.



Scheme 5.27. Catalytic cycle for the reactions of α,β-ynones.

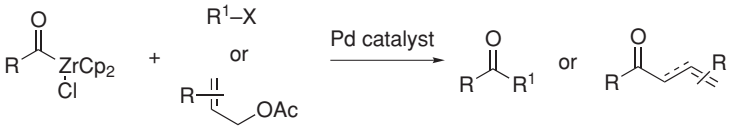
The reactions of α,β-*unsaturated* acylzirconocene chlorides with α,β-ynone compounds under identical conditions give cyclopentenone derivatives in a one-pot sequence (Scheme 5.28). Thus, from a $PdCl_2(PPh_3)_2$-catalyzed reaction of an α,β-*unsaturated* acylzirconocene chloride with an α,β-ynone in THF/toluene for 12 h at ambient temperature, a cyclopentenone derivative is obtained in 37 % yield together with the 1,4-addition product (31 % yield). Prolonged stirring (48 h) of the reaction mixture increases the yield of the cyclopentenone derivative up to 63 %. The formation of a cyclopentenone derivative is considered to be the result of a secondary process of the enolate intermediate, occurring through either an enolate-assisted Nazarov reaction [33] or an intramolecular Michael addition.



Scheme 5.28. Formation of a cyclopentenone compound.

5.4.4.4 **Pd-catalyzed coupling reactions**

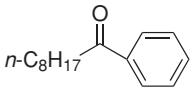
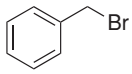
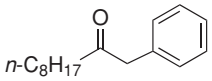
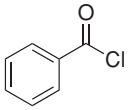
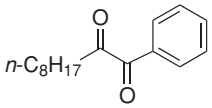
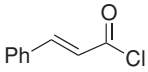
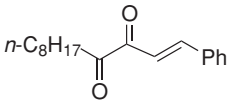
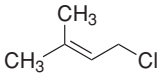
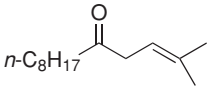
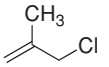
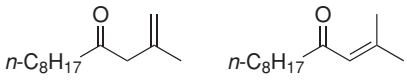
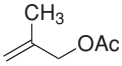
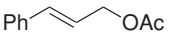
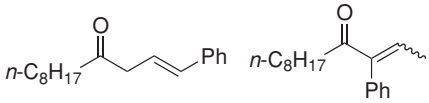
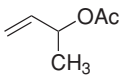
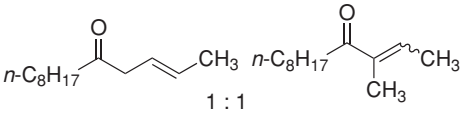
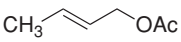
Cross-coupling reactions of acyl-metal species with organic halides have attracted our attention for the synthesis of unsymmetrical ketone derivatives. The cross-coupling reactions of acylzirconocene chlorides with organic halide or allylic acetate derivatives are carried out by utilizing a palladium catalyst (Scheme 5.29) [34]. Among the palladium catalysts examined, $PdCl_2(PPh_3)_2$ is the catalyst of choice. Other catalysts, such as $(Ph_3P)_4Pd$, $PdCl_2(PPh_3)_2$/DIBAL-H, $(CH_3CO_2)_2Pd/PPh_3$, and $PdCl_2$(DPPE), give lower yields of the products. The results of $PdCl_2(PPh_3)_2$ (5 mol%)-catalyzed coupling reactions of *n*-nonanoylzirconocene chloride with organic halides and allylic acetates in toluene at 100 °C are presented in Table 5.7.



Scheme 5.29. Pd-catalyzed cross-coupling of acylzirconocene chlorides.

Coupling with an allylic halide, e. g. methallyl chloride, gives a mixture of the β,γ-unsaturated ketone and the isomerized α,β-unsaturated ketone (1.7:1) (entry 6). The isomerization can be suppressed (to give a 10:1 ratio) by lowering the reaction temperature to 50 °C, although a longer reaction time is required (entry 6). Allylic acetate species are superior reactants to allylic halides. However, the formation of β,γ- and α,β-unsaturated ketones cannot be suppressed (entries 7–10). The reactions of the isomeric allylic acetates, giving mixtures of products in almost identical ratios, suggest that the nucleophilic attack of the acyl anion occurs through a common palladium complex intermediate (entries 9 and 10). Aryl, benzyl, and alkyl halides are poor coupling partners (giving only ~30 % yield) (entries 1 and 2), and vinyl halides are unreactive. α,β-Unsaturated acylzirconocene chlorides also react with allylic acetates under the same reaction conditions, although the yields are lower than with saturated acylzirconocene chlorides.

Table 5.7. $PdCl_2(PPh_3)_2$-catalyzed cross-coupling reactions of *n*-nonanoylzirconocene chloride. a

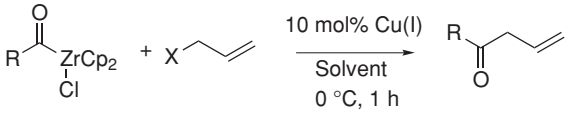
Entry	RX	Product	Yield (%) b
1			32
2			27
3			38 c
4			65 d
5			62
6		 1.7 : 1 10 : 1 e	60
7		3 : 1	86
8		 1 : 5	91
9		 1 : 1	56
10		1.2 : 1	80

a Reaction conditions; 100 °C in toluene.
b Isolated yield.
c Decarbonylated ketone was formed in 11 % yield.
d Reaction conditions; rt for 48 h.
e Reaction conditions; 50 °C for 48 h.

5.4.4.5 Cu-catalyzed cross-coupling reactions

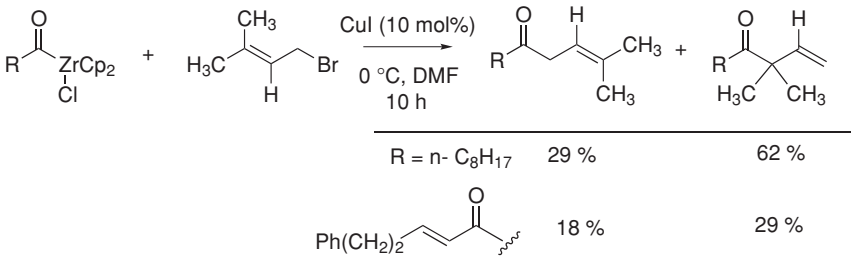
In the Pd-catalyzed cross-coupling reactions of acylzirconocene chlorides with allylic halides and/or acetates (Section 5.4.4.4), the isolation of the expected β,γ-unsaturated ketone is hampered by the formation of the α,β-unsaturated ketone, which arises from isomerization of the β,γ-double bond. This undesirable formation of the α,β-unsaturated ketone can be avoided by the use of a Cu(I) catalyst instead of a Pd catalyst [35]. Most Cu(I) salts, with the exception of $CuBr \cdot SMe_2$, can be used as efficient catalysts. Thus, the reactions of acylzirconocene chlorides with allyl compounds (Table 5.8 and Scheme 5.30) or propargyl halides (Table 5.9) in the presence of a catalytic amount (10 mol%) of Cu(I) in DMF or THF are completed within 1 h at 0 °C to give the acyl–allyl or acyl–allenyl coupled products, respectively, in good yields.

Table 5.8. Cu(I)-catalyzed coupling reactions with allyl halides. a



Entry	R	X	Cu(I)	Solvent	Yield (%) b
1	*n*-C_8H_{17}	Br	CuI	DMF	91
2	"	OTs	CuI	DMF	77
3	"	Cl	CuCl	DMF	44
4	"	Br	CuI · 2LiCl	THF	88
5	"	Br	$CuBr \cdot SMe_2$	THF	trace
6	"	Br	CuBr	DMF	78
7	"	Br	CuCl	DMF	84
8	*n*-C_5H_{11} (*E*)	Br	CuI	DMF	78

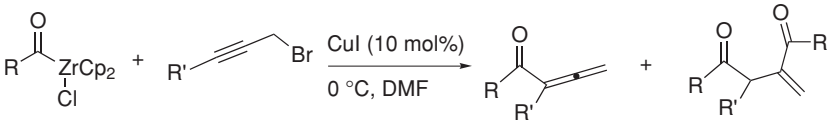
a 1.5 equivalents of acylzirconocene chloride were used.
b Isolated yields based on allylic compounds.



Scheme 5.30. Cu(I)-catalyzed coupling reactions with prenyl bromide.

Allyl tosylate is also an excellent reactant (entry 2, Table 5.8), while allyl acetate is not under Cu(I)-catalyzed conditions. Not only saturated acylzirconocene chlorides, but also α,β-unsaturated acylzirconocene chlorides give coupling products in good yields (entry 8, Table 5.8). Prenyl bromide also reacts with acylzirconocene chlorides under identical conditions to give a mixture of regioisomers (Scheme 5.30). However, a longer reaction time (10 h) is required for the completion of the reaction as compared to the reaction of allyl bromide (1 h).

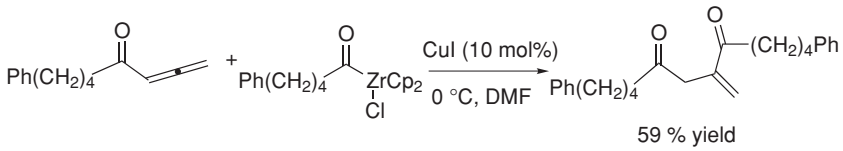
Table 5.9. Cu(I)-catalyzed reaction with propargyl halides.



Entry	R	R'	RCOZr / propargyl halide	allenyl ketone Yield (%)	1,4-dicarbonyl Yield (%)
1	$Ph(CH_2)_4$	H	1.5	65 a	< 5 a
2		H	3.0	24 a	48 a
3		H	0.5	55 b	0
4		Me	0.5	61 b	0
5	$Ph(CH_2)_2$	H	0.5	52 b	0
6		Me	0.5	47 b	0

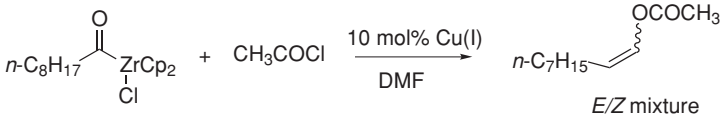
a Isolated yield based on propargyl halide.
b Isolated yield based on acylzirconocene chloride.

The formation of an allenyl ketone as the sole product can be achieved by using an excess (2 equiv.) of propargyl bromide (entries 3–6, Table 5.9). Use of an increased amount (3 equiv.) of the acylzirconocene chloride in the reaction with propargyl bromide and/or tosylate yields a significant amount of a 1,4-dicarbonyl compound derived from Michael-type addition of the acylzirconocene chloride to the initially formed allenyl ketone (entry 2, Table 5.9). The Michael-type addition of acylzirconocene chlorides to allenyl ketones under Cu(I)-catalyzed conditions has been confirmed by an independent experiment (Scheme 5.31).



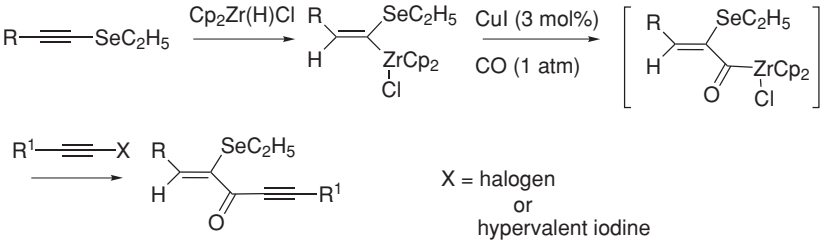
Scheme 5.31. Cu(I)-catalyzed Michael-type addition to an allenyl ketone.

Acetyl chloride reacts with an acylzirconocene chloride under Cu(I) catalysis in DMF to give the corresponding enol acetate as a mixture of *E,Z*-isomeric forms in 40 % yield (Scheme 5.32). This suggests the generation of a metal enolate species through an oxymetal carbene and subsequent 1,2-migration of the hydrogen atom. A similar reaction has been observed in the generation of acylzinc from acyl chloride and Zn in ethyl acetate [16q]. Attempted Cu(I)-catalyzed reactions of acylzirconocene chlorides with alkyl-, vinyl-, homoallyl-, and aryl halides did not afford the coupling products.

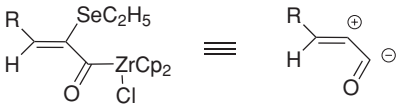


Scheme 5.32. Formation of an enol acetate.

The transmetalation of alkyl or vinylzirconocene complexes with copper has been reported to be an efficient procedure for carbon–carbon bond formation [36]. Thus, transmetalation of the acylzirconocene chloride to copper to give a transient "acyl-Cu" species might have been involved. Copper-catalyzed carbonylative coupling of (*E*)-α-(ethylselanyl)-vinylzirconocene chloride derivatives with alkynyliodonium tosylates has been reported to be a mild method for the preparation of vinyl alkynyl ketones in good yields (Scheme 5.33) [37]. The reaction proceeds via an acylzirconocene chloride species, formed in situ, and the subsequent Cu(I) (3 mol%)-catalyzed coupling reaction with the alkynyliodonium derivative gives the corresponding α-ethylselanyl-substituted vinyl alkynyl ketone derivative. This carbonylative coupling reaction is completed in a short period of time (0.5 h) in THF at ambient temperature. For these coupling reactions, the hypervalent iodine reactant is recommended since the use of the alkynyl halide as a coupling partner requires a longer reaction time, leading to a lower yield of the product. The stereochemistry of the α-(alkylselanyl)vinylzirconocene chloride is maintained during the coupling reaction. Thus, the (*E*)-α-(ethylselanyl)vinylacylzirconocene chloride generated in situ is a synthetic equivalent of an α-cationic acyl anion (Scheme 5.34).



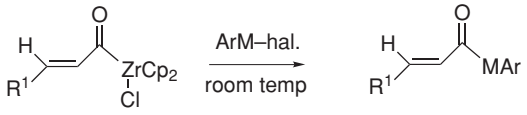
Scheme 5.33. Preparation of vinyl alkynyl ketones.



Scheme 5.34. Formal electronic charge of α-(ethylselanyl)vinylacylzirconocene chloride.

5.4.4.6 Generation of seleno- and telluroesters

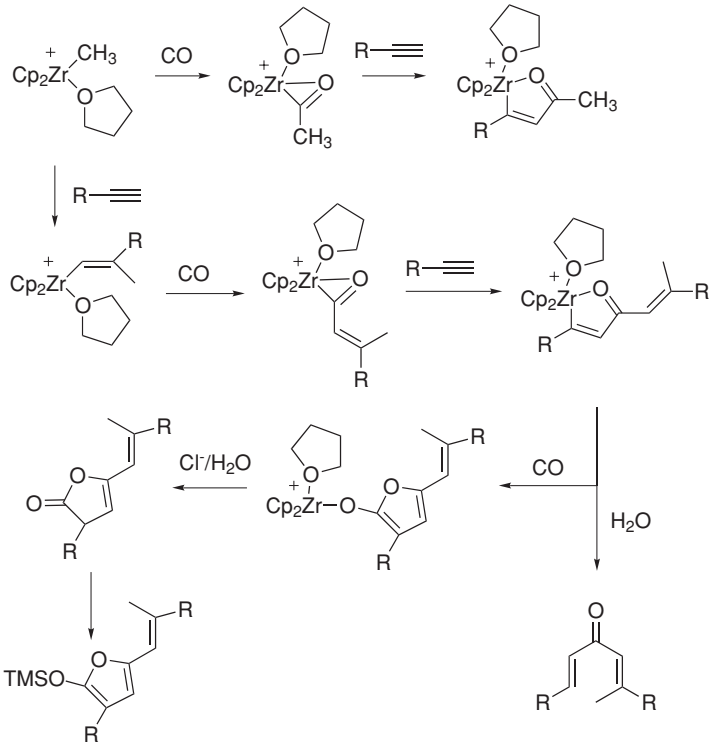
The acyl anion chemistry of acylzirconocene chlorides has also been applied to the stereoselective preparation of (*E*)-α,β-unsaturated selenoesters and telluroesters (Scheme 5.35) [38]. Although no carbon–carbon bond was formed, this reaction reflects the synthetic interest in (*E*)-α,β-unsaturated selenoesters and telluroesters, which are well-known precursors of acyl radicals and acyl anions, respectively.



Scheme 5.35. Formation of acyl-Se and acyl-Te compounds.

5.4.5 Cationic Acylzirconocene Complexes

Cationic η^2-acylzirconocenes $[Cp_2Zr(COR)(L)^+]$ have been reported to show attractive reactivity [39]. A cationic η^2-acylzirconocene can be generated in quantitative yield by treating a cationic zirconocene complex $[Cp_2Zr(R)(L)^+]$ (R = alkyl or alkenyl) with carbon monoxide (<23 °C, 1 atm) (Scheme 5.36). The cationic acylzirconocene complexes undergo regiose-

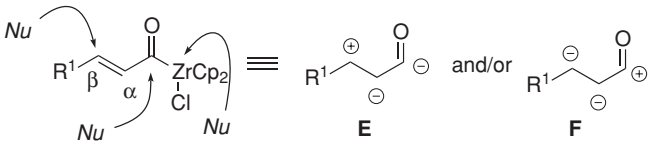


Scheme 5.36. Reactions of cationic acylzirconocene complexes.

lective insertion of terminal and internal alkynes at 23 °C to afford β-ketoalkenyl complexes in nearly quantitative yields. The regioselectivity has been rationalized on the basis of steric/electronic effects. The difference in reactivity between cationic η^2-acylzirconocenes and neutral acylzirconocene chlorides is illustrated by their reactions with unactivated alkynes (as described in Section 5.4.4.3). The utility of these complexes has been exemplified by the formation of α,β-unsaturated ketones, 1,4-divinyl ketones, γ-lactones, and furans (Scheme 5.36). The high insertion reactivity of the cationic zirconocene complexes can be ascribed to the high Lewis acidity of the cationic Zr(IV) centers, which promote coordination and activation of the inserting substrates.

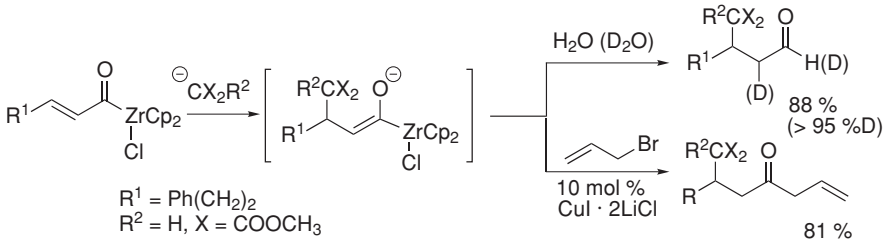
5.5
Reactivity of α,β-Unsaturated Acylzirconocene Chlorides toward Nucleophiles

There are three possible active sites in α,β-unsaturated acylzirconocene chlorides with respect to nucleophiles, namely the β-unsaturated carbon, the acyl carbon, and the Zr–chlorine bond. The reactions of α,β-unsaturated acylzirconocene chlorides with nucleophiles indicate bimodal reactivity (nucleophilic or electrophilic) at both the acyl and β-carbons (Scheme 5.37) [40].



Scheme 5.37. Possible sites of nucleophilic attack and bimodal charge of α,β-unsaturated acylzirconocene chlorides.

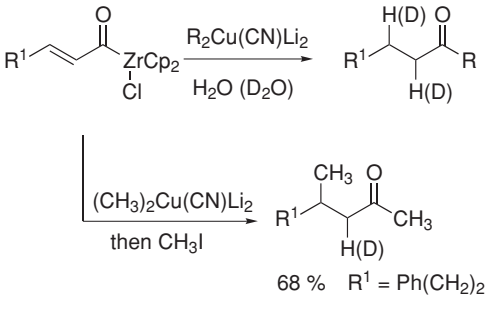
Reactions of α,β-unsaturated acylzirconocene chlorides with stable carbon nucleophiles (sodium salts of dimethyl malonate and malononitrile) at 0 °C in THF afford the Michael addition products in good yields (Scheme 5.38). Direct treatment of the reaction mixture with allyl bromide in the presence of a catalytic amount of CuI · 2LiCl (10 mol%) in THF at 0 °C gives the allylic ketone in a one-pot reaction. This sequential transformation implies the electronic nature of α,β-unsaturated acylzirconocene chloride to be of type **E** as shown in Scheme 5.37.



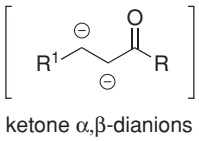
Scheme 5.38. Michael reaction of α,β-unsaturated acylzirconocene chlorides.

A higher-order cyanocuprate, $R_2Cu(CN)Li_2$, reacts with α,β-unsaturated acylzirconocene chlorides at −78 °C in THF to afford saturated ketones without giving a Michael-type product (Scheme 5.39). Treatment of the reaction mixture with D_2O gives the α,β-dideuterated ketone (of undetermined stereochemistry), and generation of a ketone α,β-dianion

equivalent [41] in the reaction medium has been suggested. Thus, the reaction of higher-order cyanocuprate indicates a formal reactivity of α,β-unsaturated acylzirconocene chlorides as described by **F** in Scheme 5.37. Other organometallic reagents (MeLi, Me_2CuLi, and MeMgBr) give either a lower yield of the Michael-type product or a complex mixture (Grignard reagents). The addition of an excess of an organic halide to the reaction mixture (α,β-unsaturated acylzirconocene chloride and $R_2Cu(CN)Li_2$) affords the β-alkylated ketone derivative.



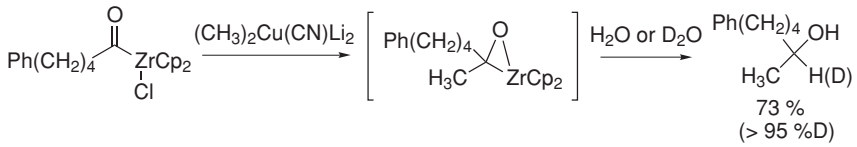
R^1	R	(%)
$Ph(CH_2)_2$	CH_3	69
	n-Bu	70
$TBDPSO(CH_2)_2$	CH_3	58



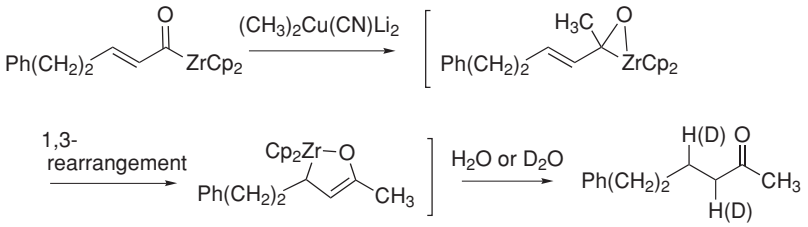
Scheme 5.39. Reactions with higher-order cyanocuprate.

Reaction of *saturated* acylzirconocene chlorides with $(CH_3)_2Cu(CN)Li_2$ gives the secondary alcohol (73 %), and D_2O work-up of the reaction mixture gives the α-deuterio alcohol. This observation suggests the formation of a ketone–zirconocene complex (Scheme 5.40; see also Section 5.3.2.1). Thus, for the reaction of α,β-unsaturated acylzirconocene chlorides with $R_2Cu(CN)Li_2$, initial formation of an unsaturated ketone–zirconocene complex followed by 1,3-rearrangement of the zirconocene moiety to an oxazirconacyclopentene, which is a ketone α,β-bis-carbanion equivalent, has been proposed (Scheme 5.41).

The assumed structures of the ketone–zirconocene and oxazirconacyclopentene complexes have not been established spectroscopically due to the excess of cuprate reagent present. However, as discussed in Section 5.3.2.2, (i) direct nucleophilic addition to the



Scheme 5.40. Reaction of a saturated acylzirconocene chloride with higher-order cyanocuprate.



Scheme 5.41. Reaction of an α,β-unsaturated acylzirconocene chloride with higher-order cyanocuprate.

acyl carbon or (ii) nucleophilic substitution of chloride followed by migration of alkyl to an acyl ligand would be involved in the formation of the ketone–zirconocene complexes. It has been reported that the transmetalation of an allylic zirconocene species with higher-order cyanocuprate generates an allylic cuprate reagent [42]. Thus, an acyl cuprate, which is known to react with α,β-enones to give a Michael-type product, might be involved. However, the addition of excess cyclohexenone to a mixture of a saturated acylzirconocene chloride and $R_2Cu(CN)Li_2$ at −80 °C does not give the Michael-type product. Comparison of the reactivity of stable carbon nucleophiles towards α,β-unsaturated acylzirconocene chlorides with that of $R_2Cu(CN)Li_2$ towards the same substrate clearly demonstrates the dichotomous reactivity at both the β- and acyl carbons in α,β-unsaturated acylzirconocene chlorides (**E** and **F**, Scheme 5.37).

5.6 Conclusion

Recent chemical accomplishments based on acylzirconocene chloride complexes indicate the potential utility of this reagent, not only as a nucleophilic donor of an "unmasked" acyl group but also as a characteristic dichotomous reagent in carbon–carbon bond-forming reactions. Although there have been many reports on the reactions of acylmetal complexes, the ready availability, stability, and notable reactivity of acylzirconocene complexes – especially acylzirconocene chloride complexes – merits their recognition as useful reagents. Further research on the reactivity of acylzirconocene species is anticipated to lead to the discovery of new synthetic applications.

Representative Experimental Procedures

Preparation of *n*-heptanoylzirconocene chloride and reaction with benzaldehyde (Scheme 5.12) To a suspension of $[Cp_2Zr(H)Cl]$ (2.0 mmol) in CH_2Cl_2 (8 mL) under argon was added 1-hexene (4.0 mmol) and the mixture was stirred for 0.5 h at ambient temperature. After stirring the mixture under an atmosphere of CO at ambient temperature for 2 h, benzaldehyde (1.0 mmol) and $BF_3 \cdot OEt_2$ (2.0 mmol) were added at −20 °C, and the resulting mixture was stirred at 0 °C for 1 h. It was then treated with aqueous $NaHCO_3$ solution and extracted with diethyl ether. The combined ethereal extracts were washed with saturated aqueous NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure to give a crude oil. Purification by flash chromatography on silica gel gave 1-hydroxy-1-phenyl-2-octanone in 79 % yield.

Preparation of *n*-nonanoylzirconocene chloride and $Yb(OTf)_3$/TMSOTf (1:1)-catalyzed reaction with *N*-benzylideneaniline (Scheme 5.15) 1-Octene (2.0 mmol) was treated with $[Cp_2Zr(H)Cl]$ (1.3 mmol) in CH_2Cl_2 (4 mL) at ambient temperature for 0.5 h under argon atmosphere, and then the mixture was further stirred under an atmosphere of CO (1 atm) at ambient temperature for 2 h. The solution was subsequently concentrated to dryness in vacuo and the residue was redissolved in THF (6 mL).

To the resulting solution of *n*-nonanoylzirconocene chloride (1.3 mmol) in THF (6 mL) was added a solution of *N*-benzylideneaniline (1 mmol), $Yb(OTf)_3$ (20 mol%), and TMSOTf (20 mol%) in THF (2 mL) at 0 °C, and the mixture was stirred at ambient tem-

perature for 24 h. It was then treated with aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure to give a crude oil. Purification by chromatography on silica gel gave 1-phenyl-1-phenylamino-decan-2-one in 64 % yield.

Pd-Catalyzed 1,2-selective reaction of *n*-nonanoylzirconocene chloride with cyclohexanone (Scheme 5.19) A solution of *n*-nonanoylzirconocene chloride in CH_2Cl_2, prepared from $[Cp_2Zr(H)Cl]$ (1.5 mmol) and 1-octene (2.0 mmol) as described above, was concentrated to dryness in vacuo. The residue was treated with dry toluene (15 mL), cyclohexanone (1 mmol), and $PdCl_2(PPh_3)_2$ (5 mol%) at ambient temperature and the resulting mixture was stirred at the same temperature for 20 h. After extractive work-up as described above, the residual oil was purified by column chromatography on silica gel to give 1-*n*-nonanoyl-2-cyclohexen-1-ol in 81 % yield.

Pd-Catalyzed 1,4-selective reaction of *n*-nonanoylzirconocene chloride with cyclohexanone (Scheme 5.20) To a solution of *n*-nonanoylzirconocene chloride (1.5 mmol) in diethyl ether (10 mL)/THF (5 mL), prepared as described above, were added cyclohexenone (1.0 mmol), $BF_3 \cdot OEt_2$ (1.0 mmol), and $Pd(OAc)_2$ (10 mol%) at 0 °C, and the resulting mixture was stirred at this temperature for 12 h. After extractive work-up as described above, purification by chromatography on silica gel gave 3-*n*-nonanoylcyclohexanone in 60 % yield.

Acknowledgements

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Abbreviations

Acac	acetylacetone
BINAP	2,2-bis(diphenylphosphanyl)-1,1′-binaphthyl
DIBAL-H	diisobutylaluminum hydride
DME	ethylene glycol dimethyl ether
DMF	*N*,*N*-dimethylformamide
dppe	1,2-bis(diphenylphosphanyl)ethane
dppf	1,1′-bis(diphenylphosphanyl)ferrocene
NBS	*N*-bromosuccinimide
Tf	triflyl = trifluoromethanesulfonyl
TBDMS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TMSCl	chlorotrimethylsilane
TMSOTf	trimethylsilyl trifluoromethanesulfonate

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6
Chiral Zirconium Catalysts for Enantioselective Synthesis

Amir H. Hoveyda

6.1
Introduction

Asymmetric catalysis is a vital and rapidly growing branch of modern organic chemistry. Within this context, Ti- and Zr-based chiral catalysts have played a pivotal role in the emergence of a myriad of efficient and enantioselective protocols for asymmetric synthesis. In this chapter, a critical overview of enantioselective reactions promoted by chiral Zr-based catalysts is provided. Since an account of this type is most valuable when it provides a context for advances made in a particular area of research, when appropriate, a brief discussion of related catalytic asymmetric reactions promoted by non-Zr-based catalysts is presented as well.

6.2
Zr-Catalyzed Enantioselective C–C Bond-Forming Reactions

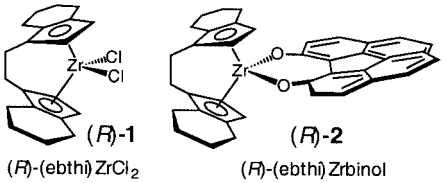
The development of catalytic C–C bond-forming reactions that proceed under mild conditions in an enantioselective fashion (>95 % enantiomeric excess) remains a critical and challenging objective in modern chemical synthesis [1]. As discussed below, Zr-containing chiral catalysts can promote uniquely efficient and highly enantioselective additions of carbon nucleophiles (such as alkylmetals and cyanide) to C=O and C=N bonds; these transformations may be used in the preparation of a wide range of medicinally important agents (e. g., non-proteogenic amino acids). Moreover, Zr-based metallocenes facilitate additions of alkylmetals to C=C bonds [2]; this attribute distinguishes these catalysts from most other classes of chiral catalysts, as although processes that involve alkylmetals and C=O bonds are relatively common, reactions of alkyl metals with alkenes does not easily occur under most circumstances [3]. In addition to the significance of C–C bonds and addressing the need for efficient and selective methods to generate them, alkene alkylations are important partly because the product of the asymmetric addition of an alkylmetal to an alkene is a *chiral* alkylmetal entity that can be further functionalized.

6.2.1

Zr-Catalyzed Enantioselective Alkylation of Alkenes with Grignard Reagents

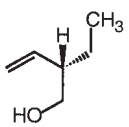
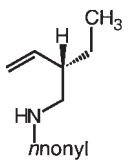
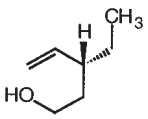
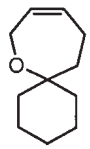
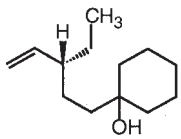
6.2.1.1 Intermolecular catalytic asymmetric alkylations

Chiral C_2-symmetric *ansa*-metallocenes, also referred to as bridged metallocenes, find extensive use as catalysts that effect asymmetric C–C bond-forming transformations [4]. In general, bridged ethylene(bis(tetrahydroindenyl))zirconocene dichloride ((ebthi)$ZrCl_2$) **1** or its derived binaphtholate ((ebthi)Zrbinol) **2** [5] and related derivatives thereof have been extensively utilized in the development of a variety of catalytic asymmetric alkene alkylations.



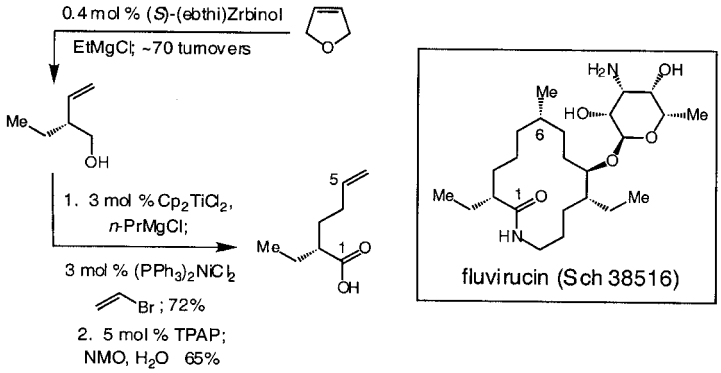
Work in the author's laboratories, which began in 1990, involving the zirconocene-catalyzed addition of Grignard reagents to alkenes (carbomagnesation), resulted in the development of catalytic transformations that are carried out at ambient temperature to afford synthetically useful products with excellent enantiomeric purities. As illustrated in Table 6.1, in the presence of 2.5–10 mol% non-racemic (ebthi)$ZrCl_2$ (or (ebthi)Zrbinol) and EtMgCl as the alkylating agent, five-, six-, and seven-membered unsaturated heterocycles undergo facile asymmetric ethylmagnesation [6].

Table 6.1. (ebthi)Zr-catalyzed enantioselective ethylmagnesation of unsaturated heterocycles[a]

Entry	*Substrate*	*Product*	*ee (%)*	*Yield (%)*
1			> 97	65
2			> 95	75
3			95	73
4			92	75

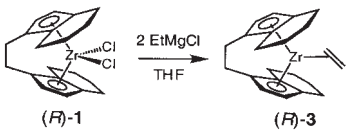
[a] Reaction conditions: 10 mol % (*R*)-**1**, 5.0 equiv. EtMgCl, THF, 22 °C for 6–12 h. Entry 1 with 2.5 mol% (*R*)-**1**.

The rate of catalytic ethylmagnesation of the terminal alkene functions of the reaction products is sufficiently slower, so that unsaturated alcohols and amines can be isolated in high yield (the second alkylation is generally not diastereoselective). The author's group has utilized the stereoselective ethylmagnesation shown in entry 1 of Table 6.1 as a key step in the first enantioselective total synthesis of the antifungal agent fluvirucin (Sch 38516) [7]. As illustrated in Scheme 6.1, further functionalization of the Zr-catalyzed ethylmagnesation product through three subsequent catalytic procedures (Ti-catalyzed hydromagnesation, Ni-catalyzed cross-coupling, and Ru-catalyzed oxidation) delivers the requisite carboxylic acid synthon in >99 % *ee*. This synthesis route underlines the utility of the Zr-catalyzed carbomagnesation protocol: the reaction product bears an alkene and an alcohol function and can thus be readily functionalized to furnish a variety of other non-racemic intermediates.



Scheme 6.1. Demonstration of the utility of (ebthi)Zr-catalyzed ethylmagnesation in the enantioselective synthesis of the macrolactam aglycon of fluvirucin.

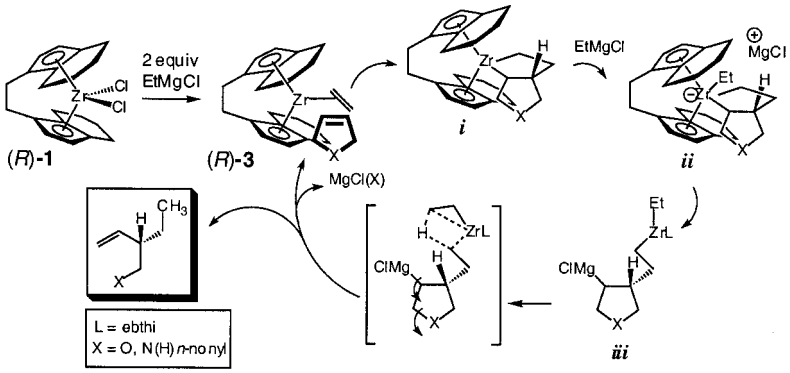
The catalytic cycle proposed to account for the enantioselective ethylmagnesations is illustrated in Scheme 6.2. Asymmetric carbomagnesation is initiated by the chiral zirconocene–ethylene complex (*R*)-**3**, formed upon reaction of dichloride (*R*)-**1** with EtMgCl [Eq. 6.1; the dichloride salt or the binol complex (*R*)-**2** may be used with equal efficiency] [8]. Coupling of the alkene substrate with (*R*)-**3** leads to the formation of the metallacyclopentane intermediate ***i***. In the proposed catalytic cycle, reaction of ***i*** with EtMgCl affords zirconate ***ii***, which undergoes Zr–Mg ligand exchange to yield ***iii***. Subsequent β-hydride abstraction, accompanied by intramolecular magnesium alkoxide elimination, leads to the release of the carbomagnesation product and regeneration of **3** [9].



(Eq. 6.1)

An important aspect of the carbomagnesation of six-membered and larger heterocycles is the exclusive intermediacy of metallacyclopentanes, in which the C–Zr bond is formed α to the heterocycle C–X bond (Scheme 6.2). Whether the regioselectivity in the zircona-

cycle formation is kinetically non-selective and rapidly reversible and only one regioisomer is active in the catalytic cycle, or whether formation of the metallacycle is kinetically selective (stabilization of electron density upon formation of C–Zr bond by the adjacent C–X) [10], has not been rigorously determined. However, as will be discussed below, the regioselectivity with which the intermediate zirconacyclopentane is formed is critical in the (ebthi)Zr-catalyzed kinetic resolution of heterocyclic alkenes.



Scheme 6.2. Catalytic cycle proposed for the (ebthi)Zr-catalyzed ethylmagnesation of unsaturated heterocycles.

Why does the (ebthi)Zr system induce such high levels of enantioselectivity in the C–C bond-formation process? It is plausible that the high enantioselection arises from minimization of unfavorable steric and torsional interactions in the complex formed between **3** and the heterocyclic substrate (Fig. 6.1). The alternative mode of addition, illustrated in Fig. 6.1, would lead to costly steric repulsions between the alkene substituents and the cyclohexyl group of the chiral ligand [6]. Reactions of simple terminal alkenes under identical conditions give little or no enantioselectivity. This is presumably because in the absence of the alkenyl substituent (of the carbon that bonds to Zr in ***i***), the aforementioned steric interactions are less significant and the alkene substrate reacts indiscriminately through the two modes of substrate–catalyst binding represented in Fig. 6.1.

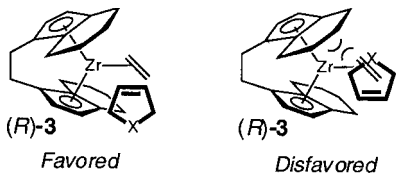
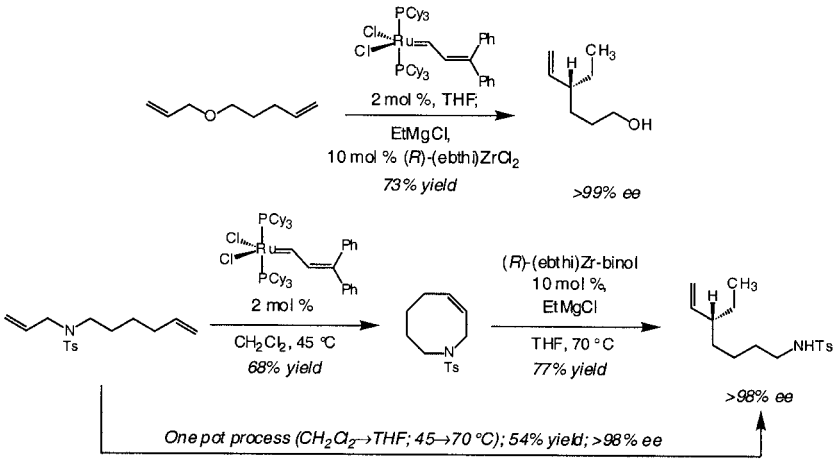


Figure 6.1. Substrate–catalyst interactions favor a specific mode of alkene insertion into the zirconocene–alkene complex.

These alkylation processes become particularly attractive when used in conjunction with powerful catalytic ring-closing metathesis protocols [11]. The requisite starting materials can be readily prepared catalytically and in high yields. The examples shown in Scheme 6.3 demonstrate that synthesis of the heterocyclic alkene and subsequent alkylation can be carried out in a single vessel to afford unsaturated alcohols and amides in good yields and with >99 % *ee* (GLC analysis) [12].



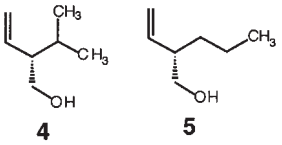
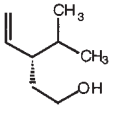
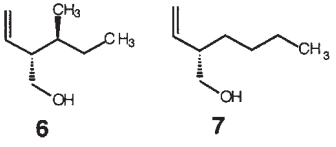
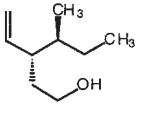
Scheme 6.3. Zr-catalyzed enantioselective ethylmagnesation and metal-catalyzed alkene metathesis make effective partners. In the two cases shown here, the alkene substrate is synthesized and enantioselectively alkylated in the same vessel.

Catalytic alkylations in which higher alkyls of magnesium are used (Table 6.2) proceed less efficiently (35–40 % isolated yield) but with similarly high levels of enantioselection (>90 % *ee*) [9]. A number of issues relating to the data illustrated in Table 6.2 merit comment. (1) With 2,5-dihydrofuran as the substrate, at 22 °C a mixture of branched (**4** or **6**) and *n*-alkyl products (**5** or **7**) is obtained. When the reaction mixture is heated to 70 °C, the branched adducts **4** and **6** become the major product isomers. In contrast, with the six-membered heterocycle, reactions at 22 °C are selective (entries 3 and 6, Table 6.2). (2) With *n*BuMgCl as the alkylating agent, high levels of diastereoselection are again observed (entries 4–6).

The aforementioned observations have significant mechanistic implications. As illustrated in Eqs. 6.2–6.4, in the chemistry of zirconocene–alkene complexes derived from longer chain alkylmagnesium halides, several additional selectivity issues present themselves. (1) The derived transition metal–alkene complex can exist in two diastereomeric forms, exemplified in Eqs. 6.2 and 6.3 by (*R*)-**8** *anti* and *syn*; reaction through these stereoisomeric complexes can lead to the formation of different product diastereomers (compare Eqs. 6.2 and 6.3, or Eqs. 6.3 and 6.4). The data in Table 6.2 indicate that the mode of addition shown in Eq. 6.2 is preferred. (2) As illustrated in Eqs. 6.3 and 6.4, the carbomagnesation process can afford either the *n*-alkyl or the branched product. Alkene substrate insertion from the more substituted front of the zirconocene–alkene system affords the branched isomer (Eq. 6.3), whereas reaction from the less substituted end of the (ebthi)Zr–alkene system leads to the formation of the straight-chain product (Eq. 6.4). The results shown in Table 6.2 indicate that, depending on the reaction conditions, products derived from the two isomeric metallacyclopentane formations can be formed competitively.

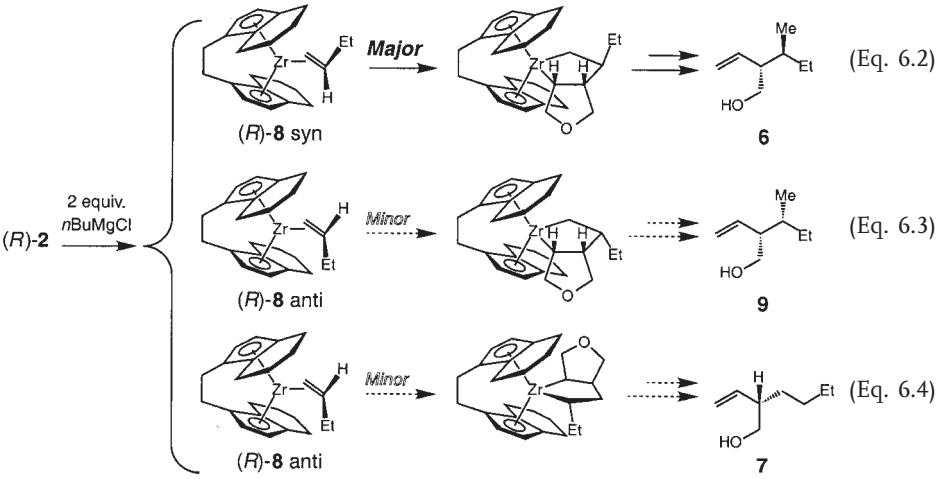
Detailed studies in these laboratories have shed light on the mechanistic intricacies of asymmetric catalytic carbomagnesations, allowing for an understanding of the above trends in regio- and stereoselectivity [9]. Importantly, these mechanistic studies have indicated that there is no preference for the formation of either the *anti* or the *syn* (ebthi)Zr–alkene isomers (e. g. **8** *anti vs.* **8** *syn*); it is only that one metallocene–alkene

Table 6.2. (ebthi)Zr-catalyzed enantioselective carbomagnesation of unsaturated heterocycles with longer chain alkylmagnesium chlorides[a]

Entry	*Substrate*	*Major product(s)*	*Temp (°C)*	*RMgCl*	*Regioselectivity*	*ee, %*	*Diastereoselectivity*
1		 **4** **5**	22	*n*PrMgCl	2 : 1	99 (**4**), 99 (**5**)	–
2			70	*n*PrMgCl	20 : 1	94 (**4**)	–
3			22	*n*PrMgCl	> 26 : 1	98	–
4		 **6** **7**	22	*r*BuMgCl	2 : 1	> 99 (**6**), > 99 (**7**)	15 : 1
5			22	*r*BuMgCl	15 : 1	90 (**6**)	13 : 1
6			22	*n*BuMgCl	> 25 : 1	> 95	> 25 : 1

[a] Reaction conditions: 5 equiv. alkyl-MgCl, 10 mol% (*R*)-**1**, 16 h; all yields: 35–40% after silica gel chromatography.

diastereomer (*syn*) is more reactive. These mechanistic studies have also indicated that zirconacyclopentane intermediates (***i*** in Scheme 6.2) do not undergo spontaneous elimination to give the derived zirconocene-alkoxide; Zr–Mg ligand exchange is likely to be a prerequisite for alkoxide elimination and formation of the terminal alkene.

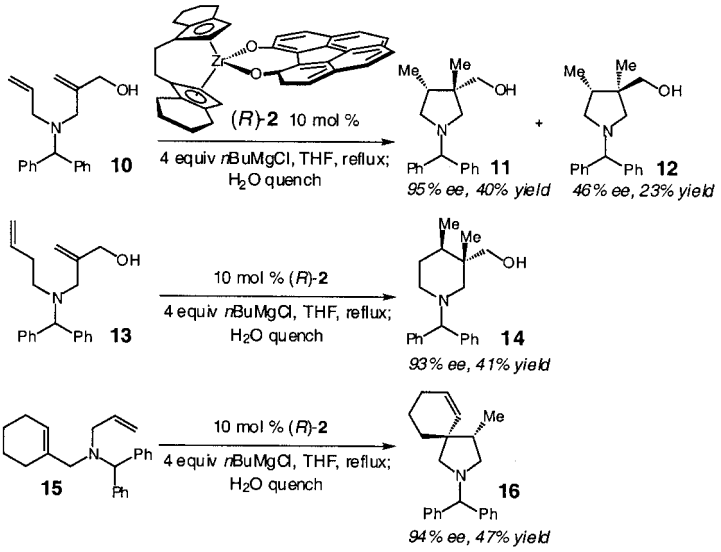


6.2.1.2 **Intramolecular catalytic asymmetric alkylations**

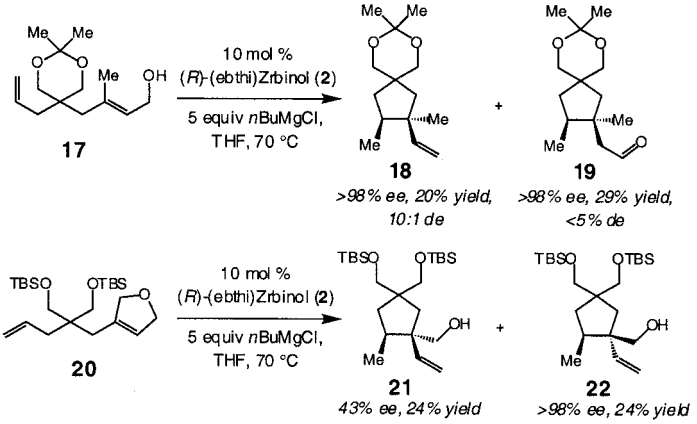
Intramolecular variants of the above Zr-catalyzed enantioselective alkylations have also been reported. As illustrated in Scheme 6.4, Mori and co-workers have reported that treatment of a variety of unsaturated amines leads to enantioselective formation of the corresponding cyclic amines in modest yields, but with high enantioselectivities [13]. Whereas diastereoselectivity is low in the formation of five-membered ring products (e. g. **10** → **11** + **12**, Scheme 6.4), asymmetric generation of the six-membered ring analogues proceeds with excellent levels of enantio- and diastereocontrol (e. g. **14**, Scheme 6.4). There are several noteworthy features of this class of C–C bond-forming reactions. (i) The Zr-catalyzed processes generate quaternary carbon centers enantioselectively [14]. (ii) Surprisingly, reactions involving two terminal alkenes are significantly less efficient and enantioselective.

Intramolecular diene cyclizations involving allylic alcohols and ethers have been under investigation in these laboratories; representative examples are shown in Scheme 6.5 [15]. The reactions are generally less efficient than when Cp_2ZrCl_2 is used as the catalyst, presumably as a result of the greater steric bulk of the tetrahydroindenyl ligand. However, as exemplified by the reaction of **17** (Scheme 6.5), both the olefinic and (remarkably) aldehyde products are formed with high enantioselectivity and olefinic product **18** is generated diastereoselectively. Catalytic asymmetric cyclization of **20**, unlike its reaction with Cp_2ZrCl_2, is non-diastereoselective (1:1 *vs.* 4:1).

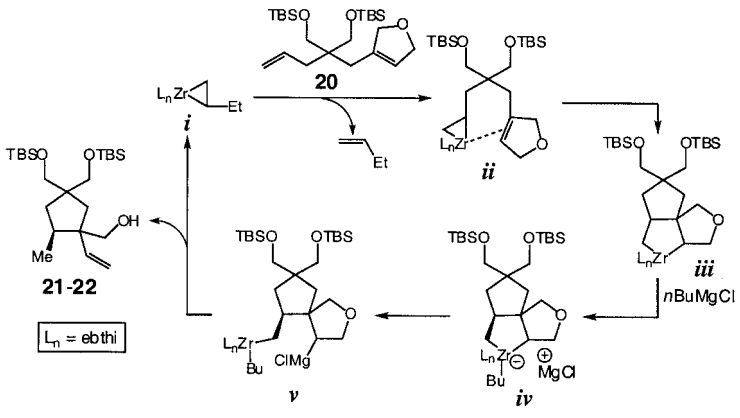
The above intramolecular diene cyclizations are likely to proceed through a similar set of reactions as shown in Scheme 6.2 for the intermolecular variants. Thus, as depicted in Scheme 6.6, formation of the zirconacyclopropane at the less hindered terminal alkene (→ ***ii***), generation of the tricyclic intermediate ***iii***, Zr–Mg exchange through the intermediacy of zirconate ***iv***, and β-H abstraction and Mg alkoxide elimination in ***v*** may lead to the formation of the observed product. Additional kinetic and mechanistic studies are required before a more detailed hypothesis can be put forward.



Scheme 6.4.
Zr-catalyzed enantioselective intramolecular diene cyclization delivers *N*-containing heterocycles having quaternary carbon stereogenic centers.



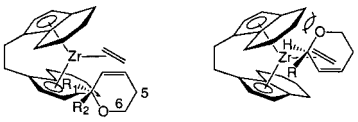
Scheme 6.5.
Zr-catalyzed enantioselective intramolecular diene cyclizations with allylic alcohol and ether substrates afford carbocycles bearing quaternary carbon stereogenic centers; the unexpected formation of the aldehyde product **19** is noteworthy.



Scheme 6.6.
Proposed mechanism for asymmetric Zr-catalyzed diene cyclization; this represents the intramolecular variant of the catalytic carbomagnesation shown in Scheme 6.2.

6.2.2
Zr–Catalyzed Kinetic Resolution of Unsaturated Heterocycles

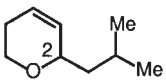
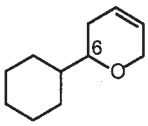
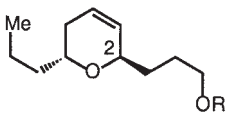
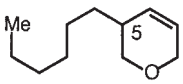
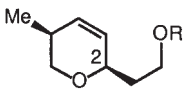
The high levels of enantioselectivity obtained in the asymmetric catalytic carbomagnesation reactions (Tables 6.1 and 6.2) imply an organized (ebthi)Zr–alkene complex interaction with the heterocyclic alkene substrates. When chiral unsaturated pyrans or furans are employed, the resident center of asymmetry may induce differential rates of reaction, such that after ~50 % conversion one enantiomer of the chiral alkene can be recovered in high enantiomeric purity. As an example, molecular models indicate that with a 2-substituted pyran, as shown in Fig. 6.2, the mode of addition labeled as **I** should be significantly favored over **II** or **III**, where unfavorable steric interactions between the (ebthi)Zr complex and the olefinic substrate would lead to significant catalyst–substrate complex destabilization.



I $R_1 = H$, R_2 = alkyl
II R_1 = alkyl, $R_2 = H$
III R = alkyl

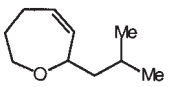
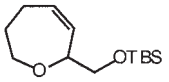
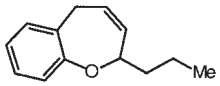
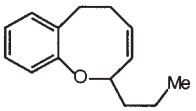
Figure 6.2. Model accounting for preferential association of one pyran enantiomer with the (*R*)-(ebthi)Zr complex.

Table 6.3. (ebthi)Zr-catalyzed kinetic resolution of unsaturated pyrans[a]

Entry	*Substrate*		*Conversion %*	*Mol % cat.*	*Unreacted subs. config., ee (%)*
1			60	10	*R*, 96
2			60	10	*S*, 41
3		**a** R = MgCl **b** R = TBS	56 60	10 10	*R*, > 99 *R*, > 99
4			58	20	*R*, 99
5		**a** R = MgCl **b** R = TBS	63 61	10 10	*R*, > 99 *R*, 94

[a] Reaction conditions: 10 mol% (*R*)-**1**, 5.0 equiv. of EtMgCl, 70 °C, THF. Mass recovery in all reactions is > 85 %.

Table 6.4. Zirconocene-catalyzed kinetic resolution of 2-substituted medium-ring heterocycles[a]

Entry	*Substrate*	*Conversion (%)*	*Time*	*Unreacted subs. config., ee (%)*
1		58	30 min	*R*, > 99
2		63	100 min	*R*, 96
3		60	8 h	*R*, 60
4		63	11 h	*R*, 79

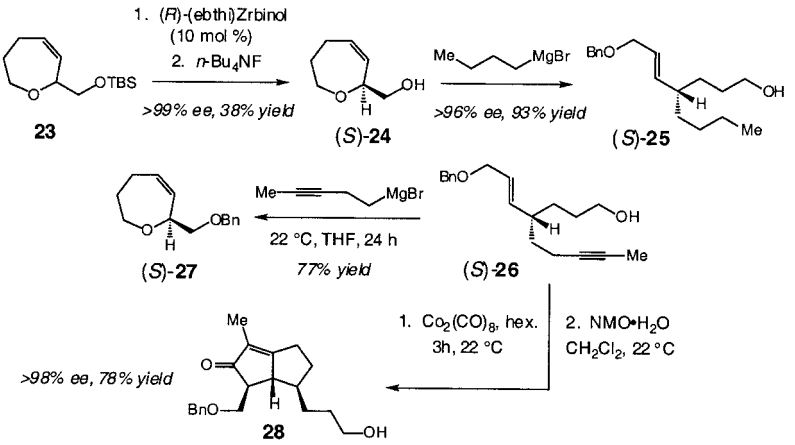
[a] Reaction conditions: indicated mol% (*R*)-**1**, 5.0 equiv. of EtMgCl, 70 °C, THF. Mass recovery in all reactions is > 85 %.

As the data in Table 6.3 indicate, in the presence of catalytic amounts of non-racemic (ebthi)$ZrCl_2$, a variety of unsaturated pyrans can be effectively resolved to furnish these synthetically useful heterocycles in excellent enantiomeric purities [16]. A number of important issues relating to the catalytic kinetic resolution of pyrans are noteworthy. (1) Reactions performed at elevated temperatures (70 °C) afford recovered starting materials with significantly higher levels of enantiomeric purity as compared to processes carried out at 22 °C. For example, the 2-substituted pyran shown in entry 1 of Table 6.3, when subjected to the same reaction conditions but at 22 °C, is recovered after 60 % conversion with 88 % *ee* (*cf.* 96 % *ee* at 70 °C). (2) Consistent with the models illustrated in Figure 6.2, 6-substituted pyrans (Table 6.3, entry 2) are not resolved effectively (the C-6 substituent should not interact strongly with the catalyst structure; see Figure 6.2); however, with a C-2 substituent also present, resolution proceeds with excellent efficiency (entry 3). (3) Pyrans that bear a C-5 substituent are likewise resolved with high selectivity (entry 4). In this class of substrates, one enantiomer reacts more slowly, presumably because its association with the zirconocene–alkene complex leads to sterically unfavorable interactions between the C-5 alkyl unit and the coordinated ethylene ligand.

As the representative data in Table 6.4 indicate, the Zr-catalyzed resolution technology may be applied to medium-ring heterocycles as well; in certain instances (e. g. entries 1 and 2), the starting material can be recovered with outstanding enantiomeric purity. Comparison of the data shown in entries 1 and 3 of Table 6.4 indicates that the presence of an aromatic substituent can have an adverse influence on the outcome of the catalytic resolution. The fact that the eight-membered ring substrate in Table 6.4 (entry 4) is resolved more efficiently may imply that the origin of this unfavorable effect is more due to the

conformational preferences of the heterocycle than the attendant electronic factors (a phenoxy group is a better leaving group than an alkoxy unit).

The availability of oxepins that bear a side chain containing a Lewis basic oxygen atom (entry 2, Table 6.4) has further important implications in enantioselective synthesis. The derived alcohol, benzyl ether, or methoxyethoxymethyl (MEM) ethers, in which resident Lewis basic heteroatoms are less sterically hindered, readily undergo diastereoselective uncatalyzed alkylation reactions when treated with a variety of Grignard reagents [17]. The examples shown below (Scheme 6.7) demonstrate the excellent synthetic potential of these stereoselective alkylations.

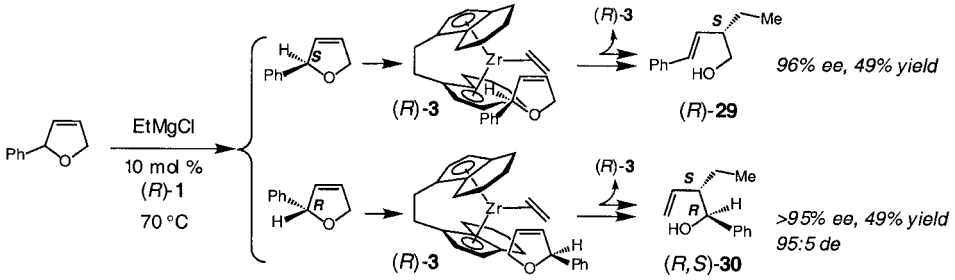


Scheme 6.7. Chiral medium-ring heterocycles, resolved by the Zr-catalyzed kinetic resolution, are subject to highly diastereoselective alkylations that afford synthetically useful compounds in optically pure form.

Thus, catalytic resolution of the TBS-protected oxepin **23**, conversion to the derived alcohol, and diastereoselective alkylation with *n*BuMgBr affords (*S*)-**25** with >96 % *ee* in 93 % yield. As shown in Scheme 6.7, alkylation of (*S*)-**27** with an alkyne-bearing Grignard reagent (→ (*S*)-**26**) allows for a subsequent Pauson–Khand cyclization reaction to provide the corresponding bicycle **28** in optically pure form. With regard to the ease with which these diastereoselective alkene alkylations take place, it is important to note that the asymmetric Zr-catalyzed additions with longer chain alkylmagnesium halides (see Table 6.2) are more sluggish than those involving EtMgCl. Furthermore, when catalytic alkylation does occur, the corresponding branched products are obtained; with *n*PrMgCl and *n*BuMgCl, *iso*Pr and *sec*Bu addition products are formed, respectively [9]. Therefore, the uncatalyzed alkylation reaction complements the enantioselective Zr-catalyzed protocol.

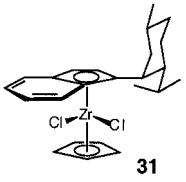
Zirconocene-catalyzed kinetic resolution of dihydrofurans is also possible, as illustrated in Scheme 6.8 [18]. Unlike their six-membered ring counterparts, both of the heterocycle enantiomers react readily, albeit through distinctly different reaction pathways, to afford – with high diastereomeric and enantiomeric purities – constitutional isomers that are readily separable (the first example of parallel kinetic resolution involving an organometallic agent). A plausible reason for the difference in the reactivity pattern of pyrans and furans is that, in the latter class of compounds, both olefinic carbons are adjacent to a C–O bond: C–Zr bond formation can take place at either end of the C–C π-system. The furan substrate and the (ebthi)Zr-alkene complex (*R*)-**3** interact such that unfavorable

steric interactions are avoided, leading to the formation of readily separable non-racemic products in the manner illustrated in Scheme 6.8.



Scheme 6.8. (ebthi)Zr-catalyzed kinetic resolution of dihydrofurans.

Subsequent to these studies by the author's group, Whitby and co-workers reported that enantioselective alkylations of the type illustrated in Scheme 6.6 can also be carried out with the non-bridged chiral zirconocene **31** [19]. Enantioselectivities are, however, notably lower when alkylations are carried out in the presence of **31**. For example, this new chiral metallocene affords **29** and **30** (Scheme 6.5) with 82 % and 78 % *ee*, respectively.

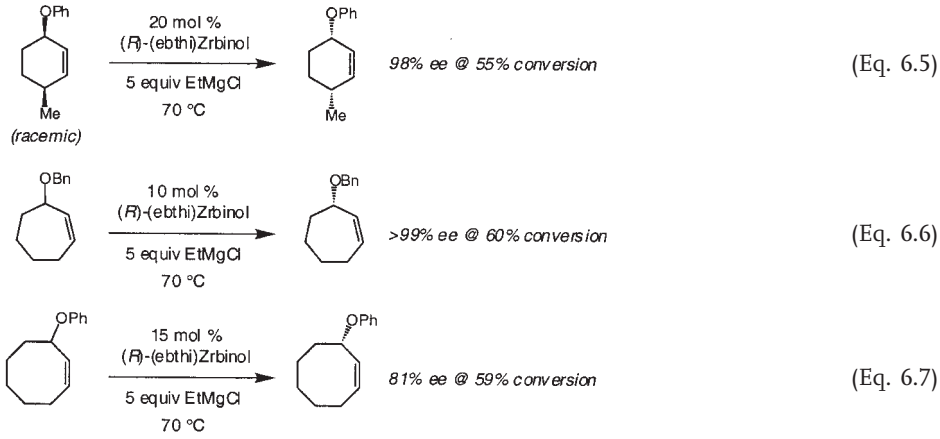


31

6.2.3

Zr-Catalyzed Kinetic Resolution of Exocyclic Allylic Ethers

As depicted in Eqs. 6.5–6.7, kinetic resolution of a variety of cyclic allylic ethers is effected by asymmetric Zr-catalyzed carbomagnesation. Importantly, besides six-membered ethers, seven- and eight-membered ring systems can readily be resolved by the Zr-catalyzed protocol.



The modes of addition shown in Figure 6.3 are similar to those shown in Figure 6.2 and are consistent with extant mechanistic work [6,9]; they accurately predict the identity of the slower reacting enantiomer. It should be noted, however, that variations in the observed *levels* of selectivity as a function of the steric and electronic nature of substituents and the ring size cannot be predicted based on these models alone; more subtle factors are clearly at work. In spite of such mechanistic questions, the metal-catalyzed resolution protocol provides an attractive option in asymmetric synthesis. This is because, although the maximum possible yield is ~40 %, catalytic resolution requires easily accessible racemic starting materials and conversion levels can be manipulated so that truly pure samples of substrate enantiomers are obtained.

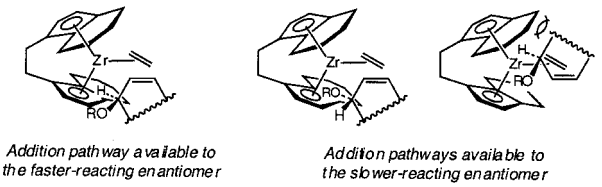
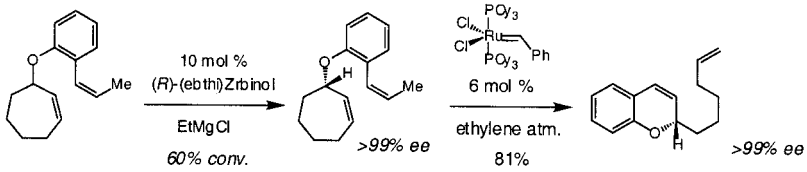


Figure 6.3. Various modes of addition of cyclic allylic ethers to an (ebthi)Zr–alkene complex.

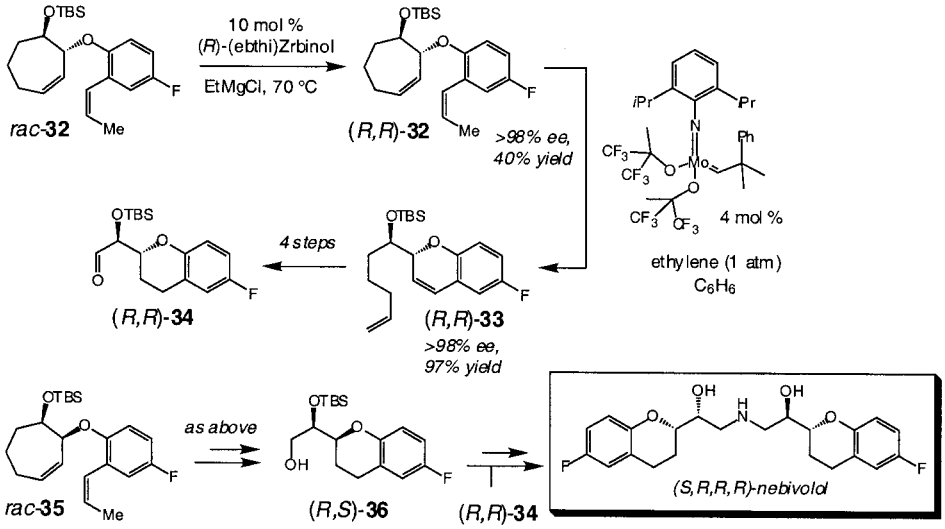
The synthetic versatility and significance of the Zr-catalyzed kinetic resolution of exocyclic allylic ethers is demonstrated by the example provided in Scheme 6.9. The optically pure starting allylic ether, obtained by the aforementioned catalytic kinetic resolution, undergoes a facile Ru-catalyzed rearrangement to afford the desired chromene in >99 % *ee* [20]. Unlike the unsaturated pyrans discussed above, chiral 2-substituted chromenes are not readily resolved by the Zr-catalyzed protocol. Optically pure styrenyl ethers, such as that shown in Scheme 6.9, are obtained by means of the Zr-catalyzed kinetic resolution, allowing for the efficient and enantioselective preparation of these important chromene heterocycles by a sequential catalytic protocol.



Scheme 6.9. Tandem Zr-catalyzed kinetic resolution and Ru-catalyzed ring-opening/ring-closing metatheses afford chiral chromenes with high optical purity.

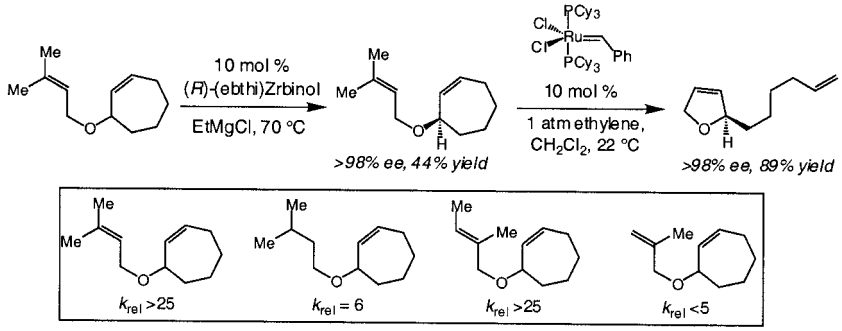
To examine and challenge the utility of the two-step catalytic resolution–chromene synthesis process [21], the author's group undertook a convergent and enantioselective total synthesis of the potent antihypertensive agent (*S,R,R,R*)-nebivolol [22]. As illustrated in Scheme 6.10, the two key fragments (*R,R*)-**34** and (*R,S*)-**36**, which were subsequently joined to afford the target molecule, were prepared in optically pure form by the catalytic resolution technology discussed above. Importantly, efficient and selective methods were established for the modification of the chromene alkenyl side chain. These studies led to a broadening of the utility of the initial methodological investigations. They demonstrated that, although the carbocyclic system may be used as the framework for the Zr- and the Mo-catalyzed reactions [23], the resulting 2-substituted chromene can be functionalized in a number of ways to afford a multitude of chiral non-racemic heterocycles [24]. Another

interesting feature of this total synthesis is that, whereas the preparation of (*R,R*)-**32** requires the use of the (*R*)-(ebthi)Zr catalyst, the synthesis of (*R,S*)-**36** is carried out by catalytic kinetic resolution with the (*S*)-(ebthi)Zr complex. Thus, the procedure of Buchwald [5k] was used to resolve *rac*-(ebthi)Zr to obtain (*R*)-(ebthi)Zrbinol and (*S*)-(ebthi)Zrbiphen to accomplish this total synthesis in an efficient manner [25].



Scheme 6.10. Tandem Zr-catalyzed kinetic resolution and Mo-catalyzed conversion of styrenyl ethers to chromenes is used in the first enantioselective total synthesis of the antihypertensive agent (*S,R,R,R*)-nebivolol.

As the representative examples in Scheme 6.11 illustrate, similar stragies may be applied to the corresponding alkenyl ethers (*vs.* styrenyl ethers) [26]. The Zr-catalyzed kinetic resolution/Ru-catalyzed metathesis protocol thus delivers optically pure 2-substituted dihydrofurans that cannot be accessed by resolution of the five-membered ring heterocycles (see Scheme 6.8). It should be noted, however, that the efficiency of the Zr-catalyzed resolution is strongly dependent, and not in a predictable manner, not only on the presence but the substitution of the acyclic alkene site of the diene substrate. The examples shown in Scheme 6.11 clearly illustrate this issue.



Scheme 6.11. Tandem Zr-catalyzed kinetic resolution and Ru-catalyzed conversion of the resulting optically pure ethers in the enantioselective synthesis of dihydrofurans. The efficiency of the catalytic resolution requires the presence of the pendant acyclic alkene and depends on its substitution.

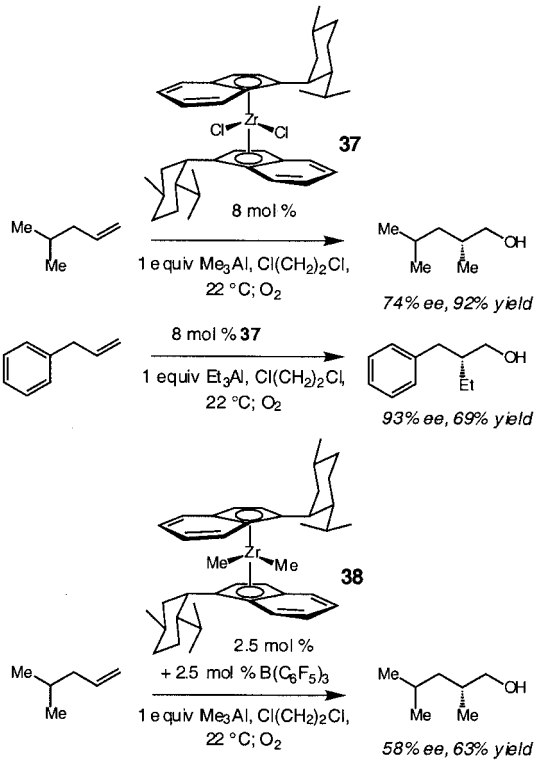
Related catalytic enantioselective processes It is worthy of note that the powerful Ti-catalyzed asymmetric epoxidation procedure of Sharpless [27] is often used in the preparation of optically pure acyclic allylic alcohols through the catalytic kinetic resolution of easily accessible racemic mixtures [28]. When the catalytic epoxidation is applied to cyclic allylic substrates, reaction rates are retarded and lower levels of enantioselectivity are observed. Ru-catalyzed asymmetric hydrogenation has been employed by Noyori to effect the resolution of five- and six-membered allylic carbinols [29]; in this instance, as with the Ti-catalyzed procedure, the presence of an unprotected hydroxyl function is required. Perhaps the most efficient general procedure for the enantioselective synthesis of this class of cyclic allylic ethers is that recently developed by Trost and co-workers, involving Pd-catalyzed asymmetric additions of alkoxides to allylic esters [30].

6.2.4
Zr-Catalyzed Enantioselective Alkylation of Alkenes with Alkylaluminum Reagents

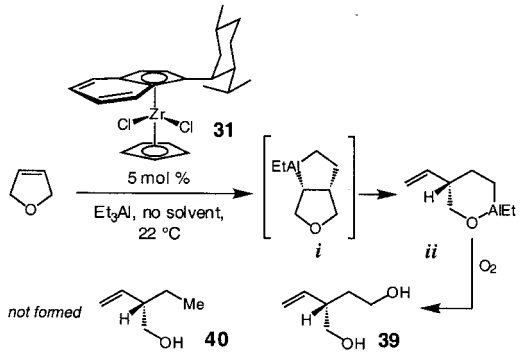
The zirconocene-catalyzed enantioselective carbomagnesation accomplishes the addition of an alkylmagnesium halide to an alkene, where the resulting carbometallation product is suitable for a variety of additional functionalization reactions (see Scheme 6.1). Excellent enantioselectivity is obtained in reactions with Et-, *n*Pr-, and *n*BuMgCl, and the catalytic resolution processes allow the preparation of a variety of non-racemic heterocycles. Nonetheless, the development of reaction processes whereby a wider variety of olefinic substrates and alkylmetals (e. g. Me-, vinyl-, phenylmagnesium halides, etc.) can be added to unfunctionalized alkenes efficiently and enantioselectively remains a challenging goal in asymmetric reaction design.

As illustrated below (Scheme 6.12), reports by Negishi and Kondakov, in which Erker's non-bridged chiral zirconocene **37** [31] was used as the catalyst, represent an impressive step towards this end [32]. A range of alkylaluminum reagents can be added with high efficiency and excellent enantioselectivity (>90 % *ee*). A remarkable aspect of this work is that through a change in reaction medium (1,1,1-trichloroethane is used as solvent), catalytic alkylations proceed through carbometallation of the alkene (direct addition of the cationic alkylzirconium species to the alkene, followed by Zr–Al ligand exchange), rather than involving the formation of a metallacyclopentane; under conditions where zirconacyclopentanes serve as intermediates, the selectivities are lower. Another notable aspect of the Negishi work is that the use of the Erker system appears to be imperative: when (ebthi)Zr is employed as the catalyst, alkylations are not nearly as efficient or stereoselective. As is also shown in Scheme 6.12, Waymouth and Shaughnessy have illustrated that cationic chiral zirconocenes, formed upon treatment of the dimethyl complex **38** with $B(C_6F_5)_3$, also promote asymmetric carboaluminations, albeit with lower levels of selectivity [33].

In 1997, Whitby reported that treatment of 2,5-dihydrofuran with Et_3Al in the presence of 5 mol% **31** leads to the enantioselective formation of **39** (Scheme 6.13), rather than the product obtained from catalytic carbomagnesations (**40**) [34]. This outcome can be rationalized on the basis of Dzhemilev's pioneering report that with Et_3Al, in contrast to the mechanism that ensues with EtMgCl (see Scheme 6.2), the intermediate aluminacyclopentane (***i***) is converted to the corresponding aluminoxacyclopentane ***ii***. To ensure the predominant formation of **39**, catalytic alkylations must be carried out in absence of solvent.



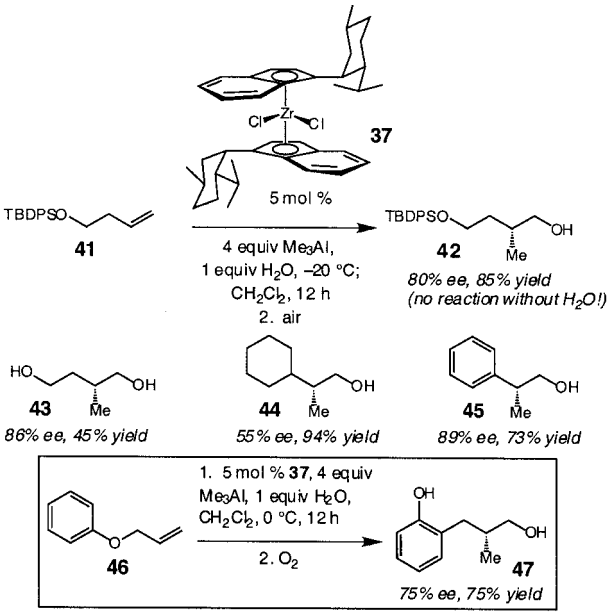
Scheme 6.12. Enantioselective carboaluminations of unactivated alkenes are promoted by neutral (**37**) and cationic (**38** + $B(C_6F_5)_3$) chiral Zr complexes.



Scheme 6.13. Zr-catalyzed enantioselective alkylation with neat Et_3Al can lead to an alternative reactivity pattern (formation of **39** rather than **40**).

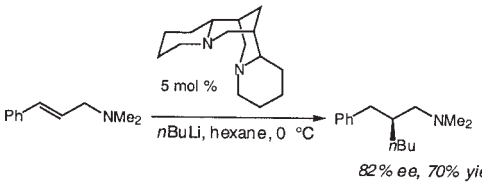
An important observation in the area of Zr-catalyzed carboaluminations of alkenes is that made by Wipf and Ribe that addition of water leads to substantial acceleration of the C–C bond-forming process [35]. Thus, as illustrated in Scheme 6.14, whereas catalytic alkylation of the silylated alkene **41** does not afford any of the desired product, upon addition of one equivalent of water, **42** is formed in 85 % yield with 80 % *ee*. As is also depicted in Scheme 6.14, carboaluminations of unsaturated alcohols are less efficient (→ **43**, but better than reactions without water), while those involving alkenes that bear an α-branched substituent are less selective (→ **44**). Another impressive example of rate

acceleration by water is the formation of **45** (73 % yield with 89 % *ee*); the Zr-catalyzed alkylation of styrene in the absence of water has been reported by Negishi to proceed to only 30 % conversion after 22 days at 22 °C [32]. In a subsequent paper, Wipf reported on a water-accelerated tandem Claisen rearrangement–catalytic asymmetric carboalumination that furnish various aromatic alcohols efficiently and with appreciable optical purity; the example shown in Scheme 6.14 is illustrative (**46** → **47**) [36].

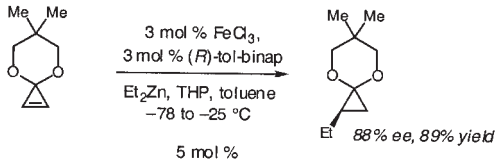


Scheme 6.14. Zr-catalyzed enantioselective carboalumination is significantly accelerated in the presence of equimolar amounts of water.

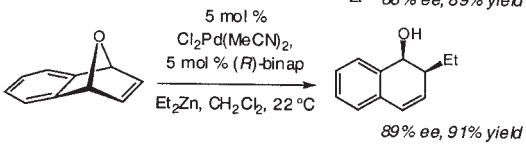
Related catalytic enantioselective processes In addition to the research summarized above, several other important developments have been reported relating to metal-catalyzed alkylation of alkenes (other than unsaturated carbonyls or allylic esters). Selected data regarding catalytic enantioselective alkene alkylations are shown in Eqs. 6.8–6.10. Marek and Normant (Eq. 6.8) have reported on a (−)-sparteine-catalyzed addition of *n*-alkyllithiums to styrenyl alkenes that bear neighboring Lewis basic directing groups [37]. Since the opposite antipode of sparteine is less readily available, this interesting approach has limited synthetic utility. Nakamura has shown that strained alkenes are enantioselectively alkylated in the presence of dialkylzincs and chiral Fe-based catalysts [38]. In addition, Lautens has reported that certain bicyclic alkenes undergo Pd-catalyzed asymmetric carbometallations followed by metal alkoxide elimination to give products such as that shown in Eq. 6.10 [39]. Unlike the Zr-catalyzed asymmetric alkylations, the latter two transformations require highly strained alkenes to proceed effectively.



(Eq. 6.8)



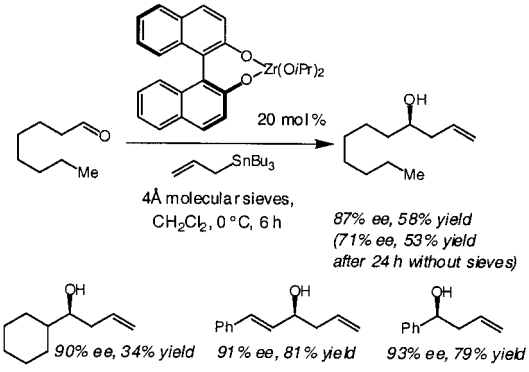
(Eq. 6.9)



(Eq. 6.10)

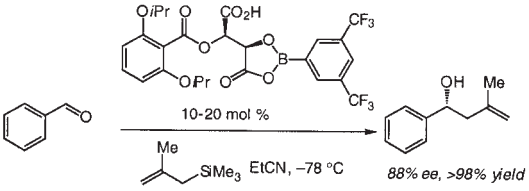
6.2.5
Zr-Catalyzed Enantioselective Allylation of Aldehydes

A case of the addition of an allylstannane to aldehydes has been reported by Tagliavini to proceed with appreciable enantioselectivity (Scheme 6.15) [40]. A notable feature of the Zr-catalyzed transformations is that they proceed more rapidly than the corresponding Ti-catalyzed processes reported by the same research team (see Scheme 6.16). Furthermore, C−C bond formation is significantly more efficient when the reactions are carried out in the presence of 4 Å molecular sieves; the mechanistic rationale for this effect is not known. It should be noted that alkylations involving aliphatic aldehydes are relatively low-yielding, presumably as the result of competitive hydride transfer and formation of the reduced primary alcohol.

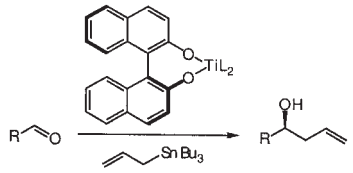


Scheme 6.15. Zr-catalyzed enantioselective addition of allylstannanes to aldehydes is more facile than the corresponding Ti-catalyzed processes.

Related catalytic enantioselective processes A number of impressive advances in the area of catalytic asymmetric allylmetal additions to carbonyls have been reported [41]. As illustrated below, procedures developed by Yamamoto (Eq. 6.11) [42] and Keck and Tagliavini (Eq. 6.12) [43] indicate that both Ti- and B-based chiral Lewis acids can effect C–C bond-forming reactions efficiently and with excellent enantioselectivity. A more recent example due to Carreira (Eq. 6.13) involves the use of the less reactive allyltrimethylsilane [44]. Another related advance is that due to Yamamoto; the Ag(binap) complex thus promotes highly asymmetric and efficient additions of allylstannane to a range of aromatic and aliphatic aldehydes (Eq. 6.14) [45]. The more recent report by Nakajima and co-workers, involving a non-metal-based catalyst (Eq. 6.15) is also worthy of note [46]. As far as stereochemical control in this general class of transformations is concerned, a number of other stoichiometric reactions have been reported that provide outstanding levels of enantioselectivity. Reaction technologies reported by Brown [47], Mukaiyama [48], Riediker [49], Corey [50], Hafner and Duthaler [51], Roush [52], Hoffman [53], and Denmark [54] serve as notable examples [55].

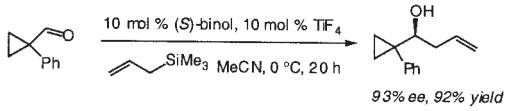


(Eq. 6.11)

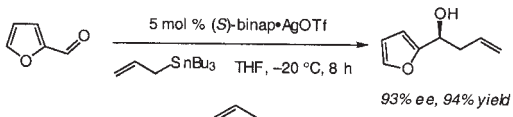


(Eq. 6.12)

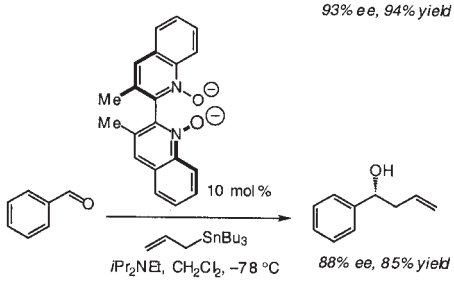
R=Ph; L = (O*i*Pr)2 (10 mol %); *95% ee, 88% yield*
R=*n*-octyl; L=Cl2 (20 mol %); *97% ee, 83% yield*



(Eq. 6.13)



(Eq. 6.14)

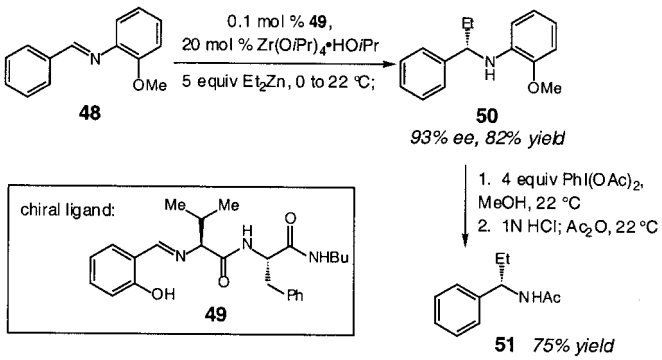


(Eq. 6.15)

6.2.6

Zr-Catalyzed Enantioselective Imine Alkylations with Alkylzinc Reagents

Based on mechanistic considerations developed in the course of a study of Ti-catalyzed cyanide additions to imines [56], recent work in these laboratories has resulted in the development of Zr-catalyzed enantioselective additions of alkylzinc reagents to imines. Application of this class of transformations delivers optically-enriched or pure amines, a class of compounds that are of great significance to medicine and biology. Screening of parallel libraries was used to establish conditions for an effective set of protocols, including the optimal metal center (Zr), solvent, reaction temperature, and amine protecting group [57]. Interestingly, as the representative examples in Scheme 6.16 illustrate, these screening studies indicated $Zr(OiPr)_4$ to be the most appropriate metal center, with dipeptide Schiff base **49** serving as the chiral ligand that leads to optimal reactivity and enantioselectivity; the corresponding Ti salt leads to significantly less efficient and enantioselective reactions. An efficient Zr-catalyzed alkylation of arylimines in the presence of 0.1–10 mol% chiral peptidic ligands and Et_2Zn has thus been established (*cf.* **48** → **50** in Scheme 6.16). These transformations afford the corresponding amines with >90% *ee* and in >66% isolated yield. As illustrated in Scheme 6.16, oxidative removal of the *o*-anisyl protecting group furnishes the derived optically enriched arylamines (→ **51**).

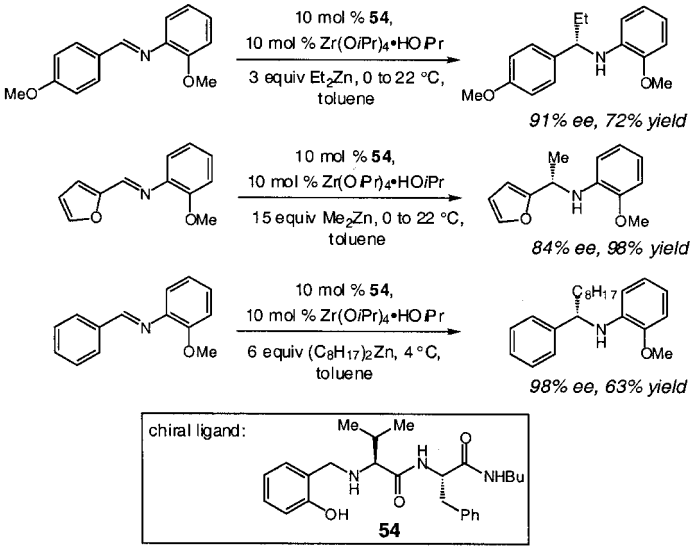


Scheme 6.16. Zr-catalyzed enantioselective addition of alkylzinc reagents to imines utilizes peptidic ligands and can be used to prepare a variety of aromatic amines in high optical purity.

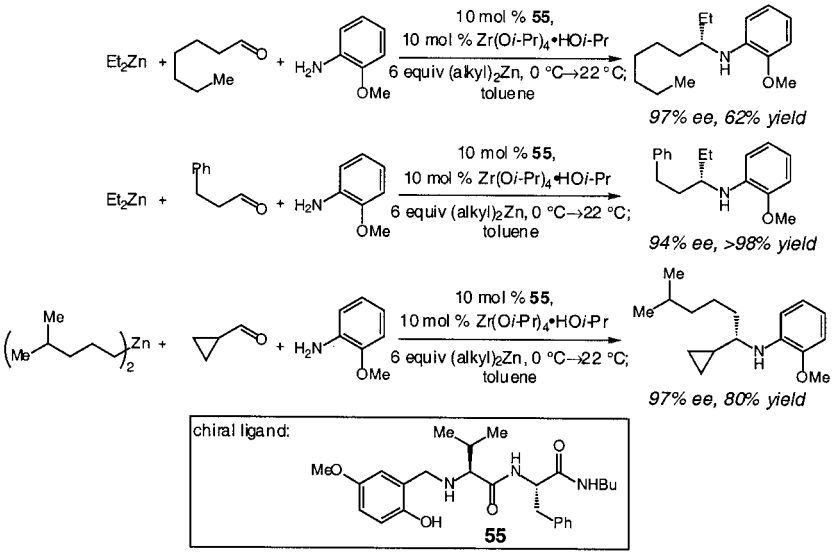
With aryl imines that bear electron-withdrawing or electron-donating substituents, Schiff-base dipeptides such as **49** prove to be less effective (amine formation with electron-withdrawing groups and <10% conversion with electron-rich units). When Et_2Zn is used in such cases, the imine substrate is reduced to afford the achiral amine product; when other dialkylzinc reagents are employed (e. g. Me_2Zn), <2% conversion is detected. The facile reduction of substrates with Et_2Zn may be due to β-H elimination of the metal-Et complexes, thereby generating active metal hydrides, which, in turn, promote amine reduction. The observed inefficiency of alkylzinc reagents that do not bear a β-H (Me_2Zn) or have less active β-H's (*n*-alkyl$_2$Zn) supports this hypothesis. It was speculated that the corresponding *amine*-based peptide ligand (e. g. **54**) may be the actual active catalyst. Thus, only in cases where it can be efficiently generated (i. e. in the presence of Et_2Zn) does the asymmetric alkylation proceed smoothly. Once again, based on a mechanistic hypothesis and because of the modularity of the chiral Schiff-base peptide structure, a variety of candidate ligands were screened. As the data in Scheme 6.17 illustrate, it was

established that the amine-based chiral ligands provide appreciable efficiency as well as enantioselectivity in the presence of all dialkylzincs, regardless of whether or not they bear an active β-H.

The more recently reported Zr-catalyzed asymmetric alkylation of aliphatic imines is shown in Scheme 6.18 [58]. Several important principles merit specific mention. (1) The catalytic asymmetric protocol can readily be applied to the synthesis of non-aryl im-



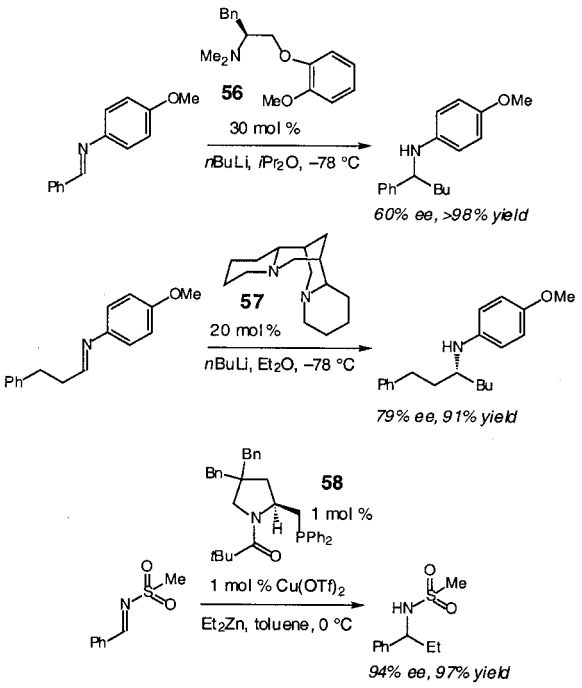
Scheme 6.17. With the peptidic amine ligand **54**, a variety of alkylzinc reagents can be added to imines in a highly enantioselective and efficient manner in the presence of $Zr(OiPr)_4 \cdot HOiPr$.



Scheme 6.18. Three-component Zr-catalyzed asymmetric alkylation of imines by alkylzincs leads to the formation of optically enriched amines not accessible by alternative methods such as catalytic hydrogenation.

ines to generate homochiral amines that cannot be prepared by any of the alternative imine or enamine hydrogenation protocols. (2) The catalytic amine synthesis involves a three-component process that involves in situ formation of the imine substrate followed by its asymmetric alkylation. This procedure is especially important vis-á-vis aliphatic substrates, since significant decomposition occurs upon isolation of aliphatic imines of the type needed here. The three-component Zr-catalyzed asymmetric imine alkylation, which is also readily applicable to the preparation of arylamines, not only provides an effective solution to the problems associated with the instability of aliphatic imines, but also suggests that such a procedure may be used to synthesize libraries of homochiral amines in a highly efficient and convenient fashion. It should be noted that peptide-based ligands such as **54** and **55** can readily be prepared from inexpensive and commercially available amino acids and salicyl aldehydes through simple procedures that can also be carried out on solid supports.

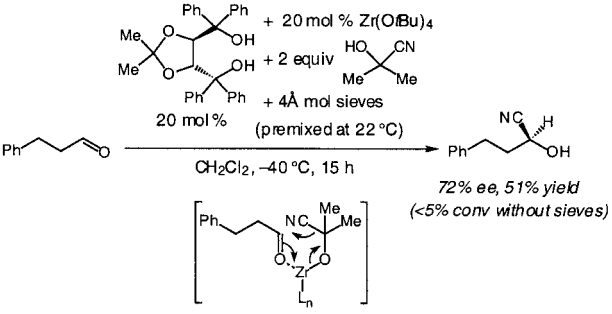
Related catalytic enantioselective processes Numerous other catalytic asymmetric protocols for enantioselective alkylations of imines have been reported (Scheme 6.19) [59]. In 1991, Tomioka utilized amino ether **56** to obtain optically enriched amines with up to 64 % *ee* [60], and later Denmark used the same *p*-methoxy group to effect enantioselective alkylation in the presence of 20 mol% (−)-sparteine (**57**) [61]. In spite of the significance of these studies, the relatively low selectivity, high catalyst loading, and the unavailability of (+)-sparteine makes these approaches less practical. More recently, Tomioka and coworkers have reported enantioselective additions of Et_2Zn to various activated imines promoted by phosphane **58** and $Cu(OTf)_2$ [62]. These transformations benefit from excellent enantioselection and low catalyst loading. However, all examples involve Et_2Zn and **58** is prepared by a somewhat lengthy sequence (thirteen steps) [63].



Scheme 6.19. Asymmetric catalytic additions of imines with non-Zr-based complexes.

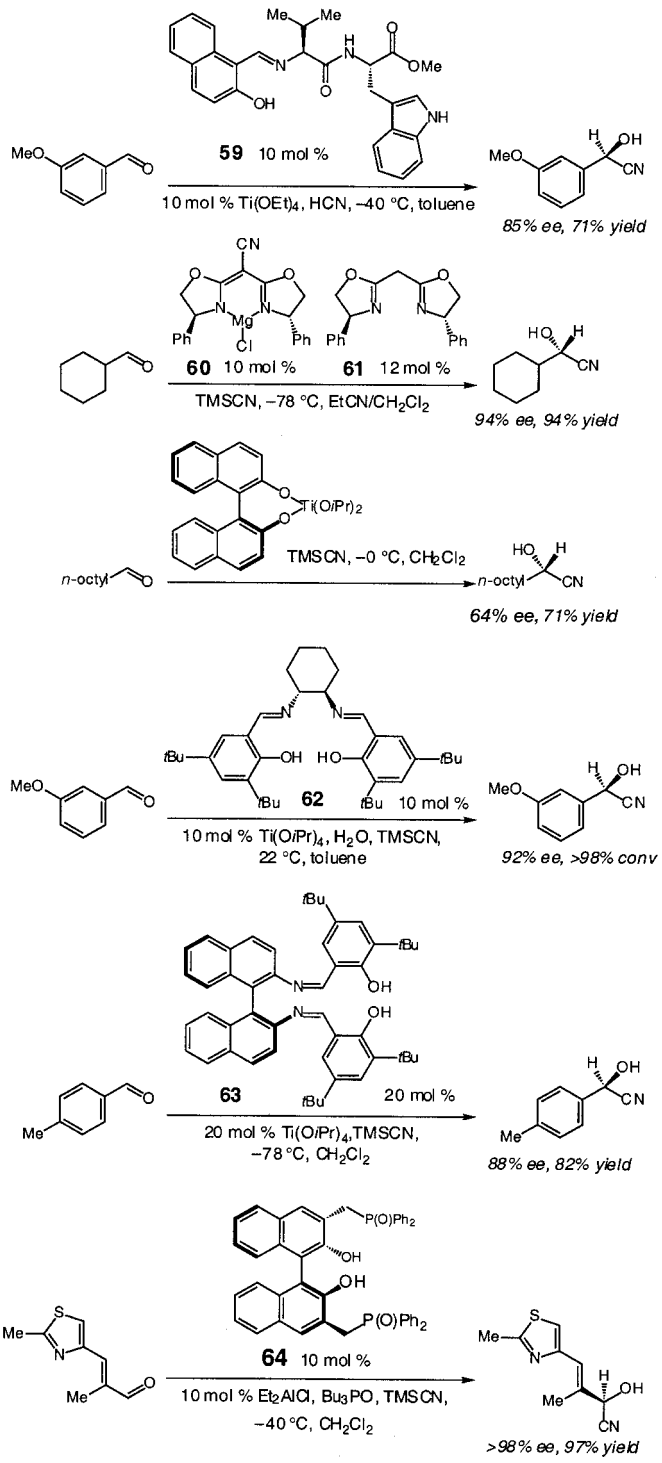
6.2.7
Zr-Catalyzed Enantioselective Cyanide Addition to Aldehydes

Maruoka and co-workers recently reported an example of a Zr-catalyzed cyanide addition to an aldehyde [64]. As is also illustrated in Scheme 6.20, the reaction does not proceed at all if 4 Å molecular sieves are omitted from the reaction mixture. It has been proposed that the catalytic addition proceeds through a Meerwein–Ponndorf–Verley-type process (*cf.* the transition structure drawn) and that the crucial role of molecular sieves is related to facilitating the exchange of the product cyanohydrin oxygen with that of a reagent acetone cyanohydrin. The example shown is the only catalytic example reported to date; the other reported transformations require stoichiometric amounts of the chiral ligand and Zr alkoxide.



Scheme 6.20. Zr-catalyzed cyanide addition to an aldehyde is facilitated by the presence of 4 Å molecular sieves.

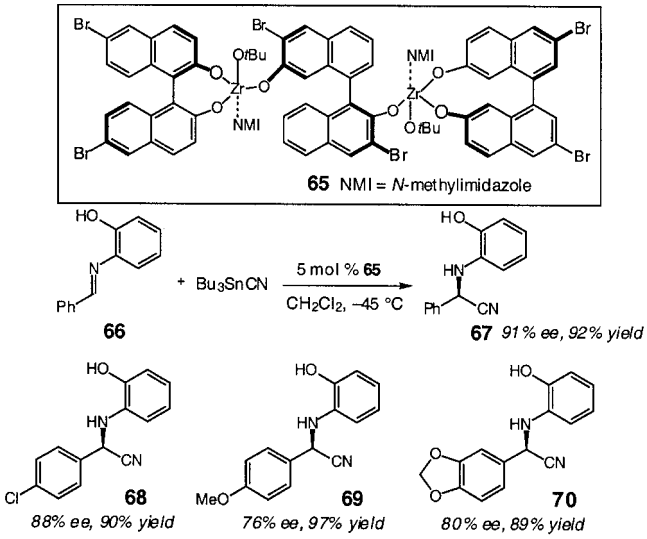
Related catalytic enantioselective processes A number of catalytic asymmetric cyanide additions to aldehydes have been disclosed by various laboratories, and a related review article focusing on this class of C–C bond-forming reactions appeared in 1992 [65]. Inoue and co-workers have published a series of papers that involve the use of dipeptide Schiff bases, such as **59** in Scheme 6.21, as chiral ligands to promote HCN addition to various aldehydes [66]; both Ti- and Al-catalyzed processes were developed by these workers [63e]. Related ligands involving amino alcohol Schiff bases have also been used by Oguni and co-workers to effect this transformation [67]. A highly selective and efficient, not to mention mechanistically intriguing, example was reported by Corey and Wang in 1993, in which, as illustrated in Scheme 6.21, a combination of **60** and **61** was employed [68]. Control experiments indicated that the presence of both **60** and **61** was required for high *ee* and yield and it was proposed that while **60** serves as a Lewis acid to associate with and activate the aldehyde substrate, **61** binds and delivers HCN. Nakai and co-workers have used the combination of binol and $Ti(OiPr)_4$ to promote enantioselective cyanohydrin synthesis (Scheme 6.21) [69]. Belokon [70] and Che [71] have also successfully utilized salen-derived chiral ligands **62** and **63** (Scheme 6.21) to obtain non-racemic cyanohydrins with high optical purities. Most recently, Shibasaki and co-workers reported a related Al-catalyzed process requiring the presence of chiral ligand **64**; these Al-catalyzed enantioselective reactions are proposed to involve bifunctional catalysis [72]. Shibasaki has used his version of the asymmetric cyanohydrin synthesis in the total synthesis of epothilone A [72b].



Scheme 6.21. Representative non-Zr-catalyzed asymmetric additions of cyanide to aldehydes.

6.2.8
Zr-Catalyzed Enantioselective Cyanide Additions to Imines (Strecker Reactions)

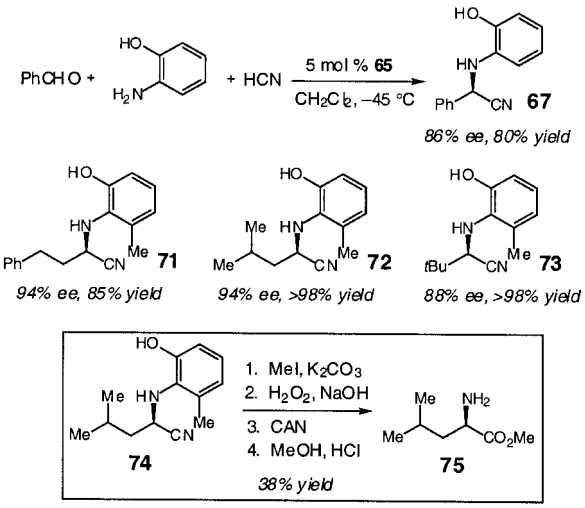
Catalytic asymmetric cyanide addition to imines constitutes an important C–C bond-forming reaction, as the product amino nitriles may be converted to non-proteogenic α-amino acids. Kobayashi and co-workers have developed two different versions of the Zr-catalyzed amino nitrile synthesis [73]. The first variant is summarized in Scheme 6.22. The bimetallic complex **65**, formed from two molecules of 6-Br-binol and one molecule of 2-Br-binol in the presence of two molecules of $Zr(OtBu)_4$ and *N*-methylimidazole, was proposed as the active catalytic species. This hypothesis was based on various NMR studies; more rigorous kinetic data are not as yet available. Nonetheless, as depicted in Scheme 6.22, reaction of *o*-hydroxyl imine **66** with 5 mol% **65** and 1–1.5 equiv. Bu_3SnCN (CH_2Cl_2, −45 °C) leads to the formation of amino nitrile **67** with 91 % *ee* and in 92 % isolated yield. As is also shown in Scheme 6.22, electron-withdrawing (→ **68**) and electron-rich (→ **69**), as well as more sterically hindered aryl substituents (→ **70**) readily undergo asymmetric cyanide addition.



Scheme 6.22. Zr-catalyzed enantioselective cyanide addition to imines in the presence of Bu_3SnCN.

To enhance the efficiency of the cyanide addition, these workers subsequently reported a three-component asymmetric synthesis of amino nitriles that avoids the use of the previously mentioned undesirable stannane [74]. Thus, as illustrated in Scheme 6.23, treatment of the requisite aniline and aldehyde with HCN (toxic but cheap and suitable for industrial use) at −45 °C in the presence of 2.5 mol% **65** leads to the formation of **67** with 86 % *ee* and in 80 % yield. As was mentioned above in the context of catalytic asymmetric three-component alkylations of imines (see Scheme 6.18), the in situ procedure is particularly useful for the less stable aliphatic substrates (*cf.* **71**–**73**, Scheme 6.23). The introduction of the *o*-Me group on the aniline is reported to lead to higher levels of asymmetric induction, perhaps because with the sterically less demanding aliphatic systems, the imine can exist as a mixture of interconverting *cis* and *trans* isomers.

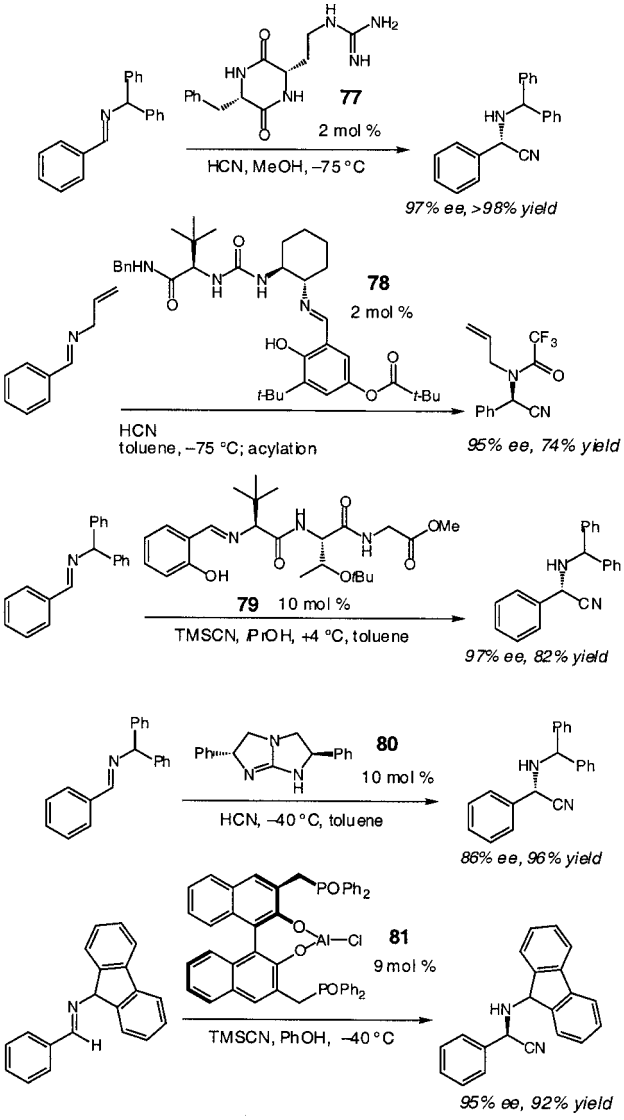
As is also illustrated in Scheme 6.23, the optically enriched amino nitriles can be converted to the corresponding α-amino esters through a four-step sequence (**74**→ **75**). Unlike the aforementioned imine alkylations with alkylzinc reagents, methylation of the phenolic OH is required, since the corresponding *o*-methoxy aniline is less reactive and affords significantly lower enantioselectivities; similar observations are made when aniline is used.



Scheme 6.23. Three-component Zr-catalyzed enantioselective cyanide additon to imines in the presence of HCN and subsequent four-step procedure for synthesis of the corresponding amino esters.

Related catalytic enantioselective processes Several non-Zr-catalyzed versions of asymmetric cyanide additions to imines have been reported by a number of research groups; representative examples are shown in Scheme 6.24. The original breakthrough by Lipton, involving catalysis by **77** [75], was followed by two different versions from Jacobsen's laboratories involving peptidic and salen-based chiral ligands (e. g. **78**) [76]. A Ti-catalyzed variant has been developed in these laboratories, whereby peptide Schiff-base systems such as **79** promote efficient and highly enantioselective C–C bond formations [77]. Another non-metal-catalyzed variant was reported by Corey, in which bicycle **80** serves as the catalyst [78]. Finally, Shibasaki and co-workers recently disclosed that **81**, equipped with a Lewis acidic Al site and nucleophilic phosphane oxides, can serve as a bifunctional catalyst to furnish amino nitriles with high optical purities [79,80]. Interestingly, mechanistic studies have shown that the Ti complex of peptide **79** probably serves as a bifunctional catalyst [53], and Corey has suggested that catalysis by **80** involves association of the guanidine functionality with a cyanide anion while the imine substrate is activated by H-bonding with the adjacent amine group of the guanidinium structure. Regarding the various amine protecting groups, the diphenylmethylene group, used in these laboratories and by Lipton and Corey, is effectively removed by inexpensive protic acids at the same time as cyanide hydrolysis; a similar strategy has been employed by Shibasaki in dealing with the *N*-fluorenyl moiety. Allyl and benzyl groups, as used by Jacobsen, are removed at a higher cost (Pd catalysis is required), but represent a more atom-economical synthesis approach than the aforementioned protections. Another advantage of the diphe-

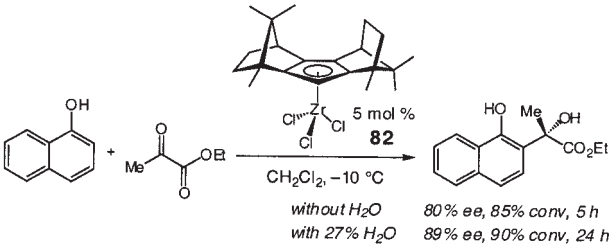
nylmethylene group is that, unlike the benzyl and allyl amines, its protection as an amide is not required for the purpose of isolation. A similar advantage exists for the *o*-hydroxyphenyl group used by Kobayashi in the Zr-catalyzed asymmetric cyanide addition to imines.



Scheme 6.24. Representative asymmetric additions of cyanide to imines promoted by non-Zr catalysts.

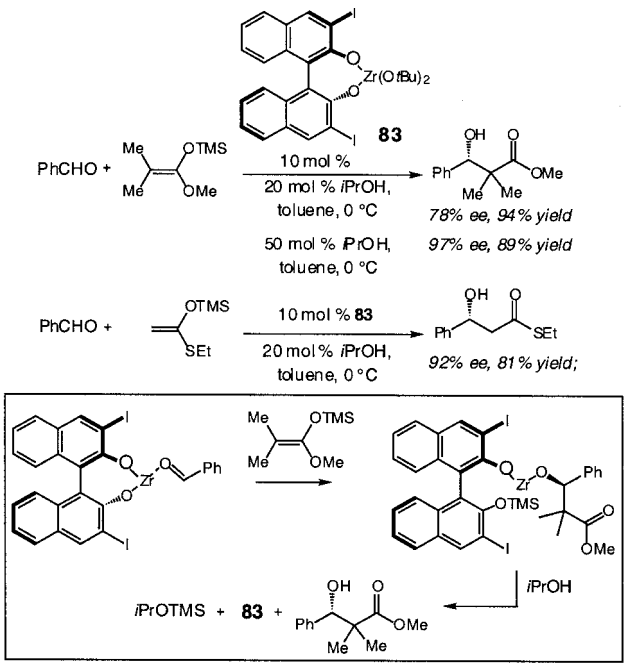
6.2.9
Zr-Catalyzed Enantioselective Aldol Additions

Erker and co-workers reported in 1990 that in the presence of the chiral Zr complex **82**, shown in Eq. 6.16, 1-naphthol adds to ethyl pyruvate with an appreciable level of enantioselectivity [81]. Higher optical purities were reported at lower temperatures, and interestingly, as later reported by Wipf for Zr-catalyzed carboaluminations of terminal alkenes (Scheme 6.14), addition of water leads to improvements in selectivity and reactivity [82].



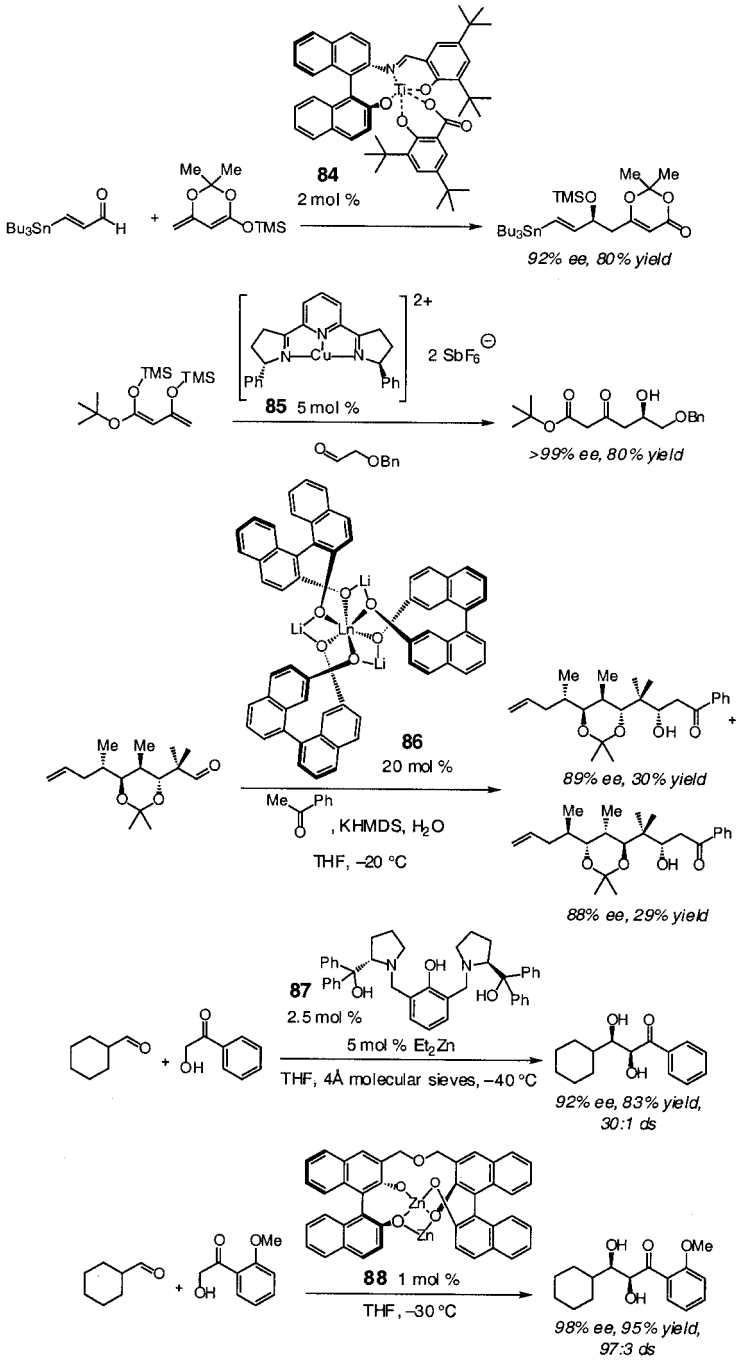
(Eq. 6.16)

More recently, Kobayashi and co-workers reported on Zr-catalyzed additions of ketene and thioketene acetals to a range of aromatic and aliphatic aldehydes (Scheme 6.25) [83]. As in the Erker study, the presence of protic additives proved critical here as well. As the example in Scheme 6.25 illustrates, the addition of larger amounts of *i*PrOH improved the yield and *ee*; it was reported that in the absence of the alcohol additive "much lower yield and enantioselectivities" were attained. The proposed catalytic cycle, depicted in Scheme 6.25, provides a plausible rationale for the role of the additive: Si transfer is facilitated by *i*PrOH to regenerate the chiral catalyst. Finally, it is worthy of mention



Scheme 6.25. Zr-catalyzed addition of silyl ketene acetals to aldehydes requiring added *i*PrOH, which is proposed to facilitate silyl transfer and release of the active catalyst after each C–C bond formation.

that other binol derivatives, bearing H, Cl, or Br at the 2- and 2′-positions, give rise to less enantioselective reactions than **83**.

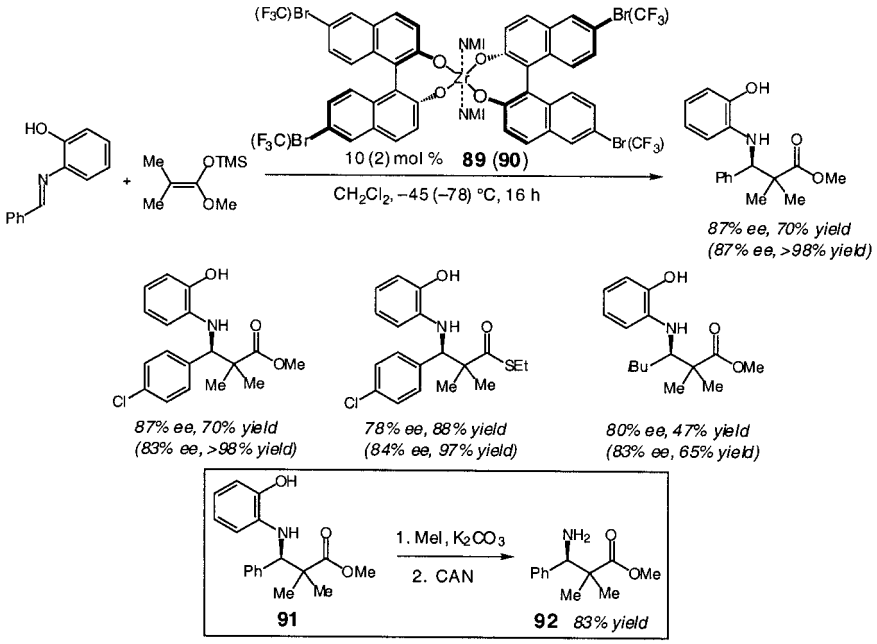


Scheme 6.26. Representative catalytic asymmetric aldol additions not promoted by Zr-based complexes.

Related catalytic enantioselective processes [84] As the examples in Scheme 6.26 show, a wide variety of catalytic asymmetric aldol additions have been reported that can be considered as attractive alternatives to the Zr-catalyzed process summarized above. The Ti-catalyzed version due to Carreira (**84**) [85], the Cu-catalyzed variant of Evans (**85**) [86], and the protocol reported by Shibasaki (**86**) [87] have all been used in syntheses of complex molecules. More recently, Trost (**87**) [88] and Shibasaki (**88**) [89] have developed two additional attractive asymmetric catalytic aldol protocols. Other related technologies (not represented in Scheme 6.26) have been described by Morken [90] and Jorgensen [91].

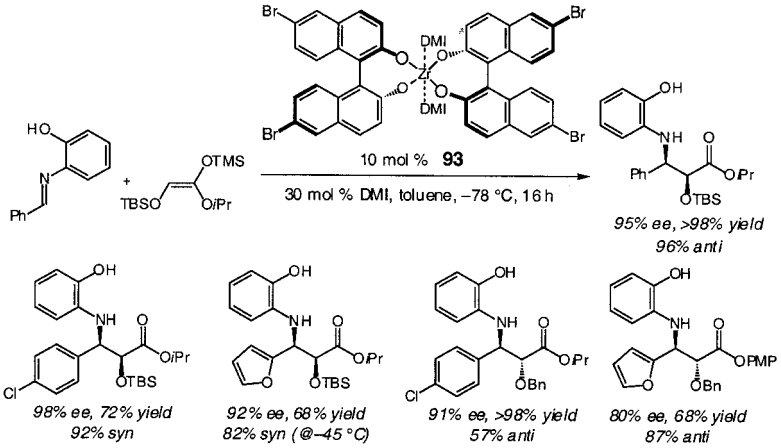
6.2.10
Zr-Catalyzed Enantioselective Mannich Reactions

Several versions of Zr-catalyzed additions of ketene acetals and derivatives to imines (Mannich reaction) have been reported in the past few years. An early disclosure by Kobayashi and co-workers is summarized in Scheme 6.27 [92]. Thus, through the use of 10 mol% of the chiral complex **89** or **90**, a range of α,α-disubstituted β-amino esters was efficiently generated with 78–87 % *ee*. The catalyst structure was proposed on the basis of spectroscopic studies; it should be noted that the presence of *N*-methylimidazole (NMI) is critical to obtaining appreciable enantioselectivities; binding of NMI to the Zr center has been suggested (see **89** and **90**, Scheme 6.27). As the results in Scheme 6.27 indicate, reactions with **90** are more efficient than those with **89** and deliver similar levels of selectivity; the higher Lewis acidity of the Zr center in **90** has been proposed to account for the observed difference in reactivity. As is also shown in Scheme 6.27, removal of the *o*-hydroxyphenol unit can be effected in two steps in high yield (**91** → **92**).



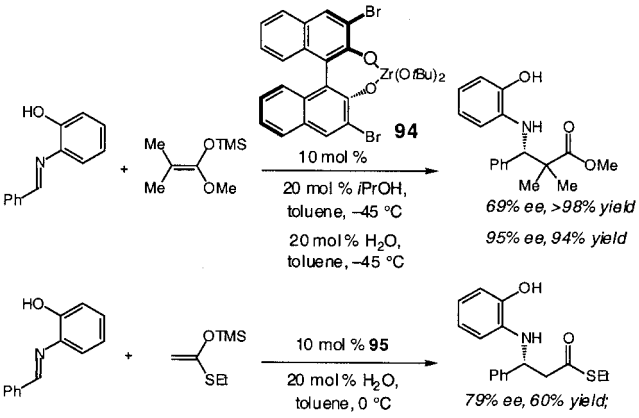
Scheme 6.27. Zr-catalyzed enantioselective Mannich reactions; when more electron-withdrawing chiral ligands are used, enantioselectivity and reactivity levels are enhanced. Deprotection is carried out in two steps.

In a related publication, Kobayashi and his team reported on Zr-catalyzed asymmetric Mannich reactions that utilize the more electron-rich oxygenated ketene acetals shown in Scheme 6.28 [93]. A noteworthy aspect of this study was that the levels of *syn*/*anti* diastereocontrol proved to be dependent on the nature of the alkoxide substituent: whereas the β-TBS acetals predominantly afforded the *syn* isomer, the OBn derivatives afforded a larger amount of the *anti* isomer. As before, the presence of an additive, this time 1,2-dimethylimidazole (DMI), proved to be important with regard to the level of π-facial selectivity. The phenol activating group can be removed by the same procedure as reported previously, with essentially identical degrees of efficiency (see Scheme 6.27).



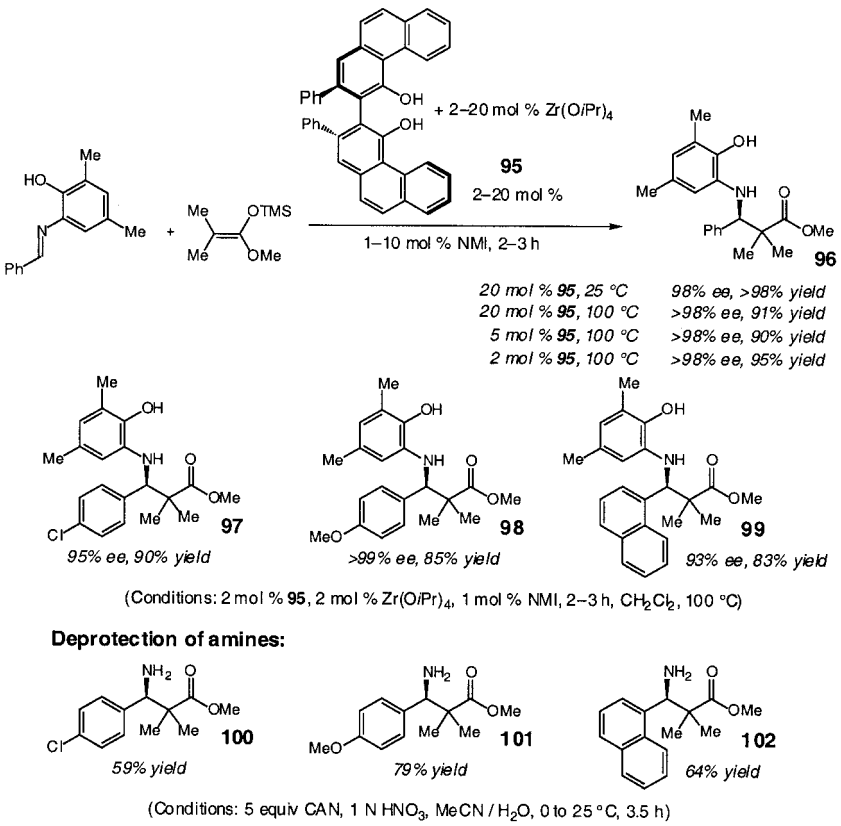
Scheme 6.28. Zr-catalyzed enantioselective Mannich reactions of functionalized ketene acetals deliver high enantio- and diastereoselectivity.

Yet another version of the Zr-catalyzed Mannich process developed by the Kobayashi group is summarized in Scheme 6.29 [78]. In this instance, the chiral catalyst (**94**) is proposed to bear a single binol molecule, where the 2,2′-dibromobinol proves to be the superior choice. Once again, protic additives, particularly H_2O, prove to be beneficial (see Scheme 6.29). This particular class of catalytic C–C bond formations is not limited to tetrasubstituted ketene acetals; as illustrated in Scheme 6.29, less substituted thioacetals prove to be effective reaction partners as well.



Scheme 6.29. Zr-catalyzed enantioselective Mannich reactions with chiral 2,2′-Br_2(binol) proceed with a higher level of enantioselectivity in the presence of water.

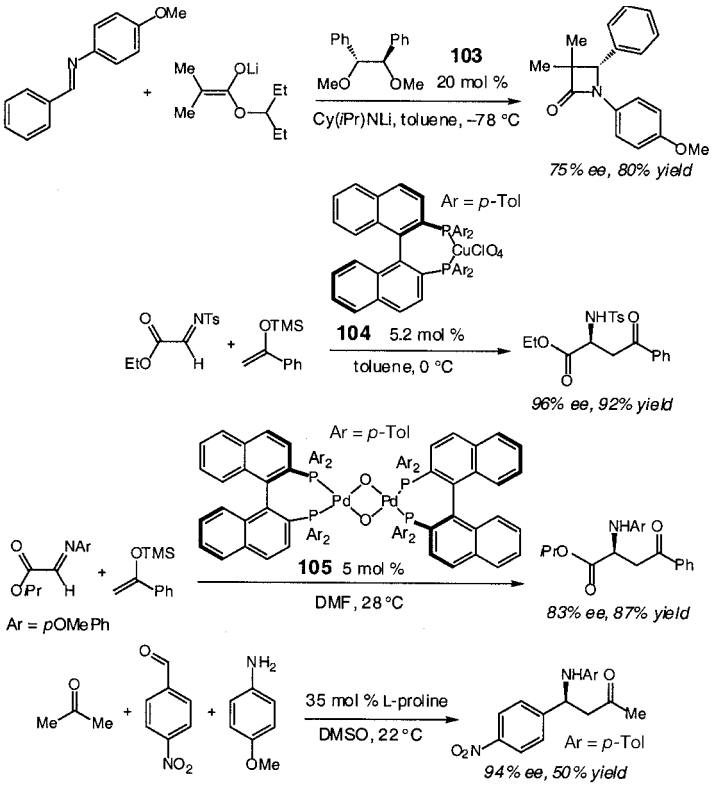
Most recently, Wulff and co-workers reported an intriguing case of Zr-catalyzed asymmetric Mannich reactions, in which VAPOL (**95**) was used as the chiral diolate ligand (Scheme 6.30) [94]. As in the earlier Kobayashi procedures (Schemes 6.27 and 6.28), the reactions were performed in the presence of catalytic amounts of NMI. An impressive aspect of the Wulff study, as shown in Scheme 6.30 (→ **96**), is that even at 100 °C exceptional levels of selectivity are attained. The presence of Me substituents on the phenol activating group also proved crucial; based on extensive modeling work, it was concluded that substrates bearing appropriate substituents fitted better in the catalyst's chiral pocket. Finally, as shown in Scheme 6.30, excellent enantioselectivities were observed with electron-rich (→ **97**), electron-poor (→ **98**) and sterically demanding (→ **99**) imines. As illustrated by deprotected β-amino esters **100**–**102**, a single-step deprotection could be used to remove the aromatic activating unit.



Scheme 6.30. Zr-catalyzed enantioselective Mannich reactions with chiral VAPOL ligands; remarkably, reactions remain as enantioselective at 100 °C as they are at 25 °C. Deprotection to give the β-amino ester is carried out in a single step.

Related catalytic enantioselective processes Representative examples of other catalytic asymmetric Mannich additions are depicted in Scheme 6.31. In 1997, Tomioka demonstrated a Li-catalyzed synthesis of functionalized β-lactams that proceeds through a catalytic enantioselective Mannich reaction (promoted by **103**) [95], and a year later Lectka and his team published a series of reports concerning additions of silyl ketene acetals

to α-imino esters as catalyzed by the chiral Cu complex **104** [96]. Then came a paper by Sodeoka on a Pd-catalyzed variant, in which the bis(palladium) complex **105** was proposed as the active catalyst. [97] In contrast to all of the above metal-catalyzed approaches, List recently put forward a three-component catalytic asymmetric Mannich reaction that is effected by optically pure proline (last entry, Scheme 6.31) [98]. Finally, it should be noted that an attractive alternative for the catalytic asymmetric synthesis of α-hydroxy,β-amino carbonyls (*cf.* Scheme 6.28) can be found in Sharpless' catalytic asymmetric aminohydroxylation protocols [99].



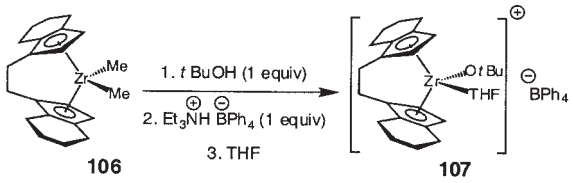
Scheme 6.31. Representative examples of non-Zr-catalyzed enantioselective Mannich reactions.

6.2.11
Zr-Catalyzed Enantioselective Cycloadditions

6.2.11.1 Cycloadditions with carbonyl dienophiles

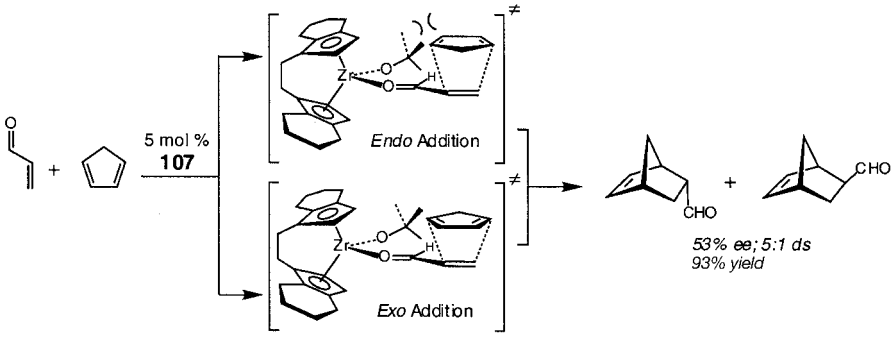
Collins and co-workers have performed studies in the area of catalytic enantioselective Diels–Alder reactions, in which *ansa*-metallocenes (**107**, Eq. 6.17) were utilized as chiral catalysts [100]. The cycloadditions were typically efficient (~90% yield), but proceeded with modest stereoselectivities (26–52% *ee*). The group IV metal catalyst used in the asymmetric Diels–Alder reaction was the cationic zirconocene complex (ebthi)Zr(O*t*Bu)·THF (**106**, Eq. 6.17). Treatment of the dimethylzirconocene [101] **106** with one equivalent of *t*-butanol, followed by protonation with one equivalent of $HEt_3N \cdot BPh_4$, resulted in the formation of the requisite chiral cationic complex (**107**),

which was used to catalyze the [4+2] cycloadditions of acrylate and acrolein derivatives with cyclopentadiene.



(Eq. 6.17)

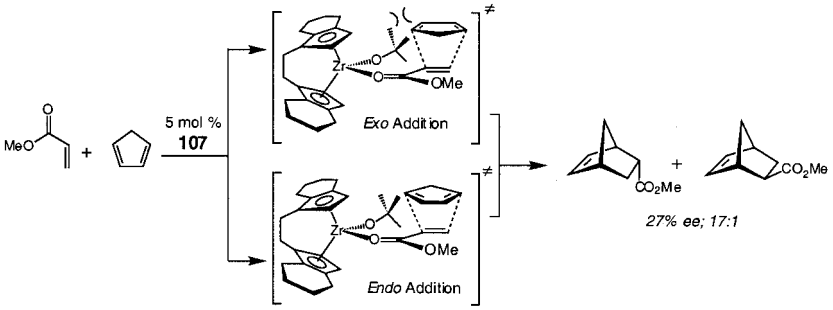
As illustrated in Scheme 6.32, in the presence of 5 mol% of **107**, the [4+2] cycloaddition of acrolein and cyclopentadiene proceeds efficiently to afford the desired cycloadduct in 93% yield with 53% *ee* as a 5:1 mixture of *endo* and *exo* isomers. Spectroscopic (^{1}H NMR) experiments indicate that the preferred orientation for binding between acrolein and the chiral metallocene is as shown. Accordingly, it has been proposed by Collins that acrolein binds to the chiral zirconocene complex such that the vinyl group is oriented away from the sterically hindered alkoxide unit in order to avoid steric interactions with the bulky *t*-butoxide ligand. It is plausible that, as can be seen in the transition structures illustrated in Scheme 6.32, approach of cyclopentadiene in the *endo* mode leads to unfavorable interactions between the diene and the *t*-butoxy ligand, thus leading to modest levels of diastereoselectivity (5:1 *endo*:*exo*). Molecular models indicate that any significant steric influence of the chiral ligand on the stereochemical outcome (both absolute and relative) of the cycloaddition is unlikely; the observed low levels of enantioselection (53% *ee*) may thus be the result of inefficient stereochemical induction by the chiral ebthi moiety [102].



Scheme 6.32. Stereoselective cationic (ebthi)Zr-catalyzed [4 + 2] cycloaddition involving an unsaturated aldehyde.

In reactions in which methyl acrylate is used as the dienophile (Scheme 6.33), cycloadditions occur with lower levels of enantioselection (23% *ee*, as compared to 53% observed for acrolein), but with significantly higher degrees of diastereoselectivity (17:1, *endo*:*exo*). Improved levels of *endo* selectivity are observed in the case of the methyl ester (Scheme 6.33); this is perhaps because, at least in part, the dienophile p-system is oriented towards the *t*-butoxy ligand, where the steric influence of the bulky substituent is expected to be more pronounced. As before, formation of the *endo* isomer may occur to a greater extent, since the transition structure that leads to the *exo* isomer would involve energetically unfavorable interactions between the diene

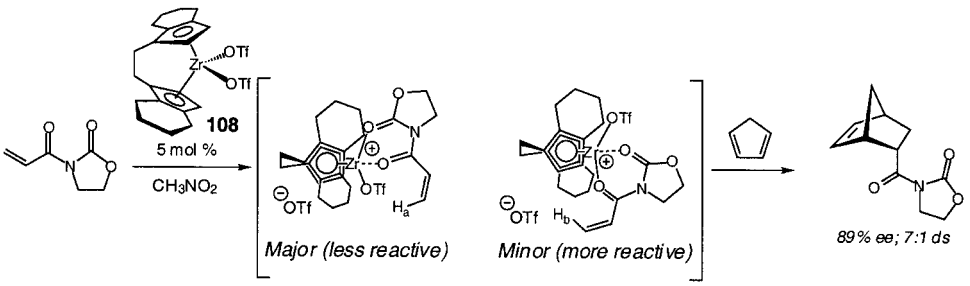
and the transition metal *t*-butoxy ligand. Collins and co-workers proposed the catalyst–substrate mode of association depicted in Scheme 6.33 on the basis of previous reports concerning the preferred stereochemistry of Lewis acid association with carboxylic esters [103].



Scheme 6.33. Stereoselective (ebthi)Zr-catalyzed cycloadditions involving a cationic zirconocene and an unsaturated ester.

Collins and co-workers have also reported on an enantioselective catalytic Diels–Alder cycloaddition, in which zirconocene and titanocene bis(triflate) complexes were used as catalysts [104]. The influence of the solvent polarity on the observed levels of stereoselectivity is noteworthy. For example, as shown in Scheme 6.34, with **108** as the catalyst, whereas in CH_2Cl_2 (1 mol% catalyst) the *endo* product was formed with 30 % *ee* (30:1 *endo*:*exo*, 88 % yield), in CH_3NO_2 solution (5 mol% catalyst) the enantioselectivity was increased to 89 % (7:1 *endo*:*exo*, 85 % yield). Extensive ^1H and ^{19}F NMR studies further indicated that a mixture of metallocene–dienophile complexes was present in both solutions (~6:1 in CH_2Cl_2 and ~2:1 in CH_3NO_2, as shown in Scheme 6.34), and that most probably it was the minor complex isomer that was more reactive and led to the observed major enantiomer. For example, whereas nOe experiments led to ca. 5 % enhancement of the CpH proton signals of the same ring when H_b in the minor complex was irradiated, no enhancements were observed upon irradiation of H_a in the major complex.

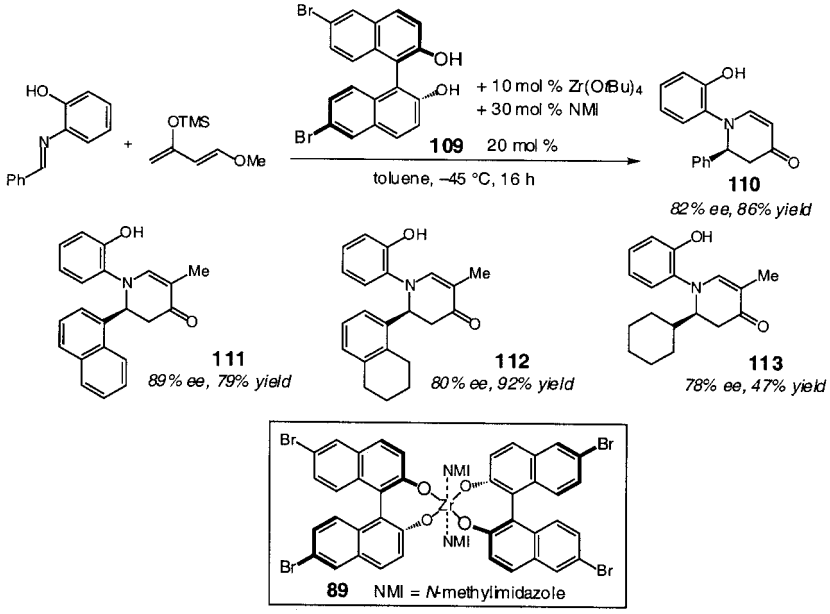
These recent results illustrate for the first time that metallocene-based chiral Lewis acids can serve effectively in providing [4+2] cycloaddition products with excellent levels of enantiofacial selectivity. Perhaps more importantly, the reported NMR studies and the observed dramatic solvent effect should pave the way for future endeavors in the rational design of better chiral metallocenes.



Scheme 6.34. Stereoselective cycloadditions with (ebthi)Zr$(OTf)_2$ as the chiral catalyst.

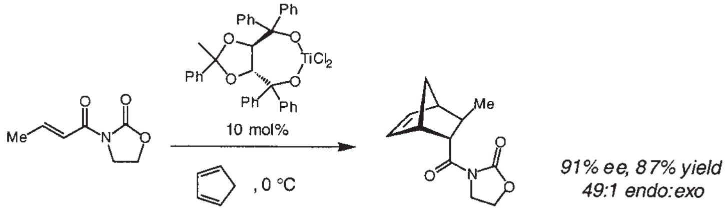
6.2.11.2 Cycloadditions with imine dienophiles

Kobayashi and his team have utilized a catalytic system similar to that used in their development of a Zr-catalyzed Mannich reaction (Schemes 6.27–6.29) to develop a related cycloaddition process involving the same imine substrates as used previously (Scheme 6.35) [105]. As the representative examples in Scheme 6.35 demonstrate, good yields and enantioselectivities (up to 90 % *ee*) are achieved. Both a less substituted version of the Danishefsky diene (→ **110**) and those that bear an additional Me group (e. g.→ **111**) can be utilized. Also as before, these workers propose complex **89**, bearing two binol units, to be the active catalytic species.

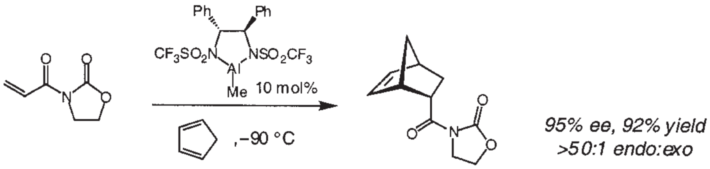


Scheme 6.35. Zr-catalyzed enantioselective addition of Danishefsky dienes to *o*-hydroxyphenylimines; the structure of the purported chiral catalyst (**89**) is also shown.

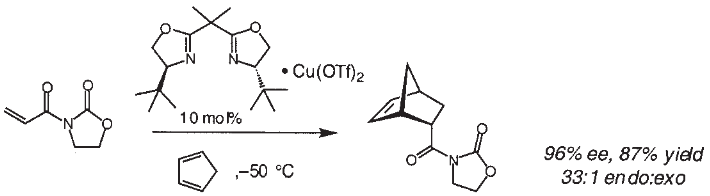
Related catalytic enantioselective processes A wide variety of other catalytic systems generally offer more selective methods for carrying out [4+2] cycloadditions [106]. Related asymmetric cycloadditions have been reported, in which, similar to Collins' work, oxazolidinones serve as dienophiles. For example, Narasaka (Eq. 6.18) [107], Corey (Eq. 6.19) [108], Evans (Eq. 6.20) [109], and Kobayashi (Eq. 6.21) [110] have published systems that offer similar, or often higher, levels of relative and absolute stereoselectivity. It should be noted that enantioselective Diels–Alder cycloaddition is far from being a "generally solved problem". The high enantioselectivities reported in the literature, although extremely important, only concern a specific, relatively small, and highly reactive class of dienes and dienophiles [111]. In brief, considering the importance of [4+2] cycloadditions in organic chemistry, future research in this area should continue to provide notable contributions to the field of asymmetric synthesis.



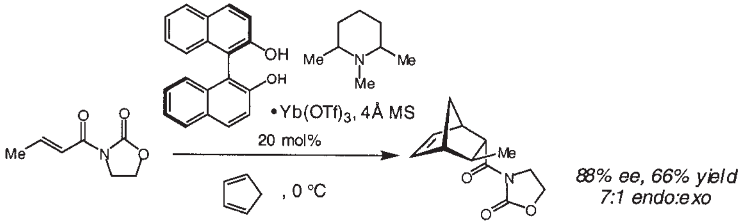
(Eq. 6.18)



(Eq. 6.19)

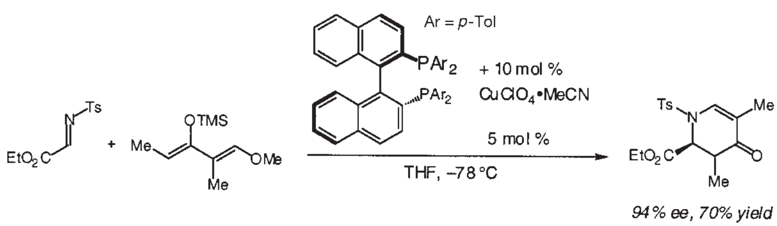


(Eq. 6.20)



(Eq. 6.21)

As far as catalytic enantioselective cycloadditions to imines are concerned, the only non-Zr-catalyzed process is a Cu-catalyzed protocol reported by Jorgensen (Eq. 6.22) [112]. It should be noted, however, that high enantioselectivities are attained only with highly substituted versions of the Danishefsky diene.

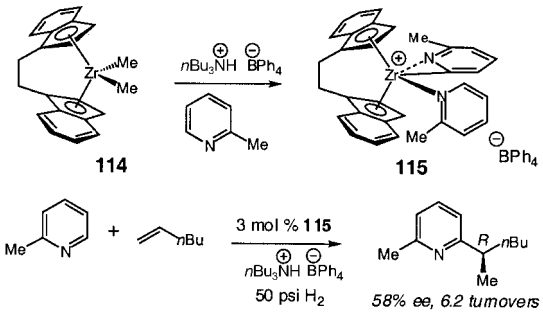


(Eq. 6.22)

6.2.12
Zr-Catalyzed Enantioselective Alkene Insertions

Inspired by the ability of cationic *ansa*-zirconocene complexes to effect stereocontrolled alkene polymerization reactions, Jordan has recently reported the stereoselective insertion of simple alkenes into both the (ebi)Zr(η^2-pyrid-2-yl) and (ebthi)Zr(η^2-pyrid-2-yl) systems [113]. As shown in Scheme 6.36, treatment of *rac*-(ebi)$ZrMe_2$ **114** with $nBu_3NH^+BPh_4^-$ in the presence of 2-picoline affords the (ebi)Zr(η^2-pyrid-2-yl) complex **115** (the derived $B(C_6F_5)$ derivatives may also be prepared and are in fact reported to be more convenient to use).

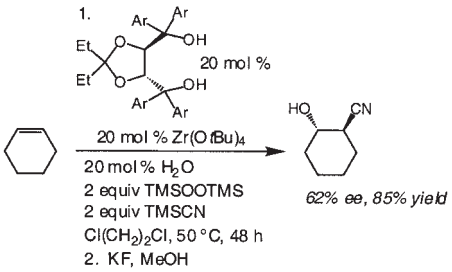
When **114** is treated with a variety of alkene substrates, facile insertion into the azazirconacycle takes place (→ **115**). The derived azazirconacyclopentanes are formed with various, but generally high, levels of diastereoselection, depending on the nature of alkene substituents. As illustrated in Scheme 6.36, the non-racemic (ebthi)Zr(η^2-pyridyl)$^+$ complex has been shown to participate in an asymmetric and catalytic C–C bond-forming reaction.



Scheme 6.36. A Zr-catalyzed enantioselective alkene insertion reaction.

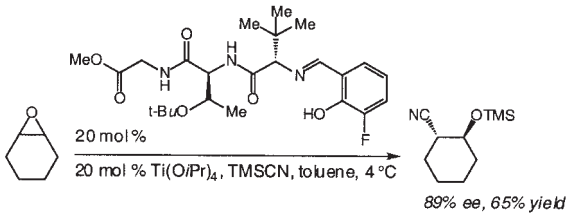
6.2.13
Zr-Catalyzed Enantioselective Additions to *Meso* Epoxides

An interesting recent report by Shibasaki deals with a Zr-catalyzed process whereby various cyclic and acyclic alkenes are directly converted to their corresponding β-cyanohydrins, presumably via an intermediate epoxide [114]. One catalytic enantioselective version has been reported, as shown in Eq. 6.23. This promising initial result augurs well for future developments of this synthetically useful transformation.

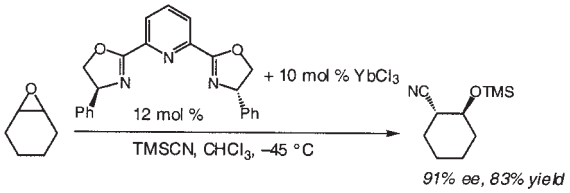


(Eq. 6.23)

Related catalytic enantioselective processes [115] Two catalytic procedures for asymmetric addition of cyanides to *meso* epoxides have been reported [116]. One is the result of work carried out in these laboratories, shown in Eq. 6.24, promoted by Ti-peptide chiral complexes, while the other, developed by Jacobsen and Schaus, is a Yb-catalyzed enantioselective reaction that is effected in the presence of pybox ligands (Eq. 6.25) [117]. Although the Shibasaki method (Eq. 6.21) is not as enantioselective as these latter methods, it has the advantage that it accomplishes both the epoxidation and subsequent desymmetrization in a single vessel.



(Eq. 6.24)

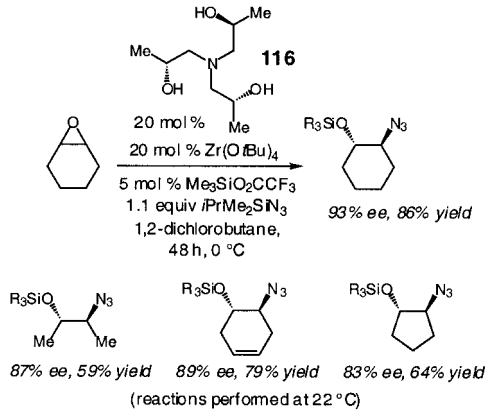


(Eq. 6.25)

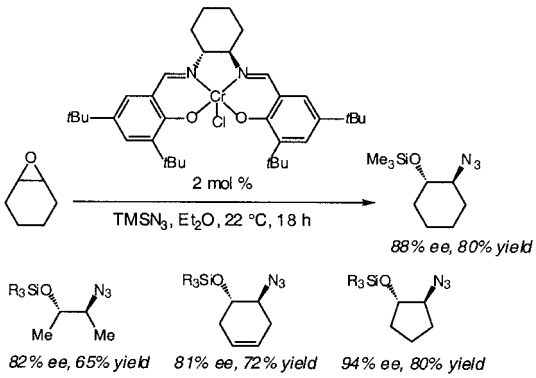
6.3
Zr-Catalyzed Enantioselective C–N Bond-Forming Reactions

In 1992, Nugent reported an intriguing Zr-catalyzed asymmetric addition of silyl azides to *meso* epoxides (Scheme 6.37) [118]. This C–N bond-forming reaction is promoted in the presence of the chiral amine triol **116** and trimethylsilyl trifluoroacetate. The discovery was based on the notion that a tightly bound multidentate ligand would be most effective for transfering chirality. Various Lewis acidic additives were then screened for their ability to enhance the reactivity. The result was the development of an efficient asymmetric method that delivers various cyclic and acyclic azido silyl ethers with appreciable levels of enantiocontrol; representative examples are shown in Scheme 6.37. More recent detailed mechanistic studies have led to the proposal of a bimetallic transition structure (see Scheme 6.37) that resembles that suggested by Jacobsen for his Cr-catalyzed variant of the same process (see below). Thus, as shown in Scheme 6.37, one Zr center serves as the Lewis acid to activate the epoxide towards nucleophilic attack, and the other transition metal center associates with an azide, delivering it to the adjacent activated substrate [119].

Related catalytic enantioselective processes Subsequent to the Nugent studies, Jacobsen and co-workers published a series of papers outlining the details of a highly efficient and enantioselective Cr-catalyzed addition of $TMSN_3$ to *meso* epoxides (Scheme 6.38) [120]. Enantioselectivities are comparable to those reported by Nugent, but the Jacobsen method requires lower catalyst loadings and has been demonstrated to be most effective in catalyzing the kinetic resolutions of a wide range of chiral epoxides [119b].



Scheme 6.37. Zr-catalyzed enantioselective desymmetrization of *meso* epoxides proceeds efficiently and with high levels of asymmetric induction.



Scheme 6.38. Cr-catalyzed asymmetric addition of silyl azides to *meso* epoxides.

6.4
Zr-Catalyzed Enantioselective C–H Bond-Forming Reactions

Much progress has been made in the *ansa*-metallocene-catalyzed hydrogenation of alkenes. Both Zr- and Ti-based catalytic systems have been used for this purpose; terminal, 1,1-disubstituted, as well as trisubstituted alkenes have been used as substrates. By far the most successful hydrogenations involve trisubstituted alkenes, for which enantioselectivities in the range 83–99 % *ee* have been reported. Initial studies in this area were carried out by Waymouth and Pino, in which the polymerization catalyst (ebthi)ZrX_2/MAO was used in the presence of H_2 to effect alkene hydrogenation [121]. Pino and Waymouth recognized that, in certain instances, alkene polymerization proceeds sluggishly because hydrogenation of the metal-alkyl intermediate takes place significantly faster than alkene

insertion, leading to the formation of hydrogenated monomers in large excess (as compared to the corresponding alkene oligomers and polymers).

The marked difference in reaction efficiency that arises when different sources of metallocene are employed in the (ebthi)Zr-catalyzed hydrogenation is illustrated in Table 6.5. The mechanism by which MAO converts the zirconium(IV) salts to the active zirconium hydride species remains unclear [122]. However, it has been proposed that a chlorine atom may form an η^2-bridge between aluminum and zirconium when the dichloride salt is used, thereby preventing formation of the active cationic metal center.

As already mentioned, and as illustrated in Table 6.6, an important prerequisite for efficient cationic (ebthi)Zr-catalyzed hydrogenation is that the alkene should not be able to polymerize in a facile manner. Whereas with 1-decene as the substrate, only 28 % of the hydrogenation product is obtained (Table 6.6, entry 1; the remainder of the product is the derived polymer), 2-methyl-1-pentene affords 97 % of the hydrogenation adduct

Table 6.5. Hydrogenation of styrene as a function of the zirconium catalyst precursor.

Catalyst precursor	*Gas*	*P_o (kPa; atm)*	*Yield %*
(ebthi)$ZrMe_2$	H_2	$2.0 \cdot 10^3$; 20	93
(ebthi)Zr-binol	D_2	$1.7 \cdot 10^3$; 17.5	89
(ebthi)$ZrCl_2$	H_2	$2.0 \cdot 10^3$; 20	0

Table 6.6. Hydrogenation of alkenes with (ebthi)$ZrMe_2$/MAO as precatalyst.

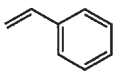
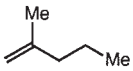
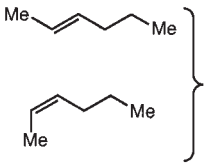
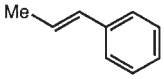
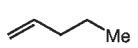
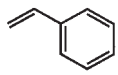
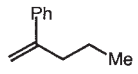
Entry	*Substrate*	*P_o (kPa; atm)*	*Conv (%)*	*Yield (%)*
1		10^3; 10	95	28
2		$2 \cdot 10^3$; 20	94	93
3		$2 \cdot 10^3$; 20	100	97
4		10^2; 1	96 4	50 (combined)
5		$2 \cdot 10^3$; 20	20	20

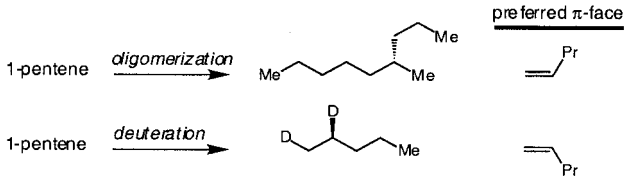
Table 6.7. Enantioselective hydrogenation and deuteration of alkenes catalyzed by (*R*)-(ebthi)Zr-binol and MAO (at 25 °C).

Substrate	*Gas*	*Cat (mol%)*	*Yield (%)*	*ee (%)*	*Product config.*
	D_2	–	10	23	*R*
	D_2	$6.0 \cdot 10^{-4}$	61	65	*R*
	H_2	$2.2 \cdot 10^{-4}$	95	36	*R*

(Table 6.6, entry 3). In a competition experiment, *trans*-2-hexene was found to be hydrogenated much faster than its corresponding *cis* isomer (entry 4).

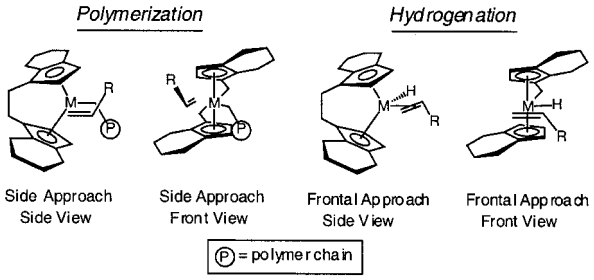
The data in Table 6.7 illustrate that when the non-racemic (ebthi)Zr system is used to catalyze the hydrogenation of prochiral alkenes, moderate levels of enantiofacial differentiation are observed (23–65 % *ee*). Enantioselective deuteration of pentene occurs in low yield but shows noticeable enantioselection (23 % *ee*). The same reaction with styrene proceeds in 61 % yield and with moderate enantioselectivity (65 % *ee*). Hydrogenation of 2-phenyl-1-pentene proceeds in excellent yield but with poor control of stereochemistry (95 % yield, 36 % *ee*).

A notable aspect of the (ebthi)ZrX_2-catalyzed hydrogenation and deuteration of alkenes is that these reactions occur with an opposite sense of stereochemistry as compared to similar oligomerization reactions. Thus, as the example in Scheme 6.39 illustrates, the prochiral π-face that is hydrogenated is the opposite face to that on which carbon–carbon bond formation takes place in the related polymerization process.



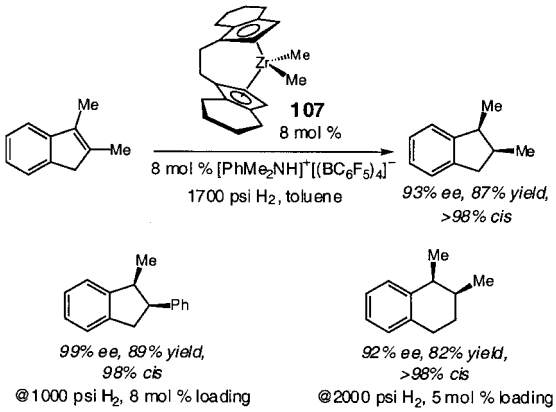
Scheme 6.39. Variations in enantiofacial selectivity in reactions catalyzed by (ebthi)Zrbinol/MAO.

Waymouth has suggested that (ebthi)Zr-catalyzed hydrogenation occurs from the opposite π-face to that which undergoes polymerization because a sterically demanding polymer chain would prefer to associate with the zirconocene catalyst in the manner shown in Scheme 6.40. Thus, the pendant groups on the alkene substrate may be oriented such that steric interactions with the ebthi ligand are minimized. This mode of catalyst–substrate interaction necessitates that the reacting alkene adopts a side-on approach towards the (ebthi)Zr system in the oligomerization or polymerization processes. In contrast, in the hydrogenation of alkenes, illustrated in Scheme 6.40, the small hydrogen atom may readily adopt the side position below the tetrahydroindenyl ligand, allowing the larger alkene to approach the metal hydride from the sterically more accessible front face.



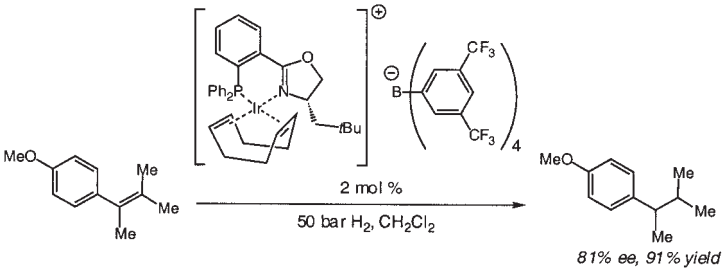
Scheme 6.40. Transition structures proposed for the polymerization and hydrogenation of alkenes by (ebthi)ZrX_2/MAO.

Tetrasubstituted alkenes are among the most challenging substrates for catalytic hydrogenation reactions. Towards this end, Buchwald and co-workers recently reported efficient and highly enantioselective Zr-catalyzed hydrogenations of a range of styrenyl tetrasubstituted alkenes (Scheme 6.41) [123]. Precedents based on efficient polymerization reactions promoted by cationic zirconocenes led these workers to consider similar catalyst species, derived from dimethylzirconocene **107**, for this purpose.



Scheme 6.41. Zr-catalyzed enantioselective hydrogenation of tetrasubstituted alkenes leads to the formation of two contiguous stereogenic centers with high enantioselectivity.

Related catalytic enantioselective processes Although great progress has been achieved in the area of metal-catalyzed hydrogenation reactions [124], examples of catalytic asymmetric hydrogenations of tetrasubstituted alkenes are rare. One other example, reported by Pfaltz and co-workers, is depicted in Eq. 6.26 (81 % *ee*, absolute stereochemistry of the product not determined) [125].



(Eq. 6.26)

6.5 Summary and Outlook

The studies summarized above clearly bear testimony to the significance of Zr-based chiral catalysts in the important field of catalytic asymmetric synthesis. Chiral zirconocenes promote unique reactions such as enantioselective alkene alkylations, processes that are not effectively catalyzed by any other chiral catalyst class. More recently, since about 1996, an impressive body of work has appeared that involves non-metallocene Zr catalysts. These chiral complexes are readily prepared (often in situ), easily modified, and effect a wide range of enantioselective C–C bond-forming reactions in an efficient manner (e. g. imine alkylations, Mannich reactions, aldol additions).

Nevertheless, much important research lies ahead. The list of important processes that do not as yet have a catalytic variant is still long. There are also unique organic transformations that are catalyzed by Zr salts but as yet do not have an asymmetric version [126]. If the above research is an indication, the catalytic enantioselective variants of many of these exciting transformations will soon be disclosed in our leading journals. Another challenge in this area remains the difficulty encountered in preparing chiral zirconocene catalysts, particularly since many of the reactions promoted by this group of chiral catalysts cannot be effected by the non-metallocene variants. Thus, the development of more practical, but equally or even more selective and efficient variations of existing methods should not be viewed as any less significant.

In conclusion, the research summarized above bears further testimony to the impressive advances made in asymmetric catalysis and synthesis during the past ten years. It also underlines the remarkable significance of this area of research not only to chemistry but to medicine and biology. The next few years will be exciting to watch indeed.

Acknowledgements

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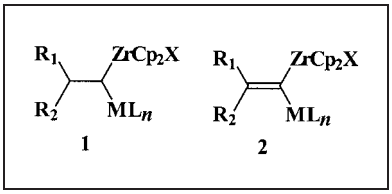
7
gem-Metallozirconocenes in Organic Synthesis

Valery M. Dembitsky and Morris Srebnik

7.1
Introduction

Many of the most important achievements in organic chemistry in the last 20–25 years have been associated in some way with the use of transition metal complexes. Among these complexes, an increasingly important place is occupied by zirconium compounds, which have a number of unique properties enabling them to be used as highly reactive reagents in organic synthesis [1–9].

The aim of this review is to summarize the available methodologies for synthesizing *gem*-metallozirconocene alkanes **1** and alkenes **2**, as well as their use in organic chemistry. These compounds are already well investigated, and they offer the potential to synthesize new classes of organometallic reagents and a wide variety of organic compounds in a highly stereoselective manner [1,5,7–11]. The carbon–metal bond in *gem*-metallozirconocenes undergoes a broad range of transformations, making these reagents useful in organic synthesis [1,5,8,12,13].



The impetus for the development of *gem*-bimetallics was initially to discover alkylidene-transfer reagents akin to Tebbe's reagent [14]. Schwartz prepared bimetallic aluminum–zirconocene derivatives by the hydrometallation of various vinyl metallic compounds [15–17]. Knochel has developed zinc–zirconium *gem*-bimetallics by hydrozirconation of vinylzincs and has used them as alkylidene-transfer reagents [18]. More recently, other *gem*-bimetallics have been developed that exhibit different reactivities of the two carbon–metal bonds. Thus, Normant and Marek have reported the allylmetallation of vinyl metals to afford zinc–magnesium and zinc–lithium *gem*-bimetallics, which react selectively with various electrophiles such as $ClSnBu_3$, H_2O, etc. [19, and references cited therein]. However, selective and sequential cleavage of the two carbon–metal bonds

with two different electrophiles presents a greater challenge. Knochel has prepared a series of zinc–boron *gem*-bimetallics by reacting zinc with α-haloboronic esters. He takes advantage of the different reactivities of the two carbon–metal bonds to synthesize various polyfunctionalized ketones [20]. Lipshutz has developed reagents based on tin and zirconium, which are obtained by the hydrozirconation of stannylacetylenes [21]. By selective cleavage of the carbon–zirconium bond with water, these reagents offer an efficient means of preparing α-alkenyl stannanes. Pelter has devised methods for the preparation of *gem*-boriolithio alkanes [22,23].

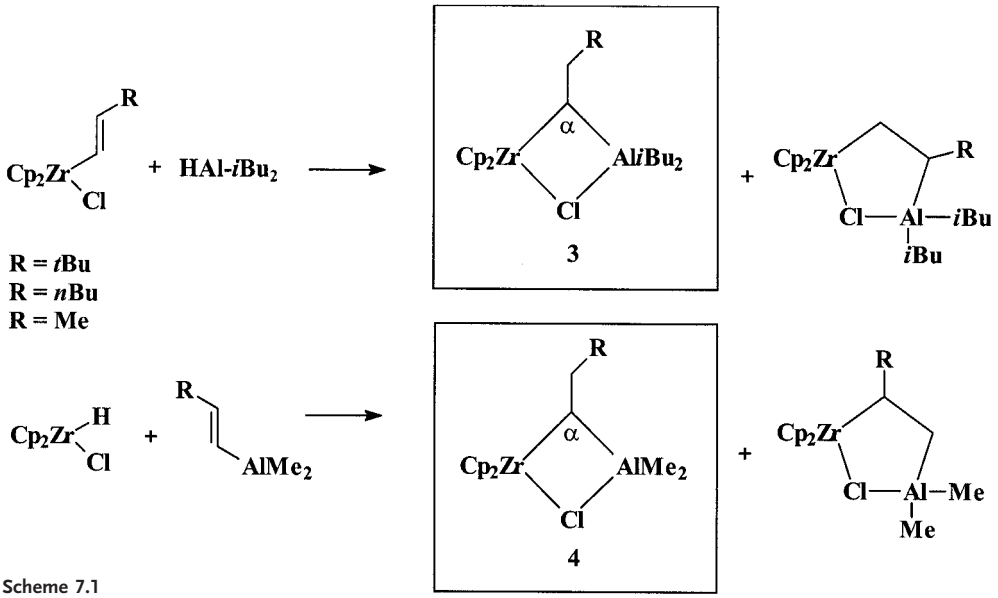
The *gem*-bimetallic compounds stabilize highly strained unsaturated compounds, allowing their use in selective carbon–carbon bond-forming reactions [6,8]. These complexes also increase the reactivity of unactivated molecules, enabling them to participate in non-traditional transformations [7,9]. A general route has been developed that allows a wider variety of unsaturated fragments to participate in these reactions. The use of these *gem*-metallozirconocenes in organic synthesis has led to the development of novel routes to a number of polyfunctionalized organic molecules [1–9].

This chapter is intended to highlight the synthesis and use of geminal bimetallic compounds such as *gem*-metallozirconocenes, but we will concentrate on the chemistry of aluminum, boron, lithium, gallium, germanium, tin, zinc, and zirconium.

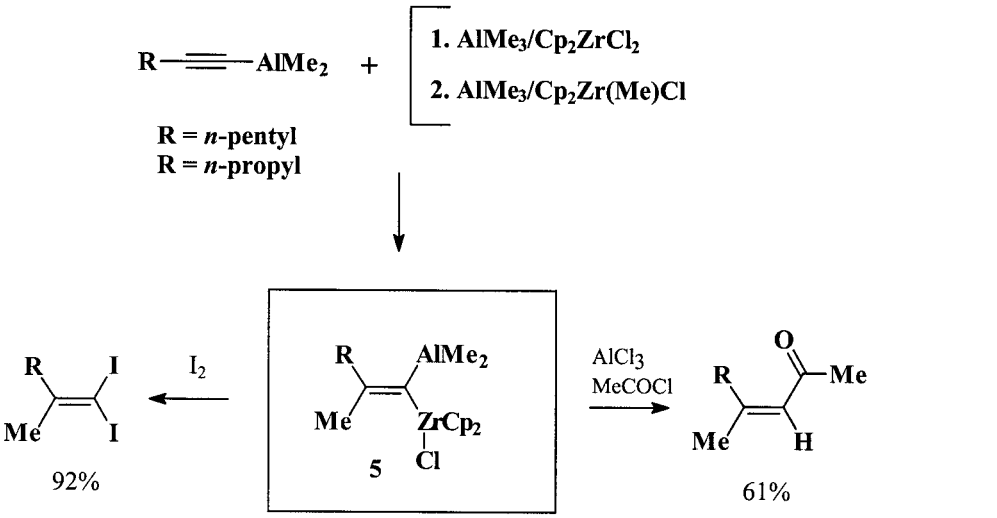
7.2
1,1-Aluminiozirconocene Complexes

Alkylidene-bridged *gem*-aluminiozirconocene complexes **3** and **4** are obtained by addition of an organometallic hydride to a metallated double bond [24]. It was found that aluminum–zirconium complexes could be obtained by two different routes: the addition of an organoaluminum hydride to an alkenylzirconium complex or the addition of $Cp_2Zr(H)Cl$ to an alkenylaluminum derivative [25]. In both cases, the direction of addition to the double bond, as revealed by ^1H NMR analysis, is apparently dependent on the steric bulk of the substituents at the double bond (Scheme 7.1). The reaction of diisobutylaluminum hydride with the *n*-hexenylzirconium complex gives a 5:1 mixture of products with the alkylidene-bridged species **3** predominating. Dimethyl-*n*-hexenylaluminum reacts with $Cp_2Zr(H)Cl$ to give a 3:2 mixture of addition products, the major isomer being **4**.

The carbometallation of 1-pentyldimethylalane with $AlMe_3$ and Cp_2ZrCl_2 or $Cp_2Zr(Me)Cl$ in a 1:1 ratio has been studied by van Horn et al. [10]. In both cases, the reaction gives the bimetallic derivative **5** in high yields (Scheme 7.2) [11].



Scheme 7.1



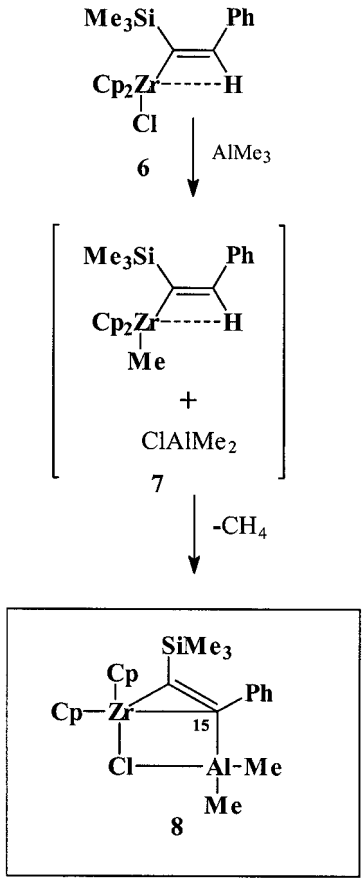
Scheme 7.2

7.2.1

Synthesis of Stable Planar Tetracoordinate Carbon Zr/Al Compounds

In 1874, van't Hoff [26] and Le Bel [27] independently surmised that tetracoordinate carbon is surrounded by substituents in a tetrahedral geometry. This perception marked the very beginning of modern organic chemistry, which is increasingly being determined by stereochemical argumentation. Some time ago, attempts were made to synthesize stable planar tetracoordinate carbon compounds [28–30].

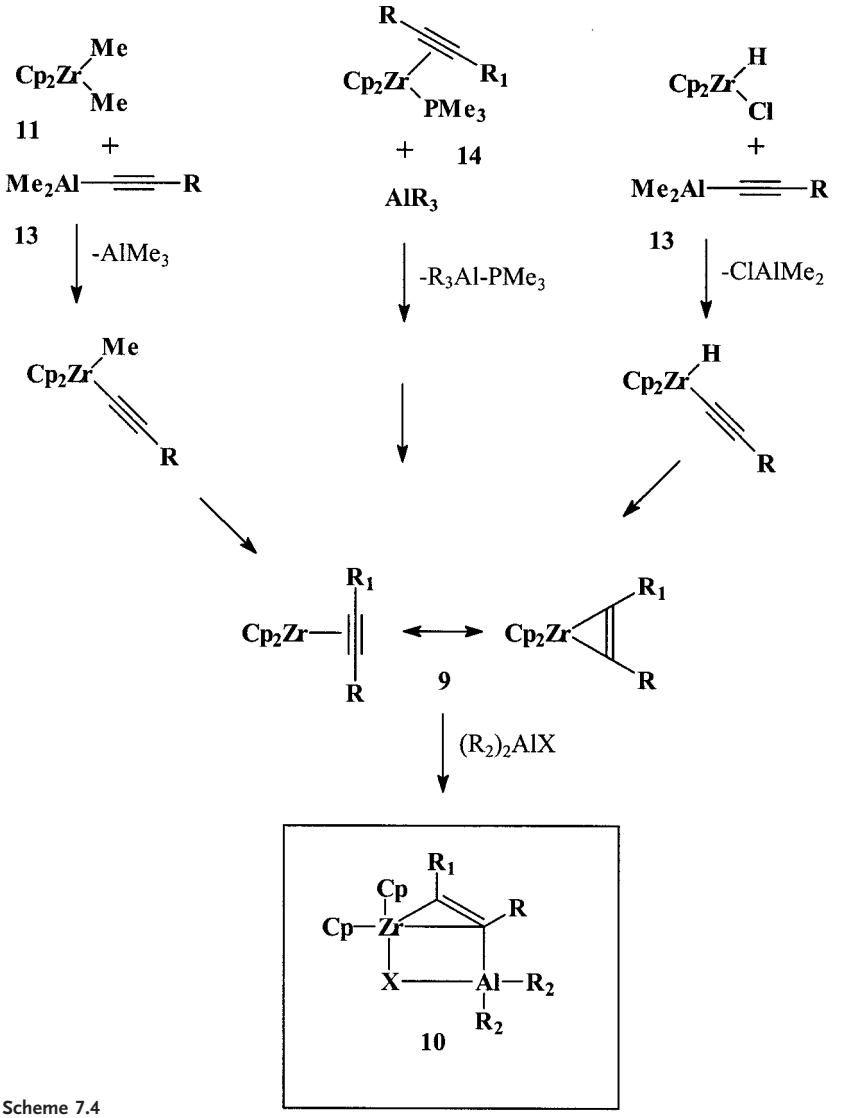
Planar tetracoordination at a carbon atom, which is stabilized through interaction with two different metal centers, has been realized in a dimetallic zirconium–aluminum complex. Thus, hydrozirconation of phenyl(trimethylsilyl)acetylene yielded the β-CH agostic alkenylzirconocene chloride complex **6**. This compound was then reacted with 1 molar equivalent of trimethylaluminum in toluene solution at ambient temperature to give the intermediate **7**. Acid/base reaction between the acidic agostic β-alkenyl hydrogen bond and the zirconium-bound methyl group gave a reactive (μ^2-alkyne)metallocene complex, which was trapped by the in situ formed dimethylaluminum chloride to give $Cp_2Zr(\mu\text{-}\eta^1,\eta^1\text{-}Me_3SiCCPh)(\mu\text{-}Cl)AlMe_2$ (**8**) in 90 % yield (Scheme 7.3) [31]. According to its X-ray data, complex **8** contains a planar central five-membered metallabicyclic ring



Scheme 7.3

system (Zr−C_{14}−C_{15}−Al−Cl) with very unusual bonding parameters, which have been studied [31].

Other synthetic methodologies have been developed by Albrecht et al. (Scheme 7.4) [32]. In situ generated (μ^2-alkyne)metallocene complexes **9** may be trapped with a variety of Lewis acidic main-group organometallics as scavengers, thereby forming compounds $Cp_2Zr(\mu\text{-}\eta^1\text{:}\eta^1\text{-}R_1\text{-}C1\text{-}C2)(\mu\text{-}X)AlR_2$ **10** (Scheme 7.4). The highly reactive (alkyne)metallocene complexes **9** are generated by reaction of either dimethylmetallocene or oligomeric **12** with aluminum alkynyl compounds **13**. Phosphane-stabilized (alkyne)metallocene complexes **14** react with Lewis acids to form a Lewis acid−phosphane adduct and the unsaturated (alkyne)zirconium species **9**, which is also stabilized. Compounds **10**, generated



Scheme 7.4

by the addition of Lewis acidic organometallics to **9**, exhibit a remarkable feature: a carbon atom (C-2) that shows four strong bonding interactions to neighboring atoms all lying perfectly in one plane. The synthesized complexes **10** containing planar tetracoordinate carbon centers are listed in Table 7.1. The crystal structures of three derivatives of bimetallic complexes of Al/Zr are represented in Figs. 7.1, 7.2, and 7.3.

Table 7.1. Compounds **10** containing planar-tetracoordinate carbon.

Compound	*R*	R_1	R_2	*X*	*Yield (%)*
10a	Ph	$SiMe_3$	Me	Cl	90
10b	Ph	Me	Me	CCPh	93
10c	*c*-C_6H_{11}	Me	Me	*c*-C_6H_{11}	52
10d	*t*Bu	Me	Me	CC*t*Bu	66
10e	$SiMe_3$	Me	Me	$CCSiMe_3$	83
10f	Ph	Ph	*i*Bu	H	62
10g	(C1=C2)$(CH_2)_4$		*i*Bu	H	70
10h	(C1=C2)$(CH)_4$		*i*Bu	H	48
10i	Me	Me	Me	Me	43
10j	Ph	Ph	Me	Me	88
10k	(C1=C2)$(CH_2)_4$		Me	Me	68
10l	(C1=C2)$(CH)_4$		Me	Me	78
10m	(C1=C2)$(CH_2)_4$		Et	Et	78
10n	H	Ph	Me	Cl	67
10o	H	Me	H	Cl	41
10p	H	*c*-C_6H_{11}	Me	Cl	27

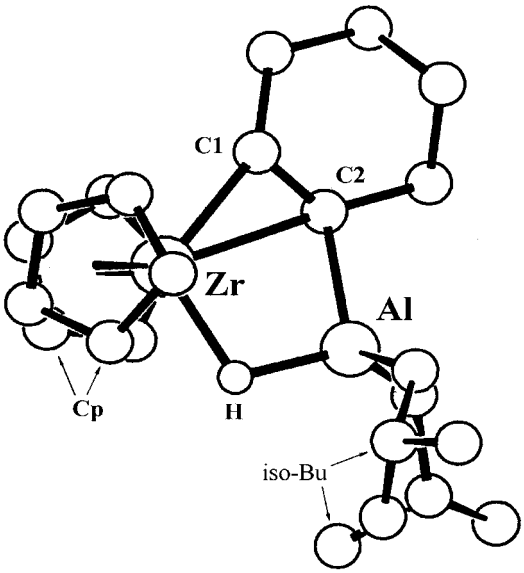


Figure 7.1. Crystal structure of the 1,1-bimetallic complex $Cp_2Zr(\mu\text{-}\eta^1{:}\eta^2\text{-}CC(CH_2)_4)(\mu\text{-}H)Al(i\text{-}Bu)_2$ **10** (X = H; R_1 = cyclo-C_6H_{11}; R_2 = *iso*-Bu_2). Adapted by the authors.

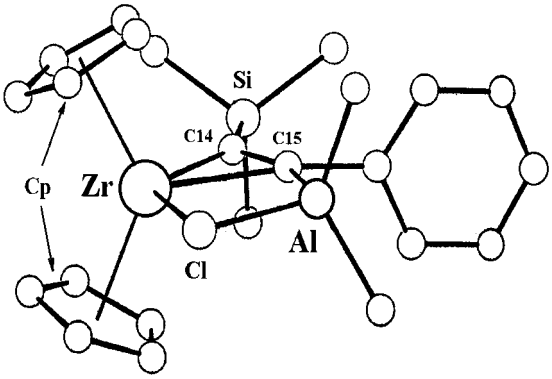


Figure 7.2. Crystal structure of the bimetallic complex $Cp_2Zr(\mu\text{-}\eta^1{:}\eta^2\text{-}Me_3SiCCPh)(\mu\text{-}H)AlMe_2$ **10a** (X = Cl; R = Ph; R_1 = $SiMe_3$; R_2 = Me); the planar-tetracoordinate carbon atom is C15. Adapted by the authors.

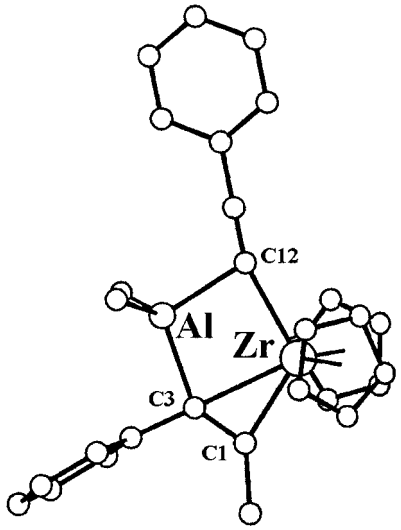


Figure 7.3. Another projection of the molecular structure of the 1,1-bimetallic compound **10** (X = C≡CPh; R_1 = Ph; R_2 = Me) with the double hydrocarbonyl-bridged $Cp_2Zr(\mu\text{-}C{\equiv}CPh)(\mu\text{-}CPh{=}CMe)AlMe_2$ complex exhibiting a planar-tetracoordinate carbon atom within the central metallacyclic ring system. Adapted by the authors.

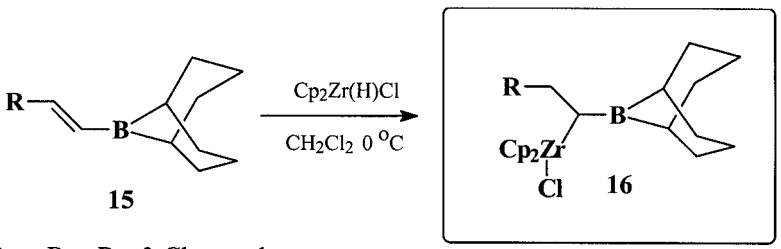
7.3
1,1-Boriozirconocene Complexes

During the last ten years, the chemistry of 1,1-boriozirconocene complexes has been studied. Both hydrozirconation and hydroboration reactions are well established, and are widely applicable to a wide variety of vinyl and acetylene derivatives [1]. Alkenylboranes and alkenylzirconium compounds can also be readily prepared. Therefore, hydrometallation of the corresponding alkenyl metals should offer a convenient method for preparing *gem*-boriozirconocenes [24].

7.3.1
gem-1,1-Boriozirconocene Alkanes

gem-Boriozirconocene alkanes may be prepared by either hydrozirconation of alkenylboranes or hydroboration of alkenylzirconium compounds. Compared with alkenylzirconium compounds, alkenylboranes are more stable and more easily accessible. Furthermore, alkenylboranes allow for much broader scope in terms of the boron ligands that can be used, such as various alkanes, diols, and amino alcohols. This makes a wide variety of alkenylboranes readily available. As a result, hydrozirconation of alkenylboranes was selected as the procedure for preparing *gem*-boriozirconocene alkanes. Initially, alkenyl-borabicyclo[3.3.1]nonanes (alkenyl-9-BBN) were chosen as the substrates for hydrozirconation. This is because the cyclononyl moiety in the alkenylborane derivatives is relatively unreactive. The organic substituents are readily transferred while the 9-BBN moiety is retained. Moreover, 9-BBN is one of the most readily available hydroborating agents and provides extremely high regioselectivities in the hydroboration of unsaturated hydrocarbons. Hydrozirconation of various 5-alkenyl-9-BBN derivatives **15** proceeded smoothly in dichloromethane, affording the expected *gem*-boriozirconocenes **16** (Scheme 7.5) [33].

However, these compounds proved to be unstable and difficult to characterize. The authors reasoned that the source of the instability was likely to be the trialkylboron moiety. Boronates are more stable than trialkylboranes since the lone-pairs of electrons on an oxygen atom can donate to the empty orbital of a boron atom. The corresponding *gem*-boriozirconocenes should also be more stable. Thus, hydrozirconation of the alkenyl-



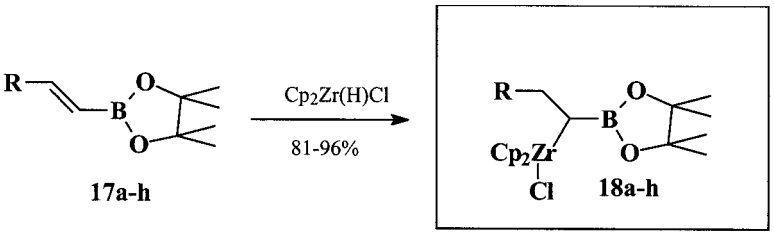
15 **16**

R = *n*Bu, *t*Bu, 3-Cl-propyl, cyclopentyl, 1-Me-propyl, 3-Ph-propyl, Ph

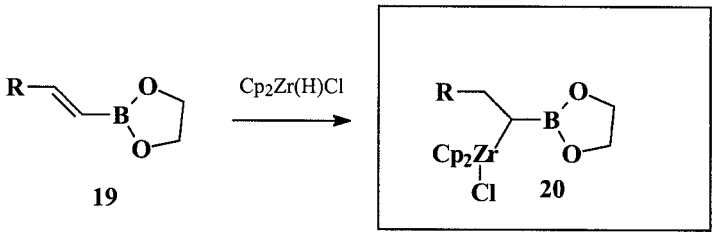
Scheme 7.5

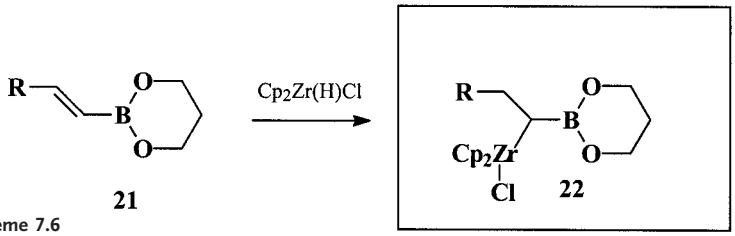
boronic esters **17** afforded clear yellow solutions of the *gem*-boriozirconocenes **18** (Scheme 7.6) [34]. As expected, compounds **18** and **20** based on boronic esters are fairly stable, and can be kept for a week in $CDCl_3$ without significant changes in their ^1H NMR spectra.

Zheng et al. [1] postulated that the driving force for placing Zr and B on the same carbon might stem from interactions between the zirconium and oxygen or boron and chlorine atoms. However, an X-ray analysis of **22** revealed that there are no intra- or intermolecular interactions between any of these atoms [35]. Compound **22** was also unambiguously characterized by ^1H-^1H double quantum filtered COSY [36] and ^{13}C-^1H heteronuclear chemical shift correlation NMR spectroscopy [37,38]. Considerable differences in the chemical shifts of the diastereotopic Cp groups were found in both the ^1H and ^{13}C NMR spectra. The NMR study unequivocally showed that the methine proton was at-



18a: R = $(CH_2)_3CH_3$
18b: R = $(CH_2)_3Cl$
18c: R = $CH(CH_3)CH_2CH_3$
18d: R = $CH(CH_2)_4$
18e: R = $C(CH_3)_3$
18h: R = $(CH_2)Ph$

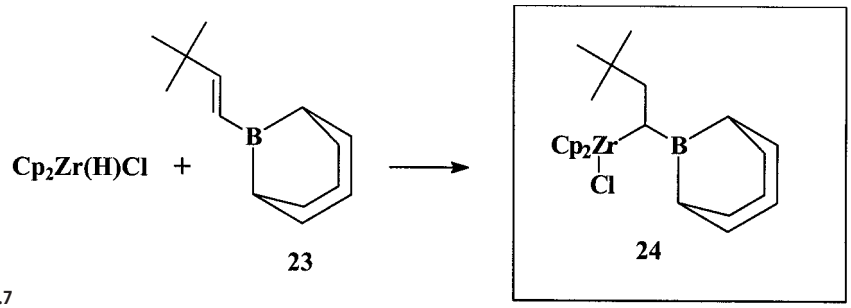




Scheme 7.6

tached to the α-carbon, and that two protons were attached to the β-carbon, which indicated that the zirconium atom was placed on the terminal carbon of the alkenyl chain in the hydrozirconation step.

Hartner and Schwartz [24] studied "long-chain" alkylidene-bridged heterobimetallic complexes and found that the addition of $Cp_2Zr(H)Cl$ to neohexenylborane **23** gave the new boron–zirconium complex **24** (Scheme 7.7).



Scheme 7.7

7.3.2
Use of *gem*-Borazirconocene Alkanes in Regioselective Synthesis

Mixed 1,1-bimetallics that undergo sequential and selective reactions at each of the carbon–metal bonds have attracted much attention lately in that they potentially offer a high degree of control in carbon–carbon bond-forming reactions [19]. Thus, Knochel has prepared a series of zinc–boron and copper–boron 1,1-bimetallics and has taken advantage of the different reactivities to synthesize various polyfunctionalized ketones [20,48]. Lipshutz et al. have developed reagents based on tin and zirconium [21,49]. Other mixed 1,1-bimetallics based on zirconocene have also been reported [11,15,18,50]. They react in the same way as Tebbe's reagent, but with greater selectivity in some instances. Pelter has been exploring the chemistry of 1-lithioboranes [22]. Prior to these studies, the chemistry of 1,1-bimetallic compounds had not been previously explored [33–35,39–47,51–54].

The different reactivities of the carbon–boron and carbon–zirconium bonds toward electrophiles are a consequence of the different bond polarities and the different electronegativities of boron and zirconium. Moreover, zirconium is a transition metal, while boron exhibits intriguing transition metal-like chemistry [55]. It is thus reasonable to presume that the combined use of boron and zirconium in organic chemistry should be synergistic, affording products and chemistry not attainable with the individual organometallics alone.

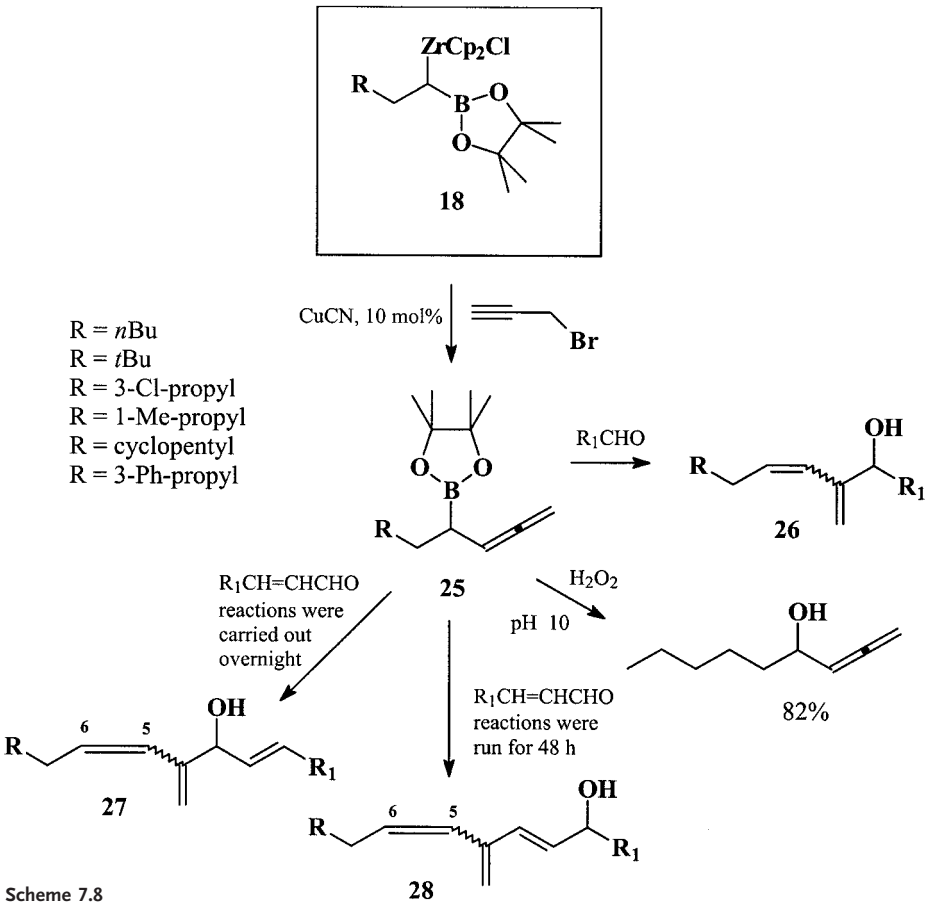
The alkenylboronic esters were synthesized according to a literature procedure [56]. Hydrozirconation of alkenylboronic esters with zirconocene hydrochloride, $Cp_2Zr(H)Cl$, prepared by Buchwald's procedure [57], took place smoothly in CH_2Cl_2, providing in each case the corresponding borazirconocene 1,1-alkane **18** [34]. Addition of propargyl bromide and a catalytic amount of copper(I) cyanide was accompanied by the disappearance of the yellow color associated with these compounds and by carbon–carbon bond

formation with exclusive cleavage of the C–Zr bond. α-Allenic boronic esters **25** were isolated in good yields (Scheme 7.8) [58–60].

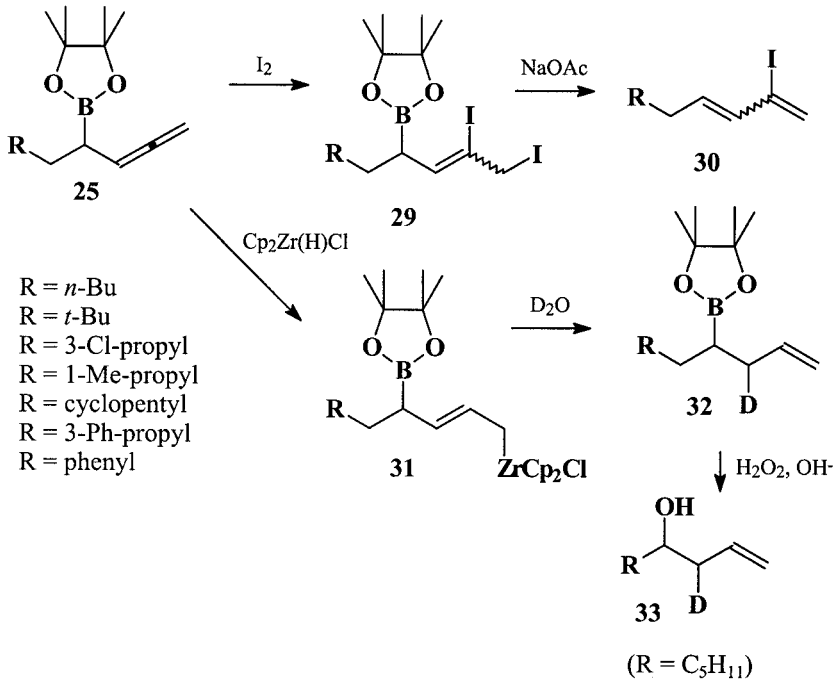
α-Allenic boronic esters **25** are also allylboranes [61,62]. Addition of an aldehyde to these boryl allenes affords the corresponding 1,3-dienyl allylic alcohols **26**. Allylboration with **25** works exceedingly well with aromatic aldehydes, except in the case of the reaction with *m*-hydroxybenzaldehyde. The low yield in the latter case may be due to the known sensitivity of allylboranes to proton sources [63]. The reaction is slower with aliphatic aldehydes, and the yields are somewhat lower too. The predominant isomer of the newly formed double bond is in all cases the (*Z*)-isomer.

Addition of an α,β-unsaturated aldehyde to **25** leads to trienes **27** or **28**, depending on the reaction conditions (Scheme 7.8). The geometry at the newly formed double bond (C_5–C_6) is predominantly *Z* in both **27** and **28**.

Iodination of terminal allenes has been reported to occur on the end carbon of the allenic system to give *cis*/*trans* mixtures of 1,2-diiodo adducts [64–66]. Reaction of a nucleophile with these adducts proceeds solely with displacement of the allylic iodine [65]. Iodi-



Scheme 7.8



Scheme 7.9

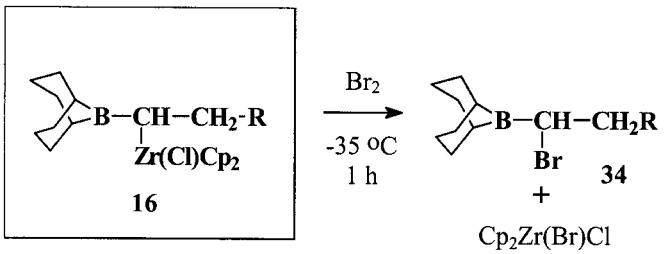
nation of **25** produced diiodo adducts **29** (Scheme 7.9). In situ reaction of **29** with sodium acetate did not lead to the expected allylic acetates, and only compound **30** was isolated [66–68]. The assignment of the allenic structure is wholly consistent with ^{1}H and ^{13}C NMR chemical shifts reported in the literature [69,70]. The reaction works well with both hindered and non-hindered **18** (Scheme 7.8) [71–74].

Hydrozirconation of **25** gave the novel bimetallic **31**. This is an interesting system in that it is both an allylborane and an allylzirconocene [75]. Although allylboranes are very reactive compounds [63], reaction with deuterium oxide occurred exclusively at the C–Zr bond and was accompanied by allylic rearrangement. Quenching of the reaction mixture with D_2O gave a single product **32**, arising from cleavage of the C–Zr bond. Oxidation of **32** led to the deuterated homoallylic alcohol **33** (Scheme 7.9).

7.3.3
Halogenation of *gem*-Boriozirconocene Complexes

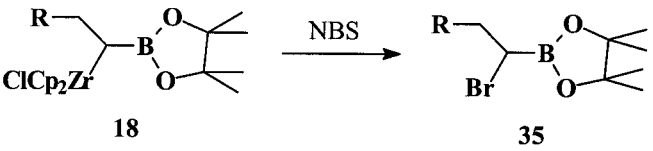
Zirconium, with an electronegativity of 1.4, is considerably more electropositive than boron, with an electronegativity of 2.0, and the carbon–zirconium bond is more polar than the carbon–boron bond. As a result, organozirconium compounds are much more reactive towards electrophiles than are organoboranes. For instance, the carbon–zirconium bond in organozirconium compounds is readily cleaved by water below ambient temperature [76], while protonolysis [77] of organoboranes requires forcing conditions, typically being performed at 120 °C. Therefore, selective cleavage of the carbon–zirconium bond in boriozirconium compounds should be readily achievable.

From a mechanistic viewpoint, cleavage of the carbon–metal bond by halogenation may proceed with either retention or inversion of the configuration at carbon, depending on the structures and the reaction conditions [78]. Halogenation of organozirconium compounds has been reported to proceed with retention of configuration [2]. On the other hand, the carbon–boron bond in organoboranes is less reactive towards halogens [79]. The presence of a base is essential for the halogenolysis of organoboranes. The reaction proceeds by an S_E2 mechanism [80]. Since halogenolysis of organozirconium compounds is a very facile process, without any need for a base, the carbon–boron bond in borazirconocene bimetallics should not be affected under the conditions used for cleavage of the carbon–zirconium bond. The expected products, α-haloboranes, are generally stable. Although the boron–zirconium bimetallics **16** based on trialkylboranes are unstable, selective cleavage of their carbon–zirconium bonds does afford α-bromoboranes **34** (Scheme 7.10) [33].



Scheme 7.10

The use of *N*-bromosuccinimide resulted in very complex mixtures and not the expected α-haloboranes. Apparently, the succinimide moiety may have acted as a base, causing various side reactions [81–85]. However, α-haloboronic esters are much more stable than α-halotrialkylboranes. Halogenation of boriozirconocene bimetallics **18** based on boronic esters proceeded very smoothly, affording the expected α-bromoboronic esters **35** (Scheme 7.11) [52].



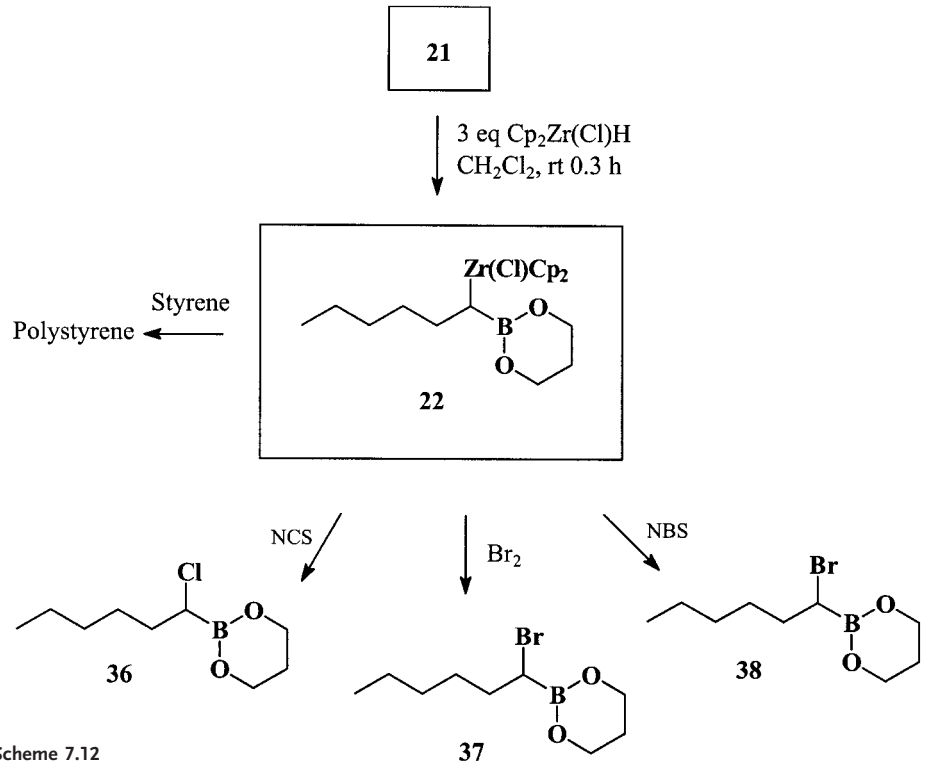
R = *n*Bu, *t*Bu, 3-Cl-propyl, cyclopentyl, 1-Me-propyl, 3-Ph-propyl

Scheme 7.11

It should be pointed out that, compared to α-bromoboronic esters, β-bromoboronic esters are much less stable. For instance, dibutyl (2-bromoethyl)boronate readily undergoes β-elimination, even under solvolytic conditions [87]. Therefore, the reaction of **18** with NBS also reaffirms the regioselectivity of the hydrozirconation step. The reaction is highly general and works equally well for the preparation of α-chloro- and α-iodoboronic

esters using *N*-chlorosuccinimide and *N*-iodosuccinimide, respectively. α-Haloboronic esters have also been obtained by hydrogen halide additions to alkenyl boronic esters and borane additions to 1-alkenyl halides. However, the regioselectivities of these additions are not always satisfactory. For instance, the hydroboration of 1-chloro-l-butene with BH_3 gave an 85:15 mixture of the products of α- and β-addition of the boron moiety [88]. To the best of our knowledge, regioselective additions of dibromoborane or catecholborane to vinyl halides, which might provide convenient conversions to α-haloboronic esters, have not been reported, whereas the addition of hydrogen iodide to dipropyl vinylboronate gave the α- and β-iodoboronic esters in a 60:40 ratio [89]. In contrast to these results, the preparation of α-haloboronic esters from alkenyl boronic esters has obvious advantages, including regiospecificity and the possibility of obtaining α-chloro-, α-bromo-, or α-iodoboronic esters in a one-pot reaction using the respective *N*-halosuccinimides. In addition to the above results, it was found that the carbon–zirconium bond in **18** (Scheme 7.11) could be readily cleaved by bromine in dichloromethane or iodine (neat).

The first example of a stable 1,1-bidentate Lewis acid based on boron and zirconium has been reported [35]. The synthesis of **22** is outlined in Scheme 7.12. Treatment of hex-1-yne with $HBBr_2 \cdot Me_2S$ followed by conversion of the dibromoboronic ester to the corresponding alkenyl boronic acid and esterification with propane-1,3-diol provided the alkenyl boronic ester. Hydrozirconation of this compound with 3 equivalents of the Schwartz reagent, $Cp_2Zr(H)Cl$ [57], afforded the desired product **22** in 86 % yield.



Scheme 7.12

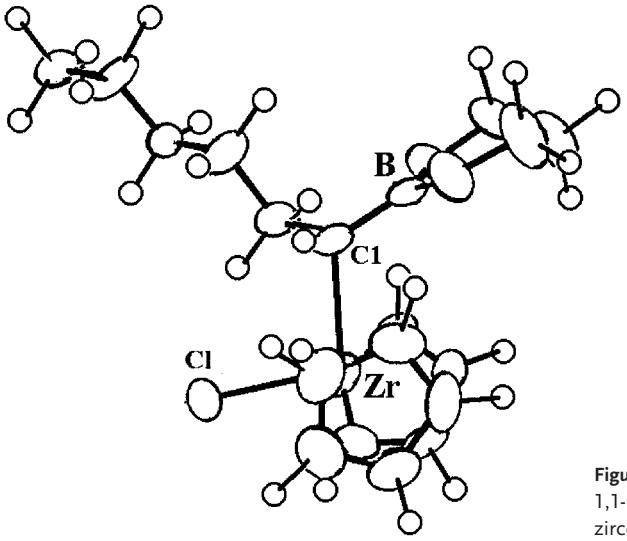


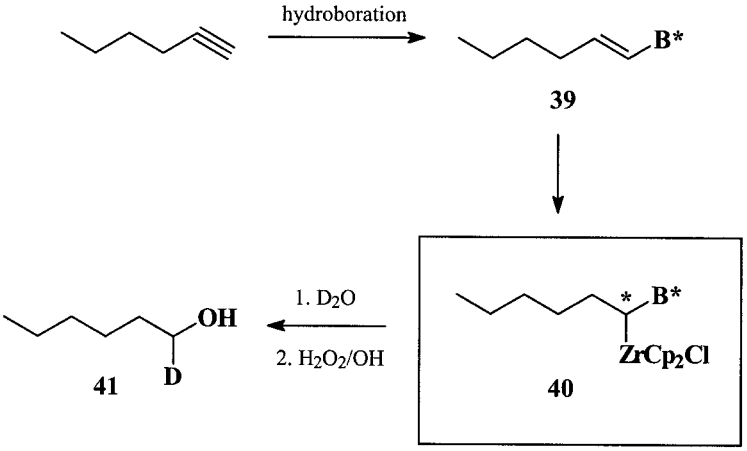
Figure 7.4. Crystal structure of the 1,1-bimetallic complex of boron and zirconium **22**. Adapted by the authors.

The reactive nature of compound **22** is illustrated by the series of transformations shown in Scheme 7.12, in which its Zr–C bond reacts selectively with electrophilic reagents to produce α-haloboronates **36**–**38**. Compound **22** also catalyzes the polymerization of styrene. The polymers thus obtained had weight-average molecular masses in the range 75000–100000 with polydispersities of 1.8–2.1. An X-ray analysis of **22** confirmed it to be a four-coordinate Zr complex with two cyclopentadienyl rings, chlorine, and the aliphatic C-1 carbon atom as the ligands (Fig. 7.4).

7.3.4
Diastereoselective Hydrozirconation

Although asymmetric synthesis is one of the most interesting and challenging problems for organic chemists, no attention has been paid to asymmetric hydrozirconation. Srebnik et al. [1], in continuing studies on the synthesis and utility of *gem*-boriozirconocenes, decided to explore this possibility. Alkenylboron compounds, the substrates for hydrozirconation, have the obvious advantage of much latitude in the choice of boron ligands. A multitude of optically active monoterpenes, 1,2-diols, and amino alcohols are readily available, and these can be efficiently converted to optically active alkenylboron compounds. It was expected that hydrozirconation of optically active alkenylboron compounds would afford optically active *gem*-borazirconocene alkanes with a high degree of diastereoselectivity and therefore optical induction. The protonolysis or deuterolysis of alkenylzirconium compounds has been reported to occur with retention of configuration [3,90]. Electrophilic carbon–zirconium bond cleavage in alkylzirconium compounds has also been shown to occur with retention of the configuration at carbon [2,3]. It has been suggested that the cleavage process involves a closed transition state. Therefore, in the process of deuterolysis, the oxygen atom of deuterium oxide coordinates to the zirconium atom through its vacant low-lying valence orbital, allowing front side attack of deuterium on the carbon–zirconium bond.

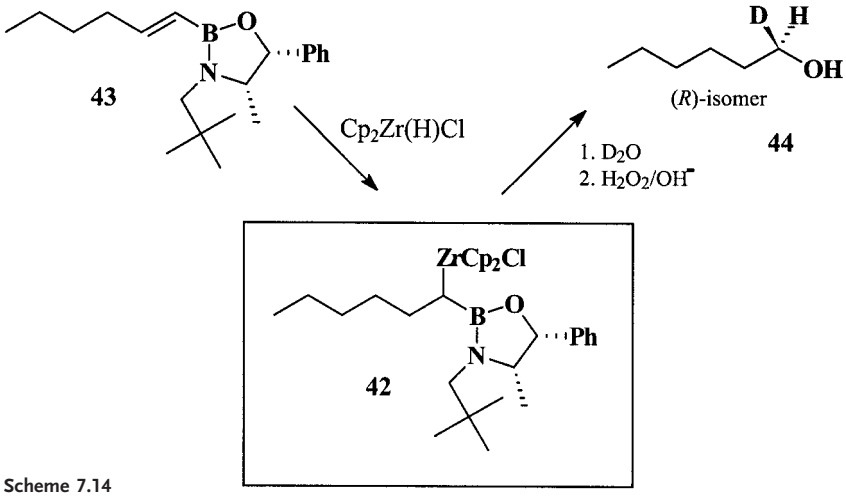
Treatment of the optically active *gem*-borazirconocene alkanes with deuterium oxide followed by alkaline oxidation affords the corresponding optically active 1-deuterio primary alcohols. The enantiomeric excess of the resulting primary alcohols represents the diastereoselectivity of the asymmetric hydrozirconation (Scheme 7.13). Based on the cost and availability of optically active ligands, three types were explored: monoterpenes, 1,2-diols, and 1,2-amino alcohols. Hydrozirconation of optically pure 1-alkenyl boranes **39** provided optically active 1,1-bimetallics **40**.



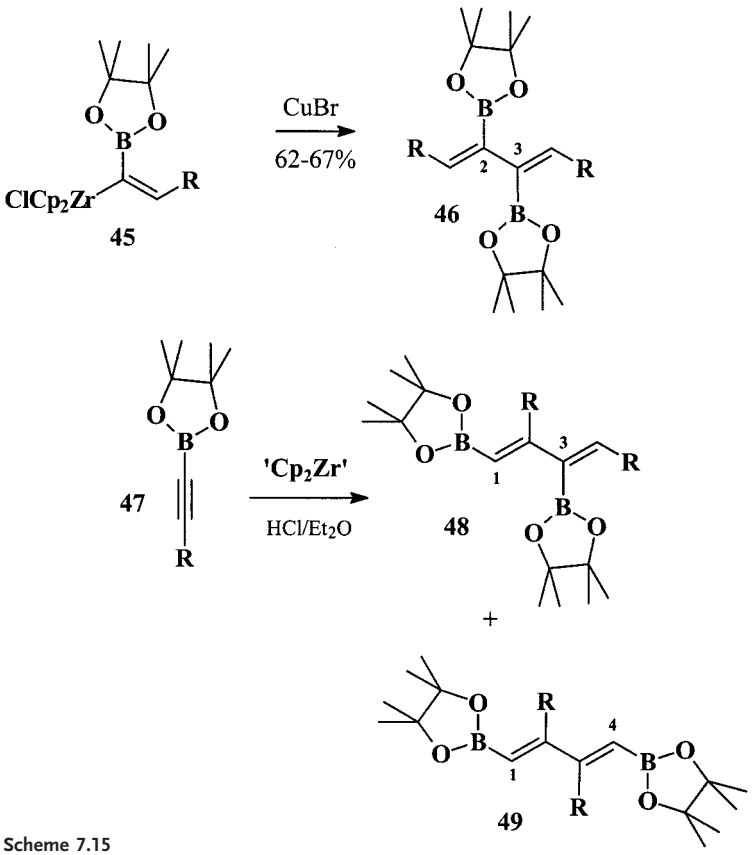
Scheme 7.13

Selective cleavage of the carbon–zirconium bond in **40** with deuterium oxide, followed by alkaline oxidation of the carbon–boron bond, afforded the optically active 1-deuterio primary alcohols **41** (Scheme 7.13). Monoterpene derivatives of alkenylboranes **39** did not undergo complete hydrozirconation. They gave low chemical yields and low incorporations of deuterium. The 1,2-diol and 1,2-amino alcohol derivatives of **39** underwent complete hydrozirconation and provided alcohols in relatively high chemical yields and with high deuterium incorporations. Neither class of compound gave high diastereoselectivities. However, the alkenyl oxazaborolidines, in addition to providing products in high chemical yields and with excellent incorporation of deuterium, also gave the best enantioselectivities. The (1*R*,2*S*)-ephedrine derivatives were superior to the diastereomeric (1*R*,2*R*)-*pseudo*ephedrine derivatives. The *N*-neopentyl derivative was particularly outstanding [53].

Oxazaborolidine 1-alkenyl boranes **43** were obtained by heating a mixture of the alkenyl boronic acid with a 1,2-amino alcohol [91] for 10 h in refluxing toluene with azeotropic removal of water. Hydrozirconation of optically pure 1-alkenyl boranes **43** (1 equiv., 0.5 M) with $Cp_2Zr(H)Cl$ provided optically active 1,1-bimetallic **42** (Scheme 7.14). Selective cleavage of the C–Zr bond in **42** with D_2O (1.5 equiv.), followed by alkaline oxidation of the C–B bond, as verified by ^1H NMR analysis, gave deuterated alcohol **44**. Although the mechanism of this new type of asymmetric reaction is not yet understood, the assignment of structure **43** is consistent with the approach of $Cp_2Zr(H)Cl$ from the less hindered face of the double bond. The pseudoephedrine derivative reagents, in which the double bond is more symmetrically disposed, give lower selectivities in the hydrozirconation step.



Scheme 7.14



Scheme 7.15

7.3.5
Preparation of Diborabutadienes by Zirconocene-Mediated Coupling

Hydrozirconation of 1-alkynyl pinacolboronates with $Cp_2Zr(H)Cl$ provides *gem*-boriozirconocenes **45**. Treatment of **45** with CuBr gives the homocoupled (1*E*,3*E*)-2,3-dibora-1,3-dienes **46** in good yield (Scheme 7.15) [92]. The zirconocene-induced coupling was studied using a series of 1-alkynyl pinacolboronates **47**. In this case, two regioisomers **48** and **49** were detected (Scheme 7.15).

7.3.6
Amination of Boriozirconocene Complexes

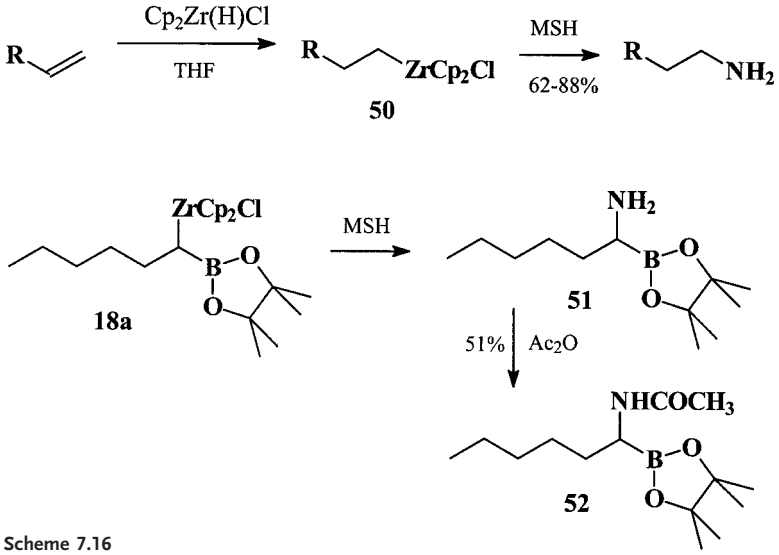
It has been found that appropriate aminating reagents can react with *gem*-borazirconocene alkanes to provide α-aminoboronic esters in reasonable yields. There is increasing interest in α-aminoboronic acid derivatives since these compounds are effective inhibitors of many serine proteases [93–95]. Previous routes [93] to these compounds rely on hydroboration, homologation with chloromethyllithium, and coupling with lithium hexamethyldisilylamide [$LiN(SiMe_3)_2$]. Newly developed *gem*-boriozirconocene alkanes have the potential to provide a convenient and efficient alternative to other metals; organozirconocene compounds readily undergo carbon–carbon bond-forming reactions, including cross-coupling with organic halides [96–99], alkene and alkyne insertions [11,100], addition of cationic organozirconium complexes to oxiranes [101] and aldehydes [102], and conjugate addition to α,β-unsaturated ketones [103–106].

The use of organozirconium compounds as carbanion equivalents is greatly facilitated by *trans* metallations to the more reactive aluminum [11,100], copper [104–106], nickel [96–98], and palladium [99] derivatives. Copper-catalyzed carbon–carbon bond-forming reactions of alkyl- and alkenylzirconocene compounds have been particularly well studied, and have found considerable application in organic synthesis [107,108].

α-Aminoboronic esters have mainly been synthesized according to Matteson's method [93]. More recently, an alternative access to α-aminoboronic esters has been reported [109], based on lithiation and catalytic hydrogenation, although this method is limited to the preparation of the pyrrole-related compounds.

Of the various electrophilic aminating reagents available for reaction with organometallic compounds, *O*-sulfonylhydroxylamines offer several advantages. They are readily available from easily accessible starting materials in a number of high-yielding steps [110,111]. One reagent, *O*-mesitylsulfonyl hydroxylamine (MSH), has been shown to be superior to the others in terms of solubility in organic solvents and reactivity as an electrophilic aminating reagent [112]. A recent investigation of amination involved hydrozirconation of an alkene followed by reaction of the resulting alkylzirconocene chloride **50** with MSH (Scheme 7.16) [2].

The amination of styrene, however, led to two products (1-phenyl-1-ethylamine and 2-phenyl-l-ethylamine) in a 1:3 ratio [113], indicating that the hydrozirconation was not completely regioselective [114,115]. Since it is well known that hydrozirconation of trisubstituted alkenes places zirconium at the least hindered carbon of the chain by a process involving zirconium migration, this class of alkenes was not investigated [5,116]. On the other hand, hydrozirconation/amination of 3-methyl-1,2-butadiene gave an allylic amine. Reaction of the latter could either occur at the terminal carbon or proceed with



Scheme 7.16

allylic rearrangement. Examination of its ^{1}H NMR spectrum revealed two non-equivalent methyl groups on a double bond. Amination had thus occurred at the terminal carbon, without allylic rearrangement, providing access to this important group of compounds. In the present methodology, only the alkyl group of $RZrCp_2Cl$ is transferred, and hence it is more efficient than the reactions involving R_3B reagents, in which one group is lost, or those involving R_2Zn reagents, the yields from which are low and mixtures are usually obtained [117,118].

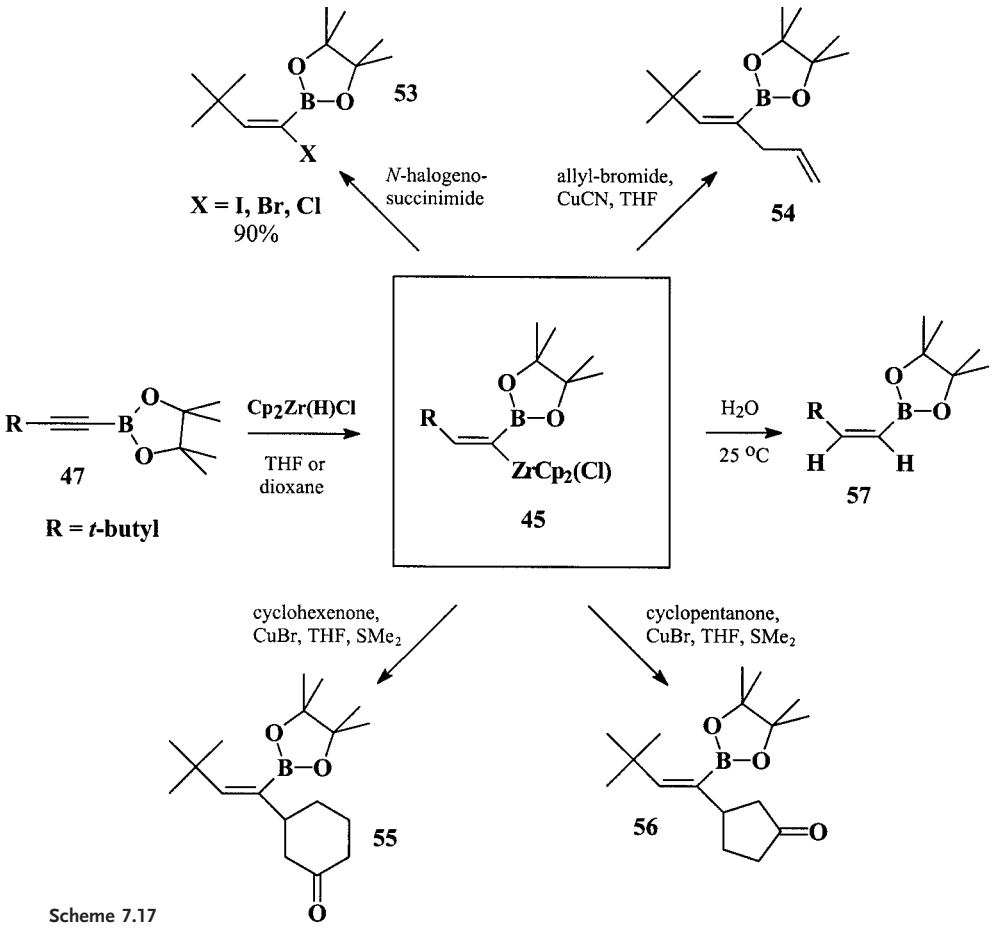
Having successfully aminated the alkylzirconocene chloride, the reaction was extended to borazirconocene 1,1-alkanes. In fact, amination of *gem*-borazirconocene alkanes **18** with MSH has proven to be a facile process [119]. Thus, when MSH is added to the *gem*-bimetallics in THF at ambient temperature, the amination is complete within 20 min (Scheme 7.16).

Compound **51** was found to be unstable and difficult to purify, as described in the literature [93–95]. Therefore, **51** was not isolated, but was instead converted to the stable pinacol 1-acetamido-l-hexylboronate derivative **52**. However, the acylated derivative **52** could not be purified by column chromatography as it was destroyed on silica gel and partially decomposed on alumina. Fortunately, we found that it dissolves in basic aqueous solution (pH $>$ 11) and can then be extracted into diethyl ether when the pH of the aqueous layer is 5–6. Finally, pure **52** was obtained by repeated washing with weak acids and bases. It should be mentioned here that exposure to a strongly acidic solution, which also dissolves compound **51**, results in its decomposition. Compared with other routes, the present two-step method involves mild reaction conditions (THF, ambient temperature) and a simple work-up procedure. It should prove very useful in providing an alternative access to α-aminoboronic esters, an important class of inhibitors of serine proteases.

7.3.7
(*E*)-1,1-Bimetallic Boriozirconocene Alkenes

A new class of *gem*-bimetalloalkenes based on dioxaborolanes and zirconocene has also been synthesized and investigated by Srebnik et al. [54].

The chemistries of $C_{sp2}-Zr$ and $C_{sp2}-B$ bonds differ considerably and this feature should allow a sequential route to substituted alkenes. Furthermore, cleavage of the $C_{sp2}-Zr$ and $C_{sp2}-B$ bonds generally occurs with retention of geometry [3,120]. Thus, *gem*-borazirconocene alkenes offer the possibility of synthesizing a multitude of stereodefined compounds. The area of mixed *gem*-bimetalloalkenes is being actively explored. In addition to the bimetallics prepared by Lipshutz [21], Knochel [48], and Marek and Normant [8], other mixed *gem*-bimetalloalkenes containing aluminum and zirconium [121], aluminum and hafnium [122], tin and boron [123], silicon and aluminum [124], and silicon and zirconium [125] have also been described.



Scheme 7.17

As representatives of this class of compounds, one hindered and one non-hindered *gem*-boriozirconocene alkene were prepared [54]. Hydrozirconation of a 1-alkynyldioxaborolane with $Cp_2Zr(H)Cl$ in either 1,4-dioxane or THF proceeded readily by a *syn* addition to give the essentially pure (*E*)-1,1-bis-metallic boriozirconocene **45** [12]. This bis-metallic complex **45** was also reacted with various electrophiles, thereby generating the alkenylboron derivatives **53**–**57** as shown in Scheme 7.17.

Vinylboronates are generally less reactive than vinylzirconocenes towards various electrophiles and hence selective reactions of the latter should be possible. It was found that selective cleavage of the carbon–zirconium bond in **45** by *N*-halosuccinimides provides (α-haloalkenyl)boronic esters **53** in excellent chemical yields and with complete regioselectivity (Scheme 7.17) [54]. An X-ray crystal structure determination of **45** confirmed the configuration of the four-coordinate Zr complex, with two cyclopentadienyl rings, Cl, and $C(sp_2)$ as the four ligands (Fig. 7.5) [54,126].

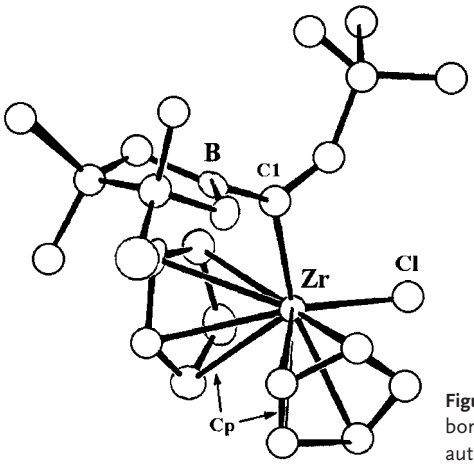


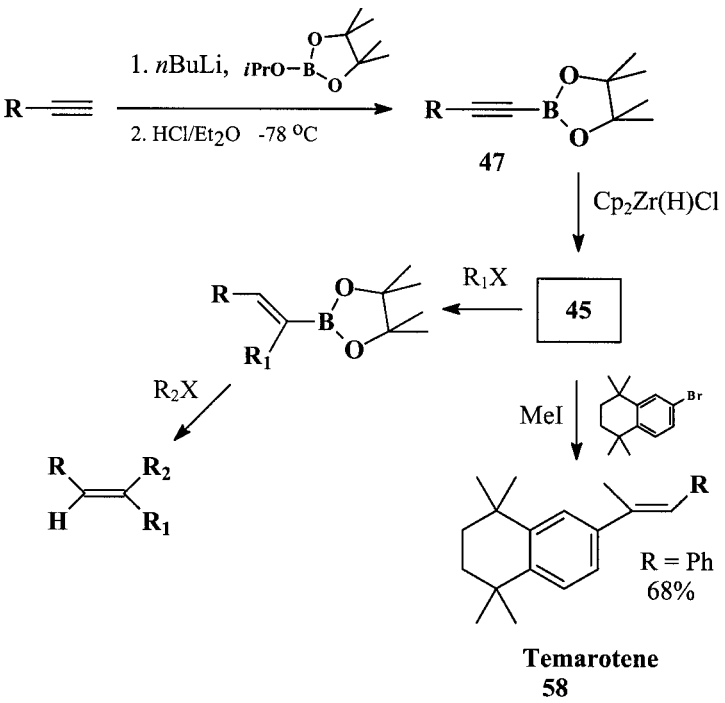
Figure 7.5. Crystal structure of the 1,1-bimetalloalkene boriozirconium complex **45** (R = *t*Bu). Adapted by the authors.

7.3.8
Hydrolysis of (*Z*)-1-Alkenylboronates

As an example of the selective reactivity of borazirconocene alkenes, their hydrolysis was examined [1]. The carbon–zirconium bond is more reactive than the carbon–boron bond towards various electrophiles, and so hydrolysis can be expected to occur with preferential cleavage of the former bond. Since hydrolysis of alkenylzirconocenes is known to proceed with retention of configuration [4,127–129], a direct utility of **45** is the preparation of (*Z*)-1-alkenylboronates **57** (Scheme 7.17) [12]. Though the *gem*-dimetalloalkenes can be isolated, in the present case it is not necessary. The desired (*Z*)-l-alkenylboronates can be obtained in a one-pot procedure by hydrozirconation followed by hydrolysis with excess H_2O. The reaction sequence is operationally simple and is compatible with various functional groups such as halides, acetals, silanes, and silyloxy protecting groups [12].

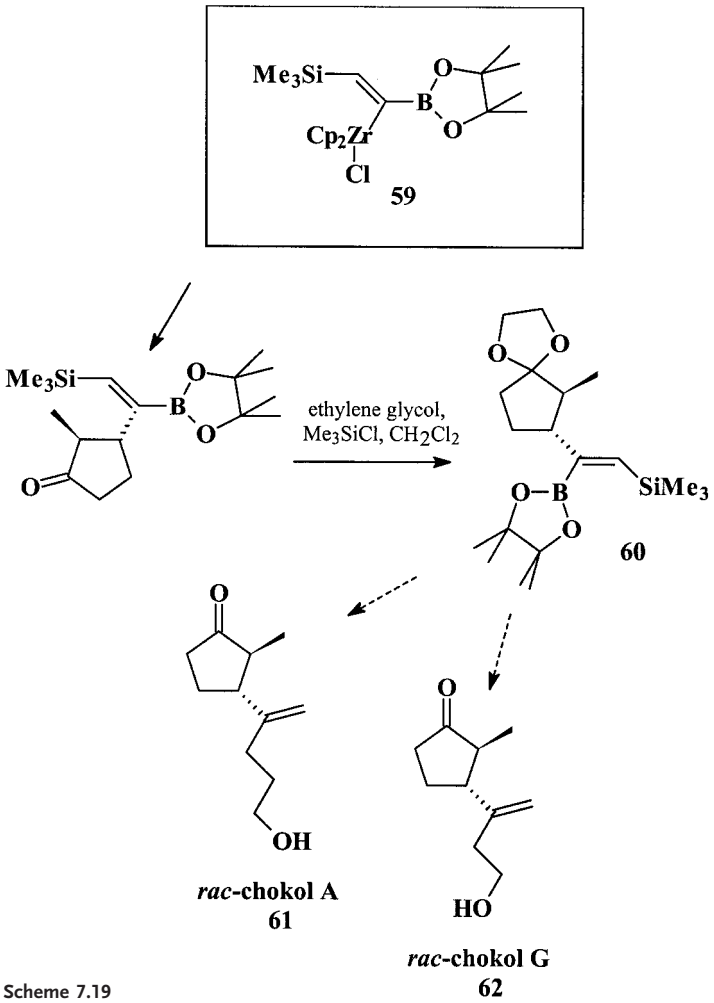
Stereospecific syntheses of temarotene (a retinoid) [130] and of chokols A and G (fungitoxic sesquiterpenes) [131–133] have been developed using 1,1-boriozirconocene complexes **45**.

The ability to form carbon–carbon bonds in a controlled manner around an alkene is the subject of continuing intense research [49,134–136]. These compounds are stable and, due to the considerably different reactivities of the C–Zr and C–B bonds, allow for selective and sequential reactions with a variety of electrophiles. Temarotene **58** is a retinoid of interest [137] because it shows no sign of hypervitaminosis A and it is not teratogenic, presumably due to the lack of a polar group [138,139]. The published synthesis of temarotene-type compounds is long and leads to mixtures of diastereoisomers, from which the desired product is eventually isolated [140–142]. However, the synthesis of temarotene **58** by the method of Srebnik et al. [130] is straightforward, as outlined in Scheme 7.18.



Scheme 7.18

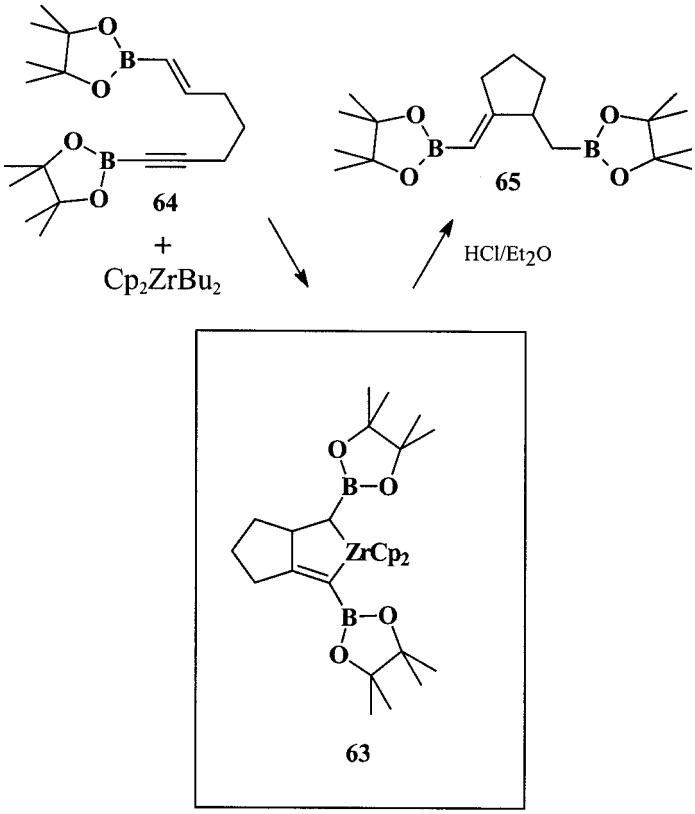
The stereoselective synthesis of *rac*-chokols A (**61**) and G (**62**) from the same precursor *gem*-boriozirconocene **59** involves a conjugate addition to 2-methylcyclopentenone to give the common intermediate **60**. The latter is then transformed through a series of reactions to provide the chokols in overall yields of 16 % and 17 %, respectively (Scheme 7.19) [131].



Scheme 7.19

7.3.9
Synthesis of Cyclic Boriozirconocenes

The formation of cyclic boriozirconocenes **63** has been observed by treating 1-alkynyl-6-alkenyl diboronates **64** with Negishi's reagent (Scheme 7.20) [133]. Hydrolysis of **63** with HCl in Et_2O gave the 1-alkenyl-1-alkyl diboronate **65** in 80 % yield.

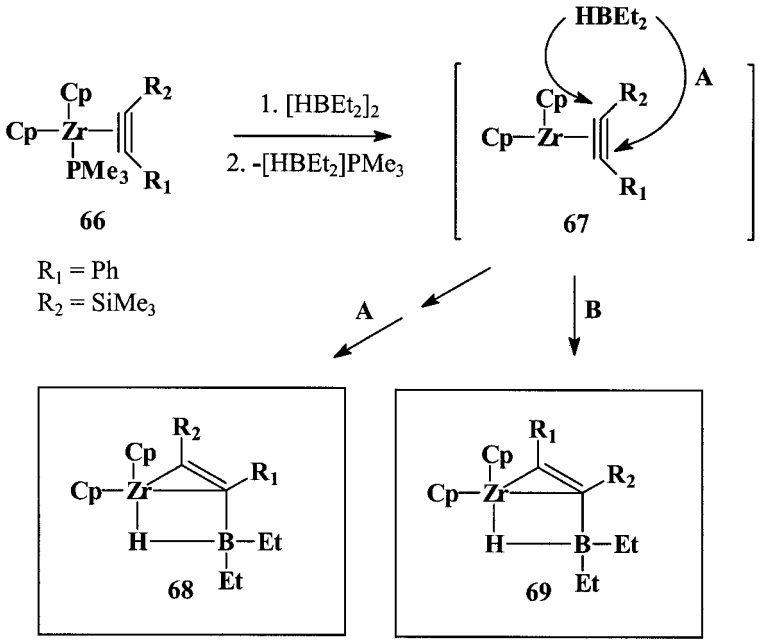


Scheme 7.20

7.3.10
Bimetallic Boriozirconocene Complexes with Planar Tetracoordinate Carbon

The *anti* van't Hoff/Le Bel compounds **68** and **69** were obtained by treating the trimethylphosphane-stabilized zirconocene acetylene complexes **66** with tetraethyldiborane in pentane. The reaction is proposed to proceed through a two-step sequence. In the first step, the trimethylphosphane ligand is removed from the starting complex to give the metallocene acetylene species **67**. This very reactive intermediate adds one equivalent of the Lewis acid to form the products **68** and **69**. If the starting complex contains an asymmetrically substituted acetylene, mixtures of the two regioisomeric products are observed, as would be expected on the basis of the outlined mechanism (Scheme 7.21). A remarkable feature is that hydroboration reactions of the acetylenes with tetraethyldiborane, which are known to be very fast even below 0 °C, are not observed in any case. The reactions are performed in pentane solution at ambient temperature. The zirconium compounds are converted to the corresponding complexes **68** (crystal structure shown in Fig. 7.6) and **69** within several days, in yields in the range 70–88 % [143].

The reaction of the trimethylphosphane-stabilized bis(trimethyl)silyl zirconocene **66** ($R_1 = R_2 = SiMe_3$) with $(HBEt_2)_2$ not only gives the *anti* van't Hoff/Le Bel compound **69**, but also the dimeric species $\{Cp[\mu\text{-}(\eta^1{:}\eta^5\text{-}C_5H_4)]ZrC(SiMe_3){=}C(H)(SiMe_3)\}_2$, which



Scheme 7.21

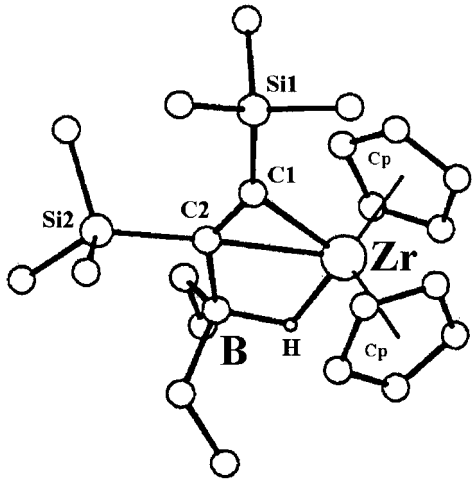
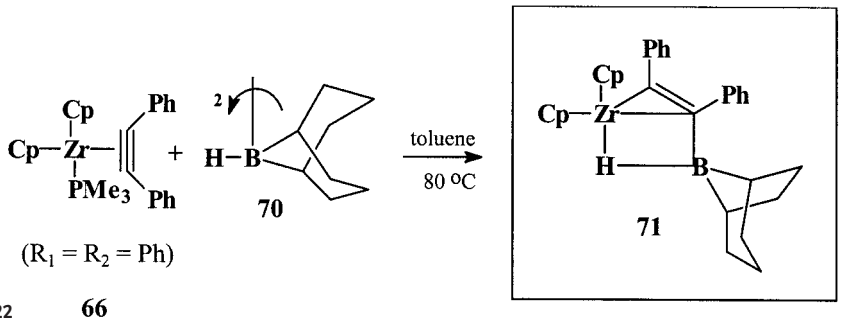


Figure 7.6. Crystal structure of the bimetallic complex $Cp_2Zr(Me_3SiCCSiMe_3)(\mu\text{-}H)(BEt_2)$ **68** ($R_1 = R_2 = SiMe_3$). Adapted by the authors.



Scheme 7.22

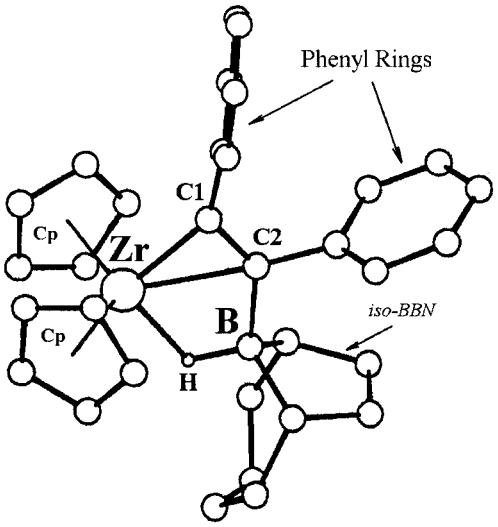
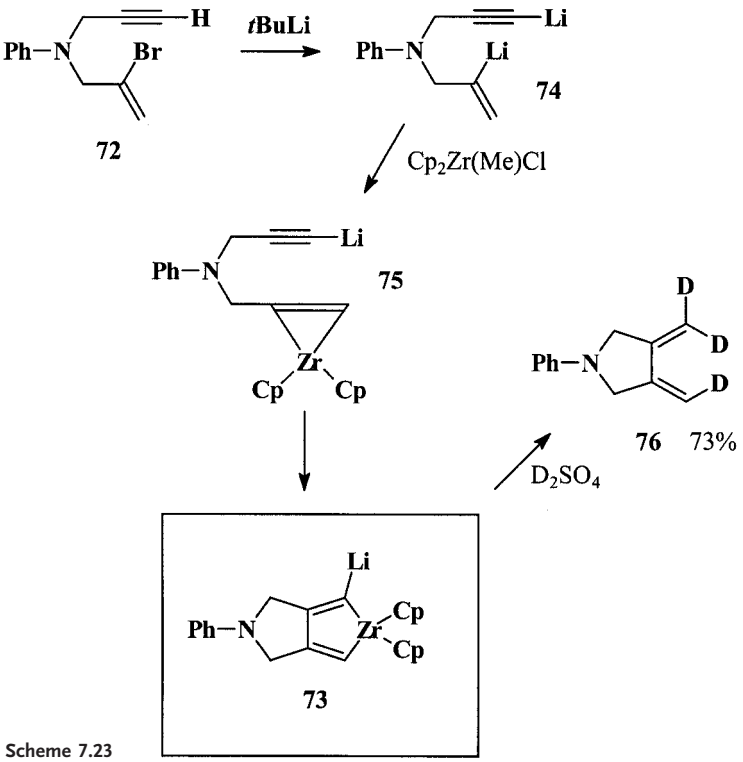


Figure 7.7. Crystal structure of the bimetallic complex CpZr(PhCCPh)(μ-H)(BB[4.2.1]N) **71**. Adapted by the authors.

was recently described by Rosenthal et al. [7,9] as a side product. On heating the zirconium complex **66** ($R_1 = R_2 =$ Ph) in toluene in the presence of 9-bis(borabicyclo[3.3.1] nonane) (BBN) **70** to 80–90 °C for eight hours, complex **71** is formed in 83 % yield. Besides the fact that **71** contains a square-planar carbon atom, this compound exhibits another remarkable feature. The borane unit shows a rearranged skeleton, identified as 9-borabicyclo[4.2.1]nonane, the so-called *iso*-BBN (Scheme 7.22). The X-ray crystal structure of **71** is shown in Fig. 7.7.

7.4
1,1-Lithiozirconocene Reagents

Reaction of *N*-(2-bromoallyl)-*N*-prop-2-ynylamines **72** with *tert*-butyllithium, followed by reaction with zirconocene methyl chloride and subsequent cyclization gives 1,1-lithiozirconioalkenes **73** via **74** and intermediate **75** (Scheme 7.23) [144,145]. Treatment of the lithiozirconium complex **73** with deuterated sulfuric acid leads to the trideuterated pyrrolidine **76**.



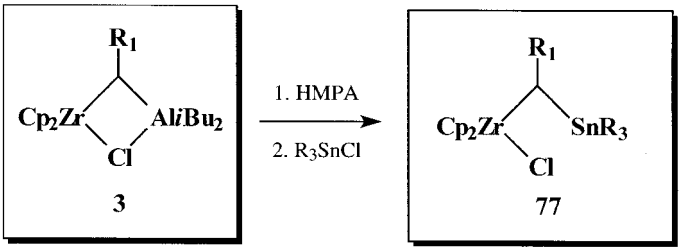
Scheme 7.23

7.5
1,1-Stanniozirconocene Reagents

7.5.1
gem-Stanniozirconocene Alkanes

Treatment of alkylidene-bridged zirconium–aluminum species with HMPA activates the C–Al bond of the alkylidene unit, making it susceptible to electrophilic attack [146]. Ligand-based activation of the C–Al bond can also be used to convert alkylidene-bridged zirconium–aluminum reagents to other bimetallic species. Thus, treatment of **3** with HMPA followed by addition of a weakly electrophilic metal salt can give rise to a new heterometallic species. Slow addition of a solution of R_3SnCl in toluene to a solution of **3** and 1

equivalent of HMPA in toluene at −40 °C, followed by stirring at room temperature for 4 h, furnishes *gem*-stannylzirconocene alkanes **77** (Scheme 7.24) in 60−100 % yield (depending on R or R_1; compounds **77a**−**c**).



77a. R = CH_3, R_1 = $(CH_2)C(CH_3)_3$, 75%
77b. R = Ph, R_1 = $(CH_2)C(CH_3)_3$, 82%
77c. R = CH_3, R_1 = $(CH_2)_4CH_3$, 58%

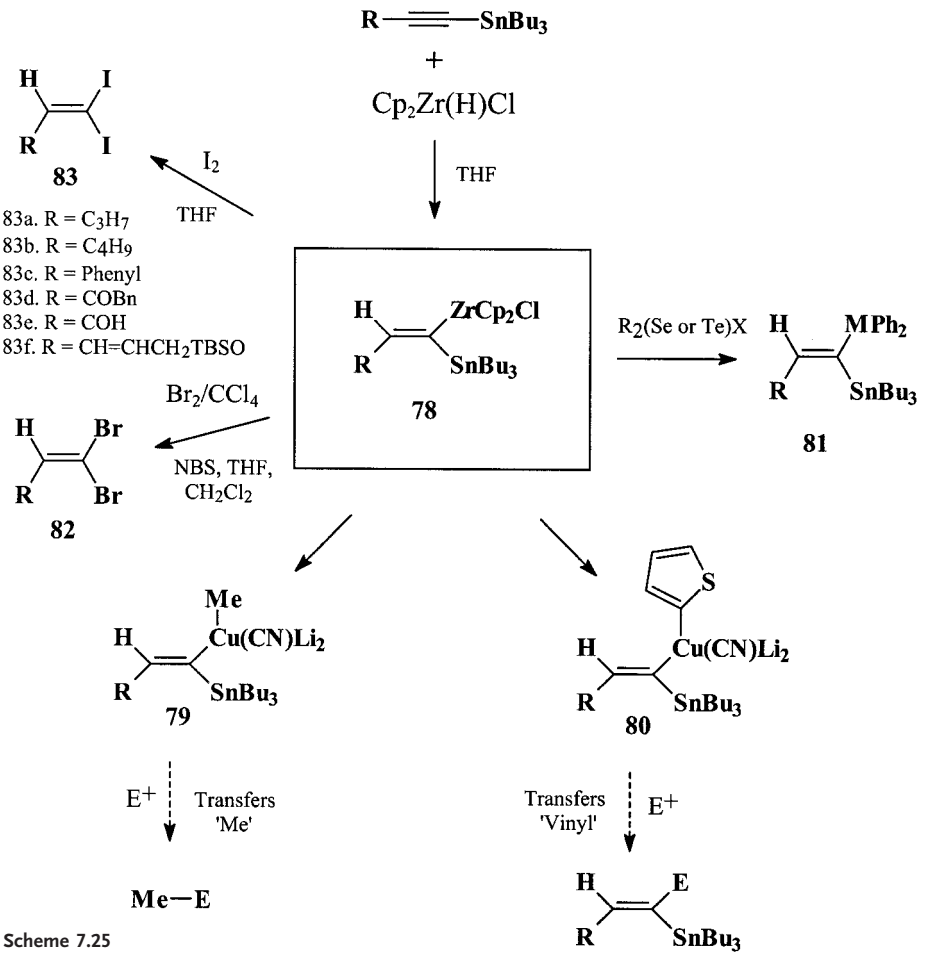
Scheme 7.24

7.5.2
Transmetalation Reactions

The addition of $Cp_2Zr(H)Cl$ to trialkylstannylacetylenes leads to the novel 1,1-dimetallo reagents stanniozirconocenes **78** (Scheme 7.25) [21,147]. Compounds **78** can be subjected to sequential manipulations of each metal; formally, they represent stereodefined 1,1-dianion equivalents. Displacement reactions can also be carried out with cuprates derived from **78**, although $CuMe_2(CN)Li_2$ is not a wise choice for this subsequent event since the transmetalated **79** is not selective in transfering a vinyl ligand (Scheme 7.25) [148]. By switching to CuMe(2-thienyl)$(CN)Li_2$, the mixed cuprate **80** is able to transfer the vinyl ligand using unactivated primary triflates, as well as allylic and benzylic halides [149].

Although 1,1-bimetalloalkenes of tin and selenium (α-selenenylvinylstannanes) may be very useful species as dilithioethene equivalents or as cation−anion synthons, to the best of our knowledge there has only been one report on their preparation and reactivity, and we have been unable to find any report concerning the synthesis of 1,1-bimetalloalkenes of tin and tellurium. Recently, Huang et al. [150] reported that the hydrostannylation of alkynylselenides gave (*E*)-1,1-bimetalloalkenes of tin and selenium under the catalysis of tetrakis(triphenylphosphane)palladium, and that these could be converted to trisubstituted alkenes. The stereo- and regioselective preparation of vinyl tellurides via alkenyl zirconocenes [151], the hydrozirconation of acetylenic tellurides [152], and the stereoselective preparation of ketene telluroacetals (1,1-bimetalloalkenes of tellurium and zirconium) have also been described [153]. New synthetic routes to 1,1-bimetalloalkenes of tin and either tellurium or selenium (**81**) involving the use of stanniozirconocene complexes have been reported [154].

A novel and highly efficient synthesis of 1,1-diiodo-, 1,1-dibromo-, and mixed (*Z*)- or (*E*)-l-iodo-l-bromo-l-alkenes using the 1,1-heterobimetallic reagents obtained by hydrozirconation of stannylacetylenes has also been described [155]. The hydrozirconation and halogenolysis steps were carried out at room temperature in THF under a nitrogen atmosphere. It is noteworthy that the developed route is compatible with various functionalities



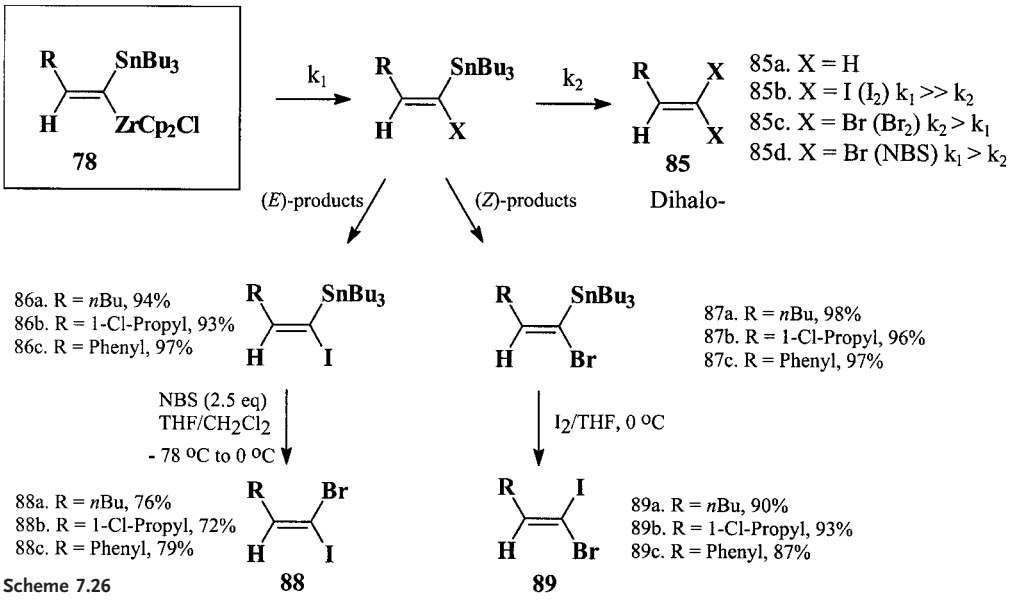
Scheme 7.25

such as hydroxyl groups or alkyl halides. The reactions are clean, and neither alkynyl halide nor over-halogenated products, for example, $RCHICI_3$ or $RCHBrCBr_3$, can be detected. The results summarized in Scheme 7.26 show the generality of this new route to trisubstituted 1,1-dihaloalkenes, in which the two carbon–halogen bonds are formed in a one-pot reaction yet are expected to be formed in a stepwise manner as the reactions of the C–Zr bond with electrophiles [21,147] are normally much faster than the reactions of the C–Sn bond. In accordance with these previous results, the new compounds **83a–c** were isolated after iodinolysis of the C–Zr bond using I_2 (1.07 equiv.) in THF at room temperature. In contrast, attempts to induce similar reactions of zirconated vinylstannane intermediates with Br_2 did not result in a clean or useful process. Reaction of **78** with 1.1 equivalents of Br_2 in CCl_4 was not chemoselective, showing competitive bromonolysis of the C–Zr and C–Sn bonds. Even the treatment of intermediates **78** with 0.9 equivalents of Br_2 in CCl_4 at −78 °C afforded a mixture of products containing the desired (*Z*)-**85c** or their (*E*)-isomers, the 1,1-dibromo-1-alkene **82**, and the (*Z*)-vinylstannane **85a** (Schemes 7.25 and 7.26).

7.5.3
Preparation of Halogenated Alkenes

Compound **85a** is formed by proton entrapment during aqueous work-up following the above reaction. The observed products (Scheme 7.26) indicate that Sn/Br exchange in **84** is somewhat faster than Zr/Br exchange in **78** ($k_1 > k_2$), whereas in **78** the Zr/halogen exchange always occurs exclusively [the (*Z*)-vinyl bromide is never obtained]. Using NBS (1.05 equiv.) in THF/CH_2Cl_2 at −78 °C to room temperature, it was possible to overcome these problems and compounds **85** were isolated in excellent yields (Scheme 7.26).

With compounds **86** and **87**, halogenolysis of the C−Sn bond was accomplished using a different halogenating agent to that used in the first step, thereby generating compounds of types **88** and **89** with complete stereocontrol. By treating **87a**−**c** with I_2 in THF at 0 °C, it was possible to obtain the isomerically pure (*Z*)-l-iodo-l-bromoalkenes **89a**−**c** in very high yields after column chromatography. In initial attempts to prepare the (*E*)-isomers, reactions of **85b** with Br_2 in CCl_4 were carried out at room temperature, 0 °C, and −78 °C. Mixtures of the isomers (*E*)-**88** and (*Z*)-**89** along with the dibromo compound **82** were obtained under all these conditions. The observed results were rationalized in terms of an addition−elimination process in the initially formed compound **88**. This side reaction was completely suppressed by performing the brominolysis with NBS in a THF/CH_2Cl_2 mixture. Under these conditions, the (*E*)-isomers **88a**−**c** were obtained exclusively and could be isolated by PTLC in the yields indicated in Scheme 7.26. Irrespective of mechanistic assumptions concerning the stereochemistries of halogenations of alkenylmetal compounds, the stereochemistries of **89a**−**c** and **88** could be assigned by ^1H and ^{13}C NMR. The vinylic proton signal is seen at δ = 6.45 for compounds **89a**,**b** and at δ = 7.65 for compound **89c**, whereas it appears at δ = 6.79−6.81 for isomers **88a**,**b** and at δ = 7.87 for **88c**.

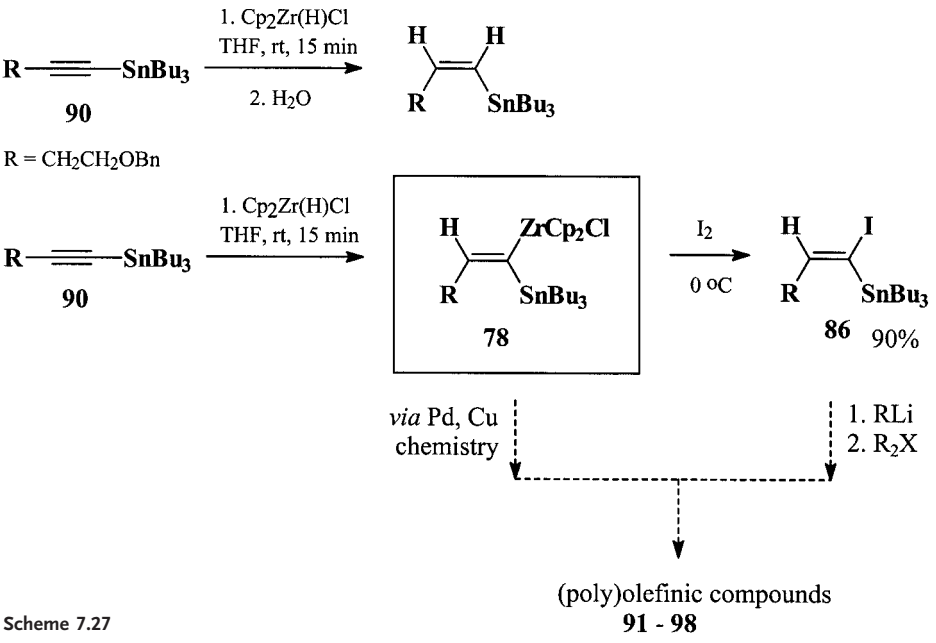


Scheme 7.26

A synthesis of potentially useful 1-iodo-1-bromo-l-alkenes has thus been developed that offers complete stereocontrol. These methods have also proven to be highly efficient for the preparation of 1,1-diiodo-1-alkenes and 1,1-dibromo-1-alkenes, which are very useful synthetic intermediates (Scheme 7.26) [155].

The preparation of (*Z*)-vinylstannanes by hydrozirconation of stannylacetylenes has been reported [21]. Earlier, a simple, efficient procedure for generating (*Z*)-vinylstannanes from acetylenic precursors **90** had also been developed (Scheme 7.27) [156–158].

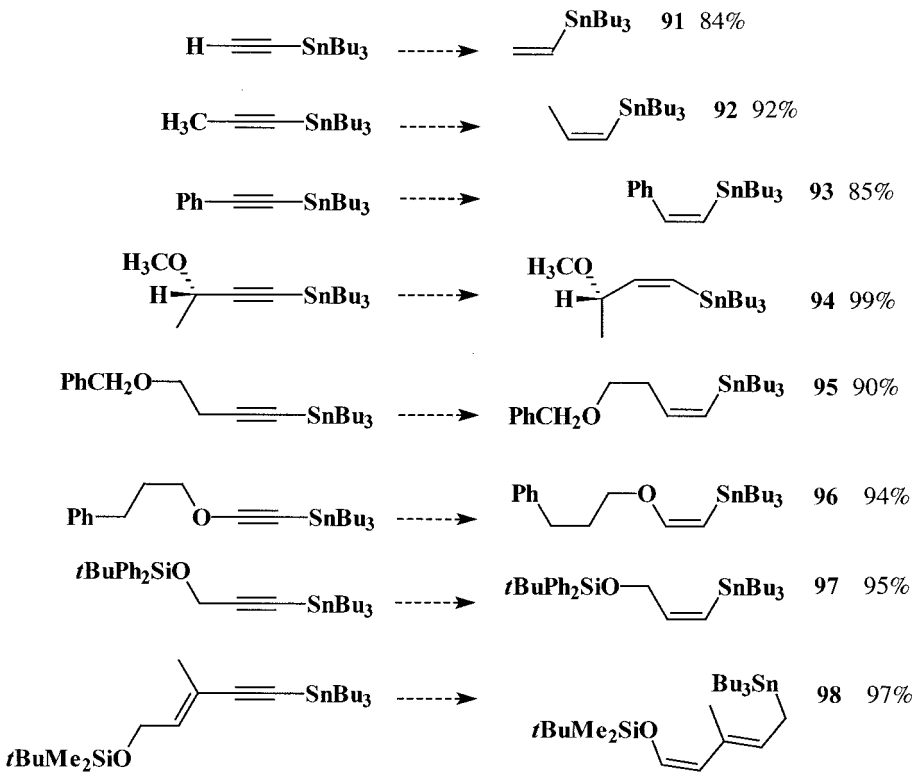
The standard procedure involves a hydrozirconation process utilizing THF as solvent, in contrast to the original Schwartz conditions, which require the use of benzene as the reaction medium [2]. These reactions are essentially stereospecific, high yielding, and, due to the greater solubility of $Cp_2Zr(H)Cl$ in THF, rapid. A survey of representative examples is given in Scheme 7.28. From this sampling, the most obvious limitation of the method is related to the propensity of this hydride source to reduce aldehydes and ketones in competition with the hydrozirconation [2,57]. Otherwise, the mild nature of these conditions allows tolerance of an assortment of desirable functionalities [159–161]. A typical synthesis is given in Scheme 7.27.



Scheme 7.27

Lastly, it should be appreciated that there is a regiochemical issue associated with the addition of $Cp_2Zr(H)Cl$ across unsymmetrical acetylenic stannanes. The long carbon–tin bond (ca. 2.2 Å) [162], the sensitivity of the hydrozirconation reaction to steric effects [2], and the polarizability of the carbon–tin bond would suggest that the Cp_2ZrCl moiety is attached at the position bearing the trialkyltin group. This was readily confirmed by quenching studies with D_2O and I_2 [163]. Although in this case the subsequent protonation step makes this question irrelevant, it is well worth recognizing the 1,1-dimetallo

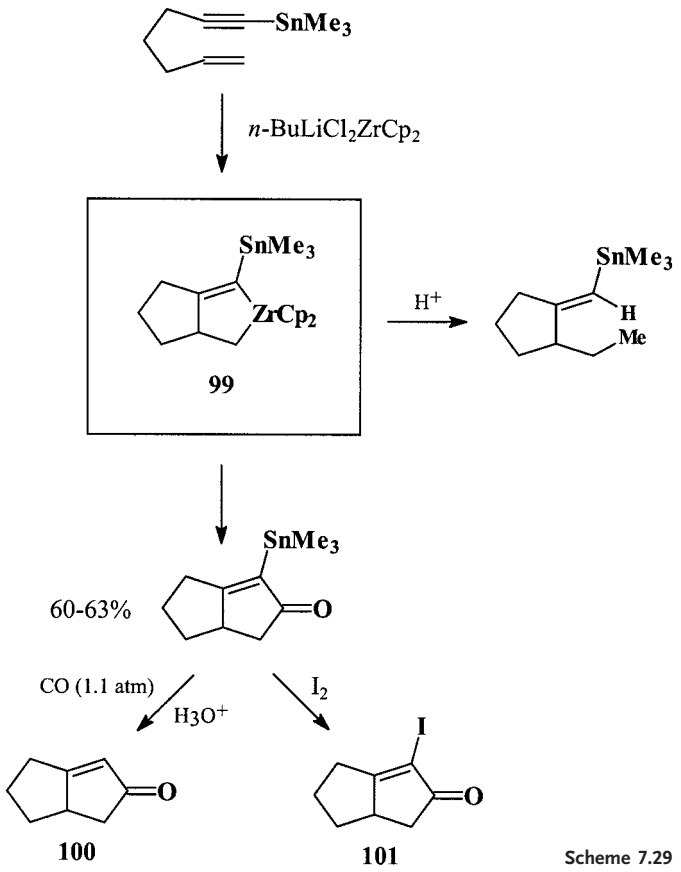
nature of the intermediates **78** involved [18,164]. In view of the significant differences in reactivity between vinylstannanes and vinylzirconocenes, e. g. toward cuprate transmetallations [165–167], species such as **78** can be regarded as stereodefined 1,1-vinyl dianions, the sequential introduction of two distinct electrophiles (E_1 and E_2) at which is controlled by the chemistry of each metal. For example, acetylenic stannane **90** can be converted into iodide **86** by virtue of the selective halogenation of intermediate **78**. Various manipulations of these compounds, e. g. using Pd^0 and Cu(I), are currently being examined and the relevant results will be reported in due course. The conversion of stannylacetylenes to (*Z*)-vinylstannanes by hydrozirconation (Scheme 7.27) is presented in Scheme 7.28.



Scheme 7.28

7.5.4
Bicyclization of Enynes

Treatment of a stannylenyne/enene compound with a low-valent zirconocene derivative results in a bicyclization reaction leading to the 1,1-stanniozirconocene complex **99** (Scheme 7.29) in moderate yield [168]. The product of carbonylation of **99** can be readily converted to **100** and **101** in high yields [169].

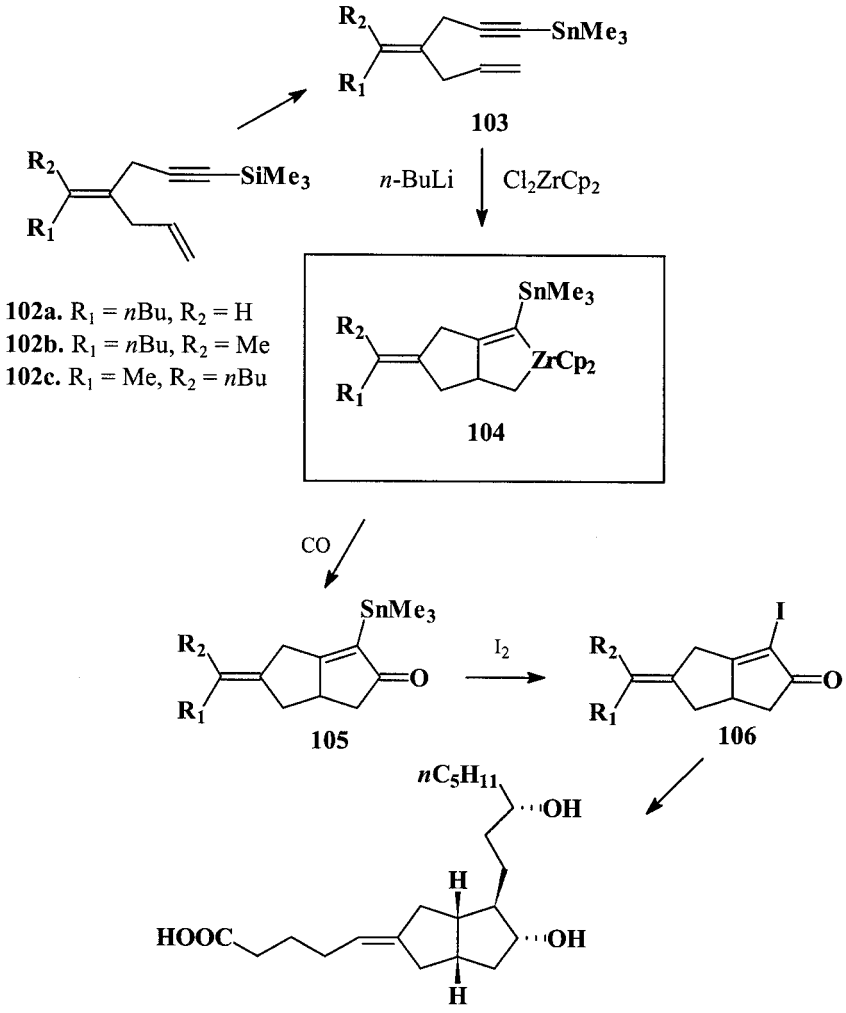


Scheme 7.29

7.5.5

Zirconium-Promoted Bicyclization of Stannylenyne Derivatives

Conversion of silylenynes **102** [6] into the corresponding $SnMe_3$ derivatives **103**, followed by a Zr-promoted bicyclization, leads to the *gem*-stanniozirconocene derivatives **104**. Carbonylation gives **105**, and subsequent iodinolysis of **105** gives **106** in good yield (Scheme 7.30). The formation of **106** proceeds with > 98% stereoselectivity, thus allowing the synthesis of carbacyclin **107** [170,171].



Scheme 7.30

7.5.6
Bicyclization of Diynes

Zirconacyclopentadiene complex **109**, containing carbon atoms that are *gem*-dimetallated by zirconium and tin, was prepared by the oxidative coupling of "Cp_2Zr" with distannyldiyne compounds [172]. Complex **109**, bearing trimethylstannyl groups, was characterized by X-ray diffraction analysis and its structure was compared with those of zirconacyclopentadiene analogues bearing *tert*-butyl or trimethylsilyl groups. The five-membered zirconacycle ring of **109** has a planar conformation. The C–Zr–C angle in **109** is smaller than those in the corresponding trimethylsilyl- and *tert*-butyl-containing ligands (Fig. 7.8). When the zirconacycle **109** bears *tert*-butyl groups at carbons C_1 and C_8, it becomes twisted and there is torsion in the angles $Zr–C_1–C_2–C_7$ and $C_1–C_2–C_7–C_8$. Another feature is the $C_1–Zr–C_8$ angle of the five-membered zirconacycle ring (Fig. 7.8). In analogy to the formation of *gem*-stanniozirconocenes (see Scheme 7.29), a *gem*-germaniozirconocene complex akin to **109** (Scheme 7.31) can also be formed.

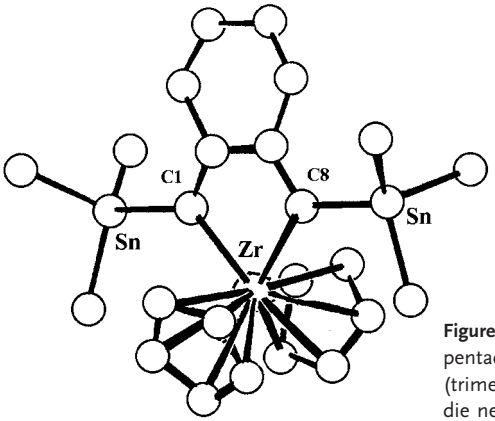
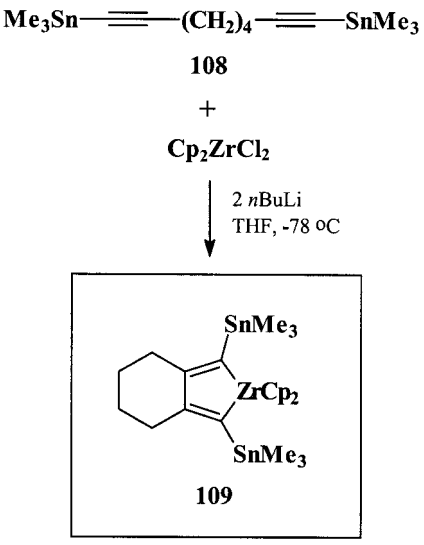


Figure 7.8. Crystal structure of the novel zirconacyclopentadiene complex, 8,8-bis(cyclopentadienyl)-7,9-bis-(trimethylstannyl)-8-zirconabicyclo[4.3.0]nona-1(9),6(7)-die ne **109**. Adapted by the authors.

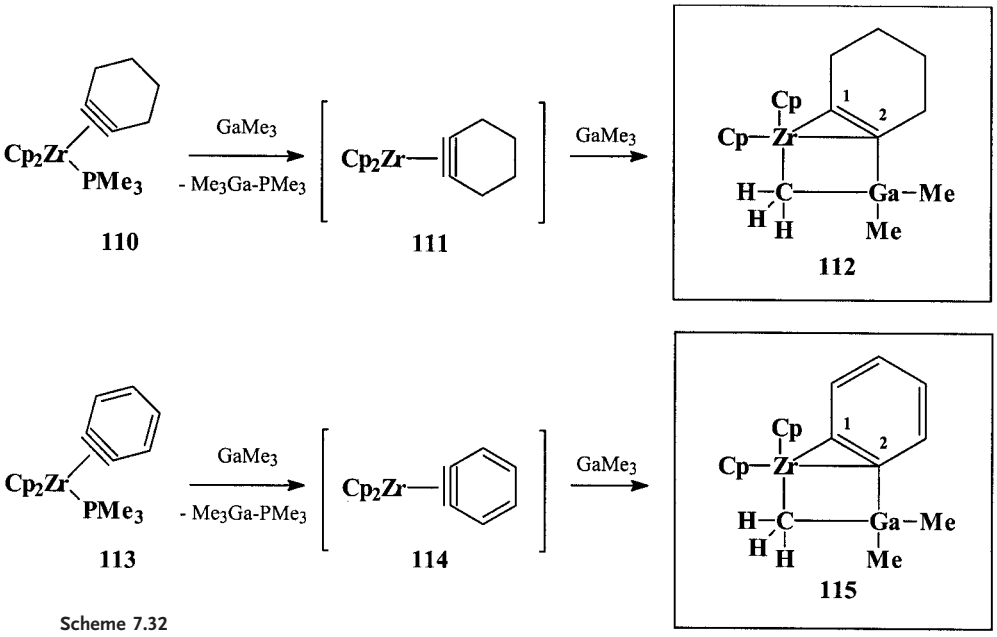


Scheme 7.31

7.6
1,1-Galliozirconocene Complexes

Recently, a variety of reactions according to the general synthetic route shown in Scheme 7.32 were carried out, which facilitated a study of hydrocarbonyl-bridged gallium/zirconium compounds [173,174]. Two representative examples of these unusually structured $R_2Ga(\mu\text{-}R^1,\mu\text{-}R^2)ZrCp_2$ complexes will be described and discussed with regard to their structural properties [175].

The σ-hydrocarbyl-bridged gallium/zirconium complexes were prepared by Buchwald's method using (η^2-cyclohexyne)(PMe_3)zirconocene **110** [176] as the starting material (Scheme 7.32). Trimethylgallium was employed as a Lewis acid to abstract the Lewis basic trimethylphosphane ligand from **110** and to subsequently serve as a coupling component to react with the in situ generated reactive (η^2-cyclohexyne)$ZrCp_2$ intermediate **111**. A fourfold molar excess of Me_3Ga had to be used. The $Me_3Ga \cdot PMe_3$ adduct formed was removed in vacuo along with the solvent and some unused trimethylgallium to give the dimetallabicyclic (η^2-cyclohexyne)$ZrCp_2/Me_3Ga$ addition product **112** in almost quantitative yield. The same synthetic pathway was found on using (η^2-1,2-didehydrobenzene)(PMe_3)$ZrCp_2$ **113** [176] as an alternative starting material. The reaction of **113** with excess trimethylgallium cleanly gave a near quantitative yield of the stable dimetallabicyclic $Cp_2Zr(\mu\text{-}\eta^1\text{:}\eta^2\text{-}C_6H_4)(\mu\text{-}CH_3)GaMe_2$ complex **115** via the very reactive (η^2-1,2-didehydrobenzene)metallocene intermediate **114** [177,178].



Scheme 7.32

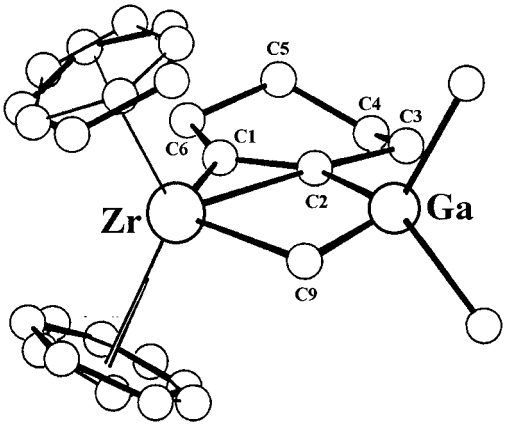


Figure 7.9. X-ray crystal structure of the Ga/Zr complex **112**. The carbon atom C-2 is planar tetracoordinate. Adapted by the authors.

Crystals of complex **112** suitable for an X-ray structure determination were obtained on cooling a solution in pentane to −30 °C. The structure determined is shown in Fig. 7.9. The most remarkable structural feature of **112** is that the gallium center is connected to the zirconium through two different σ-carboxylic bridges. One of them contains the cyclo-C_6H_8 system, which is η^1-bonded to gallium and η^2-coordinated to zirconium. It is noteworthy that carbon atom C-2 is planar tetracoordinate. It is connected to four neighboring atoms in the σ-plane, specifically to carbon atoms C-1 and C-3 and to both metal centers [175].

The C_2-C_3 distance is 1.572 Å [179–183], whereas the C_2-C_1 bond is much shorter at 1.314 Å [173,174], which is within the range of a $C(sp^2)-C(sp^2)$ carbon–carbon double bond [184]. The Zr–C(2) bond length is 2.423(5) Å. This is slightly longer than expected for an ordinary $Cp_2Zr-C(sp^2)$ single bond [185], but still shorter than the average Zr–C(Cp) separation. The C_2–Ga distance is 2.096 Å [186,187], which is also slightly longer than usually observed for gallium–carbon σ-bonds {trimethylgallium has a $Ga-C(sp^3)$ bond length of 1.967(2) Å [188–191]; this compares nicely with the $Ga-C_7$ and $Ga-C_8$ distances found in **112** of 1.968(7) Å and 1.979(7) Å, respectively}. The bonding geometry at C_2 is as expected for a typical example of an electronically stabilized planar-tetracoordinate carbon derivative. It is indicative of a three-center two-electron metal–carbon–metal σ-interaction [the corresponding bond angles of the coplanar σ-coordination at C-2 are 119.5(4)° ($C_1-C_2-C_3$), 100.3(3)° (C_3-C_2-Ga), 79.3(1)° ($Ga-C_2-Zr$), and 61.1(3)° ($Zr-C_2-C_l$)]. The planar-tetracoordinate bonding situation at the carbon atom C_2 is probably further stabilized by a π-conjugative interaction normal to the σ-ligand plane and involving the C_2-C_1-Zr moiety (Fig. 7.10).

The reaction sequence leading to **120** is probably initiated by a ligand metathesis between the alkynylgallium reagent **116** and gallido/zirconocene chloride (and not by a simple hydrozirconation reaction) [192–194]. The (hydrido)(alkynyl)$ZrCp_2$ species **118** seems to be unstable under the reaction conditions and may undergo reductive elimination. The resulting reactive (η^1-alkyne)zirconocene intermediate **119** then undergoes addition of the $ClGaMe_2$ formed in the initiating step to give the thermodynamically preferred dimetallobicyclic product **120** through intermediate reactions involving compounds **117**–**119** (Scheme 7.33). The overall reaction sequence is another example of a novel synthetic pathway to this general type of planar-tetracoordinate carbon complexes [30,122,179,180].

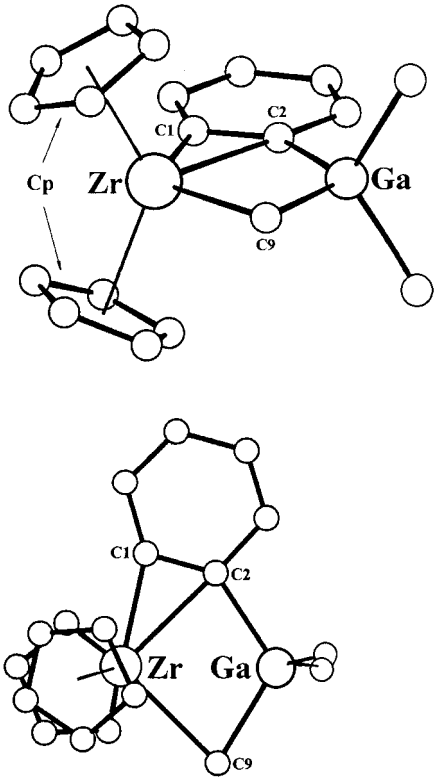
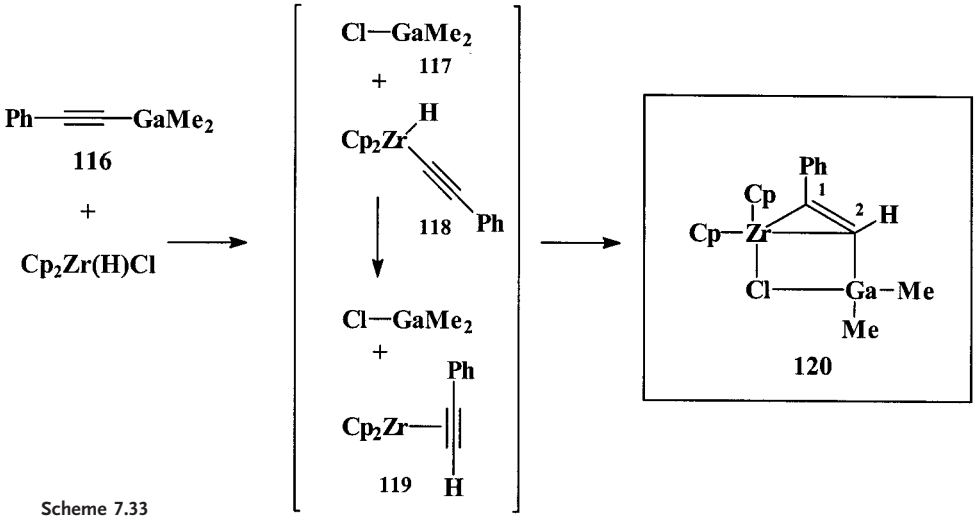


Figure 7.10. Two projections of the molecular structure of the heterodimetallic complex $Cp_2Zr(\mu\text{-}\eta^1\text{:}\eta^2\text{-}C_6H_4)(\mu\text{-}CH_3)GaMe_2$ **115**; carbon atom C-2 is planar tetracoordinate. Adapted by the authors.



Scheme 7.33

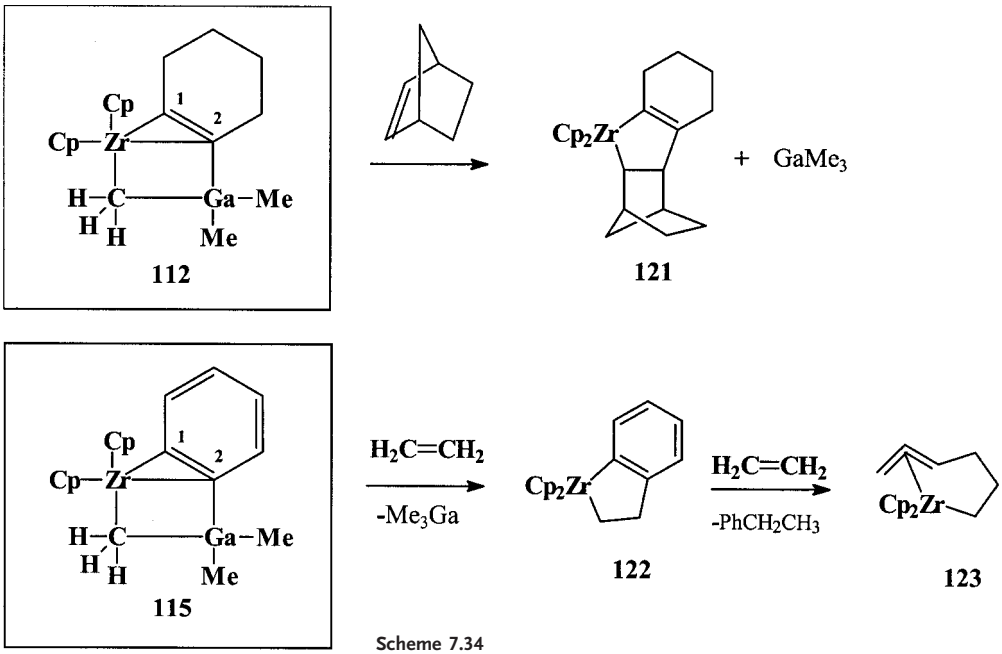
7.6.1
Exchange Reactions of Galliozirconocene Complexes

Some exchange reactions of complexes **112** and **115** have been studied. From the X-ray crystal structure analyses, it appears that trimethylgallium is rather loosely bound to the (η^2-aryne)- and (η^2-cyclohexyne)metallocene building blocks in the dimetalla-bicyclic complexes **112** and **115**, respectively (Scheme 7.34). Therefore, it was tempting to investigate whether it was possible to reverse the reactions depicted in Schemes 7.32 and 7.33 using these specific examples to carry out thermally induced exchange reactions.

The complex $Cp_2Zr(\mu\text{-}\eta^1\text{:}\eta^2\text{-}C_6H_8)(\mu\text{-}CH_3)GaMe_2$ **112** reacts readily with norbornene at room temperature to give trimethylgallium and the metallacyclic product **121**. The norbornene/(η^2-cyclohexyne)$ZrCp_2$ addition product was tentatively identified on the basis of its spectroscopic data [194].

Complex **115** reacts analogously with ethene. At ambient temperatures, trimethylgallium is rapidly liberated. At the same time, the remaining (η^2-aryne)zirconocene fragment takes up 1 equivalent of ethene to form the metallaindane system **122**. Compound **122** was identified by comparison with an authentic sample [194]. Prolonged exposure of the reaction mixture to ethene eventually led to the formation of **123**.

Acyl-bridged gallium compounds are very rare [30]. In this respect, this heavy Group 3 metal behaves quite differently to its lighter counterpart in the analogous aluminum compounds. Complexes **112** represent noteworthy exceptions to this observed difference in coordination behavior. It appears that here the heterodimetallic Zr/Ga complexes **112** are structurally and behaviorally similar to their respective Zr/Al analogues [121,122,180,182]. In these compounds, the tendency to form a stable planar-tetracoordinate geometry at the carbon C_2 of the $\mu\text{-}\eta^1\text{:}\eta^2$-RCCR'-type bridging σ-hydrocarbyl ligand

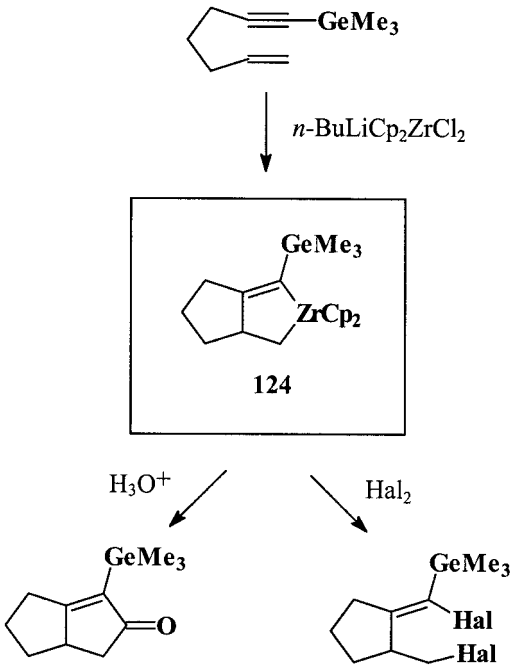


Scheme 7.34

within the dimetallabicyclic framework seems to be so pronounced that it even helps to overcome the frequently observed reluctance of the element gallium to form σ-hydrocarbonyl bridges [187,189,190,195,196].

7.7
1,1-Germaniozirconocene Complexes

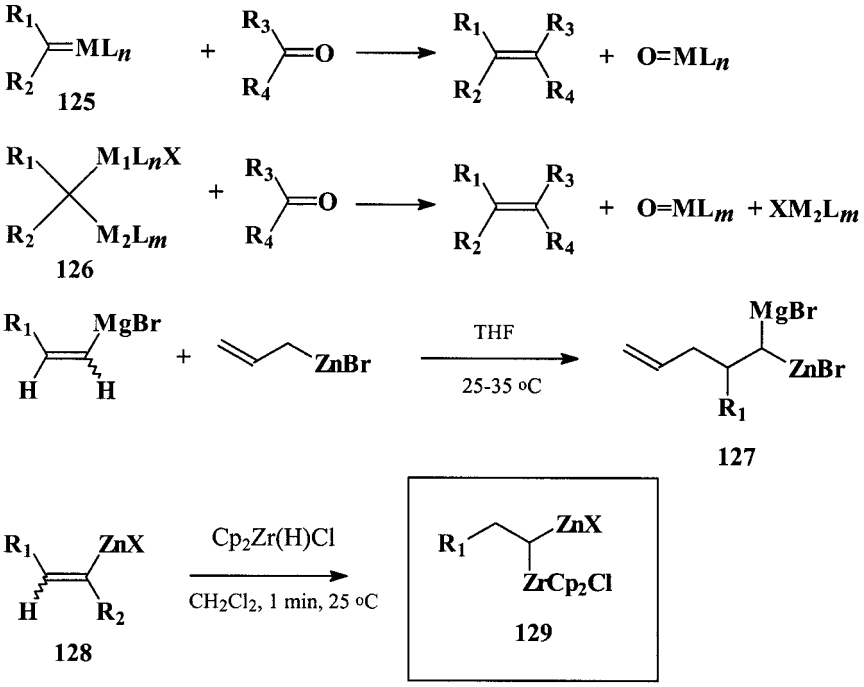
In analogy to the formation of *gem*-stanniozirconocenes (see Scheme 7.29) [197], *gem*-germaniozirconocene complex **124** can also be formed (Scheme 7.35).



Scheme 7.35

7.8
1,1-Zinciozirconocene Reagents

The methylenation of aldehydes and ketones using transition metal carbene complexes **125** or related 1,1-bimetallic organometallics **126** ($R_1 = R_2 = H$) constitutes an excellent preparation of alkenes and has found many applications in organic synthesis [198–210]. Extension of this method to alkylidenation reactions is possible in many cases, but it is often complicated by the instability of the organometallic reagents **125** and **126** (R_1 and/or R_2 _ H) and often shows only a moderate (*E*)/(*Z*) stereoselectivity (Scheme 7.36) [11,15,16,24,211–226]. In the course of recent studies concerning the reactivity of 1,1-bimetallic reagents of zinc and magnesium (**127**), it was found that a more general synthesis of these reagents, which were prepared by allylzincation of alkenylmagnesium halides, would be desirable (Scheme 7.36) [48,50,227]. Based on the work of Schwartz [17,202–204] with $Cp_2Zr(H)Cl$ [2,25,44,57,228,229], it was found that the hydro-



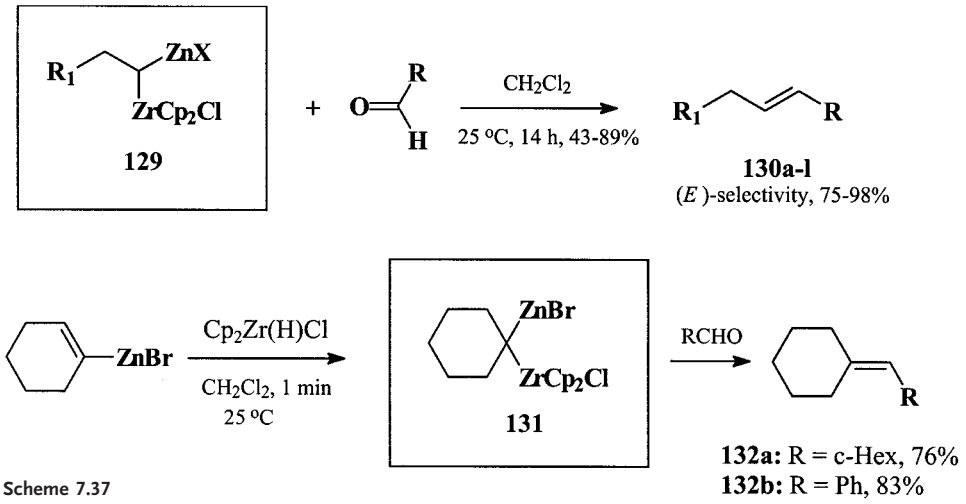
Scheme 7.36

zirconation of alkenylzinc halides **128** with $Cp_2Zr(H)Cl$ proceeds smoothly in CH_2Cl_2, leading to 1,1-bimetallic reagents that can be tentatively represented as **129**.

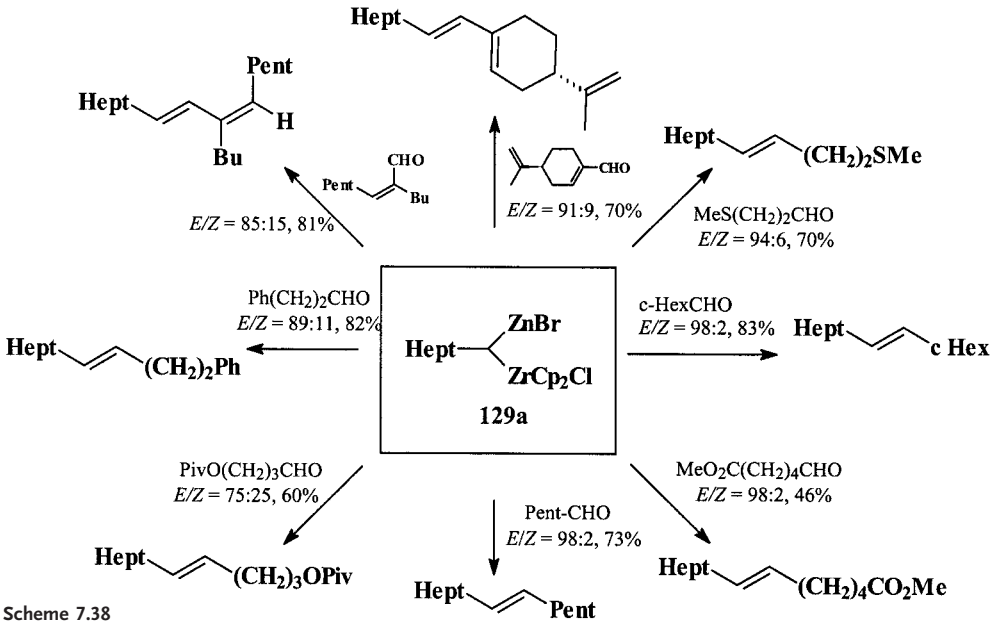
7.8.1
Preparation of Polyfunctionalized Alkenes

The preparation of polyfunctionalized alkenes and allenes using 1,1-bimetallics of zinc and zirconium has been reported [50]. Addition of a suspension of $Cp_2Zr(H)Cl$ in CH_2Cl_2 to a solution of an alkenylzinc halide **128** [**128a**: R_1 = Hex, R_2 = H; **128b**: R_1 = Ph, R_2 = H; **128c**: $R_1 = (CH_2)_3Cl$, R_2 = H; **128d**: $R_1 = (CH_2)_3CN$, R_2 = H; **128e**: $R_1 = (CH_2)_3CH(Bu)CH_2COOH$, R_2 = H; see Scheme 7.36] in the same solvent instantaneously affords a yellow solution of the relatively unstable 1,1-bimetallics of zinc and zirconium **129a–f**, to which an aldehyde or a ketone must be immediately added (Scheme 7.37) [18].

NMR spectroscopic characterization or X-ray analysis of these reactive intermediates were precluded by their instability. However, the hydrolysis of **129a** (R_1 = Hex) affords *n*-octane, and its decomposition results in the formation of a mixture of octane and octene (ca. 3:1 ratio). It should be noted that attempts to perform this reaction in other solvents such as THF, diethyl ether, or toluene led only to trace amounts of the product. The addition of phosphanes such as PPh_3 or Me_2PhP, which typically stabilize zirconium bimetallics, was found to completely inhibit the olefination reaction. A variety of functionalized [$MeO_2C(CH_2)_3CHO$, $PivO(CH_2)_2CHO$, $MeS(CH_2)_2CHO$; Scheme 7.38] and unfunctionalized [Pent-CHO, *c*-Hex-CHO, $Ph(CH_2)_2CHO$; Scheme 7.38] aldehydes produced the desired (*E*)-alkenes in acceptable yields (43–89 %) and with satisfactory (*E*)-stereoselectivities



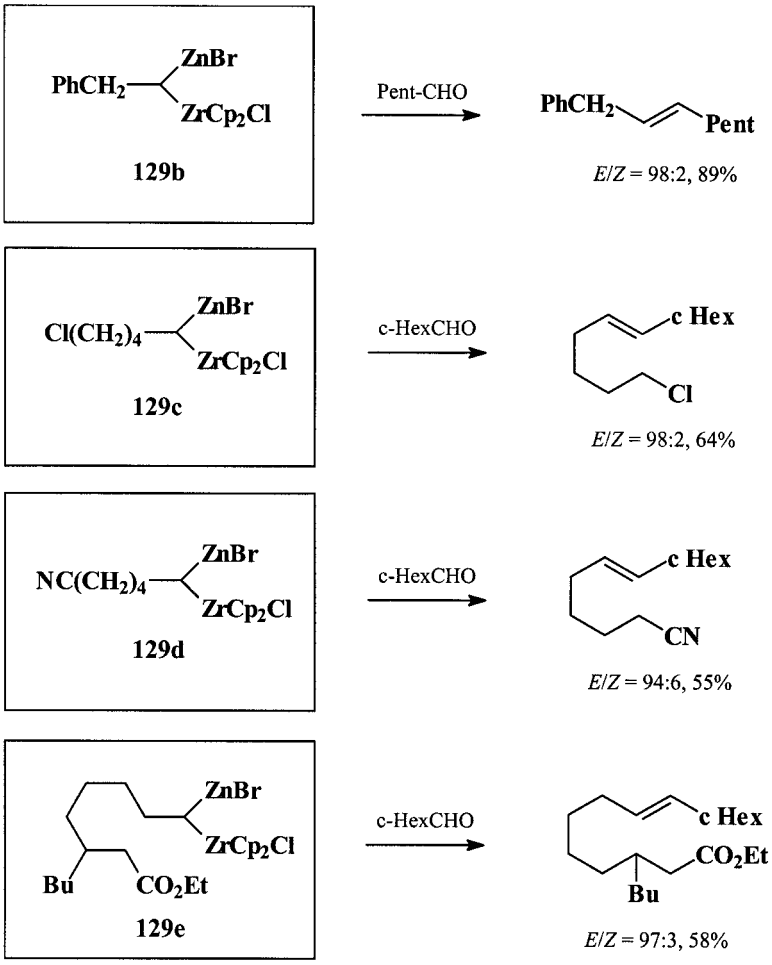
Scheme 7.37



Scheme 7.38

(75–98 % (*E*)) (Scheme 7.38). No olefination of esters such as ethyl benzoate could be achieved with this reagent, not even by performing the reaction in the presence of pyridine as a base [234].

Remarkably, the hydrozirconation can be applied to functionalized alkenylzinc reagents bearing an ester, chloride, or cyano functionality (Scheme 7.37) [230]. The functionalized bimetallic species **129c–e** gave significantly lower yields (55–64 %) but excellent stereoselectivities (>94 % (*E*); Scheme 7.39). Although the (*E*)/(*Z*) ratio was always reproducible,

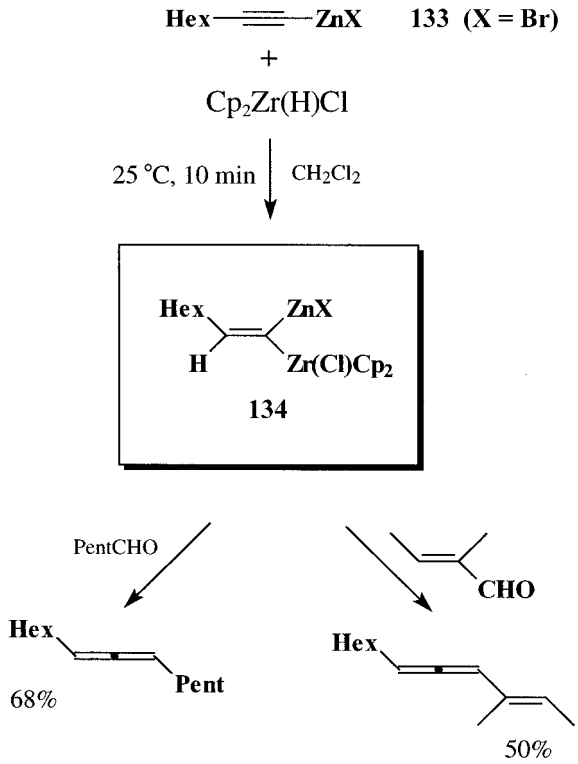


Scheme 7.39

the yields of the reaction were found to be dependent on the quality of the Schwartz reagent, $Cp_2Zr(H)Cl$ [2,44,228,229]; its preparation by the method of the Buchwald [57] gave the best results (Schemes 7.37–7.39).

When cyclohexenyllithium [231] is transmetalated by $ZnBr_2$, the product readily undergoes addition of $Cp_2Zr(H)Cl$, thereby providing the intermediate bimetallic **131**. Reactions with aliphatic and aromatic aldehydes lead to the *exo*-alkylidenecyclohexanes **132a**,**b** in yields of 76–83 % (Scheme 7.37).

Alkynylzinc bromides **133** are also cleanly hydrozirconated with $Cp_2Zr(H)Cl$ leading to 1,1-bimetalloalkenes of zinc and zirconium (**134**), which react smoothly with aldehydes to afford allenes in satisfactory yields (Scheme 7.40) [232,233].

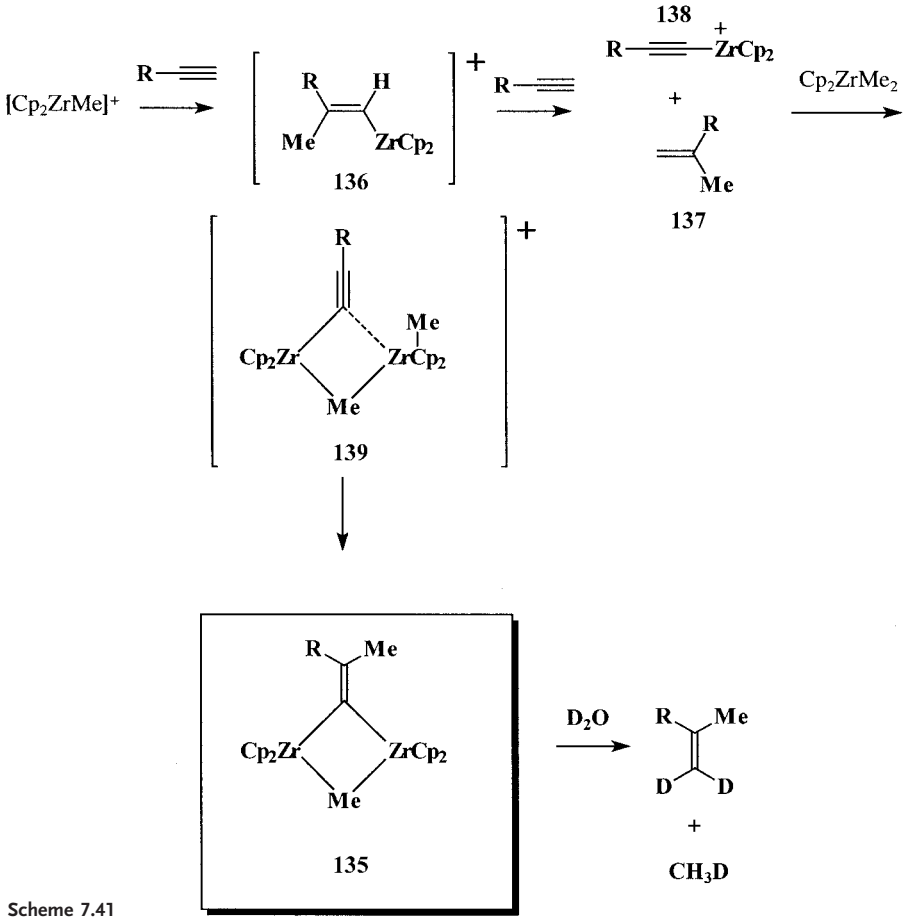


Scheme 7.40

7.9
1,1-Dizirconocene Complexes

Norton and Orpen [235] demonstrated that non-crowded alkynes react with Cp_2ZrMe_2/$(PhMe_2NH)BPh_4$ in a 2:1 ratio at −30 °C to give the *gem*-dizirconioalkene tetraphenylboron complex **135** in 70 % yield (Scheme 7.41). The first step involves alkyne insertion into $[Cp_2ZrMe(NMe_2Ph)]^+$ to give the alkenyl compound **136** [235]. Rapid σ-bond metathesis with the alkyne then liberates the alkene **137** and affords the transient alkynyl complex **138**. The Lewis base (Cp_2ZrMe_2) reacts with **138** to give a transient dizirconocene intermediate, thought to be the μ-alkynyl-μ-methyl complex **139**. Insertion of the alkynyl triple bond into a zirconium−zirconium bond in **139** leads to the complex **135**. The formation of the dideuteriated alkene and CH_3D on treating **135** with D_2O shows that this complex contains μ-methyl- and μ-alkenylidene ligands, which bridge two Cp_2Zr fragments (Scheme 7.41).

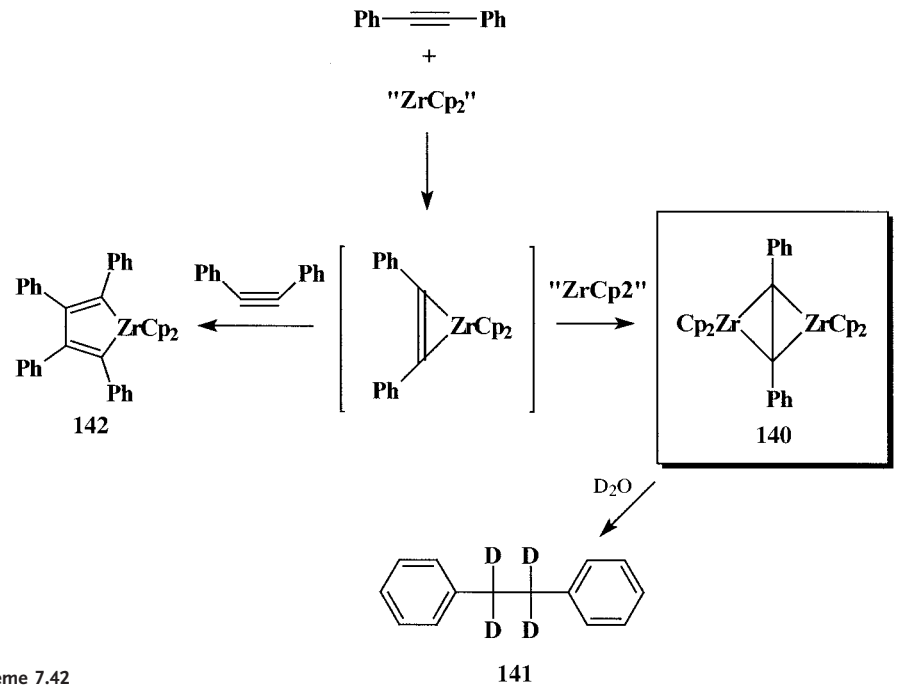
The reaction of nBu_2ZrCp_2 with 2 equivalents of PhC≡CPh provides the novel bicyclic *gem*-dizirconium complex **140** [236] (Scheme 7.42). Protonolysis of complex **140** with 3 N HCl gives bibenzyl in 88 % yield, while its deuterolysis with D_2O provides tetradeuteriobibenzyl **141** with 92 % deuterium incorporation. The dual path nature (**142** *versus* **140**) of the reaction of "Cp_2Zr" with alkynes is an important factor in designing Zr-promoted cyclizations of alkynes, enynes, and diynes.



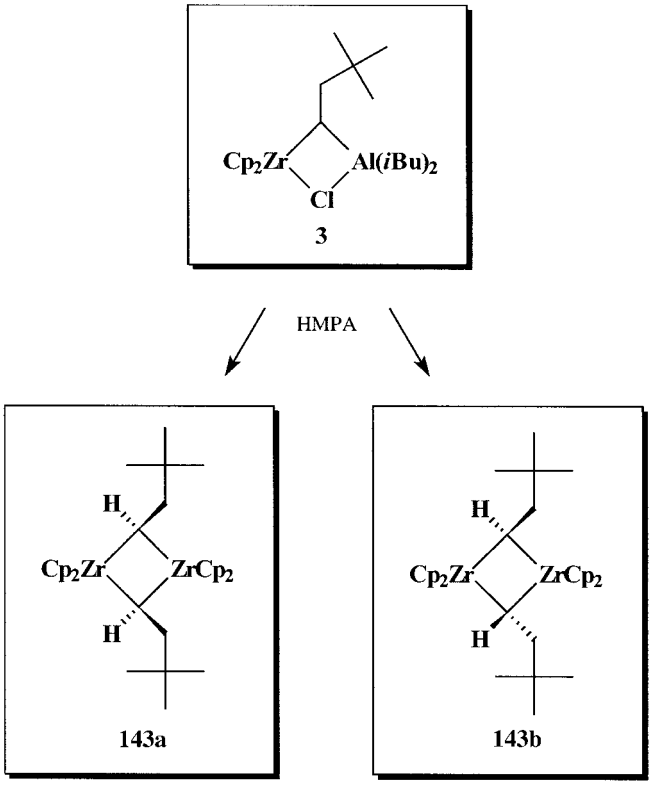
Scheme 7.41

When zirconocene(1-butene) [5] was reacted in situ with *p*-tolylchloroacetylenes, the first zircono-zirconacyclopropenes were obtained in high chemical yields [237].

Two isomeric 1,1-bis(zirconium) complexes, **143a** and **143b**, were obtained in a 3:1 ratio by transmetallation of *gem*-aluminiozirconium complexes **3** (Schemes 7.1 and 7.43) [15]. Indeed, when *gem*-aluminiozirconium complex **3** [24] was treated with 1 equivalent of hexamethylphosphoramide, red-brown crystals (31 % yield) were isolated.



Scheme 7.42



Scheme 7.43

7.10 Conclusion

gem-Metallozirconocene alkanes and alkenes are unique reagents for preparing new classes of bimetallic complexes. Sequential reactions of the zirconium–carbon and metal–carbon bonds allow for easy functionalization. Much of the work in organometallic chemistry over the past few years has focused on the development of new or improved methods for the in situ functionalization of alkenes and alkynes. The hydrozirconation of double and/or triple bonds with $Cp_2Zr(H)Cl$ allows the convenient preparation of a wide range of functionalized organozirconocenes. The chemistry summarized in this chapter shows that various geminal bimetallic complexes have been used in a wide variety of carbon–carbon bond-forming reactions. This review has also described the development of a new zirconocene-based methodology for applications in organic synthesis, including the total synthesis of natural products. Applications of *gem*-metallozirconocenes in organic synthesis have been particularly underlined in the case of *gem*-boriozirconio-, stanniozirconio-, zinciozirconio-, and bis(zirconio)alkene derivatives. The scope and limitations, as well as mechanistic details of most of the reactions discussed above need to be further delineated.

Typical Experimental Procedures

Preparation of Boriozirconocene Complex 16 (Scheme 7.5) [33] To a stirred ice-cooled suspension of the Schwartz reagent (0.26 g, 1 mmol) in dry CH_2Cl_2 (1 mL) was added a solution of B-hexenyl-9-BBN **15** (0.20 g, 1 mmol) in dry CH_2Cl_2 (1 mL). The resulting cloudy mixture became a clear yellow solution in 1 h at 0 °C (or 10 min at ambient temperature), indicating the formation of **16**.

General Preparation of 1,1-Bimetallic *gem*-Boriozirconocene 20 (Scheme 7.6) [34] A suspension of $Cp_2Zr(H)Cl$ (0.35 g, 1.36 mmol) in dry CH_2Cl_2 (2.8 mL) was stirred at ambient temperature under an atmosphere of argon. (*E*)-Pinacol 1-hexenylboronate **19** (0.9 mL of a 0.5 M solution in CH_2Cl_2; 0.45 mmol) was then added. The reaction mixture was stirred for 40 min, during which it became a clear, green-yellow solution. Evaporation of the solvent left a yellow oily residue, which was extracted with dry hexanes (4 ×x 6 mL). Pumping off the hexanes from the filtrate afforded **20** as a green oil (R = *n*Bu) (0.203 g, 96 %).

Synthesis of 1,1-Bimetalloalkenes 45 (Scheme 7.17) [12] To a stirred suspension of $Cp_2Zr(H)Cl$ (0.74 mmol, 0.191 g) in dry THF at 25 °C under an atmosphere of argon was added 2-(3,3-dimethyl-1-butynyl-4,4,5,5-tetramethyl)-1,3,2-dioxaborolane **47** (1.2 mL of a 0.5 M solution in THF; 0.60 mmol). The reaction mixture was stirred for an additional 30 min., whereupon it became clear and green-yellow in color. Addition of an excess of H_2O led to the deposition of a precipitate. After stirring for a further 30 min., the THF was evaporated and the reaction mixture was extracted with hexanes (3 ×x 10 mL). Evaporation of the solvent afforded the essentially pure (*Z*)-1,1-bimetalloalkene **45** as a colorless oil.

Synthesis of 8,8-Bis(cyclopentadienyl)-7,9-bis(trimethylstannyl)-8-zirconabicyclo[4.3.0]nona-1(9),6(7)-diene 109 (Scheme 7.31) [172] To a solution of bis(cyclopentadienyl)zirconium dichloride (585 mg, 2.0 mmol) in THF (10 mL) at −78 °C was added dropwise a solution of *n*-butyllithium in hexane (2.4 mL, 4.0 mmol). After the reaction mixture had been stirred at −78 °C for 1 h, a solution of 1,8-bis(trimethylstannyl)-1,7-octadiyne (863 mg, 2.0 mmol) in THF (2 mL) was added at the same temperature. The temperature was then allowed to rise to ambient, and the mixture was stirred for a further 3 h. The solvent was then removed under reduced pressure and the product was extracted with toluene. The extracts were filtered and the filtrate was concentrated and kept at 0 °C to afford the product **109** (723 mg, 55 % yield).

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8
Cationic Zirconocene Species in Organic Synthesis

Keisuke Suzuki, Lukas Hintermann, and Shigeo Yamanoi

8.1
General Introduction

8.1.1
Definition of Cationic Zirconocenes in this Review

Cationic zirconocenes are very reactive species. If we are writing about cationic zirconocenes in organic synthesis, the term does not necessarily mean a discrete cation in a crystalline or dissolved, well-defined salt. Usually, the zirconocene precursors in the reactions to be discussed are neutral complexes, and they first need some kind of *in situ* activation before they display cation-type reactivity. From this arises a difficulty in defining the scope of our review. Thus, as cationic reagents are not directly added to the reaction mixture, it becomes a question of mechanistic interpretation as to whether cationic zirconocene chemistry is taking place or not. The case of $[Cp_2Zr(OTf)_2(thf)]$ serves as a typical example. Whereas it has been shown by X-ray structure determination that this is a neutral complex with covalently bound triflates [1], even a weak donor (e. g. solvent, substrate) will cause ionization in solution; the resulting cationic species is very reactive and can, for example, catalyze Diels–Alder reactions (Section 8.5.3). The reagents formed from Cp_2ZrCl_2 and one or two equivalents of a silver salt ($AgClO_4$ or others), originally introduced as activators for glycosylation with glycosyl fluorides [2], display cation-like reactivity, but as yet nothing is known about their structure or ionization state.

In general, we have therefore considered examples in which typical conditions for the generation of cationic zirconocenes have been used, and where a common reactivity pattern expected for such species has been observed. In terms of the Cp_2ZrCl_2/AgX reagent, the coverage is almost comprehensive. The vast field of zirconocene-catalyzed polymerization reactions has been excluded, as this topic is rather specialized (although very broad indeed) and the polymerization reactions do not serve for the selective synthesis of single target molecules. Before moving on from the issue of polymerization, we want to stress the importance of such reactions in industry, and the wealth of mechanistic research that has been performed in connection with the cation-type zirconocene polymerization catalysts [3].

8.1.2
Conditions for the Generation of Cationic Zirconocene

Halide abstraction: Complexes of the general formula Cp_2ZrY_2 (Y = non-nucleophilic counterion) can be prepared by halide abstraction from Cp_2ZrCl_2 with AgY. The structurally characterized species $[Cp_2Zr(OTf)_2(thf)]$ was obtained with AgOTf in THF [1]. The complex is not ionized in THF and CH_2Cl_2, but partially dissociates in $MeNO_2$ or Me_2CHNO_2 [4]. On controlled addition of water to a solution in THF, the triaquo complex $[Cp_2Zr(OH_2)_3](OTf)_2 \cdot THF$ crystallizes [5] or, under slightly different conditions, the dinuclear complex $[(CpZr)_2(\mu^2\text{-}OH)_2(H_2O)_6](OTf)_4 \cdot 4THF$ is formed by protonolysis of one Cp ligand. The perchlorate salt of the latter complex cation is also known [6]. The species $Cp_2Zr(BF_4)_2$ is unstable and decomposes to Cp_2ZrF_2 and BF_3 [7]. Other fluoroanions, such as PF_6^-, SbF_6^-, or AsF_6^-, may also undergo fluoride abstraction reactions, albeit less easily.

Protonation of zirconium-methyl complexes: The complexes Cp_2ZrY_2 can also be prepared by reaction of Cp_2ZrMe_2 with the corresponding acid HY. This method has been applied to the synthesis of $Cp_2Zr(OTf)_2$ (free of coordinating solvent) from CF_3SO_3H and Cp_2ZrMe_2 [4]. Very reactive species are obtained when one or two equivalents of the acids $(HNR_3)[B(C_6F_5)_4]$ [8,9] or $[H(Et_2O)_2]$BARF (BARF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) [10] are used.

Alkyl or hydride abstraction: The Lewis acid $B(C_6F_5)_3$ [11], as well as the trityl salt $(Ph_3C)[B(C_6F_5)_4]$ [12], can abstract a methyl group from Cp_2ZrMe_2 and related zirconocenes to form cationic $[Cp_2ZrMe]^+$. In the former case, the methyl group ends up in the anion $MeB(C_6F_5)_3^-$; in the latter it is incorporated into $MeCPh_3$ (*cf.* Scheme 8.2).

Single electron transfer to dialkylzirconocenes: Single-electron oxidation of dialkylzirconocenes, e. g. with a ferrocinium [13] or silver salt [14,15], induces the following reaction leading to a cationic zirconocene [13]:

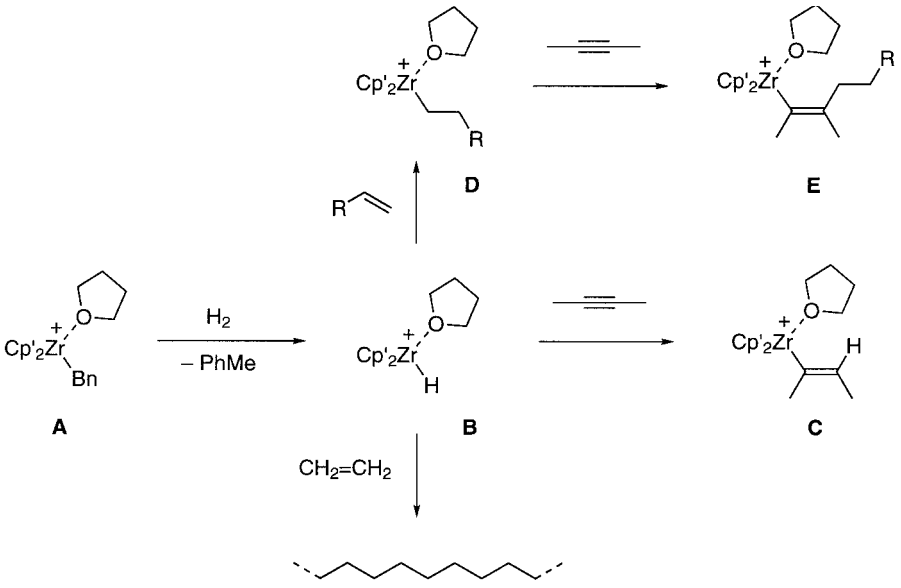
$$Cp_2ZrR_2 + [FeCp'_2]BPh_4 = [Cp_2Zr(R)(thf)]^+ BPh_4^- + 0.5\ R{-}R + FeCp'_2 \qquad (1)$$

Reaction with MAO: The additive MAO (methylaluminoxane, $-\{Al(Me){-}O\}-_n$) is special in that it may be involved in several ways in the generation of a cationic zirconocene species. It can either serve as a methylating agent (conversion of Zr−Cl to Zr−Me), or as a Lewis acid in abstracting methyl groups and/or halide. In the generation of polymerization catalysts from Cp_2ZrCl_2 and MAO, a sequence of halogen−alkyl exchanges and methyl abstraction is involved. The active species generated is thought to have the schematic composition $[Cp_2ZrMe]^+[Me{-}MAO]^-$ [3].

8.1.3
Structure and Reactivity of Cationic Zirconocenes

However transient and elusive cationic zirconocenes may be, they are real and some of their salts have been isolated and characterized, both spectroscopically and by X-ray crystallography. None of these cations is ever completely *free*; they are either coordinated by an additional ligand (typically a solvent molecule) or they interact with their counterions, no matter how *non-coordinating* these may be [16]. Scheme 8.1 shows the typical reactivity pattern of a solvent-stabilized cation $[Cp'_2ZrR(solvent)]^+$ (**A**; Cp' = η^5-C_5H_4Me)

[13]. Addition of hydrogen results in hydrogenation of the alkyl group, releasing the corresponding hydrocarbon, and a cationic hydride $[Cp_2ZrH(solvent)]^+$ (**B**). Mechanistically, one may view this as a σ-bond metathesis, but certainly not as an oxidative addition–reductive elimination sequence because a d^0 species is involved. The zirconocenium hydride **B** undergoes insertion of an alkyne or an alkene (hydrometalation) to yield an alkenylzirconium (**C**) or alkylzirconium (**D**) cation, respectively. In turn, the alkylzirconocene species **D** can undergo insertion of an alkyne (carbometalation) to give a new zirconocene-alkenyl cation (**E**). All these species can be isolated as complex salts with the counterion BPh_4^-. Hydride **B** is also a catalyst for ethene polymerization [13].

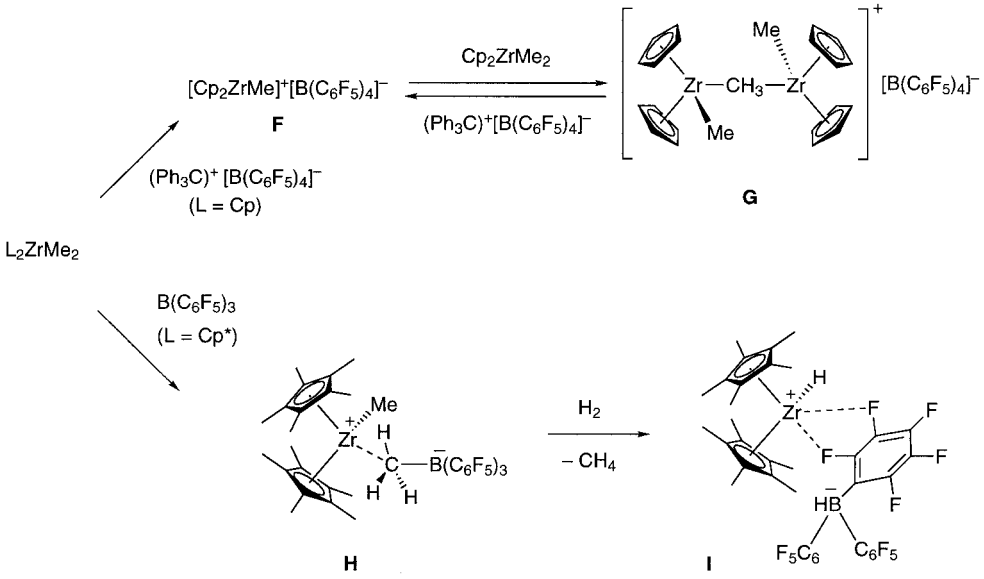


Scheme 8.1. Reaction pathways of cationic zirconocene complexes.

The above reactions are rather slow because the insertion reactivity is directly related to the rate of dissociation of the THF ligand, which is also present as the solvent. The most reactive cationic complexes are therefore *base-free*, i. e. they do not contain coordinating solvents or ligands. Logically, anion coordination is a problem in such systems. Ion pairing reduces the reactivity of the cationic zirconocenes, but in the presence of $B(C_6F_5)_4^-$, $RB(C_6F_5)_3^-$ (R = H, Me), or $BARF^-$, this interaction is only weak.

Scheme 8.2 shows pathways to and reactions of base-free zirconocene cations. The methyl-zirconocene cation **F** associates with additional Cp_2ZrMe_2 to give a methyl-bridged dinuclear species **G** [17], and the anion $Me–B(C_6F_5)_3^-$ bridges to zirconium through a methyl group in **H** [11], but on hydrogenation the cationic hydrido complex **I** is formed in which there are only weak contacts with the anion (via C–F bonds) [18].

The aforementioned reactive cationic zirconocene species can react with chlorinated solvents by chloride abstraction. However, an even more pronounced property of cationic zirconocenes is their ability to abstract and bind fluoride. Cationic complexes $[Cp_2ZrMe(thf)]^+$ are unstable with BF_4^- and PF_6^- counterions [14], and the reaction of Cp_2ZrCl_2 with $AgBF_4$ directly affords Cp_2ZrF_2 [7]. The use of $Cp_2ZrCl_2/AgClO_4$ as an



Scheme 8.2. Synthetic access to base-free cationic zirconocenes.

activator for glycosyl fluorides (*cf.* Section 8.2), notably in non-coordinating solvents such as PhMe, PhH, and CH_2Cl_2, may involve precoordination of a cationic zirconium species to the C−F bond followed by formation of a Zr−F bond. The chemistry of organometallic fluoro complexes of the d-block metals has been reviewed [19].

8.1.4
Availability

The usual precursor Cp_2ZrCl_2 is a commercially available crystalline solid that is slightly sensitive to moisture and light. Some monosubstituted (ligands RC_5H_4; R = Me, *i*Pr, *n*Bu, *t*Bu) and polysubstituted zirconocenes ($Me_2C_5H_3$, Me_5C_5) as well as the indenyl- and the 2-methylindenyl complex, all of which are homoleptic, are also commercially available.

Many chiral, enantiomerically pure zirconocenes are known [20]. In order to induce an asymmetric reaction, chiral zirconocenes have to be prepared, of which the most common are [(EBTHI)$ZrCl_2$] {EBTHI = η^{10}-ethylene-1,2-bis(tetrahydroindenyl), see Scheme 8.47 for the corresponding bis(triflate)} and Erker's [$(NMI)_2ZrCl_2$] (NMI = η^5-neomenthylindene) [21] (see Scheme 8.37). The [(EBTHI)$ZrCl_2$] complex is commercially available as a racemate or in enantiomerically pure form (for a resolution procedure, see the supplementary material of [22]), and the precursor [(EBI)$ZrCl_2$] is available as a racemate.

8.1.5
Reactions Involving Cationic Zirconocenes

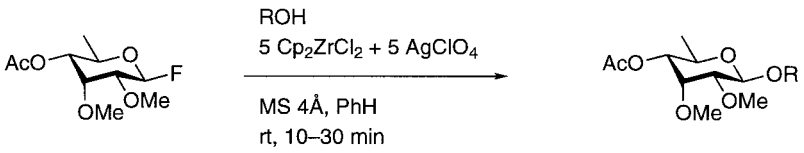
In the following sections, we discuss reactions in which cationic zirconocenes are involved as reagents, intermediates, or catalysts. As already mentioned, polymerization reactions will not be considered. Section 8.2 deals with the use of the $Cp_2ZrCl_2/AgClO_4$ system (or similar combinations) as an activator in glycoside synthesis. In Section 8.3, nucleophi-

lic alkylation reactions of aldehydes and epoxides are presented, in which cationic zirconocene species serve as Lewis acidic activators. Section 8.4 covers carbometalation of alkynes and alkenes with organozirconocene species, which can be stoichiometric or catalytic in zirconium, whereas in Section 8.5 catalytic reactions are discussed, in which cationic zirconocenes act in a similar manner to *classical* Lewis acids through coordination rather than being involved in organometallic steps. Finally, in Section 8.6, miscellaneous reactions are collected.

8.2
Glycosylations with Cp_2ZrCl_2/Silver Salt Activators

8.2.1
Cp_2ZrCl_2/Silver Salt as a New Activator of Glycosyl Fluorides

The combination $Cp_2ZrCl_2/AgClO_4$ (1:1) was introduced as a very potent activator of glycosyl fluorides in 1988 [2,23]. Reactions are very fast in CH_2Cl_2, even at −20 °C. The first examples involved the glycosidation of mycinose with various alcohols (Scheme 8.3). In order to obtain high β-selectivity with this sugar, which bears a 2-methoxy group, the reaction had to be performed in benzene [2].



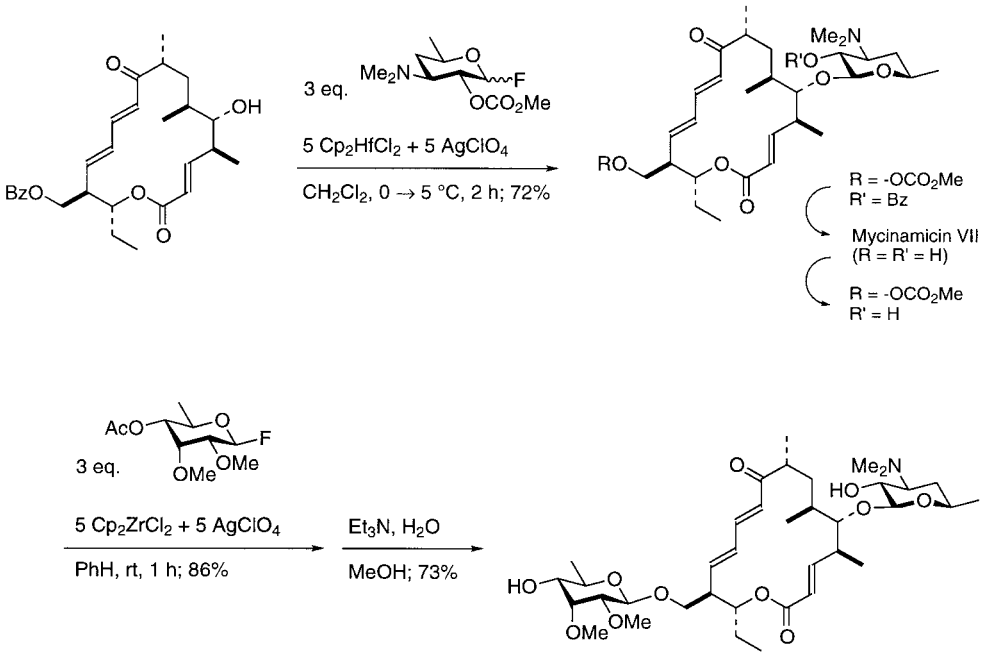
R = -CH_2Cy	92% (α/β = 1 : 16)
R = Cy	89% (α/β = 1 : 16)
R = ^{t}Bu	59% (β)

Scheme 8.3. Glycoside formation from glycosyl fluorides with a metallocene activator.

The related hafnocene reagent $Cp_2HfCl_2/AgClO_4$ (1:1) shows similar reactivity, but these congeners sometimes show different selectivity/reactivity for a given set of donor and acceptor. There has also been a report in which different chemoselectivity was observed for the two reagents (*vide infra*, Scheme 8.7). When basic functional groups such as tertiary amines are present in the glycosyl component, the Hf reagent is superior to the Zr reagent [23].

The utility of both the zirconocene and hafnocene reagents was subsequently shown in a synthesis of mycinamicin IV (Scheme 8.4) [24]. In attempted glycosylations with traditional activators, an intramolecular cyclocondensation of the aglycon occurred instead of glycoside formation, probably due to the glycosylation of the sterically hindered acceptor being very slow. By virtue of their fast glycosylation kinetics, metallocene-based reagents circumvented this problem and gave the desired β-glycosides. Interestingly, the second glycosylation step, for which the Zr reagent is used, is not hampered by the presence of the amino group in the aglycon.

An even more reactive activator of glycosyl fluorides is generated by employing a 1:2 ratio of the metallocene and silver salt in benzene [25]. The zirconium reagent proved



Scheme 8.4. Glycosylations in the synthesis of mycinamicin IV.

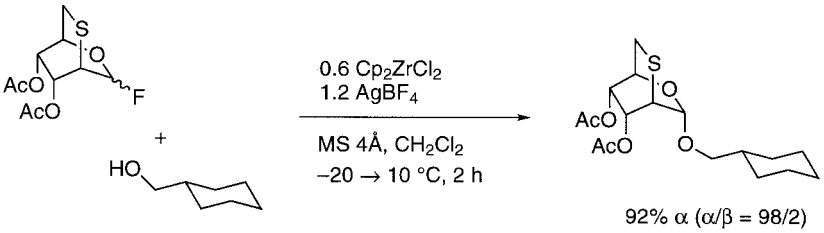
very effective in α-selective glycosylations with mannosyl fluorides. A screening of several silver salts showed that clean reactions took place with $AgClO_4$, AgOTf, and $AgBF_4$, but with $AgPF_6$ and $AgSbF_6$ side reactions occurred due to the high reactivity of the in situ formed species. Most favorable for α-selective mannosylation were the combinations $Cp_2ZrCl_2/AgClO_4$ (1:2) and $Cp_2ZrCl_2/AgBF_4$ (1:2) in benzene (room temp., 20 min) [25]. In the latter case, the actual *in situ* reagent may be BF_3, formed by fluoride abstraction from the BF_4^- anion. In line with this, a control experiment using the activator $BF_3 \cdot Et_2O$ gave similar results [25], and the reaction of Cp_2ZrCl_2 with 2 equivalents of $AgBF_4$ has been reported as a synthetic method for generating Cp_2ZrF_2 [7].

The aforementioned metallocene activators of glycosyl fluorides can be applied to glycosylations of monosaccharides as well as to those of oligosaccharides. Especially in the latter case, they often give better coupling results than other glycosyl fluoride activators. In the following section, we highlight the use of the zirconocene reagent with several substrates, and provide examples of the synthesis of complex molecular systems.

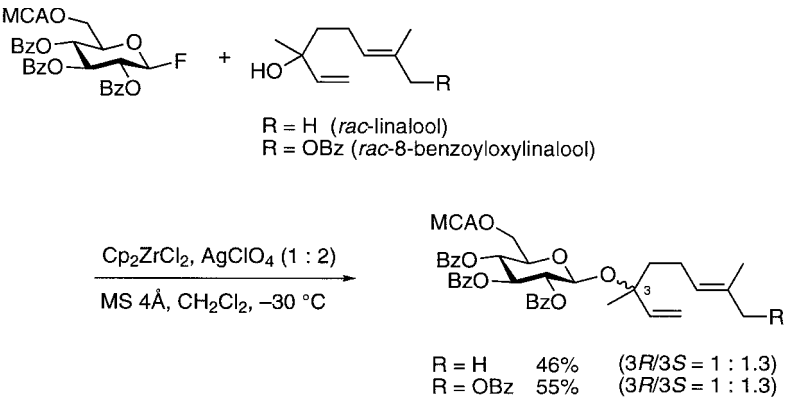
8.2.2 Applications in Synthesis

8.2.2.1 Application to glycoside and nucleoside synthesis

Toshima et al. achieved an α-stereoselective glycosidation using 2,6-anhydro-2-thioglycosyl fluoride as the donor (Scheme 8.5). Among other activators, the $Cp_2ZrCl_2/AgBF_4$ reagent (1:2) was tested and proved to be the best suited for the glycosylation of cyclohexylmethanol in high yield and with high stereoselectivity ($\alpha/\beta = 98:2$) [26].



Scheme 8.5. α-Selective glycoside formation from an anhydro thioglycosyl fluoride.



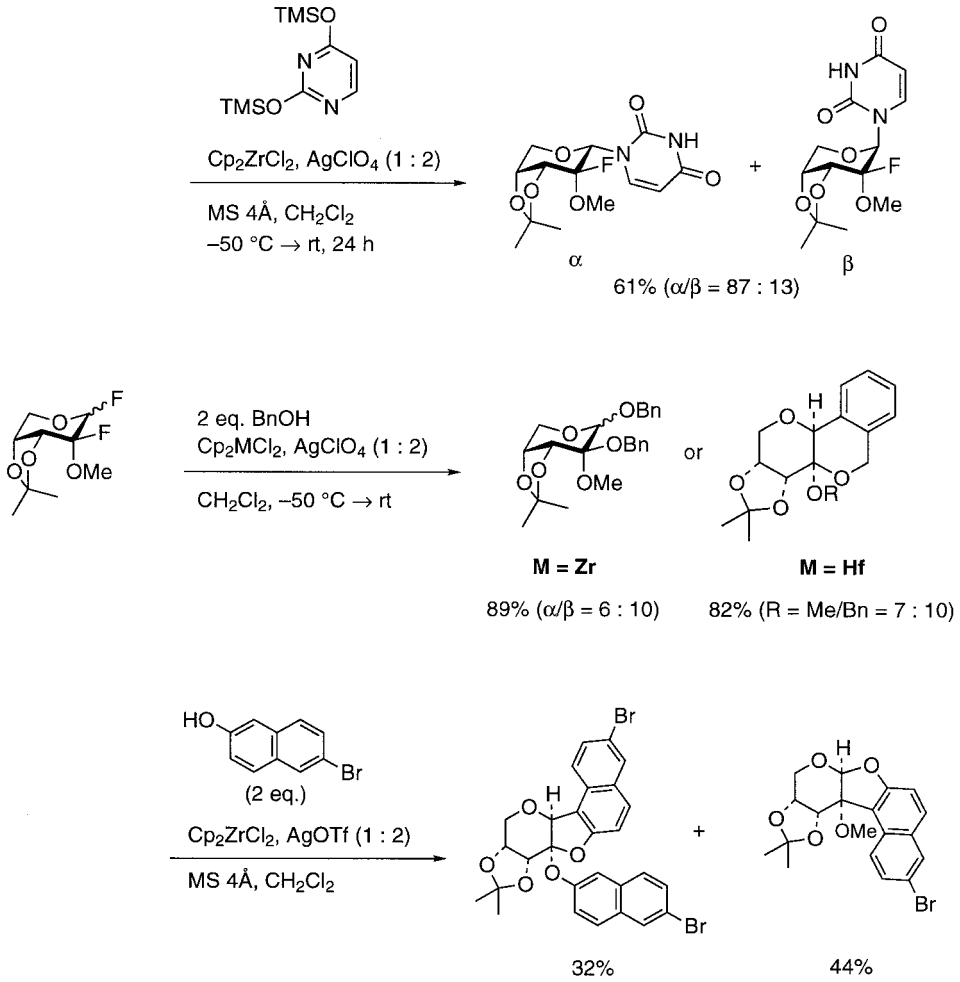
Scheme 8.6. Synthesis of terpene-glycosyl conjugates.

The zirconocene-promoted glycosylation was applied in the total synthesis of antitumor monoterpene glycosides by Konda et al. [27] (Scheme 8.6). Glycosylation of linalool and its 8-benzoyloxy derivative with a glycosyl fluoride proceeded in the presence of $Cp_2ZrCl_2/AgClO_4$ (1:2) to give the corresponding β-glycosides as mixtures of epimers in moderate yield.

Castillon et al. reported a series of interesting transformations of a 2-fluoro-2-methoxy-ribopyranosyl fluoride derivative, a 1,2-dielectrophilic synthon, with several nucleophiles in the presence of either the zirconocene or hafnocene activator [28–30] (Scheme 8.7). In the presence of $Cp_2ZrCl_2/AgClO_4$ (1:2), the reaction with bis(trimethylsilyl)uracil gave a mixture of epimeric nucleosides ($\alpha/\beta = 87:13$) in good yield, but the corresponding hafnocene reagent was even higher yielding with the same substrates [28].

When the 2-fluoro-2-methoxyribopyranosyl fluoride was subjected to conditions of benzyl glycoside formation, the zirconocene reagent ($Cp_2ZrCl_2/AgClO_4$, 1:2) facilitated the expected glycosylation, and also substituted the fluorine in the 2-position. It is then puzzling to note that the hafnocene reagent ($Cp_2HfCl_2/AgClO_4$, 1:2) displayed a different chemoselectivity, inducing a Friedel–Crafts-type cyclization to a chromane skeleton. Two products differing only in one acetal group (methoxy *vs.* benzyloxy) were formed in high yield [29].

In the reaction with 6-bromo-2-naphthol, no simple glycosides were obtained, but a mixture of tetracyclic compounds in yields of 32 % and 44 %, respectively (zirconocene activator). The hafnium reagent gave the same products in a similar ratio (21 % and 44 % yield) [30].

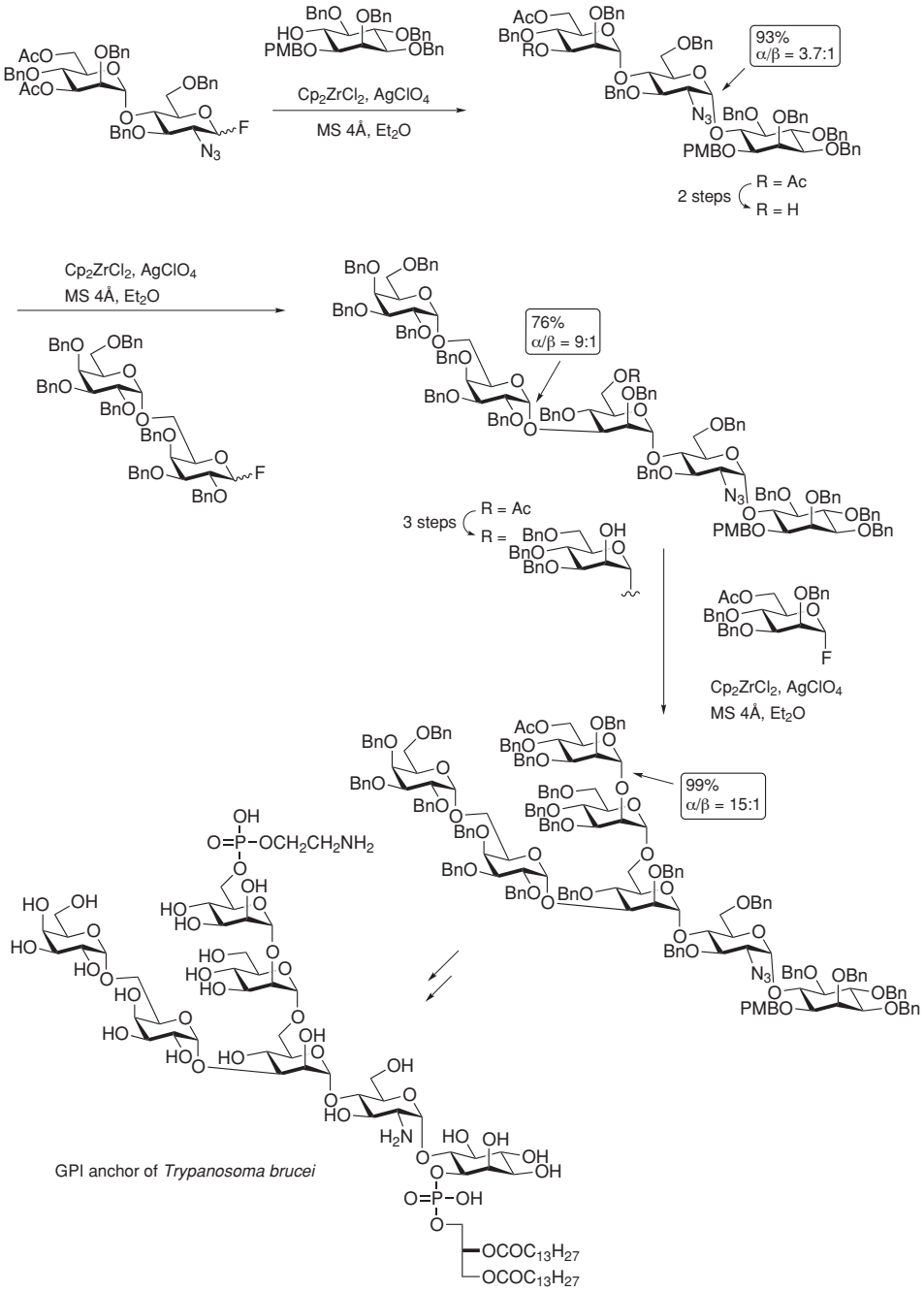


Scheme 8.7. Nucleoside synthesis, glycoside synthesis, and aromatic alkylation with a dielectrophilic donor.

8.2.2.2 Application to glycosylphosphatidylinositol (GPI) anchor and inositol phosphoglycan (IPG) synthesis

Glycoconjugates on the cell surface of parasitic protozoa of the Trypanosomatidae (including, e. g., African and American trypanosomes and *Leishmaia spp.*) influence parasite survival and infectivity. Many glycoconjugates are attached to the plasma membrane by means of glycosylphosphatidylinositol (GPI) anchors. All GPI anchors (from several different species) that have been characterized to date share an identical ethanolamine-phosphate-6-α-D-Man-(1→2)-α-D-Man-(1→6)-α-D-Man-(1→4)-α-D-GlcNH$_2$-(1→6)-D-*myo*-inositol backbone, suggesting that this sequence may be retained in all GPI anchors.

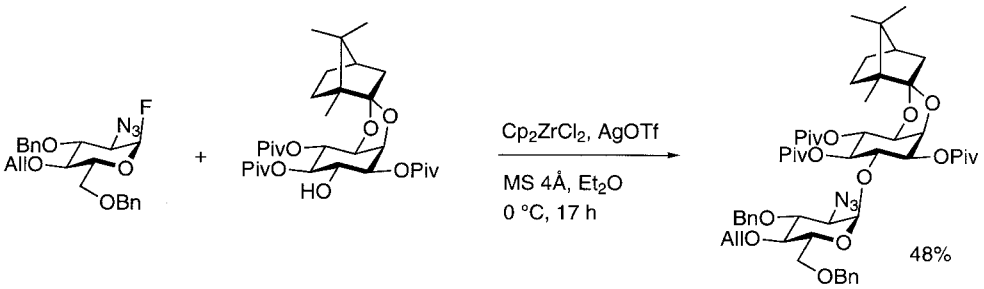
In a synthesis of a partial structure of the GPI anchor of *Trypanosoma brucei*, three of the four glycosylations were realized with the zirconocene activator ($Cp_2ZrCl_2/AgClO_4$, 1:1; Scheme 8.8). First, the coupling of a 1-D-*myo*-inositol acceptor with a disaccharide donor gave a mixture (93 %) of the desired α-linked trisaccharide and its β-isomer in a ratio



Scheme 8.8. Glycosylations in the synthesis of a GPI anchor.

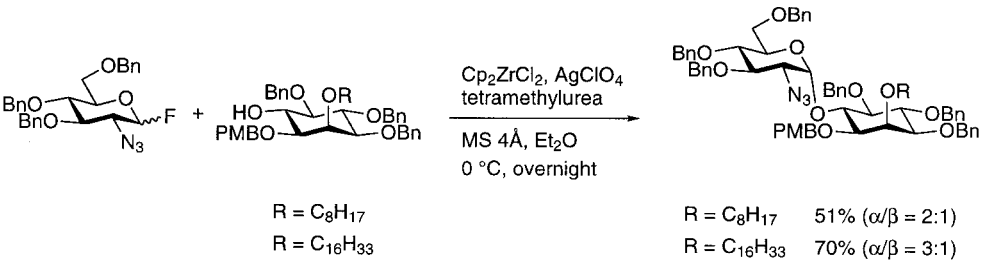
of 3.7:1. In the later sequence, two additional α-selective couplings proceeded in 76 % (α/β = 9:1) and almost quantitative yield (α/β = 15:1), respectively, the second to yield a heptaosyl core that was subsequently converted to the GPI anchor of *Trypanosoma brucei* [31–33].

Garegg et al. worked on an inositol phosphoglycan (IPG) that constitutes a partial structure of the GPI anchor [34]. On the way to this IPG, reaction of a glucosyl fluoride with a *sec*-alcohol acceptor, sterically biased by the presence of two flanking α-pivalyloxy groups, gave a reasonable yield (48 %) of the α-glycoside in the presence of the Cp_2ZrCl_2/AgOTf reagent (1:1.5 equivalents). Only traces of the β-isomer were detected (Scheme 8.9).



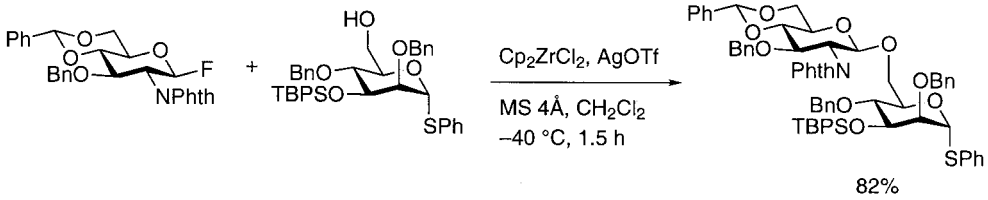
Scheme 8.9. Glycosylation of a sterically hindered, electron-poor inositol derivative.

Brimacombe and co-workers also reported glycosylations of some *myo*-inositol derivatives promoted by cationic zirconocene species in the synthesis of substrate analogues of early intermediates in the biosynthetic pathway of GPI anchors [35,36]. Glycosyl fluoride and the acceptors were treated with 4 equivalents of $Cp_2ZrCl_2/AgClO_4$ (1:1) and subsequently one equivalent of tetramethylurea to give the corresponding α-glycosides with moderate stereoselectivity (Scheme 8.10).



Scheme 8.10. Glycosylation of an inositol derivative.

Martín-Lomas et al. used a zirconocene-mediated coupling en route to an inositol-containing *pseudo*-hexasaccharide, which showed structural overlap with GPI and was designed to contain all the structural features that had been proposed for the type A inositolphosphoglycans (Scheme 8.11). The glycosylation was performed using the Cp_2ZrCl_2/AgOTf combination in a ratio of 1:2 (2 equivalents) to give, with excellent yield and selectivity, the required β-disaccharide [37]. The activation of the glycosyl fluoride in the presence of a thioglycoside is an example of the orthogonal glycosylation that can be achieved with the zirconocene reagent. Such selective activation of a glycosyl fluoride in the presence of a thioglycoside has previously been described with the hafnocene reagent [38].

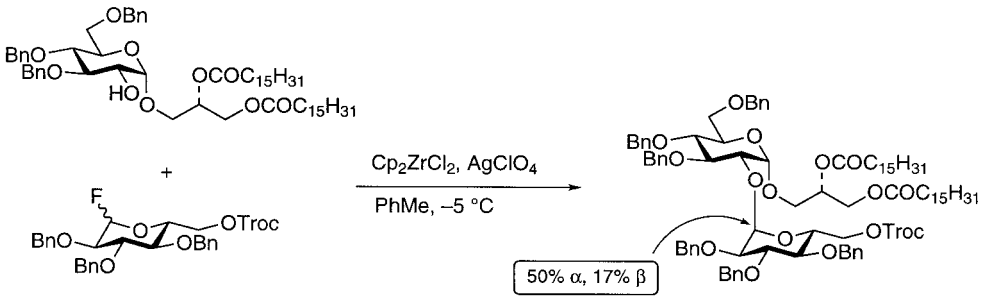


Scheme 8.11. Use of orthogonal activation strategies in the synthesis of a disaccharide donor.

8.2.2.3 **Diverse oligosaccharide syntheses**

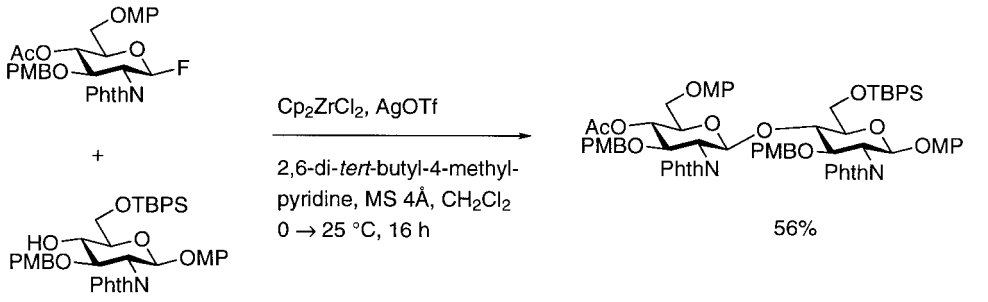
Lipoteichoic acid (LTA), which is a characteristic and widespread cell-surface constituent of gram-positive bacteria, is an amphiphile consisting of two covalently-bound distinct parts, i. e., a glycolipid and a hydrophilic poly(glycerol phosphate).

In the context of a synthesis of LTA, Kusumoto et al. reported that the glycosidation reaction of a gluco-donor and a glycolipid acceptor using $Cp_2ZrCl_2/AgClO_4$ (1:2) in toluene at −5 °C preferentially afforded the α-glycoside (α/β = 3:1), whereas the anomeric selectivity was slightly lower when $SnCl_2/AgClO_4$ was used (α/β = 2.3:1) [39] (Scheme 8.12).



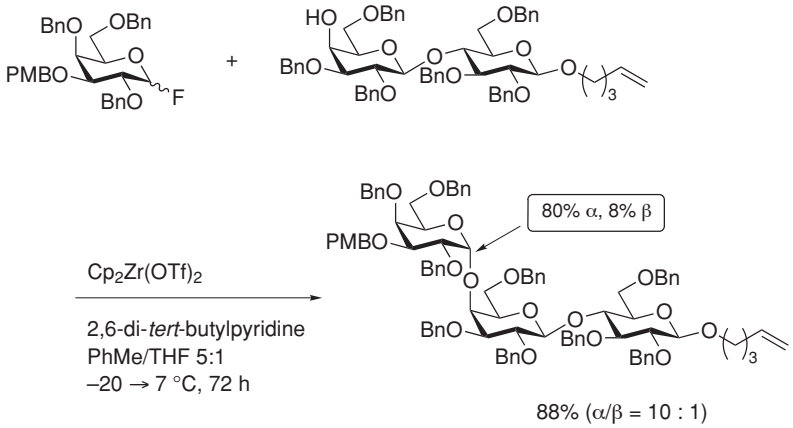
Scheme 8.12. Synthesis of glycolipids.

Nicolaou reported, in relation to a total synthesis of the NodRm-IV factors, that the coupling of a glucosamine derivative with a glycosyl fluoride mediated by $Cp_2ZrCl_2/AgClO_4$ (1:1) leads to a disaccharide with a β-glycoside linkage, as expected from the directing effect of the *N*-phthalimido group [40]. This protocol also involved the addition of an equivalent of the sterically hindered base 2,6-di-*tert*-butyl-4-methylpyridine (Scheme 8.13).



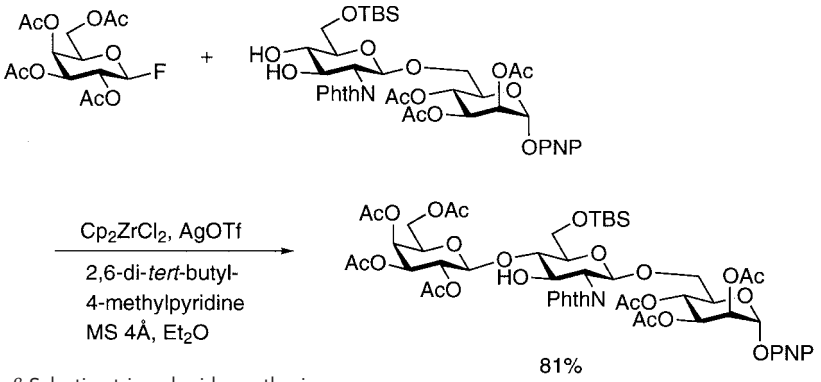
Scheme 8.13. Disaccharide synthesis in the presence of a sterically hindered pyridine.

Danishefsky recently reported a second-generation synthesis of the hexasaccharide MBr1 (globo-H) breast tumor antigen, in which $Cp_2Zr(OTf)_2$ was used in the glycosylation of a disaccharide acceptor to give an α-trisaccharide in high yield and with high selectivity (Scheme 8.14) [41]. From an experimental point of view, several aspects are worth noting in this example. First, 0.45 equivalents (based on Zr) of the isolated complex $[Cp_2Zr(OTf)_2]$ was used, rather than an excess of the in situ generated reagent. Given that the reaction solvent contained THF, one can conclude that the commercially available complex $[Cp_2Zr(OTf)_2(thf)]$ might be an alternative reagent for future use. Second, an equivalent of the sterically hindered base 2,6-di-*tert*-butylpyridine was added during the glycosylation. Third, on optimizing the procedure, the solvent mixture toluene/THF (5:1) was found to give the α-glycoside in the highest yields and with the best selectivity (10:1).



Scheme 8.14. α-Selective trisaccharide synthesis.

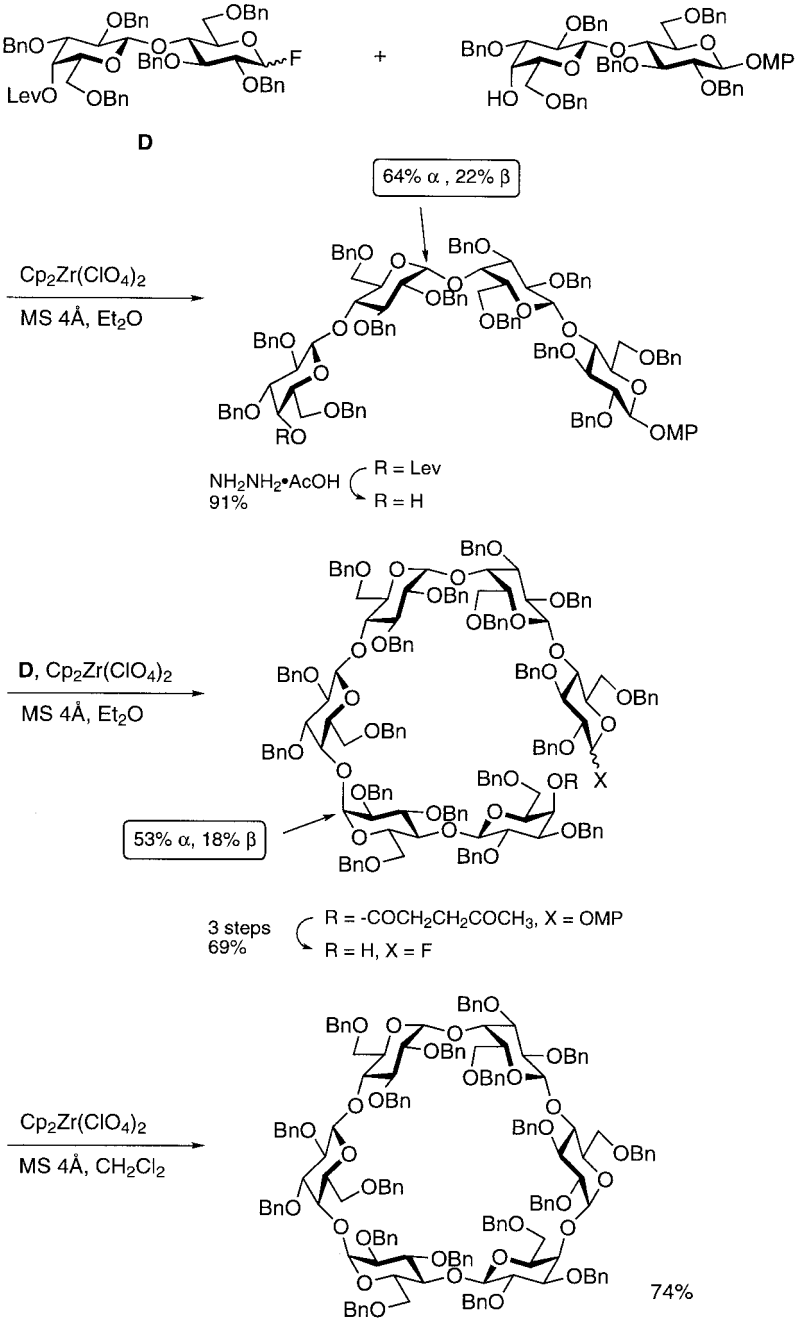
In the synthesis of a part of the gp 120 glycoprotein, galactosylation of a disaccharide acceptor containing two free hydroxy groups was achieved regioselectively using the Cp_2ZrCl_2/AgOTf reagent to afford a major β-(1→4)-linked trisaccharide in 81 % yield [42] (Scheme 8.15).



Scheme 8.15. β-Selective trisaccharide synthesis.

8.2.2.4 Cycloglycosylation

Ogawa and co-workers reported a successful cycloglycosylation using the Cp_2ZrCl_2/$AgClO_4$ (1:2) activator (Scheme 8.16). In addition, all glycosylation reactions in the synthesis were performed with the same reagent, denoted as in situ generated $Cp_2Zr(ClO_4)_2$.

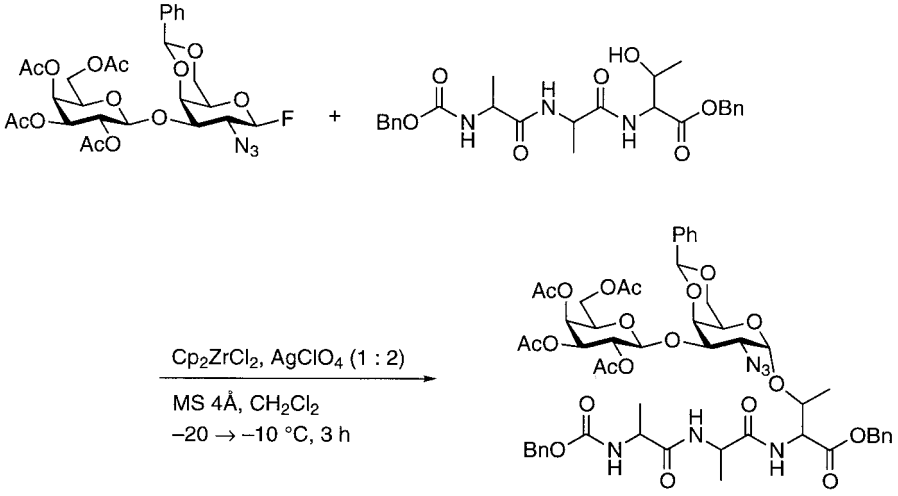


Scheme 8.16. Synthesis of a cyclolactohexose.

The linear lactohexaose cyclization precursor was built up in a [2 + 2 + 2] strategy by two consecutive α-selective glycosylations using the same disaccharide donor **D**, and this was followed by a final cyclization. The α-selectivities in the intermediate steps were only moderate (α/β = 2.9:1 in both cases), but the cyclization to the trigonally shaped protected cyclolactohexose proceeded in 74 % yield and gave a single isomer [43]. Similar strategies allowed the syntheses of cyclolactooctaose and cyclolactodecaose, again featuring the zirconocene perchlorate activator [44].

8.2.2.5 **Glycoconjugate synthesis**

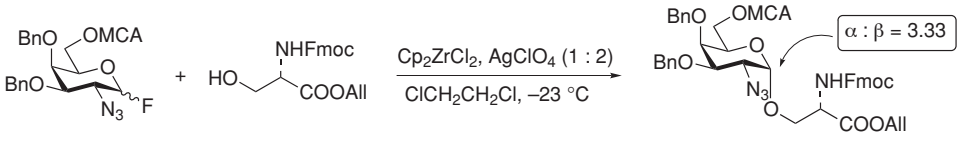
Zirconocene-promoted glycosylation was also applied in glycopeptide synthesis by Tsuda and Nishimura [45]. A disaccharide glycosyl donor was attached to the unprotected threonine residue of a tripeptide (stereochemistry not given, but probably natural) in the presence of Cp_2ZrCl_2 and $AgClO_4$ (1:2) in CH_2Cl_2 to afford the corresponding α-glycoside in 64 % yield (Scheme 8.17).



Scheme 8.17. Glycosylation of a threonine residue in a tripeptide.

Among structurally diverse glycoprotein oligosaccharides, those containing repeating *N*-acetyl-lactosamine structures attract much attention in connection with various biological events, most notably as onco-differentiation markers.

In the stereocontrolled synthesis of *O*-linked glycan, which contains a repeating lactosamine unit, Ogawa and co-workers set up the protein–carbohydrate link by glycosylation of a serine derivative in the presence of $Cp_2ZrCl_2/AgClO_4$ (Scheme 8.18). The desired α-glycoside was formed together with the corresponding β-isomer in 84 % yield (α/β = 3.33) [46].



Scheme 8.18. Glycosylation of a serine residue.

8.2.2.6 Conclusions on the use of the zirconocene/silver perchlorate activator: Modification and tuning of the reagent

Addition of a bulky pyridine base: Some workers have added an equivalent of 2,6-di-*tert*-butylpyridine or 2,6-di-*tert*-butyl-4-methylpyridine to the glycosylation mixture. While the reasons for this addition have not been discussed, one can note that according to a speculative equation for the glycosylation reaction:

$$ROH + RF + AgClO_4 + Cp_2ZrCl_2 = ROR + HClO_4 + AgCl + Cp_2ZrFCl \qquad \text{(eqn. 2)}$$

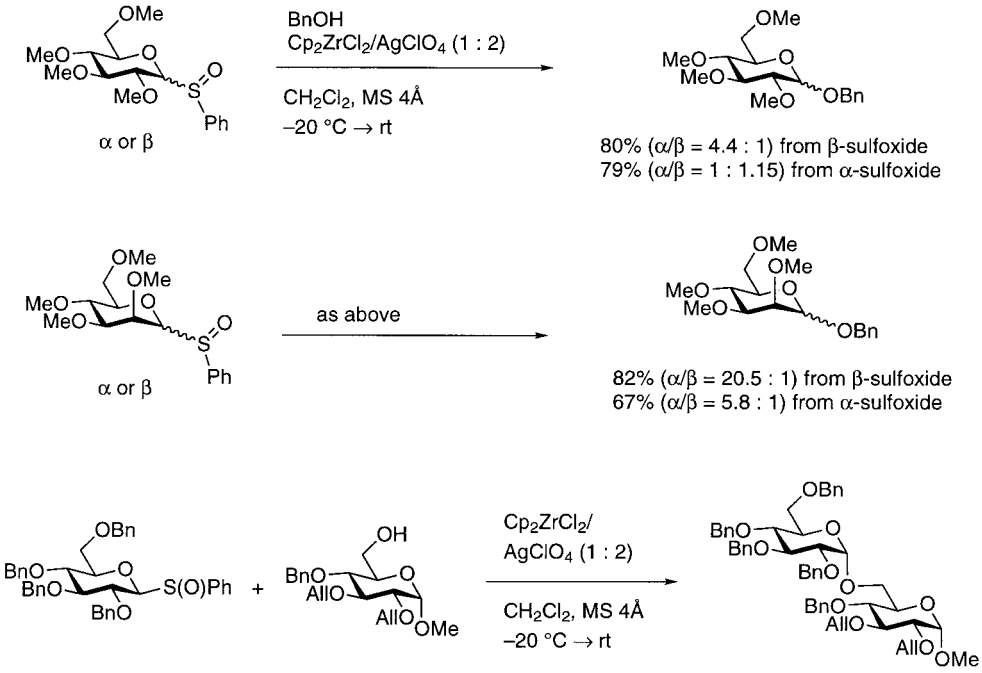
One equivalent of a strong acid is liberated, which might be trapped by the pyridine base. However, in most other reported examples, such an addition of base was not necessary. The actual products of this reaction, other than the glycoside and silver chloride, are not known. Species such as Cp_2ZrClF and Cp_2ZrF_2 are known, however, and have been described as mononuclear [19].

Excess of reagent: In the original communication, 5 equivalents of both Cp_2ZrCl_2 and $AgClO_4$ were used to bring about glycosylation [2]. This excess ensures a fast reaction, which is often the key to success in a situation of competing pathways. On the other hand, the metallocene/silver salt (1:2) activator is often used in lower quantities, down to 0.5 equivalents. This shows that each zirconium can bind two equivalents of fluoride.

In situ reagent *vs.* triflate complex: The solvent-free complex $Cp_2Zr(OTf)_2$, which is obtained by acidolysis of Cp_2ZrMe_2 with triflic acid [4], has been used as an activator in a glycosylation reaction [41]. It is probable that similar species are formed on mixing 2 equivalents of $AgClO_4$ (or other silver salts) with Cp_2ZrCl_2 in the course of the glycosylation reaction. The question thus arises as to whether it is preferable to use *in situ* activation methods or isolated complexes. The complexes in question are sensitive to moisture, and therefore handling and storage may be problematic. However, similar considerations apply to most of the silver salts used for activation. It seems that the direct use of commercially available $[Cp_2Zr(OTf)_2(thf)]$ in glycosylation reactions might offer advantages in terms of a straightforward experiment set-up, but with this complex no glycosylation has been demonstrated to date. For anions of low nucleophilicity other than triflate, no readily available zirconocenium complexes are known, and therefore the *in situ* methods for glycosylation are obligatory anyway.

8.2.3 Activation of Glycosyl Sulfoxides

It has recently been shown that the $Cp_2ZrCl_2/AgClO_4$ (1:2) reagent is also an activator of glycosyl sulfoxides bearing electron-rich ether protecting groups. Glycosylations of primary, secondary, and tertiary alcohols have proved successful. In reactions with a gluco donor, the regioselectivity of glycoside formation was found to change from α to β with increasing steric hindrance of the acceptor, whereas with a manno donor α-glycosides were consistently obtained in excess. The exact α/β ratio was also strongly influenced by the configuration of the donor. An example of disaccharide synthesis was also provided (Scheme 8.19) [47].

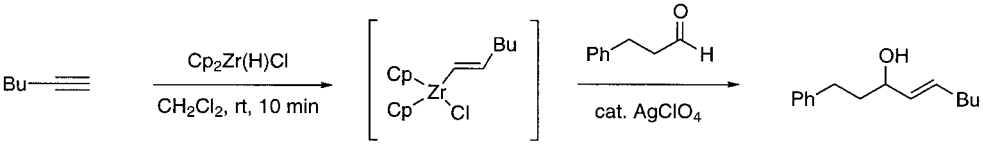


Scheme 8.19. Glycosylation reactions with a glycosyl sulfoxide.

8.3
Nucleophilic Additions to Aldehydes and Epoxides

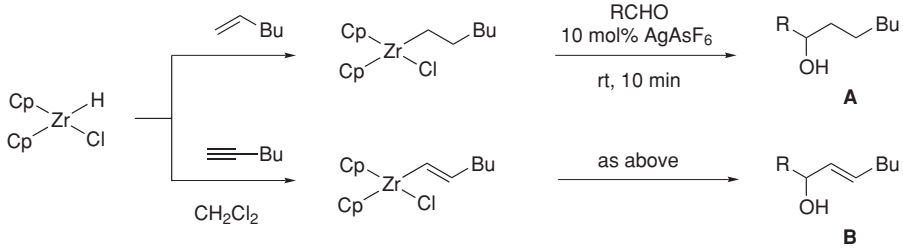
8.3.1
Silver-Mediated 1,2-Addition of Alk(en)ylzirconocene Chlorides to Aldehydes [48]

Alkyl- and alkenylzirconocene chlorides [$Cp_2Zr(R)Cl$] are readily accessible by hydrozirconation of alkenes and alkynes with the Schwartz reagent [$Cp_2Zr(H)Cl$] [49]. These organometallic species are not sufficiently reactive to cleanly add to aldehydes and ketones or to open epoxides. However, nucleophilic addition of alkenylzirconocenes to aldehydes is strongly accelerated by a catalytic amount of $AgClO_4$ [50] (Scheme 8.20). The perchlorate is more effective than other salts, the order of reactivity being: $AgClO_4$ > AgOTf > $AgSbF_6$ > $AgPF_6$ >> $AgBF_4$. Alkylzirconocene chlorides also give the addition products, but the reaction is slower and the yields are rather sensitive to the steric hindrance of the aldehyde [50].



Scheme 8.20. Hydrozirconation–carbonyl addition sequence.

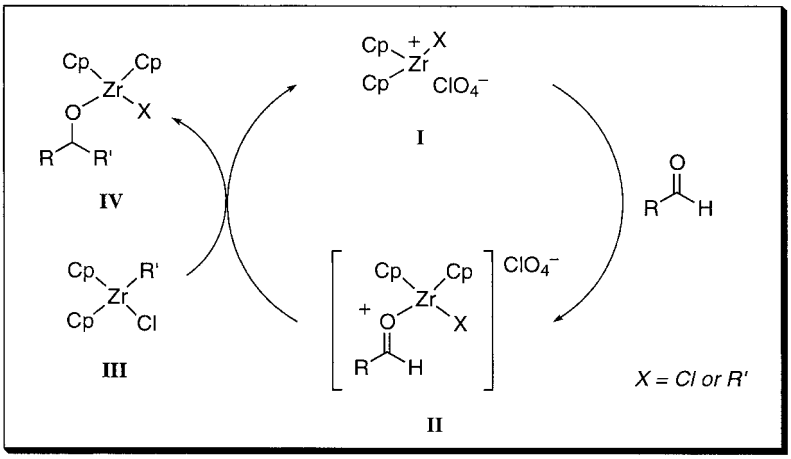
Later, it was found that $AgAsF_6$ is even more effective in promoting the addition reactions to aldehydes. Very high yields were obtained with both alkyl- and alkenylzirconocenes [51]. The use of $AgAsF_6$ is not only beneficial in terms of reactivity, but is also safer in view of the potential explosive properties of $AgClO_4$ [52] (Scheme 8.21).



Aldehyde RCHO	Yield of Alcohol	
	A	B
$PhCH_2CH_2CHO$	95%	91%
CyCHO	99%	96%
PhCH(Me)CHO	98%	91%
^{t}BuCHO	89%	88%

Scheme 8.21. Improved carbonyl addition results with $AgAsF_6$.

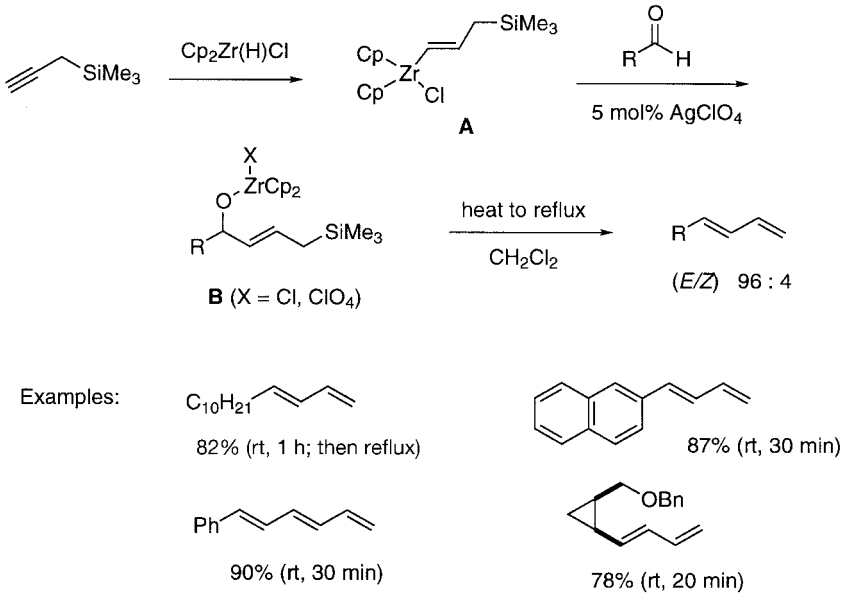
A mechanism involving the generation of a cationic alk(en)ylzirconocene (**I**; X = R') through chloride abstraction by silver(I) has been postulated (Scheme 8.22). This cationic intermediate is capable of activating the carbonyl group towards addition (**II**). Irrespective of whether an alk(en)yl group is added intra- or intermolecularly, a new cationic species is generated (either by R'-transfer or Cl-abstraction from **III**) and the reaction thus proceeds in a zirconium-catalyzed manner [50].



Scheme 8.22. Mechanism of silver-mediated carbonyl addition.

8.3.1.1 1,3-Diene synthesis from aldehydes

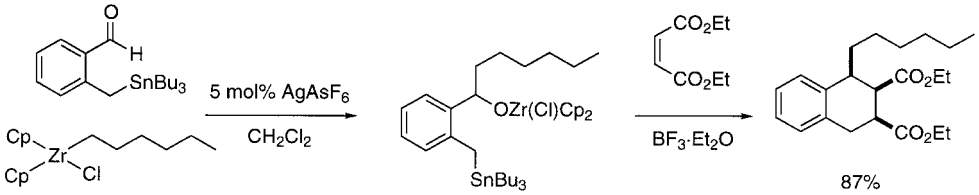
A useful application of the silver-mediated additions is 1,3-diene synthesis by three-carbon elongation of aldehydes [48,51,53]. The bimetallic reagent 3-trimethylsilyl-1-propenylzirconocene chloride (**A**; Scheme 8.23) reacts with aldehydes under the influence of a catalytic amount of Ag^+ to give the intermediate zirconocene-alkoxide **B**, which then undergoes a Peterson-type 1,4-elimination of TMS alkoxide to stereoselectively afford (*E*)-dienes (*E*/*Z* > 96:4) (Scheme 8.23). A Wittig reaction yields the same products without stereoselectivity (ca. 1:1 mixtures of *E*- and *Z*-isomers).



Scheme 8.23. Stereoselective diene synthesis.

The elimination from the zirconium alkoxide **B** (Scheme 8.23) to give the 1,4-diene also proceeds through cationic activation. An independently prepared sample of pure **B** (X = Cl) would not undergo elimination unless a catalytic amount of $AgClO_4$ (or $TMSClO_4$, which is the probable chain carrier in this elimination reaction) was added. If $AgAsF_6$ is used as the promoter for the reaction sequence, only the first (addition) step takes place and no elimination to the diene is observed [51].

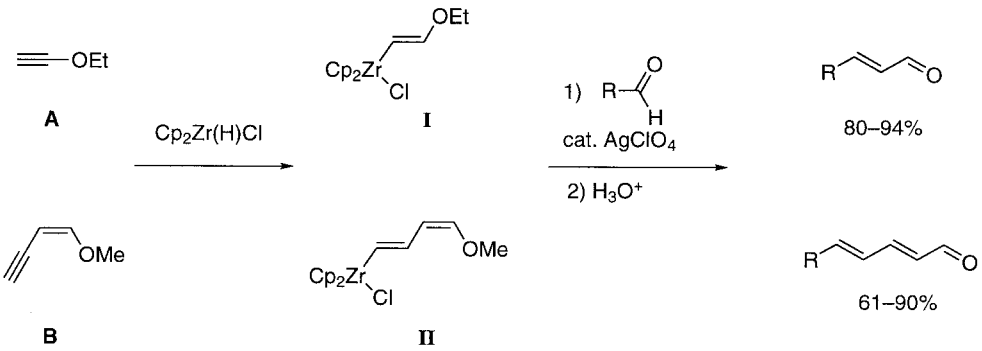
o-Quinodimethanes constitute a special type of 1,3-dienes. Scheme 8.24 shows an example in which silver-mediated addition of alkylzirconocene chloride to an aromatic aldehyde produces a zirconocene alkoxide ready for 1,4-elimination. Generation of the quinomethane is achieved using $BF_3 \cdot OEt_2$ ($AgAsF_6$ alone would not cause elimination) and the generated quinomethane is trapped by the added dienophile [51].



Scheme 8.24. Silver-mediated carbonyladdition, followed by 1,4-elimination and cycloaddition.

8.3.1.2 Homologation of aldehydes

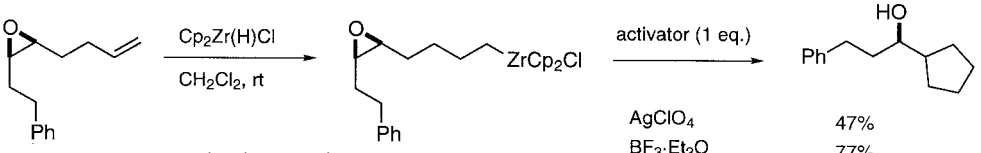
By the hydrozirconation of ethoxyethyne (**A**; Scheme 8.25) or (*Z*)-1-methoxy-1-buten-3-yne (**B**), two useful reagents for the two- (**I**) or four- (**II**) carbon homologation of aldehydes are generated in situ [54]. Silver-mediated addition to several aldehydes followed by acidic hydrolysis gives the homologous unsaturated aldehydes in good to excellent yields. By repetition, long-chain polyenals can be obtained; starting from cyclohexanecarbaldehyde, three consecutive four-carbon homologations gave the corresponding hexaenal with yields of 90 %, 80 %, and 61 % for the individual steps.



Scheme 8.25. Homologation of aldehydes to enals and dienals.

8.3.2
Nucleophilic Ring-Opening of Epoxides by Alkylzirconocene Chlorides

Like the 1,2-addition of organozirconocene chlorides, the nucleophilic ring-opening of epoxides is not usually feasible with the reagents alone. However, it has been found that an intramolecular cyclization of an alkylzirconocene possessing an oxirane ring occurs upon the addition of a stoichiometric amount of $AgClO_4$, and that this is even higher yielding with $BF_3 \cdot OEt_2$ (Scheme 8.26) [55].

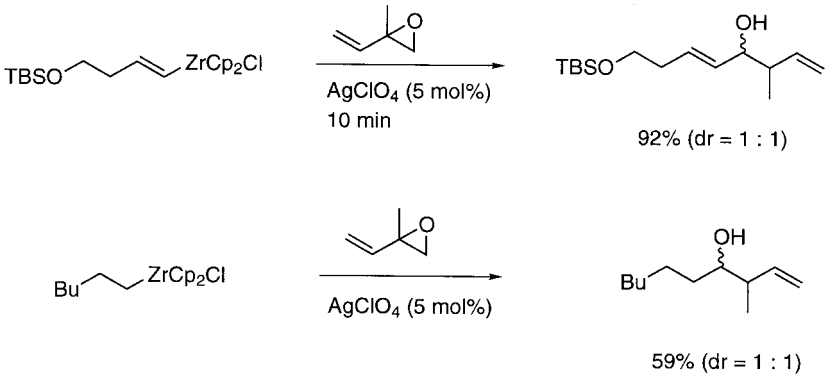


Scheme 8.26. Intramolecular epoxide opening.

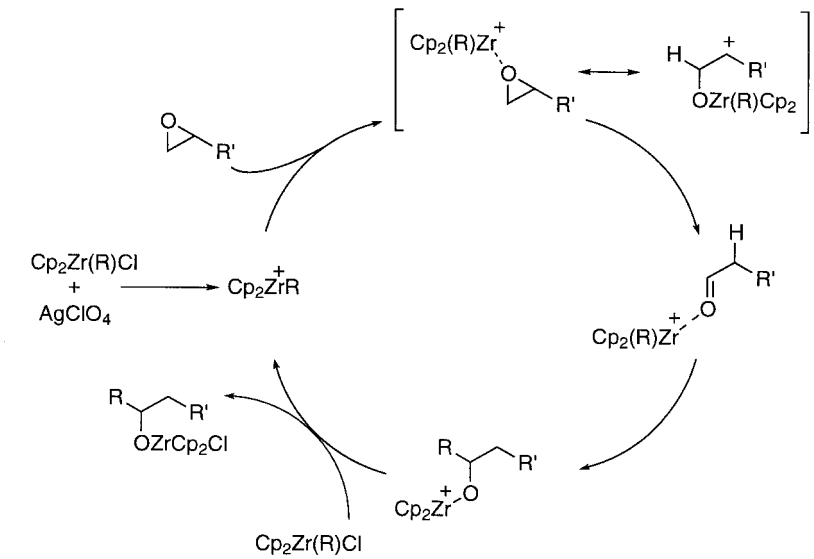
8.3.3
Nucleophilic Reactions of Organozirconocene Chlorides with Epoxides

What will happen in the intermolecular reaction of organozirconocene chlorides with epoxides in the presence of an activator? The experiment was performed by Wipf and Xu [56]. The products of this reaction bear the alk(en)yl group and the oxygen atom from the epoxide on the same carbon, showing that no simple epoxide ring-opening takes place (Scheme 8.27). The strongly Lewis acidic Cp_2RZr^+ generated by chloride abstraction from Cp_2ZrRCl with $AgClO_4$ initially induces an epoxide opening followed

by a 1,2-hydride shift. The resulting aldehyde then undergoes a nucleophilic attack of R to give an alkoxyzirconocene cation, which then abstracts a chloride from Cp_2ZrRCl to regenerate Cp_2Zr^+R. The occurrence of this rearrangement of an epoxide to the corresponding aldehyde was confirmed upon exposure of an epoxide to the Lewis acid generated in situ from Cp_2ZrCl_2 and $AgClO_4$ (*cf.* Section 8.5.2).



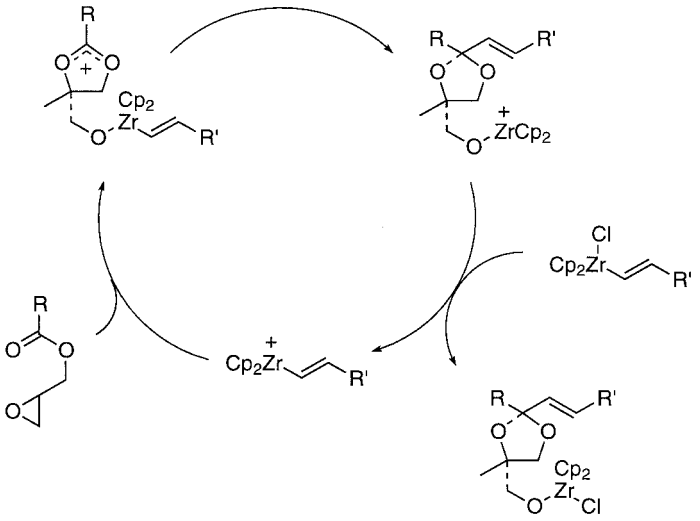
Mechanistic Scheme



Scheme 8.27. Silver-mediated reaction of alkylzirconocenes with epoxides.

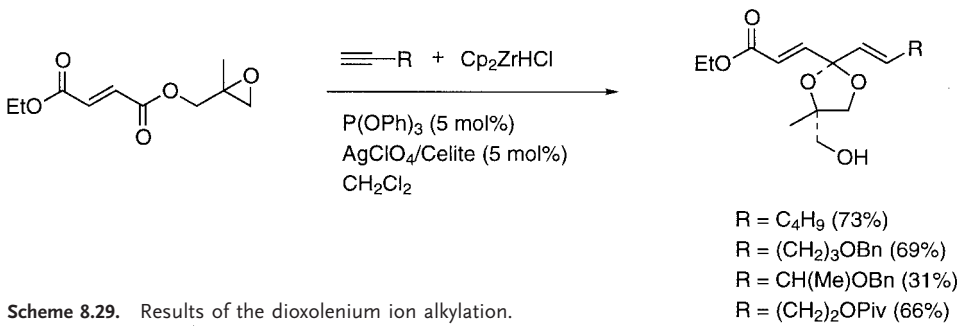
The reaction between an epoxy ester and an alkenylzirconocene chloride, again in the presence of the activator $AgClO_4$, takes a different course (Scheme 8.28) [57,58]. Assistance by the ester group leads to intramolecular ring-opening of the epoxide, and the resulting dioxolenium ion is stereospecifically alkylated by intramolecular transfer of the alkenyl ligand from zirconium, thereby forming an acetal [57]. Depending on the structure of the epoxy ester, another mode of reaction is possible, which involves the trans-

fer of the alkoxy ligand instead of the alkenyl ligand to the cation center, in which case orthoesters are the products, *cf.* Section 8.5.1.



Scheme 8.28. Internal transfer of an alkenyl group to a dioxolenium ion.

Some examples of the dioxolenium ion alkenylation reaction are shown in Scheme 8.29 [58]. The use of $AgClO_4$ on Celite (easier to handle than pure $AgClO_4$) and triphenyl phosphite was stated to improve the reproducibility in these reactions. At present, the method is not applicable to alkylzirconocene chlorides.



Scheme 8.29. Results of the dioxolenium ion alkylation.

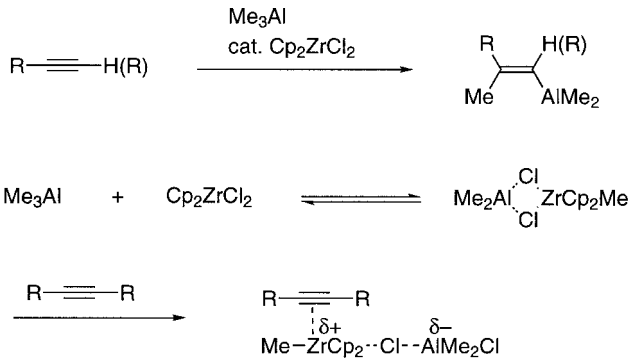
8.4 Carbometalation of Alkynes and Alkenes

Cationic zirconocene species efficiently activate alkenes toward carbon–carbon bond formation via carbometalation, as has been demonstrated in studies of alkene polymerization. Today, some zirconocene catalysts are available that allow single additions of metal-alkyls (mainly aluminum-alkyls) to alkenes or alkynes, thereby forming stable alkyl- or alkenyl-metals that do not undergo any further oligomerization. On the other hand, carbozirconation with Cp_2ZrRCl in the presence of stoichiometric or catalytic amounts of activators has also been realized.

8.4.1 Carbometalation of Alkynes

8.4.1.1 Methylalumination

In 1978, Negishi et al. reported highly regio- and stereoselective methylalumination of alkynes with Me_3Al using a zirconocene catalyst [59]. The involvement of cationic zirconocene species in the activation of carbon–carbon triple bonds was suggested in a reaction mechanism featuring electrophilic activation by aluminum (Scheme 8.30).



Scheme 8.30. Carboalumination of alkynes with $AlMe_3/Cp_2ZrCl_2$.

The method enables conversion of substituted alkynes to (*E*)-2-methyl-1-alkenylaluminum species, and, by subsequent iodinolysis, to the corresponding iodoalkenes with retention of the double-bond configuration. Depending on the substitution pattern of the starting alkyne, many useful products emerge from this reaction, which themselves can serve as building blocks for transition metal-mediated or -catalyzed coupling reactions [59–62].

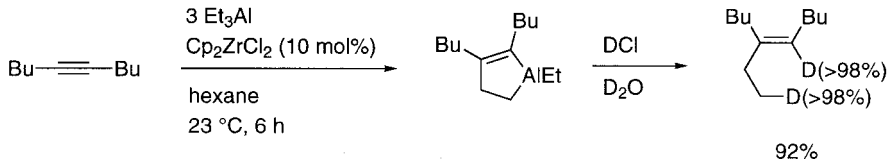
A remarkable feature of the methylalumination reaction is that the addition of water to the reaction mixture has an accelerating effect. An in situ generated aluminoxane species (similar to MAO) is most probably responsible for this effect. The methylalumination then proceeds at −23 °C without any loss of regioselectivity [63].

8.4.1.2 Other alkylaluminations

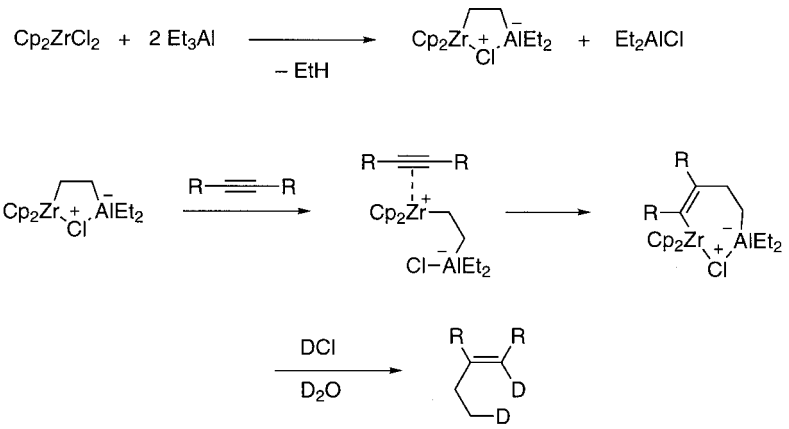
Attempts to use the isobutyl group in the carbometalation of alkynes only give rise to hydrometalated products, but ethyl and *n*-propyl groups can be successfully transferred from the corresponding dialkylaluminum chlorides. The regioselectivity in these reactions is lower than that for the methyl transfer. Indeed, the reaction mechanism may be different from that of methylalumination [62].

Despite the formal similarity of the reaction, the mechanism of Cp_2ZrCl_2-catalyzed ethylalumination [64] with $AlEt_3$ is different from that of either methylalumination with $AlMe_3$ or ethylalumination with Et_2AlCl [62]. The involvement of dimetallic species was confirmed by NMR spectroscopy as well as deuterolysis (Scheme 8.31). The proposed mechanism features an interesting zwitterionic bimetallic species, in which the zirconium center is cationic. A highly instructive treatise on the mechanistic pathways of carbometalation is presented in [65].

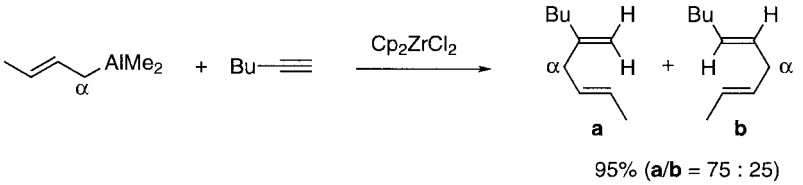
An allylaluminum species, which was generated by the reaction of allyl Grignard reagent with diisobutylaluminum chloride, was found to react with terminal alkynes in



Mechanistic Scheme:



Scheme 8.31. Ethylalumination with $AlEt_3$, catalyzed by zirconocene dichloride.

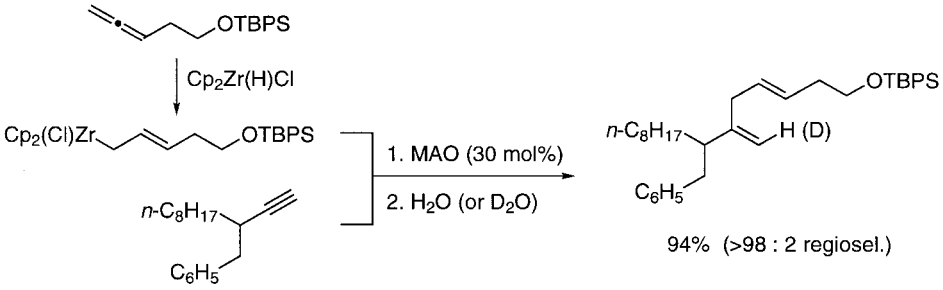


Scheme 8.32. Addition of an allyl group from aluminum to an alkyne.

the presence of zirconocene dichloride to give the carbometalated products [66]. Analogous reaction with crotylaluminum revealed that the carbon–carbon bond is established mainly between the less hindered α-position of the organoaluminum and the internal carbon of the alkynyl triple bond, although some regioisomers are also formed, the amount of which depends on the actual alkyne used (Scheme 8.32).

8.4.1.3 Allylzirconation

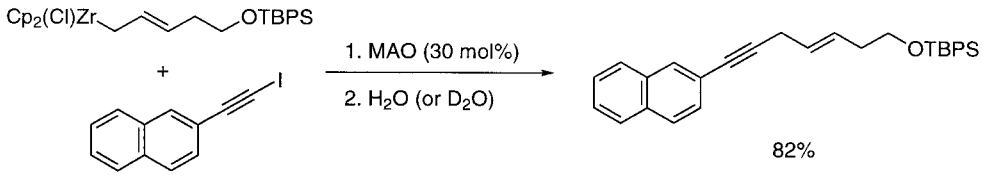
Allylzirconation of alkynes with allylzirconocene chloride reagents (obtained by hydrozirconation of allenes) takes place in the presence of a catalytic amount of methylaluminoxane (MAO) [67,68]. MAO presumably abstracts chloride to form an allylzirconocene cation, which coordinates to the alkyne triple bond. The subsequent migratory insertion is regioselective, as it is found that the new bond is mainly formed between the α-carbon of the allylzirconium species and the internal carbon of a terminal alkyne (Scheme 8.33).



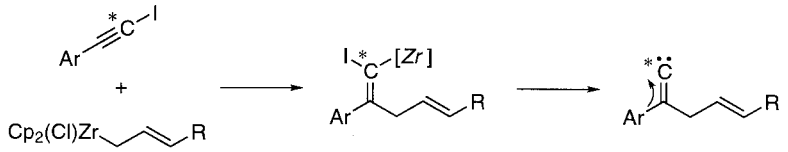
Scheme 8.33. Allylzirconium addition to alkynes, mediated by MAO.

Some attack at the terminal carbon of the alkyne also takes place, and the regioselectivity of the reaction depends very much on the steric bulk of the alkyne substituents.

When 1-iodoalkynes are coupled with allylzirconocene chlorides in the presence of a catalytic amount of MAO, disubstituted alkynes are formed (Scheme 8.34). At first sight, this might appear to be a simple substitution reaction (i.e., involving an addition/elimination sequence), but the product is in fact formed by a 1,2-rearrangement of an intermediate zirconocene carbenoid generated by allylzirconation of the 1-iodoalkyne [69]. Evidence for this was provided by an experiment with ^{13}C-labeled iodoalkyne, in which it was shown that the naphthyl group migrates during the reaction sequence.



^{13}C-labeling experiment:

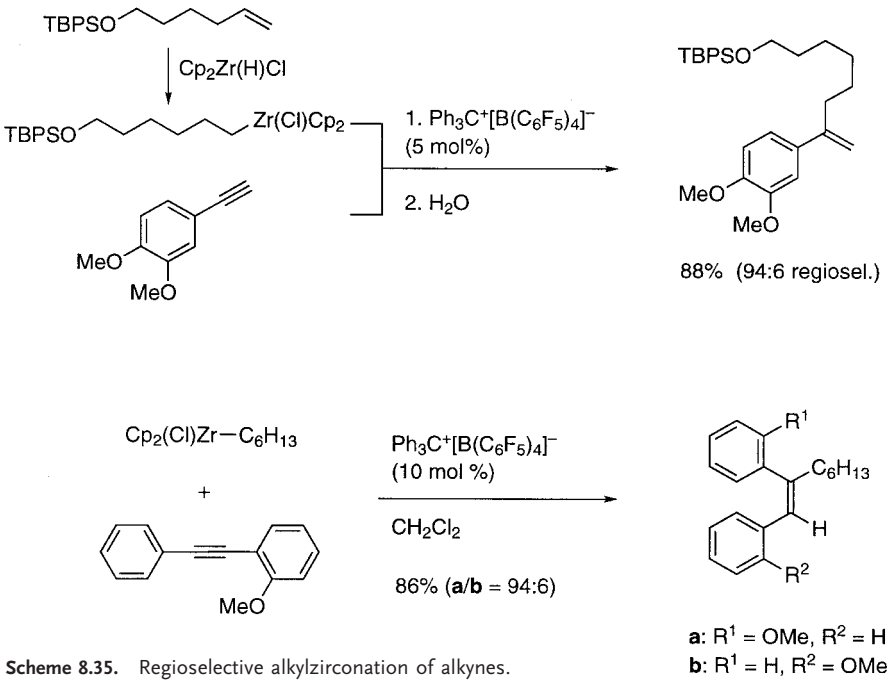


Scheme 8.34. A carbometalation–1,2-shift sequence.

8.4.1.4 **Alkylzirconation**

Whereas zirconium-catalyzed alkylalumination of alkynes is at present limited to some simple alkyl groups, it has been found that carbozirconation with $Cp_2Zr(R)Cl$ considerably expands the scope of the alkylmetalation of alkynes. The reactions are initiated by catalytic amounts of additives (typically $Ph_3C[B(C_6F_5)_4]$), which probably serve to generate cationic zirconocene species. Regioselectivity in favor of attack at the more highly substituted carbon is observed [70,71] (Scheme 8.35).

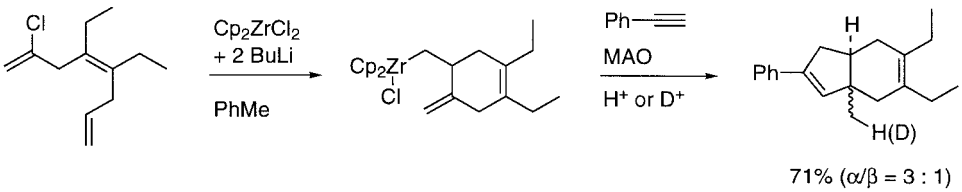
Internal alkynes, which usually show low reactivities, are carbometalated to give trisubstituted alkenes in high yields by applying this methodology. Unsymmetrical internal



Scheme 8.35. Regioselective alkylzirconation of alkynes.

alkynes bearing one *ortho*-substituted aryl group undergo regioselective alkylzirconation to give trisubstituted alkenes upon protonolysis (Scheme 8.35).

Bicyclic compounds are obtained in a sequence of intramolecular migratory insertions (i.e. alkenylzirconations of alkenes!) and an intermolecular carbometalation (Scheme 8.36). Starting with a chlorotriene, oxidative addition of the Negishi reagent (Cp_2Zr), followed by migratory insertion, gives an alkylzirconium species, which adds to a phenylalkyne in the presence of MAO. A final migratory insertion affords the product as a mixture of *cis*- and *trans*-fused bicycles [72].



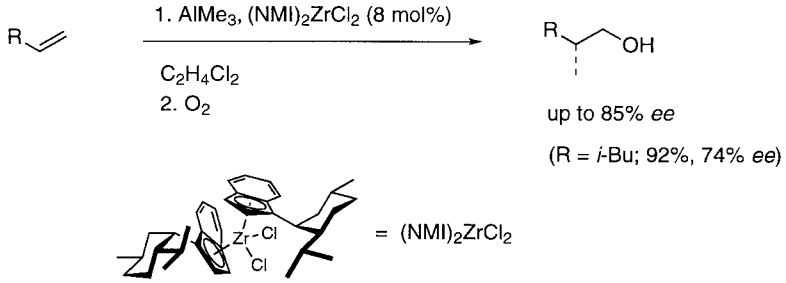
Scheme 8.36. Formation of a bicycle by an insertion–carbometallation–insertion sequence.

8.4.2
Carbometalation of Alkenes

Syntheses of isolable organometallic species by carbometallations of alkenes are difficult because many side reactions can occur, namely β-hydride elimination and chain propagation. As a consequence, only a few examples have been reported to date, mainly concerning reactions in which the initial carboalumination product is trapped through fast intra-

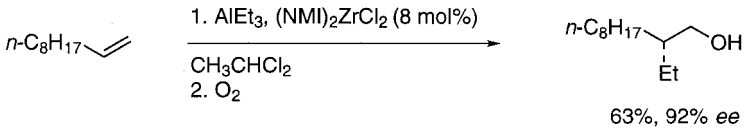
molecular cyclization [73–75]. However, it is notable that a successful asymmetric carboalumination of alkenes has been developed, using a chiral zirconocene as catalyst.

Reactions of various terminal alkenes, some of them bearing heteroatom substituents, with Me_3Al and a catalytic amount of Erker's chiral neomenthylindene-zirconocene dichloride provide, after oxidation with O_2, 2-methyl-1-alkanols in high yields with up to 85 % *ee* [76] (Scheme 8.37).



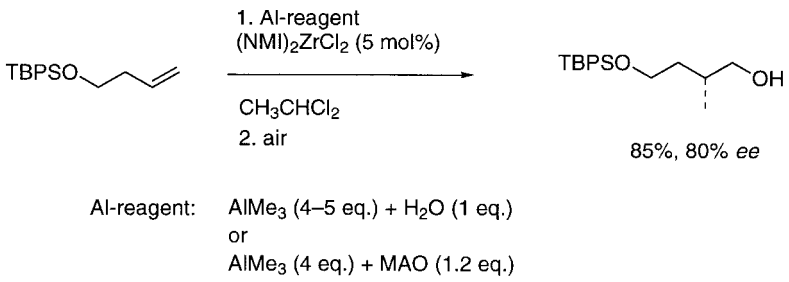
Scheme 8.37. Enantioselective methylalumination in the synthesis of isoalkyl alcohols.

The method can also be applied to ethylalumination with $AlEt_3$, in which case 2-ethyl-1-alkanols are obtained with >90 % *ee* [77] (Scheme 8.38).



Scheme 8.38. Direct enantioselective ethylalumination.

The zirconocene-catalyzed enantioselective methylalumination is accelerated by the addition of water to the reaction mixture. Styrene derivatives in particular, which are unreactive under the aforementioned conditions, readily undergo methylalumination at −5 °C. The reaction of water and $AlMe_3$ most probably yields aluminoxanes. MAO was also shown to accelerate the reaction, although less markedly [78] (Scheme 8.39).



Scheme 8.39. Asymmetric methylalumination reaction accelerated by addition of water.

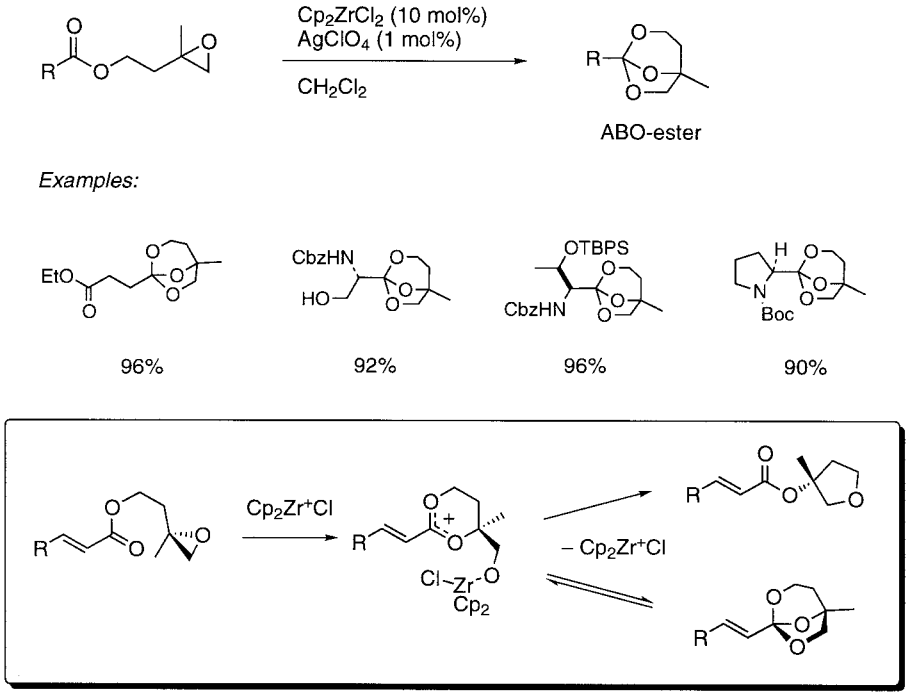
Asymmetric carbometalation has proved less successful with the $[(EBTHI)ZrCl_2]$ catalyst; this may be due to deactivation of the catalytically active cationic species by the formation of a rather stable μ-$AlMe_3$ adduct, which does not occur with the $[(NMI)_2ZrCl_2]$ catalyst system [75].

8.5
Cationic Zirconocene Complexes as Lewis Acid Catalysts

Lewis acids based on zirconocene have been employed as catalysts in several reactions. The metallic species used have mainly been the bis(triflate) and the $Cp_2ZrCl_2/AgClO_4$ reagent.

8.5.1
Epoxy Ester to Orthoester Rearrangement

The rearrangement of isopent-3-enyl epoxy esters with $Cp_2ZrCl_2/AgClO_4$ yields ABO esters (2,7,8-trioxabicyclo[3.2.1]octane; ***A**symmetric **B**icyclo-**O**ctane esters*), which are base-stable protecting groups for carboxylic acids [57,79,80] (Scheme 8.40).



Scheme 8.40. Synthesis of ABO esters; selected examples. Mechanism of formation of ABO esters and tetrahydrofurans.

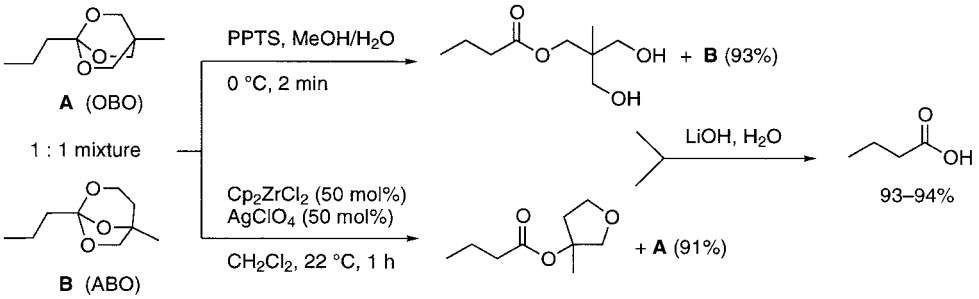
Compared to the well-known OBO esters [81], the ABO esters are more stable towards protic acids but less stable towards the Lewis acid $Cp_2ZrCl_2/AgClO_4$, which isomerizes the ABO orthoester to a tetrahydrofuranyl ester. Selective deprotection is therefore possible (Scheme 8.41).

By the same type of epoxide rearrangement, other bicyclic and tricyclic orthoesters can be synthesized [80]. However, the orthoesters are only the kinetic products and, if not sufficiently inert, can further rearrange under reaction conditions to more stable tetrahydrofuran derivatives (*cf.* Scheme 8.40). In many cases, the tetrahydrofurans are the

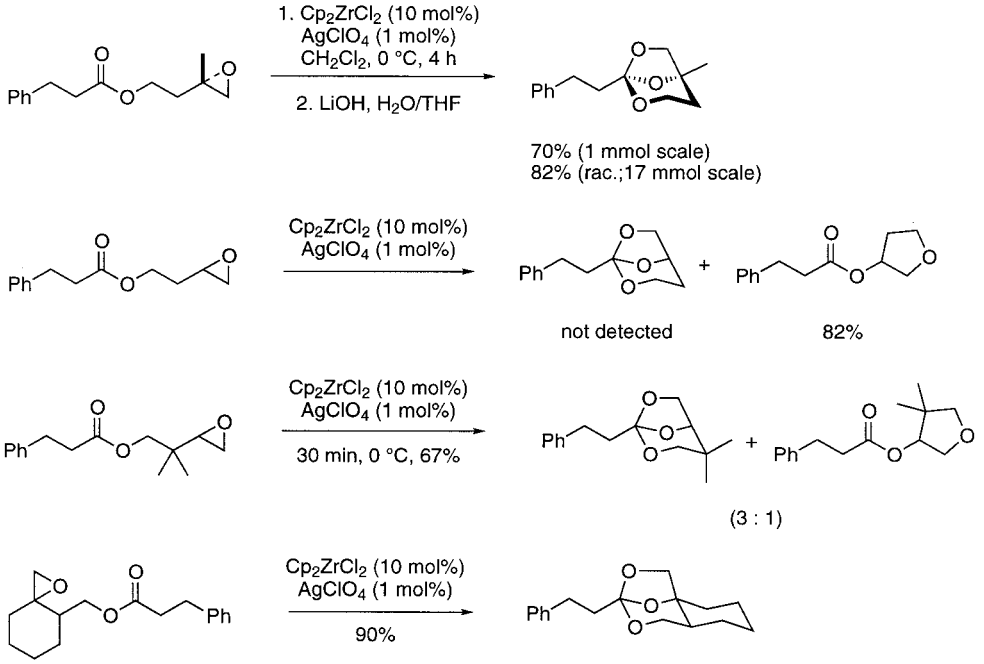
only products isolated. This is especially true for α,β-unsaturated systems, where the intermediate dioxenium ion is stabilized by conjugation (Scheme 8.42).

The rearrangement is stereospecific. Inversion of configuration occurs at the epoxide carbon, which is attacked by the ester carbonyl [79] (Scheme 8.43).

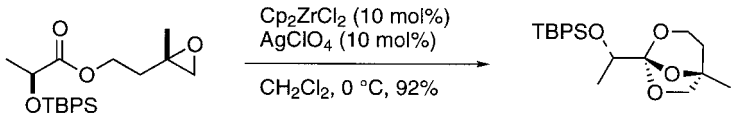
Several reaction conditions concerning the nature of the silver reagent were tested. Usually, anhydrous $AgClO_4$ was used as the initiator for the catalytic reaction, but $AgAsF_6$ was found to work equally well. When the monohydrate $AgClO_4 \cdot H_2O$ was used



Scheme 8.41. Selective deprotection of ABO and OBO esters from an ABO/OBO mixture.



Scheme 8.42. Synthesis of orthoesters by rearrangement of epoxides.

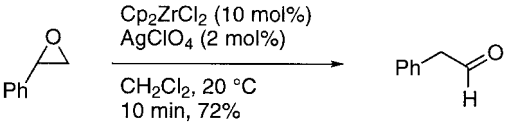


Scheme 8.43. Stereospecificity of the epoxide to orthoester rearrangement.

as the initiator, the reactions required a longer time to reach completion, but gave similar yields. High reactivity was observed with AgBARF. The reaction shown in Scheme 8.43 was catalyzed by 5 mol% Cp_2ZrCl_2 and 2 mol% AgBARF even at −78 °C (6 h, 93 % yield) [79].

8.5.2
Epoxide to Aldehyde Rearrangement

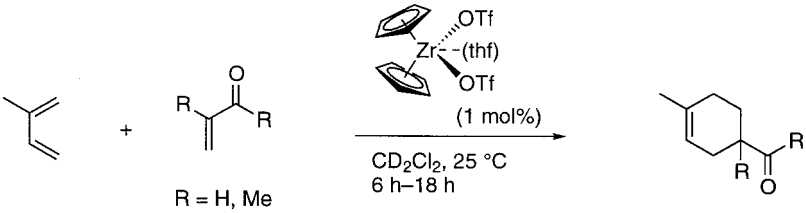
This epoxide to aldehyde rearrangement was postulated to be the first step in the silver-mediated reaction of alkylzirconocene chlorides with epoxides, in which the aldehyde is subsequently alkylated by the alkylzirconocene species (*cf.* Scheme 8.44) [56]. In a control experiment, it was shown that zirconocene dichloride (1 equivalent or less) and silver (catalytic amounts) do indeed induce the rearrangement of an epoxide to an aldehyde very quickly.



Scheme 8.44. Epoxide to aldehyde rearrangement.

8.5.3
Diels–Alder Reaction

The complex $[Cp_2Zr(OTf)_2(thf)]$ is a catalyst for the Diels–Alder reactions of α,β-unsaturated aldehydes or ketones and dienes (isoprene, cyclohexadiene, cyclopentadiene) at the 1 mol% level, giving accelerations of between 10^3 and $>10^5$ compared to the corresponding thermal reactions [82,83] (Scheme 8.45). The isomer ratio of the reaction products (*endo*/*exo* or regioisomers) is higher in catalyzed than in thermal reactions. However, because the zirconocenium triflate is also a catalyst for the polymerization of 1,3-dienes, the Diels–Alder reaction is sometimes completely suppressed in the case of less reactive dienophile-diene combinations.

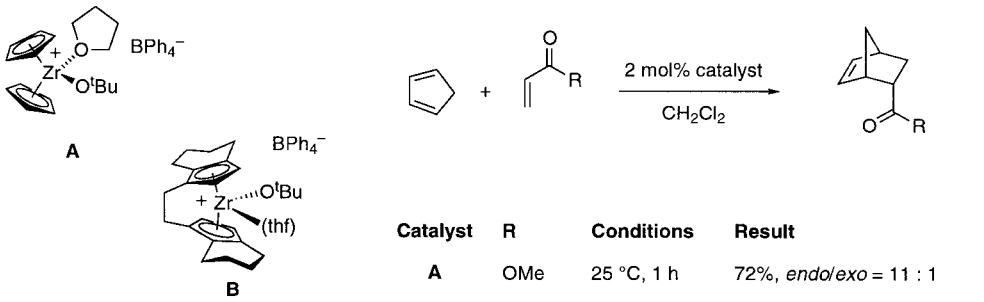


Scheme 8.45. Simple Diels–Alder catalysis by zirconocenium triflate.

The advantage of this catalyst, as compared to classical Lewis acids such as $AlCl_3$, is the low catalyst loading required. Also, solvents and reactants do not need special drying, as the catalyst is not notably deactivated by adventitious water.

Diels–Alder reactivity was also reported for a cationic zirconocene alkoxide (**A**; Scheme 8.46) at a 10 mol% level for the substrate combination methyl acrylate/isoprene [84]. Whereas the regioselectivity (*para*/*meta* = 96.2:3.8) in this process compared favorably to that with traditional Lewis acids ($AlCl_3$ in C_6H_6; regioselectivity = 95:5), the activity was quite low. The substrates methyl acrylate and cyclopentadiene (Scheme 8.46; R =

OMe) completely reacted within 1 h at room temperature at a much lower catalyst loading (2 mol%) to provide the cycloaddition product in 72 % yield (*endo*/*exo* = 11:1) [84].

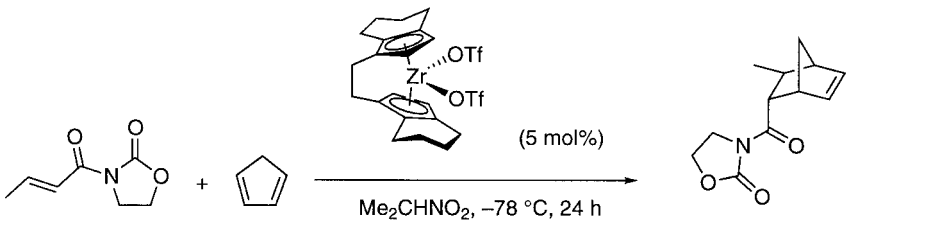


Catalyst	R	Conditions	Result
A	OMe	25 °C, 1 h	72%, *endo*/*exo* = 11 : 1
B	H	–78 °C, 3 h	93%, *endo*/*exo* = 4.8 : 1 2*R*/2*S* = 1 : 3.21 (52.4% *ee*)

Scheme 8.46. Diels–Alder catalysis by cationic alkoxyzirconocene complexes.

The asymmetric version of the reaction utilizes Brintzinger's ethylene-bis(tetrahydroindenyl) (EBTHI) *ansa*-metallocene approach [85]. Whereas complex **B** (Scheme 8.46) is still a catalyst for the Diels–Alder reaction, only low inductions are observed at room temperature. On cooling to −78 °C and using more reactive starting materials, a maximal induction of 52.4 % *ee* was attained [86].

Asymmetric Diels–Alder catalysis was more successful with dication-like versions of the Zr-EBTHI system, and using conformationally better defined acyl-oxazoline dienophiles. The bis(triflate) [Zr(EBTHI)$(OTf)_2$] (Scheme 8.47) induced high levels of *ee* (>90 %) in the cycloaddition to cyclopentadiene at low temperatures, especially in the polar solvent 2-nitropropane [87].

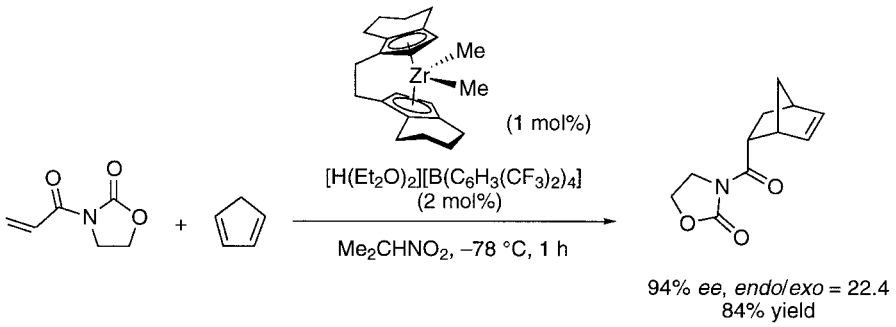


Scheme 8.47. Asymmetric Diels–Alder catalysis by an *ansa*-metallocene triflate.

NMR studies at low temperature provided evidence for the formation of a mono-cationic oxazoline–zirconocene complex in which the substrate is a bidentate ligand and one triflate is still coordinated to the zirconium [4].

A very reactive Lewis acid is obtained when the complex [(EBTHI)$Zr(Me)_2$] is converted in situ to a dicationic species by protonation with the acid H-BARF (BARF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) in the presence of the Diels–Alder substrate oxazolidinone [88] (Scheme 8.48). The dicationic species is stabilized through coordination by the oxazolidinone and by diethyl ether (derived from the acid etherate employed). The catalyst loading in the Diels–Alder reaction could be lowered to 1 mol% (Zr) and the reaction still

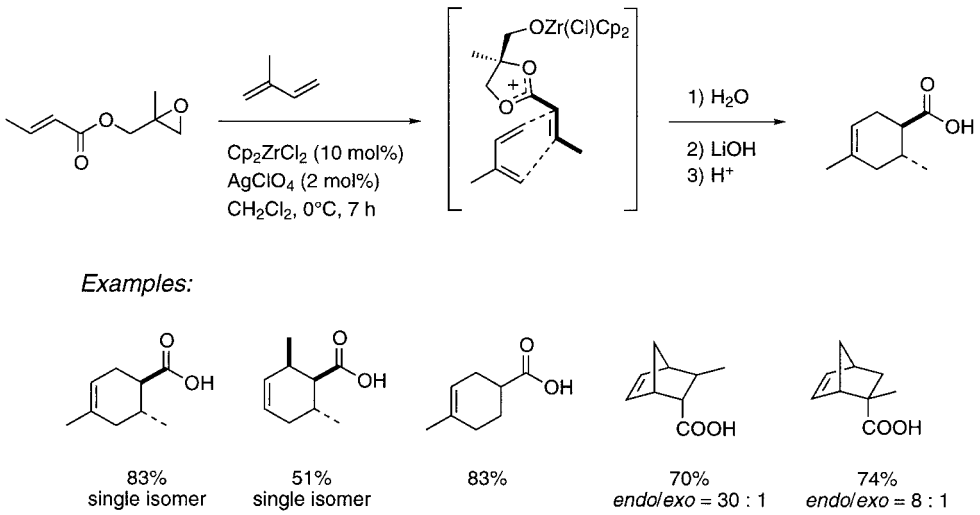
went to completion within 1 h at −78 °C to yield the product with 94 % *ee*, whereas complete conversion of the same substrate required 8 h with 5 mol% of the bis(triflate) catalyst, giving 92 % *ee* [87]. The enantioselectivity was generally better at lower catalyst loadings (88 % *ee* at 10 mol%; 94 % *ee* at 5 mol%; 95 % *ee* at 1 mol%), while the *endo*/*exo* ratio of the product remained constant at 22:1. 2-Nitropropane was again the preferred solvent, but the reactions also proceeded in CH_2Cl_2, albeit with lower *ee* values (79 % at 5 mol% Zr; 91 % at 1 mol% Zr) and with an *endo*/*exo* ratio that depended on catalyst loading (15:1 at 10 mol% [Zr], 22:1 at 1 mol% [Zr]) [88].



Scheme 8.48. Accelerated Diels–Alder catalysis with BARF counterions.

8.5.4
Cationic Diels–Alder Reaction

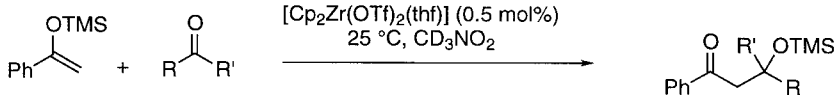
When the epoxy-isobutenyl ester of crotonic acid is treated with the $Cp_2ZrCl_2/AgClO_4$ Lewis acid, the epoxide is opened by intramolecular assistance of the ester carbonyl group, giving a dioxolenium cation (Scheme 8.49). This species is a highly electrophilic Diels–Alder dienophile that reacts with a range of dienes. THF deactivates cationic zirconocene species and is therefore not tolerated as a solvent [89].



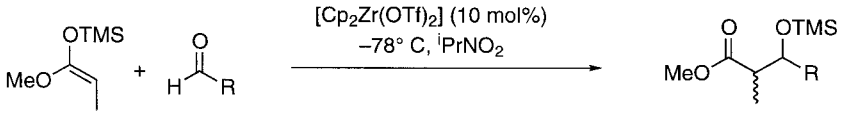
Scheme 8.49. Cationic Diels–Alder reaction.

8.5.5
Catalytic Mukaiyama Aldol Reaction

Catalytic activity in the Mukaiyama silyl aldol reaction has been reported for the complexes $[Cp_2Zr(OTf)_2(thf)]$ [83,90], $[Cp_2Zr(OTf)_2]$ [91], and $[Cp_2Zr(OtBu)(thf)]BPh_4$ [92]. Both TMS enol ethers and TMS ketene acetals were used in combination with aldehydes, and in the case of $[Cp_2Zr(OTf)_2(thf)]$ some examples with ketones were also reported (Scheme 8.50). While these reactions proceeded quite rapidly and required only low catalyst loadings (as little as 0.5 mol% $[Cp_2Zr(OTf)_2(thf)]$ could be used), they showed only slight or modest diastereoselectivity [90–92]. The results obtained for the zirconium-catalyzed Mukaiyama aldol reaction are somewhat ambiguous since it has been shown by Bosnich and co-workers that in the related catalytic reaction with $[Cp_2Ti(OTf)_2]$ the actual catalyst is not the metal Lewis acid, but in situ formed TMSOTf [93]. The interference of TMSOTf (or analogous silyl species) in catalytic Mukaiyama aldol reactions has previously been noted for other Lewis acids [94]. A mechanistic study addressing the zirconium systems was performed with the catalyst $[Cp_2Zr(OTf)_2]$ and catalysis by TMSOTf was indeed shown to be interfering [91]. Sterically hindered aldehydes react via the silyl pathway, whereas sterically unhindered or aromatic aldehydes react by a pathway that *appears to be mainly Zr-catalyzed*. The rate-limiting step in the catalysis is the regeneration of the bis(triflate) by reaction of a Zr-aldolate with TMSOTf; the latter may thus accumulate and act as a catalyst. Although the viability of zirconocenes as catalysts for this reaction has been demonstrated, the outlook for asymmetric catalysis is not ideal with the currently known systems. The use of enantiomerically pure $[(EBTHI)Zr(OTf)_2]$ as the Lewis acid resulted in *ee* values of <20 % [91].



R' = H R = Ph, Cy, ^{i}Pr, ^{t}Bu (< 7 min)
R' = Me R = Et (10 min), ^{i}Pr (2 h), ^{t}Bu (> 19 h)

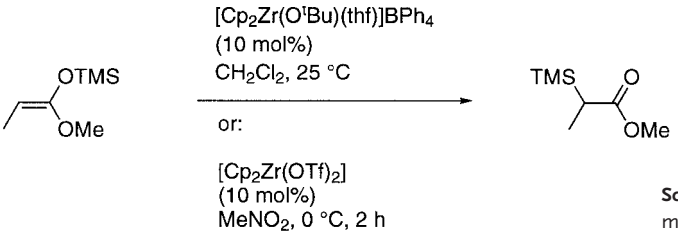


R	t/h	Yield	syn/anti
$BnOCH_2CH_2$-	5	90%	1 : 1.35
$BnOCMe_2$-	5	88%	1.57 : 1
^{t}Bu	1.5	95%	2.07 : 1

Scheme 8.50. Examples of catalytic Mukaiyama aldol reactions.

8.5.6
Silyl Ketene Acetal to α-Silyl Ester Isomerization

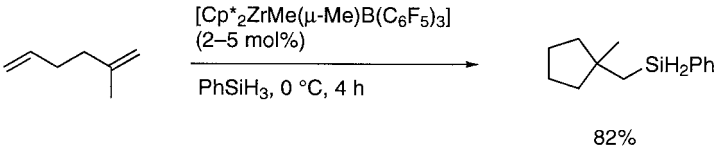
The isomerization of an *O*-silyl ketene acetal to a *C*-silyl ester is catalyzed by a cationic zirconocene–alkoxide complex [92]. This catalysis was observed as a side reaction in the zirconocene-catalyzed Mukaiyama aldol reactions and has not yet found synthetic use. The solvent-free bis(triflate) $[Cp_2Zr(OTf)_2]$ also catalyzes the reaction in nitromethane (no reaction in dichloromethane), but in this case there may be competitive catalysis by TMSOTf (*cf.* the above discussion of the catalysis of the Mukaiyama aldol reaction) [91] (Scheme 8.51).



Scheme 8.51. Catalytic O to C migration of a silyl group.

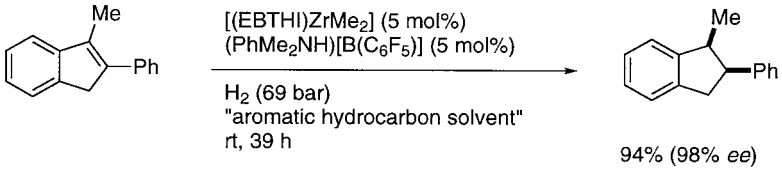
8.6
Miscellaneous Reactions

Molander et al. described a sequential cyclization–silylation of dienes that was induced by the cation-like permethylzirconocene complex $[Cp^*_2ZrMe(\mu\text{-}Me)B(C_6F_5)_3]$ [95] (Scheme 8.52).



Scheme 8.52. Cyclization–silylation of 1,5-dienes.

Buchwald et al. realized asymmetric hydrogenation of tetrasubstituted alkenes with a cationic zirconocene catalyst prepared by the protonolysis method (Scheme 8.53). The reactions were quite slow with these highly substituted alkenes, but some very good enantiomeric excesses were obtained [96].



Scheme 8.53. Asymmetric hydrogenation with cationic *ansa*-metallocene.

8.7 Conclusion

Cationic zirconocenes serve as useful reagents in such diverse fields as alkene polymerization, carbohydrate chemistry, asymmetric catalysis, and so on. Reagents that were originally developed for polymerization reactions (MAO, *ansa*-metallocenes, non-nucleophilic borate counterions) have now found use in organic synthesis and are being employed for carbometalation reactions, hydrogenation, and Diels–Alder catalysis.

We may expect that the future will see many additional uses of cationic zirconocenes in organic synthesis, in which their Lewis acidic character, coupled with the special properties of zirconium (oxophilic, fluorophilic) and its d^0-electron configuration (leading, for example, to weak back-bonding) will come into play.

Typical Experimental Procedures

Caution: $AgClO_4$ is potentially explosive and should be used with due care. It may often be replaced by AgOTf or $AgAsF_6$.

General procedure for metallocene-mediated glycosylation reaction [25] A slurry of powdered 4 Å molecular sieves (100 mg), Cp_2HfCl_2 (0.113 mmol), and $AgClO_4$ (0.227 mmol) in CH_2Cl_2 (or benzene) (0.4 mL) is stirred for 10 min. A solution of the appropriate alcohol (0.226 mmol) in CH_2Cl_2 (0.5 mL) is then added and the reaction flask is cooled to −20 °C. A solution of glycosyl fluoride (0.113 mmol) in CH_2Cl_2 (1 mL) is added, and the reaction mixture is stirred, while the progress of the reaction is followed by TLC. Standard work-up and purification by chromatography gives the glycoside product.

These conditions were optimized for Cp_2HfCl_2 activation, but are also applicable to the zirconocene version of the reaction. In the original procedure, a large excess of the metallocene dichloride and silver salt was employed to enable the rapid glycosidation of sensitive substrates, but this is not usually necessary.

Carbonyl additions: $AgAsF_6$-catalyzed addition of alkenylzirconocene chlorides to aldehydes (*cf.* Scheme 8.21) [51] A solution of 1-hexyne (93.1 mg, 1.11 mmol) in CH_2Cl_2 (3 mL) was added to the Schwartz reagent ($Cp_2Zr(H)Cl$, 270 mg, 1.05 mmol) at −78 °C with stirring. The temperature was allowed to rise to 25 °C and the reaction mixture was stirred for an additional 10 min. A solution of 3-phenylpropanal (83.1 mg, 0.619 mmol) in CH_2Cl_2 (3 mL) was then added, followed, after 5 min., by $AgAsF_6$ (20 mg, 0.068 mmol). The resulting brown suspension was stirred for 10 min. Work-up with $NaHCO_3$ and EtOAc, followed by preparative TLC (hexane/EtOAc, 4:1), gave 129 mg (94.5 %) of a colorless oil.

Carbometalation reactions; alkylzirconation of an alkyne mediated by $(Ph_3C)[B(C_6F_5)_4]$ activation (*cf.* Scheme 8.35) [70] To $Cp_2Zr(H)Cl$ (196 mg, 0.76 mmol) at 25 °C was added a solution of 1-hexene (54.7 mg, 0.65 mmol) in CH_2Cl_2 (2.4 mL), and the mixture was stirred at 40 °C for 1 h. The resulting yellow solution was cooled to 0 °C, whereupon a solution of 4-ethynyl-1,2-dimethoxybenzene (61.1 mg, 0.377 mmol) in CH_2Cl_2 (2.3 mL), followed by $(Ph_3C)[B(C_6F_5)_4]$ (17.5 mg, 0.019 mmol) were added. After stirring for 30 min. at 40 °C, the reaction was quenched by the addition of MeOH (0.5 mL) and satd. aq. $NaHCO_3$ solution

(0.5 mL). After dilution with Et_2O and drying with Na_2SO_4, filtration through SiO_2/Celite gave a crude material, which was purified by preparative TLC (hexane/acetone, 4:1) to yield 85.4 mg (95 %) of 4-(1-hexylvinyl)-1,2-dimethoxybenzene and the regioisomeric 1,2-dimethoxy-4-oct-1-enylbenzene in a ratio of 91:9.

Catalytic orthoester rearrangement (synthesis of ABO esters) [79] *General procedure for the synthesis of amino acid orthoesters from epoxy esters:* A solution of the epoxy ester (1 mmol) in CH_2Cl_2 (4 mL) is treated with Cp_2ZrCl_2 (28.8 mg, 0.1 mmol) and $AgClO_4$ (4 mg, 0.02 mmol). The reaction mixture is stirred for 4 h at room temperature, poured into satd. aq. $NaHCO_3$ solution, and extracted with EtOAc (3 × 10 mL). After drying (Na_2SO_4), the combined organic layers are filtered through SiO_2 and concentrated. The residue is purified by column chromatography (EtOAc/hexanes, 1:1).

The required epoxy esters are obtained by reaction of the free acid (0.96 mmol) with 3,4-epoxy-3-methylbutanol (1.1 mmol), DCC (1.1 mmol), and DMAP (0.048 mmol) in CH_2Cl_2/DMF (9:1, 10 mL, 1 h at 0 °C and 2 h at r. t.). Alternatively, they can be synthesized from acid chlorides using 3-methyl-3-butenol and triethylamine (1:1:2 ratio; CH_2Cl_2, 0 °C), followed by epoxidation with *m*-chloroperbenzoic acid (1.2 equivalents, CH_2Cl_2, 0 °C).

Abbreviations

BARF	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
Bn	benzyl
Bz	benzoyl
Cp*	η^5-pentamethylcyclopentadienyl
Cp'	η^5-methylcyclopentadienyl
EBI	ethylene-1,2-bis(η^{10}-indenyl)
EBTHI	ethylene-1,2-bis(η^{10}-tetrahydroindenyl)
Fmoc	fluorenylmethyloxycarbonyl
Lev	levuloyl (-$COCH_2CH_2COCH_3$)
MCA	monochloroacetyl
MP	*para*-methoxyphenyl
NMI	η^5-neomenthylindene
Phth	phthaloyl
PMB	*para*-methoxybenzyl
PNP	*para*-nitrophenyl
TBPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
Troc	2,2,2-trichloroethoxycarbonyl

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9
Titanium(II) Alkoxides in Organic Synthesis

Fumie Sato and Hirokazu Urabe

9.1
Introduction

The generation of divalent titanium complexes and their utilization in organic synthesis have attracted considerable interest over a number of years [1–3]. The divalent titanium complexes or their equivalents that have been widely used for this purpose are summarized in Fig. 9.1, where the starting materials from which they are derived are also shown [1,2,4–9]. Among these complexes, (η^2-propene)Ti(O*i*Pr)$_2$, readily prepared from Ti(O*i*Pr)$_4$ and 2 equiv. of *i*PrMgX (**1**), was introduced most recently as an equivalent of "Ti(O*i*Pr)$_2$", and it has been shown that it can be used in place of or in conjunction with other reagents shown in Fig. 9.1. Moreover, this reagent facilitates several important new synthetic transformations that are not viable using other reagents. As the combination of Ti(O*i*Pr)$_4$ and *i*PrMgX is very inexpensive as compared to other types of reagents, it is a most economical titanium(II) reagent [1]. Moreover, since the reagent does not bear any special ligands, such as cyclopentadienyl groups, phosphines, or sterically demanding aryloxy groups, other than the ligating propene and isopropoxy groups, the work-up and isolation of the product after the reaction can be carried out easily and economically. The reagent **1** is therefore a highly practical divalent titanium reagent applicable to large-scale synthesis. This chapter is largely focussed on the synthetic reactions mediated by **1**; the reactions mediated by other relevant Ti(II) reagents are mentioned where appropriate.

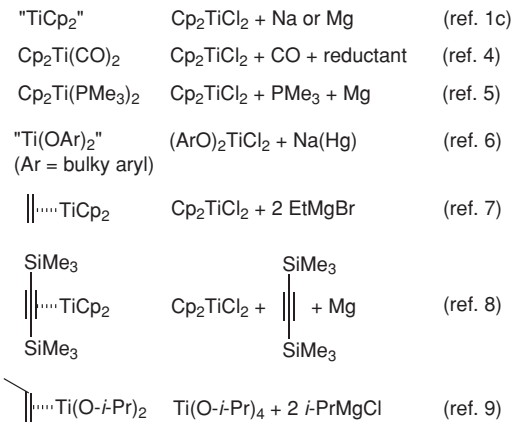
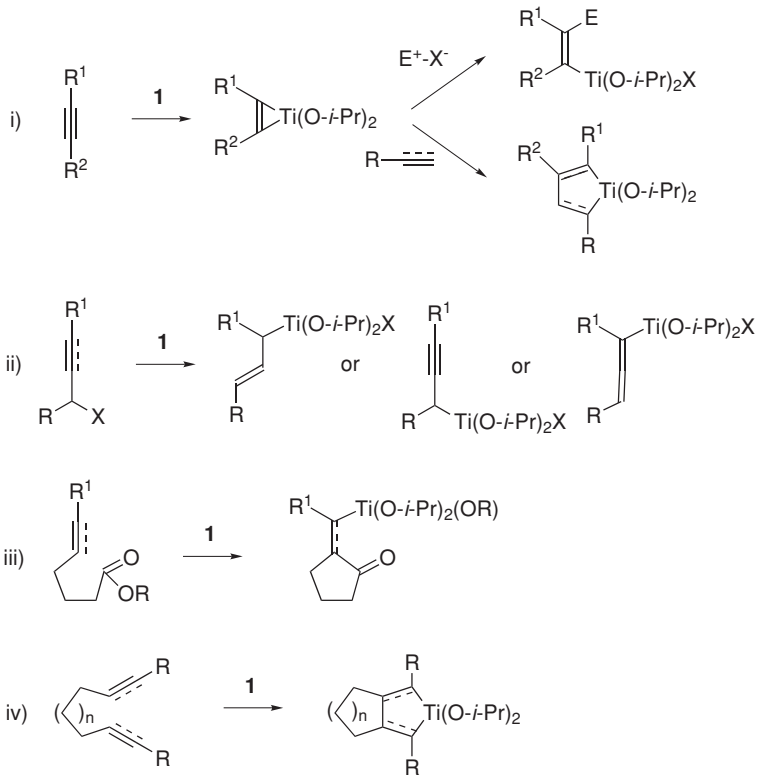


Figure 9.1. Compilation of representative Ti(II) reagents.

The synthetic reactions mediated by **1** can be classified into four categories (i)–(iv) (Scheme 9.1). The first of these is the generation of titanium–alkyne complexes by the reaction with alkynes and their further synthetic utilization. The second is the generation of allyl-, propargyl-, or allenyltitaniums by reaction with allyl or propargyl alcohol derivatives, respectively, and their use as allylating or propargylating (or, possibly, allenylating) reagents. The third is the intramolecular nucleophilic acyl substitution reaction of unsaturated esters promoted by the reagent. The fourth reaction is the intramolecular coupling of dienes, enynes, diynes, and related substrates to afford titanabicyclic compounds and their further manipulation. These four types of reactions, (i)–(iv), are described in order.

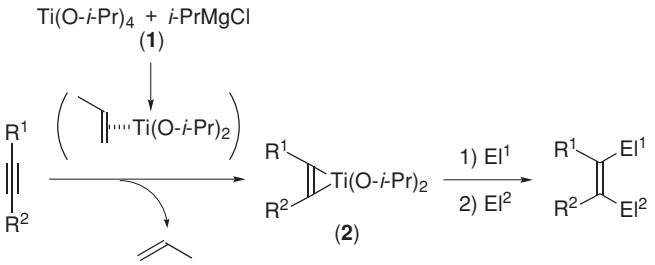


Scheme 9.1. Four categories of reactions mediated by **1**.

9.2
Generation of (η^2-alkyne)Ti(O*i*Pr)$_2$ and its Utilization in Organic Synthesis

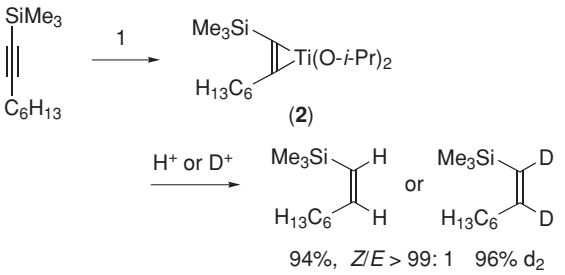
Treatment of an internal alkyne with Ti(O*i*Pr)$_4$/2 *i*PrMgCl (referred to as **1** as described above; this combination of reagents produces the actual titanium(II) species in situ) generates (η^2-alkyne)Ti(O*i*Pr)$_2$ (**2**) by exchange of the coordinated propene in (η^2-propene)-Ti(O*i*Pr)$_2$ with the alkyne substrate (Eq. 9.1) [10]. In this transformation, the nature of the alkyl group of the Grignard reagent is the key: the use of *i*PrMgX is critical and *n*PrMgX, *s*BuMgX, and *t*BuMgX cannot be used for this purpose [11]. The alkyne com-

plexes thus generated react in situ with a variety of electrophiles, including two different electrophiles in consecutive order as formulated in Eq. 9.1. The reaction thus opens up a one-pot access to a variety of di-, tri-, or tetrasubstituted alkenes starting from alkynes. While several acetylene–metal complexes, such as Cp_2Zr–, Cl_nNb–, and Cl_nTa–acetylene complexes as well as those derived from other Ti(II) reagents shown in Fig. 9.1, are known to serve as 1,2-bis-dianion equivalents [12], the advantage of the present method lies in the fact that it requires very inexpensive starting materials and very simple laboratory operations.

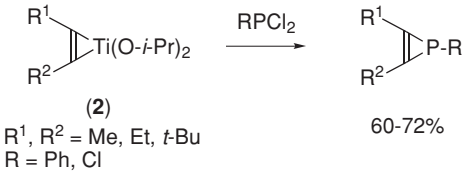


(Eq. 9.1)

Hydrolysis of the titanium–acetylene complex generated in situ provides the corresponding alkene with exclusively the *cis* configuration, thus providing a convenient one-pot method for preparing *cis*-alkenes from acetylenes. For example, Eq. 9.2 shows the synthesis of *cis*-vinylsilane [10], which was, in fact, utilized in the synthesis of intermediates to epothilone, since the reagent exhibits excellent functional group compatibility and selectivity [13]. Deuteriolysis of the reaction product provides one of the most convenient and practical routes to *cis*-dideuterioalkenes from the corresponding alkynes, as exemplified in Eq. 9.2. Other acetylene–titanium complexes could be successfully formed from a variety of acetylenes, including diynes [14] and stannylacetylenes [15]. Reaction of acetylene–titanium complexes **2** with dichlorophosphines affords phosphirenes, as shown in Eq. 9.3 [16]. It should be noted that, when the same reaction is carried out with Cp_2Ti–acetylene complex instead of **2**, the reaction is often sluggish and the yield of the product is lower.

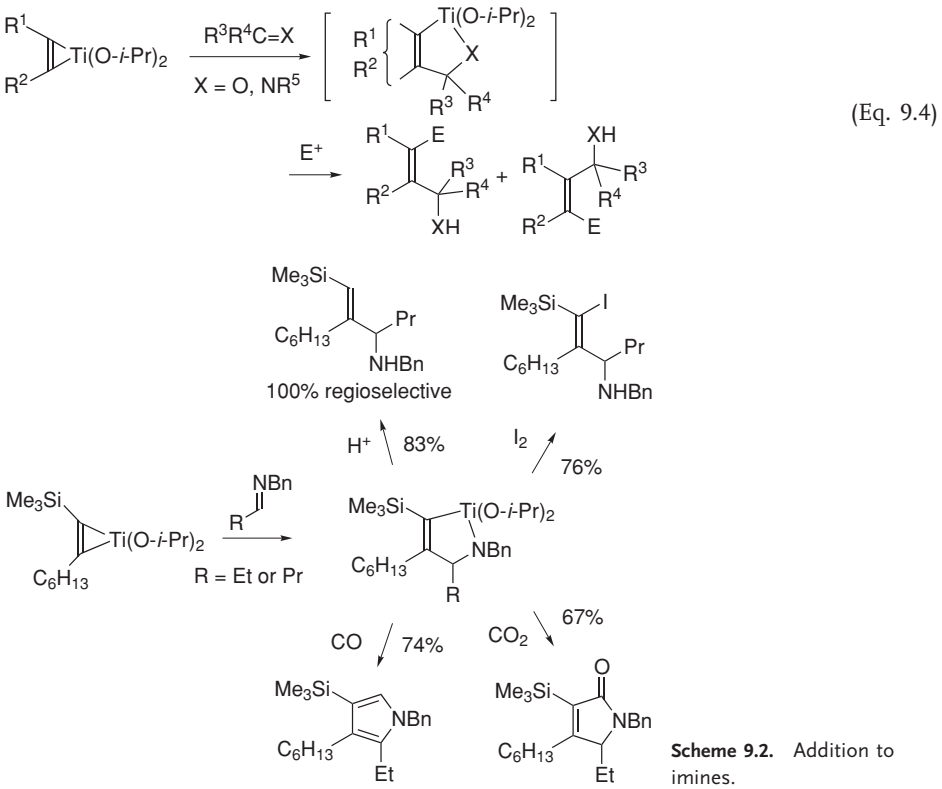


(Eq. 9.2)



(Eq. 9.3)

The titanium–acetylene complexes react with carbonyl compounds such as aldehydes and ketones [10,15,17,18] and imines [19–21] to afford oxa- and azatitanacycles, respectively, as formulated in Eq. 9.4. The remaining titanium–carbon bond in the oxa- and azatitanacycle intermediates thus produced can react with one more electrophile (E^+). For a titanium complex arising from an unsymmetrical acetylene, the reaction may form two regioisomers. However, the titanium–acetylene complexes derived from silylacetylene [10], stannylacetylene [15], phenyl alkyl acetylene [10], propargyl alcohol derivatives [17,18], and acetylenic esters [22] show a fairly high to excellent degree of regiocontrol in such addition reactions. Figure 9.2 shows the position at which the carbon–carbon bond formation takes place and the selectivity of the carbonyl addition observed for several representative acetylenes, although the regioselectivity is somewhat dependent on the steric requirement of the carbonyl compounds. Scheme 9.2 shows reactions of an acetylene complex with imines [19], including some subsequent applications to heterocycle formation [20,21]. Alternatively, formation of the imine–titanium complex followed by reaction with acetylene gave the same products [23].



(Eq. 9.4)

Scheme 9.2. Addition to imines.

Addition of the (1-silylalkyne)titanium complex to carbonyl compounds and imines occurs at the β-position to the silyl group, as shown in Fig. 9.2. However, the reaction with *s*BuOH takes place exclusively at the carbon–titanium bond α to the silyl group to give the (β-silylalkenyl)titanium species, as in Eq. 9.5 (values in square brackets denote the regioselectivity) [24], where the vinyl–titanium bond is visualized by the outcome of the iodinolysis. The overall reaction can therefore be regarded as the hydrotitanation of silylace-

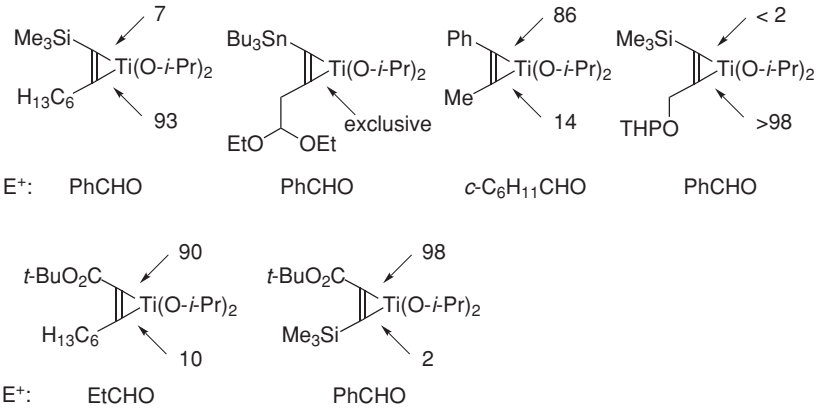
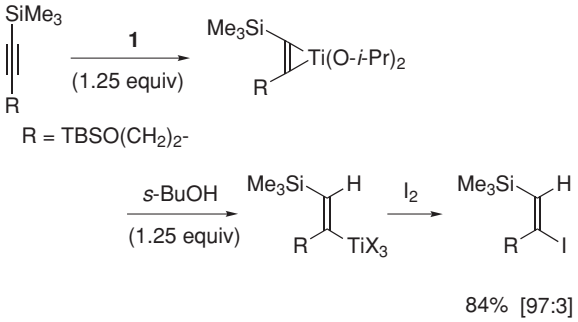
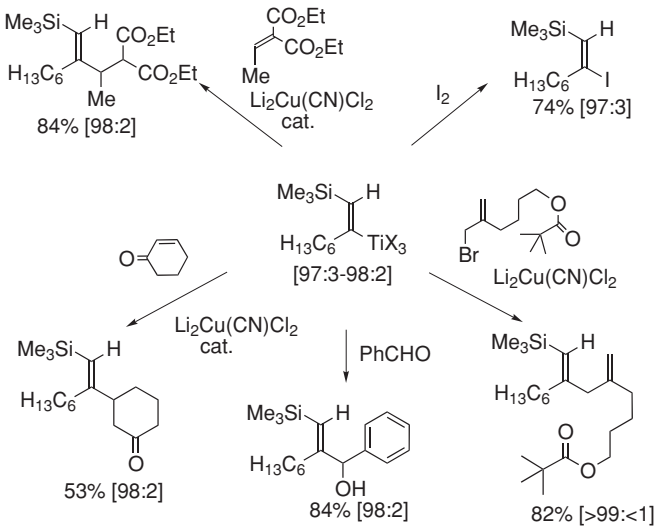


Figure 9.2. Regioselectivity for various acetylene complexes.

tylenes. As this regioselection is not attainable by other existing hydrometallation reactions, this new hydrotitanation method would seem to be an indispensable tool in organic synthesis. The resulting alkenyltitanium species readily undergoes reaction with a variety of carbon electrophiles, as shown in Scheme 9.3.

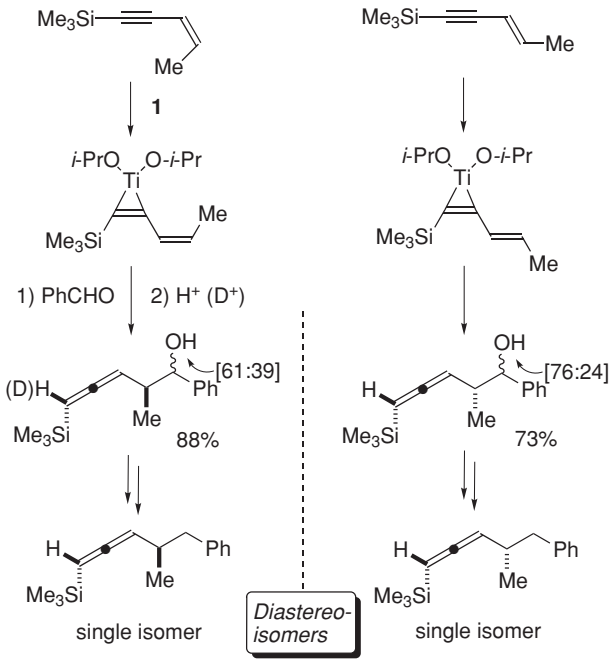


(Eq. 9.5)

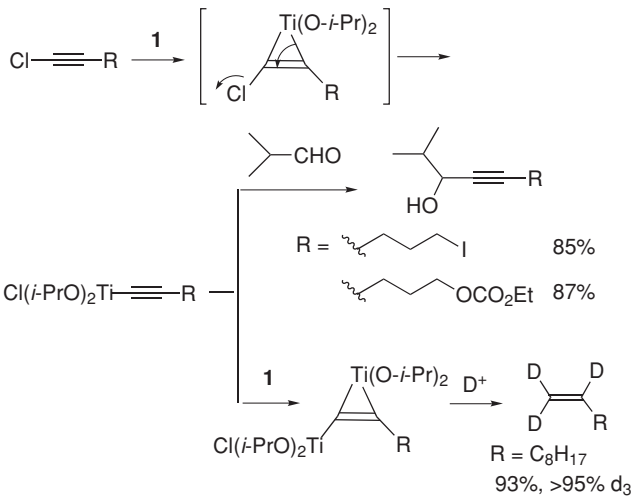


Scheme 9.3. Synthetic application of alkenyltitanium reagent (yields are based on the parent silylalkyne; ratio in square brackets refers to regioselectivity).

The titanium–acetylene complex generated from an (*E*)- or (*Z*)-enyne and **1** reacts with aldehydes, ketones, and imines at the remote olefinic carbon in a regioselective and stereospecific way to give the corresponding allenyltitanium compound, hydrolysis of which affords allenes in a similarly regioselective and stereospecific manner (Scheme 9.4) [25]. In addition to the simple hydrolysis, the resulting allenyltitanium can react with a second electrophile, such as another aldehyde, with excellent regioselectivity to afford a stereodefined adduct. As both reactions with electrophiles are highly stereoselective, an expedient method for the construction of multiple stereogenic centers from readily



Scheme 9.4. Stereospecific preparation of allenyl alcohols.

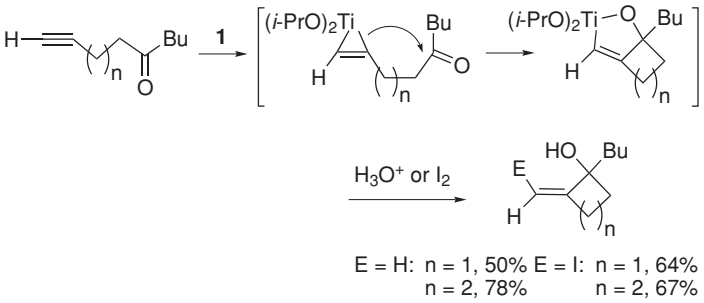


Scheme 9.5. Reaction of a haloalkyne.

available enynes has been opened up. Particularly noteworthy is the asymmetric construction of multiple stereocenters by carrying out the first reaction with an optically active imine to control the three stereogenic centers in an asymmetric manner, as will be shown later (see Eq. 9.9).

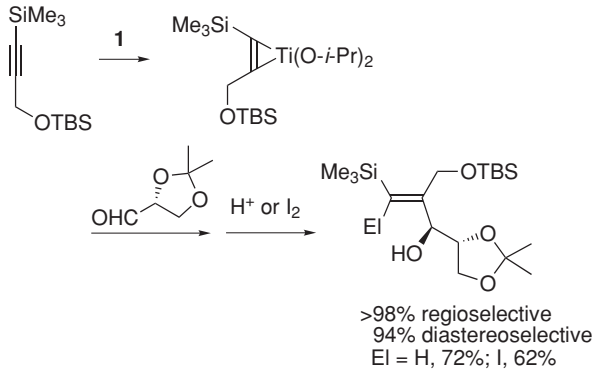
The reaction of haloalkynes with one equivalent of **1** affords alkynyltitanium compounds by β-elimination from the (η^2-haloalkyne)Ti(O*i*Pr)$_2$ intermediate, as shown in Scheme 9.5, thus providing an easy access to functionalized alkynyltitaniums [26]. When this reaction is carried out in the presence of excess **1**, a tri-titanated alkene of the type shown in Scheme 9.5 is generated in excellent yield. This is an interesting method for generating the permetallated terminal alkene [27].

Although terminal acetylenes themselves do not form stable titanium–acetylene complexes upon reaction with **1**, the reaction with terminal alkynes having a keto group at the δ- or γ-position induces an intramolecular cyclization, apparently via the above titanium–acetylene complex to afford the four- and five-membered cycloalkanols, as shown in Eq. 9.6 [28].



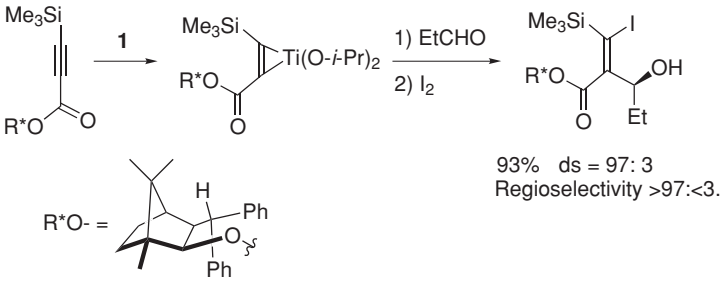
(Eq. 9.6)

Because of the recent importance of asymmetric synthesis, the preparation of optically active compounds based on the reactions of alkyne–titanium complexes has been pursued. The use of alkyne–titanium complexes having chiral alkoxy ligands on the titanium moiety has met with only limited success [11]. The substrate-controlled method has proved to be more promising, as shown in Eq. 9.7. Thus, when the titanium complex generated from a propargyl ether was treated with optically active glyceraldehyde, very high stereo- and diastereoselectivities as well as a high regioselectivity (see Figure 9.2) were recorded [18].



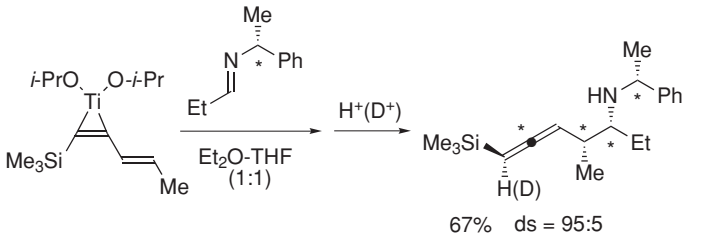
(Eq. 9.7)

It is also possible to carry out a substrate-controlled reaction with aldehydes in an asymmetric way by starting with an acetylene bearing an optically active ester group, as shown in Eq. 9.8 [22]. The titanium–acetylene complexes derived from silyl propiolates having a camphor-derived auxiliary react with aldehydes with excellent diastereoselectivity. The reaction thus offers a convenient entry to optically active Baylis–Hillman-type allyl alcohols bearing a substituent β to the acrylate group, which have hitherto proved difficult to prepare by the Baylis–Hillman reaction itself.



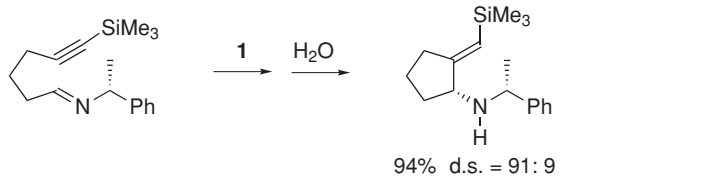
(Eq. 9.8)

Equation 9.9 shows a remarkable example of the simultaneous asymmetric construction of three stereogenic centers by the aforementioned reaction of an enyne–titanium complex (see Scheme 9.4) [25], using imines derived from optically active phenylethylamine as the electrophile.



(Eq. 9.9)

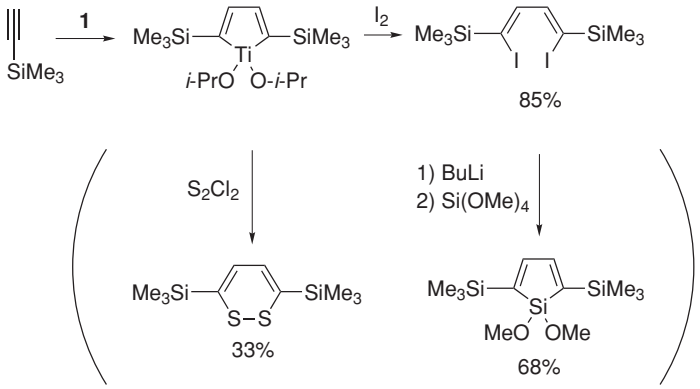
Intramolecular addition of acetylenic imines having a chiral amino substituent was found to proceed with high diastereoselectivity, providing optically active β-alkylidenecycloalkylamines, as shown in Eq. 9.10 [29].



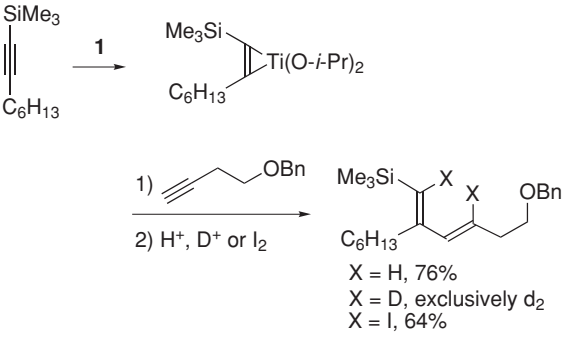
(Eq. 9.10)

Besides the above electrophiles, the acetylene–titanium complexes react regioselectively with other acetylenes providing the corresponding titanacyclopentadienes. An example of a homo-coupling reaction is shown in Eq. 9.11 [30], which also displays some synthetic applications [30,31]. Especially noteworthy is the highly regioselective cross-coupling reaction of unsymmetrical internal and terminal acetylenes, which is illustrated in Eq. 9.12

[32]. Based on the reaction shown in Eq. 9.12, a variety of conjugated dienes, including those bearing functional groups as shown in Figure 9.3, have been synthesized [32]. It should be noted that functionalized conjugated dienes are frequently found as partial structures of naturally occurring products and are also useful intermediates in organic synthesis. However, their synthesis is not necessarily an easy task, and often requires a multi-step procedure.



(Eq. 9.11)



(Eq. 9.12)

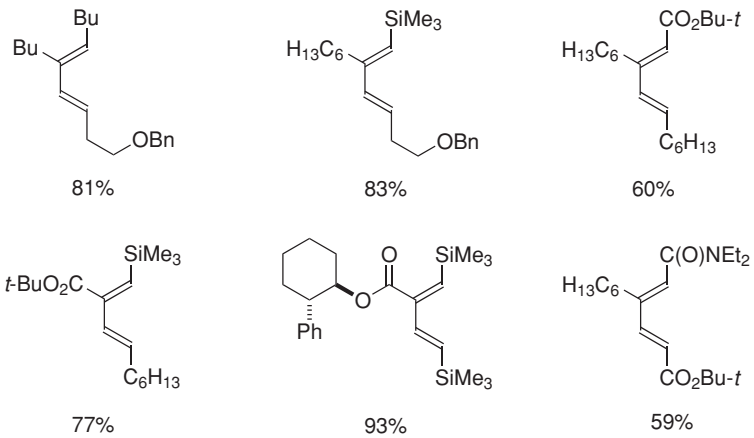
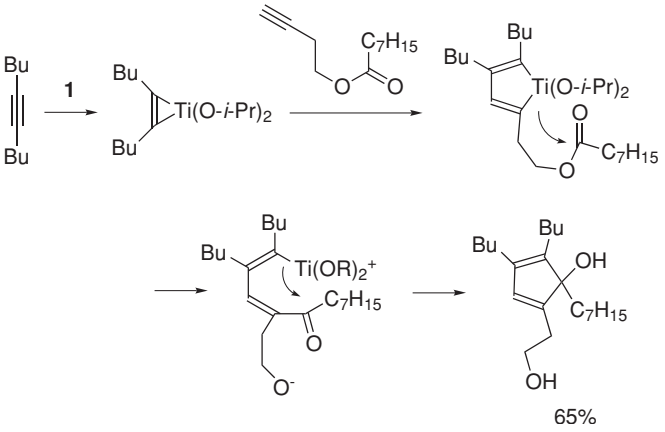


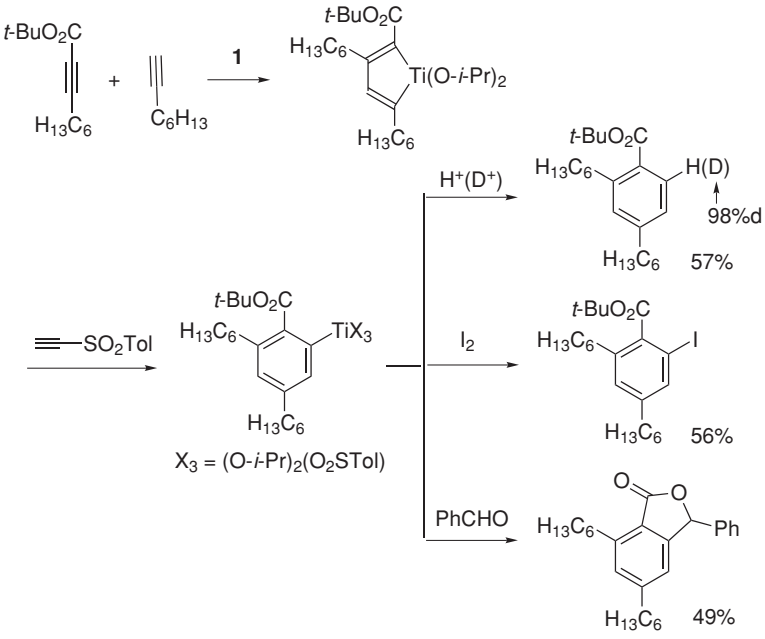
Figure 9.3. Dienes prepared by acetylene coupling reaction.

A titanacyclopentadiene generated from an acetylene having an ester group at a suitable position reacts intramolecularly with this functional group, as exemplified by Eq. 9.13. Here, both carbon–titanium bonds of the titanacycle participate in the reaction to effect ring-closure [33].

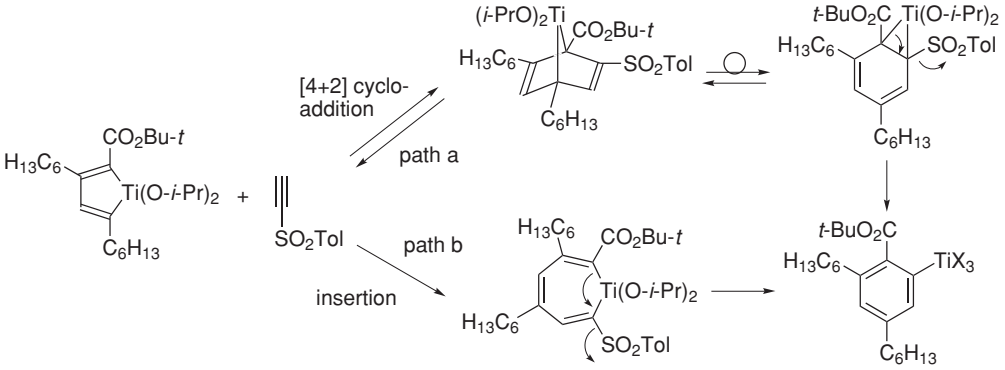


(Eq. 9.13)

As well as undergoing carbonyl addition, titanacyclopentadiene intermediates generated from two unsymmetrical acetylenes have been shown to react with ethynyl *para*-tolyl sulfone to afford an aryltitanium compound of the structure shown in Scheme 9.6 [34]. The reaction may proceed according to path a or path b, as shown in Scheme 9.7. In path a, the first step should be regioselective [4+2] cycloaddition of the titanacyclopentadiene with the sulfonylacetylene to afford the bicyclic titanacycle, at least in an equilibrium concen-



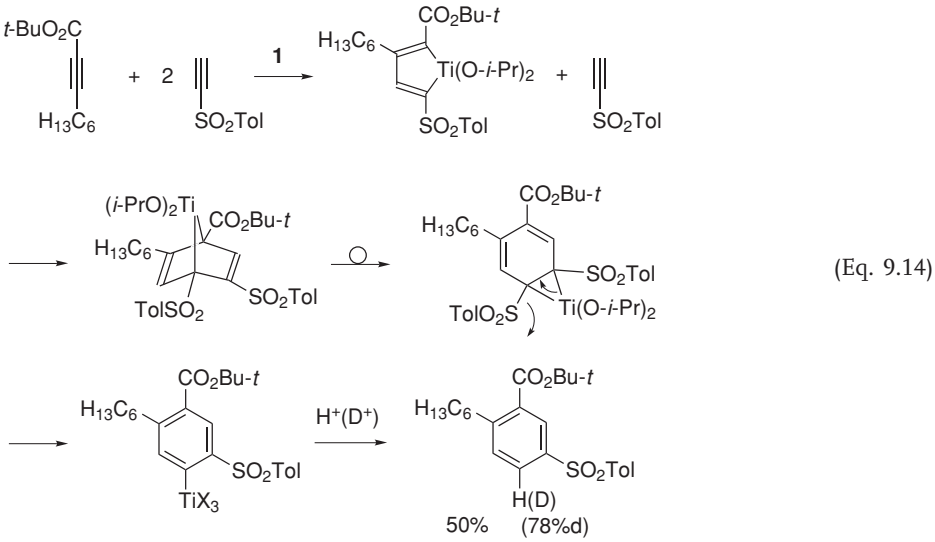
Scheme 9.6. Metalative Reppe reaction.



Scheme 9.7. Proposed reaction course for the metalative Reppe reaction.

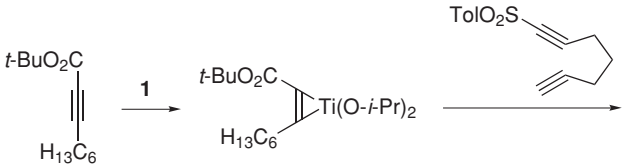
tration. Then, the carbon–titanium bond of the titanacycle rearranges to a suitable position such that 1,2-elimination of the sulfonyl group is feasible. Finally, the sulfonyl group is eliminated to shift the equilibrium towards the formation of the aryltitanium compound. Alternatively, path b involves regioselective insertion of the sulfonylacetylene into the titanacycle followed by elimination of the sulfonyl group. The resulting aryltitanium compounds react with electrophiles such as H_2O, D_2O, I_2, or an aldehyde to afford the corresponding benzene derivatives, as shown in Scheme 9.6. It should be noted that this reaction facilitates a highly chemo- and regioselective trimerization of three different kinds of unsymmetrical alkynes. The reaction also opens up, for the first time, a direct synthesis of aryltitanium compounds from three acetylenes and a metal subunit. Thus, this reaction should be referred to as a metalative Reppe reaction as compared to the conventional Reppe reaction [35].

Other representative reactions are shown in Eqs. 9.14 and 9.15, which involve the synthesis of aromatic sulfones from an acetylene and 2 equivalents of ethynyl tolyl sul-

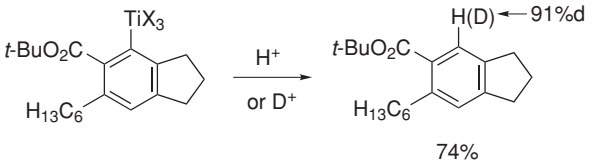


(Eq. 9.14)

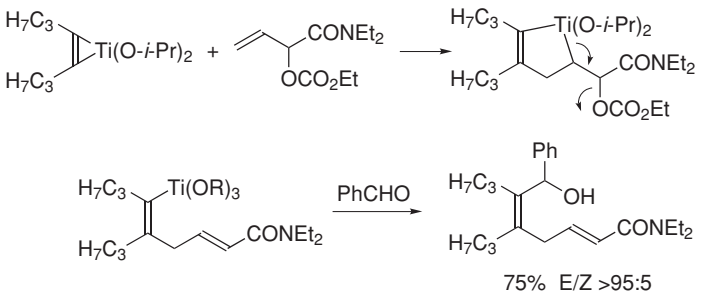
fone, and that of a bicyclic aromatic compound starting from a monosulfonylated diyne. (Other synthetic reactions based on *intra*molecular coupling reactions of bis-unsaturated compounds mediated by **1** are discussed in Section 9.5).



(Eq. 9.15)

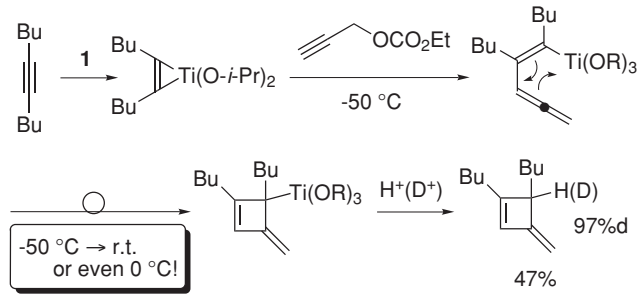


Titanium–acetylene complexes react with allylic or propargylic halides or acetates through regioselective titanacycle formation and subsequent β-elimination [36,37]. The reaction therefore provides a convenient method of preparing 1,4-alkadienes, including those bearing functional groups as exemplified in Eq. 9.16 [38].



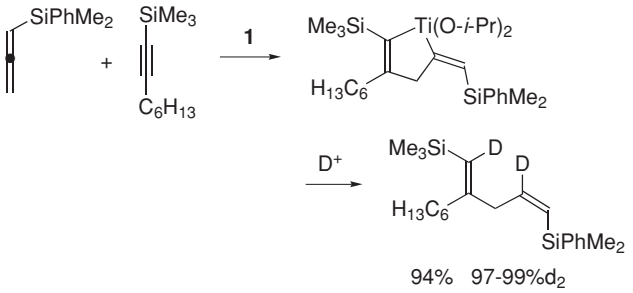
(Eq. 9.16)

Titanated vinylallenes generated from the coupling of acetylenes and propargyl carbonates [38] undergo facile, unidirectional electrocyclization to give cyclobutene derivatives under extremely mild reaction conditions as shown in Eq. 9.17 [39].

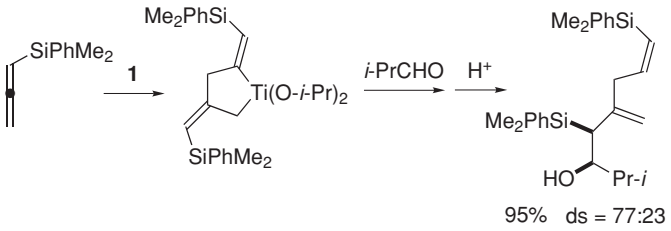


(Eq. 9.17)

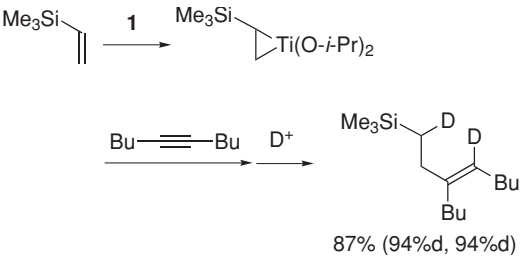
Besides the acetylene–acetylene coupling reactions shown above, acetylene–allene [40] and allene–allene coupling reactions [40] are also feasible (Eqs. 9.18 and 9.19). These reactions provide convenient methods for the synthesis of stereodefined olefinic skeletons. As an addendum, the coupling of vinylsilane with acetylenes was effected by **1** to give stereodefined homoallylsilanes, as shown in Eq. 9.20 [41].



(Eq. 9.18)



(Eq. 9.19)



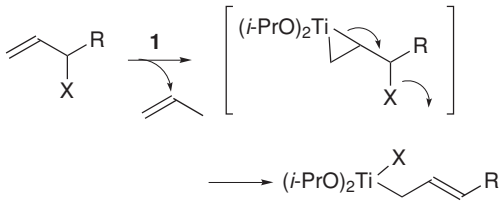
(Eq. 9.20)

9.3
Preparation of Allyl- and Allenyltitanium Reagents and their Synthetic Utility

Preparation of allyltitaniums of the type (allyl)Ti(O*i*Pr)$_3$ from the corresponding allyllithium or -magnesium compounds and ClTi(O*i*Pr)$_3$ by transmetallation and their subsequent synthetic utilization have attracted considerable interest because of the advantageous reactivity of the allyltitaniums as compared to other allylmetal complexes in terms of chemo-, regio-, and diastereoselectivity [3]. The preparation of certain allyllithium or -magnesium reagents, however, is not necessarily easy, which would seem to limit the utility of this method.

The titanium reagent **1** reacts with allyl alcohol derivatives, such as halides, acetates, carbonates, phosphates, or sulfonates to afford allyltitanium complexes of the type (η^1-allyl)TiX(O*i*Pr)$_2$, as shown in Eq. 9.21 [42]. As a variety of allylic alcohols are easily obtained,

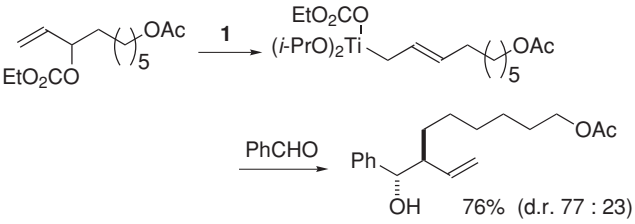
this reaction provides highly efficient and practical access to a variety of allyltitaniums, including those that are difficult to prepare by the transmetallation method outlined above.



(Eq. 9.21)

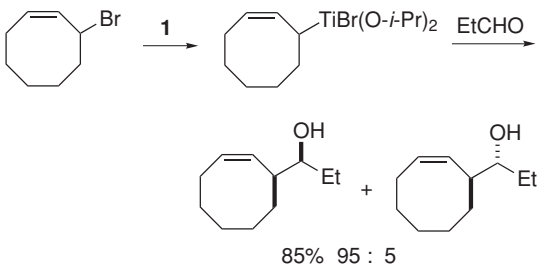
X = Cl, Br, OAc, OCO_2Et, $OP(O)(OEt)_2$, OTs, OPh

The following synthetically attractive features of the reaction are apparent. The reaction allows the preparation of allyltitaniums bearing functional groups, thus providing easy access to functionalized compounds (Eq. 9.22).



(Eq. 9.22)

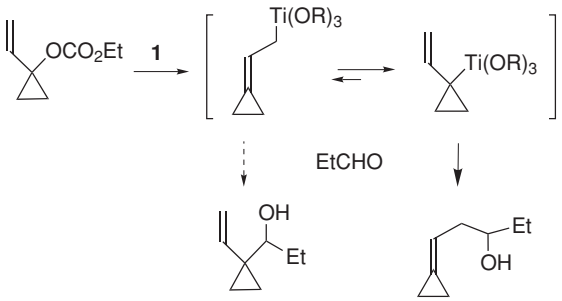
Seven-, eight-, and nine-membered cyclic allyltitanium reagents can readily be generated from the corresponding cyclic allylic halides or carbonates [43]. The resulting titanium reagents, in turn, react stereoselectively with aldehydes and imines, as exemplified by the eight-membered case shown in Eq. 9.23, thus providing a new and selective access to medium-ring carbocycles bearing a side chain at the allylic position.



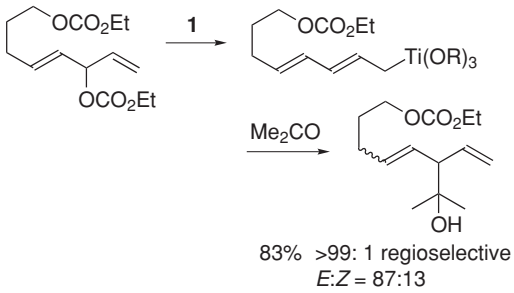
(Eq. 9.23)

Alkylidenecyclopropane derivatives can readily be prepared by the reaction of **1** with vinylcyclopropyl carbonates and subsequent trapping of the resulting allyltitaniums with aldehydes or ketones (Eq. 9.24) [44]. It should be noted that, in this case, the carbon–carbon bond formation occurs at the less substituted allylic terminus, and not at the more substituted end of the titanium reagent, the latter being the position at which addition to substituted allyltitanium reagents is usually observed.

Penta-2,4-dienyltitanium complexes, including those bearing a functional group, can readily be prepared from **1** and penta-1,4-dienyl carbonates. In turn, these react regiose-



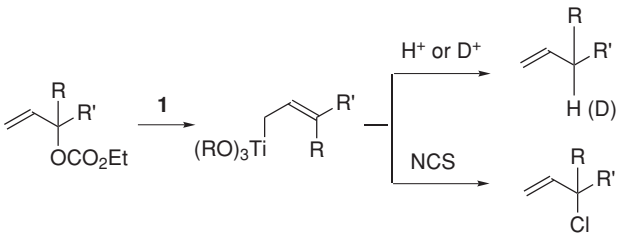
(Eq. 9.24)



(Eq. 9.25)

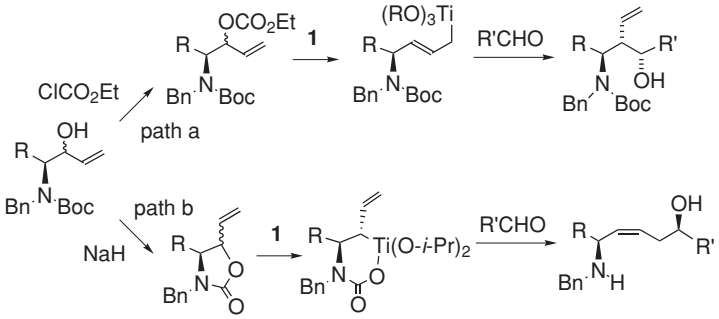
lectively with aldehydes and ketones to afford the corresponding penta-1,4-dien-3-yl carbinols in a highly specific manner, as exemplified by Eq. 9.25 [45].

Reaction of the allyltitaniums with D_2O and NCS proceeds with excellent regioselectivity, and thus a new one-pot method for converting allyl alcohol derivatives to 1-alkenes having D and Cl at the allylic position is opened up (Eq. 9.26) [46].



(Eq. 9.26)

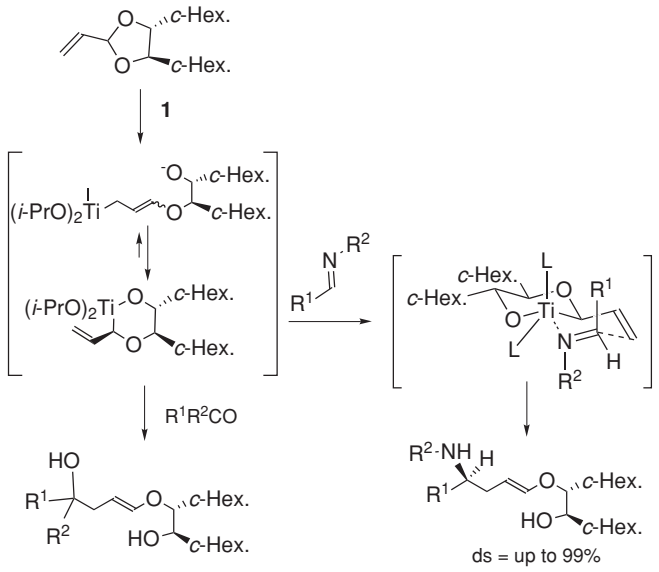
The preparation of chiral allyltitanium reagents having a stereogenic center and their utilization in asymmetric synthesis have been pursued. As shown in Eq. 9.27, chiral allyl-



(Eq. 9.27)

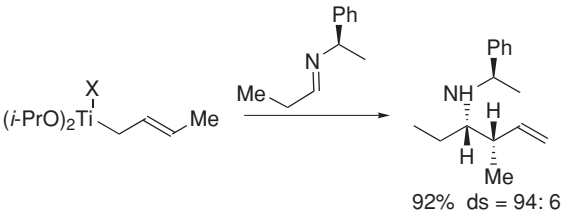
titaniums having an amino substituent at the stereogenic center can be prepared from optically active 4-amino-1-alken-3-ol derivatives. In turn, these can be made to react with aldehydes at either the α- or γ-position to the amino group by selecting ethyl carbonate (path a) [47] or cyclic carbamate (path b) [48] as the leaving group. The diastereoselectivities of both reactions are good, and so this protocol provides a new entry to the preparation of ε-aminoalkanols and β-vinyl-γ-aminoalkanols.

The allyltitanium reagent derived from optically active acrolein 1,2-dicyclohexylethylene acetal reacts with carbonyl compounds or imines in a regioselective way to provide the corresponding addition product, which has the structure shown in Scheme 9.8 [49,50]. These results indicate that the allyltitanium reagent serves as a propionaldehyde homoenolate equivalent. Although the degree of chirality transfer observed for the reaction with carbonyl compounds was low and is not indicated in the scheme, the reaction with imines was found to proceed with a high degree of chiral induction. Thus, a chiral homoenolate equivalent that reacts highly selectively with a variety of imines, including acyclic and cyclic aldimines and cyclic ketimines, has been developed for the first time.



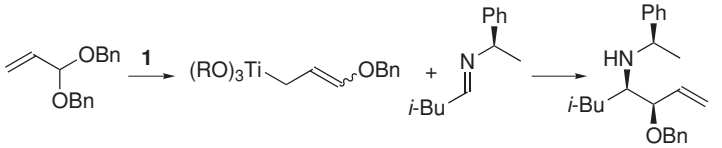
Scheme 9.8. Asymmetric addition to imines.

The synthesis of optically active compounds by the diastereoselective reaction of allyltitanium reagents with chiral electrophiles has also been reported. The reaction of allyltitanium reagents with chiral imines proceeds with excellent diastereoselectivity, as shown in Eq. 9.28, thus providing a new method for synthesizing optically active homoallylic amines with or without a β-substituent [51,52].



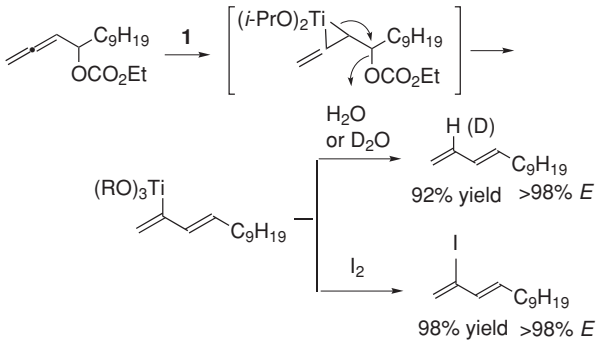
(Eq. 9.28)

In contrast to the allyltitaniums derived from acrolein cyclic acetals, such as 1,2-dicyclohexylethylene acetal shown in Scheme 9.8, those derived from acrolein acyclic acetals react with ketones and imines exclusively at the γ-position. As shown in Eq. 9.29, the reaction with chiral imines having an optically active 1-phenylethylamine moiety proceeds with high diastereoselectivity, thus providing a new method for preparing optically active 1-vinyl-2-amino alcohol derivatives with *syn* stereochemistry [53]. The intermediate allyltitanium species has also found use as a starting material for a carbozincation reaction [54].



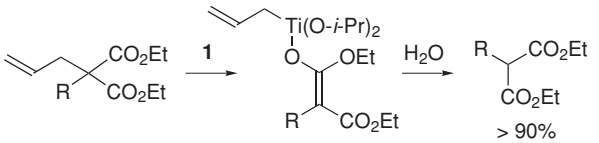
(Eq. 9.29)

The reaction of alka-2,3-dien-1-yl carbonates with **1** resulted in a similar oxidative addition to afford 1,3-dien-2-yltitanium complexes, as shown in Eq. 9.30. Subsequent iodinolysis provided one-pot access to 2-iodo-1,3-dienes, which are otherwise tedious to prepare [55].



(Eq. 9.30)

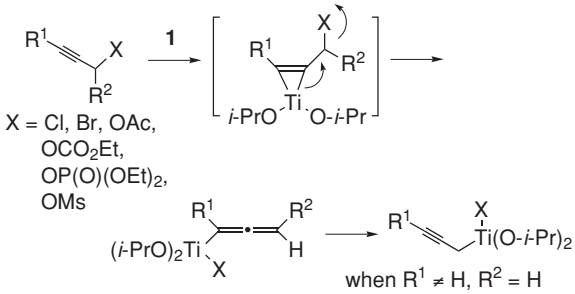
The reaction shown in Eq. 9.31, in which $CH_2{=}CHCH_2TiX_3$ is generated from **1** and $(CH_2{=}CHCH_2)RC(CO_2Et)_2$, indicates that the $RC^-(CO_2Et)_2$ anion is equally effective as a good leaving group as halide, acetate, or carbonate. By taking advantage of this reaction, the allyl moiety could be used as a protecting group for the acidic hydrogen of malonic esters [56].



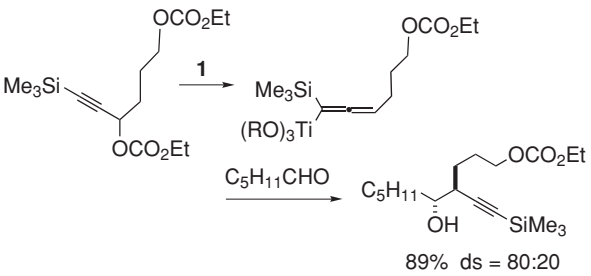
(Eq. 9.31)

The titanium reagent **1** reacts with propargyl alcohol derivatives to provide synthetically useful propargyl- or allenyltitanium compounds, as shown in Eq. 9.32 [57], which have hitherto been synthesized by a transmetallation reaction via the corresponding propargyllithium or -magnesium compounds [58]. As a variety of propargyl alcohols can easily be prepared, this direct method opens up a highly practical route for preparing a variety of homopropargyl or allenyl derivatives by their reaction with electrophiles, as illustrated

in Eq. 9.33 [57]. When stannyl chloride is used as the electrophile, propargyl- or allenyltin compounds are obtained [59]. The generation of a propargyltitanium reagent followed by its intramolecular trapping with an incipient carbonyl group leads to cycloalkanols [60]. Propargyltitanium reagents derived from pinacol acetals of ynals react selectively with aldehydes at their allenic position to give allenyl adducts, which, upon acidic treatment, spontaneously give various furans [61].



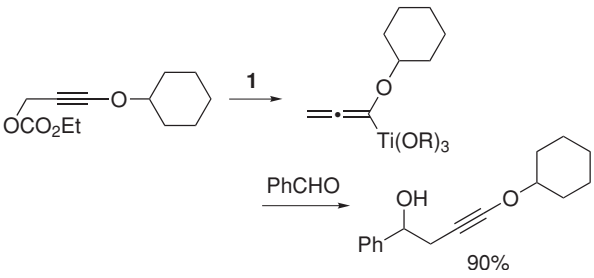
(Eq. 9.32)



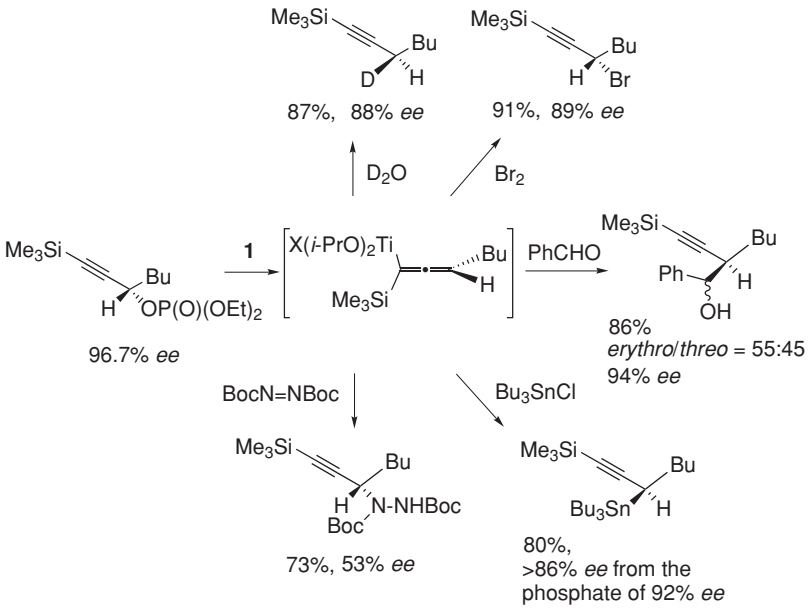
(Eq. 9.33)

The reactions of **1** with secondary propargyl phosphates (Scheme 9.9) and tertiary propargyl carbonates (Scheme 9.10) proceed with excellent stereoselectivity, although the sense of stereoselectivity is different in the two cases, thus providing a practical and general method for synthesizing chiral allenyltitaniums starting from easily accessible optically active propargyl alcohol derivatives [62–65]. The subsequent reactions of the allenyltitanium species with electrophiles shown in Schemes 9.9 and 9.10 also proceeded with good to excellent stereoselectivities. Thus, efficient access to optically active homopropargyl alcohols [62], acetylenes (having a deuterium at their propargyl position) [63], propargyl halides [63], α-hydrazinoalkynes [64], and propargylstannanes [65] has been achieved.

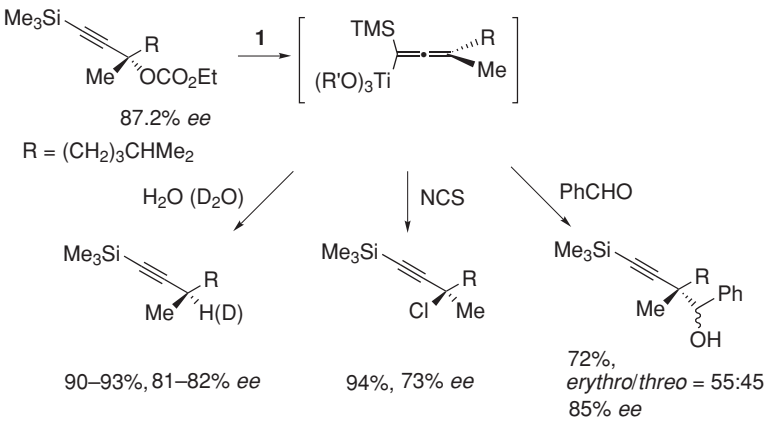
As shown in Eq. 9.34, 3-alkoxy-2-propyn-1-yl carbonates were shown to react with **1** to afford titanated alkoxyallenes, which, in turn, react regiospecifically with aldehydes to provide the corresponding γ-addition products [66].



(Eq. 9.34)



Scheme 9.9. Chirality transfer from chiral allenyltitanium reagents.



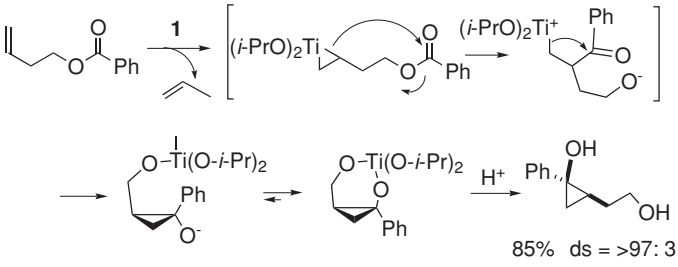
Scheme 9.10. Chirality transfer from chiral allenyltitanium reagent.

9.4
Intramolecular Nucleophilic Acyl Substitution (INAS) Mediated by 1

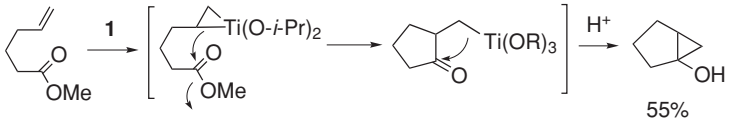
Intermolecular nucleophilic acyl substitution is a fundamental carbon–carbon bond-forming reaction. In spite of its high synthetic potential, however, its intramolecular version, that is, intramolecular nucleophilic acyl substitution (INAS) is rather rare because of the intrinsic difficulties involved in carrying it out. One difficulty associated with the INAS reaction is that a reactive nucleophilic species must be generated in the presence of carbonyl functionality, and at the same time this nucleophile is expected to react only with

the carbonyl group in an intramolecular fashion, and not intermolecularly with the one present in the reaction product. Organometallics such as zinc and boron species lack the nucleophilicity to undergo INAS reactions, while organolithiums and -magnesiums are generally too reactive.

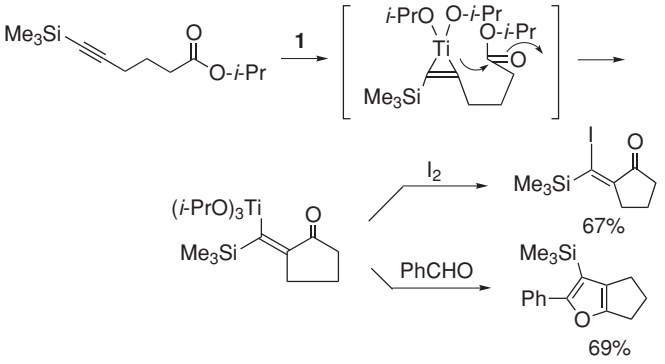
It is well recognized that organotitanium compounds do not react with esters or carbonates due to their low nucleophilicity [3]. However, INAS reaction of unsaturated esters or carbonates mediated by **1** proceeds smoothly, as shown in Eqs. 9.35 [67], 9.36 [68,69], 9.37 [70], and 9.38 [70,71]. The π-alkene or -acetylene titanium intermediates shown in these equations have highly strained titanacyclopropane or -propene structures, respectively, and the relief of the strain associated with the INAS reaction might operate as a driving force [1d,9a,9b,9c]. As the initial products generated in these INAS reactions are organotitanium compounds, the ensuing reaction occurs readily either in an intramolecular manner with an electrophile present in the products (Eqs. 9.35 and 9.36), or intermolecularly with an added electrophile (Eqs. 9.37 and 9.38). The reaction thus offers efficient and practical access to cyclopropanols (Eqs. 9.35 and 9.36), bicyclo[*n*.1.0]alkanols ($n = 3, 4, 5$) (Eq. 9.36), as well as cyclic and acyclic α,β-unsaturated ketones and lactones (Eqs. 9.37 and 9.38), starting from readily available materials.



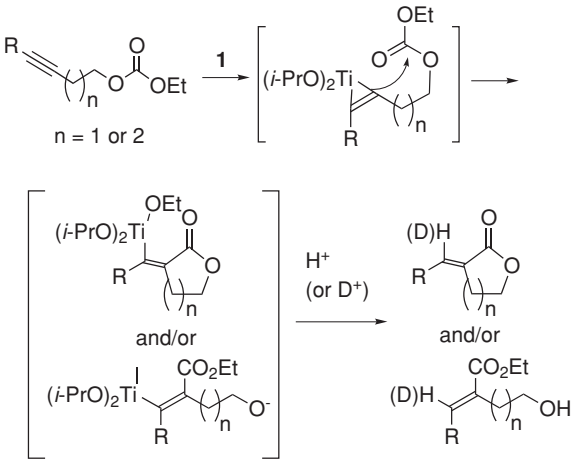
(Eq. 9.35)



(Eq. 9.36)

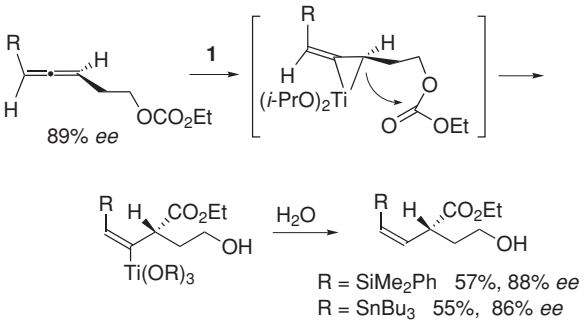


(Eq. 9.37)



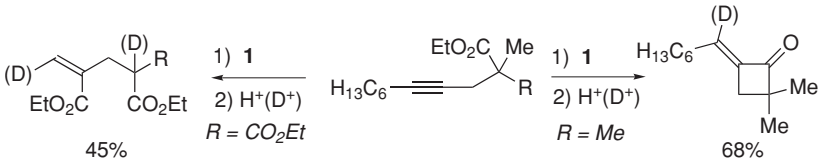
(Eq. 9.38)

INAS reactions of carbonates of 3,5-dienyl alcohols (i. e., involving a conjugated diene moiety) [72] and 3,4-dienyl alcohols (i. e., having an allene moiety) [73] also proceed smoothly to furnish the corresponding β,γ-unsaturated esters. The reaction of 4-silyl- or 4-stannyl-3,4-dienyl carbonate having axial chirality proceeds with excellent chirality transfer, as exemplified in Eq. 9.39, thereby affording a novel access to optically active α-substituted β,γ-unsaturated esters [73].



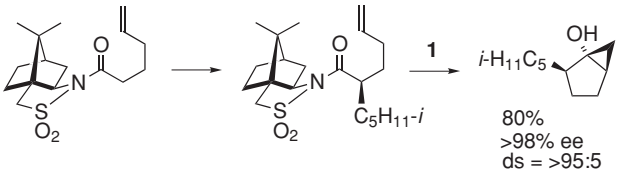
(Eq. 9.39)

Ring-closure to give small rings is also feasible, but in certain cases other types of reactions are observed, such as that shown in Eq. 9.40 [74,75].



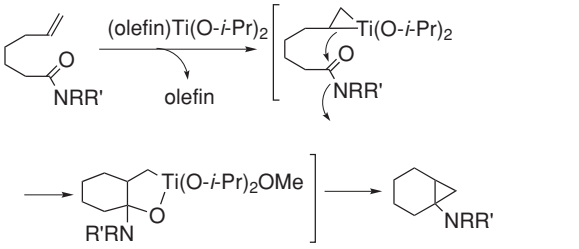
(Eq. 9.40)

Asymmetric cyclopropanol formation has been achieved with olefinic acylsulfonamides, which act like olefinic esters. Thus, their reaction with **1** provides a method for synthesizing cyclopropanols in an optically active form. As represented by Eq. 9.41, alkylation of Oppolzer's camphor sultam and reaction of the resulting unsaturated acylsulfonamides with **1** provides optically active bicyclic cyclopropanols having exclusively the structure shown in the equation [76].

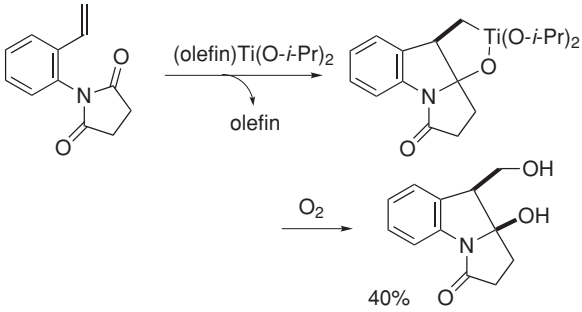


(Eq. 9.41)

The INAS reaction of ω-vinyl amides proceeds as shown in Eq. 9.42 to afford cyclopropylamine derivatives [77]. The reaction with cyclic imides derived from ω-vinylamines, furnishing acylaminal derivatives, was also found to proceed smoothly (Eq. 9.43) [78].

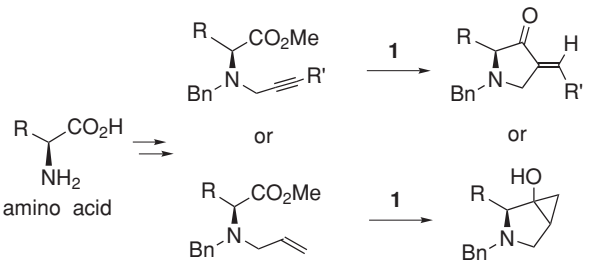


(Eq. 9.42)

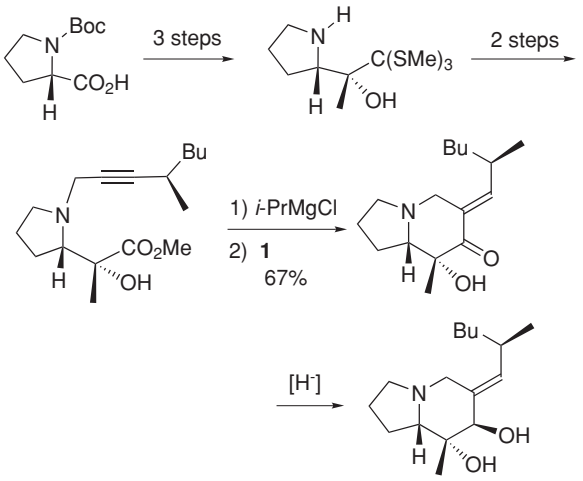


(Eq. 9.43)

The newly developed INAS reaction outlined above makes it possible to connect the carbon–carbon bond intramolecularly at an almost unprecedented position, and, moreover, the reaction products bear a functional group enabling further manipulation, such as a ketone, enone, lactone, cyclopropanol, or cyclopropylamine group. The reaction thus allows a new synthetic design in organic synthesis. The synthesis of N-heterocycles, including optically active ones, starting from readily available starting materials strongly indicated the utility of the reaction, as depicted in Eq. 9.44 [79,80]. Efficient total synthesis of allopumiliotoxin 267A, which is one component of the toxic skin secretion of certain neotropical frogs and displays significant cardiotoxic activity, was accomplished using this N-heterocycle-forming reaction as the key step (Eq. 9.45) [79].



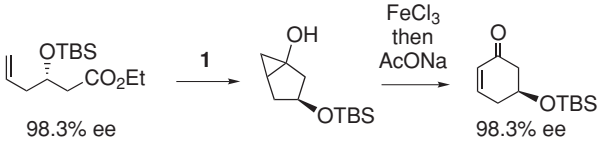
(Eq. 9.44)



Allopumiliotoxin 267A

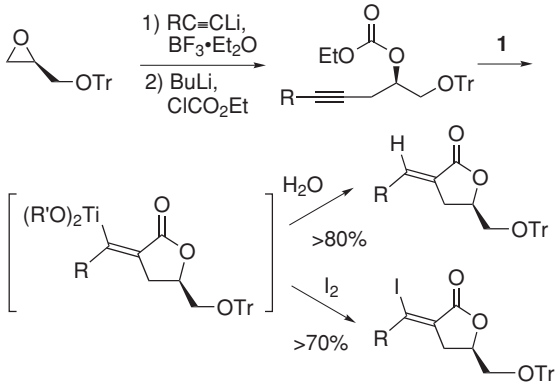
(Eq. 9.45)

The reaction also allows an efficient and practical synthesis of optically active 5-[(*tert*-butyl)dimethylsilyl]oxy-2-cyclohexenone starting from readily available starting materials, as shown in Eq. 9.46 [81,82]. 5-[(*tert*-Butyl)dimethylsilyl]oxy-2-cyclohexenone [82,83] and its analogues having additional substituents [84] or a different ring size (a seven-membered counterpart) [85] show a useful dichotomy in their stereoselectivities towards organocopper reagents. This makes them useful as effective chiral building blocks for the synthesis of substituted cyclohexane compounds, including *cis*-cyclohexa-3,5-diene-1,2-diols [86] and natural products such as penienone, penihydron [82], palitantin [87], and the A-ring precursor of 1a,25-dihydroxyvitamine D_3 [88,89] and its 19-nor derivatives [90].



(Eq. 9.46)

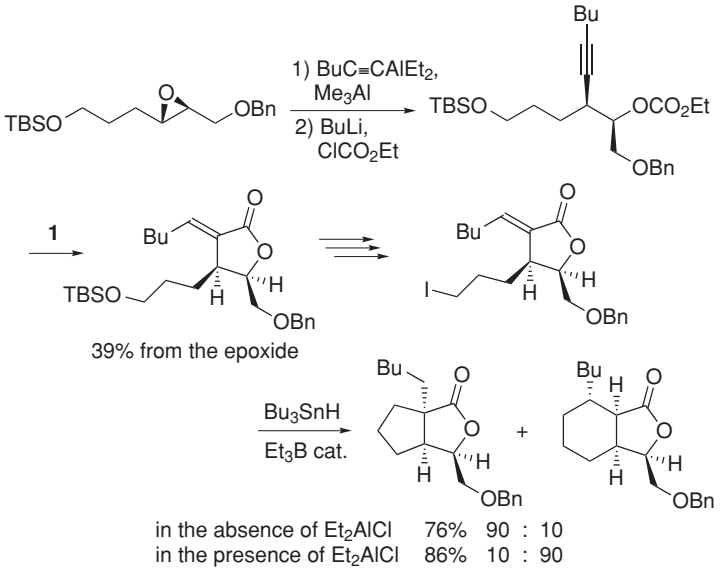
The reaction shown in Eq. 9.47 demonstrates a short synthesis of γ-[(trityloxy)methyl]-α-alkylidene-γ-butyrolactones having stereodefined mono- and disubstituted *exo*-alkylidene



(Eq. 9.47)

moieties starting from commercially available glycidyl trityl ether [91]. These lactones have been utilized as versatile building blocks and as intermediates for synthesizing chiral natural compounds.

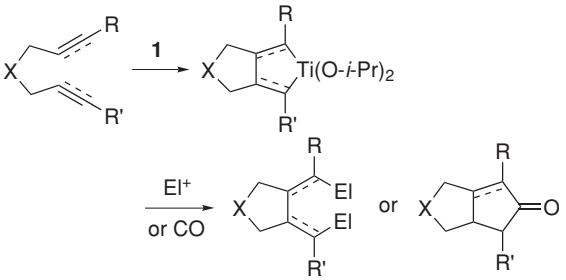
As shown in Eq. 9.48, optically active α-alkylidene lactones having an iodoalkyl substituent were prepared from the corresponding optically active epoxy alcohol by means of the Sharpless epoxidation. These represent precursors of optically active functionalized cyclopentanes and cyclohexanes, respectively, as shown in the equation [92].



(Eq. 9.48)

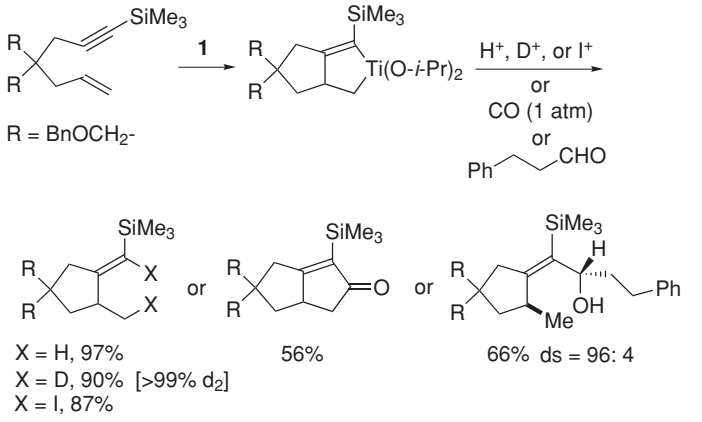
9.5
Intramolecular Coupling of Alkenes and Acetylenes

In Section 9.2, intermolecular reactions of titanium–acetylene complexes with acetylenes, allenes, alkenes, and allylic compounds were discussed. This section describes the intramolecular coupling of bis-unsaturated compounds, including dienes, enynes, and diynes, as formulated in Eq. 9.49. As the titanium alkoxide is very inexpensive, the reactions in Eq. 9.49 represent one of the most economical methods for accomplishing the formation of metallacycles of this type [1,2]. Moreover, the titanium alkoxide based method enables several new synthetic transformations that are not viable by conventional metallocene-mediated methods.

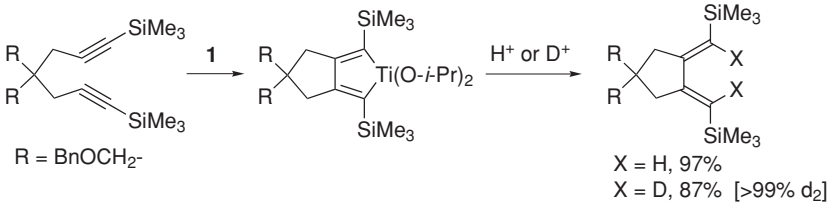


(Eq. 9.49)

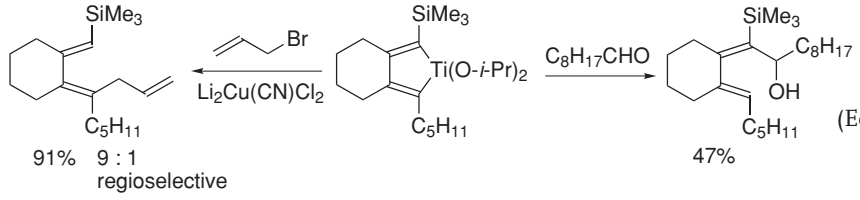
Intramolecular coupling mediated by **1** can be applied to a variety of bis-unsaturated compounds. Thus, 1,6- or 1,7-dienes, enynes, and diynes, including those having a heteroatom in the tether portion, afford the corresponding titanabicyclic compounds, as exemplified in Eqs. 9.50 and 9.51 [93–97]. The resulting titanium compounds may be protonated, deuterated, or halogenated, as shown in Eqs. 9.50 and 9.51, or they may be used for carbon–carbon bond elongation through their reactions with aldehydes or allyl bromide, which stop cleanly at the mono-addition stage, as shown in Eqs. 9.50 and 9.52. Their reactions with electrophiles usually proceed with excellent regio- and stereoselectivity, thus offering a convenient method for the preparation of five- and six-membered cyclic compounds. Intramolecular coupling of diynes followed by intramolecular double addition to the ester moiety, which is located at a suitable position with respect to the titanacycle, has proved possible, as described in Eq. 9.13 [33].



(Eq. 9.50)

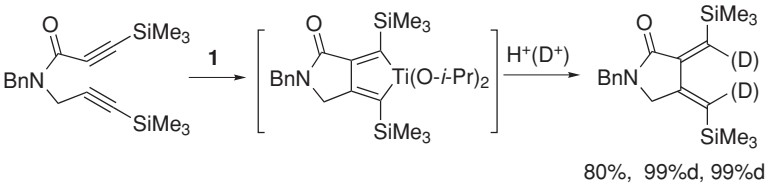


(Eq. 9.51)



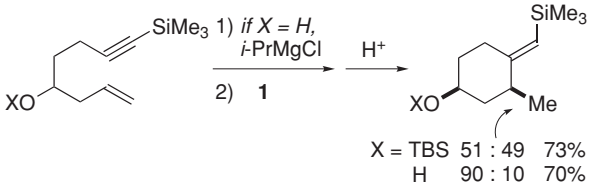
(Eq. 9.52)

The above bicyclization could be extended to functionalized diynes, permitting the preparation of lactams or lactones having a fused exocyclic conjugated diene, a representative example of which is shown in Eq. 9.53 [98].



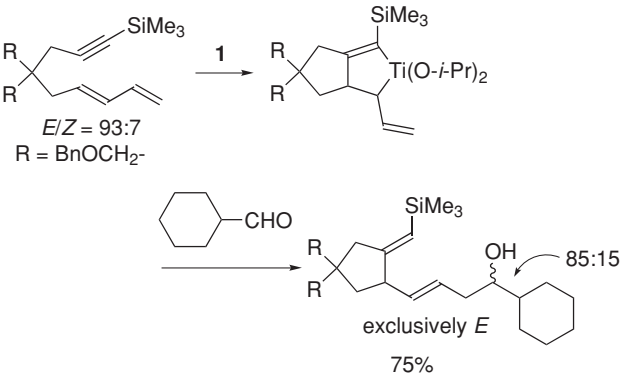
(Eq. 9.53)

Stereoselective cyclization controlled by a substituent remote from the reaction center is often difficult to achieve. However, **1**-mediated cyclization of the substrates illustrated in Eq. 9.54 proceeds in a highly stereoselective manner when the hydroxy group is converted to a magnesium alkoxide prior to cyclization [99,100]. The effect of the alkoxide group is much more favorable than that of the corresponding TBS ether.



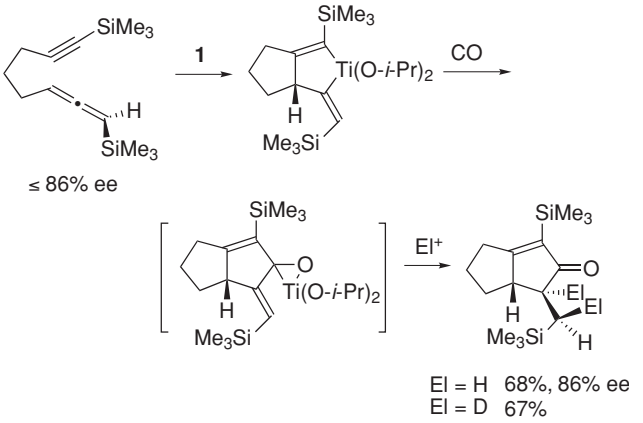
(Eq. 9.54)

The cyclization of dienynes was found to proceed equally well, as shown in Eq. 9.55, and the resulting intermediate titanacycle reacts regiospecifically with aldehydes at the remote position of the most likely allyltitanium system [101].

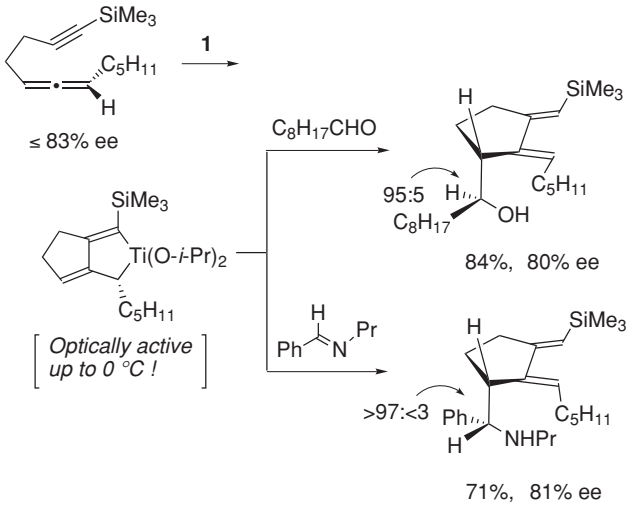


(Eq. 9.55)

The intramolecular cyclization of 1,2-dien-7-ynes and 1,2-dien-6-ynes regiospecifically affords the corresponding titanacycles, which react with protons, carbon monoxide, aldehydes, or imines to give single products, as shown in Eqs. 9.56 and 9.57 [102]. As the formation of titanacycles and their subsequent reaction with externally added reagents such as carbon monoxide (Eq. 9.56) or an aldehyde (or imine) (Eq. 9.57) proceeds with excellent chirality transfer, this represents a new method for synthesizing optically active cyclopentane derivatives from optically active allenes [102].

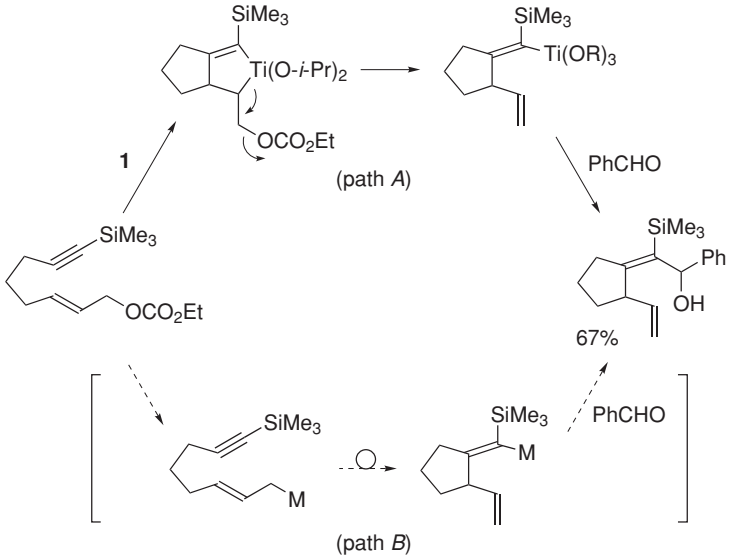


(Eq. 9.56)

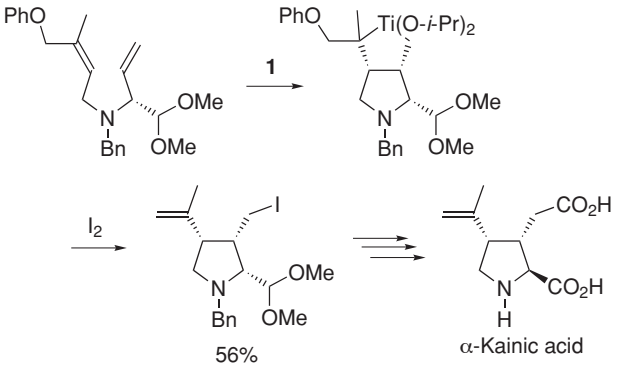


(Eq. 9.57)

If the alkenes and acetylenes that are subjected to the reaction mediated by **1** have a leaving group at an appropriate position, as already described in Eq. 9.16, the resulting titanacycles undergo an elimination (path A) as shown in Eq. 9.58 [36]. As the resulting vinyltitaniums can be trapped by electrophiles such as aldehydes, this reaction can be viewed as an alternative to stoichiometric metallo-ene reactions via allylic lithium, magnesium, or zinc complexes (path B). Preparations of optically active N-heterocycles [103], which enabled the synthesis of (−)-α-kainic acid (Eq. 9.59) [104,105], of cross-conjugated trienes useful for the diene-transmissive Diels–Alder reaction [106], and of exocyclic bis(allene)s and cyclobutene derivatives [107] have all been reported based on this method.



(Eq. 9.58)



(Eq. 9.59)

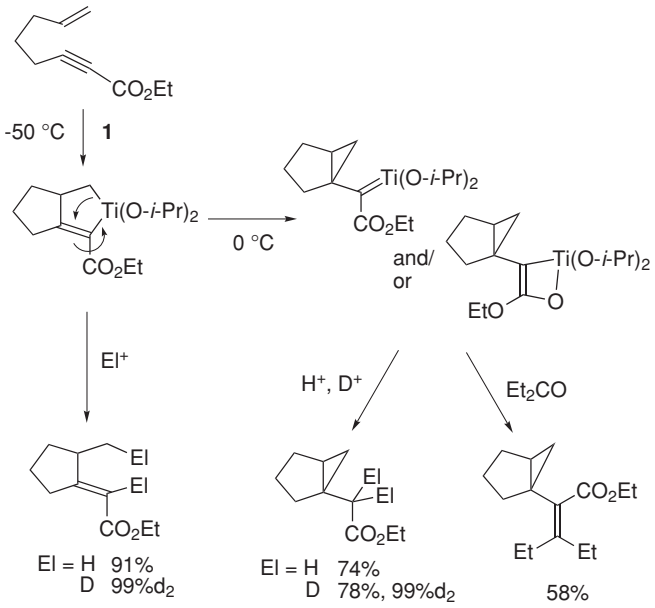
The utility of this metallo-ene-type reaction has also been demonstrated by the reaction of 1,6- or 1,7-enynes bearing a chiral 1,2-diphenylethylene acetal moiety as the leaving group. The reaction was found to proceed with excellent chiral induction to give optically active cyclopentane and cyclohexane derivatives, respectively, which was followed by reaction of the resulting vinyl titaniums with electrophiles, as exemplified in Eq. 9.60, s. p. 348 [108].

Intramolecular alkene–acetylene cyclizations of 2-en-7-ynoates and 2-en-8-ynoates proceed readily to give different products depending on the nature of the ester moiety [109,110]. Thus, cyclization of *tert*-butyl enynoate affords the titanacycle, which, in turn, reacts regioselectively with electrophiles at the titanated ester portion to afford cyclopentane or cyclohexane derivatives having stereodefined side chains (Eq. 9.61, s. p. 348) [110]. Methyl or ethyl esters having the same structure also lead to the titanacycles, but this is followed by a second ring-closure, itself initiated by the reaction with an electrophile, eventually giving bicyclic ketones as shown in Eq. 9.62, s. p. 349. The cyclization of 2,7-dienoates providing bicyclic ketones is also feasible, and this reaction has recently been used to good effect in the preparation of carbacyclin (Eq. 9.63, s. p. 349) [111].

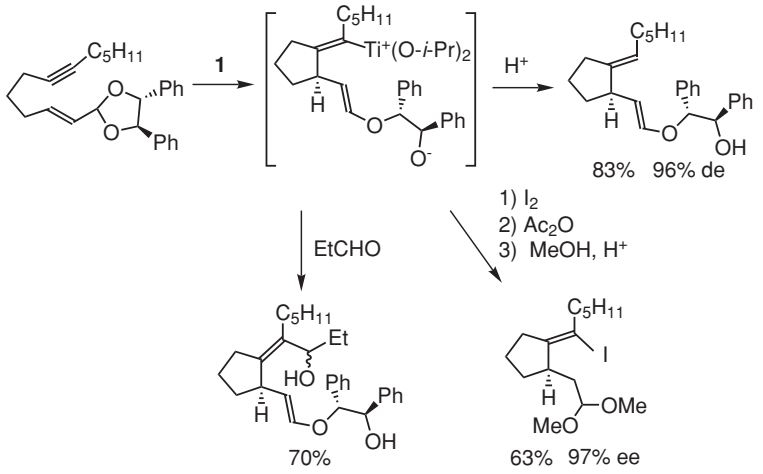
Application of the above method to chiral 2-en-7-ynoates derived from optically active 8-phenylmenthol led to asymmetric ring-closure to give bicyclic ketones bearing an angular substituent, with high *ee* values, as shown in Eq. 9.64, s. p. 349 [112].

In contrast to the reactions of olefinic esters discussed above, 7-en-2-ynoates, i. e. acetylenic esters, exhibit an interesting alternative cyclization behavior, as shown in Scheme 9.11 [109,110]. Deuteriolysis of the reaction mixture at low temperature gave the expected bis-deuterated monocyclic compound, indicating the intermediacy of a titanacycle species. However, when the reaction mixture was simply allowed to warm to as much as 0 °C, a product having a bicyclo[3.1.0]hexane skeleton was obtained in excellent yields. The initially formed titanacycle may be converted to the titanium–carbene complex and/or the α,α-bis-titanated ester, as evidenced by their deuteriolysis (to give an α,α-bis-deuterated ester) and smooth alkylidenation with diethyl ketone (to give the unsaturated ester). The synthesis of *d*-sabinene has been achieved by using this reaction as the key step [110].

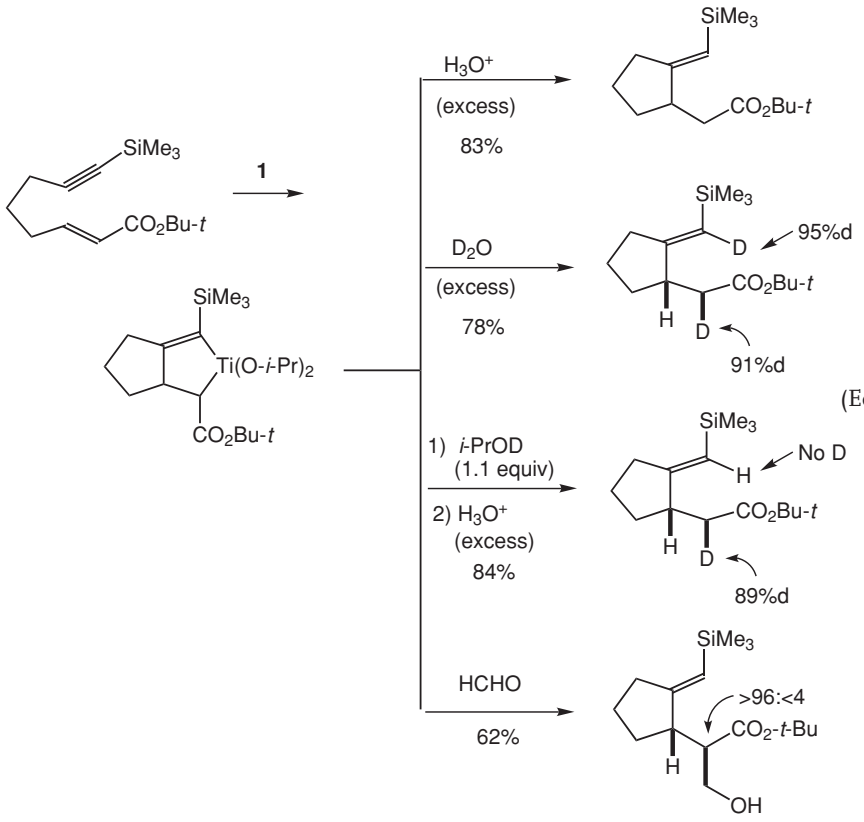
The construction of ring systems through a tandem inter- and intramolecular coupling of two unsaturated compounds is also possible using the reagent **1**. Thus, as exemplified in Eq. 9.65, s. p. 349, this transformation provides an efficient method for preparing cyclic compounds [113].



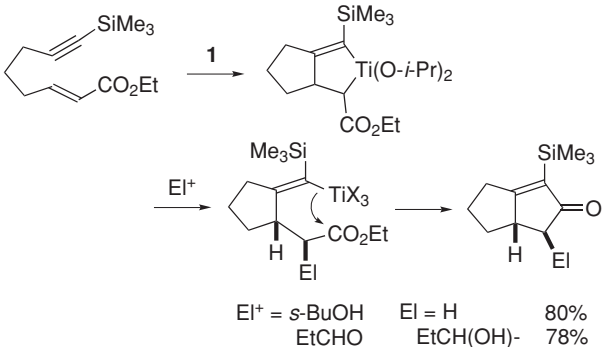
Scheme 9.11. Cyclization of 7-en-2-ynoates.


C5H11
1
Ti+(O-i-Pr)2
H+
Ph
Ph
Ph
OH
83% 96% de
EtCHO
1) I2
2) Ac2O
3) MeOH, H+
Et
HO
I
OMe
MeO
70%
63% 97% ee

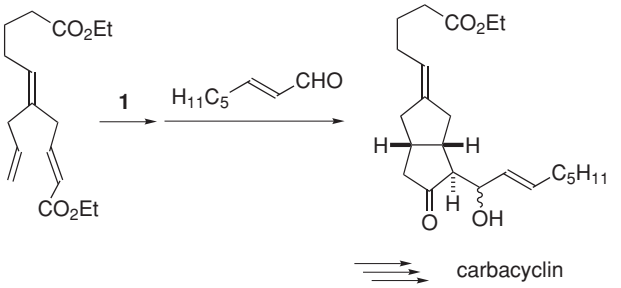
(Eq. 9.60)


SiMe3
CO2Bu-t
1
Ti(O-i-Pr)2
H3O+
(excess)
83%
D2O
(excess)
78%
95%d
91%d
1) i-PrOD
(1.1 equiv)
2) H3O+
(excess)
84%
No D
89%d
HCHO
62%
>96:<4
CO2-t-Bu
OH

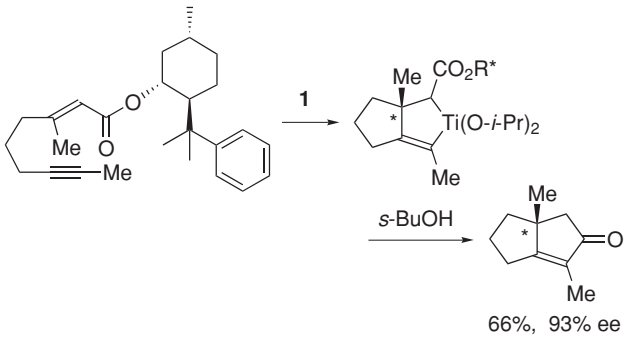
(Eq. 9.61)



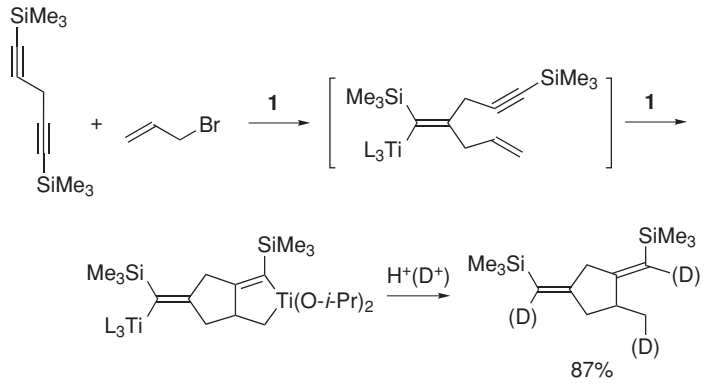
(Eq. 9.62)



(Eq. 9.63)



(Eq. 9.64)



(Eq. 9.65)

9.6 Concluding Remarks

There are already numerous synthetic reactions, and applications thereof, based on titanocene ("Cp_2Ti") and zirconocene ("Cp_2Zr") reagents. However, most of the reactions discussed in this chapter are not merely extensions of these known reactions. Indeed, they show novel selectivity or reactivity, they allow transformations that have proved unsuccessful with conventional metallocene reagents, and they facilitate reactions that have not been reported previously. The other advantageous features of the titanium alkoxide system are as follows. The starting material, $Ti(OiPr)_4$, is very inexpensive as compared to other metallocene reagents. The experimental operation is very simple: the actual reactive titanium(II) species can be generated in situ in the presence of substrates. The work-up of reactions is also very convenient because, upon hydrolysis, the titanium species either completely migrates to the aqueous layer or forms an insoluble precipitate of inorganic salts, which are readily separated from the organic products by extraction or filtration, respectively. These points are amply illustrated in the following representative procedures. Finally, we hope that this family of titanium alkoxide-mediated transformations will become increasingly utilized by synthetic chemists and will be the subject of ongoing development.

Typical Experimental Procedures

Generation and Reaction of Acetylene Complexes (Section 9.2): (*E*)-1-Cyclohexyl-2-[(trimethylsilyl)methylene]-1-octanol [10] To a stirred solution of 1-(trimethylsilyl)-1-octyne (0.14 g, 0.75 mmol) and $Ti(OiPr)_4$ (0.22 mL, 0.75 mmol) in diethyl ether (8.0 mL) was added a 1.25 M solution of *i*PrMgCl in diethyl ether (1.2 mL, 1.5 mmol) at −78 °C to give a yellow homogeneous solution. This solution was warmed to −50 °C over a period of 0.5 h, during which it became brown in color. After stirring at the same temperature for 2 h, cyclohexanone (0.054 mL, 0.53 mmol) was added at −78 °C and stirring was continued for 1 h at −75 to −70 °C. The reaction mixture was then quenched with water (0.8 mL), allowed to warm to room temperature, and filtered through a short pad of Celite. The filtrate was dried over $MgSO_4$ and then concentrated in vacuo to give an oil. ^1H NMR analysis of this crude sample showed the presence of the title alcohol and its regioisomer in a ratio of 96:4. Purification on silica gel afforded the title compound (0.12 g, 83 %) having the same isomeric composition.

Generation and Reaction of Allyltitanium Reagents (Section 9.3): 2-(4-Bromophenyl)-1-phenyl-3-buten-1-ol [42] To a solution of 1-(4-bromophenyl)allyl ethyl carbonate (285 mg, 1.0 mmol) and $Ti(OiPr)_4$ (0.296 mL, 1.0 mmol) in diethyl ether (5 mL) was added *i*PrMgBr (1.20 M in diethyl ether, 2.0 mmol) at −50 °C. The resulting yellow solution was stirred at −50 to −40 °C for 1.5 h, in the course of which it became brown. Benzaldehyde (74.3 mg, 0.70 mmol) was then added at −40 °C and the mixture was allowed to warm to 0 °C over a period of 30 min. After the addition of aqueous 1 N HCl (5 mL) at this temperature, the mixture was allowed to warm to ambient temperature. The organic layer was separated and the aqueous layer was extracted with diethyl ether (10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (5 mL), dried over

$MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel to give the title compound (176 mg, 83 %). Its ^1H NMR analysis showed that the diastereomeric ratio was >97:3 and that the stereochemistry of the major isomer was 1*RS*,2*SR*.

INAS Reaction of Esters of Acetylenic Acids (Section 9.4): (*S*)-1,2-Dibenzyl-4-[(trimethylsilyl)-methylene]piperidin-3-one [79] To a stirred solution of (*S*)-2-{benzyl-[4-(trimethylsilyl)-3-butynyl]amino}-3-phenylpropionic acid methyl ester (393 mg, 1.0 mmol) and Ti(O*i*Pr)$_4$ (0.385 mL, 1.3 mmol) in diethyl ether (10 mL) was added *i*PrMgCl (1.34 M in diethyl ether, 1.94 mL, 2.6 mmol) at −78 °C. The resulting mixture was gradually warmed to −50 °C over a period of 1 h and then stirred for 2 h at −50 to −40 °C. After the addition of saturated aqueous $NaHCO_3$ solution (0.8 mL) at −40 °C, the mixture was allowed to warm to ambient temperature. NaF (3 g) and Celite (3 g) were added and the resulting mixture was stirred for 30 min. at room temperature and then filtered through a pad of Celite. The filtrate was concentrated in vacuo to afford the crude product, which was purified by passage through a short silica gel column to afford the title compound (273 mg, 75 %).

Cyclization of Bis-Unsaturated Compounds (Section 9.5): (*E*)-1,1-Bis[(benzyloxy)methyl]-3-methyl-4-[(trimethylsilyl)methylene]cyclopentane [93] To a stirred solution of 4,4-bis-[(benzyloxy)methyl]-1-(trimethylsilyl)-6-hepten-1-yne (0.41 g, 1.0 mmol) and Ti(O*i*Pr)$_4$ (0.37 mL, 1.26 mmol) in diethyl ether (10 mL), *i*PrMgCl (1.08 M in diethyl ether, 2.55 mL, 2.75 mmol) was added dropwise at −78 °C under argon. After stirring for 30 min., the solution was warmed to −50 °C over a period of 30 min. and kept at this temperature for a few hours. The reaction was subsequently terminated by the dropwise addition of 3 N HCl (2 mL) at −78 °C. The organic layer was separated and the aqueous layer was extracted with diethyl ether and hexane. The combined organic layers were washed with aqueous $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated to an oil, which was chromatographed on silica gel to afford the title compound (0.40 g, 97 %).

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10
Organometallic Chemistry of Titanocene and Zirconocene Complexes with Bis(trimethylsilyl)acetylene as the Basis for Applications in Organic Synthesis

Uwe Rosenthal and Vladimir V. Burlakov

10.1
Introduction*)

Suitable complex fragments that are both coordinatively and electronically unsaturated are often required to realize stoichiometric and catalytic reactions of organometallic compounds with different substrates. These core complexes coordinate to the substrates, activate them, and move them in the direction of the desired products. This general mechanism is nicely illustrated by the manifold reactions of Group 4 metallocene complexes, such as the complex fragments titanocene "Cp_2Ti" and zirconocene "Cp_2Zr", which are considered as generally unstable 14-electron compounds displaying a d^2 configuration (M(II)). They possess one lone electron pair and two vacant valence orbitals. In terms of their reactivity, they can be compared to carbenes. The possible interactions between occupied and unoccupied orbitals account for the fact that these metallocenes "Cp_2M" react with a variety of unsaturated compounds to form metallacycles, which then have the potential to undergo diverse conversions with further substrates. A crucial question in this context is what kind of ligand can be used that sufficiently stabilizes the metallocene fragment, yet can be quantitatively released under mild conditions to generate the unstable and very reactive core complex.

10.1.1
Established Titanocene and Zirconocene Sources

Some systems are known to generate titanocene "Cp_2Ti" or zirconocene "Cp_2Zr" very well. A range of combined Cp_2MX_2/reducing agent systems, as well as some well-defined complexes Cp_2ML_n, have frequently been used [1]. Selected examples of such systems are a mixture of Cp_2ZrCl_2 with *n*BuLi, which forms via $Cp_2Zr(\sigma\text{-}n\text{Bu})_2$ the complex $Cp_2Zr(\pi\text{-}n\text{-butene})$ (Negishi), and a mixture of Cp_2ZrCl_2 with EtMgCl, which forms via $Cp_2Zr(\sigma\text{-Et})_2$ the complex $Cp_2Zr(\pi\text{-ethylene})$ (Takahashi). In some cases, these complexes

*) In this article the following abbrevations are used:
Cp: cyclopentadienyl, Cp^*: pentamethylcyclopentadienyl, ebthi: ethylene-bis(tetrahydroindenyl), Me: methyl, Ph: phenyl, *t*Bu: tertiary butyl.

have been stabilized by additional ligands as, for example, in $Cp_2Zr(PR_3)(\pi\text{-}n\text{-butene})$ (Binger) or $Cp_2Ti(PMe_3)(\pi\text{-ethylene})$ (Alt). Other complexes, such as $Cp_2Ti(PMe_3)_2$ (Alt) and $Cp_2Zr(\pi\text{-}1,3\text{-butadiene})$ (Erker), have also frequently been used. These complexes are summarized in a number of excellent reviews and various informative contributions in textbooks [1]. The applicability of these systems and their success in certain reactions often depend on their preparative accessibility, on the selectivity of the conversions, and on the inertness of the temporary ligand. From this point of view, all of the above mentioned systems have certain disadvantages. Nevertheless, they are frequently and successfully used in organic synthesis, sometimes without any knowledge of the elementary organometallic reactions involved. To study these basic steps of stoichiometric and catalytic reactions, there is a need for appropriate complexes that react cleanly with substrate molecules and that can give an indication of the scope and limitations of the desired chemistry. Due to the existence of the aforementioned reviews, this contribution does not cover and repeat the general and well-known facts, but is instead oriented towards unusual reaction steps that are of potential interest in organic synthesis. The results described in this chapter come mostly from novel titanocene and zirconocene reagents with bis(trimethylsilyl)acetylene.

10.1.2
Novel Titanocene and Zirconocene Reagents with Bis(trimethylsilyl)acetylene

In recent years, stable and well-defined bis(trimethylsilyl)acetylene complexes [2] of the type $Cp_2M(L)(\eta^2\text{-}Me_3SiC_2SiMe_3)$ have emerged as novel reagents [3] for group IV metallocene fragments: M = Ti, without L (**1**) [2a,2d]; M = Zr, L = THF (**2a**) [2c]; M = Zr, L = pyridine (**2b**) [2e,2j]; M = Zr, L = acetone (existing in equilibrium with the zirconacycle **2c**) [2f]; the pentamethylcyclopentadienyl complexes **3** [2b,2d] and **4** [2i], and the *rac*-ethylene-bis(tetrahydroindenyl) complexes **5** and **6** [2h].

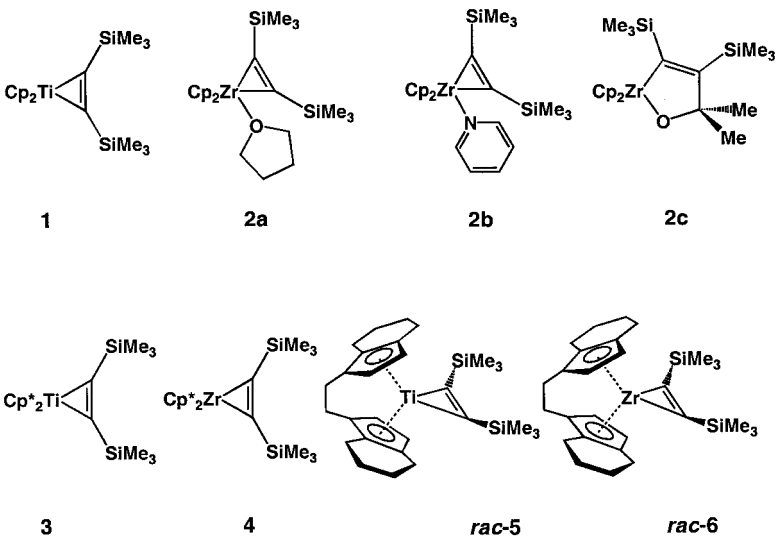
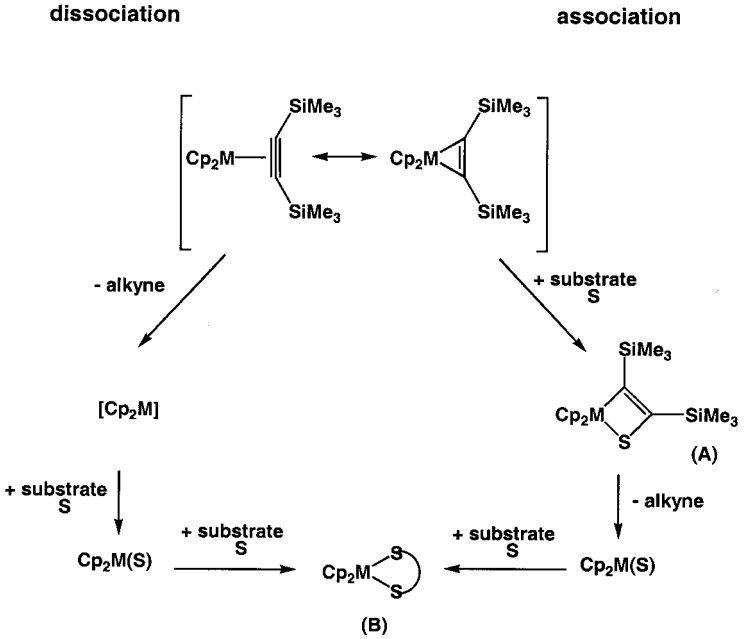


Figure 10.1. Novel titanocene and zirconocene reagents incorporating bis(trimethylsilyl)acetylene.

For one example in this series, the complex $Cp_2Zr(pyridine)(Me_3SiC_2SiMe_3)$ ("Rosenthal's complex"; **2b**), it was pointed out very recently that it "offers a number of compelling advantages over the widely used Cp_2ZrCl_2/nBuLi system and should significantly expand the scope of zirconocene-based coupling reactions" [2j].

By using different Cp ligands (Cp, Cp^*, ebthi), additional ligands (THF, pyridine, acetone), and metals (Ti, Zr), a fine-tuning of the reactions of these complexes has been feasible. Additional influences are exerted by, e. g., the substituents on the substrate, the stoichiometry used, the solvents, and other reaction conditions. Complexes of this type have also been prepared and used in connection with a multitude of substrates, and in many cases the products differ markedly from those obtained with conventional metallocene sources.

In their resonance forms, the complexes are considered as acetylenic π-complexes (+2 oxidation state) or as metallacyclopropenes (+4 oxidation state), which lead to coupling reactions of the alkyne (insertion into the metallacyclopropene) or to a substitution of the alkyne by the substrate.



Scheme 10.1. Co-reactions of the bis(trimethylsilyl)acetylene (A) or reactions of the substrate (B) at the metallocene as the basis for an associative or dissociative mechanism.

These are the two general possibilities for applications in organic synthesis: co-reactions of the alkyne with substrates (**A**) or reactions of the substrate (**B**) alone in the coordination sphere of the metal. The special feature of bis(trimethylsilyl)acetylene in reactions of these well-characterized complexes is its ability to stabilize the metallocene core and its tendency to suppress coupling reactions of the alkyne. In principle, this was found in earlier studies of reaction mixtures, firstly by Fagan and Nugent in 1988 [4] and later by Livinghouse in 1989 [5]. Investigation of the elementary organometallic steps of reactions of these complexes with substrates can provide basic information for applications in organic synthesis.

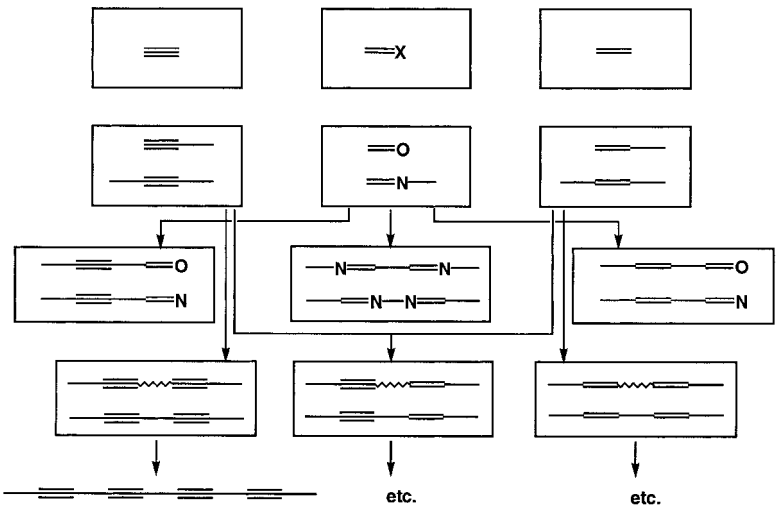
10.1.3
Mechanistic Considerations

The reaction behavior of complexes $Cp_2M(L)(\eta^2\text{-}Me_3SiC_2SiMe_3)$ (M = Ti, without L; M = Zr, L = THF, pyridine, acetone) is in all cases best explained by the easy displacement of the silyl-substituted alkyne. This can happen directly from the alkyne complex (*dissociative mechanism*) or, after coupling with the alkyne, from the formed metallacycle (*associative mechanism*). For M = Zr, strong indications have been found for an associative mechanism (see Section 10.3), while for M = Ti the substitution can also proceed dissociatively via a free titanocene [7,8a]. Interestingly, the same difference between titanium and zirconium was found by Basolo and Rausch in relation to CO substitution in complexes $Cp_2M(CO)_2$ by R_3P with the formation of $Cp_2M(PR_3)(CO)$: M = Ti, dissociative; M = Zr, associative [6]. In the case of the titanocene alkyne complexes, the dissociative route has been additionally supported by the recent reports of the first examples of free titanocenes by Lawless [7] and Mach [8a], who used the complex with bis(trimethylsilyl)-acetylene $[\eta^5\text{-}C_5Me_4(SiMe_3)]_2Ti(\eta^2\text{-}Me_3SiC_2SiMe_3)$ to generate the free titanocene $[\eta^5\text{-}C_5Me_4(SiMe_3)]_2Ti$. Interestingly, it is impossible to prepare this complex starting from $[\eta^5\text{-}C_5Me_4(SiMe_3)]_2TiCl_2$ by reduction with magnesium because coupling reactions of the substituted Cp ligands predominate [8b]. This nice example illustrates very well the potential of choosing the route via the bis(trimethylsilyl)acetylene complexes.

10.2
Reactions of Titanocene and Zirconocene Sources

Group 4 metallocenes are important as catalysts in the stereospecific polymerization of alkenes. Consequently, alkenes have been the most extensively studied substrates in reactions with metallocenes.

In the context of "modern acetylene chemistry", which serves a variety of implementations, for example new materials, special polymers, nanostructures, and supramolecular



Scheme 10.2. Combination of different functional groups to generate further substrates for investigation.

structures, substrates with C–C triple bonds have been increasingly well investigated. This includes mono-alkynes as well as linear and branched di-, oligo-, and polyynes.

Heteroalkenes themselves, or in combination with triple or double bonds, provide a broad variety of substrates. By combination of different functional groups, a more or less formal construction set for different substrates becomes available.

On the basis of these considerations, it is possible to classify and to understand the potential of metallocene-assisted reactions for organic syntheses. Additionally, it is possible to investigate which functional groups are tolerated in a considered reaction.

As mentioned above, the broad chemistry of titanocene and zirconocene has been described in many reviews [1].

This work is focused on unusual reactions of the novel metallocene reagents $Cp_2M(L)(\eta^2\text{-}Me_3SiC_2SiMe_3)$, which often give very clean organometallic elemental reactions, as the basis for applications in organic synthesis.

10.2.1
Acetylenes –C≡C–

Internal RC≡CR Symmetrically disubstituted acetylenes such as tolane PhC≡CPh react with complex **1** by substitution of the bis(trimethylsilyl)acetylene with formation of the metallacyclopentadiene **7** [2a,2d].

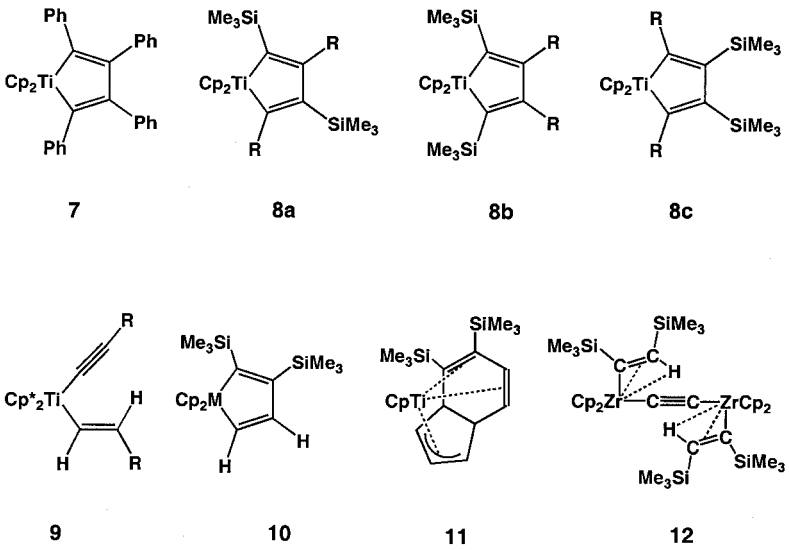
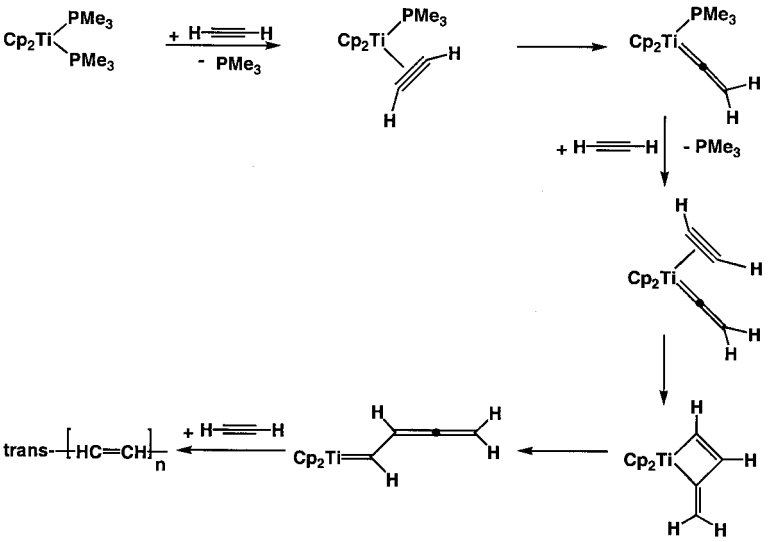


Figure 10.2. Products obtained with acetylenes.

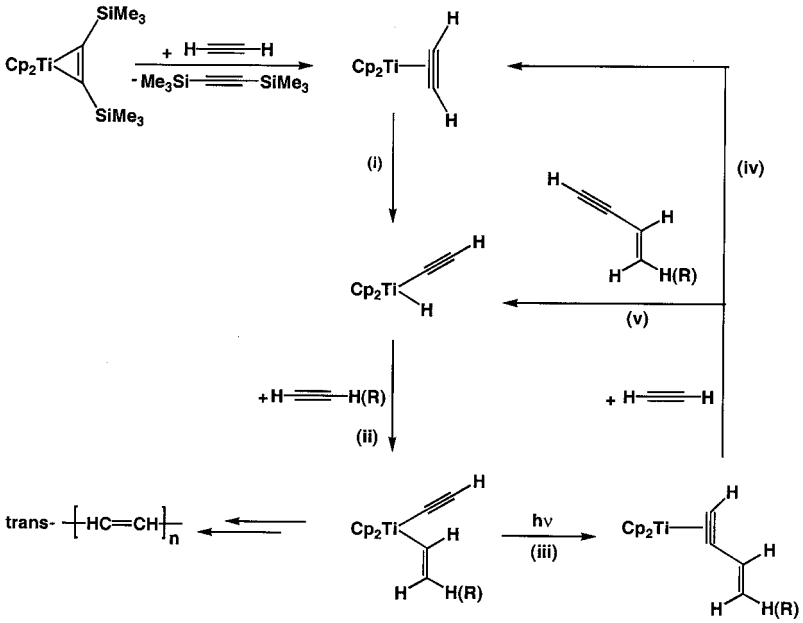
Using the unsymmetrically substituted acetylene $Me_3SiC{\equiv}CPh$, the kinetically favored substituted complex **8a** is formed initially, cycloreversion of which gives the symmetrically substituted and thermodynamically more stable product **8b**. Due to steric reasons, the other conceivable symmetric product **8c** is not formed [9]. Such metallacycles are typically very stable compounds and are frequently used in organic synthesis, as shown by the detailed investigations of Negishi and Takahashi [1m]. Bis(trimethylsilyl)acetylene complexes are a new and synthetically useful alternative.

Terminal RC≡CH Monosubstituted acetylenes of the type RC≡CH can also react with complex **1** by substitution of the bis(trimethylsilyl)acetylene with formation of metallacyclopentadienes. Due to the C−H acidity, the reaction of RC≡CH (R = Me_3Si, C_7H_9, $C_{10}H_{21}$) with complex **3** to give permethyltitanocene-1-alkenyl-acetylides **9** is more important [10]. The formation of such complexes involves substitution of $Me_3SiC{\equiv}CSiMe_3$ by RC≡CH, oxidation of the formed $Cp^*_2Ti(\eta^2\text{-}RC_2H)$ to the titanocene-hydrido-acetylide $[Cp^*_2Ti(H)(C{\equiv}CR)]$, and subsequent insertion of a further molecule of RC≡CH to yield $Cp^*_2Ti(\eta^1\text{-}(E)\text{-}CH{=}CHR)(\eta^1\text{-}C{\equiv}CR)$ (**9**). Mach has recently shown that such complexes undergo a photochemical coupling reaction of the alkenyl and acetylide groups to give the 1,4-disubstituted but-1-en-3-yne titanocene complexes $Cp^*_2Ti(3,4\text{-}\eta^2\text{-}RC_2CH{=}CHR)$ [11a]. These complexes catalyze the rapid dimerization of terminal acetylenes to give 2,4-disubstituted but-1-en-3-ynes (head-to-tail dimers) [11].

Unsubstituted HC≡CH Reactions of titanocenes and zirconocenes with unsubstituted acetylene have been thoroughly investigated by Alt, mostly using the complex $Cp_2Ti(PMe_3)_2$ [12]. Complex **1** yields *trans*-polyacetylene from unsubstituted acetylene in pyridine, whereas complexes **2**–**4** are less active catalysts in this reaction [13]. Detailed NMR investigations have shown that in the reaction of complexes **1** and **2a** with acetylene at low temperature, the corresponding disubstituted metallacyclopentadienes **10** are formed besides *trans*-polyacetylene. Warming these reaction mixtures leads, in the case of titanium, to an unusual coupling of one Cp ligand with the diene unit with the formation of a dihydroindenyl system **11** [14]. In the case of zirconium, a dimeric complex with a bridging diacetylide group and an agostic 1-alkenyl ligand $\{Cp_2Zr[C(SiMe_3){=}CH(SiMe_3)]\}_2[\mu\text{-}\sigma(1,2)\text{-}C{\equiv}C]$ **12** is formed [14] (Fig. 10.2). Both complexes are important with regard to deactivation processes of the catalyst in the polymerization of acetylene.



Scheme 10.3. Mechanism of the polymerization of acetylene proposed by H. G. Alt [12].



Scheme 10.4. Suggestions for an alternative mechanism for the polymerization of acetylene.

The combination of these findings with the aforementioned results of Beckhaus, Rosenthal, and Mach may also be interpreted in terms of an alternative mechanism for the polymerization of acetylene, which differs from that of Alt [12] (Scheme 10.3). In the absence of coupling, as in **11**, or of twofold C−H activation as found in **12**, the steps after substitution of $Me_3SiC{\equiv}CSiMe_3$ by HC≡CH and formation of $Cp_2Ti(\eta^2\text{-}HC_2H)$ are: (i) oxidative addition to give the hydrido-acetylide $Cp_2Ti(H)(C{\equiv}CH)$, (ii) insertion of a further molecule of HC≡CH to yield $Cp_2Ti(-CH{=}CH_2)(-C{\equiv}CH)$, (iii) coupling to give $Cp_2Ti(3,4\text{-}\eta^2\text{-}HC_2CH{=}CH_2)$, (iv) substitution of vinylacetylene $HC_2CH{=}CH_2$ by HC≡CH with formation of $Cp_2Ti(\eta^2\text{-}HC_2H)$ and $Cp_2Ti(H)(C{\equiv}CH)$, (v) insertion of $HC_2CH{=}CH_2$ into the newly formed $Cp_2Ti(H)(C{\equiv}CH)$ to yield $Cp_2Ti(-CH{=}CH-CH{=}CH_2)(-C{\equiv}CH)$, coupling to give $Cp_2Ti(3,4\text{-}\eta^2\text{-}HC_2CH{=}CH-CH{=}CH_2)$, and repetition of this sequence (Scheme 10.4). Thus, by an iterative process consisting of substitution, oxidative addition, and coupling, *trans*-polyacetylene is also obtained. These mechanistic suggestions, which are based on an adaptation of results relating to the dimerization of a terminal acetylene [11b] to the unsubstituted acetylene, can be combined with the various steps of Alt's mechanism.

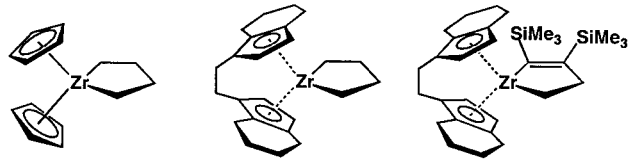
10.3
Alkenes >C=C<

The manifold chemistry of alkenes with titanocenes and zirconocenes has been reviewed in detail in some of the above mentioned contributions [1]. The reactions of the metallocene sources **1**−**6** with alkenes have only been investigated with regard to the specific question as to whether or not complexes or coupling products could be obtained.

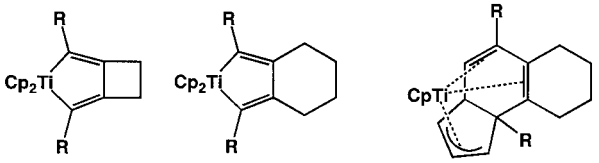
Internal RCH=CHR 2-Hexene $MeCH{=}CHC_3H_7$ is not isomerized by complex **1** to 1- or 3-hexene, nor is its *cis*:*trans* ratio changed. No olefin complexes or coupling products are obtained. The corresponding zirconocene complexes **2** likewise did not show any isomerization activity [15].

Terminal RCH=CH$_2$ 1-Hexene $C_4H_9CH{=}CH_2$ is isomerized by complex **1** in accordance with the factors influencing the thermodynamic stability of *cis*- and *trans*-2-hexene [15]. At the end of the reaction, the alkyne complex **1** was recovered almost quantitatively. No alkene complexes or coupling products were obtained. The corresponding zirconocene complex **2a** did not show any isomerization activity. Propene $CH_3CH{=}CH_2$ reacts with complex **6** with substitution of the alkyne and the formation of zirconacyclopentanes as coupling products, the structures of which are non-uniform [16].

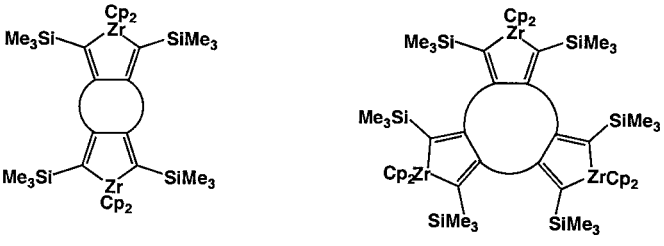
Unsubstituted H$_2$C=CH$_2$ Upon reaction with complexes **2a** or **6**, ethene gives zirconacyclopentanes such as **13** and **14** [16]. The formation of these compounds proceeds at low temperature via zirconacyclopentenes **15**, which disproportionate at room temperature to the starting alkyne complex and complex **14**. The latter is formed quantitatively in the reaction of **15** with ethene.



13 14 15



16a 16b 17



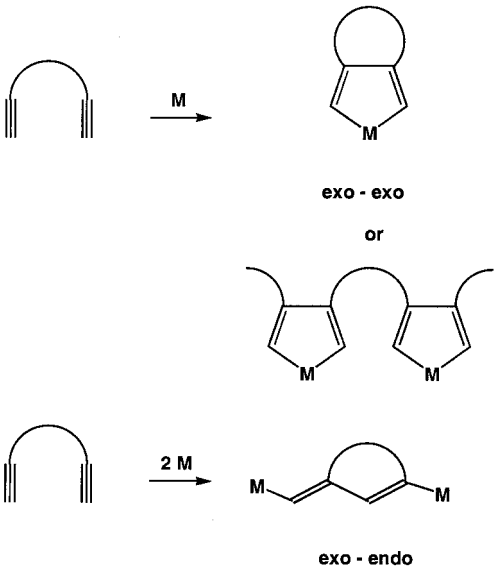
18a 18b

Figure 10.3. Selected examples of products obtained with ethene and non-conjugated diynes.

10.4 Diacetylenes

10.4.1 Non-Conjugated C≡C−X−C≡C

Coupling reactions of non-conjugated α,ω-diynes have been systematically classified by Tamao [17].



Scheme 10.5. System for different coupling reactions of non-conjugated diynes proposed by K. Tamao [17].

For titanocene and zirconocene derivatives, Negishi [1a] and Nugent [1b] were the first to establish this chemistry. Reactions of complex **1** with various α,ω-diynes $RC{\equiv}C(CH_2)_nC{\equiv}CR$ give, after substitution of the bis(trimethylsilyl)acetylene and subsequent intramolecular cyclization, bicyclic titanacyclopentadienes **16** [18a]. The spacer length determines the stability of the obtained product. Using other systems, Farona succeeded in synthesizing tricyclic compounds starting from $RC{\equiv}C{-}CH_2{-}C{\equiv}CR$ and zirconocene [18b]. The obtained titanium compounds, such as **16a/16b**, are stable for $n = 2$ and 4, but decompose for $n = 5$ to undefined products. For $n = 4$, the initially obtained complex rearranges by C−C cleavage of the C-ligand and intramolecular coupling to give the stable tricyclic η^4,η^3-dihydroindenyl titanium complex **17** [18a], which is similar to the aforementioned complex **11** and to compound **56** (vide infra).

Tilley established a new zirconocene-coupling route to poly-, cyclodi-, tri-, and tetramers, as well as to large functionalized macrocycles [2j,19]. Well-defined cyclooligomerizations of some phenylene-bridged diynes such as $Me_3SiC{\equiv}C(C_6H_4)_nC{\equiv}CSiMe_3$, $n = 2{-}4$; $Me_3SiC{\equiv}CC_6H_4{-}C_5H_3N{-}C_5H_3N{-}C_6H_4C{\equiv}CSiMe$, and $Me_3SiC{\equiv}C{-}C_5H_3N{-}C_5H_3N{-}C{\equiv}CSiMe_3$ yielding dimers **18a** and trimers **18b** with high regioselectivities were achieved using complex **2b** $Cp_2Zr(pyridine)(Me_3SiC_2SiMe_3)$ [2j].

10.4.2
Conjugated C≡C−C≡C

The nature of the products obtained from the reactions of 1,4-disubstituted 1,3-butadiynes with metallocene sources **1**−**6** depends strongly on the Cp ligands, the metal, the stoichiometry, and the reaction conditions used [3]. Generally, after elimination of the bis(trimethylsilyl)acetylene, different modes of complexation ensue. Cleavage of the butadiynes, reverse coupling with the formation of other butadiynes, or different coupling reactions of two butadiynes in the coordination sphere of one metal or between two metals may be observed as the fundamental follow-up reaction types. With complexes **3** and **4**, these reactions do not proceed, but the permethylmetallocene cores may be generated by using the chlorides $Cp^*_2MCl_2$ and magnesium. In these cases, different types of complexation or coupling reactions of the pentamethylcyclopentadienyl ligand with the butadiynes are observed. In view of the fact that the main products of these reactions have been summarized in several reviews [1r,3], herein we give only a summary of the more general aspects of this chemistry.

Complexation of 1,3-butadiynes In the reactions of complex **1** with various butadiynes, binuclear complexes with intact C_4 units between the two metal centers are found. The former diynes are transformed to "zig-zag butadiene ligands" or μ-η(1-3),η(2-4)-*trans*,-*trans*-tetradehydrobutadiene moieties between two metallocene cores. The bond type in **19** is unknown for the corresponding zirconocene complexes.

Besides this 2:1 complexation of the titanocene, a 1:1 complexation [3,20] may also be observed by employing a different stoichiometry. The butadiynes RC≡CC≡CR with R = *t*Bu and Ph generate the novel five-membered titanacyclocumulenes (metallacyclopenta-2,3,4-trienes; η^4-butadiyne complexes) **20** [3,21a]. For R = *t*Bu, this structural type could also be realized with M = Zr [3,21b]. The corresponding five-membered hetarynes had been hypothesized as reactive intermediates by Wittig in the early 1960s [22a]. More recently, such 3,3-didehydrothiophenes and -pyrroles have been discussed by Wong, who was able to trap the first compound following reactions with several alkenes [22b,22c].

Metallacyclocumulenes Five-membered metallacyclocumulenes **20** are very unusual. They are the smallest discrete cyclocumulenes to be isolated and structurally characterized. The structures of titana- and zirconacyclocumulenes show an almost planar arrangement of the metallacycle, containing three C−C double bonds, of which the central one is elongated. This elongation is ascribed to the intramolecular interaction of this bond with the metal center, which stabilizes this type of complex [21].

The distances and angles (70−74° at C-α and 147−150° at C-β) in the metallacycle correspond closely to those calculated for organic cyclocumulenes such as cyclohexa- and cycloheptatrienes [23]. According to other theoretical calculations, titana- and zirconacyclocumulenes are thermodynamically more stable than the isomeric bis(σ-acetylide) complexes [24]. The calculated data are in good agreement with the obtained experimental values. All four carbon atoms of the former diyne are viewed as having p orbitals perpendicular to the plane of the cyclocumulene. The sp-hybridized internal C atoms possess additional p orbitals in that plane, which are used to establish a coordination of the relevant bond to the metal center.

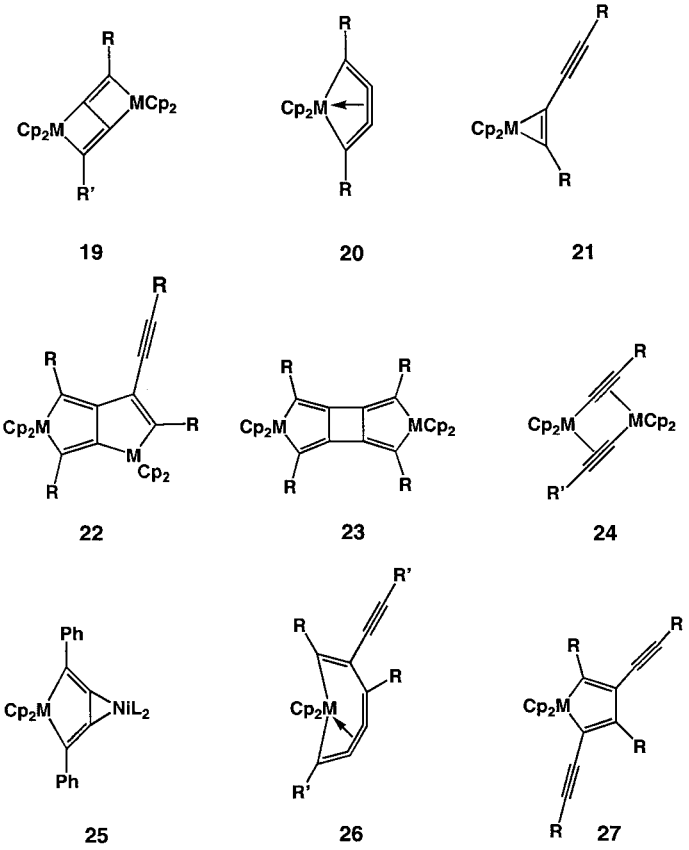
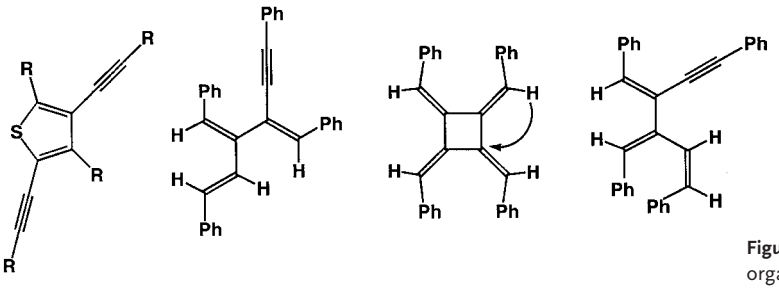


Figure 10.4. Overview of different products obtained with 1,3-butadiynes.

Reactions of the metallacyclocumulenes Some reactions of the metallacyclocumulenes are suggestive of an equilibrium between a η^4-complex (metallacyclocumulene) and a η^2-complex **21** (metallacyclopropene) [25]. Evidently, the two forms present in the equilibrium mixture can even react with each other to afford an unsymmetrical complex **22**, in which a titanacyclopentadiene is anellated to a titanacyclopentene [25]. The formation of **22** can be rationalized in terms of the insertion of the internal double bond of the titanacyclocumulene into the titanacyclopropene. Additionally, the symmetrical titanium-substituted radialene **23** is generated in the same solution [26]. This can be thought of as the product of a formal dimerization of two titanacyclocumulene molecules. Interaction of the metallacyclocumulenes **20** with additional titanocene or zirconocene sources **1**–**2c** gives either complexes with intact diynes **19** or results in C–C single-bond cleavage to give twofold σ,π-alkynyl-bridged metal(III) complexes **24**. Conversions with nickel(0) complexes show a marked dependence on the substituents R. For M = Ti or Zr and R = Ph, π-complexes of the corresponding metallacyclocumulenes are formed, which can be regarded as Ni(0)-olefin complexes **25** with two Ph_3P ligands [27]. These compounds are especially significant for two reasons. On one hand, the homobimetallic analogues of these compounds can be viewed as intermediates in the reaction leading to the two different 2:1 complexes (cleavage and complexation reaction). On the other hand, they provide unequivocal proof of the metallacyclocumulene structure of the η^4-complex. Mean-

while, π-complexes of other metals with such metallacyclocumulenes have also recently been described [28].

Coupling reactions of 1,3-butadiynes The reaction of bis(trimethylsilyl)butadiyne with zirconocene leads to a coupling product of two diyne entities at the core complex with formation of a seven-membered zirconacyclocumulene **26** (zirconacyclo-hepta-2,4,5,6-tetraene) (Fig. 10.4). Under analogous conditions with titanocene and employing two equivalents of the diyne, a regioselective coupling of the diynes to titanacyclopentadienes **27** is observed, which places one alkynyl group in a position α and the other in a position β to the metal. Both complexes react selectively with sulfur monochloride to give an identically substituted thiophene **28** [29] (Fig. 10.5).



28 **29** **30** **31**

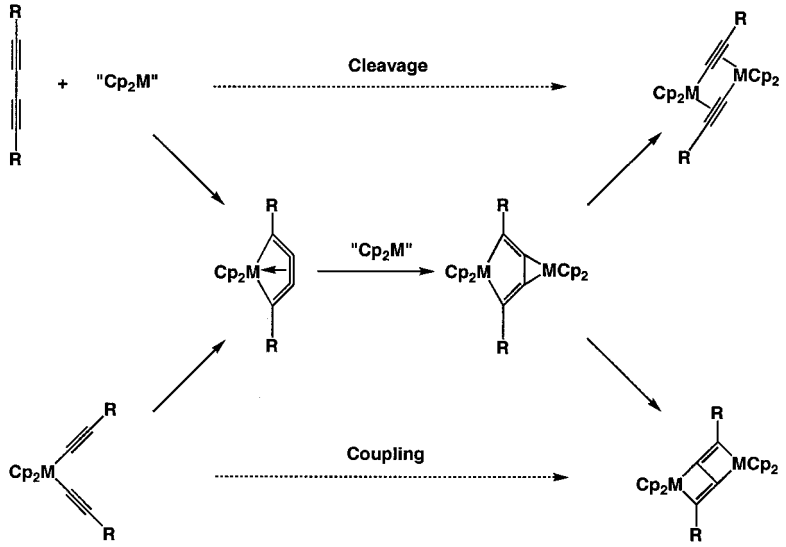
Figure 10.5. Selected organic products obtained from 1,3-butadiynes.

In addition to the previously described coupling of two diynes at a single metal center, there are examples of coupling reactions of two diynes between two metallocene fragments (complexes **22** and **23**). Acidolysis of complex **22** gives the *trans*-3,4-dibenzylidene-1,6-diphenyl-1-hexen-5-yne **29** [26]. The corresponding reaction of complex **23** (Fig. 10.4) does not lead to the expected radialene **30**, which seems to be unstable, but forms, after an H-shift, the *cis*-3,4-dibenzylidene-1,6-diphenyl-1-hexen-5-yne **31** (Fig. 10.5) [26].

Single-bond cleavage in 1,3-butadiynes Only a change in the stoichiometry can alter the reaction course; thus, cleavage products are favored if two equivalents of the metallocene are reacted with certain diynes. The generated products are, from a formal point of view, twofold σ,π-alkynyl-bridged metal(III) complexes. These were known previously, but had been synthesized by a different route. C−C single-bond activation accompanied by cleavage has provided a novel route to these compounds starting from 1,3-butadiynes. This type of cleavage reaction is favored for M = Zr as compared to Ti, an observation that is supported by theoretical calculations [30]. Additionally, the substituents R attached to the butadiynes RC≡C−C≡CR exert a strong influence, as exemplified by the trimethylsilyl group, which significantly activates the inner C−C single bond due to its β effect.

Photochemical investigations When a solution of the complex $Cp_2Ti(\sigma\text{-}C{\equiv}C\mathit{t}Bu)_2$ is irradiated, NMR spectroscopic monitoring shows that a titanacyclocumulene is first generated, and that this species then reacts with a further equivalent of titanocene to yield the dinuclear complex with μ-η(1-3),η(2-4)-*trans,trans*-butadiene units between the two

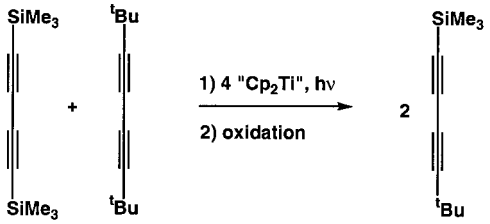
metallocene cores **19** (Fig. 10.4) [27]. This reaction cannot be used preparatively to synthesize the corresponding titanacyclocumulene, as this compound is only a non-isolable intermediate under these reaction conditions. By taking into account all these results, a general reaction scheme is deduced, whereby both the cleavage and the coupling to 1,3-butadiynes can be rationalized as a logical sequence of events [3,24].



Scheme 10.6. General scheme for alkynyl coupling and 1,3-diyne cleavage reactions via metallacyclocumulenes.

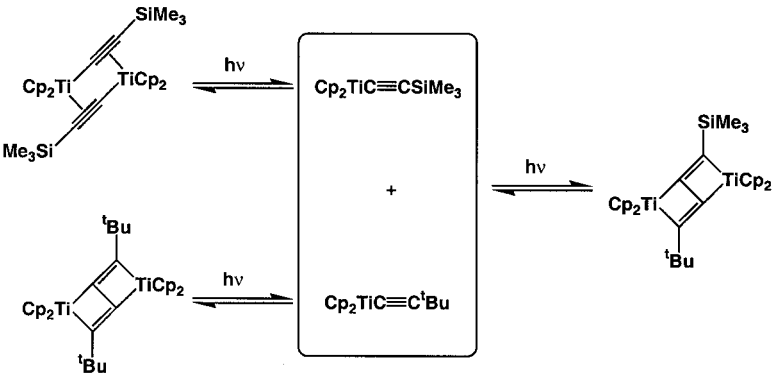
According to this scheme, both the cleavage and the coupling proceed via metallacyclocumulenes, in which the *intra*molecular coordination of the inner double bond is ultimately replaced by an *inter*molecular coordination. These intermediates then rearrange, depending on the metal M and the substituents R, to afford products in which either an intact or a cleaved C_4 linkage is present. The individual energy levels of these and comparable complexes, as well as of the proposed intermediates, have been determined by thorough calculations, and the results confirm the relative thermodynamic stabilities as observed experimentally. Thus, these theoretical results emphatically support the postulated reaction course.

Photocatalytic C–C single-bond metathesis Cleavage of symmetrically substituted butadiynes in combination with a subsequent alternating recombination of the fragments constitutes a C–C single-bond metathesis.



Scheme 10.7. Titanocene-mediated, photocatalyzed C–C single-bond metathesis with 1,3-disubstituted butadiynes.

It is of special note in this context that the first C−C single-bond metathesis reaction ever published has very recently been described using paraffins and immobilized TaH catalysts [31]. If an equimolar mixture of the butadiynes *t*BuC≡C−C≡C*t*Bu and $Me_3SiC{\equiv}C{-}C{\equiv}CSiMe_3$ is treated with an excess of the "Cp_2Ti" reagent and the mixture is then irradiated, the unsymmetrically substituted diyne $tBuC{\equiv}C{-}C{\equiv}CSiMe_3$ is obtained after oxidative work-up, along with the symmetrically substituted starting diynes [32]. The observed reaction does not proceed without titanocene. Without irradiation, higher temperatures are required and a considerable increase in decomposition reactions is observed. The reaction thus represents the first titanocene-mediated, photocatalyzed C−C single-bond metathesis in homogeneous solution. With regard to the metal, this metathesis cannot be conducted catalytically since an excess of the diyne would favor coupling reactions and the coupled complexes would predominate in the product mixture (see above). The course of reaction can be formulated in such a way that the titanocene reacts with *t*BuC≡C−C≡C*t*Bu to give the binuclear complex with an intact C_4 backbone, and with $Me_3SiC{\equiv}C{-}C{\equiv}CSiMe_3$ to give the σ,π-alkynyl-bridged cleavage product.



Scheme 10.8. Proposed mechanism for C−C single-bond metathesis through monomeric titanocene(III) monoacetylides.

Under the influence of light, both 2:1 complexes are subsequently cleaved to the extremely unstable monomeric Ti(III) complexes $[Cp_2Ti(\sigma\text{-}C{\equiv}Ct\text{Bu})]$ and $[Cp_2Ti(\sigma\text{-}C{\equiv}CSiMe_3)]$, which then dimerize to either the respective starting complexes or, in the desired way, to a differently substituted binuclear complex. The reverse reaction can also be realized.

Permethylzirconocene and 1,3-butadiynes The unstable monomeric Ti(III) complexes $[Cp_2Ti(\sigma\text{-}C{\equiv}CR)]$ seem to play a key role in the reaction sequence of our metathesis process. For this reason, the stable M(IV) complexes $Cp^*_2M(\sigma\text{-}C{\equiv}CR)_2$ (M = Ti, Zr; R = Ph, *t*Bu, $SiMe_3$) were synthesized, reduction of which, as is well-known for the analogous Cp complexes, was expected to lead to the target compounds. However, on performing these studies, it became apparent that for M = Zr and R = Ph, $SiMe_3$, these complexes rearrange very easily in sunlight to give the zirconacyclocumulenes **32** [20].

Compounds **32** could also be prepared by the reduction of $Cp^*_2ZrCl_2$ with magnesium in the presence of the butadiynes $RC{\equiv}C{-}C{\equiv}CR$ (R = Me, Ph, $SiMe_3$). The corresponding titanacyclocumulenes could not be prepared by either of the described methods. For

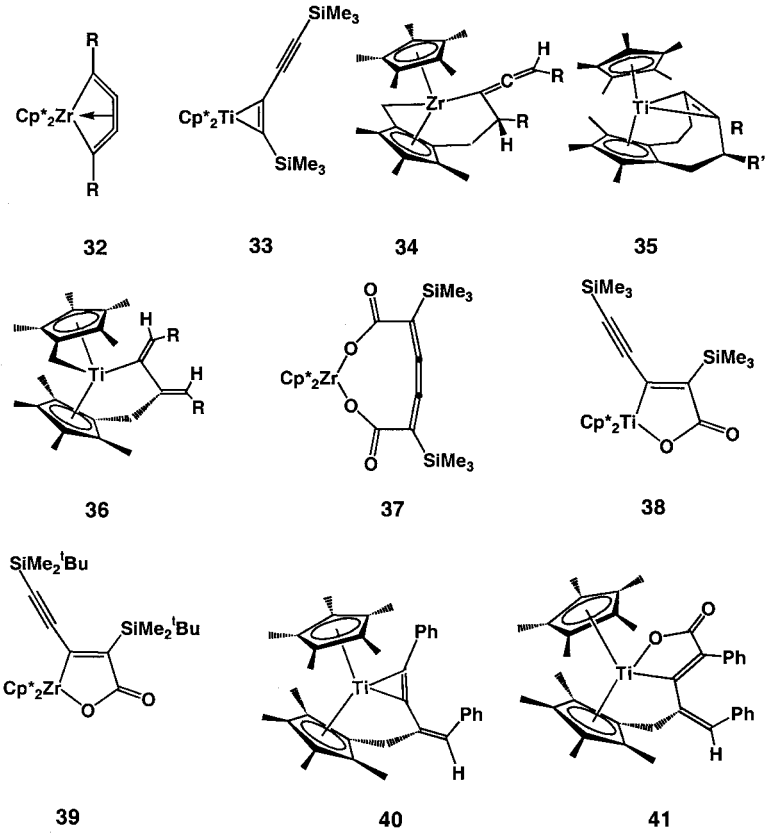
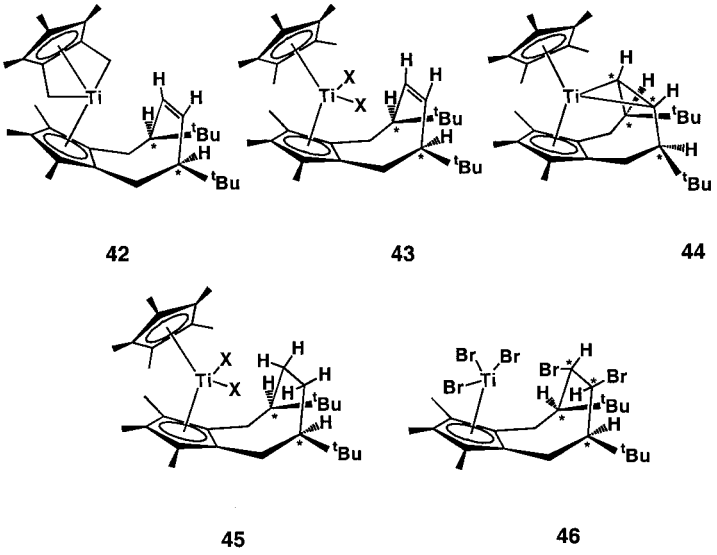


Figure 10.6. Products obtained from permethyltitanocene and permethylzirconocene with 1,3-butadiynes.

Cp^*_2Ti with R = $SiMe_3$, under the same conditions, the titanacyclopropene **33** was formed. Attempted exchange reactions starting from complexes **3** and **4** and the butadiynes failed, probably due to steric reasons. Manifold C–H activation of the methyl groups of the pentamethylcyclopentadienyl ligand and C–C couplings with particular diynes have been verified for M = Zr, R = *t*Bu (**34**); M = Ti, R = *t*Bu (**35**), and M = Ti, R = Me, Ph (**36**) [20]. These reactions depend on the metal M used and the substituents R. They are, however, worthless with regard to the synthesis of metallacyclocumulenes and cannot be applied in catalytic C–C single-bond metatheses. On the other hand, some consecutive reactions of the coupling products of permethylmetallocene complexes with butadiynes are very interesting. The products obtained were unexpected, but nevertheless very useful for further synthesis. The zirconacyclocumulene (η^4 complex) **32** with R = $SiMe_3$ takes up two molecules of CO_2, thereby forming the cumulenic dicarboxylate **37** [20]. The titanacyclopropene (η^2 complex) **33** inserts only one molecule of CO_2 with the formation of a titanafuranone **38**. The insertion of a second molecule of CO_2 into complexes **32** can also be prevented by employing the sterically demanding *t*$BuMe_2Si$ substituent on the diyne. In this case, complex **39** was obtained. The stabilities and reactivities of five-membered metallacyclocumulenes appear to be strongly influenced by steric factors. These may originate from the steric demand of the Cp or Cp* ligand, the size of the metal, or the substituents

attached to the diyne. Complex **36** seems to be in equilibrium with **40**, which can insert CO_2 to give **41**.

Another coupling product, **42**, has been obtained by thermally induced replacement of the coordinated alkyne in the permethyltitanocene source **3** by the butadiyne *t*BuC≡C−C≡C*t*Bu [33, 34].



42 **43** **44**

45 **46**

Figure 10.7. Examples of the functionalization of permethyltitanocene.

In this reaction, complex **35** has to be regarded as an intermediate, since a direct conversion of **35** into **42** is also possible. Further functionalizations of these complexes with simple reagents such as hydrogen chloride, bromine, or dihydrogen afford the novel and easily applicable chiral derivatives **43**−**46** [34].

All the chemistry ensues from the reduction of the commercially available permethyltitanocene dichloride $Cp^*_2TiCl_2$ by magnesium, which, in the presence of *t*BuC≡C−C≡C*t*Bu, gives the coupled alkyne compound **35**, and, in the presence of $Me_3SiC{\equiv}CSiMe_3$, the complex **3**. Subsequent thermolysis of **3** in the presence of *t*BuC≡C−C≡C*t*Bu yields the coupled complex **42**. Both complexes **35** and **42** react smoothly with two equivalents of HCl to yield the olefinic dichloride **43a** (X = Cl). The two protons are added either to the triple bond of **35** or to the two methylene groups of **42**. Importantly, complex **35** reacts quantitatively with molecular hydrogen to give the novel, intramolecularly coordinated titanocene−olefin complex **44**. This compound can also be obtained from **43a** by removal of the chlorine with magnesium. The reaction of **44** with HCl produces the paraffinic dichloride **45** in only a low yield; instead, complex **43** is formed, accompanied by hydrogen liberation. This implies that hydrogen addition to the double bond is less favorable than hydrogen elimination. Addition of a stoichiometric amount of elemental bromine to **44** affords the olefinic dibromide **43b** (X = Br). Complex **43a** (X = Cl), however, is unstable towards an excess of hydrogen chloride. NMR monitoring showed its slow conversion to a mixture of [Cp*$TiCl_3$] and {η^5-C_5Me_3[−CH_2CH(*t*Bu)CH=CHCH(*t*Bu)CH_2−]}$TiCl_3$]. The bromine analogues of these two complexes **46** are produced as side products in the formation of complex **43b**.

10.5 Dialkenes

10.5.1 Non-Conjugated C=C–X–C=C

1,5-Hexadiene $H_2C{=}CHCH_2CH_2CH{=}CH_2$ is isomerized at room temperature by complex **1** to (*E*,*E*)- and (*E*,*Z*)-2,4-hexadiene [15]. At the end of the reaction, the alkyne complex **1** can be isolated almost quantitatively and no alkene complexes or coupling products are obtained. In contrast, the corresponding zirconocene complex **2a** does not show any isomerization activity. Complex **1** isomerizes 1,4-cyclohexadiene to 1,3-cyclohexadiene at 60 °C, but this is accompanied by hydrogen transfer yielding benzene and cyclohexene as a competing reaction. For the corresponding zirconocene complexes **2a** and **2b**, a lower isomerization activity is found due to the more favored hydrogen-transfer reaction.

10.5.2 Conjugated C=C–C=C

1,3-Cyclohexadiene is isomerized by complex **1** at 60 °C to 1,4-cyclohexadiene, again with hydrogen transfer as a side reaction [15]. In contrast to the isomerization of aliphatic alkenes, the isomerization of cyclohexadienes seems, in principle, to be reversible. This is a specific feature of cyclohexadienes, since in acyclic systems or larger cycles the conjugated isomer is more stable than the non-conjugated one. The corresponding zirconocene complexes **2a** and **2b** give only the hydrogen-transfer reaction and no isomerization.

trans-Stilbene PhCH=CHPh does not react with complex **6**, whereas *cis*-stilbene is quickly isomerized to *trans*-stilbene. 1,1-Diphenylethylene $Ph_2C{=}CH_2$ does not react at all with complex **6** [16].

10.6 Double Bonds to Heteroatoms >C=X(–)

10.6.1 Carbonyl Compounds C=O

No defined complexes could be isolated from reactions of complex **1** with acetone $Me_2C{=}O$. Complexes **2a** and **2b** react with acetone to give the zirconafuranone **2c**, which is an interesting zirconocene precursor in view of its extremely good solubility in hydrocarbon solvents and because of its ability to dissociate into the alkyne complex [2f]. It is also possible to cleanly substitute the bis(trimethylsilyl)acetylene unit so as to obtain the complex **47**, or, alternatively, to substitute the acetone with formation of the zirconafuranone **95** (Fig. 10.14) [2f].

No products could be isolated from the reaction of **1** with formaldehyde, whereas with **2a** or **2b** the dimeric zirconafuranone **48** was formed [35].

Complexes such as **2** and **6** also insert into cyclic ketones, lactones, and carbonates to form complexes **49**–**51** [36].

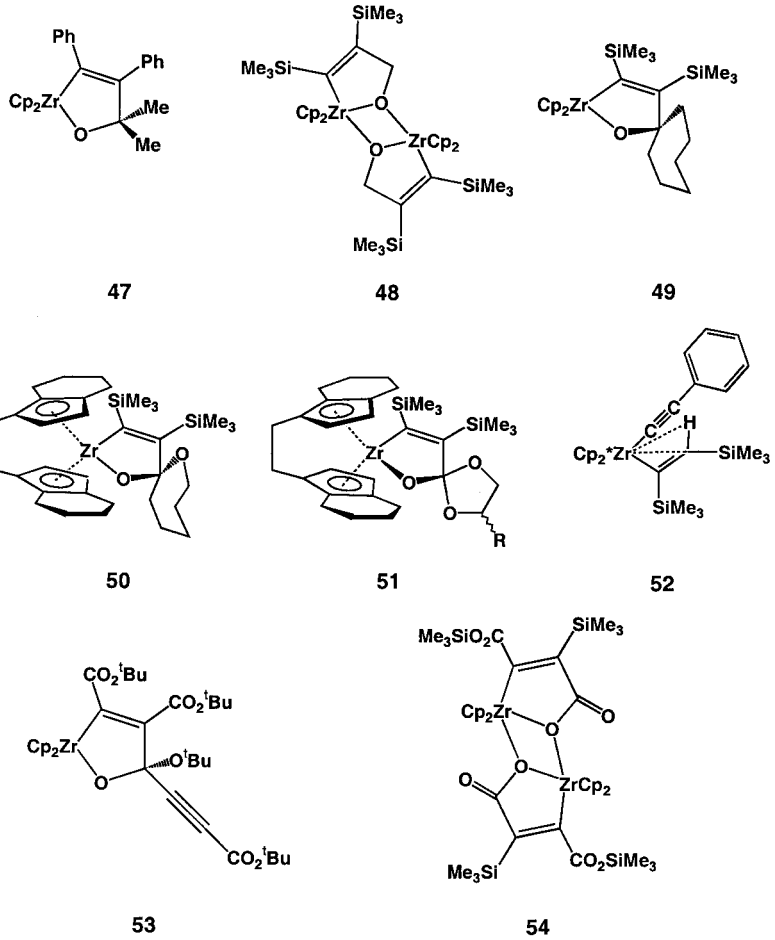


Figure 10.8. Products obtained with carbonyl compounds and phenylacetylene.

10.6.2
Imines C=N

Other substrates with C=N double bonds frequently used in organic synthesis, such as aldimines and ketimines, will be considered in Section 10.7.5.

10.7
Selected Combinations of Functional Groups

More or less formal combinations of the aforementioned functional groups allow us to extend the concept and application of these basic organometallic reactions to more complicated organic substrates. Additionally, these investigations can provide more information about which groups are tolerated in a particular reaction situation as well as to find new reactions for organic synthesis.

10.7.1
C≡C–C=C

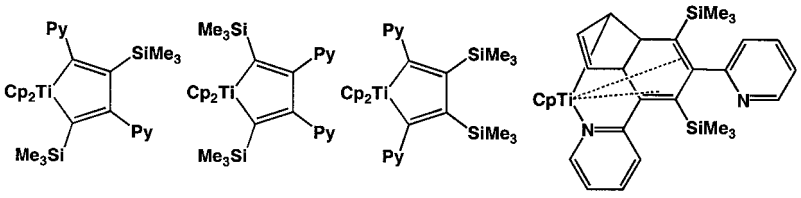
In analogy to the aforementioned reactions of alkylacetylenes, phenylacetylene reacts with complex **3** to give $Cp^*_2Ti(\eta^1\text{-}(E)\text{-}CH{=}CHPh)(\eta^1\text{-}C{\equiv}CPh)$ (**9**) [10]. In the corresponding reaction starting from complex **4** and phenylacetylene, no elimination of the alkyne is observed, but the complex $Cp^*_2Zr[C(SiMe_3){=}CH(SiMe_3)](\eta^1\text{-}C{\equiv}CPh)$ (**52**) is formed [14]. This is in good agreement with the reactions of acetylene discussed above.

10.7.2
C≡C–C=O

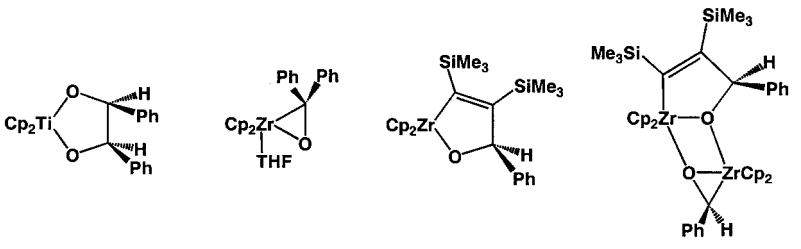
When dimethylacetylenedicarboxylates are treated with titanocene and zirconocene sources, the reactions depend strongly on the system used as well as on the substituents. The complex $Cp_2Ti(CO)_2$ reacts with $MeO_2CC{\equiv}CCO_2Me$ under drastic conditions with elimination of CO through the coupling of two triple bonds to give the expected titanacyclopentadiene of type **7** [37a]. Using **2b** and $tBuO_2CC{\equiv}CCO_2tBu$, elimination of the alkyne and coupling of one triple bond and one ester carbonyl group is observed (complex **53**). Under the same conditions, a stoichiometric reaction with $Me_3SiO_2CC{\equiv}CCO_2SiMe_3$ results in an unusual 1,3-migration of an Me_3Si group from oxygen to carbon with the formation of the dimeric complex **54** [37b].

10.7.3
C≡C–C=N

Reaction of the unsymmetrical substituted acetylene $Me_3SiC{\equiv}CPy$ with **1** yields, after substitution of the alkyne, the kinetically favored unsymmetrical substituted complex **55a** as well as the symmetrically substituted, thermodynamically more stable product **55b** [38].



55a **55b** **55c** **56**



57 **58** **59** **60**

Figure 10.9. Selected examples of products obtained with pyridyltrimethylsilylacetylene and carbonyl compounds.

Due to steric reasons, the symmetrical product **55c** is not formed. On standing in solution, complex **55a** undergoes the same unusual coupling of one Cp ligand with the diene unit with formation of a dihydroindenyl system **56** [38], as was described above for acetylene [14].

Complex **6** reacts with HC≡CPy in a similar manner as described above {akin to the reaction of complex **4** with HC≡CPh to form the complex $Cp^*_2Zr[C(SiMe_3)=CH(SiMe_3)](\eta^1\text{-}C\equiv CPh)$ (**52**)}, giving a complex with an agostic interaction, *rac*-$(ebthi)Zr[-C(SiMe_3)=CH(SiMe_3)](\eta^1\text{-}C\equiv CPy)$ [14].

10.7.4
C=C–C=O

Complex **1** reacts with benzaldehyde with elimination of bis(trimethylsilyl)acetylene to produce the titanadioxacyclopentane **57** [39]. With benzophenone or formaldehyde, no products are isolated [35].

The reactions of complex **2a** with ketones and aldehydes show a strong dependence on the substituents. With benzophenone, substitution of the silyl-substituted acetylene leads to the η^2-complex **58**, which is additionally stabilized by a THF ligand. This complex can serve as an interesting starting material for other reactions. With benzaldehyde and acetophenone, the typical zirconadihydrofuran **59**, akin to **2c**, is obtained from a coupling reaction. This complex is unstable in the case of benzaldehyde and dimerizes, after elimination of bis(trimethylsilyl)acetylene, to yield **60**. In this respect, it is similar to the above discussed complex **2c**, since both of them show a tendency to eliminate the bis(trimethylsilyl)acetylene. The reaction of methacrolein with complex **2a** depends strongly on the solvent used [40].

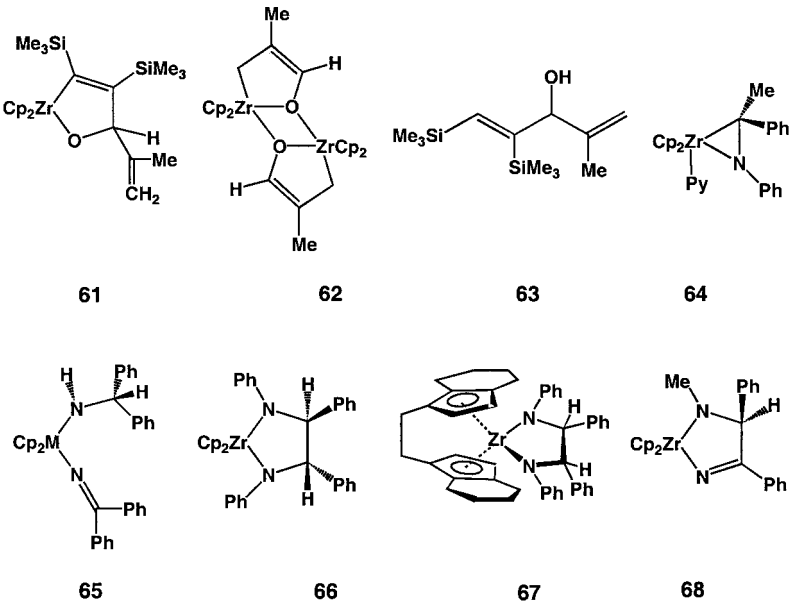


Figure 10.10. Products obtained with methacrolein, ketimines, and aldimines.

In THF, insertion into **2a** with the formation of complex **61** is found, whereas in *n*-hexane, elimination of the bis(trimethylsilyl)acetylene leads to the formation of **62**. With acids, the dialkene **63** is liberated from complex **61**.

10.7.5
C=C–C=N

Various phenyl-substituted ketimines and aldimines react with metallocenes **1** and **2**, in a manner that depends on the substituents present [41]. In all cases, elimination of the alkyne is observed. Complex **2b** reacts with PhN=CMePh to give the η^2-complex **64**, which is stabilized by an additional pyridine ligand [41a]. In the reactions of **1** or **2a** with the ketimine $HN{=}CPh_2$, hydrogen transfer generates complexes **65**. Two molecules of the aldimine PhN=CHPh are coupled by **2a** to give the cyclic diamido complex **66** [41b]. The corresponding complex **67** is formed using complex **6** [2h]. With the aldimine MeN=CHPh and complex **2a**, a similar complex eliminates methane with the formation of complex **68** [3a].

2-Vinylpyridine reacts with complexes **2** and **6** with the formation of complexes **69** and **70**, respectively; these are mono-azadienes, in which the aromaticity of the pyridine ring has been lost [42].

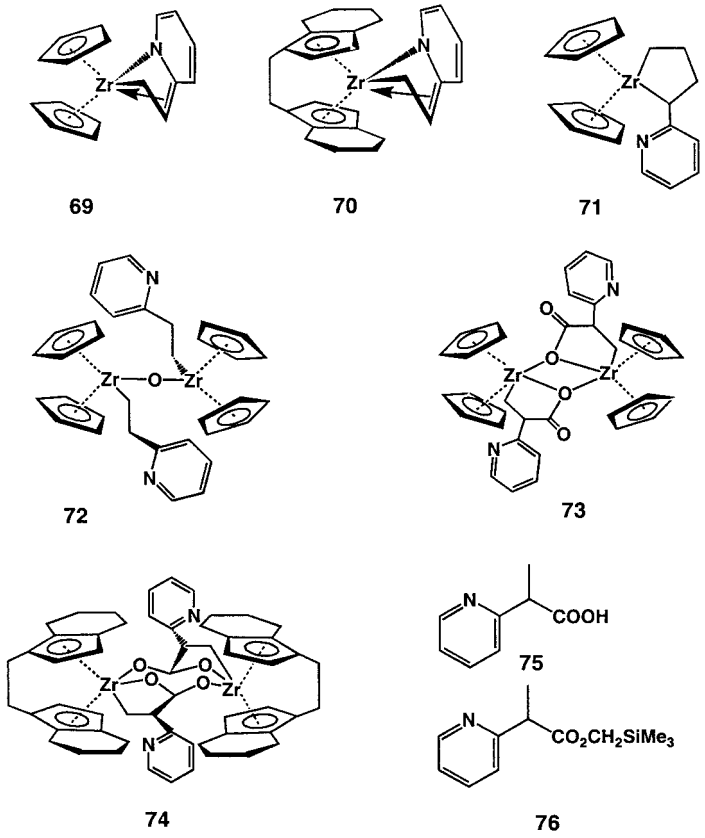


Figure 10.11. Overview of products obtained with 2-vinylpyridine.

These complexes show an interesting chemistry, e. g. they undergo coupling with ethene to give zirconacyclopentane **71** or with water to give zirconoxane **72**, or they can undergo insertion of carbon dioxide with formation of the complexes **73** and **74**. In all of these reactions, the pyridine moiety is restored. With acids, complex **73** liberates the corresponding carbonic acids **75** or esters **76**.

10.7.6
N=C–C=N

1,4-Diazabutadienes RN=CHCH=NR react with complexes **1** and **2** with liberation of the alkyne and formation of the corresponding diazadiene complexes **77** [43].

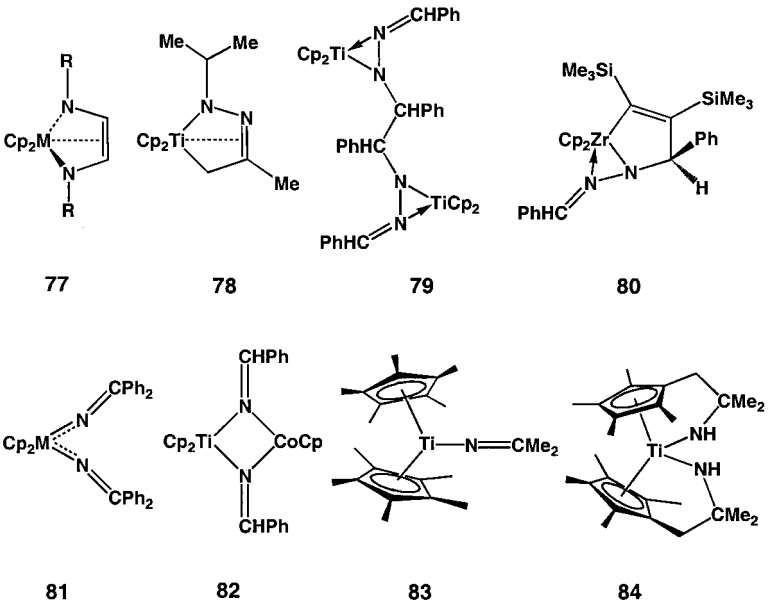


Figure 10.12. Selected examples of products obtained with 1,4- and 2,3-diazabutadienes.

This is a general and new method for obtaining 1-metalla-2,5-diazacyclopent-3-enes of titano- and zirconocenes in high yields.

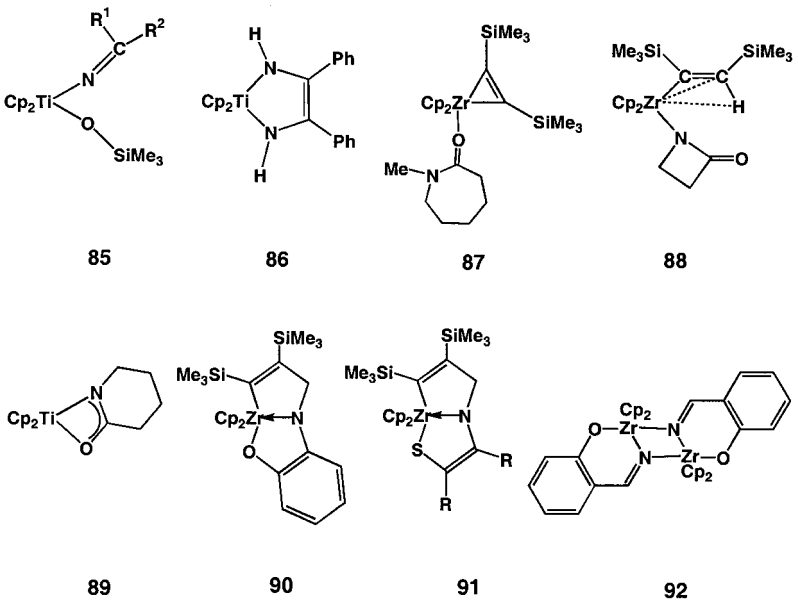
10.7.7
C=N–N=C

In the analogous reaction of differently substituted azines RR'C=NN=CRR', the products depend strongly on the metal used (Ti and Zr) as well as on the substituents R and R' [43]. With R = R' = Me and M = Ti, substitution of the alkyne by the azine and subsequent CH activation of the complex **78** is observed. With R = Ph and R' = H, the acetylene is also substituted and, through a reductive coupling of two azine molecules, the binuclear Ti(III) complex **79** is formed. Using the zirconocene **2a**, and with azine substituents R = Ph and R' = H, no substitution of the alkyne is observed, but one of the C=N double bonds of the azine inserts into the Zr–C bond of the starting complex to yield complex **80**.

With R = R' = Ph and using complexes **1** or **2a**, the central N–N single bond of the azine is cleaved by both metals. In this case, the bis(imido) complexes **81** were formed, treatment of which with complexes such as $CpCo(C_2H_2)_2$ can give heterobimetallic bis(alkylideneamido)-bridged complexes such as **82**. Mach has used this concept for the reaction of methyl-substituted titanocenes with acetoneazine. With **3**, monomeric Ti(III) complexes **83** and, after activation of the methyl groups, coupled products such as **84** could be obtained [44].

10.8 Miscellaneous

Ketoximes and aldoximes Ketoximes and aldoximes are uniquely substituted C=N systems that react differently with titanocene and zirconocene. Aliphatic and alicyclic *O*-silylated ketoximes $R_2C{=}N{-}OSiMe_3$ react with complex **1** with elimination of the alkyne and N–O bond cleavage to give imido-silanolates **85** [45].



85 **86** **87** **88**

89 **90** **91** **92**

Figure 10.13. Products obtained with ketoximes, aldoximes, and selected heterocyclic compounds.

The corresponding aldoxime $PhCH{=}N{-}OSiMe_3$ reacts with complex **1** to give titanocene nitrile complexes and the titana-diazacyclopentene **86** [46].

Lactams Lactams represent a special type of C=N system due to the tautomerization between the lactam (keto amine) and lactim (hydroxyimine) forms. The lactim form is much more favored for cyclic than for non-cyclic amides of carbocyclic acids. In the reaction of complex **2b** with *N*-methyl-ε-caprolactam, a simple ligand exchange reaction occurs and complex **87** can be isolated. With β-propiolactam, the alkenyl-amido complex **88** is formed, which indicates an agostic interaction. The reaction of complex **1** with ε-caprolactam gives, after elimination of the alkyne and of molecular hydrogen, complex **89** with a deprotonated lactam in a η^2-amidate bonding fashion [47].

Heterocyclic compounds Heterocyclic C=N systems, such as benzoxazole and related thiazoles, react with complex **2b** to yield the ring-expanded adducts, e. g. complexes **90** and **91**, by formal C−X (X = O, S) bond cleavage and coupling with the alkyne. In the case of benzisoxazole, the alkyne is not coupled but eliminated, and ring-enlargement of the benzisoxazole leads to the N-bridged dimer **92** [48].

Carbon Dioxide O=C=O The reactions of the metallocene sources **1**−**6** with carbon dioxide depend strongly on the metal and ligands used. Complex **1** gives, by elimination of half of the alkyne, the dimer **93**, which forms the titanafuranone **94** after aerial oxidation [49].

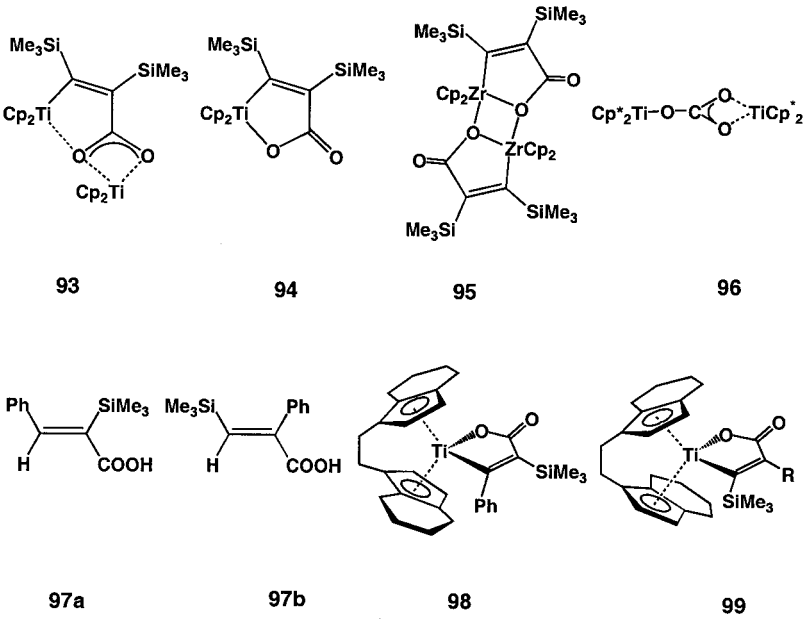


Figure 10.14. Products obtained with carbon dioxide.

Complex **2** reacts with CO_2 to give **95** by quantitative coupling of the alkyne [50]. Only elimination of the alkyne and no coupling was observed in the reaction of **3** with carbon dioxide, which gave the carbonate-bridged complex **96** along with $Cp^*_2Ti(CO)_2$ [51]. These reactions are interesting because they provide, after hydrolysis, regioselectively unsaturated carbonic acids **97** from unsymmetrical substituted alkynes, e. g. $PhC{\equiv}CSiMe_3$, and carbon dioxide. Insertion at the Me_3Si-substituted carbon atom is typical for titanium and zirconium with most of the ligands used, i. e. Cp and Cp^*, and gives the corresponding α-cinnamic acid **97a** [9]. By using the *rac*-ebthi system, the same regioselectivity was found in **98**. By using the *meso*-ebthi ligand, insertion occurred at the C−Ph carbon bond leading to complex **99**, acidic treatment of which gave **97b** [52]. These results show that insertions of carbon dioxide into metallocene alkyne complexes are governed by both the substitution pattern of the alkyne and the steric environment around the metal center.

Alkynylsilanes C≡C–SiH Acetylene exchange in complexes **1** and **3** by the alkynylsilanes RC≡CSiMe$_2$H (R = *t*Bu, Ph, SiMe$_3$, SiMe$_2$H) yields complexes in which an agostic interaction between the Si–H bond and the metal center is indicated for complex **100**, but not for **101** [53].

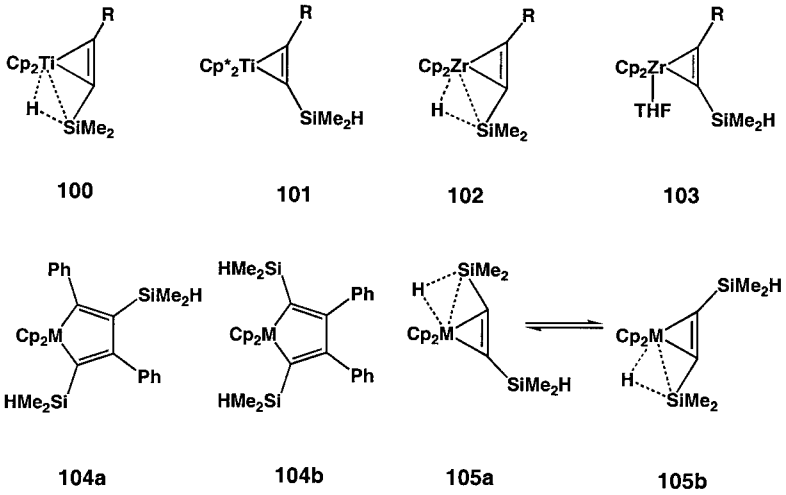
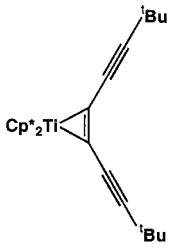


Figure 10.15. Products obtained with alkynylsilanes containing Si–H groups.

This depends mostly on the differing degrees of bulkiness of the Cp and Cp* ligands. With complex **2a**, analogous zirconocene complexes **102** are isolated, in which there is also such an Si–H metal interaction. Upon coordination by an additional THF ligand, this agostic interaction disappears, as in **103**. With PhC≡CSiMe$_2$H and **1** or **2a**, the coupling products **104a** and **104b** are also formed. Interaction of **1** or **2a** with the difunctionalized substrate HMe$_2$SiC≡CSiMe$_2$H results in a flip-flop coordination (complex **105**). The titanocene and zirconocene complexes, with intramolecularly coordinating alkynylsilanes, can serve as suitable model compounds for studying the intermolecular interaction of similar alkyne complexes with silanes, which are used in catalytic reactions such as the hydrosilylation of aldimines and ketimines and the dehydrogenative polymerization of silanes [54]. The above products allow study of the influence of different Cp ligands and metals on the catalytic activity of the complexes.

Triynes –C≡C–C≡C–C≡C– The permethyltitanocene core is complexed by triynes RC≡C–C≡C–C≡CR through the central triple bond and the η^2-complex **106** is formed.

The corresponding permethylzirconocene moiety is complexed by triynes RC≡C–C≡C–C≡CR through two triple bonds in a η^4-fashion and complex **107** is obtained. Detailed NMR investigations have revealed a "sliding" of the permethylzirconocene along the triyne backbone **108** [55]. This result is important because it shows there to be a lot of species in the mixture; this is the reason for the low selectivity in some reactions.



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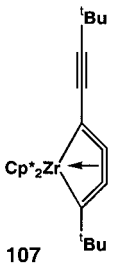

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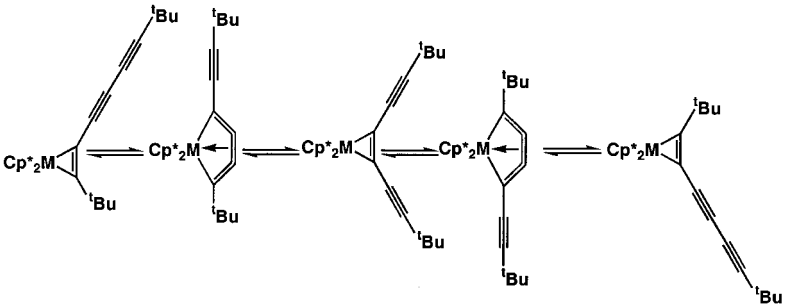

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Figure 10.16. Different complexation modes of triynes and "sliding" along the triyne backbone.

Tetraynes $-C{\equiv}C-C{\equiv}C-C{\equiv}C-C{\equiv}C-$ *and* $(-C{\equiv}C)_2Si(C{\equiv}C-)_2$ The reaction behavior of titanocene and zirconocene towards linear octatetraynes $RC{\equiv}C-C{\equiv}C-C{\equiv}C-C{\equiv}CR$ is very similar to that found for the 1,3-butadiynes [56]. Two equivalents of complex **1** react with $Me_3SiC{\equiv}C-C{\equiv}C-C{\equiv}C-C{\equiv}CSiMe_3$ to form **109**.

Four equivalents of complex **1** react with tBuC≡C−C≡C−C≡C−C≡CtBu to give complex **110** with an intact C4 chain. Under the same conditions, the corresponding zirconocene complex **2a** forms complex **111** through twofold C−C single-bond cleavage. If two butadiyne moieties are separated by a *para*-phenylene unit, as in $RC{\equiv}C-C{\equiv}C-C_6H_4-C{\equiv}C-C{\equiv}CR$, the titanium complex **112** is obtained. Depending on the stoichiometry, the two zirconocene complexes **113** and **114** can also be obtained [56 b].

Reactions of the branched tetraalkynylsilanes **115** $(RC{\equiv}C)_4Si$ (R = tBu, Ph, Me_3Si) with the metallocene sources **1** or **2a** lead, through twofold migration and C−C coupling of the alkynyl groups, to a novel type of dinuclear carbon-rich *spiro*-complexes **116** [57].

The conversions proved to be independent of the metal, the substituents, or the stoichiometry employed. Similar products **117** have recently been found by Takahashi following reactions of dialkynylsilanes $(RC{\equiv}C)_2SiR_2$ with zirconocene complexes [58].

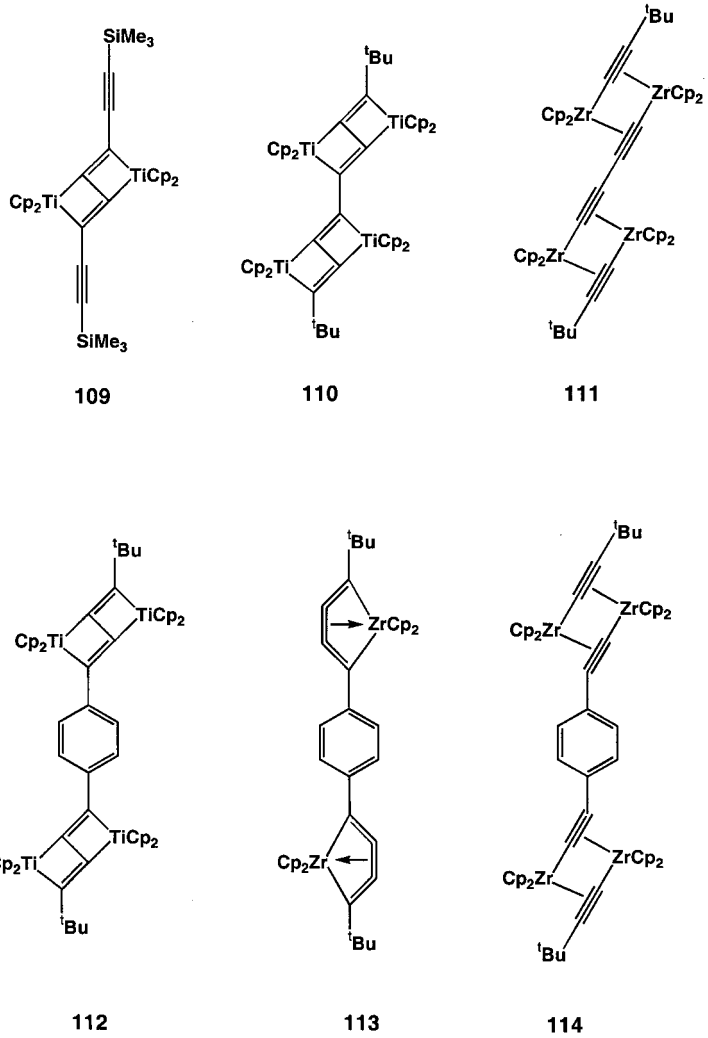
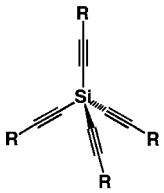


Figure 10.17. Products obtained with linear tetraynes.

Hexaynes $(C_6H_3)(C{\equiv}C{-}C{\equiv}C{-})_3$ Tris(butadiynyl)benzenes such as 1,3,5-$(RC{\equiv}C{-}C{\equiv}C)_3$-$C_6H_3$ give the complexes **118** when six equivalents of titanocene are used. Treatment with three equivalents of zirconocene gives the tris(cyclocumulene) **119**, and treatment of the latter with three additional equivalents yields the threefold C–C cleaved product **120** [59].

Together with the aforementioned results for tetraynes, these complexes show the possibility of extending the reaction pattern from 1,3-butadiynes to more complicated molecules.



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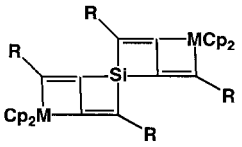

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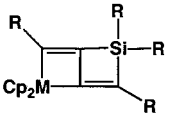

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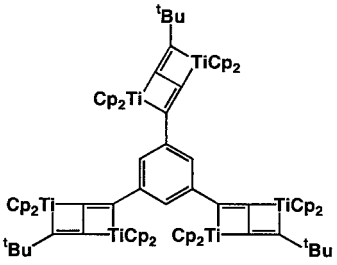

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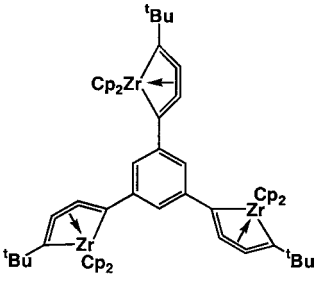

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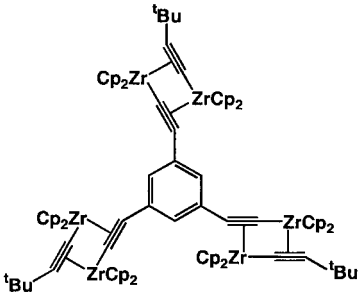

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Figure 10.18. Products obtained with tetraalkynylsilanes and hexaynes.

Fullerene The reaction of **1** with an equimolar amount of fullerene-60 in toluene at room temperature gives the first fullerene complex of titanium $Cp_2Ti(\eta^2\text{-}C_{60})$ **121** [60]. An X-ray diffraction study of this complex has shown that it has the structure of a titanacyclopropane derivative, which should have a high potential for further derivatization of the fullerene.

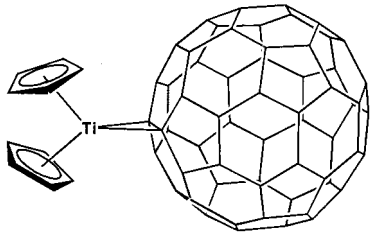

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Figure 10.19. Complexation of fullerene-60 with titanocene.

10.9 Summary and Outlook

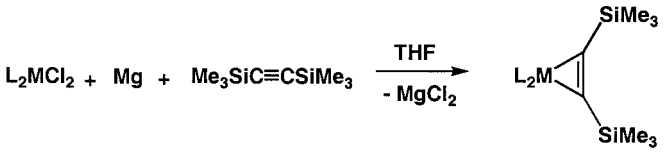
The results presented herein show the high synthetic potential of complexes of the type $Cp_2M(L)(\eta^2\text{-}Me_3SiC_2SiMe_3)$ (M = Ti, L = –, **1**; M = Zr, L = THF, **2a**; pyridine, **2b**; acetone, **2c**) as well as of the corresponding substituted complexes $Cp^*_2M(\eta^2\text{-}Me_3SiC_2SiMe_3)$ (M = Ti, **3**; Zr, **4**) and *rac*-(ebthi)$M(\eta^2\text{-}Me_3SiC_2SiMe_3)$ (M = Ti, **5**; Zr, **6**) as novel reagents for group IV metallocene fragments. The complexes obtained from addition and substitution reactions of these compounds with the functional groups of several substrates have provided a lot of information concerning the applications of titanocene and zirconocene in organic synthesis. The elementary steps and reactions to give other species open the door for further subsequent reactions leading either to organic compounds or to more complicated organometallics, allowing the evaluation of a broad range of other chemistry.

As mentioned above, these novel metallocene sources have a number of compelling advantages over the widely used Cp_2ZrCl_2/*n*BuLi and some other systems [1]. These can be summarized as follows [2j]:

- The complexes can readily be prepared in large quantities direct from the commercially available dichloride complexes, Cp_2MCl_2.
- They are stable at room temperature, and can be stored for long periods under an inert atmosphere.
- They allow close control over the stoichiometries of reactions, even at elevated temperatures.
- The side products of the reactions, e. g. bis(trimethylsilyl)acetylene, THF, pyridine, acetone, etc., are soluble and volatile and are thus easy to remove.
- They allow coupling reactions in a broad variety of solvents, in particular non-polar solvents such as pentane.
- They can induce chemo-, regio-, and stereoselectivity in the coupling reactions in the presence of certain functional groups.

Typical Experimental Procedures

All operations were carried out under inert atmosphere (argon) using standard Schlenk techniques. Prior to use, solvents were freshly distilled from sodium tetraethylaluminate under argon. Deuterated solvents were treated with sodium or sodium tetraethylaluminate, distilled, and stored under argon.



1 M = Ti, L = Cp
3 M = Ti, L = Cp*
4 M = Zr, L = Cp*
***rac*-5** M = Ti, L_2 = ebthi
***rac*-6** M = Zr, L_2 = ebthi

Scheme 10.9. Synthesis of titanocene (**1**, **3**, *rac*-**5**) and zirconocene (**4**, *rac*-**6**) complexes with bis(trimethylsilyl)acetylene without additional ligands.

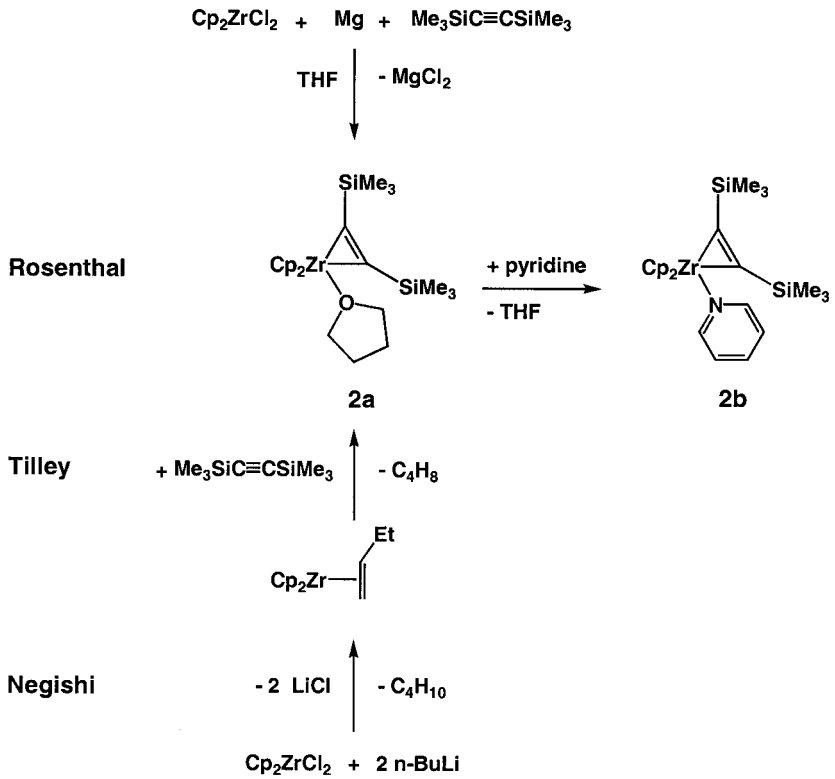
Synthesis of the titanocene source $Cp_2Ti(\eta^2\text{-}Me_3SiC_2SiMe_3)$ (1) A mixture of Cp_2TiCl_2 (1.00 g, 4.02 mmol), finely divided magnesium turnings (0.10 g, 4.11 mmol), and bis(trimethylsilyl)acetylene (0.92 mL, 4.06 mmol) in THF (25 mL) was stirred at room temperature under argon for 3 h. Thereafter, the dark solution obtained was filtered and the filtrate was concentrated to dryness in vacuo. The residue was redissolved in *n*-hexane (20 mL) and this solution was filtered again. Cooling of the filtrate to −78 °C resulted in the deposition of golden-yellow crystals of $Cp_2Ti(\eta^2\text{-}Me_3SiC_2SiMe_3)$ (**1**), which were separated from the mother liquor by decantation and were dried in vacuo at room temperature. The yield was 0.71 g (51 %); m. p. 81−82 °C (dec.) under argon [2a,2d].

Synthesis of the zirconocene source $Cp_2Zr(THF)(\eta^2\text{-}Me_3SiC_2SiMe_3)$ (2a) A mixture of Cp_2ZrCl_2 (2.10 g, 7.18 mmol), finely divided magnesium turnings (0.18 g, 7.41 mmol), and bis(trimethylsilyl)acetylene (1.62 mL, 7.15 mmol) in THF (25 mL) was stirred at room temperature under argon for 3 h. It was then concentrated in vacuo until a nearly dry material remained. This solid was collected on a G3 frit and washed with THF/pentane (1:3, 15 mL) and then extracted with this solvent mixture (50−60 mL). The extract was concentrated to dryness in vacuo, to leave the orange complex **2a** (2.50 g, 75 %); m. p. 139−141 °C (dec.) under argon [2c].

Synthesis of the zirconocene source $Cp_2Zr(pyridine)(\eta^2\text{-}Me_3SiC_2SiMe_3)$ (2b) (Scheme 10.10) *Rosenthal's route* [2e], *starting from* **2a**: A solution of $Cp_2Zr(THF)(\eta^2\text{-}Me_3SiC_2SiMe_3)$ (**2a**; 1.32 g, 2.85 mmol) in THF (20 mL) was stirred at room temperature and treated with pyridine (0.25 mL). After 1 h, the resulting dark-red solution was filtered and the filtrate was concentrated to dryness in vacuo. The residue was extracted with *n*-hexane at 50 °C and on cooling the extract the product crystallized. The yield of very pure complex **2b** was 0.89 g (66 %); m. p. 125−126 °C (dec.) under argon [2e]. Direct synthesis of **2b** starting from Cp_2ZrCl_2 through the preparation of complex **2a** in situ gives less pure samples.

Tilley's route [2j], *starting from Cp_2ZrCl_2 and proceeding via the Negishi reagent or via $Cp_2Zr(THF)(\eta^2\text{-}Me_3SiC_2SiMe_3)$* **2a**: To Cp_2ZrCl_2 (5.00 g, 17.1 mmol) and bis(trimethylsilyl)acetylene (2.91 g, 17.1 mmol) in THF (100 mL), *n*-BuLi (21.4 mL, 34.2 mmol) was added dropwise at −78 °C. The resulting mixture was stirred for 10 min. at −78 °C and was then allowed to warm to room temperature over a period of 2 h. Pyridine (1.38 mL, 17.1 mmol) was added and the solution was concentrated in vacuo to a volume of 20 mL. Pentane (250 mL) was then added, and the solution was filtered, concentrated to half of its original volume in vacuo, and then cooled to −80 °C to induce crystallization. The yield of complex **2b** was 6.844 g (85 %).

Synthesis of the zirconocene source *rac*-(ebthi)$Zr(\eta^2\text{-}Me_3SiC_2SiMe_3)$ (6) A mixture of *rac*-(ebthi)$ZrCl_2$ (1.00 g, 2.34 mmol), finely divided magnesium turnings (0.07 g, 2.88 mmol), and bis(trimethylsilyl)acetylene (0.42 mL, 1.85 mmol) in THF (25 mL) was stirred at 45 °C under argon for 2 h. The initially colorless solution gradually turned green. After removal of the solvent in vacuo, redissolution of the residue in *n*-hexane, filtration of the resulting solution, and repeated removal of the solvent, 0.89 g (72 %) of the dark-green complex *rac*-(ebthi)$Zr(\eta^2\text{-}Me_3SiC_2SiMe_3)$ (**6**) was obtained; m. p. 137−142 °C (dec.) under argon [2h].



Scheme 10.10. Synthesis of zirconocene complexes (**2a** and **2b**) with bis(trimethylsilyl)acetylene containing additional ligands following the routes used by Rosenthal and Tilley.

Substitution and formation of the titanacyclocumulene 20 (Fig. 10.4) To a solution of $Cp_2Ti(\eta^2\text{-}Me_3SiC_2SiMe_3)$ (**1**; 1.385 g, 3.97 mmol) in *n*-hexane (3 mL) was added a solution of 1,4-di-*tert*-butyl-1,3-butadiyne (0.645 g, 3.97 mmol) in *n*-hexane (7 mL). After standing at room temperature for 2 h, the green solution was freed of small amounts of a dinuclear complex (**19**; M = Ti and R = R' = *t*Bu) by filtration and the product was allowed to crystallize at −40 °C. Greenish crystals of the titanacyclocumulene (**20**; M = Ti and R = R' = *t*Bu) were formed, which were washed with cold *n*-hexane and dried in vacuo. The yield was 0.482 g (36 %), m. p. 172−173 °C under argon [21a].

Coupling of >C=N− and formation of the zirconacycle 67 (Fig. 10.10) A solution of N-benzylideneaniline (0.14 g, 0.76 mmol) in THF (10 mL) was added to a solution of *rac*-(ebthi)$Zr(\eta^2\text{-}Me_3SiC_2SiMe_3)$ (**6**; 0.20 g, 0.38 mmol) in THF (15 mL). The resulting mixture was stirred for 10 min. at 40 °C, during which a color change from green to violet occurred. After the solution had been stirred for 1 h at room temperature, the solvent was removed in vacuo and the foamy solid residue was redissolved in boiling diethyl ether. Crystals of the zirconacycle **67** were deposited overnight at room temperature, from which the mother liquor was decanted off. The crystals were washed with cold *n*-hexane and dried in vacuo to give 0.24 g (86 %) of the zirconacycle, m. p. > 280 °C [2h].

Coupling of $-C\equiv C-C\equiv C-$ and reaction with SCl_2: formation of the thiophene derivative 28 (Fig. 10.5) (a) To a solution of $Cp_2Ti(\eta^2\text{-}Me_3SiC_2SiMe_3)$ (**1**; 0.727 g, 2.09 mmol) in *n*-hexane (3 mL) was added a solution of 1,4-bis(trimethylsilyl)-1,3-butadiyne (0.811 g, 4.17 mmol) in *n*-hexane (7 mL). After filtration and leaving the filtrate to stand at room temperature for 5 h, red-brown crystals were obtained (0.691 g). The mother liquor was decanted off and placed in a refrigerator. After 1 d, a second crop (0.261 g) of the complex had crystallized. The crystals were washed with cold *n*-hexane and dried in vacuo. The yield of the titanacyclopentadiene **27** was 0.952 g (80.5 %); m. p. 162–163 °C under argon [21a]. (b) To a solution of the titanacyclopentadiene (0.265 g, 0.47 mmol) in THF (10 mL) was added sulfur monochloride (0.04 mL, 0.5 mmol). The red mixture was stirred at 55 °C for 6 h, the red-brown solution obtained was concentrated to dryness, and the residue was extracted with *n*-hexane (4 × 3 mL). The combined extracts were purified by flash chromatography on activity grade III alumina (8 × 2 cm) to yield 0.089 g (49.7 %) of the tetrasubstituted thiophene **28** as a pale-yellow liquid [29].

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11
Titanium-Mediated Syntheses of Cyclopropanols and Cyclopropylamines

Armin de Meijere, Sergei I. Kozhushkov, and Andrei I. Savchenko

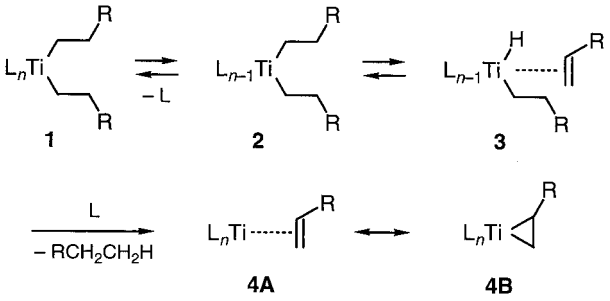
11.1
Introduction

Among the wide variety of organometallic compounds, the relatively inexpensive and safely handled non-transition-metal derivatives, in particular organolithium, organomagnesium, organozinc, and organoaluminum reagents, are definitely the most widely used in organic synthesis [1]. The majority of synthetically useful transformations of these reagents, including carbon–carbon bond-forming reactions, may sometimes undergo a dramatic change in their rates or even modes when conducted in the presence of a transition metal compound [2–9]. The use of the latter, especially of group IV transition metal derivatives, sometimes not only allows one to modify the reactivity of non-transition organometallics, but also to perform new kinds of transformations due to a structural reorganization of the carbanionic moiety. Among group IV metal derivatives, titanium catalysts or mediators, such as titanium chlorides, titanium alkoxides, and titanocene derivatives, are especially attractive for practical use as they are the least expensive of reagents and are conveniently handled. In the form of the Sharpless epoxidation [10–15] and the McMurry coupling reagents [16–21], chemo- and stereoselective reactions of carbonyl compounds [22–24] as well as alkene metathesis reactions [25], titanium derivatives have found numerous synthetic applications, all of which have been reviewed.

This chapter compiles the synthetic applications of an important class of rather novel low-valent titanium reagents, which are formed in situ from titanium alkoxides and organometallic compounds, especially organomagnesium halides. Their application leads to cyclopropanols from carboxylic esters (lactones) and to cyclopropylamines from *N*,*N*-dialkylcarboxamides, respectively [26], processes that have been developed in the last 14 years. These discoveries have led to synthetically extremely useful transformations of organic compounds that could not even have been thought of in classical organic chemistry, yet are well on their way to being routinely applied in modern organic synthesis. The increasing importance of these reactions is demonstrated by their first successful applications in the syntheses of natural products and of compounds with potentially useful properties, which are also discussed herein.

11.2
Reaction Modes of Titanium Alkyl Derivatives Possessing β-Hydrogen Atoms

Alkyl derivatives of titanium and other transition metals having β-hydrogen atoms are known to be prone to β-hydride elimination reactions as their most characteristic transformation [23,27–32], which occurs particularly readily when two or more alkyl groups are bound to the metal. This leads to the formation of the corresponding alkanes, along with polyalkenes and low-valent titanium derivatives [33–38]. The latter intermediates, which may be formed by a bimolecular disproportionation, are essentially 1,2-dimetalloalkylene derivatives [35]. This thermal decomposition of alkyltitanium derivatives may also occur by β-elimination of the metal hydride [3,39–42]. This mechanism includes a ligand dissociation step from **1** with formation of a coordinatively unsaturated dialkyltitanium derivative, followed by elimination of the metal hydride from one of the alkyl groups in **2** with concomitant transfer of the resulting alkene to the vacant coordination site to form an alkenealkylhydrido complex **3** (Scheme 11.1). Re-addition of a ligand to **3** accompanied by reductive elimination of an *n*-alkane eventually leads to the alkenetitanium complex **4** (Scheme 11.1) [27,43–47].

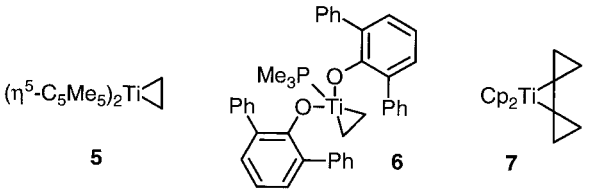


Scheme 11.1. Thermal decomposition of alkyltitanium derivatives by β-elimination of metal hydride.

The question as to whether a transition metal complex of type **4** is best described as an alkene π-complex **4A** or as a metallacyclopropane **4B**, which is of practical importance, has been addressed in several computational studies on the relationship between alkene π-complexes and three-membered rings [48–52]. It has been concluded that the titanium complexes of type **4** are best represented as titanacyclopropanes, i. e. by resonance structure **4B**, if one is willing to accept the notion that **4A** and **4B** are limiting resonance forms [52].

The first isolable alkenetitanium complex, the bis(pentamethylcyclopentadienyl)-titanium–ethylene complex **5**, was prepared by Bercaw et al. by reduction of bis(pentamethylcyclopentadienyl)titanium dichloride in toluene with sodium amalgam under an atmosphere of ethylene (ca. 700 Torr) or from $\{[(\eta\text{-}C_5Me_5)_2Ti]_2(\mu\text{-}N_2)_2\}$ by treatment with ethylene [42]. X-ray crystal structure analyses of **5** and of the ethylenebis(aryloxy)trimethylphosphanyltitanium complex **6** [53] revealed that the coordination of ethylene causes a substantial increase in the carbon–carbon double bond length from 1.337(2) Å in free ethylene to 1.438(5) Å and 1.425(3) Å, respectively. Considerable bending of the hydrogen atoms out of the plane of the ethylene molecule is also observed. By comparison with structural data for other ethylene complexes and three-membered heterocyclic compounds, the structures of **5** and **6** would appear to be intermediate along the continuum between a Ti(II)-ethylene (**4A**) and a Ti(IV)-metallacyclopropane (**4B**) (Scheme 11.1) as

limiting structures [42]. No crystal structure analysis, but a full NMR spectroscopic characterization has been reported for the interesting bis-spirocyclopropanated titanacyclopropane **7**, which is readily formed upon reaction of $Cp_2Ti(PMe_3)_2$ with bicyclopropylidene [54].

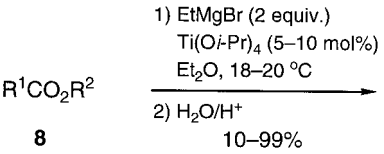


5 **6** **7**

11.3 Preparation of Cyclopropanols

11.3.1 From Organomagnesium Precursors

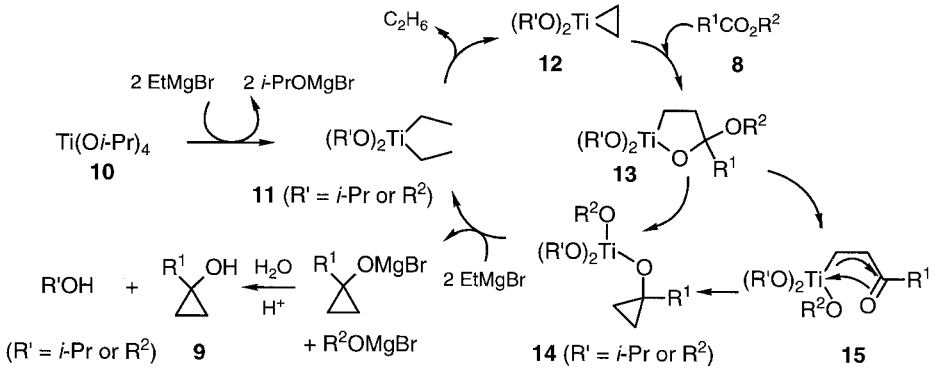
The first synthetically useful reaction of titanium complexes of type **4**, leading to the formation of two new carbon–carbon bonds, was developed by Kulinkovich et al. [55]. They found that treatment of a carboxylic acid ester with a mixture of one equivalent of titanium tetraisopropoxide and an excess of ethylmagnesium bromide at −78 to −40 °C affords 1-alkylcyclopropanols **9** in good to excellent yields (Scheme 11.2) [55,56]. This efficient transformation can also be carried out with sub-stoichiometric amounts of $Ti(OiPr)_4$ (5–10 mol%) [57,58]. In this case, an ethereal solution of two equivalents of EtMgBr is added at room temperature to a solution containing the ester and $Ti(OiPr)_4$. Selected examples of this transformation are presented in Table 11.1 (for more examples, see ref. [26a]).



8 **9**

Scheme 11.2. $Ti(OiPr)_4$-catalyzed preparation of 1-alkylcyclopropanols **9** from carboxylic acid esters and ethylmagnesium bromide. For details, see Table 11.1.

Mechanistically, this reaction can be rationalized as depicted in Scheme 11.3. It is assumed that two equivalents of the Grignard reagent react with $Ti(OiPr)_4$ to form the thermally unstable diethyltitanium intermediate **11**, which rapidly undergoes β-hydride elimination (see Scheme 11.1) and reductive elimination to yield ethane and the reactive intermediate titanacyclopropane **12**. The putative titanacyclopropane **12** then acts as a 1,2-dicarbanionic equivalent in that it performs an overall twofold alkylation of the alkoxycarbonyl group. This most probably occurs by insertion of the ester carbonyl group into one of the titanium–carbon bonds to give an oxatitanacyclopentane **13**, followed by ring-contraction, most probably initiated by attack of an alkoxide moiety from a titanium or magnesium alkoxide or even attack of another molecule of ethylmagnesium bromide on the titanium, with concurrent loss of the alkoxide group from the former carbonyl carbon atom to yield the titanium cyclopropanolate **14** or an analogue with one ethyl group on



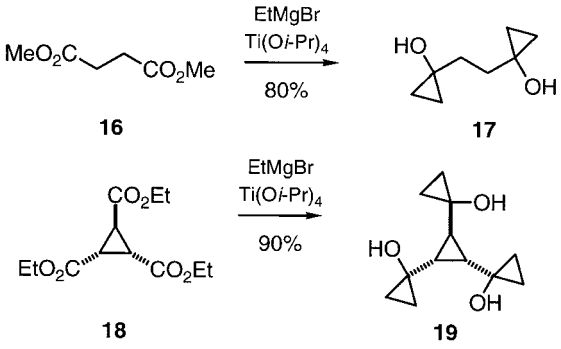
Scheme 11.3. Mechanistic rationalization of $Ti(OiPr)_4$-catalyzed cyclopropanation of carboxylic acid esters.

Ti (Scheme 11.3). The latter reacts with one or two more molecules of the Grignard reagent to reform the intermediate **11** – completing a catalytic cycle – and to give the magnesium cyclopropanolate that is eventually hydrolyzed to **9**. Alternatively, attack of an alkoxide or ethylmagnesium bromide moiety on the titanium in **13** could induce ring-opening to a titanium homoenolate **15**, which could close the three-membered ring and yield **14** by intramolecular nucleophilic attack on the carbonyl group (Scheme 11.3).

This mechanism has recently been probed by carrying out density functional theory calculations at the B3LYP/6-31G* level of theory [73]. Addition of an ester to titanacyclopropane **12** was found to be fast, exothermic, and irreversible, while the cyclopropane-forming step was concluded to occur directly from **13** to **14**, to be rate-determining, and to determine the experimentally observed *cis* diastereoselectivity (see below).

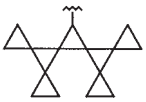
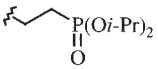
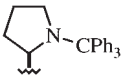
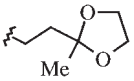
This cyclopropanol formation proceeds smoothly with alkenyl- (except ethenyl) [74], cycloalkyl- [58–60,72], and arylcarboxylates [56,58], as well as with carboxylates containing a β- [65,75] or γ-halogen [66], an acetal [71,76], and quite a number of other functional substituents, including dialkoxyphosphonyl groups [69] (see Table 11.1).

Diesters and even triesters have been converted to bis- and tris(cyclopropanol)s, respectively. Dimethyl succinate gave the bis(cyclopropanol) derivative **17** in 80 % yield, while triethyl *trans*-cyclopropanetricarboxylate (**18**) yields the tris(cyclopropanol) **19** (90 %) (Scheme 11.4; selected examples in Table 11.2) [77,78]. Higher homologous dicarboxylic acid diesters are likewise smoothly converted with ethylmagnesium bromide in the presence of $Ti(OiPr)_4$ to provide the corresponding bis(cyclopropanol)s [71,78].



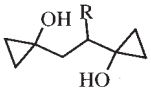
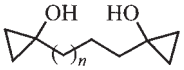
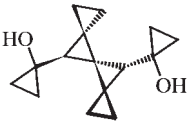
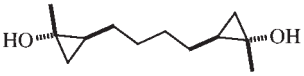
Scheme 11.4. Conversion of di- and triesters to bis- and tris(cyclopropanol)s [77,78].

Table 11.1. 1-Alkylcyclopropanols **9** from carboxylic acid esters and ethylmagnesium bromide in the presence of titanium tetraisopropoxide (see Scheme 11.2).

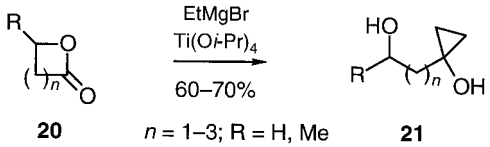
Entry	*Starting Ester* R^2	*Conditions*[a] *[mol% Ti(OiPr)$_4$]*	*Product* R^1	*Yield (%)*	*Ref.*
1	Me	A	Me	74	[55,56]
	Et	B [4–10]	Me	84	[58]
2	Me	A	Et	82	[55,56]
	Me	B [5–10]	Et	79	[57]
3	Me	A	*n*-C_5H_{11}	93	[55,56]
	Me	B [4–10]	*n*-C_5H_{11}	94	[57,58]
4	Me	A	*i*Pr	88	[55,56]
	Me	B [4–10]	*i*Pr	88	[58]
5	Me	B [22]	*c*Pr	99	[59,60]
6	Et	B [20]	1-(*trans*-4-*n*Pr-*c*-Hex)	95	[61]
7	Me	B [10]	$CH{=}C(Me)_2$	23	[62]
8	Me	B [10]	$(CH_2)_{14}CH{=}CH_2$	> 90	[63]
9	Et	A	Ph	93	[55,56]
	Et	B [4–10]	Ph	64	[58]
10	Et	B [22]		93	[64]
11	Me	B [10]	$BrCH_2CH_2$	86	[65]
12	Et	B [10]	$ClCH_2CH_2CH_2$	85	[66]
13		C	*c*Pr_2NCH_2	28	[67]
14	*i*Pr	B [14]	*n*-$C_{14}H_{29}CH(OiPr)$	70	[68]
15	Me	A		67	[69]
16	Me	B [20]		99	[70]
17	Me	B [10]		84	[71]
18	Et	B [24]		81	[72]

[a] A: Ester (1.0 equiv.), Ti(O*i*Pr)$_4$ (1 equiv.), EtMgBr (3 equiv.). B: Ester (1.0 equiv.), Ti(O*i*Pr)$_4$ (0.05–0.5 equiv.), EtMgBr (2–4 equiv.). C: MeTi(O*i*Pr)$_3$, EtMgBr (3 equiv. each).

Table 11.2. Bis- and tris(cyclopropanol)s from di- and tricarboxylic acid ethyl esters and ethylmagnesium bromide in the presence of titanium tetraisopropoxide.

Entry	*Conditions[a] [mol% Ti(OR)$_4$]*	*Product*	*Yield (%)*	*Ref.*
1	A [20]		68 (R = Me) 64 (R = Et) 85 (R = *i*Pr)	[78]
2	A [20]		90 (*n* = 1) 90 (*n* = 2) 85 (*n* = 5)	[78]
3	A [22]		51	[59]
4	A, B [50][b]		10	[79]

[a] A: Ti(O*i*Pr)$_4$; B: ClTi(O*i*Pr)$_3$.
[b] The reaction was carried out in the presence of 1,7-octadiene using *i*PrMgBr.

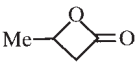
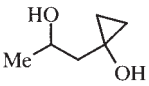
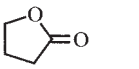
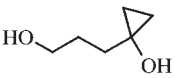
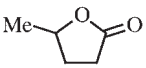
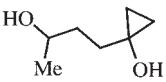
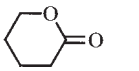
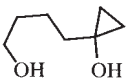
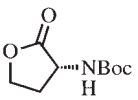
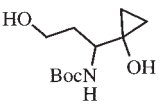
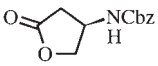
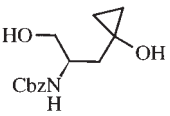


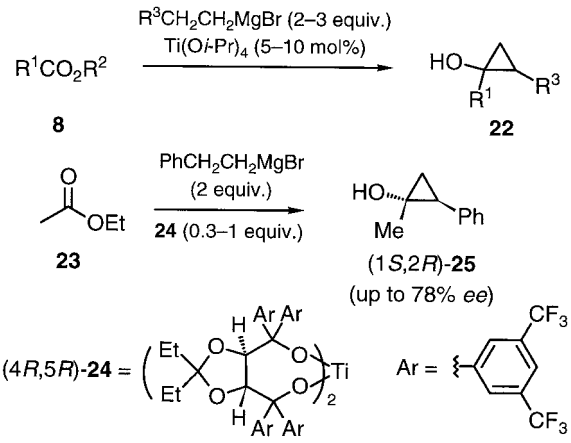
Scheme 11.5. Transformations of differently substituted β-, γ-, and δ-lactones **20** to 1-hydroxyalkylcyclopropanols. For details, see Table 11.3.

In the recently reported reaction of differently substituted β-, γ-, and δ-lactones **20** [80], 20 mol% of Ti(O*i*Pr)$_4$ proved sufficient to obtain the corresponding β-, γ-, and δ-hydroxyalkyl cyclopropanols **21** in 60–70 % yield (Scheme 11.5, Table 11.3, entries 1–3). However, 36 mol% of the titanium reagent was found to be necessary to obtain *N*-protected (aminohydroxyalkyl)cyclopropanols (Table 11.3, entries 5 and 6) from the corresponding 2-*N*-Boc- and 3-*N*-Cbz-2-butyrolactones in yields of 65 % and 70 %, respectively.

1,2-Disubstituted cyclopropanols **22** can be prepared from esters and appropriately 2-substituted ethylmagnesium halides in the presence of titanium tetraisopropoxide [56,81,82]. In the absence of any chelating substituents in the substrate, the products **22** are formed with high diastereoselectivity, i. e. the two substituents on the 1,2-disubstituted cyclopropanol preferentially end up in a mutually *cis* relationship (Scheme 11.6; selected examples in Table 11.4) [81,83]. However, the sequence of events in the formal reductive bis-alkylation of an alkoxycarbonyl group with 2-substituted titanacyclopropane intermediates is not at all clear [77,83]. In the presence of certain titanium bis(TADDOLate)s **24**, generated in situ from chlorotriisopropyloxytitanium and the corresponding TADDOL, 2-phenyl-1-methylcyclopropanol (**25**) is obtained from ethyl acetate and (2-phenylethyl)magnesium bromide (64 %) with an enantiomeric excess of up to 78 % [81].

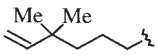
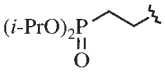
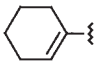
Table 11.3. Cyclopropanediols **21** from substituted β-, γ-, and δ-lactones **20** and ethylmagnesium bromide in the presence of titanium tetraisopropoxide [80].

Entry	*Conditions [mol% $Ti(OiPr)_4$]*	*Lactone*	*Product*	*Yield (%)*
1	A [20]			70
2	A [20]			60–70
3	A [20]			60–70
4	A [20]			60–70
5	A [36]			65
6	A [36]			70



Scheme 11.6. Routine and enantioselective preparation of 1,2-disubstituted cyclopropanols from esters and 2-substituted ethylmagnesium halides. For details, see Table 11.4.

Table 11.4. 1,2-Disubstituted cyclopropanols **22** from carboxylic acid esters **8** and 2-substituted ethylmagnesium halides in the presence of titanium tetraisopropoxide or chlorotitanium triisopropoxide.

Entry	*Starting Ester* R^2	*Product* R^1	R^3	*Conditions*[a] *[mol% $Ti(OR)_4$]*	*Yield (%) (d. r. Z/E*[b]*)*	*Ref.*
1	Me	Me	Ph	A	62	[56]
2	Et	Me	Me	B [4–10]	57	[58]
3	Me	Me	Me	A	67	[61]
4	Et	Me	*n*Bu	B [10]	75	[62]
5	Me	Me	Me	C[c] [10]	90	[78]
6	Me	H	*n*-C_6H_{13}	C [10]	72	[81]
7	Me	Me	Ph	C [10]	83	[81]
8	Me	Et	Et	A	74	[56]
9	Me	Et	Ph	B [10]	73	[62]
10	Me	*n*-C_6H_{13}	*n*Bu	A, B [10]	n. r.[d]	[84]
11	Me	*n*-C_6H_{13}	*n*-C_6H_{13}	C[c] [10]	88	[81]
12	Me	*c*-Pr	Me	B [10]	57 (2.2:1)	[62]
13	Me		Et	C [50]	61	[85]
14	Me	$PhCH_2CH_2$	Me	C[c] [10]	83	[81]
15	Et	Ph	Me	A	62	[56]
	Me	Ph	Me	B [10]	27 (1:1)	[62]
16	Et	Ph	Ph	A, B [4–10]	31	[58]
17	Me	$Me_2C{=}CH$	Me	B [10]	24	[62]
18	Me	Me_3SiCH_2	Ph	A	44	[63]
19	Me		Et	A	71	[69]
20	Me		$(i\text{Pr})_3SiOCH_2CH_2$	C [catal.]	77	[79]
21	Me	$Br(CH_2)_5$	$MeO_2C(CH_2)_3$	D[c]	16	[62]

[a] A: $R^3CH_2CH_2MgBr$, $Ti(OiPr)_4$ (3 equiv. each, stoichiometric method). B: $R^3CH_2CH_2MgBr$ (2–4 equiv.), $Ti(OiPr)_4$ (0.05–0.5 equiv., catalytic version). C: $R^3CH_2CH_2MgBr$, $ClTi(OiPr)_3$ (3 equiv. each). D: $MeTi(OiPr)_3$.

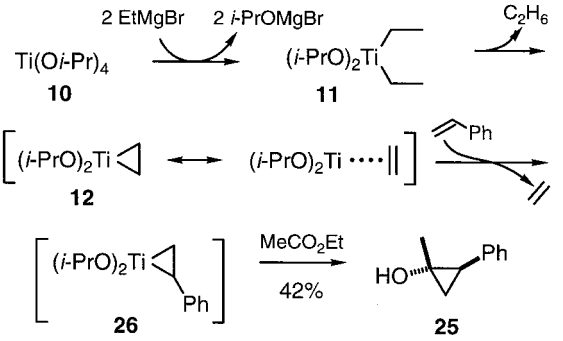
[b] d. r. = diastereomeric ratio, quoted only when reported in the original paper.

[c] Reaction was carried out by addition of alkyl halide to the mixture containing magnesium turnings.

[d] n. r. = not reported.

11.3.2
Via Ligand-Exchanged Titanium–Alkene Complexes

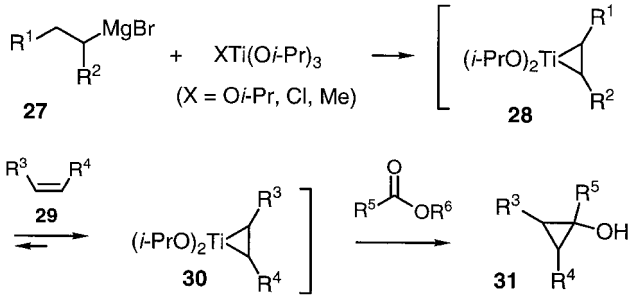
As noted above (see Scheme 11.1), a titanacyclopropane **4B** is just the dominating resonance structure of a titanium–alkene complex. It is thus quite understandable that such titanacyclopropanes **12** formed from dialkyltitanium diisopropoxides (Scheme 11.3) can undergo ligand exchange with other added alkenes. The consequence of such a ligand exchange was first identified by Kulinkovich et al. and was applied in the development of an alternative economical method for the preparation of 1,2-disubstituted cyclopropanols [83]. In a first attempt, (*E*)-1-methyl-2-phenylcyclopropanol (**25**) was obtained in 42 % yield by the addition of two equivalents of ethylmagnesium bromide in diethyl ether to a boiling ethereal solution of styrene (2 equiv.) and a catalytic amount (0.05 equiv.) of titanium tetraisopropoxide (Scheme 11.7) [83]. Apparently, the titanacyclopropane intermediate **12** formed from ethylmagnesium bromide and Ti(O*i*Pr)$_4$ undergoes rapid ligand exchange with styrene to give the phenyl-substituted titanacyclopropane **26**, which subsequently reacts with ethyl acetate to give **25**.



Scheme 11.7. Ligand exchange of titanacyclopropanes **12** with added alkenes [83].

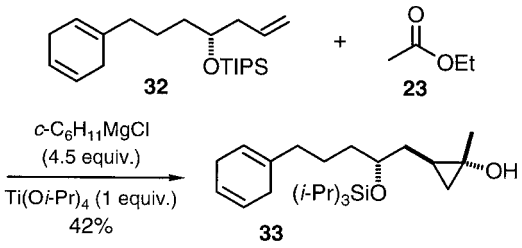
In contrast to styrene, when 1-heptene and some other alkenes are added to the reaction mixture, ligand exchange with the parent titanacyclopropane intermediate **12** in the presence of only catalytic quantities of Ti(O*i*Pr)$_4$ is insufficiently rapid to afford the corresponding 1,2-disubstituted cyclopropanols in satisfactory yields. Cha et al. [79,85,86], as well as Sato et al. [87], have independently found that upon treatment of esters with an excess of an organomagnesium compound in the presence of close to equimolar amounts of titanium tetraisopropoxide as well as one equivalent of various terminal alkenes, 1,2-disubstituted cyclopropanols with substituents stemming from the respective alkene can be obtained in moderate to good yields (Scheme 11.8; selected examples in Table 11.5) [87–96]. The best results have been achieved using isopropyl- [87], butyl- [89], cyclopentyl-, and cyclohexylmagnesium halides [79,85,88].

In a formal sense, overall transformation of an ester with the titanium reagent generated in situ by ligand exchange with an alkene to give a 1,2-disubstituted cyclopropanol may be considered as a hydroxycyclopropanation of the alkene **29** [79,85,87–100]. With the exception of norbornene [79], only terminal alkenes have been hydroxycyclopropanated in this way (Table 11.5). The presence of other remote functional groups, such as di- and trisubstituted alkenyl [79,85,96,97], bromo [79], hydroxy [90], silyloxy [79,85,86,91,97,98], alkoxy [98], acetal [92], dialkylamino [86,99,100], and acyloxy groups



Scheme 11.8. Preparation of substituted cyclopropanols by ligand exchange. For details, see Table 11.5.

[87], is tolerated. Thus, the triene **32** can be selectively cyclopropanated at the terminal monosubstituted double bond to give the 1,2-disubstituted cyclopropanol **33** with the two alkyl groups having a mutually *cis* orientation (Scheme 11.9) [79].



Scheme 11.9. Selective cyclopropanation of the triene **32** [79].

Table 11.5. Substituted cyclopropanols **31** from carboxylic acid esters and alkenes via ligand-exchanged titanium intermediates generated from Grignard reagents and $XTi(OiPr)_3$ (X = O*i*Pr, Cl, Me).

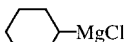
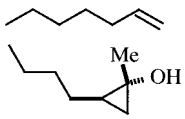
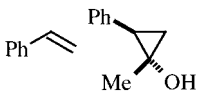
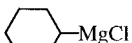
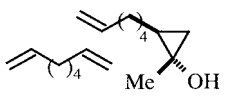
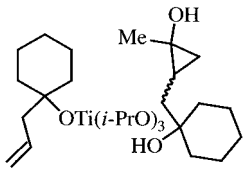
Entry	*Starting Ester*		*Grignard Reagent (equiv.)*	*Alkene*	*Condi-tions[a] (mol%)*	*Yield (%) (cis:trans[b])*	*Ref.*
	R^5	*R^6*	*Product*				
1	Me	Et	 (4.5)		A, B	95 (>98:2)	[79]
2	Me	Et	RMgBr (2–4.5); R = Et, *n*-Pr, *i*Pr , *n*Bu		(10) A A (10–100)	42 30–78[c] (>98:2)	[83] [89]
3	Me	Et	 (4.5)		A, B	49 (>98:2)	[79]
4	Me	Et	EtMgBr (4)		A	26	[90]

Table 11.5. Continued.

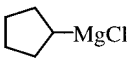
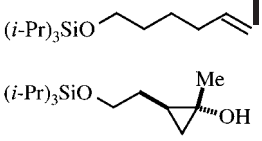
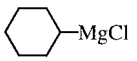
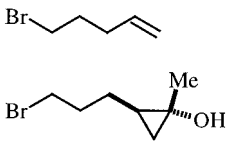
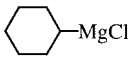
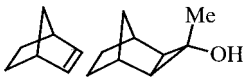
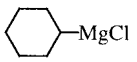
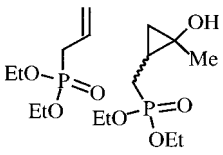
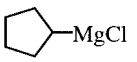
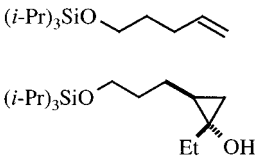
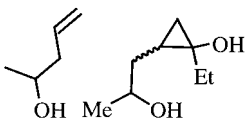
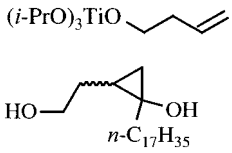
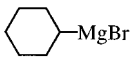
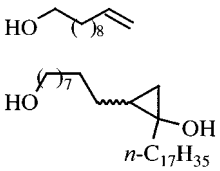
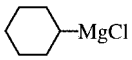
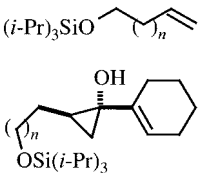
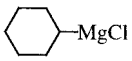
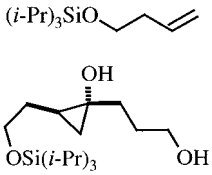
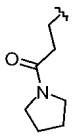
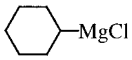
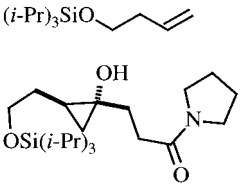
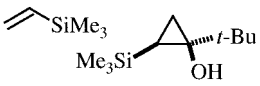
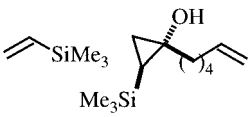
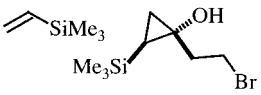
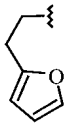
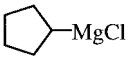
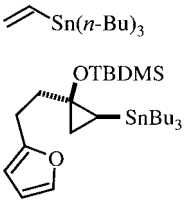
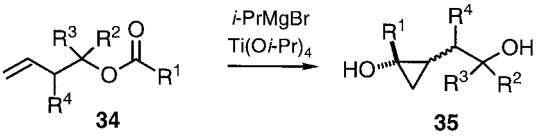
Entry	Starting Ester		Grignard Reagent (equiv.)	Alkene	Conditions[a] (mol%)	Yield (%) (cis:trans[b])	Ref.
	R^5	R^6		Product			
5	Me	Et	 (4.5)		A, B	81 (>98:2)	[91]
6	Me	Et	 (4.5)		A, B	64 (>98:2)	[79]
7	Me	Et	 (4.5)		A, B	37	[79]
8	Me	Me			A	54 (3:1)	[69]
9	Et	Et	 (4.5)		A, B	65 (>98:2)	[91]
10	Et	Et	*i*PrMgBr (4)		A	71	[94]
11	*n*-$C_{17}H_{35}$	Et	EtMgBr (4)		A	41	[90]
12	*n*-$C_{17}H_{35}$	Et	 (6)		A	>56	[88]

Table 11.5. Continued.

Entry	Starting Ester R^5	R^6	Grignard Reagent (equiv.)	Alkene / Product	Conditions[a] (mol%)	Yield (%) (cis:trans[b])	Ref.
13		Me	 (4.5)		A, B	55 ($n = 1$) 46 ($n = 4$) (>98:2)	[79]
14			 (4.5)		A, B	33 (>98:2)	[79]
15		Me	 (4.5)		A, B (80)	58 (>98:2)	[91]
16	*t*Bu	Me	*i*PrMgCl (2.9)		B (150)	82 (7:93)	[95]
17		Me	*i*PrMgCl (2.9)		B (150)	62 (88:12)	[95]
18		Et	*i*PrMgCl (2.9)		B (150)	42 (77:23)	[95]
19		Me	 (3.9)		B (110)	51[d]	[96]

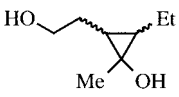
[a] A: $Ti(OiPr)_4$; B: $ClTi(OiPr)_3$.
[b] *cis* and *trans* are with respect to the relative positions of the alkyl substituents.
[c] Yield of the crude crystalline product is given.
[d] As the respective cyclopropanols were found to be unstable, they were isolated as trimethylsilyl or *t*-butyldimethylsilyl ethers following protection under standard conditions.

Functional substituents on the terminal alkene may have a significant influence on the stereochemistry of the hydroxycyclopropanation [74,85–87,90,97]. For example, homoallyl acetate **34** (R^1 = Me, R^2 = R^3 = R^4 = H) gives the corresponding 2-(2′-hydroxyethyl)-1-methylcyclopropanol **35** with a slight excess of the *trans* diastereomer (*trans*/*cis* = 58:42) in excellent yield (93 %) (Scheme 11.10 and Table 11.6, entry 1) [87]. Other homoallyl esters yield the corresponding 1-substituted 2-(2′-hydroxyethyl)cyclopropanols with a much higher preference for the (*E*)-diastereomer (*E*/*Z* up to >97:3). These reactions have been classified by the authors as intramolecular nucleophilic acyl substitution (INAS) reactions, although the possibility of an initial transesterification of the starting compounds catalyzed by titanium tetraisopropoxide [101] has not been excluded by any experimental evidence.



Scheme 11.10. INAS reaction of homoallyl acetates of type **34**. For details, see Table 11.6.

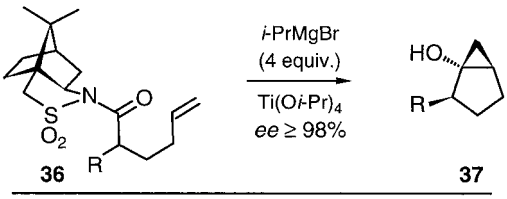
Table 11.6. 1,2-Disubstituted cyclopropanols of type **35** from homoallyl and 3-butenyl carboxylates of type **34** by intramolecular nucleophilic acyl substitution (INAS) reaction (see Scheme 11.10).

Entry	R^1	R^2	R^3	R^4	*Grignard Reagent (Equiv.)*	*Conditions (mol%)*[a]	*Yield (%) (cis:trans*[b]*)*	*Ref.*
1	Me	H	H	H	*i*PrMgBr (4)	A (200)	93 (42:58)	[87]
2	Me	Et	H	H	*i*PrMgBr (4)	A (200) up to 0 °C A (200) up to 20 °C	33 (59:41) 70 (5:95)	[87]
3	Me	H	H	Me	*i*PrMgBr (4)	A (200)	74 (>3:97)	[87]
4	*n*-C_5H_{11}	H	H	H	*i*PrMgBr (4)	A (200)	95 (12:88)	[87]
5	*i*Pr	H	H	H	*i*PrMgBr (4)	A (200)	88 (12:88)	[87]
6	1-Propenyl	H	H	H	*i*PrMgBr (4)	A (200)	78 (7:93)	[87]
7	Ph	H	H	H	*i*PrMgBr (4) *n*BuMgCl (5)	A (200) B (50)	85 (>3:97) 78 (1:7)	[87] [85a]
8					*i*PrMgBr (4)	A (200)	<5	[87]

[a] A: Ester (1.0 equiv.), $Ti(OiPr)_4$ (2.0 equiv.), *i*PrMgBr (4.0 equiv.), Et_2O, −45 to −40 °C, 1 h or −40 to 20 °C, 2 h, then 20 °C, 2 h. B: Ester (1.0 equiv.), $ClTi(OiPr)_3$ (0.5 equiv.), *n*BuMgCl (5.0 equiv.), Et_2O, r. t., 1–2 h.
[b] *cis* and *trans* are with respect to the relative positions of the alkyl substituents.

This hydroxycyclopropanation of a terminal double bond also works perfectly well in an intramolecular situation, e. g. with terminally alkenyl-substituted esters, to yield substituted 1-hydroxybicyclo[*n*.1.0]alkanols [85a,85b,100], aminobicyclo[*n*.1.0]alkanols [85c], and heterocyclic analogues [99a,99b,100], in which five- and six-membered rings are formed (Table 11.7).

Sato et al. developed an interesting enantioselective synthesis of bicyclic cyclopropanols **37** from *N*-acylcamphorsultam derivatives **36**. Products with enantiomeric excesses of up to 98 % were obtained (Scheme 11.11) [102].



R	Yield (%)	Diastereomeric Ratio
$PhCH_2$	86	99:1
n-C_6H_{13}	58	95:5
t-$BuMe_2SiO(CH_2)_5$	84	95:5
i-Bu	80	95:5
t-BuO_2CCH_2	56	92:8
$Me_2C{=}CHCH_2$	87	95:5

Scheme 11.11. Enantioselective synthesis of bicyclic cyclopropanols **37** [102].

Table 11.7. Substituted cyclopropanols by intramolecular hydroxycyclopropanation of a terminally alkoxycarbonyl-substituted alkene (selected examples).

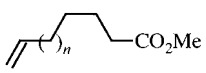
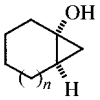
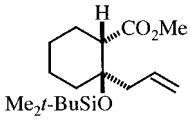
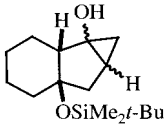
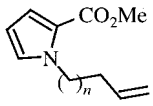
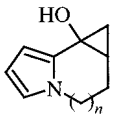
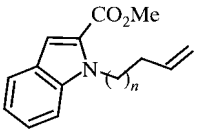
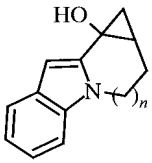
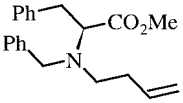
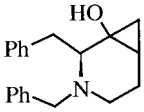
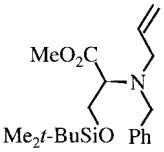
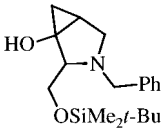
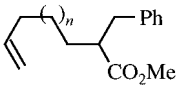
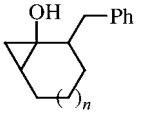
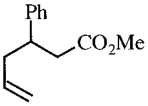
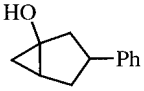
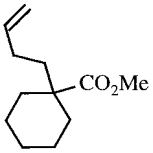
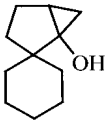
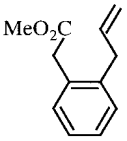
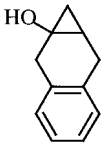
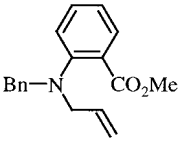
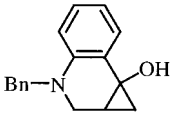
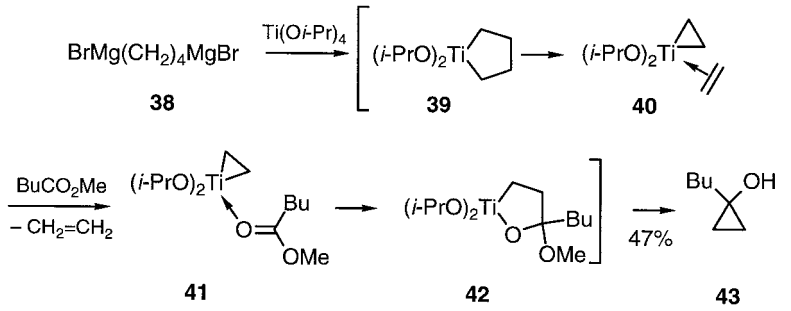
Entry	*Starting Unsaturated Ester*	*Grignard Reagent (Equiv.)*	*Conditions[a] [mol% XTi(OiPr)$_3$[a]]*	*Product*	*Yield (%) (d. r.)[b]*	*Ref.*
1		*n*BuMgCl (3–5)	B [50] B [50] B [50]		55 ($n = 0$) 62 ($n = 1$) 11 ($n = 2$)	[85a]
2		*n*BuMgCl (5)	B [50]		70 (2:1)	[85a]
3		*i*PrMgBr (2.6)	A [130]		80 ($n = 0, 1$)	[99]

Table 11.7. Continued

Entry	Starting Unsaturated Ester	Grignard Reagent (Equiv.)	Conditions[a] [mol% XTi(OiPr)$_3^a$]	Product	Yield (%) (d. r.)[b]	Ref.
4		*i*PrMgBr (2.6)	A [130]		94 (n = 0) 74 (n = 1)	[99]
5		*i*PrMgBr (2.6)	A [130]		75 (73:27) (n = 0) 76 (92:8) (n = 1)	[99]
6		*i*PrMgBr (2.6)	A [130]		86	[99]
7		*i*PrMgBr (4.0)	A [200]		77 (66:34) (n = 0) 73 (89:11) (n = 1)	[100]
8		*i*PrMgBr (4.0)	A [200]		83 (61:39)	[100]
9		*i*PrMgBr (4.0)	A [200]		88	[100]
10		*i*PrMgBr (4.0)	A [200]		98	[100]
11		*i*PrMgBr (4.0) (2.6)	A [200] A [130]		94	[100] [99]

[a] A: Ti(O*i*Pr)$_4$; B: ClTi(O*i*Pr)$_3$.
[b] Diastereomeric ratio given only when reported in the original literature.

1-Substituted cyclopropanols were also obtained, albeit in moderate yields, upon reaction of esters such as methyl pentanoate with 1,4-bis(bromomagnesium)butane (**38**) in the presence of titanium tetraisopropoxide. This corroborates the formation of a titanacyclopropane–ethylene complex **40** from an initially formed titanacyclopentane derivative **39** (Scheme 11.12) [103]. Apparently, an ester molecule readily displaces the ethylene ligand from **40**, and a subsequent insertion of the carbonyl group into the Ti–C bond, a formal $[2_s + 2_\pi]$ cycloaddition, leads to the oxatitanacyclopentane **42**, the precursor to 1-butylcyclopropanol (**43**).

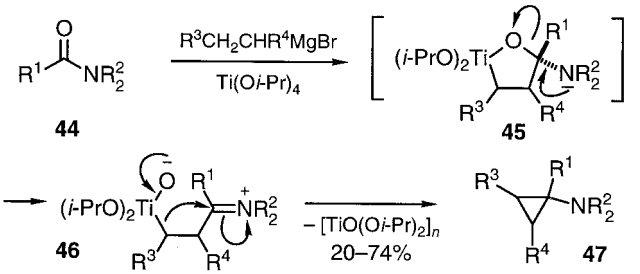


Scheme 11.12. Mechanistic test for the formation of a titanacyclopropane-ethylene complex **40** from a titanacyclopentane derivative **39** [103].

11.4 Preparation of Cyclopropylamines

11.4.1 From Organomagnesium Precursors

A very useful and highly versatile preparation of cyclopropylamines has been developed by de Meijere et al. [62,69,104–111]. *N,N*-Dialkylaminocyclopropanes **47** with up to three additional substituents are readily obtained from carboxylic acid *N,N*-dialkylamides **44** and ethyl- as well as substituted ethylmagnesium halides in the presence of titanium tetraisopropoxide or, even better, methyltriisopropoxytitanium. These transformations also proved to be possible using sub-stoichiometric amounts of the titanium reagent, but the yields are significantly higher using stoichiometric amounts. In some cases, extended reaction times and/or slightly elevated temperatures can also lead to better yields. Particularly high yields are obtained from *N,N*-dialkylformamides (Scheme 11.13, and selected exam-



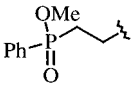
Scheme 11.13. Preparation of *N,N*-dialkylaminocyclopropanes **47** from carboxylic acid *N,N*-dialkylamides **44**. For details, see Table 11.8.

ples in Table 11.8). Yields are consistently lower from amides with bulky substituents next to the carbonyl group or on the nitrogen, but even the sterically crowded *N*,*N*-di-*tert*-butylformamide can be converted to di-*tert*-butylcyclopropylamine (Table 11.8, entry 8), albeit in only 20% yield [104]. The diastereoselectivities in the formation of 2-substituted and 1,2-disubstituted *N*,*N*-dialkylcyclopropylamines are generally lower than those achieved in generating the corresponding cyclopropanols from esters.

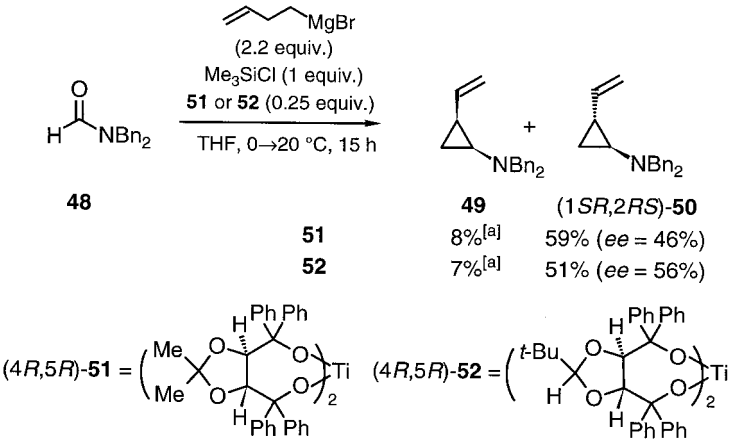
As far as the mechanism is concerned, this transformation of carboxamides to cyclopropylamines differs in some important details from that of esters to cyclopropanols. Due to the poorer leaving group ability of the dialkylamino group in the oxatitanacyclopentane intermediate **45**, which is initially formed by insertion of the carbonyl group of the amide into the titanium–carbon bond of a titanacyclopropane, this intermediate does not undergo ring-contraction like the corresponding oxatitanacyclopentane **12** derived from an ester (see Scheme 11.3). Instead, **45** undergoes ring-opening to an iminium-titanium oxide zwitterion **46**, which cyclizes to the cyclopropylamine **47** with loss of an oxotitanium diisopropoxide species (Scheme 11.13).

In the presence of titanium bis(TADDOLate)s such as **51** and **52** (25 mol%), generated from titanium tetraisopropoxide and the corresponding TADDOL, as well as chlorotri-

Table 11.8. *N*,*N*-Dialkylcyclopropylamines **47** from *N*,*N*-dialkylcarboxamides **44** and ethyl- as well as substituted ethylmagnesium bromides in the presence of titanium tetraisopropoxide (selected examples).

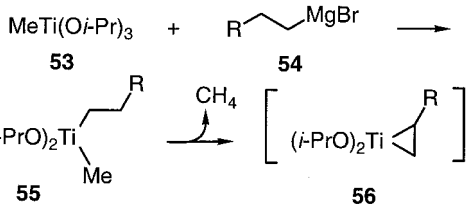
Entry	R^1	R^2	R^3	R^4	*Yield (%) (d. r.)*	*Ref.*
1	Me	Bn	H	H	60	[104]
2	Et	Bn	H	H	63	[104]
3	*n*Pr	Bn	H	H	52	[104]
4	*n*Pr	Bn	*n*Bu	H	35	[104]
5	H	Bn	H	H	73	[104]
6	H	$-(CH_2)_5-$	H	H	74	[104]
7	H	$-(CH_2)_2O(CH_2)_2-$	H	H	74	[104]
8	H	*t*Bu	H	H	20	[104]
9	H	Bn	Me	H	63 (1:1)	[104]
10	H	Bn	*n*Bu	H	52 (1:2.3)	[104]
11	Me	Bn	Et	H	47	[62]
12		Me	Et	H	42 (10:1)	[69]
13	H	Bn	$-(CH_2)_4-$		34	[62]
14	Me	Me	*n*Bu	H	38 (>25:1)	[108]
15	H	Bn	$CH_2=CH-$	H	42 (>25:1)	[108]
16	$-CH_2CH_2-$	$-CH_2CH_2-$, Bn	H	H	21	[108]
17	$-(CH_2)_4-$	$-(CH_2)_4-$, Me	H	H	33	[108]

methylsilane (1 equiv.), *cis*- and *trans*-2-ethenyl-1-dibenzylaminocyclopropanes **49** and **50** could be prepared from dibenzylformamide **48** and 1-buten-4-ylmagnesium bromide in a ratio of 1:7 [111]. The latter was obtained with an enantiomeric excess of up to 56 % (Scheme 11.14; the absolute configuration was not determined; *cf.* also Scheme 11.6). With a sub-stoichiometric amount of the titanium reagent present, but with no trimethylsilyl chloride, the yields of **49** and **50** were only 6 % and 41 %, respectively, with the *ee* for **50** being only 24 %.



Scheme 11.14. Preparation of enantiomerically enriched *trans*-2-ethenyl-1-dibenzylaminocyclopropane **50** [111]. [a] Enantiomeric excess not determined.

Since benzyl groups can be removed from *N*,*N*-dibenzylcyclopropylamines by catalytic hydrogenation over palladium catalysts, primary cyclopropylamines are accessible by this methodology. Thus, the theoretically interesting tricyclopropylamine [106,107] could be prepared from benzylcyclopropylformamide by a sequence of reductive cyclopropanation of the formyl group, hydrogenolytic debenzylation, *N*-formylation, and repeated reductive cyclopropanation [106,107].



Scheme 11.15. Formation of the reactive titanacyclopropane intermediate **56** from methyltitanium triisopropoxide and a Grignard reagent.

Improved yields of cyclopropylamines **47** could be obtained by using methyltitanium triisopropoxide (**53**) instead of titanium tetraisopropoxide [108], as well as by adding the Grignard reagent to the mixture of the amide and the titanium reagent at ambient rather than low temperature (Schemes 11.15 and 11.16, and Table 11.9) [67,69]. In principle, methyltitanium triisopropoxide requires only one equivalent of the alkylmagnesium halide to generate a dialkyltitanium diisopropoxide intermediate **55**, and in this particular case β-hydride elimination can only occur at the non-methyl substituent so that methane

Table 11.9. *N*,*N*-Dialkylcyclopropylamines **47** from *N*,*N*-dialkylcarboxamides **44** and ethyl- as well as substituted ethylmagnesium bromides **27** in the presence of methyltitanium triisopropoxide.

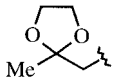
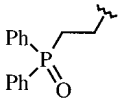
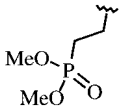
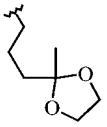
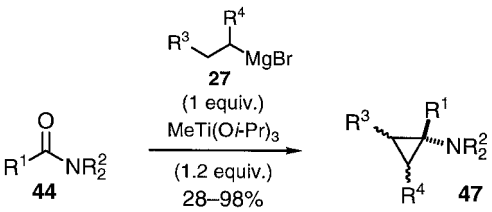
Entry	R^2	R^1	R^3	R^4	*Yield (%) (d. r.)*	*Ref.*
1	Bn	H	H	H	95	[67,109]
2	Bn	H	Me	H	89 (1:1.1)	[67]
3	Bn	Et	H	H	70	[67,109]
4	Bn	Pr	H	H	62	[67,109]
5	Me	$-CH_2CH_2CH_2-$		H	28	[62,108]
6	Bn	H	$CH_2=CH$	H	98 (1:7)	[67]
7	Bn	$BnOCH_2$	Et	H	48 (1:5)	[109,110]
8	Bn	$BnOCH_2$	*i*Pr	H	42 (1:3)	[110]
9	Bn	*i*Pr	H	H	44	[67,109]
10	*i*Pr	H	H	H	86	[67]
11	Bn	H	Ph	H	98 (1:2.3)	[67]
12	Bn	H	tBuO$(CH_2)_3$	H	59 (1:2)	[67]
13	Bn	H		H	92 (1:1.5)	[67]
14	$(CH_2)_5$	H	Ph	H	92 (1:1.5)	[67]
15	Bn	$ClCH_2CH_2$	H	H	49	[109]
16	Bn	$BnOCH_2CH_2$	Me	H	33 (1:3)	[109]
17	Bn		$CH_2=CH$	H	61	[67]
18	Bn	$BnCH_2O$	$BnOCH_2CH_2$	H	40 (1:3)	[109]
19	Me		$CH_2=CH$	H	83 (1:3)	[67,69]
20	Me		Ph	H	82 (1:1.4)	[67,69]
21	Bn	H	$-CH_2CH_2CH_2-$		89	[67]
22	Me	H	$CH_2=CH$	H	57 (17:1)	[108]
23	Me	H	$BnOCH_2CH_2$	H	54 (1.1:1)	[108]
24	Bn	H	THPO$(CH_2)_2$	H	34 (2.1:1)	[108]

Table 11.9. Continued.

Entry	R^2	R^1	R^3	R^4	Yield (%) (d. r.)	Ref.
25	Me	H		H	53 (1.8:1)	[108]
26	$-(CH_2)_5-$	Ph	H	H	73	[67]
27	Et	H	H	H	83	[67]
28	Bn		H	H	85	[67]
29	Me	H	$-CH_2CH_2-$		72	[67]
30	Bn	H	$-CH_2CH_2-$		87	[67]
31	Bn	H	$-CH(CH_3)CH_2-$		87	[67]

is liberated selectively. This is an advantage – and likewise for the production of certain cyclopropanols from esters – with valuable, e. g. functionally substituted, Grignard reagents, since one does not sacrifice one equivalent of the reagent as an alkane in the formation of the corresponding titanacyclopropane **56** (Scheme 11.15). By using an excess of the alkylmagnesium halide, in spite of the presence of the sacrificial methyl substituent on the titanium reagent, the yields based on the carboxamide substrate can be increased to as high as 92–98 % (Table 11.9, entries 1, 6, 11, 13, and 14). This is particularly beneficial in cases where the carboxamide is more precious than the Grignard reagent. This modification has also been successfully applied in the intramolecular reductive cyclopropanation of *N,N*-dialkylcarboxamides, in which the Grignard reagent **27** was generated in situ from ω-bromocarboxamides and metallic magnesium (Table 11.9, entry 5).

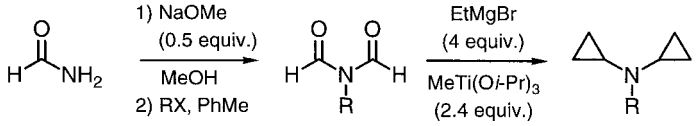


Scheme 11.16. Preparation of *N,N*-dialkylcyclopropylamines **47** in the presence of methyltitanium triisopropoxide. For details, see Table 11.9.

It is remarkable that even cyclobutylmagnesium bromides react cleanly with titanium alkoxides to yield reactive titanacyclopropane intermediates that reductively cyclopropanate *N,N*-dialkylformamides. This constitutes the first synthesis of the highly strained *N,N*-dialkylbicyclo[2.1.0]pent-5-ylamines (Table 11.9, entries 29–31).

The reductive cyclopropanation with in situ generated titanacyclopropanes can also be applied to alkyldiformylamines **58**, which are easily prepared from inexpensive formamide (**57**). Both formyl groups are converted to cyclopropyl groups, and the alkyldicyclopropyl-

amines **59** are obtained in yields ranging from good to very good (Scheme 11.17) [67]. This new method for the preparation of dicyclopropylamines compares favorably with the previously published [112] reductive amination of cyclopropanone alkyl silyl acetals with primary amines, as the reagents used in this current protocol are commercially available and are far less expensive.



57 **58** **59**

RX	R	%	%
$(MeO)_2SO_2$	Me	70	67
$(EtO)_2SO_2$	Et	71	82
n-BuOMs	*n*-Bu	74	53
All-Br	All	52	0
BnBr	Bn	97	57

Scheme 11.17. The twofold reductive cyclopropanation of alkyldiformylamines **58** [67].

11.4.2
Via Ligand-Exchanged Titanium–Alkene Complexes

In view of their versatile new synthesis of dialkylcyclopropylamines from *N,N*-dialkylcarboxamides through titanacyclopropane intermediates generated from Grignard reagents and $XTi(OiPr)_3$ (X = O*i*Pr, Me) [104,108], de Meijere et al. also turned their attention to the additional synthetic potential of titanacyclopropane intermediates generated by ligand exchange [69,105,113]. This approach was also applied by Cha et al. [86,96,114] to a whole range of alkenes, and has since been established as an efficient method for the formal dialkylaminocyclopropanation not only of mono-, but also of some disubstituted alkenes and cycloalkenes (for selected examples, see Table 11.10).

The optimized protocol has also been applied to a wide range of open-chain and cyclic dienes (for selected examples, see Table 11.11) [113]. The latter generally give higher yields than non-terminal alkenes and cycloalkenes, except for strained ones such as *N*-benzylpyrroline, cyclopentene, and norbornene (Table 11.10, entries 20–22).

Surprisingly, reactions with substituted 1,3-dienes such as isoprene, 4-methyl-1,3-pentadiene, and myrcene all gave the alkenyldibenzylaminocyclopropanes derived from putative attack on the more highly substituted double bond of the conjugated diene unit, and not the expected products that would have been formed by attack on the least substituted double bond (entries 1–4, Table 11.11). As these expected products could not be detected in any case, and as control experiments with 2,3-dimethylbutadiene and 2,5-dimethyl-2,4-hexadiene did not yield any cyclopropylamines, it must be concluded that the alkenyldiisopropyloxy-titanacyclopropane **60**, with the least substituted double bond of the conjugated diene attached to the titanium, is kinetically – and possibly thermodynamically – favored. The formamide **48** then undergoes cycloaddition with this alkenyltitanacyclopropane **60** through a metallaene reaction with a six-center transition state to yield an oxatitanacycloheptene **61**. This intermediate can cyclore-

Table 11.10. *N,N*-Dialkylcyclopropylamines **47** from *N,N*-dialkylcarboxamides and alkenes via ligand-exchanged titanium intermediates obtained from Grignard reagents and $XTi(OiPr)_3$ (X = O*i*Pr, Cl, Me, OR).

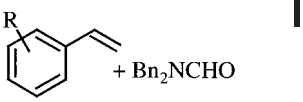
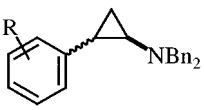
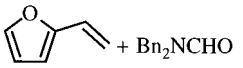
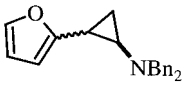
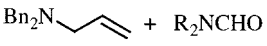
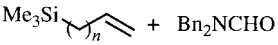
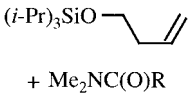
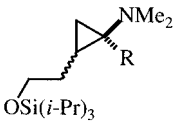
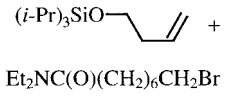
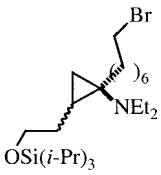
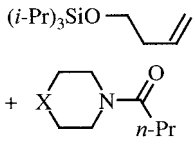
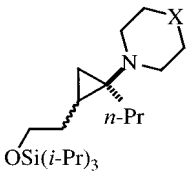
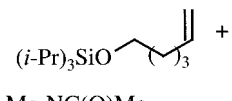
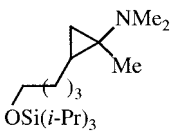
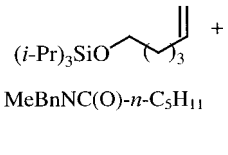
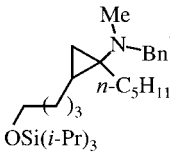
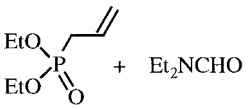
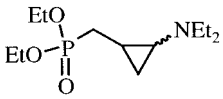
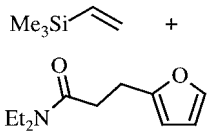
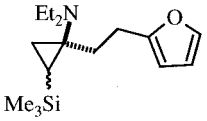
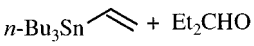
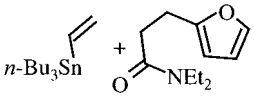
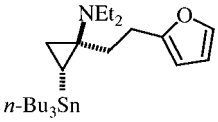
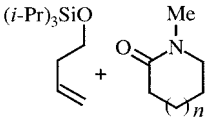
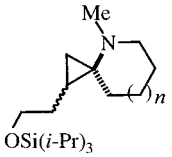
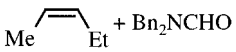
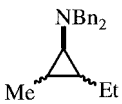
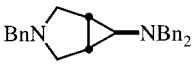
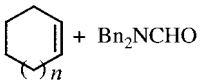
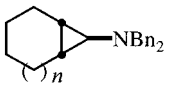
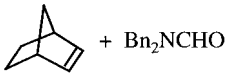
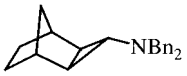
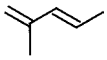
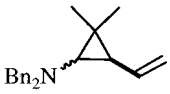
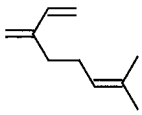
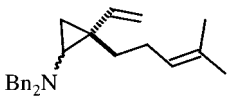
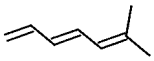
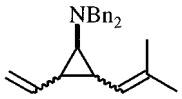
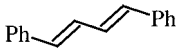
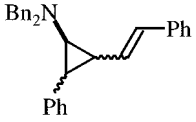
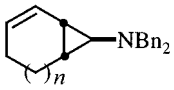
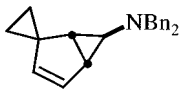
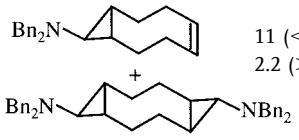
Entry	*Alkene, Starting Amide*	*Product*	*Yield (%) (d. r.)*	*Ref.*
				
1	R = H	R = H	66 (1:3.2)	[105, 113]
2	R = 4-OMe	R = 4-OMe	45[a] (1:1.2)	[113]
3	R = 2-CF_3	R = 2-CF_3	13[a] (1:4)	[113]
4	R = 3-CF_3	R = 3-CF_3	56 (1:11)	[113]
5	R = 4-CF_3	R = 4-CF_3	18[a] (0:1)	[113]
6			43 (1:4)	[113]
7			44[a] (R = Me) (1:5) 39[a] (R = Bn) (1:4)	[113]
8			38[a] (*n* = 0) (0:1) 28[a] (*n* = 1) (0:1)	[113]
9			61 (R = H) (1:2.2) 68 (R = Me) (6.3:1) 56 (R = *n*-Pr) (5.3:1)	[85, 114]
10			60 (7.6:1)	[85]
11			69 (X = CH_2) (7.3:1) 77 (X = O) (3.1:1)	[85, 114]
12			n. r.[b]	[115]

Table 11.10. Continued.

Entry	Alkene, Starting Amide	Product	Yield (%) (d. r.)	Ref.
13			n. r.[b]	[115]
14			36[a] (1.6:1)	[69]
15			68 (1:6.5)	[96]
16			57	[96]
17			68	[96]
18			21 ($n = 0$) (1.0:0) 79 ($n = 1$) (6.2:1)	[96]
19			26[a] (1:2:6)	[113]
20			87	[105b, 113]
21			28 ($n = 0$) 28 ($n = 1$) 33 ($n = 3$)	[113]
22			43 (<2:98)	[86]

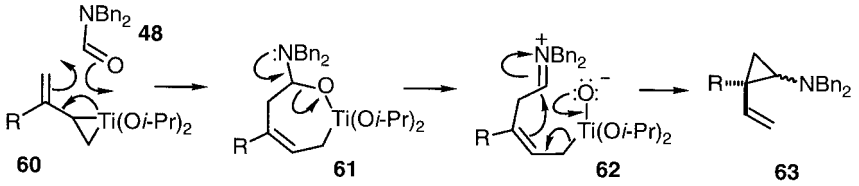
[a] Not optimized.
[b] n. r. = Not reported.

Table 11.11. 2-Alkenyl-1-(*N*,*N*-dibenzylamino)cyclopropanes formed from *N*,*N*-dibenzylformamide (**48**) and titanium-diene complexes generated in situ by ligand exchange.

Entry	*Alkene*	*Product*	*Yield (%) (d. r.)*	*Ref.*
1			56 (R = H) (1:2.7) 59 (R = Me) (>98:2)	[113, 116]
2			64 (1:5.3)	[113, 116]
3			27 (1:3)	[113, 116]
4			51 (>98:2)	[113, 116]
5			54 (1:1.5:1.5)	[113, 116]
6			9 (1:0)	[113]
7			(n = 0): No conversion (n = 1): 58 (2:98)	[113]
8			trace	[113]
9			11 (<2:98) 2.2 (>2:98)	[113]

vert to an iminium-allyltitanium oxide 1,8-zwitterion **62**, which can then only cyclize to a cyclopentenylamine or to the observed, more highly substituted cyclopropylamine **63** (Scheme 11.18) [116].

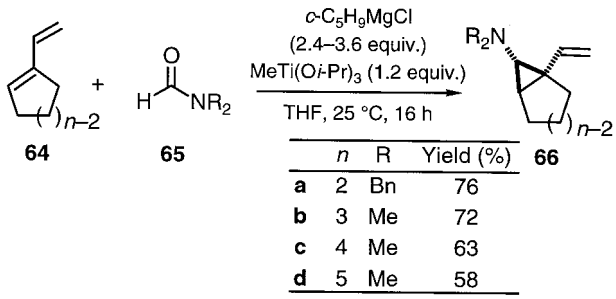
The formation of the same cyclopropylamine from 2-methyl-1,3-pentadiene as from 4-methyl-1,3-pentadiene (entries 2 and 3 in Table 11.11) can most probably be attributed to initial isomerization of the former to the latter under the conditions employed. The fact that the conjugated 6-methyl-1,3,5-heptatriene yields only the 2,3-dialkenylcyclopro-



Scheme 11.18. Aminocyclopropanation of the more highly substituted double bond in a conjugated diene: a mechanistic rationalization [116].

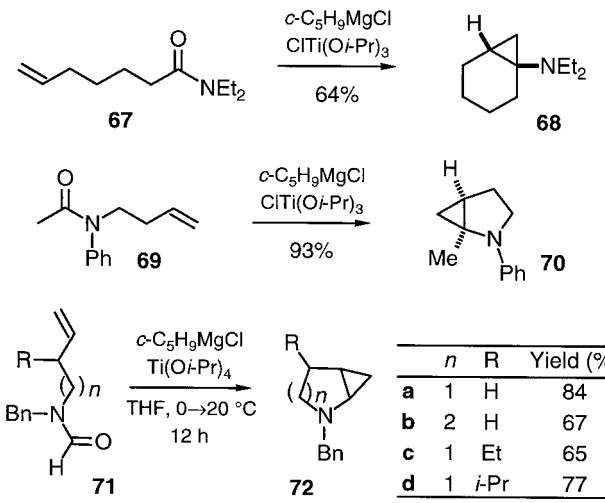
pylamine (entry 5) arising from attack at the central double bond of the triene is in full accord with the notion that the reacting species are actually the less substituted titanacyclopropanes of type **60** and that the transformation to the oxatitanacycloheptene of type **61** occurs as a metallaene reaction [116].

In the analogous reactions of 1-ethenylcycloalkenes **64**, only the endocyclic double bond is involved in the aminocyclopropanation to furnish the (*n*+3)-(dialkylamino)-1-ethenylbicyclo[*n*.1.0]alkanes **66**. It is noteworthy that the yield of **66** steadily increases on going from the larger seven-membered ring **64d** to the smaller four-membered ring **64a**, so that the best yield is obtained for the most highly strained 1-ethenylbicyclo[2.1.0]pent-5-ylamine **66a** (Scheme 11.19) [67,117].



	n	R	Yield (%)
a	2	Bn	76
b	3	Me	72
c	4	Me	63
d	5	Me	58

Scheme 11.19. Aminocyclopropanation of 1-ethenylcycloalkenes **64**.

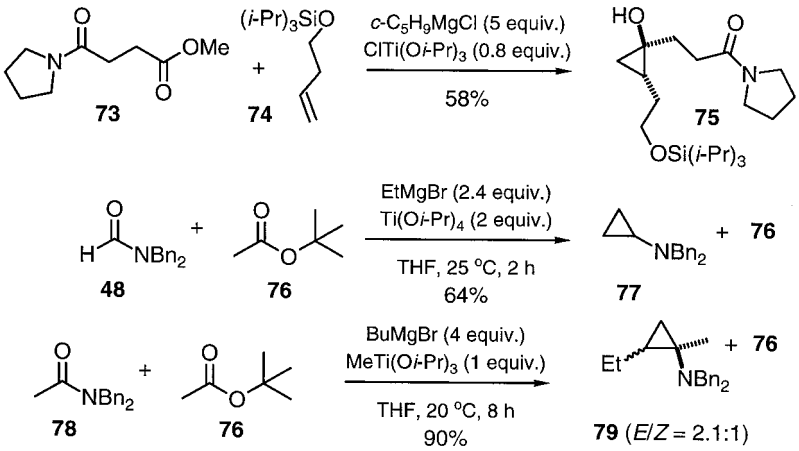


	n	R	Yield (%)
a	1	H	84
b	2	H	67
c	1	Et	65
d	1	*i*-Pr	77

Scheme 11.20. Intramolecular aminocyclopropanations of terminal alkenes [86,118].

Versions of these aminocyclopropanations of terminal alkenes can also be applied intramolecularly. Terminally ethenyl-substituted *N,N*-dialkylcarboxamides such as **67** yield 1-(dialkylamino)bicyclo[*n*.1.0]alkanes such as **68**, while (ω-alkenylamino)carboxamides such as **69** and **71** lead to 1-alkyl-2-azabicyclo[*n*.1.0]alkanes such as **70** and **72** (Scheme 11.20) [86,118], and *N*-allylamino acid *N,N*-dialkylamides furnish bicyclic diamines (see below).

In the hydroxycyclopropanation of alkenes, esters may be more reactive than *N,N*-dialkylcarboxamides, as is illustrated by the exclusive formation of the disubstituted cyclopropanol **75** from the succinic acid monoester monoamide **73** (Scheme 11.21) [91]. However, the reactivities of both ester- as well as amide-carbonyl groups can be significantly influenced by the steric bulk around them [81,91]. Thus, in intermolecular competitions for reaction with the titanacyclopropane intermediate derived from an alkylmagnesium halide and titanium tetraisopropoxide or methyltitanium triisopropoxide, between *N,N*-dibenzylformamide (**48**) and *tert*-butyl acetate (**76**) as well as between *N,N*-dibenzylacetamide (**78**) and *tert*-butyl acetate (**76**), the amide won in both cases and only the corresponding cyclopropylamines **77** and **79**, respectively, were obtained (Scheme 11.21) [62,119].

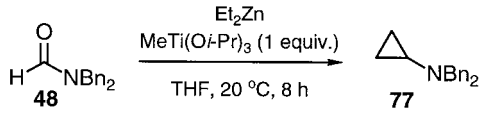


Scheme 11.21. Competition between aminocyclopropanation and hydroxycyclopropanation reactions [91,119].

11.4.3
From Organozinc Precursors

As diorganylzinc reagents are less nucleophilic than organomagnesium compounds and can easily be prepared with a variety of functional groups, including ester moieties [120], their potential application in the preparation of functionalized aminocyclopropanes would appear to be very promising. In a first attempt it was found that, in the presence of methyltriisopropoxytitanium, diethylzinc reacts with dibenzylformamide (**48**) under conditions commonly employed for alkylmagnesium halides, to give *N,N*-dibenzylaminocyclopropane (**77**), albeit in only 21 % yield [67]. A systematic study of this reaction revealed that the yield could be significantly improved by the addition of alkali metal alkoxides, and

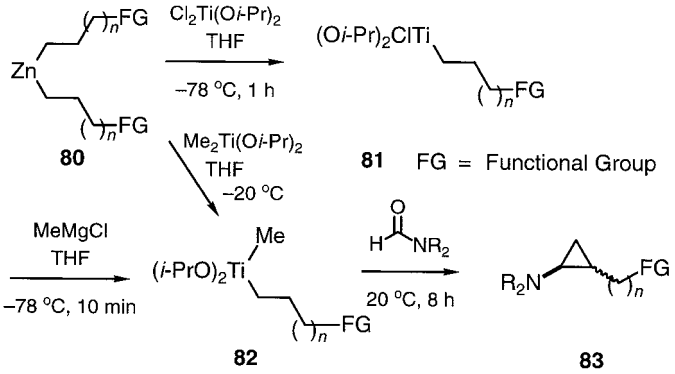
an optimum yield of 89 % was achieved by using 2 equiv. of NaO*i*Pr and 2 equiv. of Et_2Zn (Scheme 11.22) [119].



Base Additive (equiv.)	Et_2Zn (equiv.)	Yield (%)
None	2	21
NaO*i*-Pr (1)	2	52
NaOEt (2)	2	82
NaO*i*-Pr (2)	2	89
NaO*i*-Pr (2)	1	82
NaO*i*-Pr (2)	0.5	43

Scheme 11.22. Reactions of diethylzinc with dibenzylformamide **48** in the presence of methyltriisopropoxytitanium and an added alkoxide base [119].

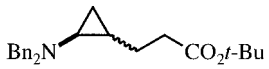
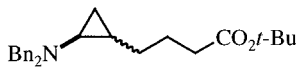
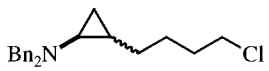
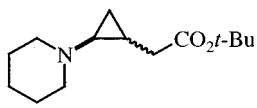
However, it was found that under the conditions optimized for diethylzinc, the reductive cyclopropanations of *N,N*-dialkylcarboxamides could not be carried out with differently functionalized organozinc reagents. Nevertheless, monoalkylation of dichlorotitanium diisopropoxide with a diorganozinc reagent **80**, followed by treatment with methylmagnesium chloride to substitute the second chlorine atom in **81** with a methyl group, provided the titanium intermediates of type **82**. These exhibit essentially the same reactivity pattern as the titanium intermediates generated from Grignard reagents, and transform *N,N*-dialkylformamides to yield the correspondingly substituted dialkylaminocyclopropane derivatives **83**. The reagent **82** can also be prepared directly from **80** and dimethyltitanium diisopropoxide (Scheme 11.23 and Table 11.12) [119].



Scheme 11.23. Preparation of various functionally substituted aminocyclopropanes from diorganozinc reagents **80** and *N,N*-dialkylcarboxamides [119].

This new protocol provides easy access to various functionally substituted aminocyclopropanes, including cyclopropylamino acid derivatives [119], although the yields and diastereoselectivities obtained with this approach leave room for further improvement.

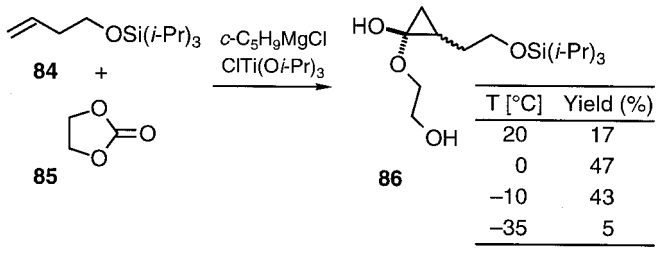
Table 11.12. Functionally substituted *N*,*N*-dibenzylcyclopropylamines **83** from *N*,*N*-dialkylformamides and organozinc precursors (see Scheme 11.23).

Product	*Conditions*[a]	*Yield (%)*	*E/Z* Ratio
	A	49	1.1:1
	B	40	1.2:1
	A	36	1.2:1
	B	24	1.1:1
	A	21	1.1:1
	A	19	1.1:1
	B	27	1.2:1
	A	61	1.2:1
	B	65	1.2:1
	A	57	1.1:1
	B	61	1.1:1
	B	60	2.0:1
	B	63	1.3:1
	B	60	1.8:1

[a] A: $Zn(CH_2CH_2FG)_2$ (1.5 equiv.), $Cl_2Ti(OiPr)_2$ (1.3 equiv.), MeMgCl (5 equiv.), THF, −78 to 20 °C, 8 h.
B: $Zn(CH_2CH_2FG)_2$, $Me_2Ti(OiPr)_2$, MeMgCl (1 equiv. each), THF, −30 to 20 °C, 8 h.

11.5
Applications in Natural Product Syntheses and Syntheses of Compounds with Potentially Useful Properties

Several applications of cyclopropanols and cyclopropylamines prepared by the described methodology in the syntheses of natural products as well as compounds of practical use, e. g. for the construction of a cyclopropane ring present in a given target molecule [59,60,92,121] or a key intermediate [65,66,75,122], have been reported since the discoveries of these transformations. For example, dialkyl carbonates can be converted to cyclopropanone hemiacetals **86** in moderate yields using titanacyclopropane intermediates generated by ligand exchange with terminal alkenes [91,97]. The best yields of **86** were obtained with the cyclic ethylene carbonate **85** at −10 to 0 °C. At higher reaction temperatures (even ambient), the yield decreased considerably (Scheme 11.24) [97].



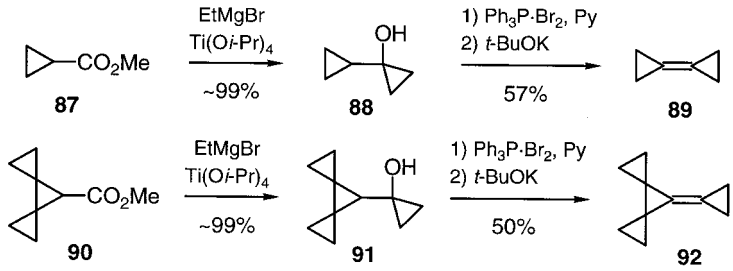
T [°C]	Yield (%)
20	17
0	47
–10	43
–35	5

Scheme 11.24. Conversion of ethylene carbonate (**85**) to the cyclopropanone hemiacetal **86** [97].

11.5.1

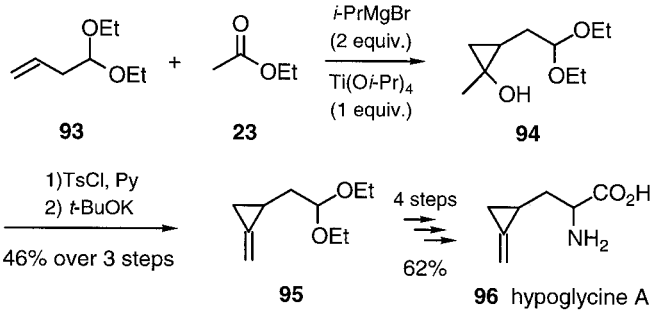
Transformations of Cyclopropanols with Retention of the Cyclopropane Ring

This methodology offers the best means of preparing the key precursors to bicyclopropylidene (**89**) [59,60] and its bis-spirocyclopropanated analogue **92** [59], since methyl cyclopropanecarboxylate (**87**) and ethyl dispiro[2.0.2.1]heptane-7-carboxylate (**90**) are virtually quantitatively converted to 1-cyclopropylcyclopropanol (**88**) and 1-(dispiro[2.0.2.1]-hept-7-yl)cyclopropanol (**91**), respectively (Scheme 11.25) [59]. The same approach has successfully been applied for the preparation of other strained bicyclopropylidene derivatives [72,121].



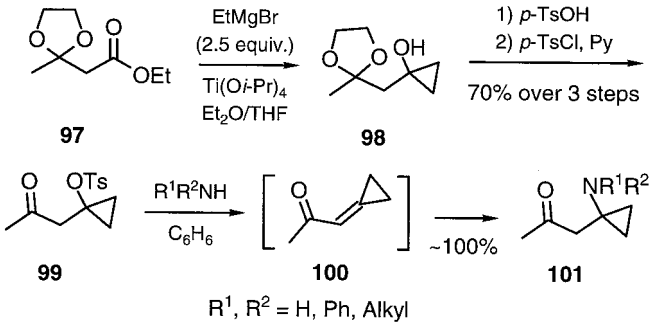
Scheme 11.25. Preparation of the key precursors to bicyclopropylidene (**89**) and its bis-spirocyclopropanated analogue **92** [59].

Thus, in a novel synthesis of hypoglycine A (**96**), hydroxycyclopropanation of ethenylacetaldehyde diethyl acetal (**93**) followed by formal dehydration of the cyclopropanol **94** via its tosylate intermediate gave the methylenecyclopropane species **95**, a key precursor to the target amino acid (Scheme 11.26) [92].



Scheme 11.26. Novel synthesis of hypoglycine A (**96**) by hydroxycyclopropanation of ethenylacetaldehyde diethyl acetal (**93**) [92].

A carbonyl group in the β-position of a cyclopropanol tosylate fragment, as in **99**, facilitates the elimination so that it occurs upon treatment of the tosylate **99** with a primary or secondary amine. An ensuing Michael addition of the amine to the α,β-unsaturated ketone **100** then yields the β-(1-aminocyclopropyl)ketone **101**, the product of a formal substitution of the hydroxy group in the cyclopropanol precursor to **99** (Scheme 11.27) [123].



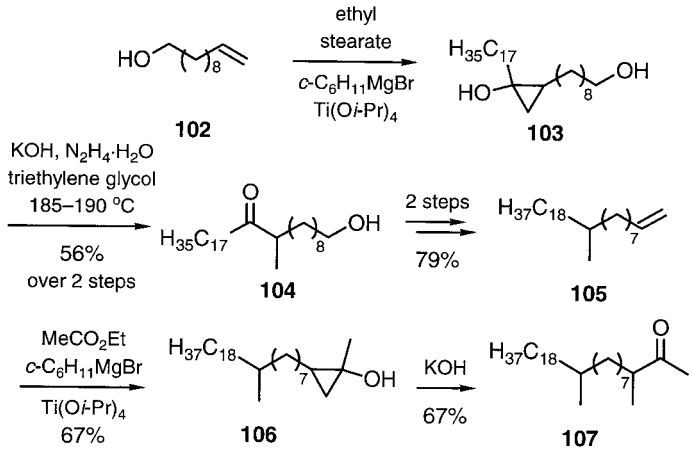
Scheme 11.27. Straightforward transformation of the cyclopropanol **98** into aminocyclopropane derivative **101** [123].

11.5.2
Transformations of Cyclopropanols with Cleavage of the Cyclopropane Ring

Cyclopropanols are prone to ring-opening reactions. The wide variety of such ring-opening reactions and their applications in the preparation of synthetically useful organic compounds has been reviewed [124]. The main ring-opening mode of cyclopropanols, under both basic and acidic conditions, leads to the formation of differently substituted saturated and unsaturated ketones. For instance, synthetically useful α-methyl ketones [88] have been prepared by the regioselective cleavage of 1,2-dialkylcyclopropanols upon treatment with potassium hydroxide [125]. *N*-Bromosuccinimide is usually the reagent of choice for brominative ring-opening of 1-substituted cyclopropanols leading to 2-bromoethyl ketones [65,124]. Bromine in aqueous MeOH has been used for the regioselective conversion of 1,2-dialkylcyclopropanols to 2-bromoethyl alkyl ketones [88], and the pyridine–bromine complex, which is commonly employed to prepare differently substituted 1,8-dibromo-3,6-octanediones [78], proved to be also applicable to the bromination of the acid-sensitive functionally substituted cyclopropanol **98** [93]. The resulting β-bromo ketones can easily be dehydrobrominated, thereby furnishing the corresponding vinyl ketones [66,76,78,93] or α-methylene ketones [84]. Several natural products have been prepared using this type of ring-cleavage reaction as a key step.

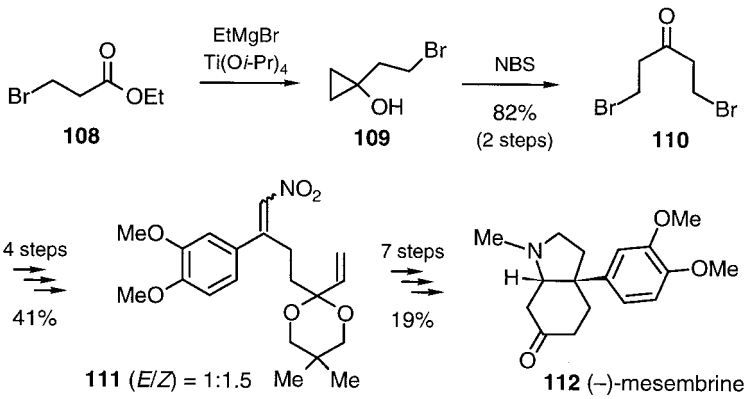
A convenient new approach to 3,11-dimethylnonacosan-2-one (**107**), a component of the sex pheromone of the German cockroach *Blattella germanica*, using 1,2-disubstituted cyclopropanols as key intermediates has been elaborated [88]. The construction of the branched chain of **107** was based on the regioselective base-induced cleavage of 1,2-disubstituted cyclopropanols **103** and **106** to give the corresponding α-methyl ketones **104** and **107** [88]. The key intermediates **104** and **106** were prepared by hydroxycyclopropanation of the alkenes **102** and **105** with ethyl stearate and ethyl acetate, respectively (Scheme 11.28).

An efficient total synthesis of the *Sceletium* alkaloid (−)-mesembrine **112** has been accomplished in seven steps and 19% overall yield from the functionally substituted



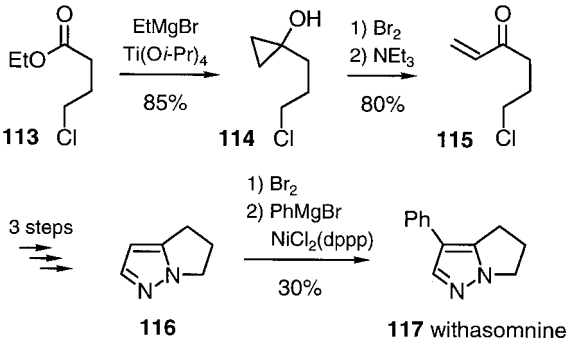
Scheme 11.28. 1,2-Disubstituted cyclopropanols as key intermediates in a new access to 3,11-dimethylnonacosan-2-one (**107**) [88].

nitroalkene **111** by applying a domino [4+2]/[3+2]-cycloaddition sequence as a key step for the construction of the quaternary carbon center in the target molecule [75]. The precursor nitroalkene **111** was prepared in four steps (41 % overall yield) from 1,5-dibromopentan-3-one (**110**), for which the previously reported approach [65] to 1,5-dihalopentan-3-ones based on the transformation of alkyl 3-haloalkanoates with the Ti(O*i*Pr)$_4$/EtMgBr reagent and subsequent ring-opening bromination of the substituted cyclopropanol, in this case **109**, with *N*-bromosuccinimide, was applied (Scheme 11.29).



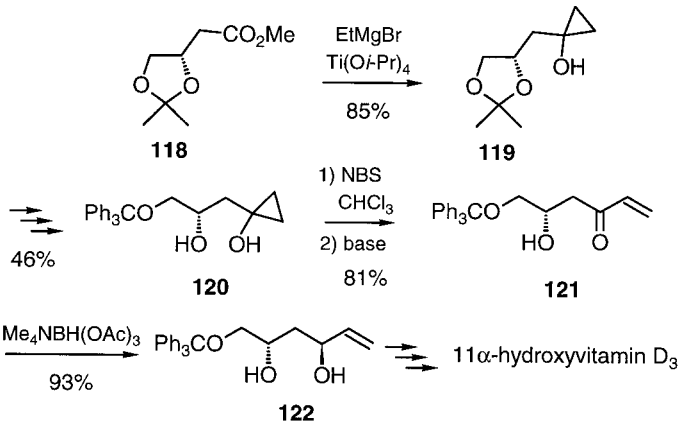
Scheme 11.29. Total synthesis of the *Sceletium* alkaloid (−)-mesembrine **112** [75].

The transformation of ethyl 4-chlorobutyrate with the Ti(O*i*Pr)$_4$/EtMgBr reagent also proceeds with high yield (85 %) to give 1-(3-chloropropyl)cyclopropanol (**114**), which, by ring-opening bromination with bromine and subsequent dehydrobromination, gave the vinyl ketone **115** as a key intermediate in the synthesis of the pyrazole alkaloid withasomnine **117** by selective bromination of **116** and subsequent nickel-catalyzed cross-coupling with phenylmagnesium bromide (Scheme 11.30) [66].



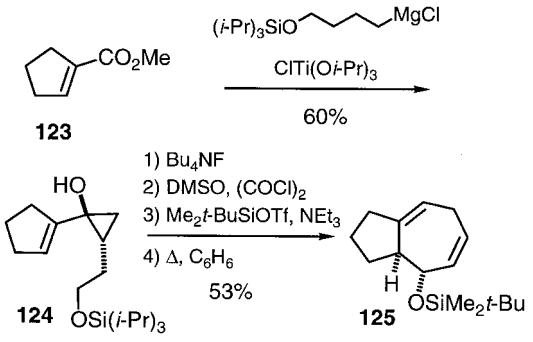
Scheme 11.30. Synthesis of the pyrazole alkaloid withasomnine **117**, with cyclopropanation of ethyl 4-chlorobutyrate (**113**) as an initial step [66].

The transformation of an ester group into a vinyl ketone moiety has also been used for the preparation of the *anti*-diol **122** as a key intermediate in the synthesis of the 11α-hydroxyvitamin D_3 [76]. To obtain **122**, the ester **118**, which is easily accessible from L-(+)-malic acid ester, was used as the chiral enantiomerically pure starting material to give, by reaction with ethylmagnesium bromide in the presence of titanium tetraisopropoxide, the cyclopropanol derivative **119**. After appropriate manipulations of the protecting groups on the 1,2-diol unit, the cyclopropanol derivative **120** was transformed into the vinyl ketone **121**. Diastereoselective reduction of the latter with $Me_4NBH(OAc)_3$ gave the key intermediate **122** in high yield (Scheme 11.31).



Scheme 11.31. The transformation of an ester group in **118** into a vinyl ketone moiety in the preparation of the *anti*-diol **122** [76].

An interesting application of a 1,2-disubstituted cyclopropanol in a seven-membered ring-annelation methodology has been developed by Cha et al. [82]. The cyclopropanol **124**, obtained from methyl 1-cyclopentenecarboxylate (**123**) and 4-(triisopropylsilyloxy)-butylmagnesium chloride, was converted to a 1,2-dialkenylcyclopropanol bis-silyl ether, which, by a subsequent facile Cope rearrangement, afforded the cycloheptadiene-annelated cyclopentane derivative **125** in 32 % overall yield (Scheme 11.32).

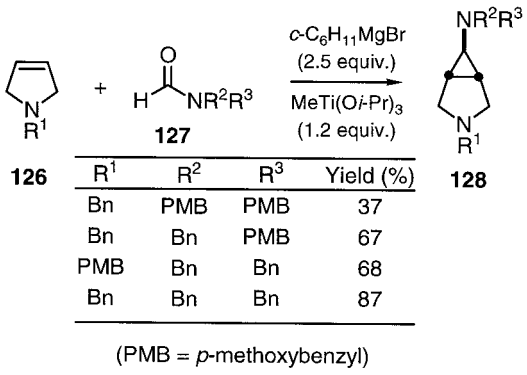


Scheme 11.32. Transformation of methyl 1-cyclopentenecarboxylate (**123**) to cycloheptadienyl-annelated cyclopentane derivative **125** via cyclopropanol **124** [82].

11.5.3
Transformations of Cyclopropylamines

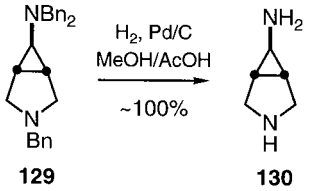
Among the biologically interesting cyclopropylamines, one of the important targets was 3-azabicyclo[3.1.0]hexylamine **130**, a key component of the commercial antibiotic trovafloxacin [126]. In fact, *N*-protected 2,5-dihydropyrroles **126** were found to undergo rapid ligand exchange, especially with the titanacyclopropane generated from cyclohexylmagnesium halides and $XTi(OiPr)_3$ (X = O*i*Pr, Me), and the resulting intermediates were found to react efficiently with *N,N*-disubstituted formamides **127** to give the tris-protected *exo*-6-amino-3-azabicyclo[3.1.0]hexanes **128** in up to 87% yield [105b,113]. The unprotected diamine **130** was obtained by catalytic hydrogenation under appropriate conditions (Scheme 11.33) [113].

The structurally related 1-amino-substituted azabicyclo[3.1.0]hexanes **132** were prepared by intramolecular cyclopropanation of *N'*-allylaminoacetic acid *N,N*-dimethylamides **131** as diastereomeric mixtures (Scheme 11.34) [127].

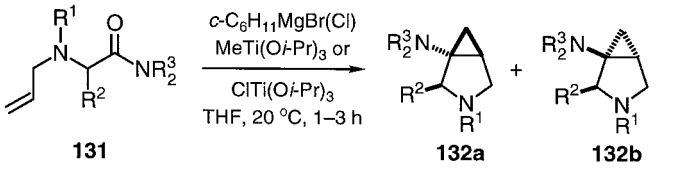


R^1	R^2	R^3	Yield (%)
Bn	PMB	PMB	37
Bn	Bn	PMB	67
PMB	Bn	Bn	68
Bn	Bn	Bn	87

(PMB = *p*-methoxybenzyl)



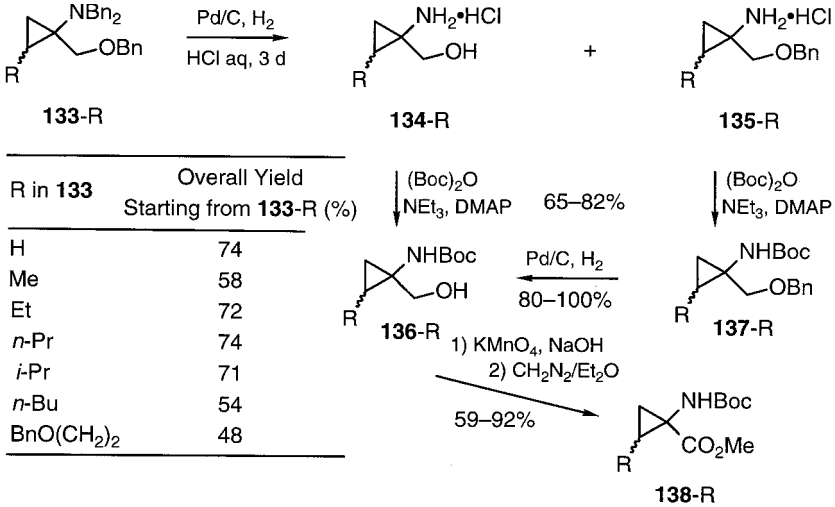
Scheme 11.33. Aminocyclopropanation of *N*-protected 2,5-dihydropyrroles **126** and debenzylation of the *exo*-6-amino-3-azabicyclo[3.1.0]hexane **129** [105b,113].



131 132a 132b

R^1	R^2	R^3	Yield (%)	Ratio **132a/132b**	Ref.
Bn	Bn	Me	83	2.6 : 1	[127a]
Bn	*p*-TBSOBn	Me	83	2.6 : 1	[127a]
Bn	TBDMSOCH$_2$	Me	89	2 : 1	[127b]
Bn	H	Bn	50	–	[127b]
Me	H	Bn	48	–	[127b]

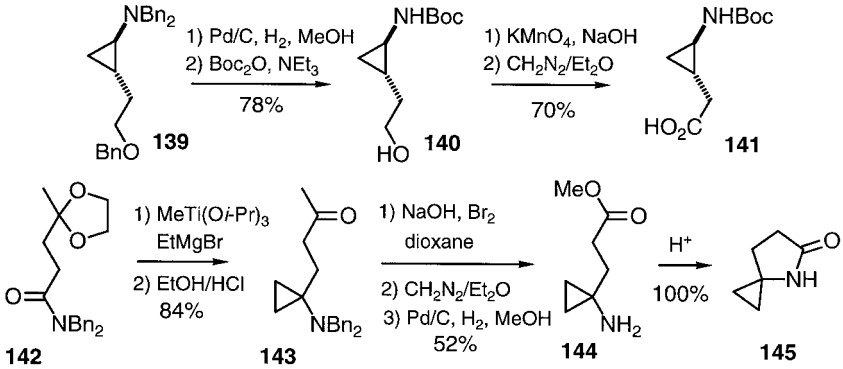
Scheme 11.34. Preparation of 1-amino-substituted azabicyclo[3.1.0] hexanes **132** [127].



133-R 134-R 135-R 136-R 137-R **138-R**

R in **133**	Overall Yield Starting from **133**-R (%)
H	74
Me	58
Et	72
n-Pr	74
i-Pr	71
n-Bu	54
BnO(CH$_2$)$_2$	48

Scheme 11.35. Preparation of various protected substituted 1-aminocyclopropanecarboxylic acid (ACC) derivatives **138**-R from *N*,*N*-dibenzylamino(benzyloxymethyl)cyclopropanes **133**-R [109,110].



139 **140** **141** **142** **143** **144** **145**

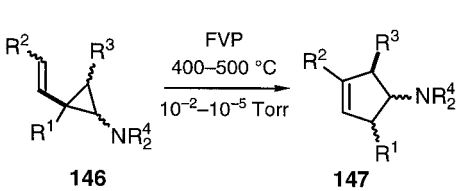
Scheme 11.36. Preparation of 3,4-methano-γ-aminobutyric acid **141** and 4-spirocyclopropane-γ-butyrolactam (**145**) [109,110,119b].

Applying only a few simple operations, the dibenzylaminocyclopropanes **133**-R, prepared as described above from *N*,*N*-dibenzyl-α-benzyloxyacetamide in 33–48 % yield (see Scheme 11.16 and Table 11.9), have been transformed into *N*-Boc-protected methyl esters of amino acids **138**-R containing a cyclopropane moiety (Scheme 11.35) [109,110]. Several such analogues of natural amino acids, also referred to as methanoamino acids, exhibit important biological activities [128].

Similarly, the *N*-Boc-protected 3,4-methano-γ-aminobutyric acid **141** and the 4-spirocyclopropane-γ-butyrolactam **145** have been obtained in overall yields of 55 % and 44 %, respectively (Scheme 11.36) [109,110,119b].

Upon flash vacuum pyrolysis or under silver nitrate catalysis, a variety of 2-ethenyl-substituted cyclopropylamines **146** cleanly undergo a vinylcyclopropane to cyclopentene rearrangement [129] and afford high yields (up to 95 %) of 4-aminocyclopent-1-enes **147**, some of which have unprecedented substitution patterns (Scheme 11.37) [130].

Analogously, under similar conditions, the (*n*+3)-(dimethylamino)-1-ethenylbicyclo[*n*.1.0]alkanes **66** (see Scheme 11.19) undergo ring-enlargement to (*n*+1)-dimethylaminobicyclo[*n*.3.0]alkenes **148** (Scheme 11.38) [117]. As was demonstrated for **148** ($n = 2$), this thermal rearrangement can be brought about more cleanly by heating the starting material **66** in decalin at 220 °C for 1 h (90 % yield). The overall sequence starting from a cycloalkanone and proceeding via a 1-ethenylcycloalkene to yield bicyclo[*n*.3.0]alkenes **148** constitutes a new cyclopentene annelation methodology. Through quaternization with methyl iodide followed by Hofmann elimination, compounds **148** may be transformed into mixtures of fused cyclopentadienes **150** and **151** in 64–78 % overall yield (Scheme 11.38) [117,131].

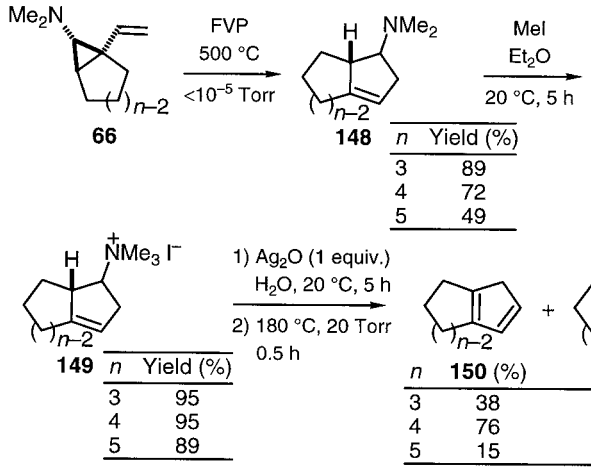


146 **147**

R^1	R^2	R^3	R^4	Yield (%)
H	H	H	Me	90
H	H	H	Bn	95
Me	H	H	Bn	90
[a]	H	H	Bn	54
H	Ph	Ph	Bn	27

[a](3-Isopropylidene)propyl

Scheme 11.37. Vinylcyclopropane to cyclopentene rearrangement of 2-alkenyl-substituted cyclopropylamines **146** [130].



66 **148**

n	Yield (%)
3	89
4	72
5	49

149

n	Yield (%)
3	95
4	95
5	89

n	**150** (%)	**151** (%)
3	38	42
4	76	6
5	15	57

Scheme 11.38. Vinylcyclopropane to cyclopentene rearrangement in (*n*+3)-(dimethylamino)-1-ethenylbicyclo[*n*.1.0]alkanes **66** [117].

11.6 Conclusion

Monocarbanionic organometallic reagents in the presence of stoichiometric or sub-stoichiometric (semi-catalytic) quantities of certain titanium derivatives may act as dicarbanionic equivalents in reactions with electrophiles. The key step in the transformation of a monocarbanionic into a 1,2-dicarbanionic organometallic is a disproportionation reaction of a dialkyltitanium intermediate to form a titanacyclopropane derivative. These highly reactive organometallic compounds apparently exhibit the properties of reagents with two carbon–metal σ-bonds and are able to react as equivalents of 1,2-dicarbanionic moieties with the carbonyl groups of carboxylic esters and *N*,*N*-dialkylcarboxamides to give cyclopropanols and *N*,*N*-dialkylcyclopropylamines, respectively. They can also undergo ligand exchange with alkenes to afford new titanacyclopropanes, which may subsequently react as 1,2-dicarbanionic equivalents. In the recently reported systematic evaluation of several titanium alkoxides and aryloxides [132], chlorotitanium triisopropoxide and/or methyltitanium triisopropoxide were found to be the reagents of choice for the ligand-exchange modification, whereas the original Kulinkovich protocol proved to be insensitive to the nature of the titanium alkoxide. In many cases, these titanium-mediated reactions of non-transition organometallics proceed in good yields and with high chemo- and stereoselectivity. These features, in conjunction with the simplicity of the experimental procedures and the low cost of the reagents, make these reactions favorable for an ever increasing range of applications in organic synthesis.

Typical Procedures

1-Cyclobutylcyclopropanol [133] To a well-stirred solution of ethyl cyclobutanecarboxylate [134] (56.47 g, 0.441 mol) and titanium tetraisopropoxide (26.3 mL, 88.2 mmol, 20 mol%) in anhydrous diethyl ether (200 mL), ethylmagnesium bromide (0.980 mol, 276 mL of a 3.55 M solution in Et_2O) was added over a period of 3 h. The temperature was maintained at between 20 and 25 °C with a water bath. After the addition was complete, the mixture was stirred for an additional 0.5 h at the same temperature, then cooled to −5 °C, whereupon the reaction was quenched by the careful addition of ice-cold 10% aqueous sulfuric acid (500 mL) while the temperature was maintained between −5 and 0 °C with an acetone/dry ice bath. The mixture was stirred at 0 °C for an additional 1 h and then the aqueous phase was extracted with Et_2O (100 mL). The combined ethereal phases were washed with saturated aq. $NaHCO_3$ solution (2 × 200 mL) and brine (200 mL), dried, and concentrated at water-pump pressure at 20 °C to give 48.92 g (99%) of 1-cyclobutylcyclopropanol. The spectroscopic data of the product were identical to those reported in the literature [135].

2-(2,2-Diethoxyethyl)-1-methyl-1-cyclopropanol (94) [93] To a gently boiling solution of vinylacetaldehyde diethyl acetal (7.73 mL, 44.4 mmol), ethyl acetate (4.42 mL, 44.4 mmol), and $Ti(OiPr)_4$ (6.53 mL, 22.2 mmol) in anhydrous Et_2O (30 mL), a solution of *n*BuMgBr (133.2 mmol) in Et_2O (110 mL) was added dropwise over a period of 3 h. After the addition was complete, the reaction mixture was stirred for an additional 1 h and then poured into 10% aqueous NaOH (150 mL). The aqueous layer was extracted

with Et_2O (4 × 50 mL). The combined organic solutions were dried ($MgSO_4$) and, after evaporation of the solvent under reduced pressure, the crude product **94** was purified by column chromatography on Al_2O_3. Yield 6.69 g (80 %). The spectroscopic data of the product were identical to those reported in the literature [92].

1-Acetonyl-1-hydroxycyclopropane ethylene acetal (98) [123] A solution of ethylmagnesium bromide (62.5 mmol) in a mixture of anhydrous THF (10 mL) and Et_2O (30 mL) was added to a solution of acetoacetic ester ethylene acetal **97** (4.36 g, 25 mmol) and $Ti(OiPr)_4$ (1.42 g, 5 mmol) in THF (60 mL) kept at 15−20 °C over a period of 2 h. The reaction mixture was stirred for an additional 1 h and was then treated with saturated NH_4Cl solution (30 mL) and extracted with Et_2O (3 × 50 mL). The combined ethereal extracts were washed with brine (50 mL) and dried (Na_2SO_4). The product was distilled under reduced pressure (b. p. 79−81 °C/2 Torr); yield 3.18 g (80 %). Its spectroscopic data were identical to those reported in the literature [71].

(1*R*,2*R*,5*S*)-3-Benzyl-1-dimethylamino-2-(*tert*-butyldimethylsilyloxymethyl)-3-azabicyclo-[3.1.0]hexane (132) [127b, c] To a well-stirred solution of 2-(allylbenzylamino)-2-(*tert*-butyldimethylsilyloxy)-*N,N*-dimethylpropionamide (**131**; 2.15 g, 5.7 mmol) and methyltitanium-triisopropoxide (2.06 g, 8.6 mmol) in anhydrous THF (150 mL), cyclohexylmagnesium bromide (34 mmol, 35 mL of a 0.98 M solution in Et_2O) was added dropwise at room temperature. After the addition was complete, the mixture was stirred for an additional 4 h and then poured into ice/water (100 mL) and stirred for an additional 1 h. Et_2O (100 mL) was added and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined ethereal phases were washed with saturated $NaHCO_3$ (100 mL) and brine (100 mL), dried, and concentrated at atmospheric pressure. The product was purified by column chromatography on silica gel (hexane/Et_2O, 2:1); yield 1.834 g (89 %), *endo*/*exo* = 2:1. ^{1}H NMR (*endo*): δ = 7.28−7.18 (m, 5 H), 4.21 (d, *J* = 13.5 Hz, 1 H), 3.9 (dd, *J* = 4.3, 19.6 Hz, 1 H), 3.71 (dd, *J* = 4.8, 10.6 Hz, 1 H), 3.31 (d, *J* = 13.5 Hz, 1 H), 3.02 (t, *J* = 4.5 Hz, 1 H), 2.72 (d, *J* = 8.9 Hz, 1 H), 2.47 (s, 6 H), 2.36 (dd, *J* = 4.0, 8.9 Hz, 1 H), 1.33−1.26 (m, 1 H), 1.04 (t, *J* = 4.3 Hz, 1 H), 0.91 (s, 9 H), 0.61 (dd, *J* = 4.3, 8.6 Hz, 1 H), 0.07 (s, 6 H); ^{13}C NMR: δ = 139.8 (C), 128.5 (2 CH_{ar}), 128.5 (2 CH_{ar}), 128.0 (CH_{ar}), 65.3 (CH_2), 62.5 (CH), 58.7 (CH_2), 54.2 (CH_2), 42.0 (2 CH_3), 26.0 (3 CH_3), 23.3 (CH), 18.3 (C), 14.7 (CH_2), 1.1 (3 CH_3). ^{1}H NMR (*exo*): δ = 7.30−7.22 (m, 5 H), 4.00 (d, *J* = 13.9 Hz, 1 H), 3.88−3.85 (m, 2 H), 3.78 (d, *J* = 13.9 Hz, 1 H), 3.06−3.01 (m, 2 H), 2.61 (d, *J* = 7.8 Hz, 1 H), 2.21 (s, 6 H), 1.64−1.57 (m, 1 H), 0.94 (s, 9 H), 0.89−0.85 (m, 1 H), 0.66 (dd, *J* = 3.5, 8.5 Hz, 1 H), 0.08 (s, 3 H), 0.07 (s, 3 H).

3-Benzyl-6-*exo*-(dibenzylamino)-3-azabicyclo[3.1.0]hexane (128) [105b,113] To a stirred solution of *N*-benzylpyrroline (**126**; 1.49 g, 9.37 mmol) and $Ti(OiPr)_4$ (2.84 g, 10.0 mmol) in anhydrous THF (5 mL), methylmagnesium chloride (10.2 mmol, 3.4 mL of a 3 M solution in THF) was added dropwise over a period of 5 min at 0−5 °C. A solution of *N,N*-dibenzylformamide (**48**; 2.25 g, 10.0 mmol) in anhydrous THF (10 mL) was then added in a single portion. The resulting solution was allowed to warm to ambient temperature and was stirred for a further 10 min. Cyclohexylmagnesium bromide (21.4 mmol, 14 mL of a 1.53 M solution in THF/benzene, 3:1) was then added dropwise by means of a cannula over a period of 50 min at ambient temperature, and the resulting

mixture was heated under reflux for 15 min. Water (2 mL) was subsequently added to the still hot reaction mixture, which was then diluted with pentane (15 mL). The colorless precipitate obtained was removed by filtration and washed with pentane (50 mL). The resulting solution was concentrated under reduced pressure and then filtered through silica gel (60 g) eluting with pentane/EtOAc (1:1). The solvents were removed under reduced pressure to furnish 3.25 g of almost pure **128** (according to its ^{1}H NMR spectrum), which could be further purified by kugelrohr distillation (170 °C/10^{-4} Torr) to give 3.0 g (87 %) of **128** as a pale-yellow oil. ^{1}H NMR: δ = 1.34 (br. s, 2 H), 2.29 (br. s, 1 H), 2.36–2.40 (br. d, J = 8.5 Hz, 2 H), 2.96 (d, J = 8.8 Hz, 2 H), 3.63 (s, 2 H), 3.73 (s, 4 H), 7.20–7.35 (m, 15 H, 3 Ph); ^{13}C NMR: δ = 25.6, 44.9, 54.4, 58.8, 59.1, 126.7, 126.8, 127.9, 128.1, 128.4, 129.5, 138.9, 139.5.

Benzyl-*N*,*N*-dicyclopropylamine (59) [67] To a well-stirred solution of benzyl-*N*,*N*-diformylamine (**58**; 816 mg, 5.0 mmol) and methyltitanium triisopropoxide (2.88 g, 12.0 mmol) in anhydrous THF (50 mL), ethylmagnesium bromide (20.2 mmol, 11.2 mL of a 1.80 M solution in Et_2O) was added dropwise at room temperature. After the addition was complete, the reaction mixture was stirred for a further 16 h and then water (5 mL) was added. The resulting mixture was filtered, the precipitate was washed with Et_2O (50 mL), and the combined ethereal phases were dried with K_2CO_3 and concentrated under reduced pressure. Column chromatography (50 g of silica gel, 20 × 2.5 cm column, hexane/Et_2O, 10:1, R_f = 0.38) gave **59** (534 mg, 57 %) as a colorless oil. ^{1}H NMR: δ = 0.37–0.50 (m, 8 H, CH_2 Cpr), 1.80–1.89 (m, 2 H, CH Cpr), 3.85 (s, 2 H, CH_2), 7.25–7.36 (m, 5 H, Ph); ^{13}C NMR: δ = 6.2 (4 CH_2, Cpr), 35.7 (2 CH, Cpr), 60.4 (CH_2), 126.7, 127.8, 129.9 (CH), 137.5 (C). IR: $\tilde{\nu}$ = 3087, 3011, 2921, 2819, 1494, 1454, 1355, 1218, 1176, 1022, 754, 702 cm^{-1}.

Acknowledgements

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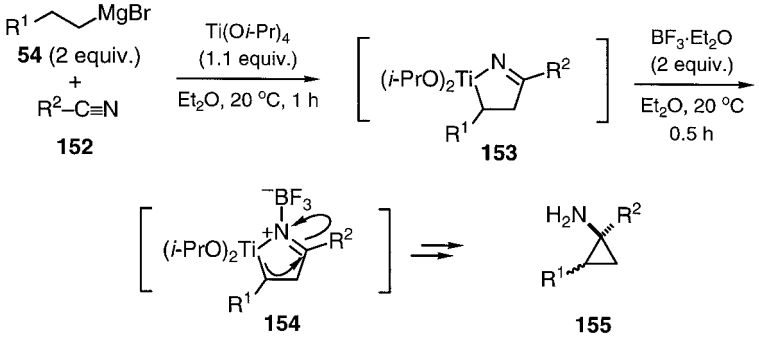
Addendum

In order to keep this chapter as up to date as possible, several new contributions that have appeared in the literature since the original manuscript was submitted are compiled here.

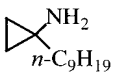
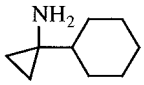
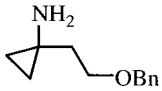
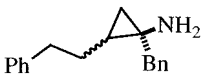
Early attempts to convert aliphatic nitriles into primary cyclopropylamines, in the same way as *N*,*N*-dialkylcarboxamides **44** are transformed to *N*,*N*-dialkylcyclopropylamines **47** under the action of Grignard reagents and Ti(O*i*Pr)$_4$, were unfruitful [136]. However, Szymoniak et al. have found that the addition of a Lewis acid such as boron trifluoride etherate is necessary to activate azatitanacyclopentene **153** resulting from insertion of

the nitrile **152** into the titanium–carbon bond of the initially formed reactive titanacyclopropane intermediate (Scheme 11.39) [137]. Under the action of BF_3, the ring-contraction of **154** occurs readily and, after basic work-up, the unprotected primary cyclopropylamines **155** are isolated in good yields (Table 11.13) [137].



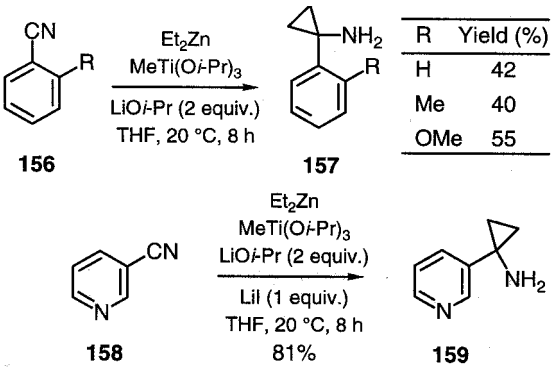
Scheme 11.39. Preparation of primary cyclopropylamines **155** from aliphatic nitriles **152** [137]. An intramolecular version of this reaction has also very recently been reported [127c].

Table 11.13. Cyclopropylamines **155** from aliphatic nitriles **152**, Grignard reagents, and $Ti(OiPr)_4$ in the presence of $BF_3 \cdot OEt_2$ (see Scheme 11.39).

Entry	*Grignard Reagent* R^1	*Starting Nitrile 152* R^2	*Product*	*Yield (%) (d.r.[a])*
1	H	Bn		70
2	H	*n*-C_9H_{19}		70
3	H	Cyclohexyl		52
4	*n*-C_4H_9	Bn		57 (64:36)
5	H	$BnO(CH_2)_2$		54
6	$Ph(CH_2)_2$	Bn		51 (68:34)

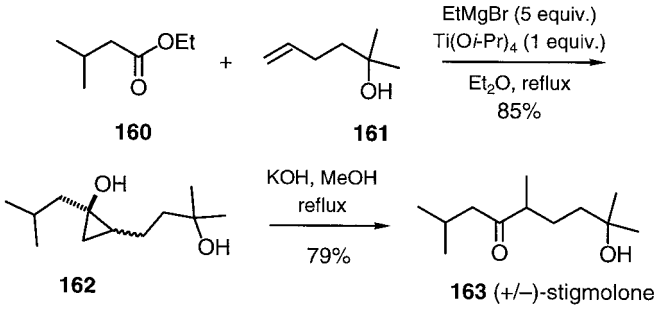
[a] d. r. = diastereomeric ratio

Surprisingly, aromatic nitriles were found not to yield 1-arylcyclopropylamines under these conditions. However, this deficit is compensated for by a complementary method developed by de Meijere et al. using diethylzinc in the presence of methyltitanium triisopropoxide and lithium isopropoxide (Scheme 11.40). While aliphatic nitriles **152** gave primary cyclopropylamines **155** in only 12–16 % yield with this reagent mixture, aromatic nitriles **156** and **158** furnished 1-arylcyclopropylamines **157** and **159** in moderate (28–40 % for substituted benzonitriles **156**) to good (70 % for 3-cyanopyridine **158**) yields (Scheme 11.40) [138].



Scheme 11.40. Synthesis of 1-arylcyclopropylamines from aromatic nitriles by reaction with diethylzinc in the presence of $MeTi(OiPr)_3$ and $NaOiPr$ [138].

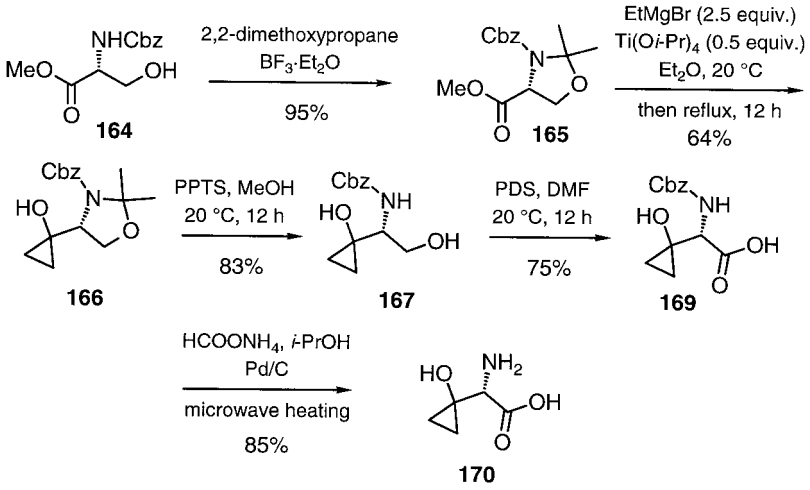
Progress has also been reported in applying titanium-mediated cyclopropanation reactions as a key step in the preparation of natural products. For example, racemic stigmolone (8-hydroxy-2,5,8-trimethylnonan-4-one) **163**, a pheromone of the myxobacterium *Stigmatella aurantiaca*, has been synthesized in 67 % overall yield by the titanium-mediated hydroxycyclopropanation of 2-methyl-5-hexen-2-ol **161** with ethyl isovalerate **160** followed by base-induced ring-opening of the resulting 2-(3-hydroxy-3-methylbutyl)-1-isobutyl-1-cyclopropanol **162** (Scheme 11.41) [139].



Scheme 11.41. Two-step synthesis of (+/−)-stigmolone **163** [139].

An elegant six-step synthesis of enantiomerically pure (*S*)-cleonin **170** [140], a key component of the antitumor antibiotic cleomycin, starting from (*R*)-serine has been elaborated by Taddei et al. [141]. The methoxycarbonyl group of the protected serine ester **165** was converted to a hydroxycyclopropyl moiety by the Kulinkovich reaction. Oxazolidine ring-opening in the resulting **166**, followed by PDC oxidation and Pd-catalyzed removal of the Cbz protecting group, gave enantiomerically pure (*S*)-cleonin **170** in 26 % overall

yield starting from (*R*)-serine (Scheme 11.42) [141]. This methodology has also been successfully applied in the preparation of several non-natural cyclopropyl-substituted glycines [141].



Scheme 11.42. First stereocontrolled synthesis of (*S*)-cleonin [141].

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12
Titanocene-Catalyzed Epoxide Opening

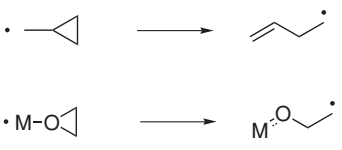
Andreas Gansäuer and Björn Rinker

12.1
Introduction

Over the past three decades, radicals have been increasingly utilized as reactive intermediates in organic synthesis [1]. Their ease of generation, high functional group tolerance, and predictable behavior in many transformations have led to numerous developments of novel methods for the efficient formation of C–C bonds. Most of these methods involve typical free-radical reactions, for which the usual selectivities are substrate-controlled [2]. Reagent-controlled radical transformations have emerged more recently [3]. In this context, epoxides, which can readily be prepared by a number of methods [4], are a very interesting class of radical precursors. They can easily bind to radical-generating Lewis acidic electron-transfer reagents and therefore allow reagent-controlled formation of radicals and subsequent reagent-induced radical reactions. To date, titanocene complexes have proven to be the most promising reagents in this context [5]. In this chapter, we present current results in this field and focus on the recently developed catalytic reaction conditions.

12.2
Stoichiometric Opening of Epoxides by Electron Transfer

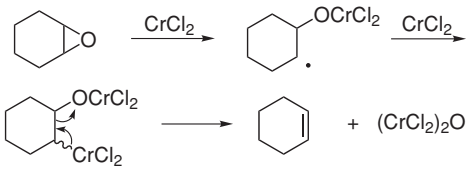
Due to their high reactivity, epoxides have been used in a plethora of synthetic applications, most notably in nucleophilic substitutions. The strained three-membered ring can, however, also be successfully employed as an electron acceptor in reductive ring-opening by low-valent metal complexes. The general concept behind this type of transformation has been outlined by Nugent and RajanBabu and is illustrated in Scheme 12.1 [5]. The overall transformation can thus be regarded as an analogue of the well-established opening of cyclopropylcarbinyl radicals to give butenyl radicals [6].



Scheme 12.1. Opening of epoxides with low-valent metal complexes.

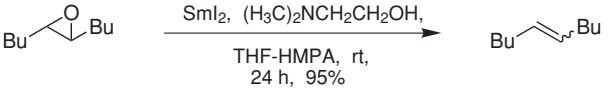
In the case of epoxides, β-metaloxy radicals are formed. These constitute interesting intermediates for organic synthesis because they can either be further reduced to give β-metaloxy metal species or can be used in typical transformations of radicals.

The participation of β-metaloxy metal species in this context was first discussed by Kochi, Singleton, and Andrews in 1968 [7] in relation to their deoxygenation of styrene and cyclohexene oxide by chromium(II) reagents, as shown in Scheme 12.2.



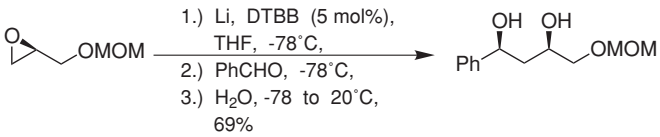
Scheme 12.2. Deoxygenation of cyclohexene oxide with chromium(II) chloride.

The proposed mechanism includes a reductive epoxide opening, trapping of the intermediate radical by a second equivalent of the chromium(II) reagent, and subsequent β-elimination of a chromium oxide species to yield the alkene. The highly potent electron-transfer reagent samarium diiodide has also been used for deoxygenations, as shown in Scheme 12.3 [8].



Scheme 12.3. Deoxygenation of epoxides with samarium diiodide.

The mixture of (*E*) and (*Z*) isomers obtained is indicative of a radical ring-opening mechanism because the initially formed intermediate is trapped with low stereoselectivity to yield two diastereomeric samariumoxy samarium species, which undergo elimination to give the alkene isomers. In order to exploit the carbanionic reactivity of the dimetallated intermediate in C−C and C−X bond-forming reactions, it is necessary to produce a thermally stable organometallic compound. This goal was first achieved by Bartmann in 1986 by the use of radical anions of biphenyl [9]. Cohen [10] and Yus [11] have applied this methodology in the synthesis of more complex molecules. An example is shown in Scheme 12.4.

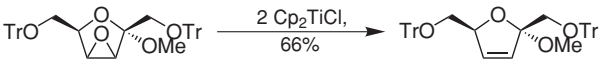


Scheme 12.4. Opening of epoxides in the presence of aromatic radical anions.

According to calculations by Houk and Cohen, the first intermediate in these reactions is the radical anion of an epoxide [12].

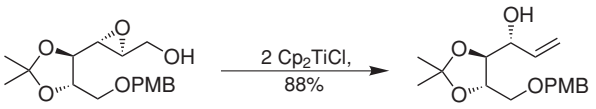
The β-metaloxy radical was first exploited for synthetic purposes in C−H and C−C bond-forming reactions by Nugent and RajanBabu through the use of titanocene(III) chloride as an electron-transfer reagent [5]. They established that the β-titaniumoxy radicals formed after electron transfer can be reduced by hydrogen atom donors, e. g. 1,4-cyclohexadiene or *tert*-butyl thiol, that they add to α,β-unsaturated carbonyl compounds, and that they can react intramolecularly with olefins in 5-*exo* cyclizations.

It should not be forgotten, however, that titanocene(III) complexes are also excellent reagents for the deoxygenation of epoxides, as demonstrated independently by Schobert [13] and by Nugent and RajanBabu [5d]. An example of a reaction yielding a highly acid-sensitive product in reasonable yield is shown in Scheme 12.5.



Scheme 12.5. Deoxygenation in the presence of titanocene chloride.

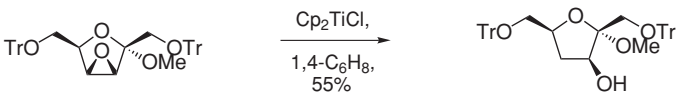
Another interesting application of the deoxygenation reaction is shown in Scheme 12.6. Sharpless epoxides are transformed to enantiomerically pure allylic alcohols [14]. It should be noted that the disadvantage of the loss of one-half of the allylic alcohol, as in the case of kinetic resolutions of allylic alcohols, is not a problem when this protocol is employed.



PMB = *p*-MeOC$_6$H$_4$CH$_2$

Scheme 12.6. Synthesis of enantiomerically pure allylic alcohols with titanocene chloride.

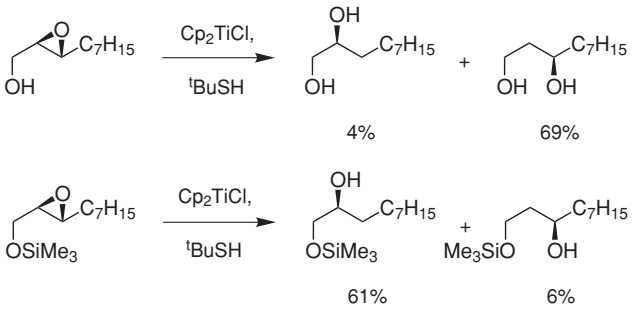
Transformations exploiting typical radical reactivity have been used in a number of synthetic applications. These are discussed first, before attention is turned to the development of the catalytic reaction conditions. The reductive opening of epoxides usually yields the less substituted alcohol through formation of the higher substituted radical. In analogy to the calculations of Cohen and Houk [12], one may envisage a titanocene(IV)-bound epoxide radical anion as the intermediate. The observed regioselectivity of epoxide-opening could then be explained in terms of the avoidance of substantial steric interactions between the ligands and the bulkier substituent of the epoxide. Thus, the more highly substituted β-titanoxy radical would be formed. This selectivity is complementary to that of the Bartmann ring-opening [9]. Although one might also envisage a reversible epoxide opening to give the more stable radical, this typical Curtin–Hammett scenario [15] seems unlikely as the selectivity of epoxide opening is independent of the radical trap employed. An example of a reduction of an epoxide is shown in Scheme 12.7.



Scheme 12.7. Reductive epoxide opening with titanocene chloride.

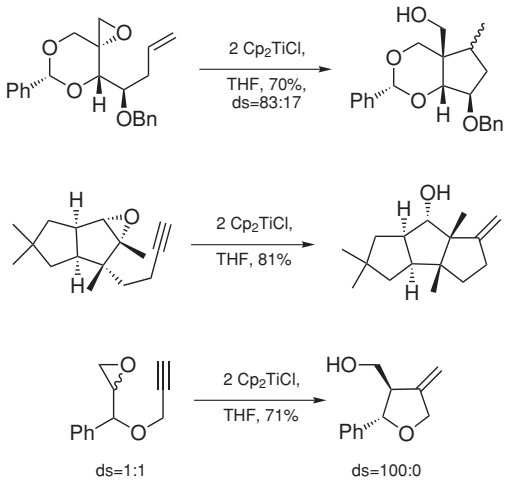
When the epoxide is 1,2-disubstituted, steric and electronic effects are responsible for the preferential formation of one product. In this context, benzyl radicals are always produced irrespective of the substitution pattern of the epoxide. For these intermediates, the more reactive *tert*-butyl thiol is the hydrogen atom donor of choice. Chelation of titanium can be used to good effect for regioselective epoxide opening, as shown in Scheme 12.8 [5d].

More recently, Doris et al. have described the reductive ring-opening of α-keto epoxides [16]. In this manner, β-hydroxy ketones can be obtained in high yields. The synthesis of enantiomerically pure compounds can easily be realized. The titanocene(III) reagents are distinctly superior to samarium diiodide, which is also known to induce this transformation.



Scheme 12.8. Chelation as a means for controlling the regioselectivity of epoxide opening.

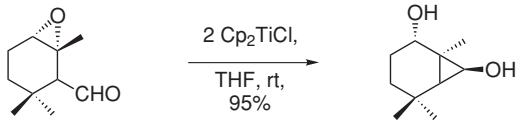
The formation of C−C bonds is generally considered to be more important than the formation of C−H bonds. It is therefore not surprising that these reactions have attracted more attention. Of special importance in organic synthesis are 5-*exo* cyclizations [17], and the titanocene-mediated reactions are a valuable tool for carrying out these transformations. Three examples are shown in Scheme 12.9.



Scheme 12.9. Titanocene-mediated *5-exo* cyclizations.

The observation of a stereoconvergent cyclization by Roy et al. [18], as shown in the third example, is of special interest from a synthetic point of view because it exploits the configurational lability of radicals in a favorable manner. The other examples, i. e. Nugent and RajanBabu's cyclization of a carbohydrate-derived epoxide [5d] and Clive's quinane synthesis [19], amply demonstrate the usefulness of the titanocene-initiated epoxide opening.

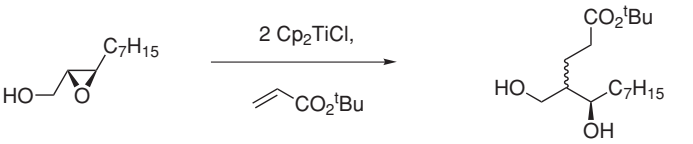
The cyclization of the radicals is not restricted to carbon−carbon multiple bonds as radical traps. An intriguing cyclization utilizing aldehydes as radical acceptors has been reported by Fernández-Mateos et al. [20]. The reaction shown in Scheme 12.10 constitutes a rare example of a highly efficient 3-*exo* cyclization.



Scheme 12.10. Titanocene-mediated highly efficient 3-*exo* cyclization.

Although intermolecular additions to α,β-unsaturated carbonyl compounds have not been used as often, these transformations are also attractive from a synthetic point of view for the synthesis of δ-lactones or δ-hydroxy esters. An example is shown in Scheme 12.11 [5d].

Control of diastereoselectivity has so far remained difficult, however.



73%, mixture of isomers

Scheme 12.11. Intermolecular addition to α,β-unsaturated carbonyl compounds.

12.3 Titanocene-Catalyzed Epoxide Opening

12.3.1 Titanocene-Catalyzed Reductive Epoxide Opening to Alcohols

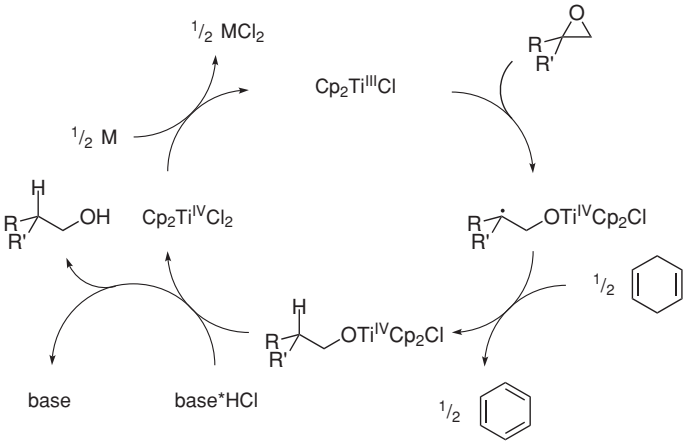
In the stoichiometric applications of titanocene complexes, no attempt to use ligands other than simple cyclopentadienyl has yet been reported. In principle, the use of more complex titanocenes [21] is very interesting because a simple means of exerting reagent control in radical reactions would be at hand. Reagent control can be exercised either at the stage of radical generation or during the ensuing reaction of the generated radical, or indeed in both steps. Intriguing goals in this context are enantioselective ring-openings of *meso* epoxides through electron transfer, ligand-controlled diastereoselective 5-*exo* cyclizations, and diastereoselective addition reactions to α,β-unsaturated carbonyl compounds. Clearly, the stoichiometric use of titanocene complexes that have to be prepared by multistep syntheses is not attractive for these purposes.

Therefore, we decided to initiate a program directed towards the development of a titanocene-catalyzed epoxide opening [3c]. Since titanocene dichloride is formed in the stoichiometric reaction after the protic quench, the challenge to be met is the regeneration of the redox-active species in situ, the fundamental requirement for a catalytic reaction. This underlying problem is depicted in Scheme 12.12.

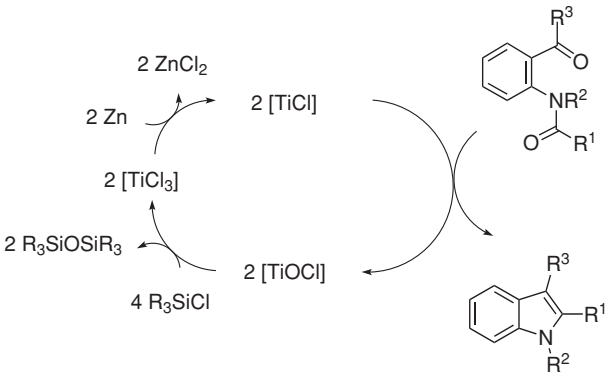
Solutions to similar problems of achieving catalytic turnover [22] in McMurry couplings [23], Nozaki–Hiyama reactions [24], and pinacol couplings [25] have been reported by Fürstner and by Hirao. The key step in these reactions is the in situ silylation of titanium and vanadium oxo species with Me_3SiCl and reduction of the metal halides by suitable metal powders, e. g. zinc and manganese dust, as shown in Scheme 12.13.

This method was later applied to samarium diiodide initiated reactions [26] and to titanocene-catalyzed pinacol couplings [27]. The first examples of enantioselective reactions using Me_3SiCl as a mediator for catalysis have very recently been reported by Cozzi et al., as shown in Scheme 12.14 [28].

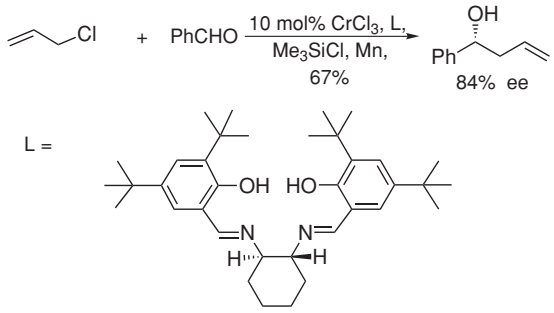
In the case of the epoxide openings, Me_3SiCl is not an appropriate reagent for the cleavage of a titanium alkoxide because of the high oxophilicity of silicon. This results in the



Scheme 12.12. Planned titanocene-catalyzed reductive epoxide opening.



Scheme 12.13. Fürstner's McMurry reaction that is catalytic in titanium.

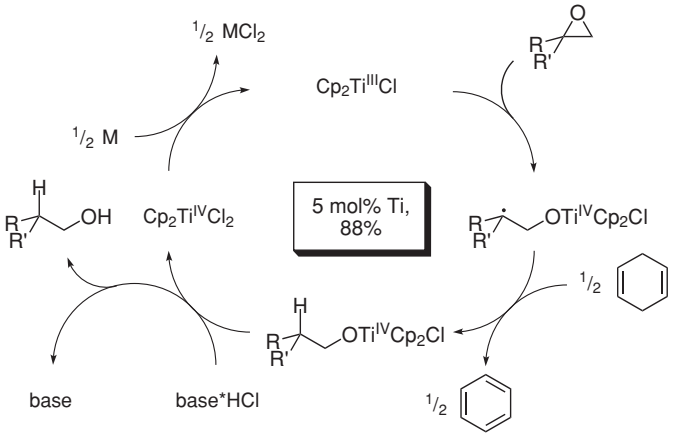


Scheme 12.14. Cozzi's catalytic enantioselective Nozaki–Hiyama reaction.

formation of silylated chlorohydrins from the epoxide. Therefore, we decided to investigate buffered forms of hydrochloric acid as mediators for catalytic turnover. This concept relies on the stability of radicals under protic conditions. On closer examination of the intermediates in the stoichiometric reaction (Scheme 12.12), a number of characteristics of the acid to be employed become apparent:

1. the acid must not be strong enough to open epoxides through S_N1 or S_N2 reactions;
2. the acid must be strong enough to protonate alkoxides so as to enable turnover; the pK_a values of typical alcohols in water are in the range 15–18;
3. the acid must not oxidize the stoichiometric reductant or the titanocene(III) complex;
4. the base liberated must not complex and deactivate any titanium species in the proposed catalytic cycle.

With these conditions in mind, we decided to investigate amine hydrochlorides as mediators [29]. Since pyridine hydrochloride is known to open epoxides to give the corresponding chlorohydrins [30] in chloroform, the employed acid must be weaker than pyridine hydrochloride but should be at least three orders of magnitude more acidic than typical alcohols to ensure quantitative protonation. Therefore, the acid should have a pK_a of 6–12 in water. Among the acids investigated, collidine and lutidine hydrochlorides proved to be excellent mediators for achieving catalytic turnover in the presence of manganese dust as the stoichiometric reductant [31]. Zinc dust, on the other hand, performed distinctly less well. Presumably, the zinc dichloride formed during reduction of titanocene dichloride acted as a Lewis acid, complexing and slowly opening the epoxide. Since the reaction is sensitive to moisture, we prefered to use collidine hydrochloride as the acid because it is distinctly less hygroscopic than lutidine hydrochloride. Under the optimized conditions, the desired product was obtained in good yield. Compared to the stoichiometric conditions [5], the amount of titanocene is reduced at the expense of employing stoichiometric amounts of collidine. A stoichiometric amount of the reductant is utilized in both cases. The resulting catalytic cycle is shown in Scheme 12.15.



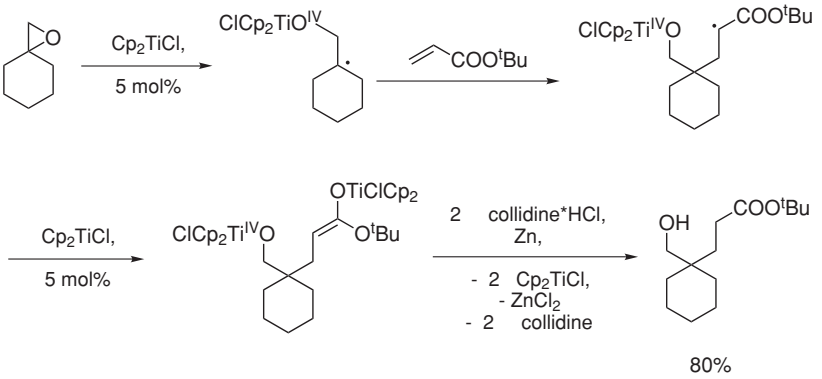
Scheme 12.15. Titanocene-catalyzed reductive epoxide opening.

The catalytic system preserves the attractive features of the stoichiometric reaction, i. e. the high regioselectivity of epoxide opening and the exceptional functional group tolerance. Thus, electrons are transferred with high selectivity from manganese to titanium and not from manganese to the organic substrates. Among the groups tolerated are aromatic ketones, tosylates, halides, and aliphatic aldehydes.

The opening of α, β-epoxy ketones, as recently reported by Doris et al., can also be carried out with catalytic amounts of titanocene dichloride [16]. Thus, the relatively sensitive β-hydroxy ketones are also readily tolerated under the catalytic conditions.

12.3.2
Titanocene-Catalyzed Additions to α,β-Unsaturated Carbonyl Compounds

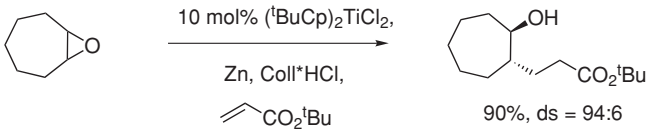
With an operating catalytic cycle for the reductive opening of epoxides at hand, we decided to investigate the preparatively more important formation of carbon–carbon bonds. Intermolecular addition reactions to α,β-unsaturated carbonyl compounds have been described for the stoichiometric process of Nugent and RajanBabu [5]. The general concept behind the catalytic conditions is outlined in Scheme 12.16.



Scheme 12.16. Titanocene-catalyzed addition to α,β-unsaturated carbonyl compounds.

As in the reductive ring-opening, titanocene–oxygen bonds have to be protonated. Here, a titanium enolate, which is generated after reductive trapping of an enol radical, has to be protonated, in addition to a simple titanocene alkoxide. As before, 2,4,6-collidine hydrochloride constitutes a suitable acid to achieve catalytic turnover, but here zinc dust turned out to be the reductant of choice [31c]. The features of the stoichiometric reaction are preserved under our conditions. Acrylates and acrylonitriles are excellent radical acceptors in these reactions. Methyl vinyl ketone did not yield the desired addition product. Under the standard reaction conditions, α-substituted acceptors are readily tolerated, but β-substitution gives the products only in low yields.

The problem of diastereoselectivity in additions to cyclic radicals arising from the opening of bi- or tricyclic epoxides, e. g. cycloheptene oxide or norbornene oxide, has been addressed only recently [32]. In the former case, reasonable selectivities can be obtained with titanocene dichloride (*trans*:*cis* = 76:24), but excellent selectivities are observed with bis(*tert*-butyl)titanocene dichloride (*trans*:*cis* = 94:6), as shown in Scheme 12.17.



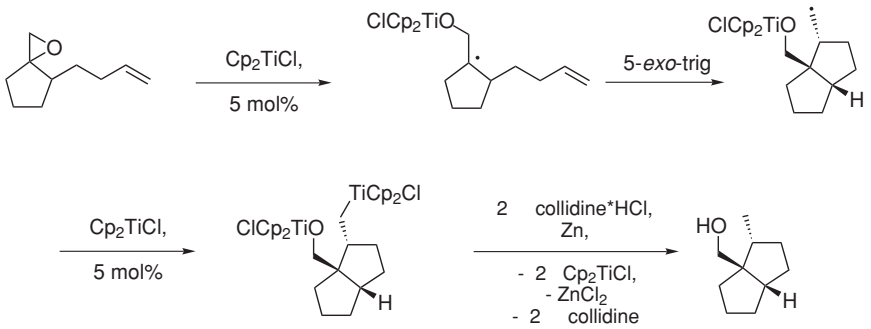
Scheme 12.17. Control of diastereoselectivity in intermolecular additions.

In the case of norbornene systems, complete *exo* selectivity was observed by Giese et al. [33] during radical additions carried out by the mercury method. In the titanocene-catalyzed epoxide openings, Cp_2TiCl_2 gives an *exo*:*endo* ratio of 4:1 [34], whereas $(t\text{BuCp})_2TiCl_2$ gives a 53:47 mixture [35]. Thus, the reagent control of the titanocene leads to a complete loss of the substrate-induced selectivity.

12.3.3
Titanocene-Catalyzed 5-*exo* Cyclizations

Probably the most important applications of radicals in organic chemistry are 5-*exo* cyclization reactions. Numerous applications of this exceptionally useful transformation, including several elegant syntheses of natural products, have been reported [17]. Although a general concept for a catalytic reagent-controlled cyclization is still lacking, such a method would clearly be very useful for the design of novel transformations.

As a first step towards this goal, we managed to develop a titanocene-catalyzed 5-*exo* cyclization of radicals derived from suitably unsaturated epoxides. The mechanism of the cyclization is depicted in Scheme 12.18 [31].



Scheme 12.18. Titanocene-catalyzed 5-*exo* cyclization.

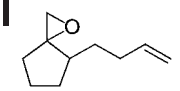
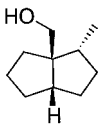
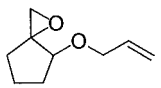
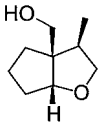
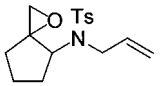
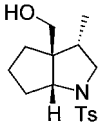
The key step in achieving catalytic turnover is protonation of the titanium–oxygen and titanium–carbon bonds, which is readily achieved by employing collidine hydrochloride as a protic acid. An interesting feature of the cyclization shown above is its diastereoconvergent nature. From a diastereomeric mixture of the epoxides, the cyclization product is obtained as essentially a single isomer. Unfortunately, this is not always the case, as shown in Table 12.1 [36].

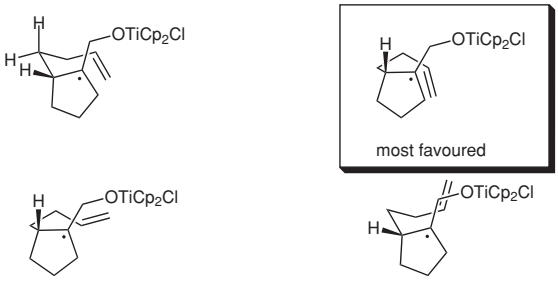
Models accounting for the observed selectivities can be obtained from simple analysis of transition structures, according to the work of Spellmeyer and Houk [37]. These authors have calculated the transition states for cyclizations of radicals to be those shown in Scheme 12.19, but with a hydrogen atom being replaced by the CH_2OTiCp_2Cl group.

The presence of this bulky group leads to a higher diastereoselectivity than in the unsubstituted case because interactions of the alkene with the titanocene group lead to the exclusive formation of one diastereoisomer, presumably through the most favored transition structure shown in Scheme 12.19, in which steric interactions should be minimized.

We are currently employing substituted titanocene complexes to achieve reagent-controlled cyclizations.

Table 12.1. Titanocene-catalyzed formation of [3.3.0] systems. For the sake of clarity, only the major isomer is shown.

Substrate	*Product*	*Yield, Selectivity*
		66, >98:<2
		68, 58:42
		62, 86:14

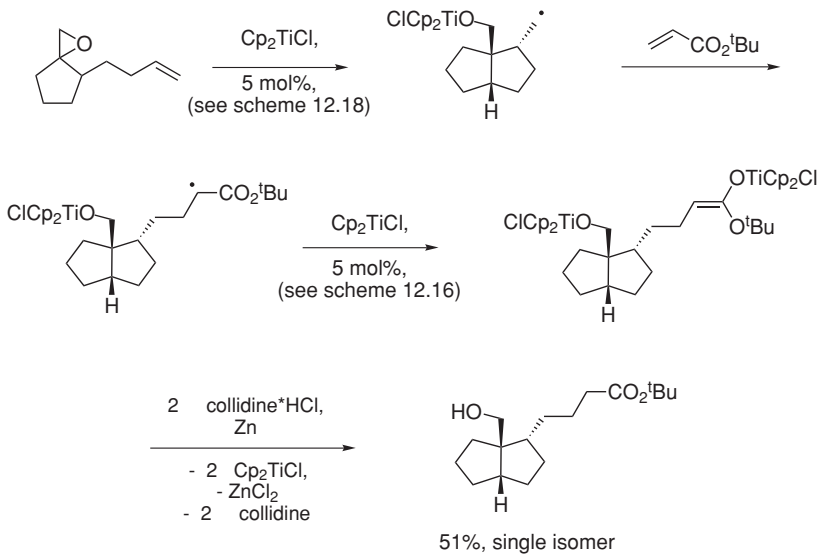


Scheme 12.19. Transition state models for cyclization based on the work of Spellmeyer and Houk.

Alkynes are interesting radical acceptors for cyclization reactions because the products contain double bonds that can be subjected to further transformations. In the case of terminal alkynes, the desired products can be obtained in high yields as single isomers. With non-terminal alkynes as acceptors, the alkene products are generated as mixtures of (*E*)- and (*Z*)-isomers in high yields but with low selectivity [36].

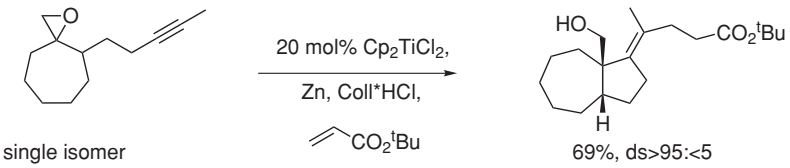
12.3.4
Titanocene-Catalyzed Radical Tandem Reactions

A very attractive feature of radical chemistry is the generation of a novel radical after cyclization or any other radical translocation. This feature allows the inclusion of a second carbon–carbon bond-forming event and can, in principle, be extended even further. The resulting tandem reactions [38] can be extremely useful for the construction of complex molecules. Impressive early results have been reported by Stork in applications directed towards the synthesis of prostaglandins [39]. Our catalytic conditions also allow the realization of tandem reactions. An example including a mechanistic proposal is shown in Scheme 12.20.



Scheme 12.20. Titanocene-catalyzed radical tandem reactions.

The key features of the catalytic cycle are trapping of the radical generated after cyclization by an α,β-unsaturated carbonyl compound, reduction of the enol radical to give an enolate, and subsequent protonation of the titanocene alkoxide and enolate. The diastereoselectivity observed is essentially the same as that achieved in the simple cyclization reaction. An important point is that the tandem reactions can be carried out with alkynes as radical acceptors. The trapping of the formed vinyl radical with α,β-unsaturated carbonyl compounds occurs with very high stereoselectivity, as shown in Scheme 12.21.



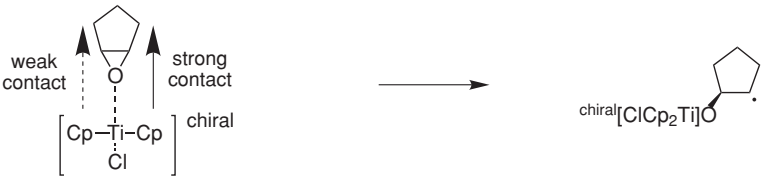
Scheme 12.21. Selective formation of a tetrasubstituted olefin by a tandem radical reaction.

Thus, our radical tandem reactions offer highly stereoselective access to tri- and tetrasubstituted alkenes that are otherwise difficult to prepare.

12.3.5
Catalytic Enantioselective Epoxide Opening

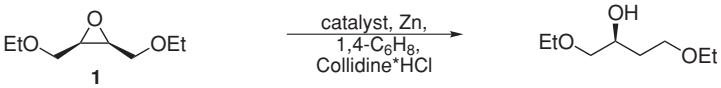
Using the catalytic system described above, the enantioselective opening of *meso* epoxides could also be pursued. Although many excellent examples of ring-opening of *meso* epoxides by S_N2 reactions have recently been reported, the reaction planned here is conceptually different [40]. In the S_N2 reaction, the path of the incoming nucleophile has to be controlled. In the titanocene-catalyzed reaction, the intermediate radical has to be formed selectively. If an intermediate similar to that invoked in the Bartmann ring-open-

ing [9] is postulated here, the selectivity-determining interaction should be that of the epoxide radical anion with a titanocene(IV) complex, as shown in Scheme 12.22.



Scheme 12.22. Concept for enantioselective *meso* epoxide opening by electron transfer.

According to the introductory remarks, reagent control is thus exercised in the radical-forming step. Thus, two diastereomeric radicals are initially formed due to the chirality of the titanocene complex. The diastereoselectivity of the ensuing reaction may also be controlled by the ligand sphere of the titanium. After protic cleavage of the titanium–oxygen bond, enantiomeric products are formed. This admittedly very simple mechanistic interpretation paves the way for the rational design of the cyclopentadienyl ligands. To achieve efficient differentiation in the steric interaction of the catalyst with the *meso* epoxide, the ligand should be able to interact with the substrate in regions distant from the initial binding site, i. e. the epoxy group. Thus, efficient chirality transfer from the periphery of the titanocene complex to regions of the substrate distant from the binding site of the catalyst has to be achieved. Examination of the extensive literature on titanocene and cyclopentadienyl complexes [21] suggested that ligands derived from terpenes would be suitable for this purpose. In *ansa*-metallocenes, which have recently been used with great success, the chirality is centered around the metal. Chirality transfer to the periphery of these complexes is not obvious in studies of molecular models and from the crystallographic structures. Epoxide **1** was chosen as the substrate, as shown in Scheme 12.23, because it is readily accessible from (*Z*)-butenediol in two steps and the absolute stereochemistry of the ring-opened product can be established by synthesis of authentic samples from malic acid [41].

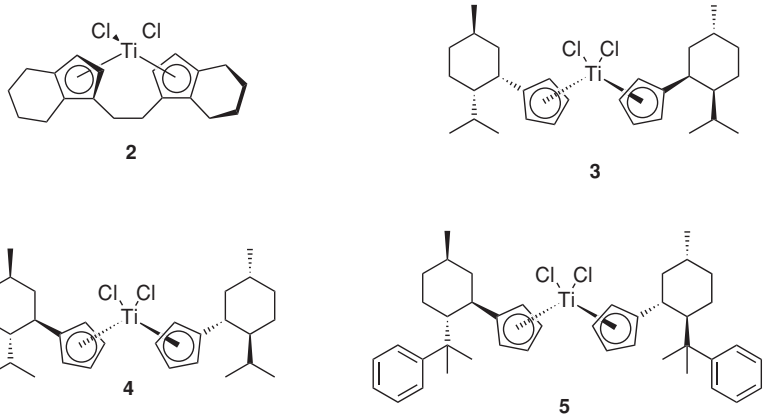


Scheme 12.23. Enantioselective test reaction for catalyst optimization.

The results of investigations of a number of titanocene complexes shown in Scheme 12.24 are summarized in Table 12.2.

Table 12.2. Reductive opening of epoxide **1** with various titanocene complexes.

Cat, mol % cat	*yield [%]*	*(R) : (S)*
2, 10	55	78 : 22
3, 10	45–51	60–76 : 40–24
4, 10	76	3 : 97
5, 10	72	3.5 : 96.5

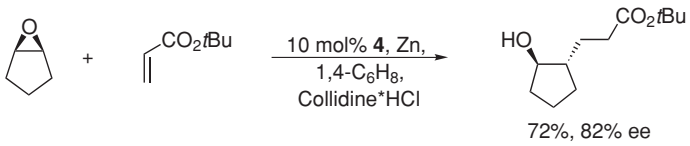


Scheme 12.24. Titanocene catalysts used for enantioselective ring-opening of **1**.

Brintzinger's complex **2** [42] (10 mol%) performed poorly in terms of both the enantioselectivity of the epoxide opening (56 %) and the product yield (55 %). The titanocene complex **3** [42] obtained from (1*R*,2*S*,5*R*) menthol gave variable results due to its sensitivity to traces of moisture (*ee* = 20–52 %). Clearly, the axially positioned cyclopentadienyl group is not ideal.

A satisfactory result was obtained with the ligand **4** [43], which was synthesized from *neo*-menthol and contains an equatorial cyclopentadienyl group. The enantioselectivity of the opening attained synthetically useful levels (97:3) and the isolated yields were reasonable. Complex **5** [44], incorporating a ligand derived from phenylmenthone, also performed well. An enantioselectivity of 96.5:3.5 was observed. Phenylmenthol has already been extensively and successfully used as a chiral auxiliary [45].

These results suggest that both **4** and **5**, after reduction to the redox-active species, contain a chiral pocket well-suited for the steric differentiation of the enantiotopic groups of *meso* epoxide **1**. The corresponding bis(*tert*-butyl) ether epoxide represented a more difficult example due to the increased steric demand of the bulky groups. With **4**, an enantioselectivity of 92.5:7.5 was obtained, whereas **5** gave a lower ratio of 87.5:12.5. An interesting and demanding problem is presented by the opening of bicyclic *meso* epoxides, e. g. cyclopentene oxide, and trapping of the resulting radical with an acrylate, e. g. *tert*-butyl acrylate. Besides the enantioselectivity of epoxide opening, the diastereoselectivity of the C–C bond-forming step has to be controlled. Complex **4** proved to be the most selective catalyst, giving reasonable enantioselectivity while preserving high diastereoselectivity, as shown in Scheme 12.25. Titanocene **5** gave lower selectivities.



Scheme 12.25. Ring-opening of cyclopentene oxide in the presence of **4**.

A comparison of the structures of **4** and **5**, both in the crystalline form and in solution, has been carried out [46]. The results obtained suggest that the structures are essentially the same in both states of aggregation and that crystal structure data can therefore be used for catalyst optimization.

12.4 Conclusion

The opening of epoxides by electron transfer has led to a number of synthetically useful reactions. To date, the stoichiometric reagents showing the most promising selectivities are titanocene(III) reagents introduced by Nugent and RajanBabu [5]. The recent emergence of a reaction catalytic in titanium has increased the usefulness of this reaction even further [31,36,41,45]. The key step in the catalytic protocol involves protonation of titanium–oxygen and titanium–carbon bonds. This novel approach has for the first time allowed the use of substituted titanocenes in influencing the diastereoselectivity and enantioselectivity of radical reactions. It remains to be seen how general this approach of reagent control in radical chemistry is going to be.

Acknowledgements

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Typical Experimental Procedures

2-Methyl-4-phenylbutan-1-ol (Scheme 12.15) To a suspension of collidine hydrochloride (236 mg, 1.50 mmol) in dry THF (10 mL) was added 2-methyl-2-phenylethyl oxirane (165 µL, 1.00 mmol), 1,4-cyclohexadiene (0.425 mL, 4.25 mmol), titanocene dichloride (12.5 mg, 0.05 mmol), and manganese (82 mg, 1.50 mmol). After stirring for 16 h, excess manganese was removed by decantation and MTBE (50 mL) was added. The organic layer was washed sequentially with H_2O (30 mL), 2 N HCl (30 mL), H_2O (30 mL), satd. aq. $NaHCO_3$ solution (30 mL), and H_2O (30 mL), and dried ($MgSO_4$). After removal of the volatiles, the crude product was purified by flash chromatography on silica gel (25 % MTBE/75 % PE) to give 144 mg of the desired product (88 %).

***tert*-Butyl 1-(hydroxymethyl)cyclohexylpropanoate** (Scheme 12.16) To a mixture of collidine hydrochloride (394 mg, 2.5 mmol), the epoxide (120 µL, 1.0 mmol), zinc dust (100 mg, 1.5 mmol), and *tert*-butyl acrylate (370 µL, 2.5 mmol) in dry THF (10 mL) was added titanocene dichloride (12.5 mg, 0.05 mmol) and the resulting mixture was stirred for 60 h. After the addition of MTBE (50 mL), the mixture was washed sequentially with H_2O (30 mL), 2 N HCl (30 mL), H_2O (30 mL), satd. aq. $NaHCO_3$ solution (30 mL), and H_2O (30 mL), and dried ($MgSO_4$). After removal of the volatiles, the crude product

was purified by flash chromatography on silica gel (25 % MTBE/75 % PE) to give 193 mg of the desired product (80 %).

(3-Methyl-hexahydropentalen-3a-yl)methanol (Scheme 12.18) To a mixture of collidine hydrochloride (394 mg, 2.50 mmol), the epoxide (152 mg, 1.0 mmol), and zinc (131 mg, 2.0 mmol) in dry THF (10 mL) was added titanocene dichloride (12.5 mg, 0.05 mmol) and the resulting mixture was stirred for 61 h. After the addition of MTBE (50 mL), the mixture was washed sequentially with H_2O (30 mL), 2 N HCl (30 mL), H_2O (30 mL), satd. aq. $NaHCO_3$ solution (30 mL), and H_2O (30 mL), and dried ($MgSO_4$). After removal of the volatiles, the crude product was purified by flash chromatography on silica gel (15 % MTBE/85 % PE) to give 102 mg of the desired product (66 %).

***tert*-Butyl 3-(*S*)-(2-(*R*)-Hydroxycyclopent-1-yl)propanoate** (Scheme 12.25) To a suspension of collidine hydrochloride (394 mg, 2.5 mmol) in dry THF (10 mL) was added cyclopentene oxide (87 μL, 1.0 mmol), 1,4-cyclohexadiene (94 μL, 1.0 mmol), *t*-butyl acrylate (290 μL, 2.0 mmol), **4** (53 mg, 0.1 mmol), and zinc dust (131 mg, 2.0 mmol). The green suspension was stirred for 22 h and then poured onto MTBE (50 mL). The organic layer was washed sequentially with H_2O (30 mL), 2 N HCl (30 mL), H_2O (30 mL), satd. aq. $NaHCO_3$ solution (30 mL), and H_2O (30 mL). After drying ($MgSO_4$), the volatiles were removed in vacuo and the residue (294 mg) was microdistilled (140 °C, 10 mbar). Purification by chromatography on silica (CH/EE, 9:1) gave 154 mg of the desired product as a colorless oil (72 %); $[\alpha]_D^{20} = -19.6$ ($c = 1$ in CH_2Cl_2).

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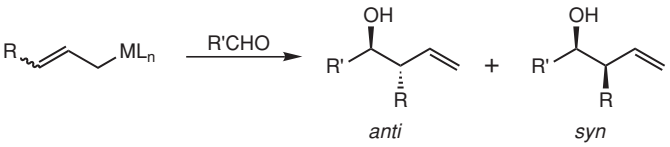
13
Synthesis and Reactivity of Allyltitanium Derivatives

Jan Szymoniak and Claude Moïse

13.1
Introduction

The reactions of allylmetal reagents with carbonyl compounds and imines have been extensively investigated during the last two decades [1]. These carbon–carbon bond-forming reactions possess an important potential for controlling the stereochemistry in acyclic systems. Allylmetal reagents react with aldehydes and ketones to afford homoallylic alcohols (Scheme 13.1), which are valuable synthetic intermediates. In particular, the reaction offers a complementary approach to the stereocontrolled aldol process, since the newly formed alkenes may be readily transformed into aldehydes and the operation repeated.



Scheme 13.1. Synthesis of homoallylic alcohols by addition of allylmetal compounds to aldehydes.

Allylmetals of the crotyl-type based on B, Si, and Sn have been widely used to achieve stereocontrolled transformations, for example for constructing polypropionate stereosequences [2]. Allyltitanium reagents have also attracted great attention since the pioneering work of Seebach [3] and Reetz [4], considerable progress in this field being accomplished over the past ten years. A number of allyltitanium derivatives have been prepared from cheap and available starting materials. It has been demonstrated that the replacement of the main group counterion of allyl carbanions by titanium increases the selectivity, which can also be adjusted by judicious choice of the ligands at the titanium. Thus, allyltitanium reagents react in situ with electrophiles under mild conditions, often with high chemo-, regio-, and stereoselectivity. Some reviews partially cover the preparation, properties, and synthetic uses of these versatile reagents [5].

In this chapter, allyltitanium reagents are grouped according to ligands, but above all for the sake of simplicity and for historical reasons. They are divided into three groups: those possessing two cyclopentadienyl ligands (allyl bis(cyclopentadienyl) titanium reagents, Section 13.2), those with one cyclopentadienyl ligand (allyl mono(cyclopentadienyl) tita-

nium reagents, Section 13.3), and those without any cyclopentadienyl ligand ((allyl)TiX_3, Section 13.4). The chapter covers the main developments in the field of allyltitanium chemistry, with an the emphasis on the results from the last years.

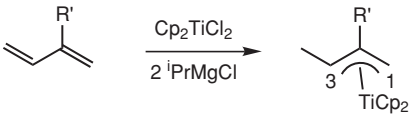
13.2
Allyl Bis(cyclopentadienyl)titanium Reagents

The Cp (η^5-C_5H_5) and Cp* (substituted Cp) ligands are effective electron donors, aromatic and non-labile, that confer low Lewis acidity as well as thermal and hydrolytic stability to early transition metal compounds. In particular, titanocene complexes (Cp_2TiL_n) [6], readily available from titanocene dichloride, are ubiquitous in the organometallic chemistry of early transition metals. On the other hand, the allyl ligand exhibits two modes of binding, η^1 and η^3, of which the former is sterically preferred, while the latter is electronically preferred. Both η^1-allyltitanocene(IV) and η^3-allyltitanocene(III) complexes (**1** and **2** in Scheme 13.2) have been synthesized and used as allylating reagents.

1 **2** **Scheme 13.2.** η^1- and η^3-allyltitanocene complexes **1** and **2**.

13.2.1
Preparation and Properties of η^3-Allyltitanocenes

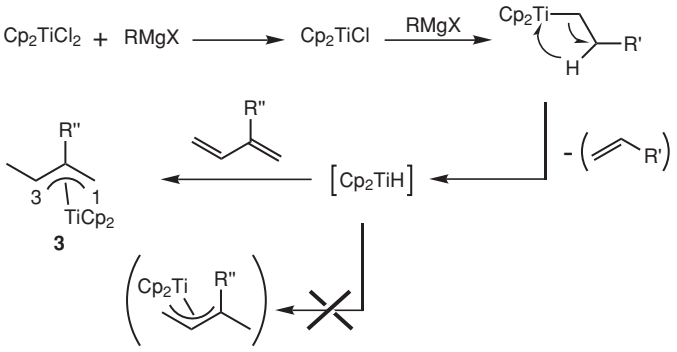
η^3-Allyltitanocenes can be prepared from Cp_2TiCl_2 by the action of allyl Grignard reagents [7] or by hydrotitanation of conjugated dienes [8]. The development and widespread synthetic use of η^3-allyltitanium compounds has mostly relied on this last method, which is convenient and offers the possibility of preparing η^3-allyltitaniums bearing functional groups. The method was discovered in 1966 by Martin and Jellinek [8]. They reported that the reaction of conjugated dienes with Cp_2TiCl_2 and 2 equivalents of an alkyl Grignard reagent possessing a β-hydrogen produces η^3-allyltitanocenes, as illustrated in Scheme 13.3.



Scheme 13.3. η^3-Allyltitanocenes from 1,3-dienes, Cp_2TiCl_2, and a Grignard reagent.

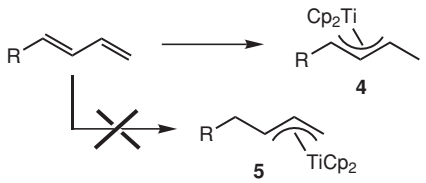
A series of η^3-allyltitanium compounds has been prepared, and their π-structures have been confirmed by spectroscopic methods and X-ray analysis [9]. In these complexes, the alkyl substituents at C-1 and C-3 preferably occupy the *syn* position with respect to the H (or R) at C-2 due to steric reasons. The proposed mechanism for their formation is outlined in Scheme 13.4 [8].

A sequence of reduction of Cp_2TiCl_2 to Cp_2TiCl, subsequent transmetallation, and β-hydrogen elimination gives Cp_2TiH. The hydrotitanation of dienes with Cp_2TiH occurs with total regioselectivity to afford the sterically favored complex **3** (with a *syn* orientation of Me at C-3, as in Scheme 13.3). Moreover, the most symmetrical complex, that is the one in



Scheme 13.4. Proposed mechanism for the hydrotitanation of 1,3-dienes.

which the environments of C-1 and C-3 of the allyl are as similar as possible, is formed preferentially (i. e. **4** rather than **5** in Scheme 13.5).

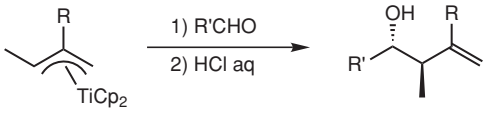


Scheme 13.5. Regioselective formation of the most symmetrical η^3-allyltitanocene complex.

The regioselective formation of η^3-allyltitanocenes is clearly attractive for further synthetic applications.

13.2.1.1 Reactions with aldehydes and ketones

Fourteen years after the aforementioned findings, Sato [10] and Teuben [11] independently discovered that η^3-allyltitanocenes have nucleophilic properties, and that they can be employed as effective allyl-transfer reagents toward various electrophiles. The reactions with aldehydes and ketones proceed under mild conditions (Et_2O or THF, r. t., 0.5–1 h) to furnish homoallylic alcohols in excellent yields (70–95 %) [10–13]. α,β-Unsaturated carbonyl compounds undergo exclusive 1,2-addition [10]. Good compatibility with other functional groups (except for C=N) is observed. Cp_2TiCl_2 can be partially recovered by hydrolyzing the reaction mixture with aq. HCl followed by aerial oxidation (oxychlorination of Cp_2TiCl to Cp_2TiCl_2). η^3-Allyltitanocene complexes react with aldehydes and ketones in a regiospecific way, at the more substituted γ-carbon of the allyl (Scheme 13.6) [10].



Scheme 13.6. Regioselective addition of η^3-allyltitanocenes to aldehydes.

Moreover, the reaction with aldehydes occurs with good to excellent *anti* stereoselectivity, typically 100:0 to 9:1 for R' = alkyl or alkenyl, and 9:1 to 7:3 for R' = phenyl [10,12]. The diastereoselectivity even increases when using Cp-substituted crotyltitanocenes

(RCp_2Ti(crotyl), R = Me, *i*Pr) [13]. Both the regio- and the diastereoselectivity in the allyltitanation reactions of aldehydes can be explained in terms of a six-membered chair-like transition state (Figure 13.1).

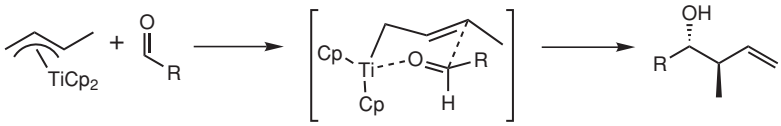
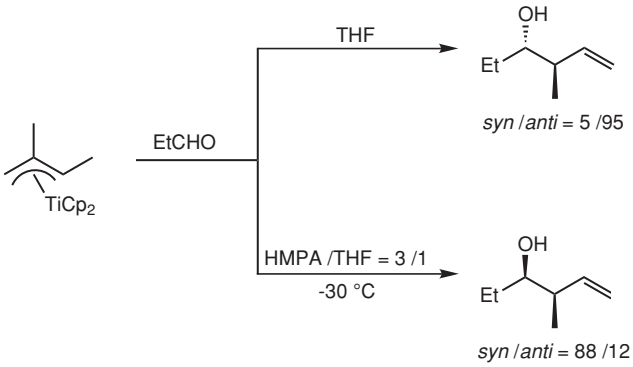


Figure 13.1. The origin of regio- and diastereoselection in the allyltitanation of aldehydes.

A change in the allyl hapticity (η^3 to η^1 slippage) leading to the less substituted titanium–carbon σ bond accounts for the observed γ-regioselectivity. The *anti* diastereoselectivity stems from a pseudo-equatorial orientation of the aldehyde group. The diastereoselectivity of the reaction can be reversed through the use of a more coordinating co-solvent such as HMPA (Scheme 13.7) [14]. This reversal of *anti* to *syn* diastereoselectivity can be rationalized in terms of an open transition state.



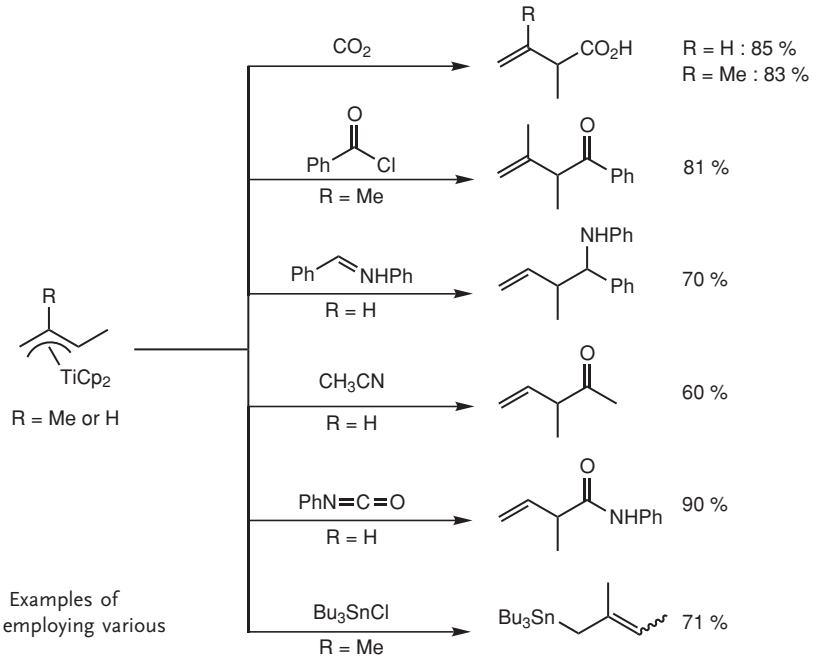
Scheme 13.7. Reversal of *anti* to *syn* diastereoselectivity by using HMPA as a co-solvent.

13.2.1.2 **Other electrophiles and diene precursors**

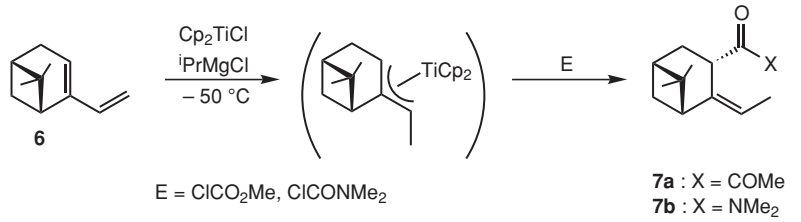
The opportunity of employing various electrophiles and functionalized diene precursors greatly enhances the synthetic potential of η^3-allyltitanocenes. Besides aldehydes and ketones, carbon dioxide [11,15,16], acid chlorides [17], imines [11], nitriles [11], isocyanides [11], and organotin halides [18] react to afford the corresponding allylated products after hydrolysis. Examples are given in Scheme 13.8.

In all cases, complete γ-regioselectivity has been noticed. The reaction with R_3SnCl represents a convenient method for preparing allyltin derivatives of the type shown in Scheme 13.8. The reaction with sterically less hindered acid chlorides gives tertiary alcohols as by-products. More recently, methyl chloroformate [19] and dimethyl carbamoyl chloride [20] have been employed as electrophiles. These reactions allow the direct conversion of 1,3-dienes into β,γ-unsaturated esters or amides. Interestingly, the nopadiene-derived complex **6**, which proved to be inert towards CO_2, reacts regio- and stereoselectively with $ClCO_2Me$ and $ClCONMe_2$ to afford the unique β-pinene derivatives **7a** and **7b** (Scheme 13.9) [19,20].

η^3-Allyltitanocenes react with acetals in the presence of a Lewis acid to provide homoallylic ethers [21]. The intramolecular reaction involving tethered dienyl acetals also takes

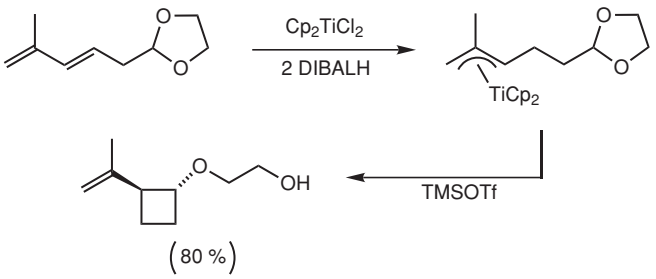


Scheme 13.8. Examples of allyltitanation employing various electrophiles.



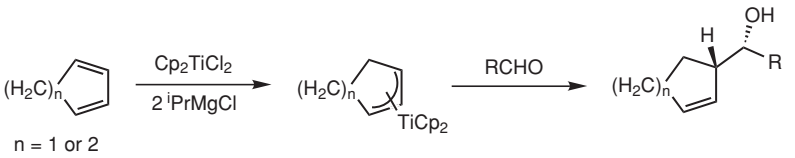
Scheme 13.9. Regio- and stereoselective formation of β-pinene derivatives from nopadiene.

place (Scheme 13.10) [22]. The reaction provides a convenient access to small and medium-sized vinylcycloalkanes ($n = 3-6$) and to bicyclic fused compounds.



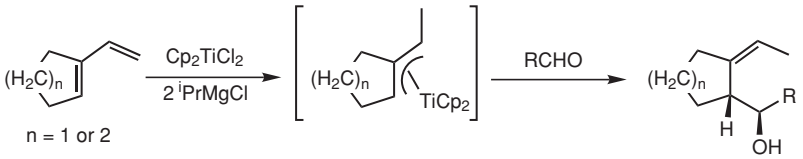
Scheme 13.10. Intramolecular crotyltitanation of a tethered acetal promoted by TMSOTf.

Not only acyclic but also cyclic dienes can be employed to form η^3-allyltitanium complexes. The complexes derived from 1,3-cyclopenta- and 1,3-cyclohexadiene undergo highly stereoselective addition with aldehydes (Scheme 13.11) [23].



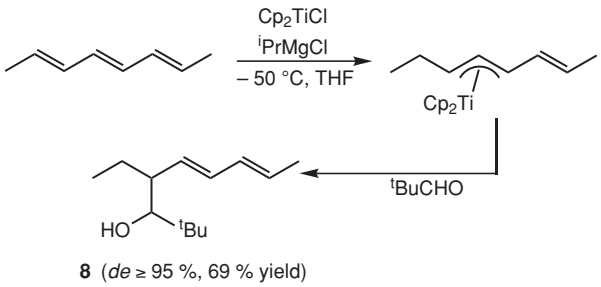
Scheme 13.11. Allyltitanation of aldehydes from cyclic dienes as precursors.

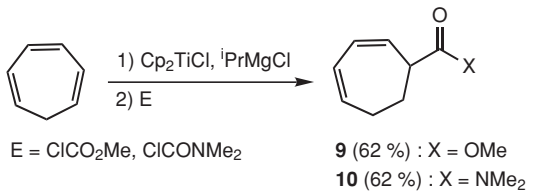
The complexes derived from 1-vinylated cyclopentene and cyclohexene undergo completely regio- and stereoselective reactions, as indicated in Scheme 13.12 [23].



Scheme 13.12. Allyltitanation of aldehydes from 1-vinylated cyclopentene and cyclohexene.

A similar result obtained with nopadiene is presented above (Scheme 13.9). Linear and cyclic trienes furnish alkenyl-η^3-allyltitanium complexes, which can react with aldehydes to produce dienyl alcohols (Scheme 13.13) [24].

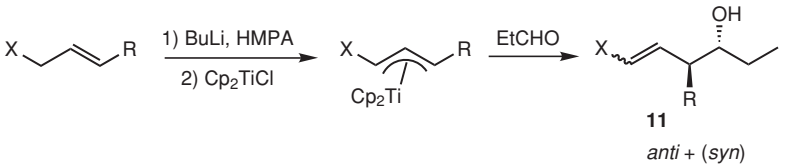




Scheme 13.13. Allyltitanation of aldehydes from conjugated trienes.

Starting from 2,4,6-octatriene and pivaldehyde, the conjugated homoallylic alcohol **8** is obtained as the sole product. Cycloheptatriene-derived complexes react with aldehydes and CO_2 to afford mixtures of the isomeric 1,3- and 1,4-cycloheptadienyl carbinols or acids, respectively. Interestingly, analogous reactions with methyl chloroformate or dimethyl carbamoyl chloride produce the conjugated dienyl ester **9** or amide **10** as unique products [19,20].

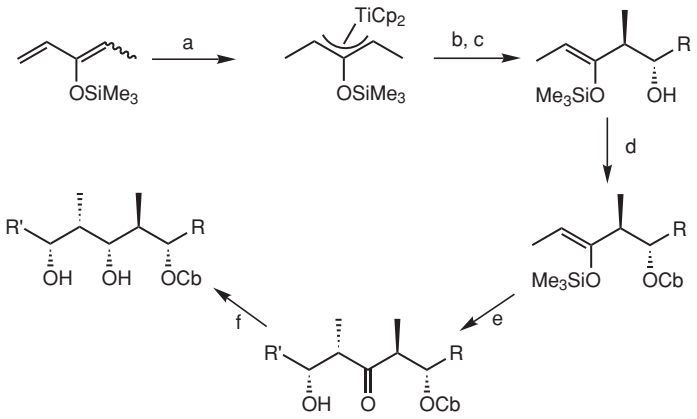
Hetero-substituted η^3-allyltitanocenes have also been studied. Functionalized η^3-allyltitanium complexes (X = $SiMe_3$, OPh, SPh) have been prepared by transmetallation of Cp_2TiCl with the corresponding allyllithiums, and were found to react regiospecifically with propionaldehyde to give functionalized homoallylic alcohols **11** (Scheme 13.14) [25].



X	$SiMe_3$	$SiMe_3$	OPh	SPh
R	Me	$SiMe_3$	Me	Me
anti /*syn*	86/14	100/0	100/0	66/34

Scheme 13.14. Functionalized η^3-allyltitanocene reagents.

Silyltitanation of 1,3-dienes with $Cp_2Ti(SiMe_2Ph)$ selectively affords 4-silylated η^3-allyltitanocenes, which can further react with carbonyl compounds, CO_2, or a proton source [26]. Hydrotitanation of acyclic and cyclic 1,3-dienes functionalized at C-2 with a silyloxy group has been achieved [27]. The complexes formed undergo highly stereoselective addition with aldehydes to produce, after basic work-up, *anti* diastereomeric β-hydroxy enol silanes. These compounds have proved to be versatile building blocks for stereocontrolled polypropionate synthesis. Thus, the combination of allyltitanation and Mukayiama aldol or tandem aldol-Tishchenko reactions provides a short access to five- or six-carbon polypropionate stereosequences (Scheme 13.15) [28].



(a) Cp_2TiCl (preformed), ^iPrMgCl, -20 °C; (b) RCHO; (c) $NaHCO_3$ aq;
(d) PhNCO, r. t.; (e) R'CHO, $TiCl_4$, CH_2Cl_2; (f) DIBALH, Et_2O, -78 °C.

Scheme 13.15. Polypropionate building blocks via the stereoselective allyltitanation–Mukayiama aldol sequence.

This strategy has recently been extended to optically active stereosequences, either by using a chiral protective group (carbamate) as an inductor, or by using (*S*)- or (*R*)-BINOL-$TiCl_2$ as the catalyst for the Mukayiama reaction [29].

13.2.1.3 Asymmetric reactions with η^3-allyltitanocenes

Efforts have been made to apply η^3-allyltitanium chemistry to the asymmetric synthesis of homoallylic alcohols and carboxylic acids. The synthesis and reactions of chiral η^3-allyltitanocenes with planar chirality, or containing Cp ligands with chiral substituents, have been reported [6c,15,30–32]. The enantiofacial selectivity in the allyltitanation reactions has been examined for the complexes **12** [15], **13** [30], **14** [31], **15**, **16**, and **17** [32] depicted in Figure 13.2.

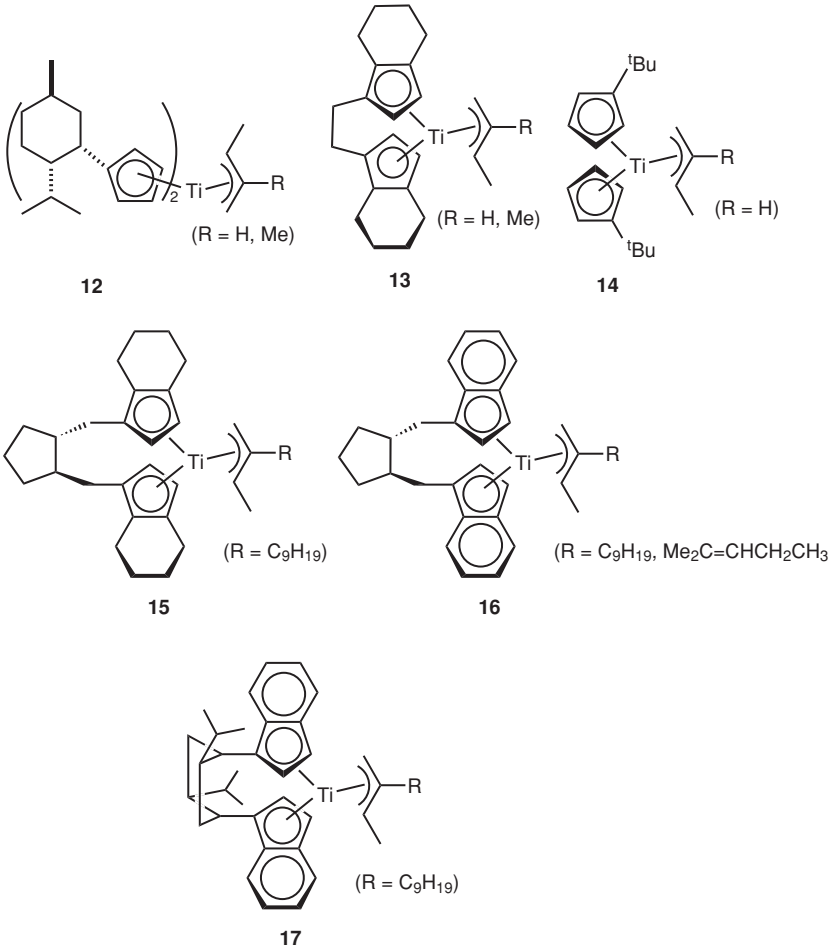
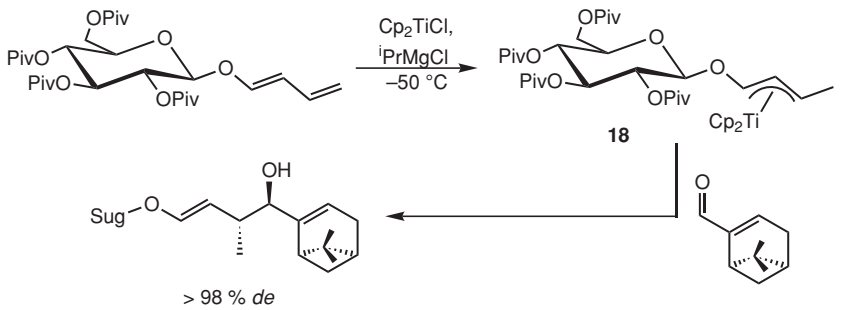


Figure 13.2. Chiral η^3-allyltitanocene derivatives.

Reactions of aldehydes with complexes **13**–**17** provide optically active homoallylic alcohols. The enantioselectivities proved to be modest for **13**–**16** (20–45 % *ee*). In contrast, they are very high (≥ 94 % *ee*) for the (*ansa*-bis(indenyl))(η^3-allyl)titanium complex **17** [32], irrespective of the aldehyde structure, but only for the major *anti* diastereomers, the *syn* diastereomers exhibiting a lower level of *ee* (13–46 % *ee*). Complex **17** also gives high chiral induction (≥ 94 % *ee*) in the reaction with CO_2 [32], in contrast to complex **12** (R = Me 11 % *ee*; R = H 19 % *ee*) [15]. Although the aforementioned studies of enan-

tioselectivity induced by the optically active η^3-allyltitanocenes are interesting from a mechanistic point of view, their synthetic utility seems rather limited. Indeed, a stoichiometric amount of a precious, optically active titanocene dichloride is needed, although this may be partially recovered after the reaction. Some other asymmetric reactions involving η^3-allyltitanocenes have been carried out. η^3-Tiglyltitanium complexes bearing α- or β-glucopyranosyl auxiliaries have been prepared from the corresponding anomeric carbohydrate dienes [33]. The reactions of these complexes with different aldehydes give rise to varying diastereofacial selectivities, depending on both the complex and the aldehyde. A matched pair of a chiral aldehyde ((−)-myrtenal) and the β-glucopyranosyl complex **18** gives *de* > 98 % (Scheme 13.16).

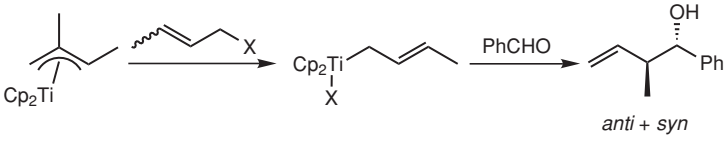


Scheme 13.16. Matched effect in the asymmetric allyltitanation results in a high diastereofacial selectivity.

Asymmetric reactions of a nopadiene-derived η^3-allyltitanocene complex with aldehydes have been studied [34]. In several cases, new terpenoid chirons have been prepared with *de* ≥ 95 %. Reactions of the η^3-tiglyltitanocene complex with a series of chiral aldehydes resulted in modest facial selectivities [35]. Complex structural effects on selectivity have been observed.

13.2.2
Preparation and Reactions of η^1-Allyltitanocenes

These σ-complexes have been less extensively studied than the η^3-allyltitanium derivatives. η^1-Allyltitanocenes can readily be prepared from the corresponding magnesium compounds by reaction with Cp_2TiCl_2 or by reaction of preformed η^3-allyltitanium complexes with but-2-enyl halides [36]. Crotyl-type reagents, which are accessible only in the *E*-isomeric form, add to aldehydes with an *anti* selectivity (Scheme 13.17).

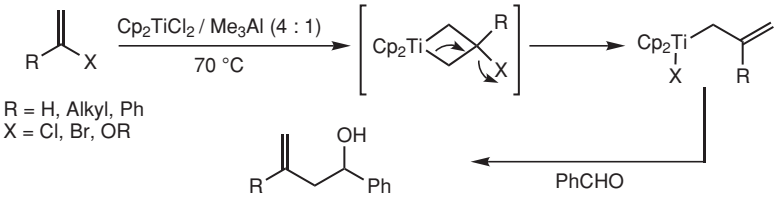


X	Cl	Br	I
anti /*syn*	60/40	100/0	94/6

Scheme 13.17. Preparation of η^1-crotyltitanocenes and addition to benzaldehyde.

The stereoselectivity proved to be dependent on the nature of the halide ligand X and was found to be complete for X = Br. Reversal of the diastereoselectivity from *anti* to *syn* has been accomplished by adding $Et_2O \cdot BF_3$ [37]. The predominant *syn* selectivity in the presence of this Lewis acid is consistent with a non-cyclic antiperiplanar transition state.

More recently, two interesting reactions leading to η^1-allyltitanocenes have been described. Takeda and co-workers reported that allyl sulfides undergo an oxidative addition reaction with a "Cp_2Ti" equivalent, prepared by the reduction of Cp_2TiCl_2 with 2 equivalents of *n*-BuLi [38]. The thus formed allyltitanocenes $Cp_2(SPh)Ti(allyl)$ add to aldehydes with an *anti* selectivity (*anti*/*syn* ≥ 97:3) and in good yields. Taguchi and Hanzawa developed an efficient procedure for generating η^1-allyltitanocene species from non-allylic starting materials, namely vinyl halides, vinyl ethers, and carboxylic esters [39]. The reaction uses a Cp_2TiCl_2/Me_3Al (1:4) reagent system and is likely to proceed through the formation of a titanacyclobutane followed by β-elimination of the halogen or alkoxy group (Scheme 13.18).



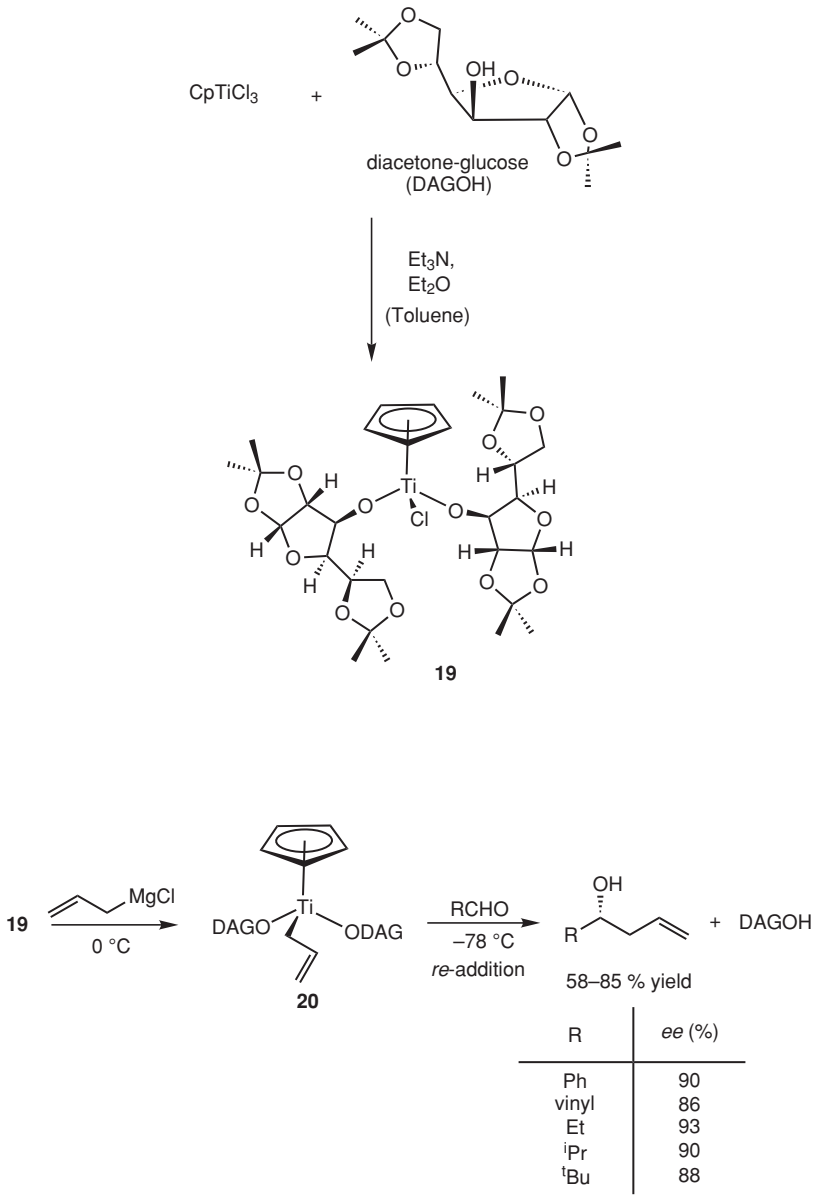
Scheme 13.18. η^1-Allyltitanocene complexes from vinyl derivatives.

Enantioselective reactions involving η^1-allyltitanocenes are almost unknown. An attempt to realize an asymmetric transfer of the allyl group has been reported by Reetz [40], who employed a chiral titanium precursor with two different Cp groups and a stereogenic center at the metal ($CpCp^{tBu}(C_6F_5)Cl$) [41]. However, the addition of the derived allyltitanium reagent to aldehydes was found to proceed with a low chiral induction (*ee* up to 11 %) in this case.

13.3 Allyl Mono(cyclopentadienyl)titanium Reagents

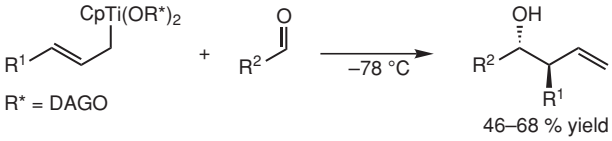
Although allyltitanocenes have emerged as highly diastereoselective reagents, no highly enantioselective and/or practically useful chiral allyltitanocene has so far been reported. Since 1989, Hafner and Duthaler have made important progress in the field of asymmetric allyltitanation. They have introduced new chiral allyl monocyclopentadienyltitanium complexes that add to aldehydes with an impressive enantiocontrol [42]. Thus, high enantiofacial discrimination has been achieved with a markedly differentiated arrangement on titanium: a single Cp ligand and a rigid alkoxy chiral inductor.

The first successful enantioselective allyltitanium reagent bearing a carbohydrate has been obtained, as shown in Scheme 13.19. The reaction of $CpTiCl_3$ with commercially available 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (diacetone glucose, DAGOH) in the presence of Et_3N afforded cyclopentadienyl chlorotitanate **19** [42], which was isolated and fully characterized (X-ray diffraction) [43]. Complex **19** can be stored either as a stock solution in diethyl ether or toluene, or as a crystalline solid after precipitation with hexane. The reaction of **19** with allylmagnesium chloride gave the allylic reagent **20**, which was added in situ to aldehydes at −78 °C to afford homoallylic alcohols with good yield and



Scheme 13.19. Enantioselective allyltitanation of aldehydes with allyl $TiCp(ODAG)_2$.

very high enantioselectivity (*re* side addition; about 90 % *ee*) (Scheme 13.19). Both the chiral inductor and $CpTiCl_3$ could be recovered and recycled to give **19**. Allyltitanium reagents with different acetal protection of their glucose ligands gave similar stereoselectivities as **20**. CpTi(ODAG) complexes analogous to **20** and bearing substituted allyl groups (R on C3 = vinyl, Ph, Me) also proved to be highly enantioselective toward aldehydes (Scheme 13.20) [42b,42c]. Finally, reactions of **20** with ketones, which had to be carried out at higher temperature (0 °C), gave lower enantiomeric excesses (ca. 50 % *ee*).

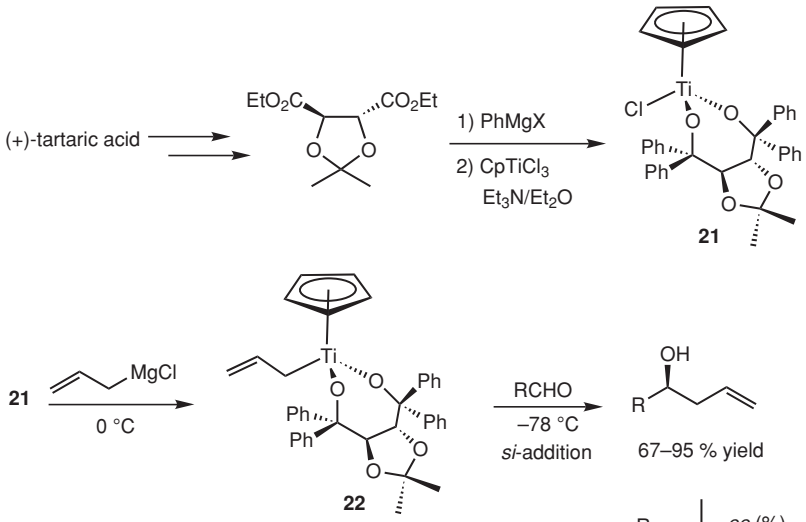


R^1	R^2	*ee* (%)
vinyl	^{i}Bu	90
Ph	^{i}Bu	88
Me	^{i}Pr	83

Scheme 13.20. Enantioselective allyltitanation of aldehydes with substituted allyl $TiCp(ODAG)_2$ reagents.

The above interesting approach to the asymmetric allyltitanation reaction does, however, have a limitation. Thus, L-glucose is much more expensive that the D-form and, consequently, homoallylic alcohols of the opposite configuration cannot easily be obtained by this method. In an attempt to induce the opposite *si* face selectivity, other acetonide derivatives of monosaccharides from the xylose, idose, and allose series were tested [42b,42c]. The enantiofacial discrimination was, however, much lower than that with DAGOH and both *re* and *si* face selective additions to aldehydes were observed.

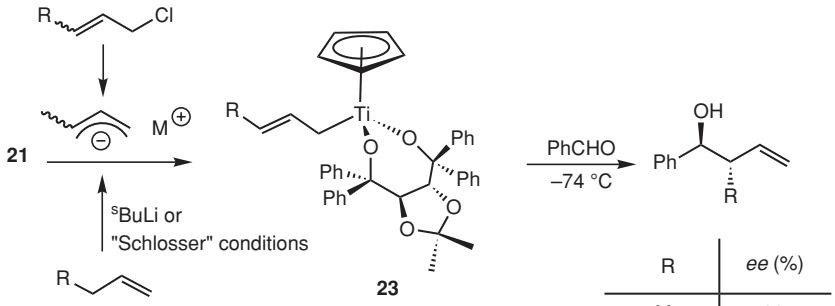
Bidentate chiral auxiliaries have since been examined. While camphane-2,3-diol and β-binaphthol gave disappointing results, tartrate-derived (TADDOL) ligands were found to be very promising as chiral inductors [44]. Particularly interesting results were obtained by using complex **21**, readily available from natural (*R*,*R*)-(+)-tartaric acid (Scheme 13.21).



R	*ee* (%)
Ph	95
$CH_3(CH_2)_8$	97
^{i}Pr	97
^{t}Bu	97

Scheme 13.21. Enantioselective allyltitanation of aldehydes with a chiral tartrate-derived reagent.

The corresponding allylic reagent (*R,R*)-**22**, prepared by transmetallation with an allylic Grignard compound, adds to aldehydes with excellent enantioselectivity (≥ 95 % *ee*), which is higher than that obtained with **20**. The marked influence on enantioselectivity is exerted by the steric bulk of substituents (Ph) on the carbinol groups. The enantiomeric excess of 95 % in the reaction of **22** with PhCHO decreased to just 12 % *ee* when the Ph groups were replaced by Me groups [44]. Most notably, the replacement of DAGO in complex **20** by TADDOL in complex **22** reverses the selectivity (*si* and *re* face additions, respectively). The opposite selectivities seen with **20** and **22** make these chiral allyltransfer reagents complementary. Moreover, since the (*S,S*)-tartrate-derived reagent ((*S,S*)-**22**) is also available, it can be used instead of **20** to prepare the same enantiomer. The tartrate-bearing reagents **23** can be employed to transfer substituted allyl groups [42b,44]. As depicted in Scheme 13.22, the predominant or sole product (≥ 95 % *ee*, ≥ 95 % *de*) in the reactions of **23** with benzaldehyde is the *anti* diastereomer, obtained by selective *si* face attack of the substituted allyl terminus. Aliphatic aldehydes give similar results.



R	*ee* (%)
Me	98
Ph	98
$SiMe_3$	98
OEt	92

Scheme 13.22. Substituted allyl tartrate-derived reagents.

Like other allyltitanation reactions, the method is thus restricted to the preparation of branched regioisomers with the *anti* configuration. In fact, the NMR spectra of the substituted allylic reagents **23** showed fast 1,3-shifts, favoring the (*E*)-isomer with titanium σ-bonded to the less substituted carbon. The reactions with chiral aldehydes led to generally high diastereofacial selectivities. Finally, some insight into the mechanism of the asymmetric induction was gained from the correlation of X-ray and Ti NMR data. Asymmetric distortion of the titanium coordination geometry has been suggested to be essential for enantioselective discrimination [44a].

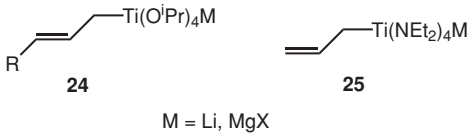
Easy to prepare and highly selective tartrate-derived reagents may be successfully employed for synthesizing chirons and useful building blocks. In a recent series of papers, Cossy et al. have reported new routes to enantiopure subunits and biologically active molecules based on enantioselective allyltitanation [45]. By using the reagents (*R,R*)- and (*S,S*)-**22**, enantiomeric alcohols of high optical purity (93–98 %) were prepared from α,β-acetylenic aldehydes [45a]. Similarly, optically active 1,2-diol units were synthesized from α-alkoxy-substituted aldehydes [45b]. *Syn*- and *anti*-diols were obtained with excellent

selectivities (93–95 % *de*) from unprotected chiral β-hydroxy aldehydes [45c]. Enantioselective allyltitanation was used as the key step in the total syntheses of (+)-sedamine [45d] and of the lactone units related to compactin and mevinolin [45e]. The complexes (*R*,*R*)- and (*S*,*S*)-**22** were also employed for the desymmetrization of *meso* dialdehydes, which were further transformed to chiral lactones [45f].

13.4 Allyltitanium Reagents without Cyclopentadienyl Groups

13.4.1 Synthesis by Transmetallation and Selective Allylation Reactions

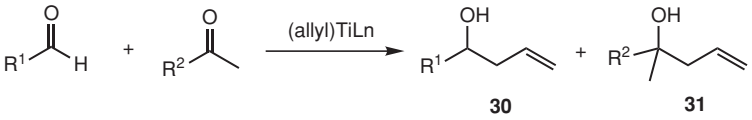
Allyltitanium compounds of the type (η^1-allyl)TiX_3 (X = OR, NR_2) were extensively studied in the early 1980s, mainly by Seebach [3,46] and by Reetz [4,47]. They can be obtained by transmetallation of allylic Li-, Mg-, or Zn-based organometallics with Ti. The (η^1-allyl)-$Ti(OR)_3$ complexes are more easily prepared from $ClTi(OR)_3$ and Mg or Li reagents [48]. Analogously, the allylic aminotitanium complexes (η^1-allyl)$Ti(NR_2)_3$ are accessible by titanation of the Li or Mg allylic precursors with $ClTi(NR_2)_3$ [47–49]. Moreover, allyltitanium ate complexes such as **24** and **25** (Scheme 13.23) can be generated by the addition of allylmagnesium or -lithium reagents to $Ti(OiPr)_4$ and $Ti(NEt_2)_4$, respectively [49,50].



Scheme 13.23. σ-Allyltitanium ate complexes bearing alkoxy and amino groups.

Although allyltitanium compounds lacking cyclopentadienyl ligands are quite reactive, this does not affect their chemo-, regio-, or stereoselectivity. The ability of these reagents to discriminate between aldehydes and ketones has been tested in competition experiments. Notable examples are depicted in Table 13.1 [4,50a].

Table 13.1. Ketone *vs.* aldehyde chemoselective addition of allyltitanium derivatives.

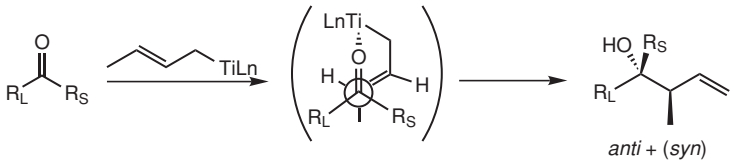


	TiLn / **30** : **31** ratio			
	$Ti(O^iPr)_3$ **26**	$[Ti(O^iPr)_4]^-$ **27**	$Ti(NMe_2)_3$ **28**	$[Ti(NMe_2)_4]^-$ **29**
$R^1 = C_6H_{13}$, $R^2 = C_5H_{11}$	86:14	98:2	13:87	4:96
R^1 = Ph = R^2	84:16	98:2	50:50	1:99

Whereas alkoxytitanium reagents (allyl)Ti(O*i*Pr)$_3$ (**26**) and [(allyl)Ti(O*i*Pr)$_4$]$^-$ MgCl$^+$ (**27**) are aldehyde-selective (**30**:**31** ratio $>$ 1), aminotitanium reagents (allyl)Ti(NMe$_2$)$_3$ (**28**) and [(allyl)Ti(NMe$_2$)$_4$]$^-$ MgCl$^+$ (**29**) are ketone-selective (**30**:**31** ratio $<$ 1). The case of aminotitanium reagents **28** and **29** represents a rare example of chemoselectivity in favor of carbanion addition to ketones. Particularly high aldehyde/ketone or ketone/aldehyde chemoselectivities are achieved with the *ate* complexes **27** and **29**, respectively. Allyltitanium complexes without Cp groups also show chemoselectivity towards dicarbonyl compounds as well as carbonyl compounds having additional functional groups. They add selectively to enones in a 1,2-fashion and usually faster than to the saturated analogues [4,5a].

Crotylmagnesium derivatives, as mixtures of regio- and stereoisomers, react with the alkoxy- and aminotitanium reagents to provide *E*-configured allyltitanium compounds in a stereoconvergent manner. Their addition to various aldehydes and ketones occurs with moderate to good *anti* diastereoselectivity. The effect of the substrate and the ligand structure on stereoselectivity has been examined, and although no general rule can be advanced, some significant trends are apparent in Table 13.2 [46a,48a,49].

Table 13.2. Substrate- and ligand-dependent diastereoselectivity in the crotyltitanation reaction.

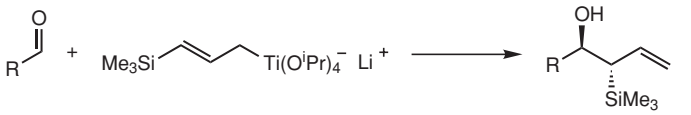


R_L	R_S	TiLn	*anti* / *syn*	R_L	R_S	TiLn	*anti* / *syn*
Ph	H	Ti(OPh)$_3$	85 : 15	Ph	Me	Ti(OPh)$_3$	88 : 12
Ph	H	Ti(O^{i}Pr)$_3$	80 : 20	Ph	Me	Ti(NEt$_2$)$_3$	85 : 15
^{i}Pr	H	Ti(O^{i}Pr)$_3$	88 : 12	^{t}Bu	Ph	Ti(OPh)$_3$	96 : 4
^{i}Pr	H	Ti(OPh)$_3$	96 : 4	^{i}Pr	Me	Ti(O^{i}Pr)$_3$	88 : 12

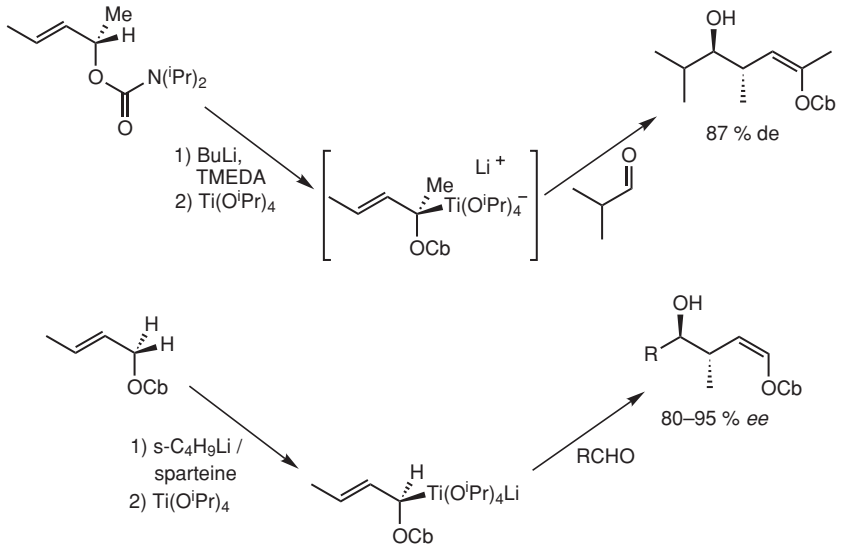
The phenoxytitanium reagent (crotyl)Ti(OPh)$_3$ is often more selective than other alkoxy- or aminotitanium reagents. Higher selectivities are observed with aliphatic than with aromatic aldehydes. Most significantly, highly diastereoselective addition to ketones can be achieved using these reagents; this is in contrast to other allylmetals, which are much less stereoselective or only slightly reactive toward ketones. Allyltitanium triphenoxide adds to the substituted epoxides regioselectively at the more substituted carbon to afford the corresponding alcohols in good yields [51].

Allyltitanium reagents bearing heteroatoms such as S, Si, P, etc. have also been reported [5a,5b,46a]. The silylated reagents react regioselectively at the γ-carbon atom, whereas both γ- and α-regioselectivities are observed for the sulfur-substituted derivatives. Hetero-substituted allyltitanium reagents generally show very high *anti* stereoselectivity (Scheme 13.24).

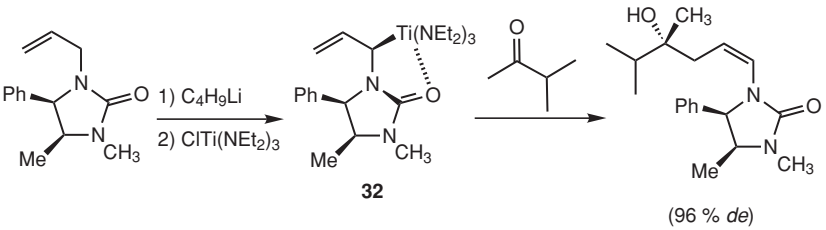
Titanated allyl carbamates are reported to react regio- and stereospecifically with aldehydes [52]. An elegant and synthetically useful method based on diastereoselective and enantioselective homoaldol reactions has been developed (Scheme 13.25) [53].



Scheme 13.24. Addition of silylated σ-allyltitanium ate complexes to aldehydes.



Scheme 13.25. Diastereoselective and enantioselective homoaldol reactions using titanated allyl carbamates.



Scheme 13.26. Highly enantioselective homoaldol addition with a chiral titanium *N*-allylurea reagent.

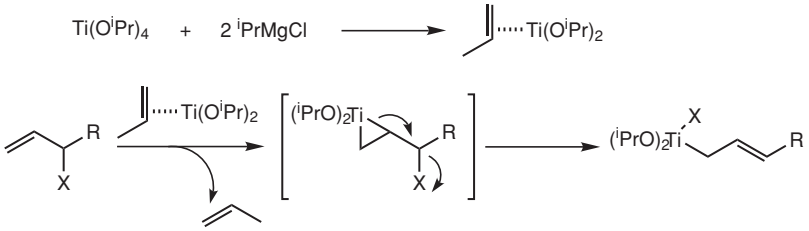
Generally speaking, since the α-carbon of a substituted allylic fragment is a stereogenic center, chirality may be transferred to the carbonyl compounds. Thus, very high diastereofacial selectivity has been obtained in the reaction of **32** with isopropyl methyl ketone due to a rigid transition state (Scheme 13.26) [54].

13.4.2

Allyltitaniums from Allyl Halides or Allyl Alcohol Derivatives and Ti(II) and their Synthetic Utility

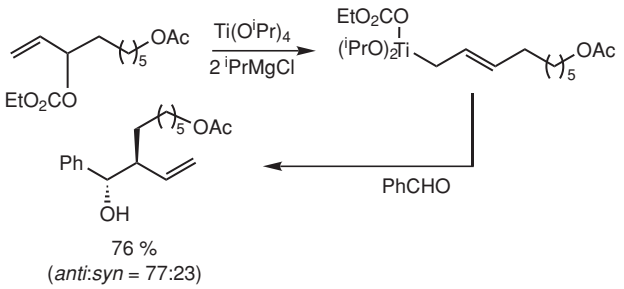
Despite the high level of selectivity obtained with (η^1-allyl)TiX_3 reagents, their synthetic limitations remain due to their method of preparation, which involves allylic lithium or magnesium precursors. Alternative direct syntheses from carbon–carbon unsaturated organic molecules and a titanium reagent have recently extended the synthetic utility of allyltitanium compounds. The renaissance in this field is mainly due to the impressive development of Ti(II) chemistry in the mid-1990s. Therefore, this section will be limited to the most relevant findings to avoid redundancy with Chapter 9 of this book.

The versatile Ti(II) chemistry available using preformed (alkene)Ti(O*i*Pr)$_2$ species was opened up by the discovery of the Kulinkovich cyclopropanation reaction [55]. Since 1995, Sato and collaborators have developed a wide range of elegant and synthetically useful reactions based on the Ti(O*i*Pr)$_4$/*i*PrMgCl reagent [56]. In particular, it was reported that the Ti(II) complex (η^2-propene)Ti(O*i*Pr)$_2$, preformed from Ti(O*i*Pr)$_4$ and 2 equivalents of *i*PrMgCl, reacts with allylic compounds, such as halide, acetate, carbonate, phosphate, sulfonate, and aryl ether derivatives, to afford allyltitanium compounds as depicted in Scheme 13.27 [57].



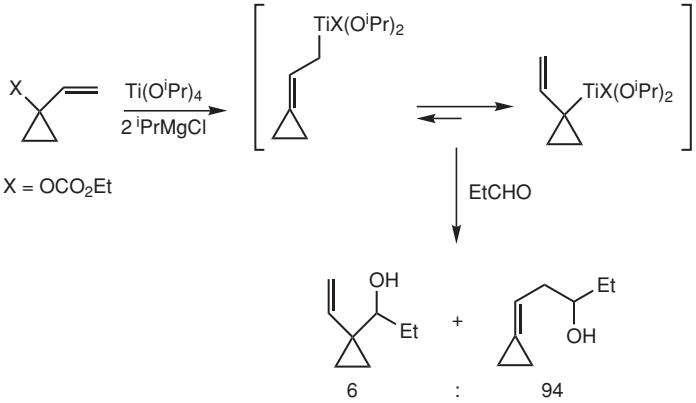
Scheme 13.27. Preparation of allyltitanium compounds from allylic derivatives.

The reaction proceeds through ligand exchange and a subsequent β-elimination akin to the oxidative addition of "Cp_2Zr" to allylic ethers [58]. In this way, allyltitanium compounds can be obtained from readily available allylic alcohol derivatives and inexpensive Ti(O*i*Pr)$_4$. The method allows the preparation of functionalized allyltitaniums bearing functional groups such as ester or halide (Scheme 13.28).



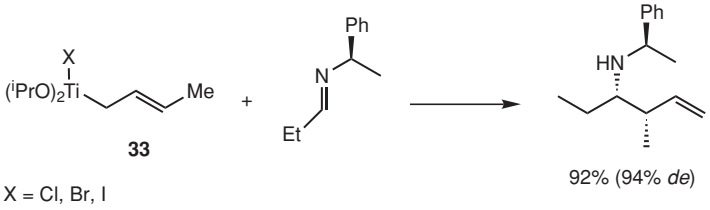
Scheme 13.28. Functionalized allyltitanium compounds from allylic derivatives.

Reactions with seven- to nine-membered cyclic allylic carbonates or halides give the corresponding cyclic allyltitanium compounds. These reagents add to aldehydes and imines with moderate to excellent diastereoselectivities [59]. The allyltitanium compound generated from 1-vinylcyclopropyl carbonate reacts regioselectively with aldehydes and ketones at the less substituted carbon atom to provide alkylidenecyclopropane derivatives, as shown in Scheme 13.29 [60]. The regiochemical outcome of the reaction can be rationalized by assuming an equilibrium between two allyltitanium species that favors the less strained tertiary structure.



Scheme 13.29. Regioselective conversion of 1-vinylcyclopropyl carbonate into alkylidenecyclopropane derivatives.

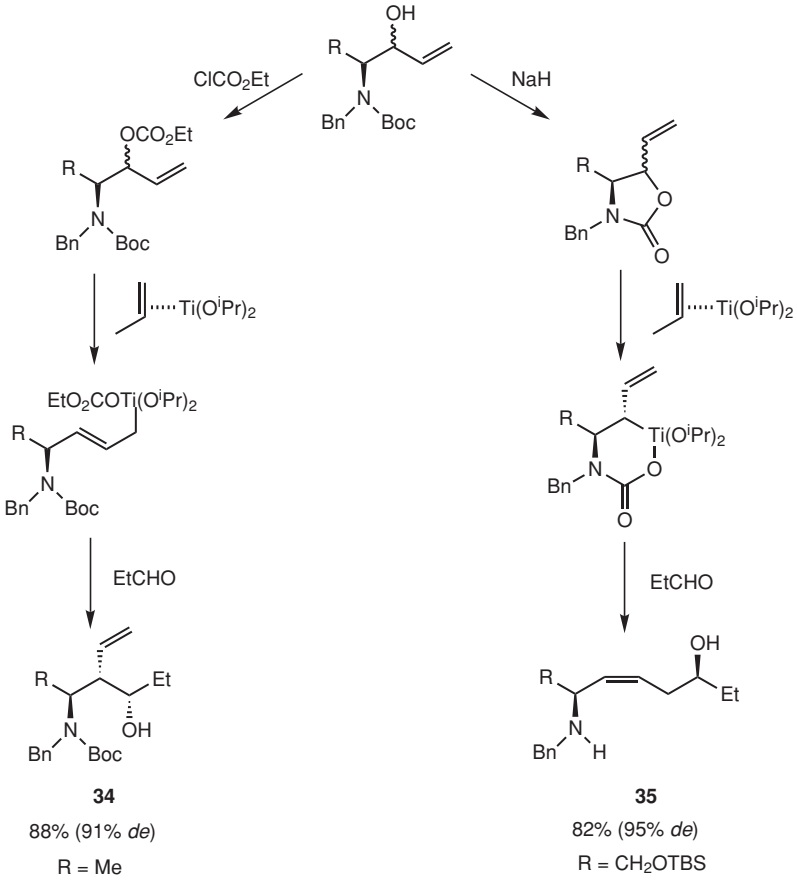
Asymmetric reactions have also been developed. The reactions of allyltitaniums with chiral aldimines derived from optically active 1-phenylethylamine afford optically active homoallylic amines with excellent diastereofacial selectivities. Thus, the Cram *syn* addition products are obtained highly predominantly when using crotyltitanium reagent **33**, as exemplified in Scheme 13.30 [61].



Scheme 13.30. Addition of crotyltitanium reagents to a chiral aldimine.

Various chiral allyltitaniums having a stereogenic center in the allyl moiety have been prepared by the Sato method and these have been reacted with aldehydes and imines [62]. An interesting example concerns chiral allyltitanium compounds bearing an amino substituent at the stereogenic center, which could be prepared from optically active 4-aminoalk-1-en-3-ol derivatives. These reagents add to aldehydes highly diastereoselectively (*de* $\geq$ 90 %) and in a regioselective manner depending on the allylic precursor derivative. Whereas the allyltitaniums formed from the carbonate precursors gave rise to the

formation of β-vinyl-γ-amino alcohols **34**, those formed from cyclic carbamates afforded predominantly 1,5-amino alcohols **35** (Scheme 13.31).



Scheme 13.31. Regiocontrolled addition of chiral allyltitanium derivatives to aldehydes.

Allyltitanium complexes derived from a chiral acetal have been reacted with carbonyl compounds and imines [63]. While the chiral induction proved to be low with carbonyl compounds, high induction was observed with imines. This complex represents the first chiral homoenolate equivalent that reacts efficiently with imines. Finally, the reactions with electrophiles other than carbonyl compounds and imines, namely a proton source, NCS, and I_2, furnished the corresponding alkene, chloro, and iodo derivatives in good yields [64].

13.5 Conclusion

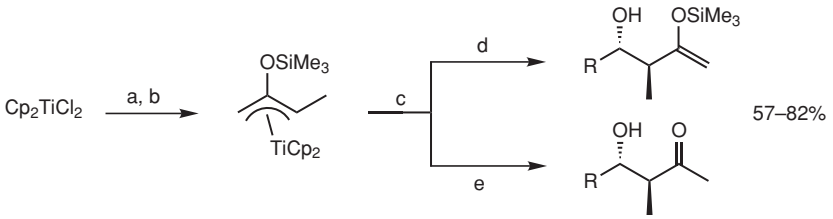
The last decade has seen significant progress in the field of allyltitanium chemistry. A broad range of allyltitanium compounds, including functionalized derivatives, is now available. They can be prepared through several synthetic methods from structurally

diverse organic precursors. The versatility of these compounds as allyl-transfer reagents has recently been demonstrated. Allyltitaniums have proved to be mild and selective, particularly in their addition to carbonyl compounds, which generally proceeds with high chemo-, regio-, and stereoselectivity. Furthermore, the opportunity of employing efficient chiral titanium reagents as well as other electrophiles further increases the synthetic potential of the allyltitanation reaction. It can be anticipated that allyltitanium derivatives will be useful reagents for the practising synthetic chemist in the forthcoming years.

Typical Experimental Procedures

All manipulations should be carried out in dry flasks under argon. Syringe techniques are best employed.

Preparation of 2-trimethylsilyloxy-η³-crotyltitanocene and *in situ* reactions with aldehydes [27]



R = alkyl (Et, *n*-C_5H_{11}, ^{i}Pr, ^{t}Bu) : exclusively *anti*

R = Ph : *anti* /*syn* = 70/30

(a) 1 equiv. ^{i}PrMgCl, 25 °C, THF; (b) –15 °C, 1 equiv. ^{i}PrMgCl, 1 equiv. H_2C=CH–C(OSiMe_3)=(
(c) RCHO, –15 °C, 10 min; (d) aq $NaHCO_3$; (e) *2 M* HCl

Scheme 13.32. Preparation of 2-trimethylsilyloxy-η³-crotyltitanocene and stereoselective reactions with aldehydes.

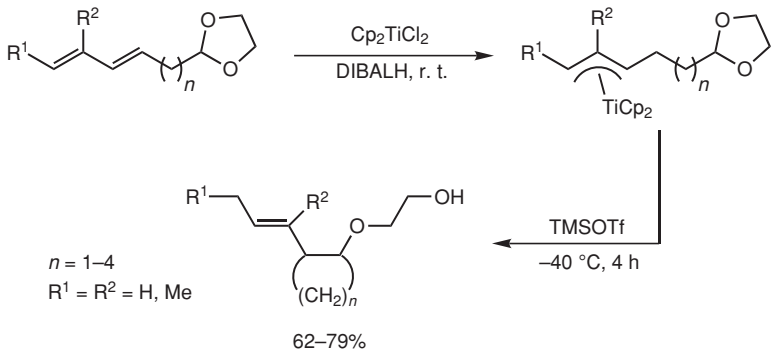
At room temperature, *i*PrMgCl (2 mL, 2 M solution in THF) was added dropwise by means of a syringe to a stirred suspension of Cp_2TiCl_2 (1.00 g, 4.03 mmol) in THF (25 mL). After stirring for 15 min., the resulting green solution of Cp_2TiCl was cooled to −15 °C. Solutions of *i*PrMgCl (4 mmol) in THF (2 mL) and of silyloxydiene (6 mmol) in THF (ca. 1 mL) were then slowly added simultaneously by means of syringes to give a violet reaction mixture. After stirring for 5 min., the neat aldehyde (4.5 mmol) was added by means of a syringe at −15 to −10 °C. After a further 10 min., either acidic or basic work-up was performed to afford the corresponding β-hydroxy ketone or β-hydroxy enol silyl ether, respectively.

Acidic work-up: The reaction mixture was quenched with 2 M HCl (4 mL) and air was passed through the stirred solution for 5 min. The solution was then diluted with Et_2O/hexane (4:1, 120 mL) and the precipitate of Cp_2TiCl_2 was recovered by filtration (0.7 g, 70 %). The organic layer was washed with small portions of H_2O, dried ($MgSO_4$), and concentrated in vacuo. A second small portion of Cp_2TiCl_2 was separated by filtration through a thin layer of Celite. The filtrate was concentrated in vacuo to provide the crude β-hydroxy ketone, which was further purified by flash chromatography.

Basic work-up: The reaction mixture (−10 °C) was poured into a separatory funnel containing cold Et_2O (120 mL), and treated with ice-cold satd. aq. $NaHCO_3$ solution (30 mL). The Et_2O layer was separated and the aqueous layer was extracted with further cold Et_2O. The combined organic phases were washed with H_2O, dried ($MgSO_4$), and concentrated in vacuo. The residue was treated with Et_2O/hexane (1:1, 30 mL) and the small residual amount of titanium derivatives was removed by filtration through a frit. The bulk of the Cp_2TiCl_2 could be recovered by acidifying the aqueous layer. After concentration of the organic filtrate in vacuo, the crude β-hydroxy enol silyl ether was purified by flash chromatography on a short silica gel column.

General procedure for the intramolecular crotyltitanation of acetals [22]

The crotyltitanium complex was prepared in situ at room temperature by treating Cp_2TiCl_2 (1.00 g, 4.03 mmol) with two equivalents of DIBALH (2 ×x 4 mL, 2 M solution in THF) and dienyl acetal (4 mmol). The solution was then cooled to −40 °C, whereupon TMSOTf (0.8 mL, 4 mmol) was slowly added and the resulting mixture was stirred for 4 h at −40 °C. The cold mixture was then quenched with satd. aq. $NaHCO_3$ solution and extracted twice with diethyl ether. The combined organic phases were washed with water, dried over $MgSO_4$, and concentrated in vacuo. Chromatographic purification (hexane/diethyl ether, 1:1, *v*/*v*) afforded 1-alkoxy-2-vinylcycloalkanes in 62−79 % overall yield (Scheme 13.33).

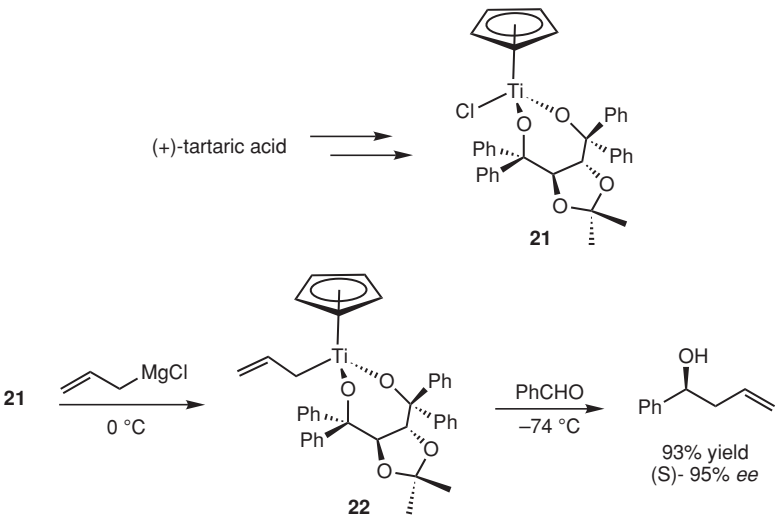


Scheme 13.33. Intramolecular crotyltitanation of acetals.

Enantioselective allyltitanation of aldehydes with a chiral tartrate-derived titanium complex [44]

At 0 °C, a solution of allylmagnesium chloride (0.8 M in THF, 5.3 mL, 4.25 mmol) was added dropwise under argon to a solution of (*R*,*R*)-**21** (3.06 g, 5 mmol) in diethyl ether (60 mL) over a period of 10 min. After stirring for 1.5 h at 0 °C, the slightly orange suspension was cooled to −74 °C, whereupon a solution of benzaldehyde (403 mg, 3.8 mmol) in diethyl ether (5 mL) was added over a period of 2 min. Stirring at −74 °C was continued for 3 h. The reaction mixture was then treated with 45 % aqueous NH_4F solution (20 mL), stirred for 12 h at room temperature, and filtered through Celite. The filtrate was extracted with diethyl ether (2 ×x 50 mL) and the combined organic phases were washed with brine, dried with $MgSO_4$, and concentrated. The solid residue was stirred with pentane (50 mL). Subsequent filtration furnished 1.68 g of white crystalline (4*R*)-*trans*-2,2-di-

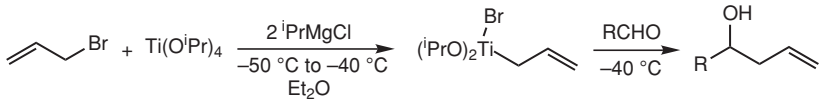
methyl-α,α,α',α'-tetraphenyl-1,3-dioxolane-4,5-dimethanol (ligand). Chromatography of the residue from the filtrate (CH_2Cl_2/hexane/diethyl ether, 4:4:1) finally afforded 521 mg (93 %) of (1*S*)-1-phenyl-3-buten-1-ol (95 % *ee*), as determined by capillary GLC.



Scheme 13.34. Enantioselective allyltitanation of aldehydes.

Typical procedure for the preparation of allyltitanium derivatives from allyl halides via oxidative addition, and *in situ* reaction with aldehydes [57,59]

To an equimolar mixture of $Ti(OiPr)_4$ and 3-bromo-1-propene in diethyl ether, 2 equiv. of *i*PrMgCl was added at −50 °C. After the reaction mixture had been stirred for 1 h at −50 to −40 °C, the aldehyde was added at −40 °C and the reaction mixture was stirred



Scheme 13.35. Preparation of allyltitanium derivatives from allyl halides and reaction with aldehydes.

for a further 0.5 to 1 h. Hydrolytic work-up (1 M HCl, then extraction with diethyl ether), followed by chromatographic purification on silica gel afforded the corresponding homoallylic alcohol in good yield (77−94 %). An analogous procedure was also applied to allyl alcohol derivatives.

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14
Titanium-Based Olefin Metathesis and Related Reactions

Takeshi Takeda

14.1
Introduction

Titanium carbene complexes $L_2Ti{=}CR^1R^2$ are a useful class of titanium-based reagents. These organotitanium species react with unactivated non-polar carbon–carbon multiple bonds as well as polar multiple bonds, such as carbonyls and nitriles, and are thus useful tools in organic synthesis [1]. Alkenes form titanacyclobutanes upon treatment with titanium carbene complexes. Since the main degradation process of the titanacycle is generation of a new olefin and a new carbene complex, the net reaction of a titanium carbene complex with an alkene can be regarded as an olefin metathesis. An analogous reaction of the carbene complexes with carbon–oxygen double bonds provides a powerful tool for Wittig-like carbonyl olefination. This chapter focuses on the use of titanium carbene complexes in olefin metathesis and related synthetically useful reactions that involve the formation of four-membered titanacycle intermediates.

14.2
Reactions of Titanium Carbene Complexes with Carbon–Carbon Double Bonds

14.2.1
Olefin Metathesis

A combination of the cleavage of the sp^2–sp^2 double bonds of a pair of alkenes and the reconstruction of a pair of new alkenes (Scheme 14.1) is a useful synthetic method for the construction of carbon frameworks.

Scheme 14.1. Metathesis between two olefins.

This reaction is invariably catalyzed by transition metal compounds and its mechanism is of special interest. The first explanation for this transformation is based on the so-called "pairwise mechanism", in which two olefins coordinate to a transition metal center to form a transient cyclobutane-like intermediate [2]. However, this idea was later replaced

by the metal carbene mechanism (Scheme 14.2), in which an intermediate metallacyclobutane **1** is produced by the cycloaddition of a metal carbene **2** to an olefin **3** [3].

Scheme 14.2. Reaction of a metal carbene complex with an olefin.

The term "olefin metathesis" originally implied the interchange of sp^2 carbon atoms between two olefins, as shown in Scheme 14.1. Since the elucidation of its mechanism, the reaction of a metal carbene with an olefin, in which the double bonds of the metal carbene and olefin are cleaved and a new metal carbene and a new olefin are constructed, the process illustrated in Scheme 14.2 has been referred to as olefin metathesis [1d].

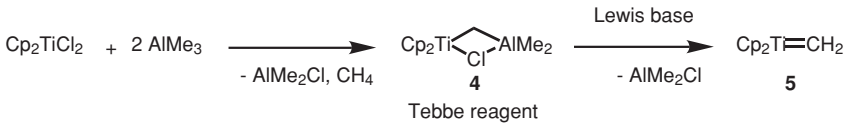
Catalysts and reagents for this transformation include a wide variety of transition metal compounds. Among them, organotitanium species constitute an important class of reagents. In the early stages of these studies, titanium species prepared by the treatment of titanium tetrachloride or bromide with organoalanes (R_3Al) or organoaluminates ($LiAlR_4$) were investigated as catalysts for ring-opening metathesis polymerization (ROMP) [4] of cyclic olefins such as cyclobutenes [5], cyclopentenes [5a,6], and norbornenes [7] (Scheme 14.3). Since the discovery of the Tebbe reagent, the reactions of acyclic olefins with structurally well-defined organotitanium compounds have been investigated for their potential in organic synthesis.

Scheme 14.3. ROMP of cyclic olefins.

14.2.2

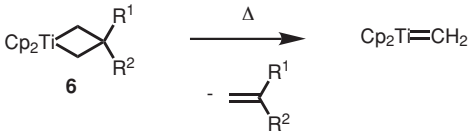
Formation of Titanocene-Methylidene and its Reaction with Olefins

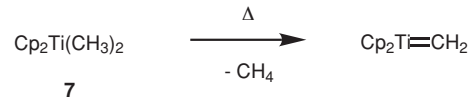
In 1978, Tebbe and co-workers reported the formation of the metallacycle **4**, commonly referred to as the Tebbe reagent, by the reaction of two equivalents of trimethylaluminum with titanocene dichloride. The expulsion of dimethylaluminum chloride by the action of a Lewis base affords the titanocene-methylidene **5** (Scheme 14.4) [8].



Scheme 14.4. Formation of titanocene-methylidene from the Tebbe reagent.

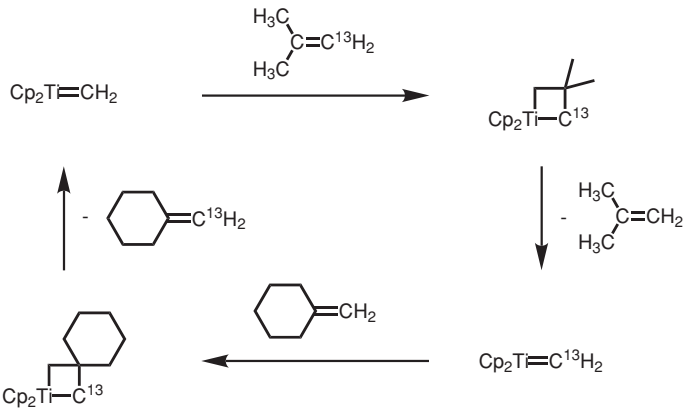
Aluminum-free titanocene-methylidene can be generated by thermolysis of titanacyclobutanes **6**, which are prepared by reaction of the Tebbe reagent with appropriate olefins in the presence of pyridine bases [9]. Alternatively, the titanacyclobutanes are accessible from titanocene dichloride and bis-Grignard reagents [10] or from π-allyl titanocene precursors [11]. The α-elimination of methane from dimethyltitanocene **7** provides a convenient means of preparing titanocene-methylidene under almost neutral conditions [12] (Scheme 14.5).





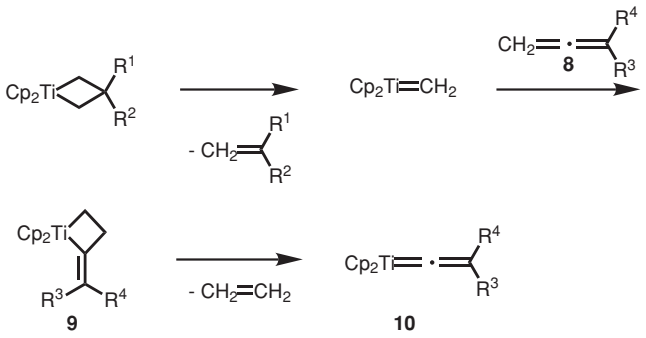
Scheme 14.5. Formation of titanocene-methylidene from titanacyclobutanes and dimethyltitanocene.

Tebbe and co-workers reported the first olefin metatheses between titanocene-methylidene and simple terminal olefins [13]. They showed cross-metathesis between isotopically labeled isobutene and methylenecyclohexane to be catalyzed by titanocene-methylidene. This process is referred to as "degenerate" olefin metathesis as it does not yield any new olefin (Scheme 14.6). The intermediate titanacyclobutane has been isolated and characterized [14], and its stability [15] and mechanism of rearrangement [16] have been investigated.



Scheme 14.6. Titanocene-methylidene-catalyzed metathesis between two olefins.

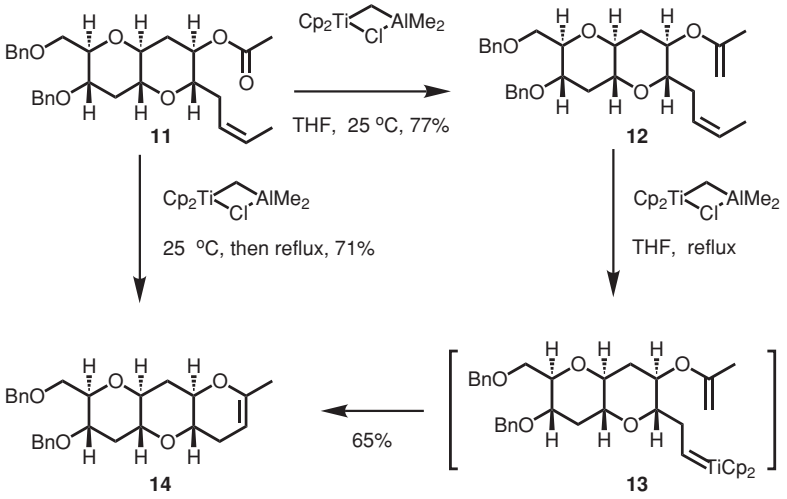
One of the synthetically useful titanium-based olefin metatheses is the reaction of titanocene-methylidene with terminal allenes **8**. Productive olefin metathesis occurs when titanacyclobutanes are treated with **8** (Scheme 14.7) [17] and the resulting α-alkyli-



Scheme 14.7. Olefin metathesis of titanocene-methylidene with substituted allenes.

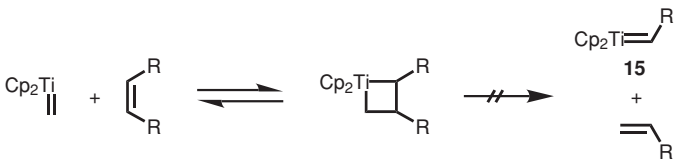
denetitanacyclobutanes **9** can be employed as precursors of titanocene-alkenylidene **10**, which is suited for further transformations (see Section 14.3.2).

Tandem carbonyl olefination–olefin metathesis utilizing the Tebbe reagent or dimethyltitanocene is employed for the direct conversion of olefinic esters to six- and seven-membered cyclic enol ethers. Titanocene-methylidene initially reacts with the ester carbonyl of **11** to form the vinyl ether **12**. The ensuing productive olefin metathesis between titanocene methylidene and the *cis*-1,2-disubstituted double bond in the same molecule produces the alkylidene-titanocene **13**. Ring-closing olefin metathesis (RCM) of the latter affords the cyclic vinyl ether **14** (Scheme 14.8) [18]. This sequence of reactions is useful for the construction of the complex cyclic polyether frameworks of maitotoxin [19].



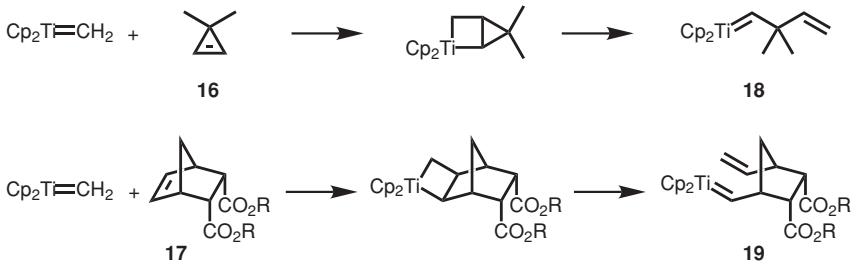
Scheme 14.8. Formation of cyclic enol ethers by carbonyl methylenation–olefin metathesis.

Despite the successful reactions mentioned above, olefin metathesis utilizing titanocene-methylidene is not necessarily regarded as a useful synthetic tool. Indeed, the steric interaction between the substituent at the carbon α to titanium and the bulky cyclopentadienyl ligand disfavors the formation of the titanocene-alkylidene **15**. Hence, cleavage of the titanacycle affords only titanocene-methylidene and the starting olefin (Scheme 14.9).



Scheme 14.9. Reaction of titanocene-methylidene with internal olefins.

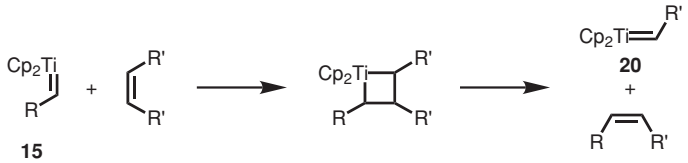
On the contrary, if a highly strained cyclic olefin such as the cyclopropene **16** [20] or the norbornene derivative **17** [21] is employed, the titanacycle is cleaved to form the corresponding titanocene-alkylidene **18** or **19**. This reaction is clearly enhanced by the concomitant release of intrinsic strain energy (Scheme 14.10).



Scheme 14.10. Reaction of titanocene-methylidene with strained cyclic olefins.

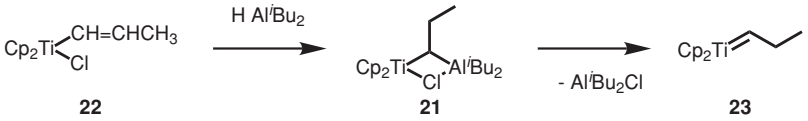
14.2.3
Formation of Titanocene-Alkylidenes and their Application to Olefin Metathesis

Another approach to synthetically useful olefin metathesis involves the utilization of higher homologues of titanium-methylidene **15**, as shown in Scheme 14.11. If the resulting titanium carbene complex **20** is more stable than the starting alkylidene complex **15**, this reaction can be employed for the generation of various titanocene-alkylidenes and as a method for the preparation of unsaturated compounds.



Scheme 14.11. Reaction of titanocene-alkylidenes with olefins.

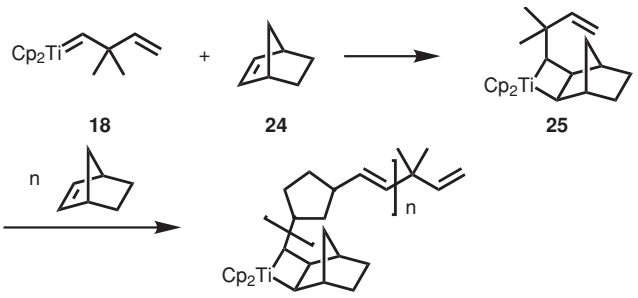
The major obstacle to this approach is that there are few reagents capable of generating higher homologues of titanocene-methylidene. Although the procedure is not straightforward, the titanacycle **21** formed by the addition of diisobutylaluminum hydride to the double bond of (1-propenyl)titanocene chloride **22** serves as a titanocene-propylidene **23** equivalent in carbonyl olefination (Scheme 14.12) [22].



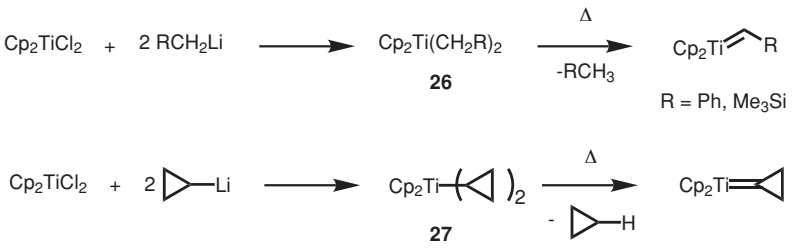
Scheme 14.12. Formation of titanocene-alkylidenes from alkenyltitanocene chlorides.

The alkyl-substituted titanium carbene complex **18** reacts with norbornene **24** to form a new titanacycle **25**, which can be employed for the ROMP of **24** (Scheme 14.13). The titanacycle generated by the reaction of the Tebbe reagent with **24** is also used as an initiator for the same polymerization [23]. These preformed titanacyclobutanes also initiate ROMP of various other strained olefin monomers [24].

An alternative means of preparing alkylidene complexes of titanium is by the α-elimination reaction of dialkyltitanocenes (Scheme 14.14) [25]. The limitation of this method is that only dialkyltitanocenes having no β-hydrogen, such as **26** or dicyclopropyltitano-



Scheme 14.13. ROMP initiated by the titanocene-alkylidene **18.**

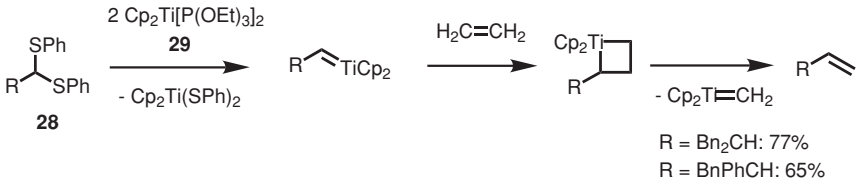


Scheme 14.14. Preparation of titanocene-alkylidenes from dialkyltitanocenes.

cene **27**, can be employed for the preparation. Indeed, if a β-hydrogen is present, an elimination might take place during thermolysis of the dialkyltitanocene. The titanocene-alkylidenes thus prepared are also used for the ROMP of norbornene [26].

14.2.4
Preparation of Titanocene-Alkylidenes from Thioacetals and their Application to Olefin Metathesis

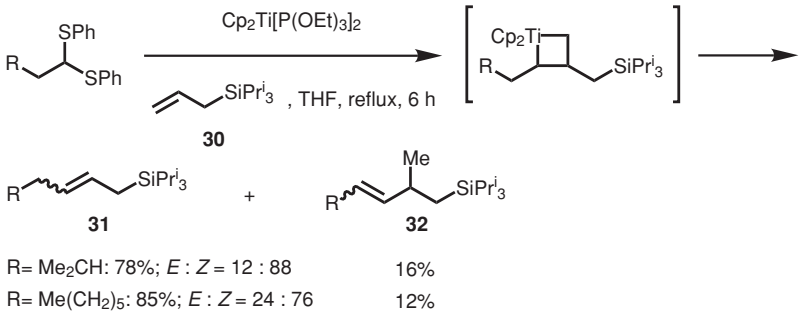
The organotitanium compounds produced by desulfurization of the diphenyl thioacetals of aldehydes **28** with the titanocene(II) species $Cp_2Ti[P(OEt)_3]_2$ **29** react with carbon–carbon double bonds to form the olefin metathesis-type products. Thioacetals **28** may be transformed into terminal olefins by desulfurization with **29** under an ethene atmosphere (Scheme 14.15) [27]. This reaction is believed to proceed through a titanacyclobutane intermediate, formed by cycloaddition of the titanocene-alkylidene with ethene.



Reagent: $Cp_2Ti[P(OEt)_3]_2$ (3 eq). Conditions: THF, r.t. (15 min) then reflux (30 min).

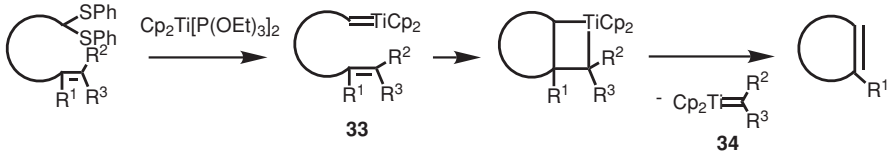
Scheme 14.15. Olefin metathesis of titanocene-alkylidenes generated from thioacetals with ethene.

The reactions of titanium-alkylidenes prepared from thioacetals with unsymmetrical olefins generally produce complex mixtures of olefins. This complexity arises, at least in part, from the concomitant formation of the two isomeric titanacyclobutane intermediates. However, the regiochemistry of the titanacyclobutane formation is controlled when an olefin bearing a specific substituent is employed. Reactions of titanocene-alkylidenes generated from thioacetals with trialkylallylsilanes **30** afford γ-substituted allylsilanes **31**, along with small amounts of homoallylsilanes **32** (Scheme 14.16) [28].



Scheme 14.16. Transformation of thioacetals into γ-substituted allylsilanes.

Another synthetic application of olefin metathesis using a thioacetal-titanocene(II) system is the ring-closing olefin metathesis (RCM) of carbene complexes possessing an olefin moiety, e. g. **33** (Scheme 14.17). The success of the RCM apparently depends on the substituents at the carbon–carbon double bond (i. e. the substituent(s) on the resulting carbene complex **34**).



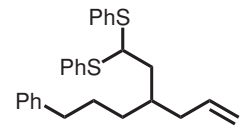
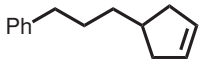
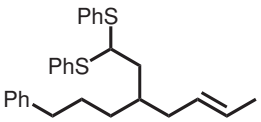
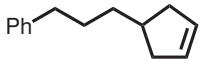
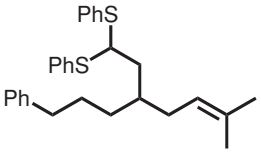
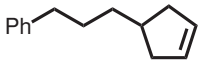
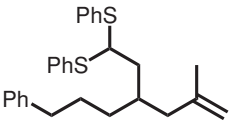
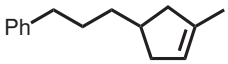
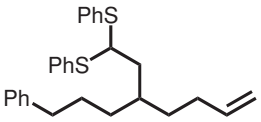
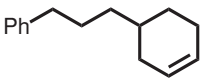
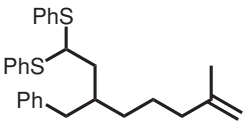
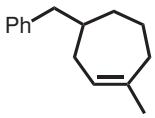
Scheme 14.17. RCM of titanocene-alkylidenes generated from alkenyl thioacetals.

Thioacetals having a terminal or 1,2-disubstituted double bond are transformed into the corresponding cycloalkenes upon treatment with titanocene(II) species first at room temperature and then at elevated temperature. On the other hand, only a small amount of cycloalkene is produced under the same reaction conditions from thioacetals having a trisubstituted double bond (Table 14.1) [29,30].

This RCM has proven to be a useful synthetic method for the construction of a variety of heterocycles. Mono and bicyclic unsaturated ethers and sulfides are obtained from alkenyl thioacetals having an ether or sulfide linkage (Table 14.2) [30].

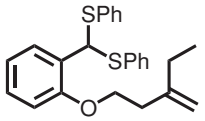
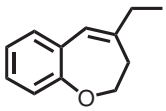
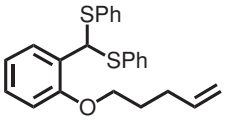
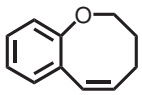
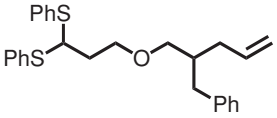
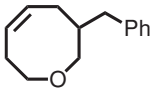
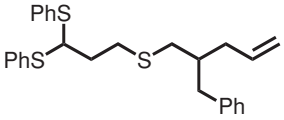
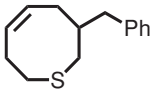
Nitrogen heterocycles can also be prepared by the RCM of unsaturated amines having a diphenyl thioacetal moiety (Table 14.3) [31].

Table 14.1. Preparation of carbocyclic compounds from alkenyl thioacetals.

	Thioacetal	Product	Yield
1			71%
2			67%
3			8%
4			87%
5			50%
6			81%

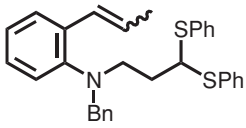
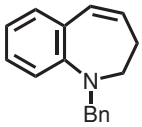
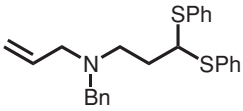
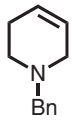
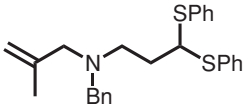
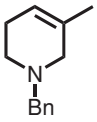
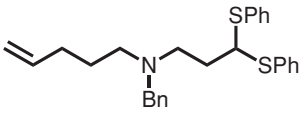
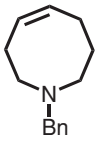
Reagent: $Cp_2Ti[P(OEt)_3]_2$ (3 eq). Conditions: THF, r.t. (1–2 h) then reflux (1 h).
Concentration of the thioacetal: 0.1–0.015 M.

Table 14.2. Preparation of cyclic ethers and sulfides from alkenyl thioacetals.

	Thioacetal	Product	Yield
1			69%
2			65%
3			63%
4			50%

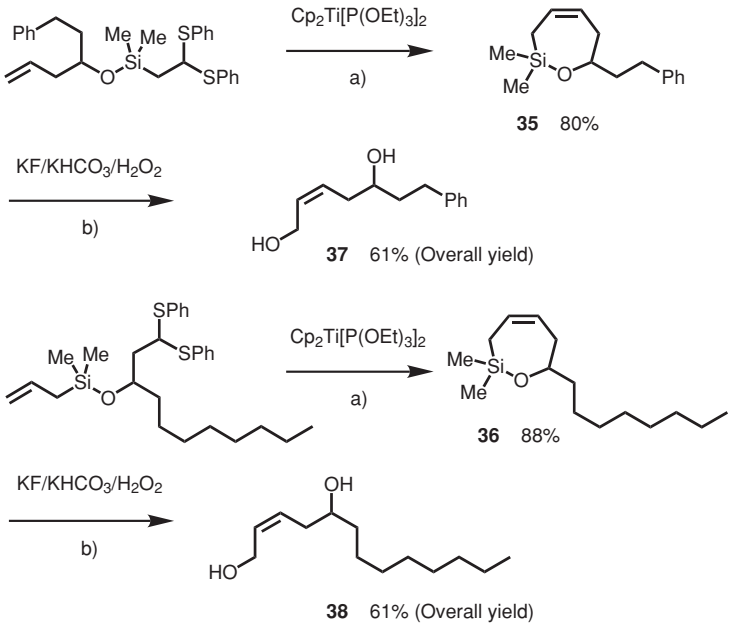
Reagent: $Cp_2Ti[P(OEt)_3]_2$ (3–4 eq). Conditions: THF, r.t. (1–5 h) then reflux (1–3 h). Concentration of the thioacetal: 0.1–0.01 M.

Table 14.3. Preparation of cyclic amines from alkenyl thioacetals.

	Thioacetal	Product	Yield
1			77%
2			35%
3			61%
4			73%

Reagent: $Cp_2Ti[P(OEt)_3]_2$ (3–4 eq). Conditions: THF, r.t. (2 h) then reflux (1–2 h). Concentration of the thioacetal: 0.03 M.

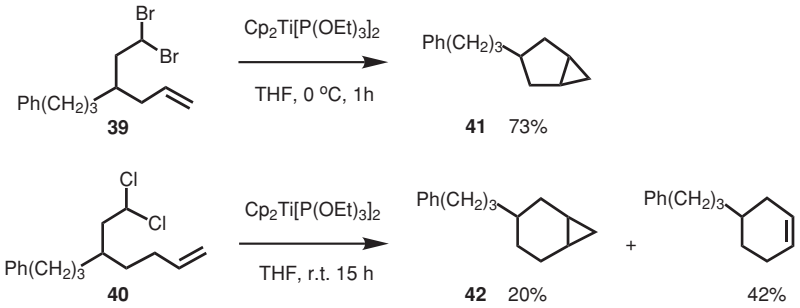
An interesting application of the cyclization of alkenyl thioacetals is the stereoselective preparation of olefinic diols. Thus, oxidative cleavage of the silicon–carbon bond [32] in the ring-closed metathesis products, i.e. cyclic allylsilanes such as **35** and **36**, affords (*Z*)-alk-2-ene-1,5-diols **37** and **38** (Scheme 14.18) [33].



a) Reagent: $Cp_2Ti[P(OEt)_3]_2$ (4 equiv.). Conditions: THF, r.t. (4 h) then reflux (1 h) Concentration of the thioacetal: 0.03 M. b) Conditions: THF/MeOH, 40 °C, 24 h.

Scheme 14.18. Stereoselective preparation of olefinic diols from alkenyl thioacetals.

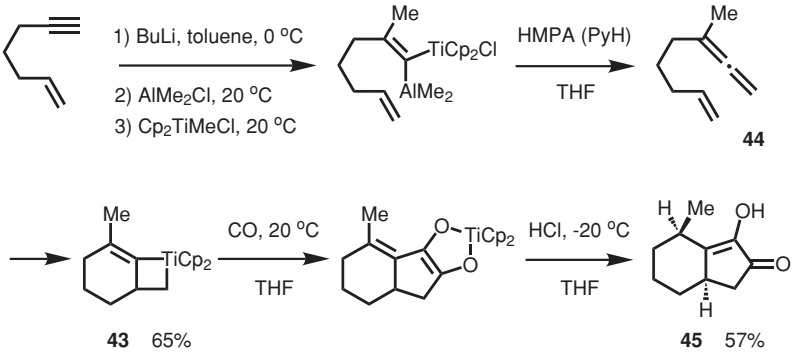
From a mechanistic point of view, the titanocene(II)-promoted intramolecular cyclopropanation of *gem*-dihalides possessing a terminal double bond is interesting. Although the products of ring-closing metathesis, i.e. cycloalkenes, are produced in certain cases, the treatment of 6,6- and 7,7-dihalo-1-alkenes (e.g. **39** and **40**) with titanocene(II) species affords bicyclo[3.1.0]hexane and bicyclo[4.1.0]heptane derivatives **41** and **42**, respectively (Scheme 14.19) [34].



Scheme 14.19. Titanocene(II)-promoted intramolecular reaction of alkenyl *gem*-dihalides.

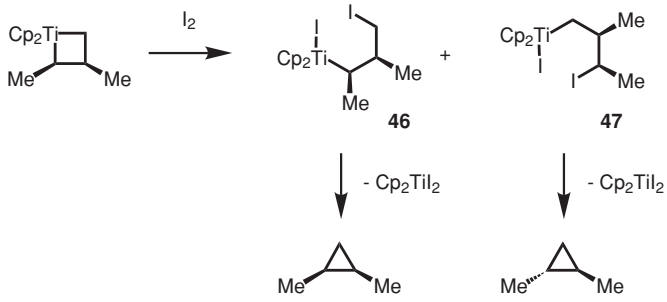
14.2.5
Other Transformations of Titanacyclobutanes

Titanacyclobutanes also serve as useful synthetic intermediates; the titanacycle **43**, prepared by the intramolecular reaction of the alkenylidene complex **44**, affords the α-diketone **45** and the other functionalized cyclic compounds by further transformations (Scheme 14.20) [35].



Scheme 14.20. Transformation of titanacyclobutanes into functionalized carbocycles.

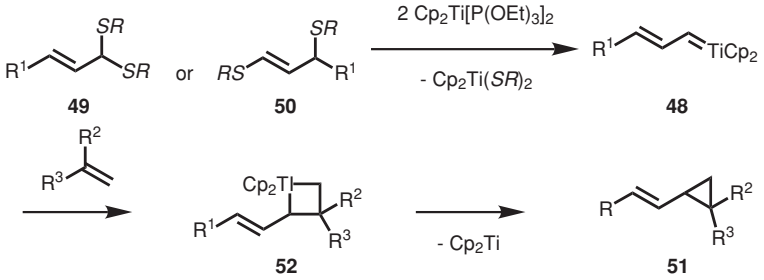
Although the reaction of a titanium carbene complex with an olefin generally affords the olefin metathesis product, in certain cases the intermediate titanacyclobutane may decompose through reductive elimination to give a cyclopropane. A small amount of the cyclopropane derivative is produced by the reaction of titanocene-methylidene with isobutene or ethene in the presence of triethylamine or THF [8]. In order to accelerate the reductive elimination from titanacyclobutane to form the cyclopropane, oxidation with iodine is required (Scheme 14.21) [36]. The stereochemistry obtained indicates that this reaction proceeds through the formation of γ-iodoalkyltitanium species **46** and **47**. A subsequent intramolecular S_N2 reaction produces the cyclopropane.



Scheme 14.21. Formation of cyclopropanes by the oxidative cleavage of titanacyclobutanes.

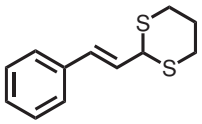
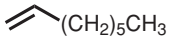
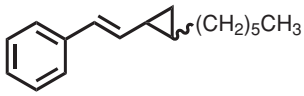
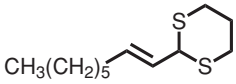
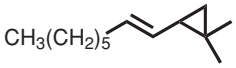
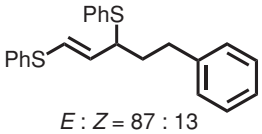
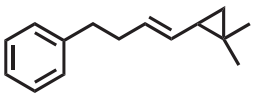
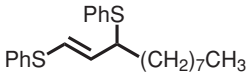
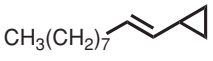
An unusual reductive elimination can ensue from titanacyclobutanes possessing an alkenyl group at the carbon α to the titanium atom. Thus, alkenylcarbene complexes **48**, prepared by the desulfurization of β,γ-unsaturated thioacetals **49** or 1,3-bis(phenylthio)propene derivatives **50** with a titanocene(II) reagent, react with terminal olefins to produce alkenylcyclopropanes **51** (Scheme 14.22, Table 14.4) [37]. This facile reductive

elimination might be attributed to the labile allylic carbon–titanium bond of the titanacyclobutane **52**.



Scheme 14.22. Formation and reductive elimination of alkenyltitanacyclobutanes.

Table 14.4. Preparation of alkenylcyclopropanes from β,γ-unsaturated thioacetals and related compounds.

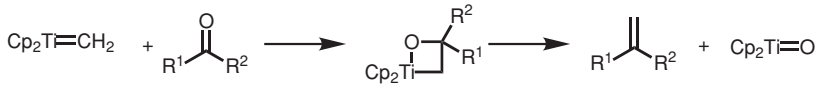
	Organosulfur Compound	Olefin	Product	Yield
1			 *ratio of isomers* = 60 : 40	72%
2	 *E* : *Z* = 96 : 4		 *E* : *Z* = 82 : 18	86%
3	 *E* : *Z* = 87 : 13		 *E* : *Z* = 85 : 15	93%
4	 *E* : *Z* = 79 : 21	= a	 *E* : *Z* = 98 : 2	76%

Reagent: $Cp_2Ti[P(OEt)_3]_2$ (2 eq), olefin (2–10 eq). Conditions: THF, r.t. (4 h).
a Prepared in situ by the reduction of 1,2-dibromoethane with magnesium.

14.3
Reactions of Titanium Carbene Complexes with Carbon–Oxygen Double Bonds [38]

14.3.1
Methylenation of Carbonyl Compounds

A reaction that is mechanistically related to olefin metathesis is the Wittig-like olefination of carbonyl compounds, which proceeds through the formation of oxatitanacyclobutane **53** and subsequent elimination of titanocene oxide **54** (Scheme 14.23). The Tebbe reagent [39], titanacyclobutanes [9a,39d], and dimethyltitanocene [12,40] are used as precursors of titanium-methylidene for methylidenation. This carbonyl olefination using titanium-based reagents has several advantages over conventional methods, such as the Wittig reaction [41], related reactions of phosphonate carbanions [42], and Peterson olefination [43]. Because of the low basicity of the reagent, it can be employed for the olefination of highly enolizable ketones. Moreover, base-sensitive or sterically hindered aldehydes and ketones can also be efficiently converted to terminal olefins. The most striking feature of titanocene-methylidene is that it can be employed for the olefination of carboxylic acid derivatives (Table 14.5).

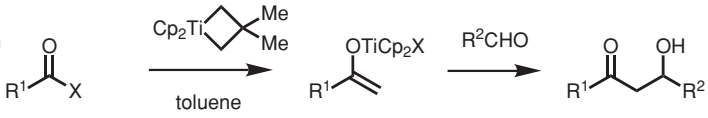


R^1 = alkyl, OR^3
R^2 = H, alkyl, OR^3, NR^3R^4, SR^3, SeR^3, $SiMe_3$.

Scheme 14.23. Reaction of titanocene-methylidene with carbonyl compounds.

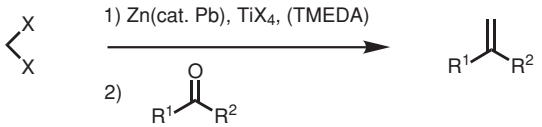
Reactions of titanocene-methylidene generated from titanacyclobutanes with acyl chlorides **55** [46] or acid anhydrides **56** [47] lead initially to the titanium enolates **57** (Scheme 14.24), which then afford aldols upon treatment with the carbonyl compounds. On the other hand, five-membered cyclic anhydrides are methylenated with dimethyltitanocene (Table 14.5, entry 7) [45].

Scheme 14.24. Formation of titanium enolates by the reaction of titanacyclobutanes with acyl chlorides or acid anhydrides.



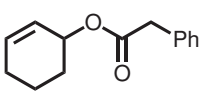
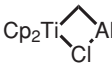
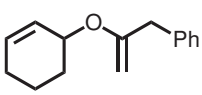
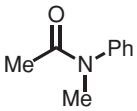
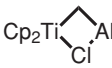
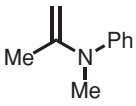
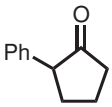
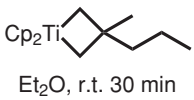
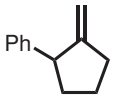
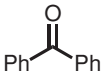
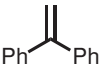
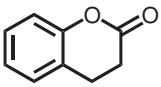
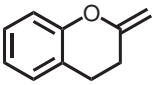
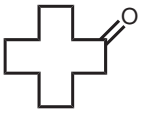
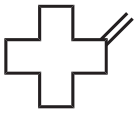
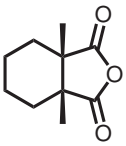
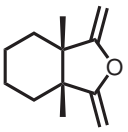
55: X = Cl
56: X = RCOO
57

Another titanium-based reagent for the methylenation of carbonyl compounds is that prepared from dibromomethane/zinc/titanium tetrachloride and related systems (Scheme 14.25) [48]. These systems transform a wide variety of carboxylic acid derivatives to terminal olefins in the same way as titanocene-methylidene does.



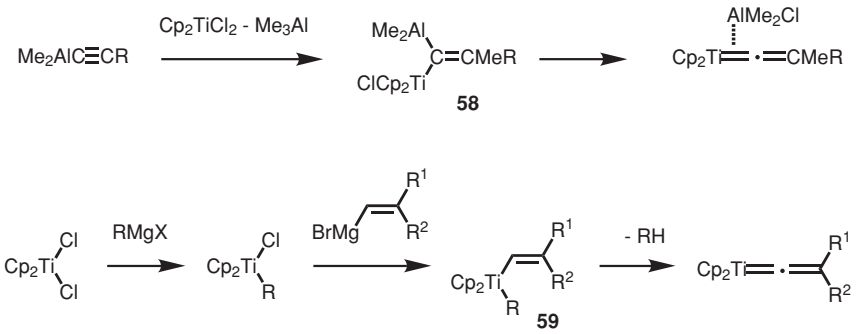
Scheme 14.25. Carbonyl olefination utilizing a $CH_2X_2/Zn/TiCl_4$ system.

Table 14.5. Carbonyl methylenation utilizing titanocene-methylidene precursors.

	Carbonyl compound	Reagent / conditions	Product	Yield	Ref.
1		 / toluene-THF, 0 °C - r.t. 30 min		96%	[39a]
2		 / toluene-THF, 0 °C - r.t. 30 min		97%	[39b]
3		 Et_2O, r.t. 30 min		98%	[39d]
4		$Cp_2Ti{=}CH_2 \cdot ZnX_2$ / toluene		quant	[44]
5		Cp_2TiMe_2 / toluene, 60-65 °C / 12-26 h		80%	[12b]
6		Cp_2TiMe_2 / toluene, 60-65 °C / 12-26 h		83%	[12b]
7		Cp_2TiMe_2 / THF, 65 °C / 20-26 h		79%	[45]

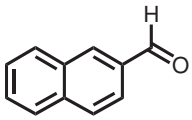
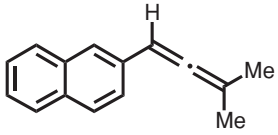
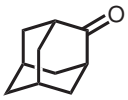
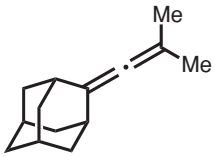
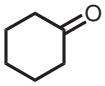
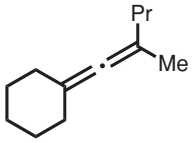
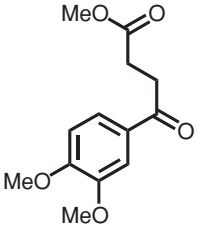
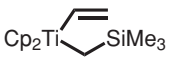
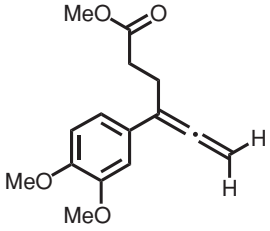
14.3.2
Alkylidenation of Carbonyl Compounds

As noted above, titanocene-alkylidenes can be prepared using various methods and starting materials. Like the methylidene complex, higher alkylidene complexes are useful for the transformation of carbonyl compounds to highly substituted olefins. Ketones and aldehydes are converted into substituted allenes by treatment with titanocene-alkenylidenes prepared by olefin metathesis between titanocene-methylidene and substituted allenes (see Scheme 14.7) [17]. Titanocene-alkenylidene complexes can also be prepared from



Scheme 14.26. Preparation of titanocene-alkenylidene complexes.

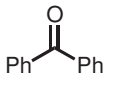
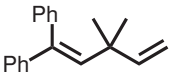
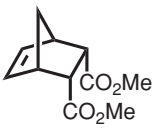
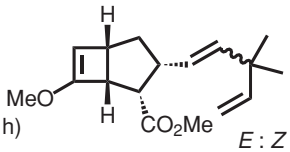
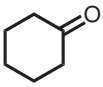
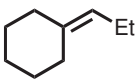
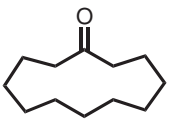
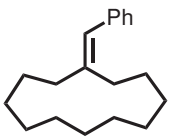
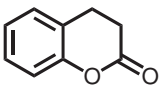
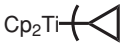
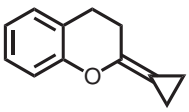
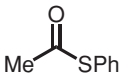
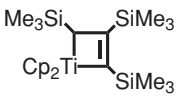
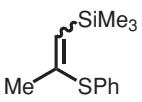
Table 14.6. Allenation of aldehydes and ketones.

	Carbonyl compound	Reagent / conditions	Product	Yield	Ref.
1		 , $Me_2C{=}C{=}CH_2$ / benzene, rt, 12 h		53%	[17]
2		 , $Me_2C{=}C{=}CH_2$ / benzene, rt, 12 h		75%	[17]
3		$PrMeC{=}C(AlMe_2)TiCp_2Cl$		83%	[49]
4		 / THF, 0 °C - rt		81%	[50]

the 1,1-dimetalloalkene **58** [49] or the alkylalkenyltitanocene **59** [50] (Scheme 14.26), and may be successfully applied in the allenation of aldehydes and ketones (Table 14.6).

Alkylidene complexes of titanium generated by productive metathesis between titanocene-methylidene and highly strained cyclic olefins react with carbonyl compounds to form the olefination products (Table 14.7, entries 1 and 2) [20,21]. This process has been applied to the synthesis of (±)-$\Delta^{(9,12)}$-capnellene [21]. Higher homologues of dimethyltitanocene are employed for the benzylidenation (entry 4) [25a] and cyclopropylidenation (entry 5) [25c]. On heating with carbonyl compounds, these reagents produce phenyl-substituted olefins and alkylidenecyclopropanes, respectively, via the corresponding titanocene-alkylidenes. Tris(trimethylsilyl)titanacyclobutene, prepared by the reaction of bis(trimethylsilylmethyl)titanocene with bis(trimethylsilyl)acetylene, is a useful reagent for the conversion of various carbonyl compounds into alkenylsilanes (entry 6) [25d]. It is suggested that the olefination takes place through the titanocene-trimethylsilyl-

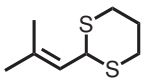
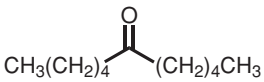
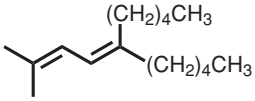
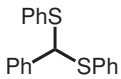
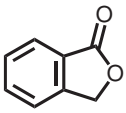
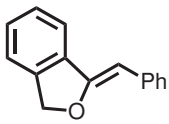
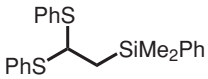
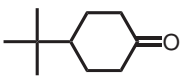
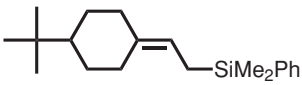
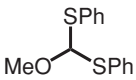
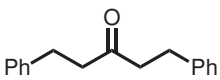
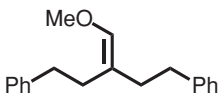
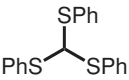
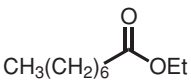
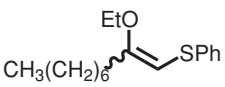
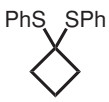
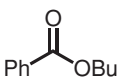
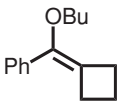
Table 14.7. Carbonyl olefination utilizing titanocene-alkylidenes.

	Carbonyl compound	Reagent / conditions	Product	Yield	Ref.
1		 / toluene, 23 °C, 10h		83%	[20]
2		 / toluene, r.t. (4 h) - 55 °C (15 h)	 *E* : *Z* = 3.9 : 1.0	53%	[21b]
3		$ClCp_2TiCH{=}CHMe$, HAl^iBu_2 / toluene, -40 °C - r.t. 30 min		50%	[22]
4		$Cp_2Ti(CH_2Ph)_2$ / toluene, 45 - 55 °C, 16 - 26 h		86%	[25a]
5		 / toluene, 50 °C		67%	[25c]
6		 / toluene, 60 °C		95%	[25d]

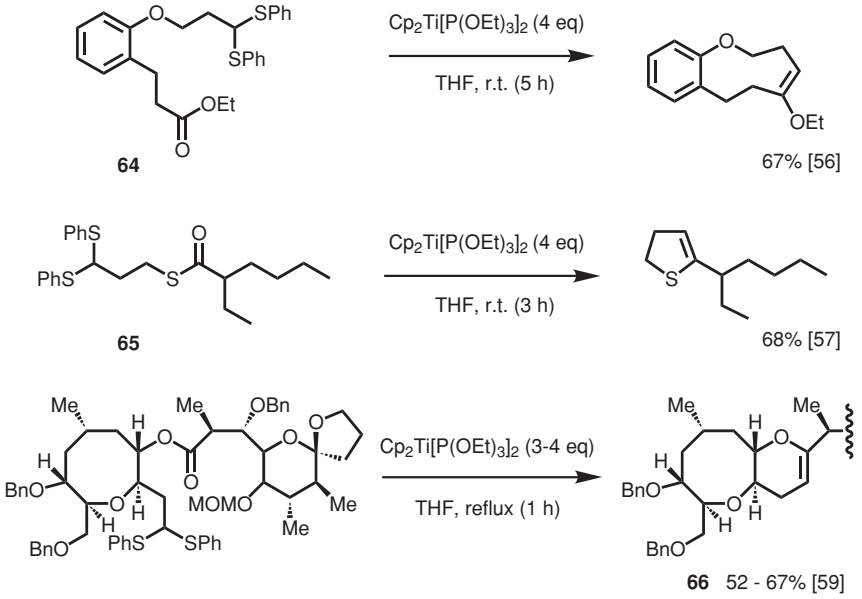
methylidene and/or its alkyne complex. Although bis(trimethylsilylmethyl)titanocene itself effects the same transformation, the reaction requires very high temperature (>100 °C) [25b].

Titanium carbene and vinylcarbene complexes formed by the desulfurization of thioacetals react with carbonyl compounds to afford alkenes and dienes (Table 14.8) [51]. Since thioacetals are stable under acidic as well as basic reaction conditions and are readily accessible from various starting materials, carbonyl olefination utilizing the thioacetal-titanocene(II) system enjoys a wide range of synthetic applications. Allylsilanes are obtained using thioacetals bearing a trialkylsilyl group (e. g. **60**) [52]. Olefinations of carbonyl compounds using orthothioesters **61** and **62** afford enol ethers and alkenyl sulfides, respectively [53]. Titanocene-cyclobutylidene is produced from 1,1-bis(phenylthio)cyclobutane **63**, and its reaction with ketones, esters, and thioesters affords alkylidenecyclobutanes [54].

Table 14.8. Carbonyl olefination utilizing a thioacetal-titanocene(II) system.

	Thioacetal	Carbonyl Compound	Product	Yield	Ref.
1				88%	[51]
2				75%	[51]
3	 **60**			81%	[52]
4	 **61**			63%	[53]
5	 **62**		 ($E:Z = 63:37$)	88%	[53]
6	 **63**			74%	[54]

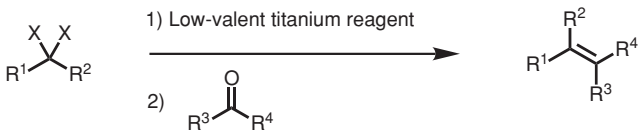
Reagent: $Cp_2Ti[P(OEt)_3]_2$ (3–6 eq), Thioacetal (1.1–2 eq). Conditions: THF, r.t. - reflux.



Scheme 14.27. Intramolecular carbonyl olefination utilizing a thioacetal-titanocene(II) system.

Intramolecular carbonyl olefinations of esters using phosphorus-containing carbanions are generally unsuccessful because, except in the case of certain five- and six-membered cyclic compounds in which the double bond formed is stabilized through π-conjugation, these reactions afford acylation products [55]. This difficulty has been overcome by the use of a thioacetal-titanocene(II) system (Scheme 14.27). Enol ethers of cyclic ketones and dihydrothiophenes are obtained by the intramolecular carbonyl olefination of alkyl ω,ω-bis(phenylthio)alkanoates (e. g. **64**) [56] and (*S*)-[3,3-bis(phenylthio)propyl] thioalkanoates (e. g. **65**) [57], respectively. Although the preparation of simple monocyclic enol ethers by the titanocene(II)-promoted intramolecular reaction of ω,ω-bis(phenylthio)alkyl alkanoates is rather complicated owing to the concomitant formation of oligomers [58], this intramolecular carbonyl olefination has been successfully applied to the synthesis of J-ring of ciguatoxin **66** [59].

Titanium-based reagents generated by the reduction of *gem*-dihalides with low-valent metal species are widely used for the alkylidenation of carbonyl compounds (Scheme 14.28). As in the case of methylidenation, the system *gem*-dibromide/$TiCl_4$/Zn/TMEDA



Zn(cat. Pb)/$TiCl_4$/TMEDA: R^1 = Alkyl; R^2 = H; R^3 = Alkyl, RS; R^4 = OR, SR, $OSiR_3$, NR_2

$Cp_2Ti[P(OEt)_3]_2$ (**29**): R^1 = Alkyl; R^2 = Alkyl; R^3 = Alkyl; R^4 = H, Alkyl, OR [61, 62]

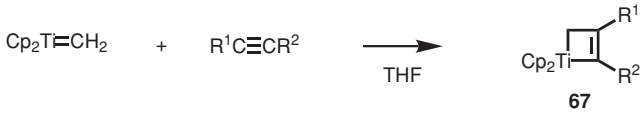
Scheme 14.28. Carbonyl alkylidenation utilizing *gem*-dihalides and low-valent titanium reagents.

transforms carboxylic acid derivatives such as esters, thioesters, amides, lactones, and silyl esters into the corresponding heteroatom-substituted olefins [60]. A similar transformation can be accomplished by the combined use of $Cp_2Ti[P(OEt)_3]_2$ (**29**) and *gem*-dichlorides [61]. The advantage of this modification is that esters and lactones may be converted into trisubstituted enol ethers. This procedure has also been applied to the dichloromethylenation and chloromethylenation of ketones using carbon tetrachloride and chloroform, respectively [62].

14.4 Reactions of Titanium Carbene Complexes with Triple Bonds

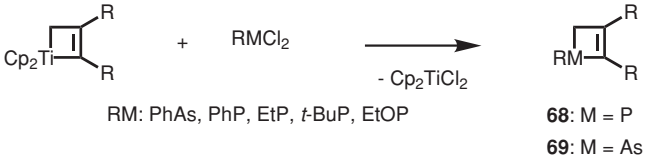
14.4.1 Reaction of Titanium Carbene Complexes with Alkynes

Similarly to alkenes, alkynes react with various titanium-methylidene precursors, such as the Tebbe reagent [13,63], titanacyclobutanes [9b, 64], and dimethyltitanocene [65] to form the titanium-containing unsaturated cyclic compounds, titanacyclobutenes **67** (Scheme 14.29). Alternatively, 2,3-diphenyltitanacyclobutene can be prepared by the reaction of the complex titanocene(II) bis(trimethylphosphine) with 1,2-diphenylcyclopropene [66]. Substituent effects in titanacyclobutenes [67], the preparation of titanocene-vinylketene complexes by carbonylation of titanacyclobutenes [68], and titanacyclobutene-vinylcarbene complex interconversion [69] have been investigated.



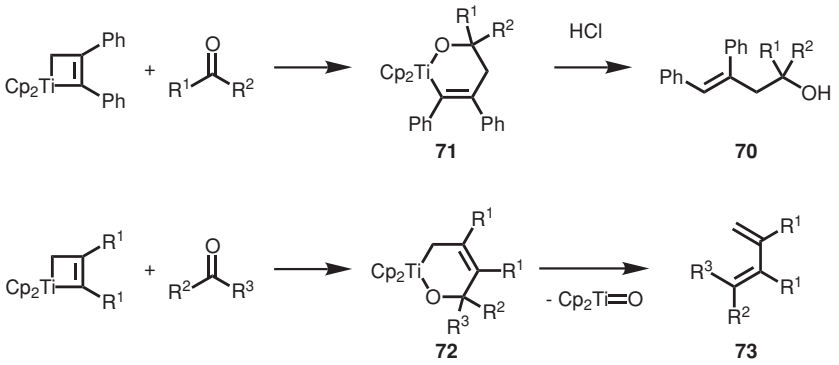
Scheme 14.29. Formation of titanacyclobutenes by the reaction of titanocene-methylidene with alkynes.

Titanacyclobutenes are useful intermediates for the synthesis of various organic compounds. The titanium atom in titanacyclobutane can be replaced by phosphorus [70,71] or arsenic [71] to form phospha- **68** and arsa-cyclobutanes **69**, respectively (Scheme 14.30).



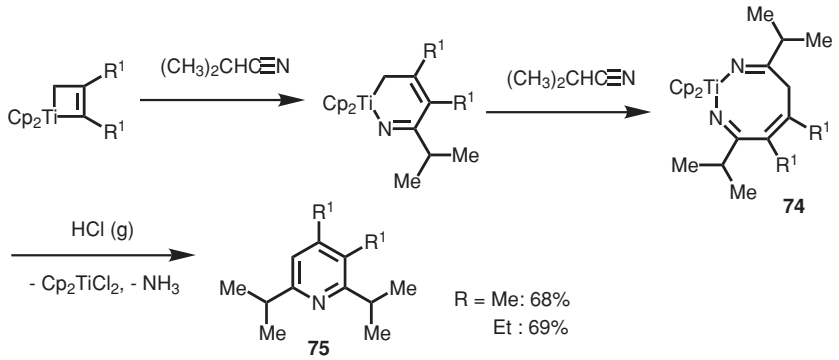
Scheme 14.30. Transformation of titanacyclobutenes into phospha- and arsa-cyclobutenes.

The mode of reaction of titanacyclobutenes with carbonyl compounds is largely dependent on steric factors (Scheme 14.31) [72]. Ketones and aldehydes tend to insert into the titanium–alkyl bond of 2,3-diphenyltitanacyclobutene, and homoallylic alcohols **70** are obtained by hydrolysis of the adducts **71** [65a,73]. On the contrary, when dialkyl-substituted titanacyclobutenes are employed, the reaction with aldehydes preferentially proceeds through insertion into the titanium–vinyl bond. Thermal decomposition of the adducts **72** affords conjugated dienes **73** with *E*-stereoselectivity as a result of a concerted retro [4+2] cycloaddition [72].



Scheme 14.31. The two modes of reaction of titanacyclobutene with carbonyl compounds.

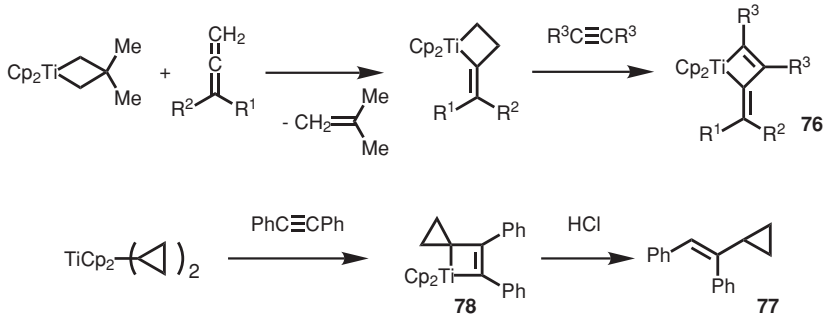
In marked contrast to the above results, double nitrile insertion into both the titanium–alkyl and titanium–vinyl bonds occurs to form the diazatitanacycles **74**. Treatment of these titanacycles with dry hydrogen chloride affords the tetrasubstituted pyridine derivatives **75** (Scheme 14.32) [74]. On the other hand, 2,3-diphenyltitanacyclobutene reacts with various nitriles to afford the products of mono-insertion, which afford the corresponding unsaturated ketones upon hydrolysis [73,74].



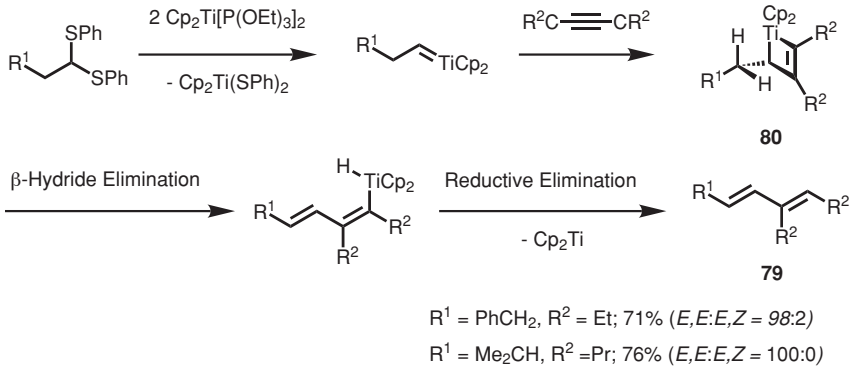
Scheme 14.32. Preparation of tetrasubstituted pyridines by the reaction of titanacyclobutenes with nitriles.

Methylenative dimerization takes place when terminal alkynes are treated with the titanocene/methylidene/zinc halide complex generated from titanocene dichloride and $CH_2(ZnI)_2$. The process is believed to involve the formation of a titanacyclobutene intermediate [75].

The formation of highly substituted titanacyclobutenes utilizing titanocene-alkylidenes has been investigated (Scheme 14.33). Alkylidenetitanacyclobutenes **76** are produced by the reaction of titanocene-alkenylidene complexes with alkynes [76]. The alkenylcyclopropane **77** can be synthesized by thermolysis of dicyclopropyltitanocene in the presence of diphenylacetylene, which is assumed to proceed through formation of the titanacyclobutene **78** [25c].



Scheme 14.33. Formation of titanacyclobutenes by the reaction of titanocene-alkylidene precursors with alkynes.



R^1 = $PhCH_2$, R^2 = Et; 71% (*E,E:E,Z = 98:2*)

R^1 = Me_2CH, R^2 =Pr; 76% (*E,E:E,Z* = 100:0)

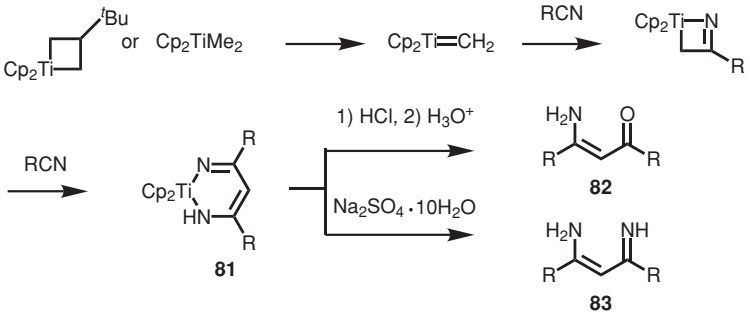
Scheme 14.34. Stereoselective preparation of conjugated dienes by the titanocene(II)-promoted reaction of thioacetals with alkynes.

The carbene complexes generated by desulfurization of thioacetals with the titanocene(II) species react with internal alkynes to produce the conjugated dienes **79** with high stereoselectivity (Scheme 14.34) [77]. The process appears to involve *syn*-elimination of β-hydride from the alkyl substituent that originates from the carbene complex after the formation of titanacyclobutene **80**.

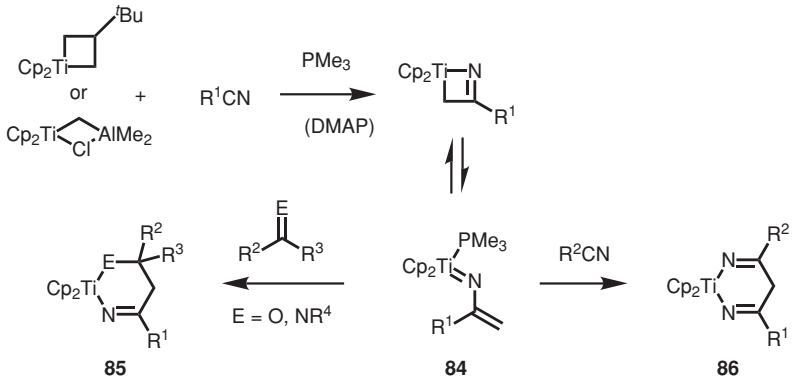
14.4.2
The Reaction of Titanium Carbene Complexes with Nitriles

Since the hybridization and structure of the nitrile group resemble those of alkynes, titanium carbene complexes react with nitriles in a similar fashion. Titanocene-methylidene generated from titanacyclobutane or dimethyltitanocene reacts with two equivalents of a nitrile to form a 1,3-diazatitanacyclohexadiene **81**. Hydrolysis of **81** affords β-ketoenamines **82** or 4-amino-1-azadienes **83** (Scheme 14.35) [65,78]. The formation of the azatitanacyclobutene by the reaction of methylidene/zinc halide complex with benzonitrile has also been studied [44].

In the presence of trimethylphosphine or 4-dimethylaminopyridine, titanocene vinylimido complexes **84** are produced by treating the in situ generated titanocene-methy-



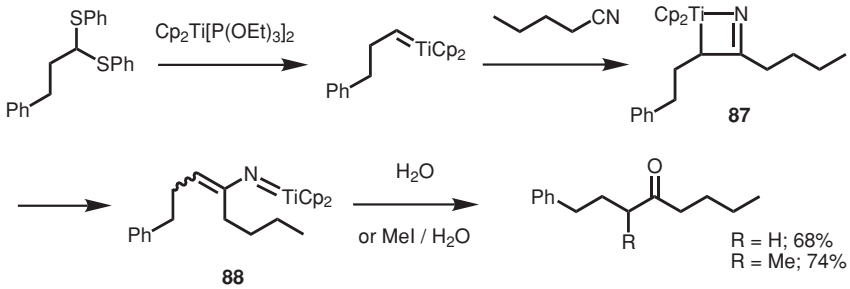
Scheme 14.35. The reaction of titanocene-methylidene with nitriles.



Scheme 14.36. Formation and reactions of titanocene vinylimido complexes.

lidene with nitriles. These titanium species are reactive towards organic molecules having a multiple bond, such as ketones, imines, and nitriles (Scheme 14.36) [79]. Functionalized ketones are produced by hydrolysis of the resulting six-membered titanacycles **85** and **86**.

The reaction of titanocene-alkylidenes generated from thioacetals with nitriles followed by hydrolysis affords ketones. Like the reaction of titanocene-methylidene, this reaction may proceed via the azatitanacyclobutene **87** and/or the vinylimido complex **88**, which reacts with an organic halide to form an α-substituted ketone [80] (Scheme 14.37).



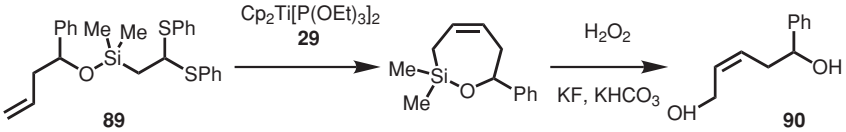
Scheme 14.37. Preparation of ketones by the titanocene(II)-promoted reaction of thioacetals with nitriles.

14.5 Conclusion

The potential synthetic utility of titanium-based olefin metathesis and related reactions is evident from the extensive documentation outlined above. Titanium carbene complexes react with organic molecules possessing a carbon–carbon or carbon–oxygen double bond to produce, as metathesis products, a variety of acyclic and cyclic unsaturated compounds. Furthermore, the four-membered titanacycles formed by the reactions of the carbene complexes with alkynes or nitriles serve as useful reagents for the preparation of functionalized compounds. Since various types of titanium carbene complexes and their equivalents are now readily available, these reactions constitute convenient tools available to synthetic chemists.

Typical Experimental Procedures

Ring-closing metathesis of [2,2-bis(phenylthio)ethyl]dimethyl-(1-phenylbut-3-enyloxy)silane (89) and subsequent oxidation [33]

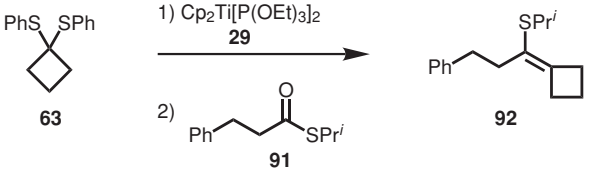


Scheme 14.38. Ring-closing metathesis of [2,2-bis(phenylthio)ethyl]dimethyl-(1-phenylbut-3-enyloxy)-silane (**89**) and subsequent oxidation to (*Z*)-5-phenylpent-2-ene-1,5-diol (**90**).

A 1-L round-bottomed flask, equipped with a magnetic stirring bar, a thermometer, and a rubber septum, was charged with titanocene dichloride (3.74 g, 15 mmol) and finely powdered 4 Å molecular sieves (0.75 g). The stirred mixture was heated to 100 °C by means of a heating bath for 1 h under reduced pressure (2 mmHg). After cooling, the reaction vessel was flushed with argon, and then magnesium turnings (0.40 g, 16.5 mmol; purchased from Nacalai Tesque Inc., Kyoto, Japan) were added. THF (60 mL) and triethyl phosphite (5.1 mL, 30 mmol) were successively injected through the septum. During the addition of triethyl phosphite, the reaction mixture was cooled in a water bath to maintain the temperature below 30 °C. After stirring for 3 h at room temperature, the resulting solution of $Cp_2Ti[P(OEt)_3]_2$ (**29**) in THF was treated with a solution of the silane **89** (2.25 g, 5 mmol) in THF (107 mL), and the reaction mixture was stirred for 4 h at room temperature and then refluxed for 1 h. After cooling to room temperature, it was diluted with hexane (300 mL). The insoluble materials were removed by filtration through Celite and washed with hexane (150 mL). The filtrate and washings were concentrated under reduced pressure, and the residue was redissolved in hexane (300 mL). The insoluble material was again removed by filtration through Celite and washed with hexane (150 mL). After removal of the solvent from the filtrate and washings, triethyl phosphite and the polar by-products were quickly separated by column chromatography (silica gel deactivated with 5 % H_2O; hexane/AcOEt, 100:1). A mixture of the crude

cyclic ether thus obtained, KF (1.45 g, 25 mmol), and $KHCO_3$ (1.15 g, 11.5 mmol) was dissolved in THF/MeOH (50 mL of each). Hydrogen peroxide (30 %, 23 mL) was then added dropwise to this solution over a period of 15 min. at 40 °C, and the reaction mixture was stirred for 24 h. After cooling, the organic materials were extracted with AcOEt. The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure, and the residue was purified by PTLC (hexane/AcOEt, 1:1) to give (*Z*)-5-phenylpent-2-ene-1,5-diol (**90**) (0.576 g, 65 %).

Cyclobutylidenation of (*S*)-isopropyl 3-phenylpropanethioate (91) [54,81]



Scheme 14.39. Cyclobutylidenation of (*S*)-isopropyl 3-phenylpropanethioate (**91**).

To a solution of the titanocene(II) reagent **29** in THF (42 mL) in a 300-mL round-bottomed flask, prepared from titanocene dichloride (6.54 g, 26.3 mmol), magnesium turnings (0.766 g, 31.5 mmol), triethyl phosphite (8.96 mL, 52.5 mmol), and finely powdered 4 Å molecular sieves (1.31 g) according to the procedure described above, was added a solution of 1,1-bis(phenylthio)cyclobutane (**63**; 2.29 g, 8.40 mmol) in THF (14 mL). The reaction mixture was stirred for 15 min. and then a solution of (*S*)-isopropyl 3-phenylpropanethioate (**91**; 1.46 g, 7.00 mmol) in THF (21 mL) was injected dropwise over a period of 10 min. The reaction mixture was refluxed for 1 h, then cooled, whereupon 1 M aq. NaOH solution (150 mL) was added. The insoluble materials produced were removed by filtration through Celite and washed with diethyl ether. The aqueous layer was separated and extracted with diethyl ether. The combined ethereal extracts were dried (Na_2SO_4), filtered, and concentrated. The residual liquid was purified by column chromatography (silica gel, hexane) to afford 1.33 g (77 %) of (1-isopropylthio-3-phenylpropan-1-ylidene)cyclobutane (**92**).

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