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SYNTHETIC APPLICATIONS OF ORGANOCHLOROZIRCONOCENE COMPLEXES

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Contents

1. Introduction

Organozirconocenes have emerged as one of the most useful classes of transition metal derivatives for use in organic synthesis. A wide range of zirconocene-mediated transformations and the relative ease of preparation of alkenyl- and alkylchlorozirconocenes contribute to the broad appeal of this chemistry. Hydrozirconation of alkynes or alkenes is often performed at room temperature and does not require special glassware or glove-box techniques. The relative stability of organozirconocenes is reflected by a considerable tolerance toward functional groups (FG) in the substrate. The polarization of the carbon-zirconium bond is comparable to Grignard reagents, however, due to the steric crowding around the zirconium atom, the organometallic bond is quite shielded and only small electrophiles attack the complex directly. Much of the development of the chemistry of organozirconocenes has therefore focused on indirect reaction pathways where other metals participate in carbon-carbon bond formations, or where access to the metal center is facilitated by the preparation of formally cationic complexes.

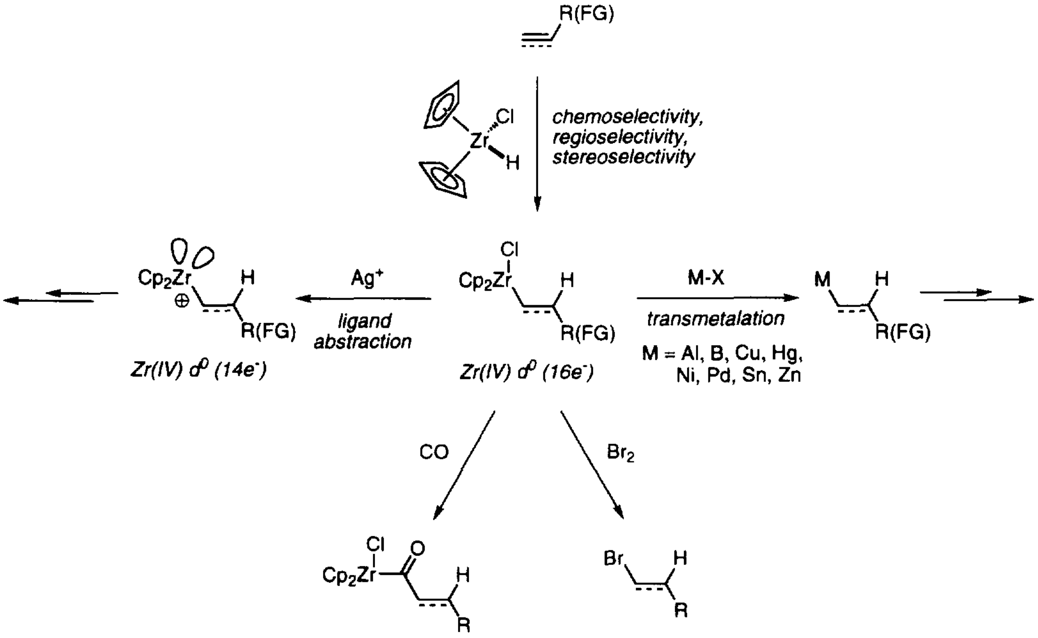


Figure 1. Summary of typical preparation and reactions of organozirconocenes.

This review summarizes the preparation of organochlorobis(cyclopentadienyl)zirconium(IV) complexes and their subsequent organic transformation and transmetalation chemistry. The discussion will mainly focus on developments since 1990, since excellent reviews are available that cover the earlier work.[1,2,3,4,5] For a treatment of the wealth of chemistry of zirconium(II) complexes and their applications in carbometalation,[6] cyclozirconation,[7] and Ziegler-Natta olefin polymerization,[8,9,10] the reader is referred to a series of recent reviews in these areas.[11,12,13]

2. Background

Zirconium is among the twenty most abundant elements in the earth's crust and therefore very readily available and relatively inexpensive compared to other transition metals.[14] After the preparation of the first zirconocene, Cp_2ZrBr_2, in 1953,[15] further development of the chemistry of Group 4 metallocenes was initially slow, but rapidly expanded in the 1970's, and the rate of publication is still increasing at a considerable pace.[16] Landmark events for applications of organochlorobis(cyclopentadienyl)zirconium(IV) complexes in organic chemistry were the preparation of zirconocene hydrides by Wailes and Weigold in 1970[17] and the use of hydrozirconation for the functionalization of organic compounds by Schwartz et al. in 1974.[18] Whereas the metathetical exchange reaction between a metal halide and a main group organometallic represents the most general route toward transition metal derivatives, hydrozirconation targets readily available alkene and alkyne precursors and thus by-passes alkyl or alkenyl halides and strongly basic lithium or magnesium reagents for the use of organozirconocenes in organic synthesis.[19]

Two cyclopentadienyl groups occupy three coordination sites each in organochlorobis(cyclopentadienyl)zirconium(IV) complexes and provide effective steric shielding as well as electron donating power to the metal (Figure 2). Carbon-zirconium bond lengths vary between 2.3 and 2.5 Å,[16a] and both the methyl-zirconium and the hydrogen-zirconium bond energies range around 75-85 kcal/mol.[20,21] The chlorine-zirconium bond distance is relatively constant at 2.4 to 2.5 Å, and its bond dissociation enthalpy lies close to 110 kcal/mol.[16a] It can be assumed that with increasing bulkiness of the carbon center, the strength of the C-Zr bond decreases.[21] Representative ^{91}Zr NMR chemical shifts have recently been reported.[22]

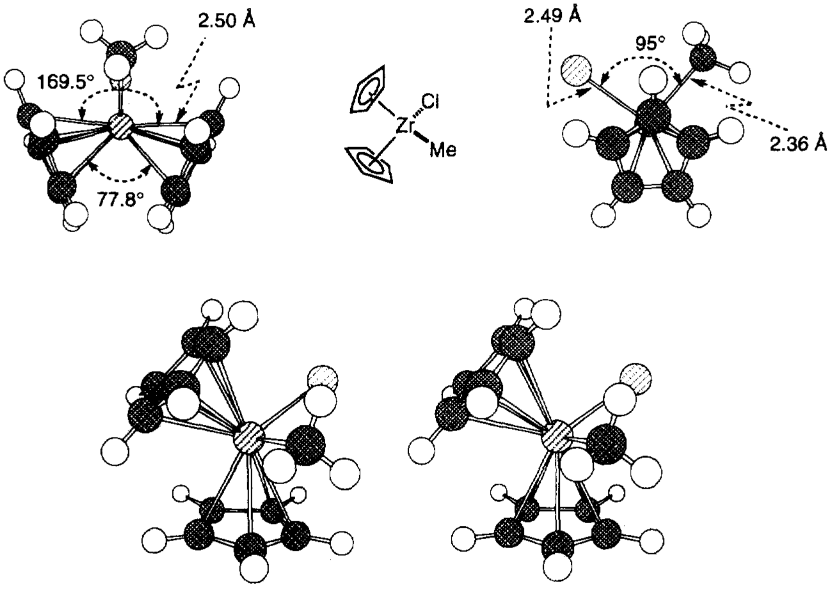
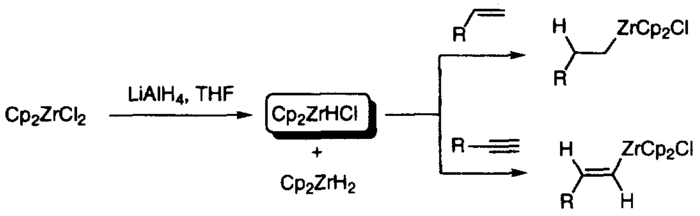


Figure 2. Bond lengths, bond angles, and stereo-representations of the x-ray structure of $Cp_2Zr(Cl)Me$.[23]

3. Preparation of Zirconocene Hydrochloride (Schwartz Reagent)

The zirconium hydride $Cp_2Zr(H)Cl$ was first prepared by Wailes et al. by reduction of Cp_2ZrCl_2 with 0.25 equiv of $LiAlH_4$ in THF as well as by magnesium metal reduction of Cp_2ZrCl_2.[17] Due to the pioneering studies of Schwartz and his group on the synthetic use of Cp_2ZrHCl, this reagent is also generally referred to as "Schwartz reagent". The use of $LiAlH_4$ as reducing agent can lead to considerable overreduction to the very insoluble Cp_2ZrH_2, and the more hindered $LiAl(O\text{-}t\text{-}Bu)_3H$ was recommended as a more selective agent (Scheme 1).[24]



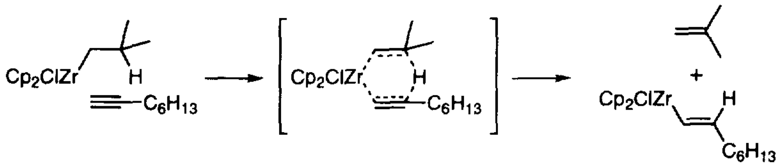
Scheme 1

Alternatively, Red-Al ($Na[AlH_2(OCH_2CH_2OMe)_2]$) was applied by Schwartz and coworkers for the preparation of Cp_2ZrHCl. In this protocol, however, a ca. 30% contamination of the reagent with sodium chloride remained.[25] To prevent isolation problems resulting from impurities and overreduction, Buchwald et al. have developed an experimentally simple procedure for large scale preparations of pure Schwartz reagent.[26] Since a relatively rapid reaction between Cp_2ZrH_2 and CH_2Cl_2 forms Cp_2ZrHCl which is only slowly transformed further into Cp_2ZrCl_2,[17] they introduced a washing step with CH_2Cl_2 which converts most of the zirconocene dihydride to the desired monohydride after the reduction. The use of filtered solutions of $LiAlH_4$ in Et_2O prevented contamination with salt impurities and simplified the product isolation by filtration of the precipitated reagent.

The poor solubility of Schwartz reagent in commonly used organic solvents such as THF, benzene, toluene and CH_2Cl_2 is advantageous for its preparation, but undesirable for subsequent transformations, and more soluble derivatives bearing substituents on the Cp-rings such as $(Me_5C_5)_2ZrHCl$ = $Cp^*{}_2ZrHCl$,[27,28] $Cp^*CpZrHCl$,[29] and $[(Me_2Si)(C_5H_4)_2ZrHCl]$[30] have been prepared. A protocol for a polymer-supported version is also available.[31] However, these reagents are also less readily accessible and more expensive than Cp_2ZrHCl. In general, the preparation of modified Schwartz reagents with more highly solubilizing substituents is plagued by overreduction to the dihydrides.[32] An indirect route to $Cp^*{}_2ZrHCl$ used an exchange reaction between the dihydride and the dichloride.[30] Related hydride transfers can be used for the *in situ* preparation of organozirconocenes. Erker and coworkers reported an improved hydrozirconation rate in a mixture of $(MeCp)_2ZrCl_2$ and $[(MeCp)_2ZrH_2]_2$ in THF or toluene. The small quantity of $(MeCp)_2ZrHCl$ generated in the equilibrium was available for the *in situ* hydrozirconation step and its greater solubility increased the rate of the overall process.[33,34]

Recently, $Cp_2Zr(H)OTf$, a more soluble alternative for Schwartz reagent was reported by Luinstra et al. for the hydrozirconation of alkenes.[35] Substitution of the chloride in Schwartz reagent for the larger triflate anion gave a well-defined and very reactive dimeric hydrozirconating reagent, which was soluble in THF up to a concentration of 0.1 M and reacted with TMS-acetylene to give the monoalkenyl complex $Cp_2Zr[(E)\text{-}CH{=}CH(SiMe_3)](OTf)$. $Cp_2Zr(H)OTf$ was synthesized by treatment of the borohydride complex $Cp_2ZrBH_4(OTf)$, obtained almost quantitatively from the synproportionation of $Cp_2Zr(OTf)_2$[36] and $Cp_2Zr(BH_4)_2$, with 1 equiv of NEt_3 in toluene.

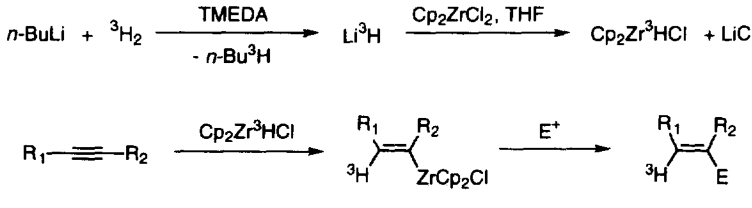
Sometimes it is more convenient to generate Schwartz reagent *in situ* and carry out the hydrozirconation in the same reaction vessel because Cp_2ZrHCl does not have an extended shelf-life.[37] *In situ* procedures using *t*-BuMgCl[38] or $LiEt_3BH$[39] in conjunction with Cp_2ZrCl_2 have been reported. Lipshutz et al. developed a useful *in situ* protocol for alkynes. Treatment of Cp_2ZrCl_2 with $LiEt_3BH$ in THF led to the formation of $Cp_2Zr(H)Cl$. Subsequently added terminal alkynes underwent hydrozirconation without compromising acid-sensitive functional groups.[39] In 1991, Negishi et al. further extended their *in situ* procedure with *t*-BuMgCl to the hydrozirconation of alkynes.[40] Treatment of 1-octyne with *i*-$BuZrCp_2Cl$, preformed quantitatively by treatment of Cp_2ZrCl_2 with *t*-BuMgCl, cleanly produced (*E*)-1-octenyl zirconocene chloride. Subsequent protonolysis gave 1-octene in 95% yield. The mechanism for the zirconocene transfer from *i*-$BuZrCp_2Cl$ to 1-octyne is not clear, but both a β-elimination to give Schwartz reagent followed by reaction with the alkyne or a concerted six-electron process are feasible (Scheme 2).



Scheme 2

A combination of $(i\text{-}C_4H_9)_3Al$ and Cp_2ZrCl_2 can also be used as hydrometalating reagent.[41] In this case, however, only organoaluminum compounds are formed via hydrozirconation and transmetalation.

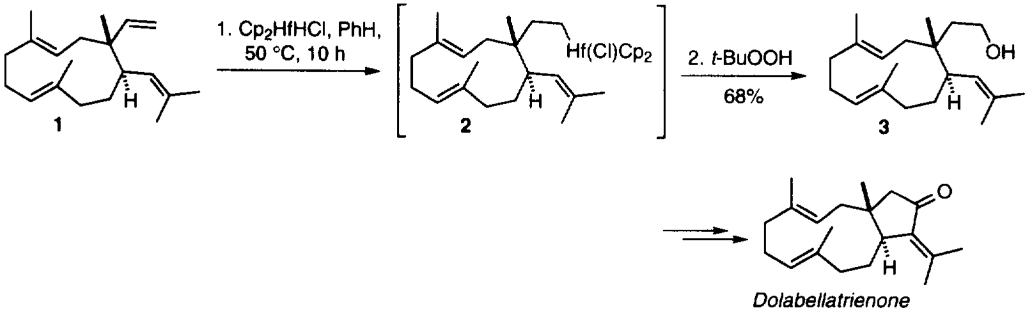
Recently, a new *in situ* preparation of Schwartz reagent by the reaction of LiH with Cp_2ZrCl_2 was reported. This method is useful for the synthesis of labeled reagents using Li^2H or Li^3H, allowing for the selective isotope-labeling of an acetylene or an olefin substrate (Scheme 3).[42]



Scheme 3

It is important to note that these *in situ* generated reagents are not necessarily structurally identical with isolated Cp_2ZrHCl and can lead to undesirable side-products or different kinetic behavior. Especially the presence of metal salts, *e.g.* aluminum halides, $MgCl_2$, or LiCl, can inhibit further transformations of the zirconocene.[43,44]

Although the molecularity of Schwartz reagent is not firmly established, solid-state infrared spectra suggest hydride bridging ligands.[45] The dihydride $(Cp_2ZrH_2)_x$ is polymeric, relatively unreactive, insoluble, and therefore a poor hydrozirconating agent.[17,46] In addition to the hydrozirconation of alkynes and alkenes, both mono- and dihydride have been used as C=O and C=N reducing agents.[47] The hafnium analog of the Schwartz reagent, Cp_2HfHCl, is difficult to obtain in pure form and of considerably higher cost. Based on the limited number of applications of hafnocene hydrochloride, it appears to be somewhat more sensitive to steric demand and more efficacious in apolar solvents.[48,49] Attempted hydroboration or hydrozirconation of dolabellatrienone intermediate **1** with Schwartz reagent were unsuccessful; however, reaction of **1** with Cp_2HfHCl in benzene at 50 °C for 10 h led to selective hydrometalation of the vinyl group vs. the unusually reactive endocyclic double bonds. The desired alcohol **3** was obtained after oxidation with *t*-butyl hydroperoxide (Scheme 4).[49]

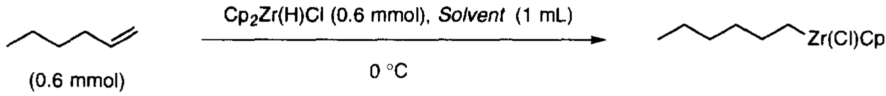


Scheme 4

In apolar solvents such as benzene and hexane, the low solubility of Cp_2ZrCl_2 can induce a disproportionation of organochlorobis(cyclopentadienyl)zirconium(IV) complexes to the corresponding bis(organo)zirconium compounds and precipitated Cp_2ZrCl_2,[50] similar to the Schlenk equilibrium.

4. Hydrozirconation

The insertion of C,C-double and -triple bonds into the Zr-H bond represents the default stepping stone for the preparation of synthetically useful organochlorobis(cyclopentadienyl)-zirconium(IV) complexes. This process is closely related to the hydroboration reaction, but, interestingly, hydrozirconation via a four-atom, concerted transition state is formally symmetryallowed due to the vacant d-orbitals on Zr,[51] whereas hydroboration is formally symmetry-forbidden.[52] The actual mechanistic details of the hydrozirconation process are still poorly understood; the insolubility and the oligomeric character of Schwartz reagent obscure the reaction kinetics. It is, however, clear that the solvent has a major effect on the reaction rate (Figure 3).[53] Hydrozirconation is orders of magnitude faster in THF than in hydrocarbon solvents such as benzene, and the most efficient solvent identified so far appears to be oxetane.[54] Therefore, there is a direct correlation between the donor-capabilities of the solvent and the rate of hydrozirconation, which is indicative of a rate-limiting dissociation of the oligomer before hydrometalation occurs. In oxetane solution, the reaction becomes first order both in Cp_2ZrHCl and alkene, whereas in THF it is zeroth order in Schwartz reagent. Accordingly, we can hypothesize that in the strongly solvolytic oxetane deaggregation of zirconocene hydrochloride and hydrozirconation have comparable rates, or hydrozirconation is actually rate-limiting. Further kinetic studies are clearly needed to provide a better experimental understanding of this fundamental process.



Solvent	Half-life [min] (GC)
Benzene	2210
THF	113
Oxetane	37
Morpholine	40
10% Oxetane/THF	95
25% Oxetane/THF	60
10% Oxetane/Benzene	545
10% Oxetane/CH_2Cl_2	109
THF (2 equiv Cp_2ZrHCl)	105
THF (2 equiv Hexene)	58
Oxetane (2 equiv Cp_2ZrHCl)	22
Oxetane (2 equiv Hexene)	24

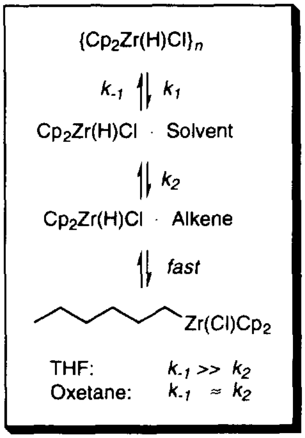
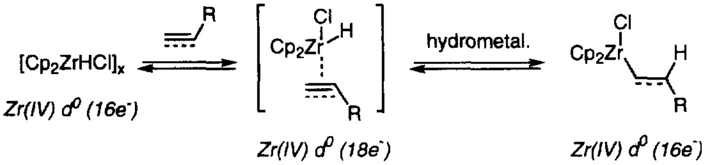


Figure 3. Experimental comparison of the solvent dependence of the rate of hydrozirconation of 1-hexene.[53]

In an *ab initio* MO study on hydrozirconation, Morokuma and coworkers have concluded that attack of ethylene and acetylene at Zr is most favorable between the Cl and H ligands.[55] Further insertion of olefin into the organochlorobis(cyclopentadienyl)zirconium(IV) complex is substantially more difficult than hydrozirconation, a result that is experimentally well established. The π-complex shown in Scheme 5 represents a transient structure or a saddle point according to Morokuma's calculation. Since the electron configuration of Zr(IV) is d^0, stabilization of such a complex by metal→olefin backdonation is not possible. Thermodynamically, the σ-bound $16e^-$ zirconocene is favored by >10 kcal/mol. This represents a major difference to derivatives of late-transition metals, which generally do not readily exhibit hydrometalation reactions due to the stability of their alkene complexes.[1] The calculated activation barrier for the hydrozirconation of ethylene is very small, between 0 and 15 kcal/mol at the MP2 and RHF level, respectively (Figure 4). Most of the RHF activation energy is derived from distortion of the Cp_2Zr-complex. In the transition state, formation of the Zr-C bond has progressed further than formation of the new H-C bond. The final product is the result of an overall *cis*-addition of zirconium and hydrogen across the C,C-double or triple bond, a result that is in agreement with all available experimental evidence.



Scheme 5

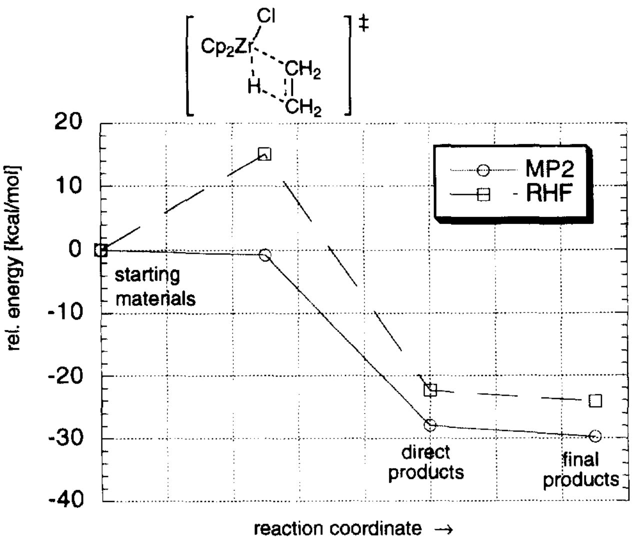
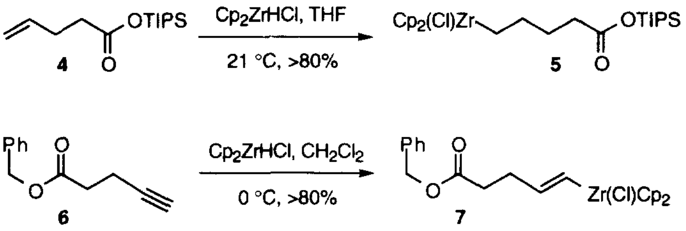


Figure 4. Calculated relative energies for the hydrozirconation of ethylene.[55] In the final products the methyl group was allowed to rotate to the most stable conformation.

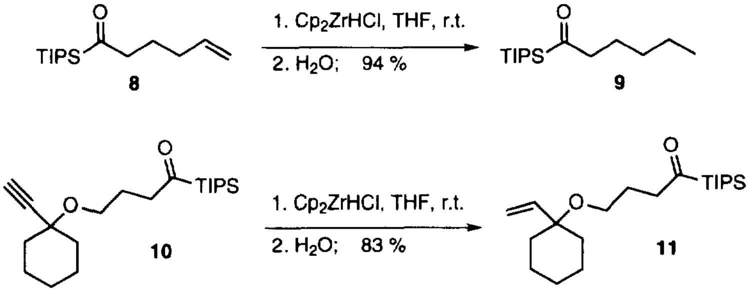
A. Functional Group Compatibility of Hydrozirconation

The chemoselectivity of Schwartz reagent toward alkynes and alkenes and thus its general functional group compatibility is limited. Most epoxides, isonitriles, aldehydes, ketones, nitriles and esters are reduced competitively with the hydrozirconation of alkenes and alkynes.[1,56,57] Enones and enoates undergo 1,2-reduction.[58,59] Silyl esters,[60] *t*-butyl esters,[61] and even benzyl esters and nitriles,[60] however, are tolerated by an equivalent of reagent in the presence of a particularly reactive site of unsaturation, such as a terminal alkyne or vinyl function. Hydrozirconation of 4-pentenoate **4**[43] and 4-pentynoate **6**[62] led to the organozirconocenes **5** and **7**, respectively, in high yield, and no significant level of reduction of the ester functions was detected in the reaction mixture (Scheme 6). In both cases, hydrozirconation in THF or CH_2Cl_2 was complete in less than 30 min at room temperature or 0 °C.



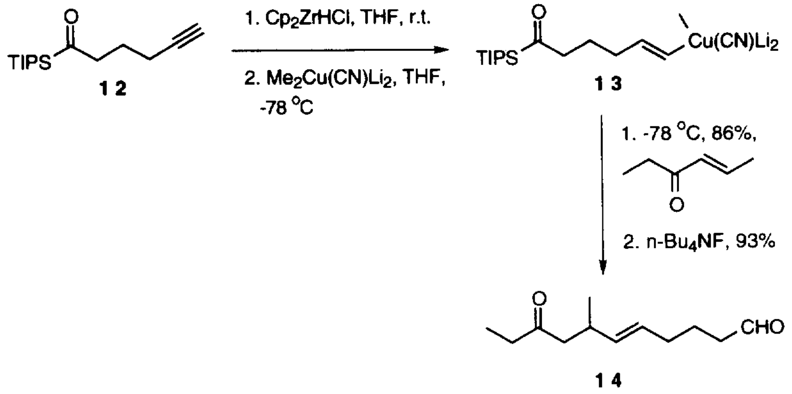
Scheme 6

An interesting protocol for the protection of carbonyl functions during hydrozirconation was recently reported by Lipshutz et al. Triisopropyl (TIPS) acyl silanes **8** and **10** were readily converted to the corresponding zirconocenes and resisted further 1,2-addition (Scheme 7).[63] Further transformations of the zirconium moiety, for instance via transmetalation to copper(I), were successful, and the aldehyde could subsequently be regenerated by desilylation with TBAF (Scheme 8).

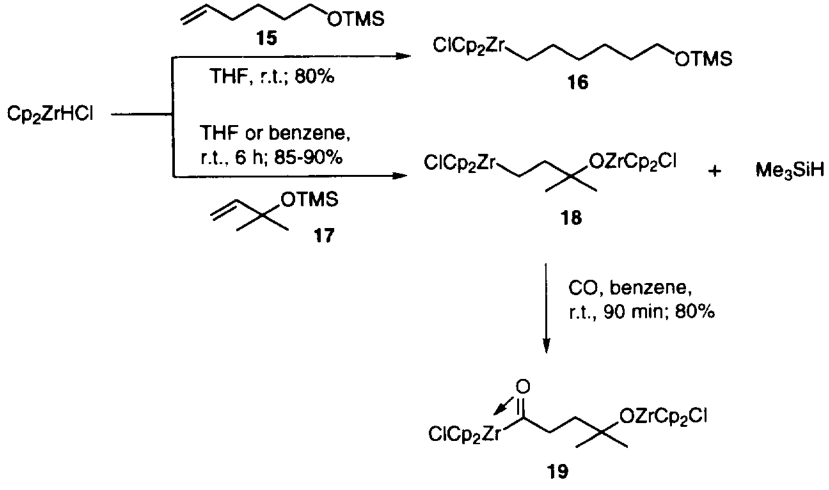


Scheme 7

Obviously, alcohols and acids are not compatible with the strongly hydridic character of Cp_2ZrHCl and are converted to the corresponding anions under the reaction conditions. Silyl ethers are generally stable, even though exceptions are known.[64] The trimethylsilyl ethers of unsaturated alcohols yield different compounds on reaction with Cp_2ZrHCl depending on the length and branching of the alkenyl chain. Hexenol derivative **15** gave the usual product of hydrozirconation **16**, whereas the silylated 2-methylbut-3-en-2-ol **17** underwent reductive cleavage of the Si-O bond to afford trimethylsilane and the yellow complex **18** as main products (Scheme 9).[64]

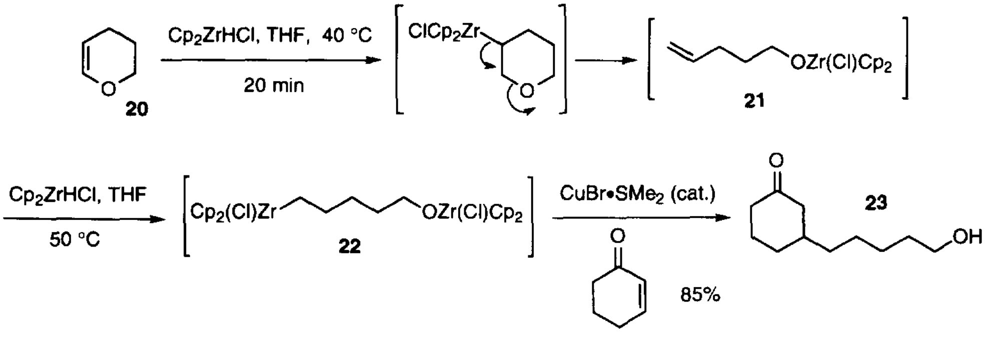


Scheme 8



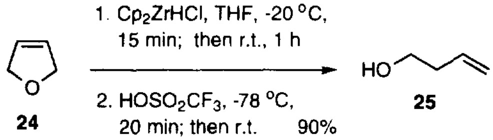
Scheme 9

Acetals, THP-ethers,[60] oxazolines, amides, imides,[63] carbamates,[63] sulfides, halides,[60,74] and alkyl and aryl ethers are generally stable under mild reaction conditions, if these functional groups are not in vinylic, allylic or possibly homoallylic positions of the alkene moiety. Secondary carboxamides can be reduced to imines with excess Cp_2ZrHCl.[47e] Annby and Karlsson have found that internally unsaturated ethers,[65] sulfides, phenylsulfones and ammonium iodides underwent substantial elimination of the functional group after rearrangement of the zirconium moiety towards the carbon bearing the heteroatom.[2,66,67,68,69] This process can be synthetically useful. The first example of a zirconium-promoted ring opening was reported by Wipf and Smitrovich in 1991.[62] They found that hydrozirconation of 3,4-dihydro-2*H*-pyran led to the acyclic compound $Cp_2ZrClO(CH_2)_3CH{=}CH_2$ (**21**), which could be further hydrozirconated and added to an organic electrophile (Scheme 10).

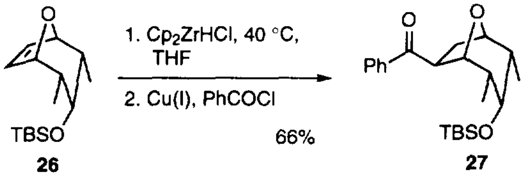


Scheme 10

In an extension of this protocol, Cenac et al. found that hydrozirconation of phosphorus-, nitrogen- or oxygen-containing unsaturated five membered rings such as phospholene, 1-benzyl-3-pyrroline or 2,5- and 2,3-dihydrofuran followed by addition of various electrophiles led via ring opening to a variety of acyclic unsaturated phosphanes, alcohols, ethers and esters (Scheme 11).[70] For elimination to occur, the overlap between the zirconium-carbon bond and the leaving group has to be stereoelectronically favorable. Hydrozirconation-acylation of bicyclic ether **26**, for example, does not lead to ring opening at 40 °C (Scheme 12).[71]



Scheme 11

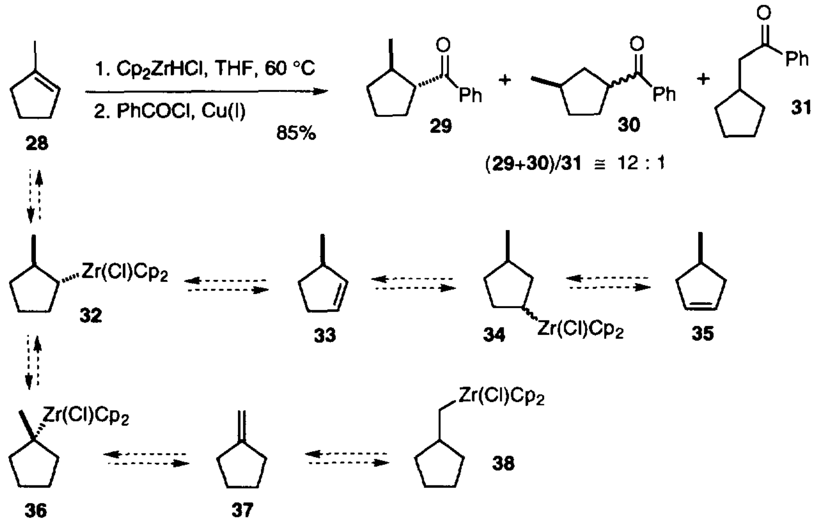


Scheme 12

As previously noted, the reactivity of the organozirconocene products of hydrozirconation of alkenes and alkynes is much lower than that of Schwartz reagent, and, in the absence of metal catalysts, even addition to aldehydes and acid chlorides is extremely sluggish. Accordingly, any improvement in the double/triple bond-chemoselectivity of the hydrozirconation step will directly translate into a wider range of functionalized organozirconocenes available for further transformations.

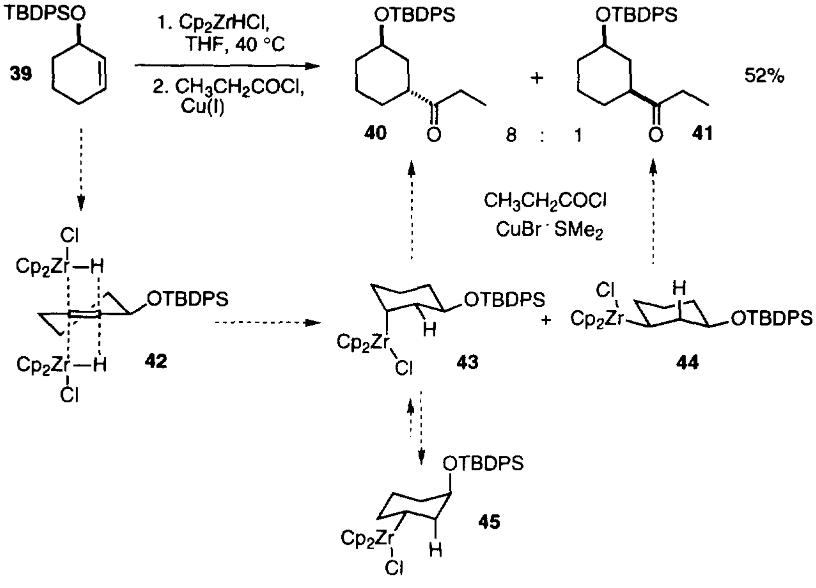
B. Hydrozirconation of Alkenes and Allenes

Empirically, the rate of hydrozirconation appears to decrease in the order of: terminal alkyne > terminal monosubstituted alkene ≈ internal alkyne > internal disubstituted alkene ≈ 2,2-disubstituted terminal alkene ≈ conjugated polyene > trisubstituted alkene. For example, an enyne is selectively hydrozirconated at the alkyne moiety,[72] and an unsymmetrical diyne reacts preferentially at the less substituted triple bond.[73] For cyclic alkenes, the rate of hydrozirconation is strongly dependent on the ring size and ring strain. Bicyclic alkenes, for example, react quite readily, whereas cycloheptene and cyclooctene are very resistant substrates. Even in the latter cases, a large deuterium incorporation from Cp_2ZrDCl is noticed, indicating a possible thermodynamic instability of the cycloheptyl and cyclooctyl zirconocenes due to transannular interactions.[2] In general, tetrasubstituted alkenes do not react. Due to the rapid β-elimination of secondary alkylchlorozirconocene species, migration of the zirconium along the carbon chain produces terminal organometallics even with internal alkenes (see Section 4C). Under mild conditions, isomerization does not proceed beyond a tertiary position,[1] but with increased temperature, this limitation can be overcome. Hydrozirconation of the trisubstituted alkene **28** followed by copper(I)-catalyzed acylation provided a mixture of four ketones in 85% yield (Scheme 13).[74] In spite of the apparent instability of the tertiary zirconocene **36**, the phenyl ketone **31** derived from **36** via **37** and **38** accounts for almost 8% of the product.



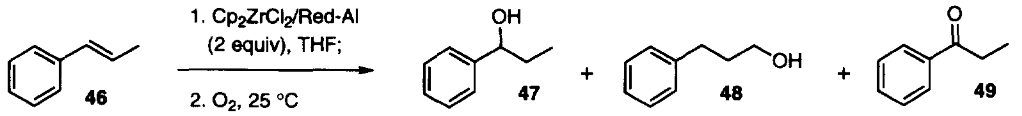
Scheme 13

The control of the selectivity of hydrozirconation of cyclohexenes with Schwartz reagent appears more facile. The hydrozirconation/copper-catalyzed acylation sequence of protected cyclohexenol **39** provides some interesting insight into the stereochemical course of these reactions (Scheme 14).[74] Predominant attack of Zr-H from the cyclohexene α-face led to the *trans*-isomer **43**, whereas the analogous but less favorable addition from the β-face of the molecule resulted in a *cis* relationship between zirconium and silyloxy substituents. Subsequent Cu(I)-assisted acylation provided ethyl ketones **40** and **41** in 52% yield in an 8 : 1 ratio.



Scheme 14

Kinetically controlled hydrozirconation appears to select for Zr-C bond formation at the site of the more negative electrostatic potential. Hydrozirconation of styrene results in 2:1 to 10:1 ratios of terminal and benzylic zirconocenes.[1,62] For the alkyl-substituted styrene **46**, the site of kinetic attack of zirconium is the benzylic position, and isomerization slowly converts this species to the terminal zirconocene (Scheme 15).[75] This regioselectivity can be explained by preferential addition of zirconium at the alkene terminus with the more negative atomic charge. The presence of the phenyl ring significantly polarizes the double bond and increases the relative atomic charge at the distal vs. the proximal sp^2-carbon (Figure 5).[76,77] Accordingly, kinetically controlled attack by Schwartz reagent favors formation of the benzylic organometallic to give **47** or **49** after exposure to oxygen. This analysis can also be nicely visualized by a representation of the electron-density surface encoded with the electrostatic potential.[76] Thermodynamic equilibration promotes formation of the sterically less hindered zirconocene precursor of primary alcohol **48**.



Hydrozirconation at 25 °C for 4 h: **47** : **48** : **49** = 15 : 1 : 3
Hydrozirconation at 25 °C for 24 h: **47** : **48** : **49** = 5 : 2 : 1
Hydrozirconation at 40 °C for 4 h: **47** : **48** : **49** = 4 : 3 : 1
Hydrozirconation at 40 °C for 48 h: **47** : **48** : **49** = 1 : 14 : 0

Scheme 15

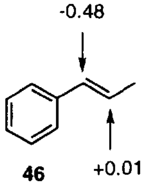
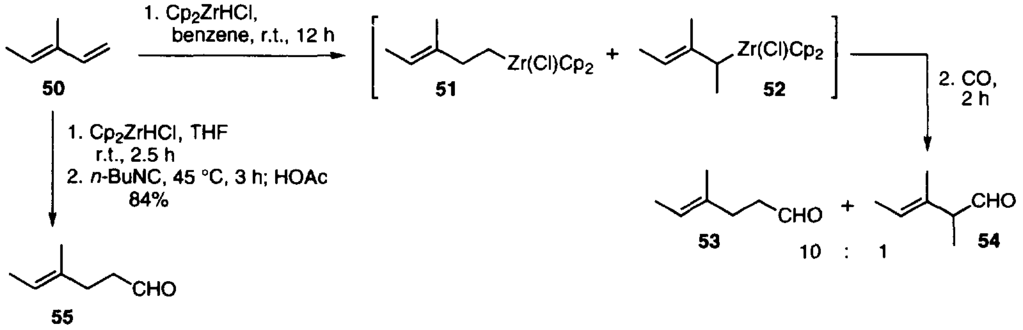


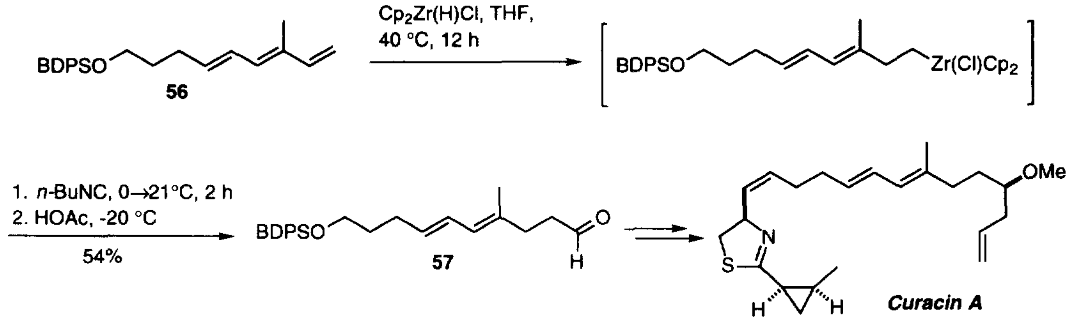
Figure 5. 3-21G(*) atomic charges obtained from fits to the electrostatic potentials.[76,77]

Conjugated dienes are preferentially hydrozirconated at the sterically more accessible double bond. Bertelo and Schwartz reported the formation of a mixture of terminal and allylic zirconium species with diene **50**, which led to two aldehydes **53** and **54** in a 10 : 1 ratio upon trapping with CO (Scheme 16).[78] With the bulkier trapping reagent *n*-butyl isocyanide, the aldehyde **55** was isolated as the sole product in 84% yield.[79]



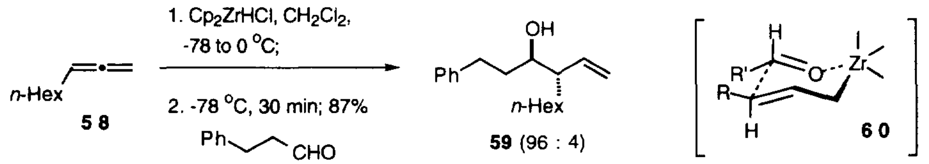
Scheme 16

In the hydrozirconation of polyunsaturated substrates, partial isomerization of double bonds can be a serious side reaction.[80,81] The level of chemo- and regioselectivity depends on reaction conditions and substrate structure. It is, however, possible to achive synthetically useful functionalizations of conjugated polyenes. Hydrozirconation of triene **56**, for example, was a key reaction in the total synthesis of curacin A by Wipf and Xu, and a single aldehyde **57** was isolated after insertion into isocyanide and acidic workup (Scheme 17).[82]



Scheme 17

The hydrozirconation of allenes requires special experimental precautions, and the order of addition of reagents and the reaction temperature are crucial for a successfull transformation. After first adding Schwartz reagent to CH_2Cl_2 at -78 °C, followed by allene **58**, hydrozirconation at the terminal position resulted in a red solution of the organozirconocene.[83] Subsequent reaction with 3-phenylpropanal gave the adduct **59** in high regio- and stereoselectivity, probably via the chair-like transition state **60** (Scheme 18).[84]

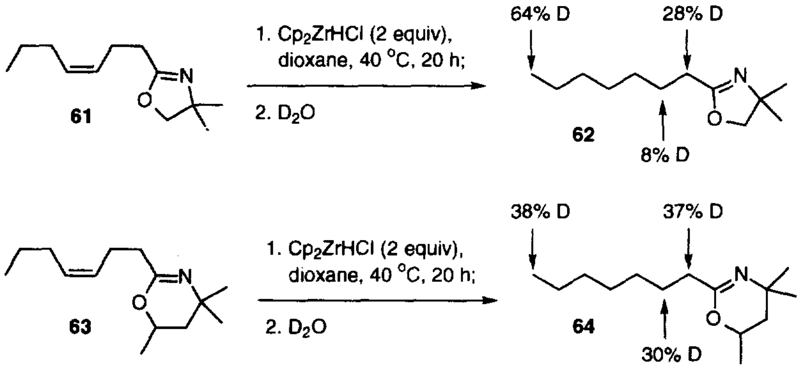


Scheme 18

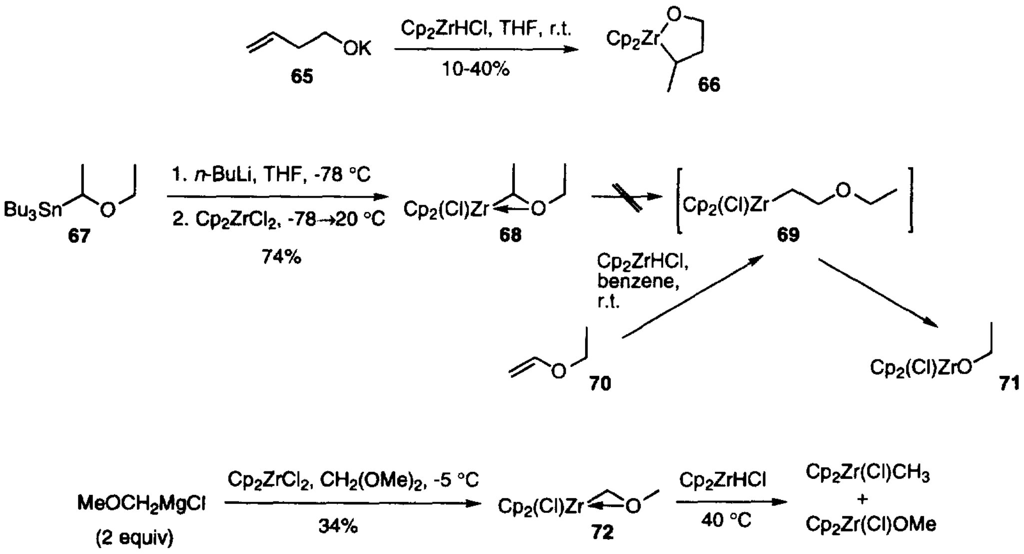
The facile isomerization of zirconocenes discussed in more detail in section 4C complicates the stereocontrol in the transformations of internal acyclic alkenes and allenes, and no detailed studies have yet addressed this important issue. Also, opportunities for enantioselective hydrozirconation using, for example, chiral *ansa*-metallocenes[6c,85,86,87,88,89,90] have not yet been utilized.

C. Hydrozirconation-Isomerization

Any alkene hydrometalation is basically a reversible process and can lead to migration of the double bond. Among existing procedures, hydroalumination and hydroboration require considerable higher temperatures for isomerization than hydrozirconation.[1] At room temperature in benzene, 1-octene, *cis*-4-octene and *trans*-4-octene all yield the *n*-octylzirconocene derivative.[18] The regiochemistry of hydrozirconation-isomerization is influenced by steric hindrance and the presence of chelating heteroatoms and aryl rings.[2] Hydrozirconation of oxazoline **62** and oxazine **63** followed by cleavage of the Zr-C bond with deuterium oxide revealed several positional isomers (Scheme 19).[91] The terminal alkene **65** provided the secondary zirconocene **66**,[92] and the zirconocene **68**, prepared from Cp_2ZrCl_2 and organolithium reagent derived from **67**,[93] did not isomerize to the terminal methylene carbon (Scheme 20). In contrast, hydrozirconation of alkene **70** let to a kinetically controlled formation of the primary zirconocene **69** followed by a rapid β-elimination to give alkoxide **71**. The secondary zirconocene **68** reacted smoothly with carbon monoxide and isocyanide and decomposed only slowly at 145 °C in toluene. In a related study, treatment of Cp_2ZrCl_2 with methoxymethyl Grignard reagent led to the 3-membered metallacycle **72**,[94] which upon exposure to Schwartz reagent inserted its CH_2 group into the Zr-H bond in an ylide-type fashion.[95]

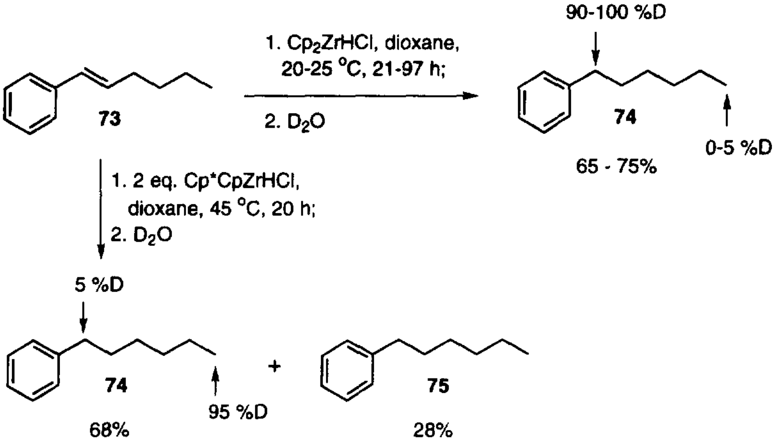


Scheme 19



Scheme 20

Aryl rings appear to electronically favor the kinetic attack of zirconocenes at the benzylic position.[75,96] Since the major driving force for isomerization of alkylzirconocenes is steric hindrance, any increase in the size of the zirconium complex would be expected to facilitate the migration. This has indeed been confirmed experimentally. Annby and Karlsson have reported the preferential preparation of terminal alkylzirconocenes from conjugated aromatic olefins with $Cp^*CpZrHCl$ ($Cp^* = \eta^5\text{-}C_5Me_5$) (Scheme 21).[34] The ω-deuterated alkane **74** was obtained in much lower yield using standard Schwartz reagent.

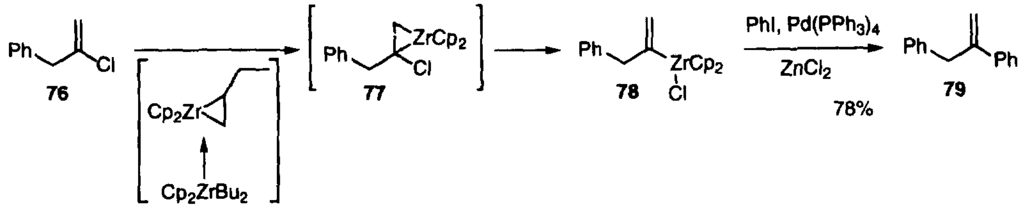


Scheme 21

Little is known about the mechanism of zirconium migration along an alkyl chain. Spectroscopic monitoring of the reaction only reveals starting material and terminal zirconocene. Accordingly, the rate of isomerization of secondary zirconocenes is faster than the rate of hydrozirconation of internal alkenes, and the organic group appears to remain associated with the zirconium complex throughout this process.[1]

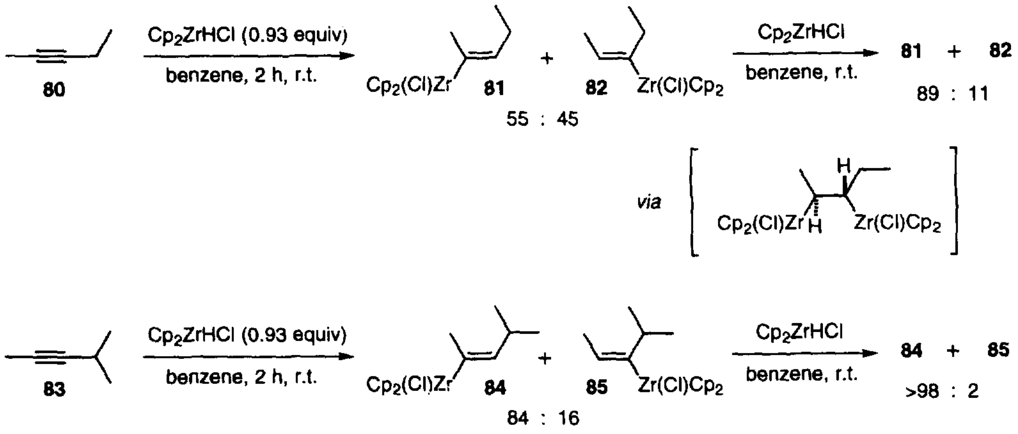
D. Hydrozirconation of Alkynes

Syn-addition of Schwartz reagent onto a terminal alkyne followed by treatment with electrophiles provides a *trans*-functionalized alkene with a high (>98%) level of stereochemical purity.[97] This protocol has become very popular in organic synthesis and is relatively insensitive to the presence of functional groups. Photochemical isomerization of alkenylzirconocenes allows, in principle, the preparation of both (*E*)- and (*Z*)-isomers of the organometallic reagent.[98] Alternatively, the oxidative insertion of zirconocene "Cp_2Zr" into 2-haloalkenes allows the synthesis of internalized organochlorozirconium(IV) complexes **78** (Scheme 22).[50]



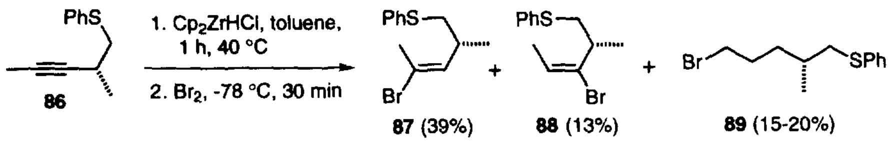
Scheme 22

For unsymmetrically substituted internal alkynes, hydrozirconation provides mixtures of regioisomers that are enriched in alkenylzirconocene placing the zirconium-carbon bond geminal to the sterically less demanding substituent.[99] The initial (kinetic?) selectivity is low, but excess Schwartz reagent readily isomerizes the adduct presumably via the dimetalated alkane to give improved thermodynamically controlled regioselectivity (Scheme 23).[99,100]

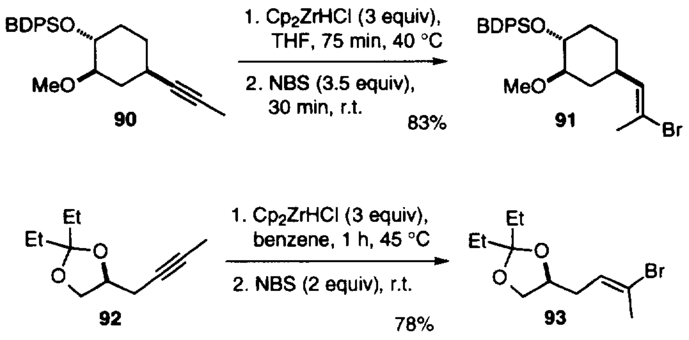


Scheme 23

The hydrozirconation of more highly substituted internal alkynes reveals a more complex picture for regioisomeric product formation. En route to rapamycin, Schreiber and coworkers reported a mixture of isomers and saturated alkane in the hydrozirconation-bromination of thioether **86** (Scheme 24).[101] On small scale, the reaction was cleaner and provided mostly the less hindered bromide **87**. In contrast, Ireland and Smith et al. obtained the vinyl bromides **91** and **93** in 78% and 83% yield, respectively (Scheme 25).[102,103]

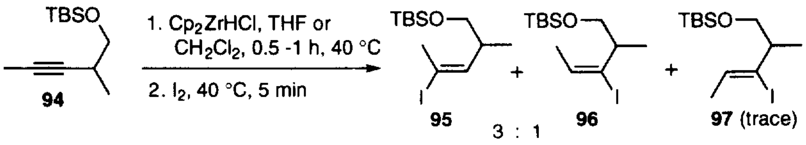


Scheme 24



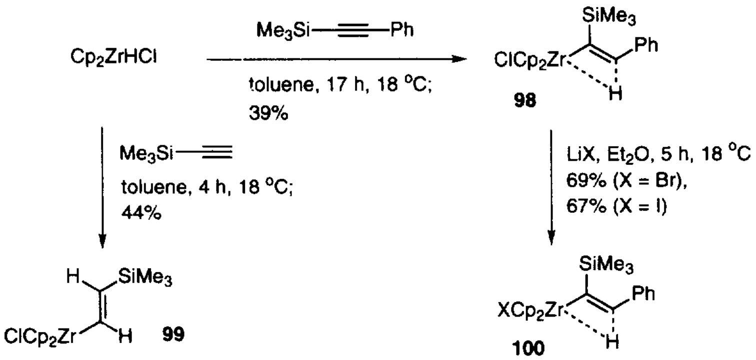
Scheme 25

The hydrozirconation of silyl ether **94** in THF or CH_2Cl_2 gave a 3:1 ratio of regioisomers **95** and **96** besides minor amounts of *trans*-isomer **97** (Scheme 26).[104] The use of Cp_2HfHCl did not improve this regioselectivity.



Scheme 26

Reaction of phenyl(trimethylsilyl)acetylene with Schwartz reagent yields the β-CH-agostic alkenylzirconocene chloride **98**, and subsequent halogen exchange with LiBr or LiI produces the alkenylzirconocene halide **100** (Scheme 27). In contrast, hydrozirconation of (trimethylsilyl)acetylene gives **99**, positioning the bulky $SiMe_3$ substituent at the β-position of the σ-alkenyl ligand, which lacks the β-agostic metal-C-H interaction that is characteristic of **100**.[105]



Scheme 27

E. Bimetallic Zirconocenes

The first bimetallic zirconocenes prepared by hydrozirconation of unsaturated organometallics were Zr-Al, Zr-B, and Zr-Zn derivatives obtained by Schwartz and coworkers (Figure 6).[106,107] The direction of the addition to the double bond was dependent on the steric bulk of the substituents. Bis-zirconocene **105** could be prepared by tandem hydrozirconation of acetylene, and the agostically stabilized **106** was obtained by hydrozirconation of an alkynylzirconium species.[100,108] Carbozirconation of pentynylalane gave the Zr-Al bimetallic species **107**.[109]

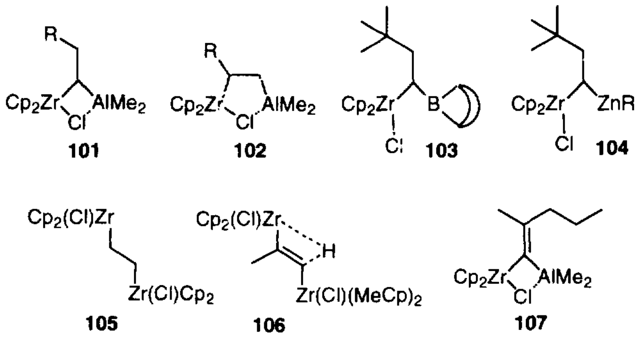
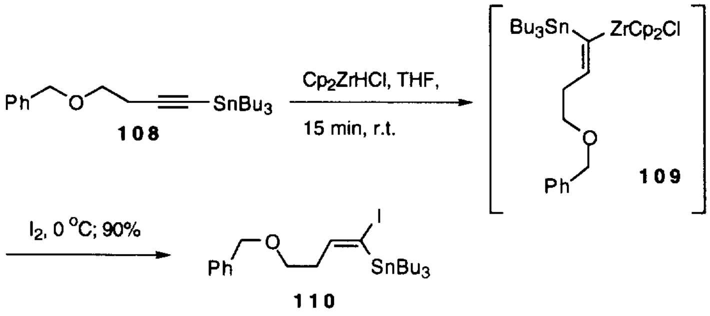


Figure 6

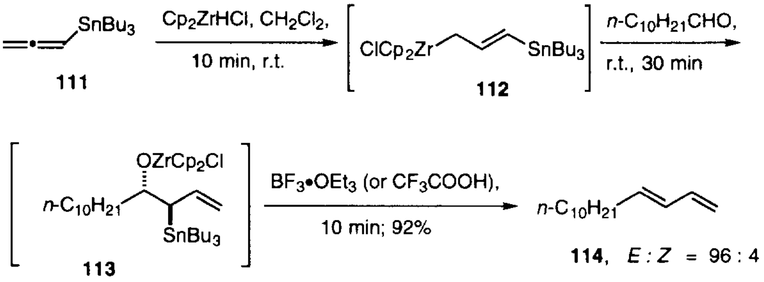
The synthetic chemistry of 1,1-bimetallics containing zirconium has not yet been extensively applied, but since these early studies, many additional combinations of zirconium with zinc,[110,111] tin,[112,113,114,115,116] aluminum,[117] as well as boron,[118,119,120,121,122,123,124,125] have been reported. Hydrozirconation of alkynyl and alkenyl Ru-complexes and Re-carbenes gave 1,2- and 1,1-bimetallic species, respectively.[126,127]

The Lipshutz group has prepared *gem*-stannazirconocene alkenes and reacted them with α,β-unsaturated enones and allylic halides.[112,116,116] Treatment of tin acetylenes with Cp_2ZrHCl followed by proton quench afforded the (*Z*)-vinylstannanes in high yields,[113] which, for example, were useful reagents in the preparation of tetronasin segments.[114] Similarly, 1-tributylstannylbutyn-3-ol benzyl ether **108** was hydrozirconated and selectively halogenated with iodine to give iodide **110** (Scheme 28). The long carbon-tin bond, the sensitivity of the hydrozirconation reaction to steric affects, and the polarizability of the carbon-tin bond were instrumental in directing the $Cp_2(Cl)Zr$ moiety geminal to the trialkyltin group.



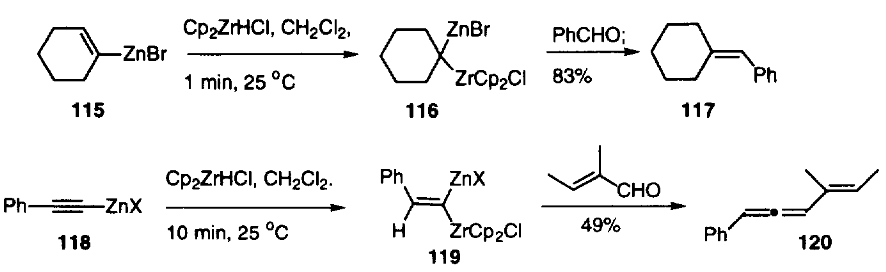
Scheme 28

Suzuki and coworkers have reported the hydrozirconation of allenylstannane **111** to give (*E*)-allylzirconocene species with a γ-Bu_3Sn substituent, and applied them in highly regio- and stereoselective reactions with aldehydes and ketones to give vicinal tin alkoxides **113** (Scheme 29).[115] Further *in situ* treatment with Lewis ($BF_3{\cdot}OEt_2$) or protic acids (CF_3COOH) effected a β-elimination to give terminal 1,3-dienes with high (*E*)-selectivity.



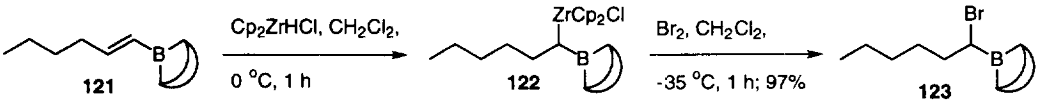
Scheme 29

Knochel et al. investigated the hydrozirconation of various alkenylzinc- and alkynylzinc halides with Cp_2ZrHCl to give 1,1-dimetalloalkanes and 1,1-dimetalloalkenes of zinc and zirconium, and studied their further reactions with aldehydes and ketones.[111] The reaction tolerated the presence of a wide range of functional groups in the dimetallic species as well in the carbonyl compounds; however only a moderate stereoselectivity was observed. The addition of a suspension of Cp_2ZrHCl in CH_2Cl_2 to a solution of alkenylzinc halide **115** afforded instantaneously a yellow solution of the relatively unstable 1,1-bimetallic **116**, to which the aldehyde or ketone was immediately added (Scheme 30). The hydrozirconation of alkynylzinc halides **118** afforded 1,1-dimetalloalkenes of type **119**, which reacted with aldehydes to provide allenes **120**. It is interesting to note that with alkene **115**, the zirconium is adding geminal to the zinc substituent to give the sterically more hindered complex.



Scheme 30

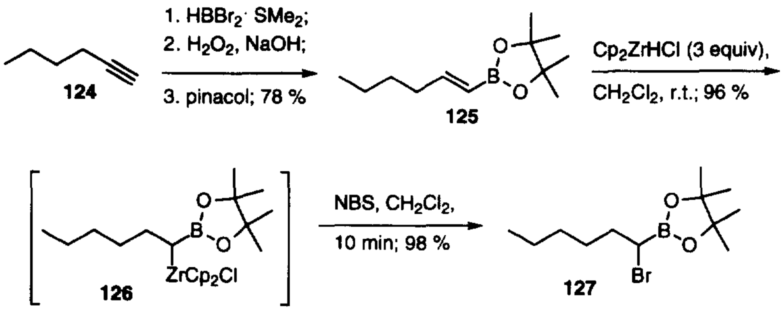
Srebnik et al. reported the preparation and selective reaction of highly functionalized zirconium-boron 1,1-dimetallic reagents.[118] Hydrozirconation of various B-alkenyl borabicyclo[3.3.1]nonanes (B-alkenyl-9-BBN) with Schwartz reagent afforded 1,1-bimetallics of boron and zirconium (Scheme 31). These compounds reacted selectively with bromine to afford α-bromoboranes, whereas olefination of ketones, even in the presence of zinc chloride, was not accomplished. Hydrozirconation was performed in CH_2Cl_2 and THF, whereas diethyl ether, hexanes and benzene were found to be unsuitable. Both electronic and steric factors greatly influenced the course of hydrozirconation of B-alkenylboranes.



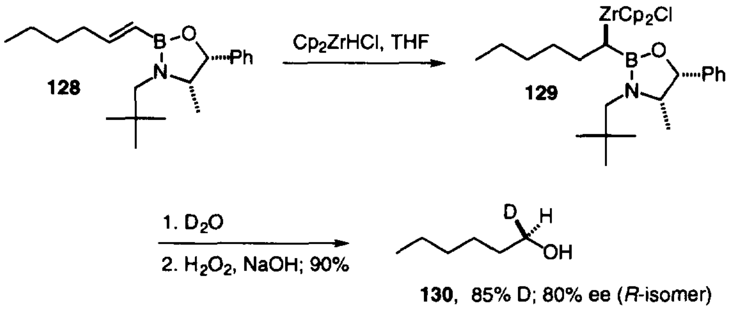
Scheme 31

Bimetallics based on zirconium and trialkylboranes have a poor stability; these compounds are very sensitive to moisture and oxygen and decompose rapidly in $CDCl_3$. To achieve a higher degree of stability, oxygenated boranes were used by Srebnik et al. The (*E*)-alkenylboronic ester **125**, prepared by hydroboration of alkynes with $HBBr_2{\cdot}Me_2S$ followed by the esterification of the intermediate boronic acid derivative with pinacol, was hydrozirconated with 3 equiv of Schwartz reagent to give fairly stable bimetallic agents (Scheme 32). *In situ* addition of *N*-halosuccinimide or bromine provided α-halo boronic esters.[119,121,123,124,125]

This concept can also be applied to a diastereocontrolled hydrozirconation. Optically pure 1-alkenyl boranes derived from monoterpenes, 1,2-diols and 1,2-amino alcohols were investigated, and *N*-neopentyl oxazaborolidine derivatives were found to provide excellent diastereoselectivities. Hydrozirconation of optically pure 1-alkenyl boranes **128** with Cp_2ZrHCl to give the optically active 1,1-bimetallic **129**, followed by cleavage of the more reactive C-Zr bond with D_2O and alkaline oxidation of the C-B bond afforded optically active 1-deuterio primary alcohols **130** (Scheme 33). (1*R*,2*S*)-*N*-Neopentyl norephedrine-derived oxazaborolidines in THF afforded the best chemical yields combined with high diastereoselectivities.[120]



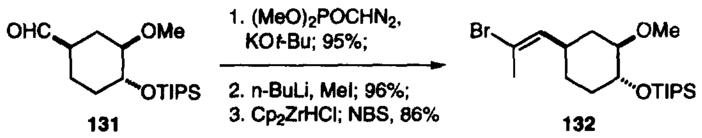
Scheme 32



Scheme 33

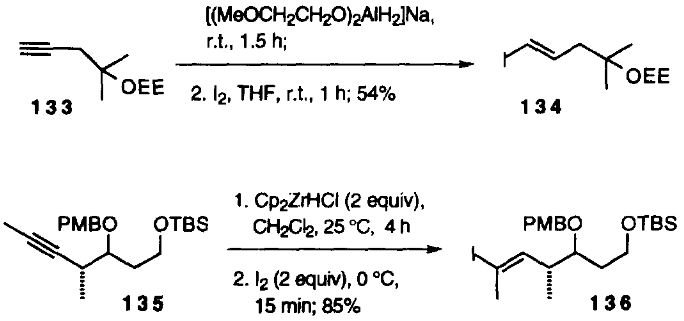
5. Halogenation of Organozirconocenes

Electrophilic halogenation of alkyl- and alkenylzirconium(IV) complexes with Br_2, I_2, *N*-bromo- or chlorosuccinimide, or iodobenzene dichloride affords the corresponding organic halides.[18,78,99] The reaction proceeds with retention of configuration at carbon,[99,128] and has become widely used especially for the conversion of alkynes to vinyl halides.[101,102,103,129] Hydrozirconation-halogenation has been used for the synthesis of an intermediate of the immunosuppressive agent FK-506.[130] Homologation of the aldehyde **131** to the vinyl bromide **132** was achieved in three steps via conversion of the aldehyde function into a terminal acetylene, methylation of the acetylene and a stereo- and regioselective hydrozirconation reaction, followed by treatment of the vinylzirconium intermediate with *N*-bromosuccinimide (Scheme 34).



Scheme 34

Hydrozirconation-iodination was used for the synthesis of steroid side chains, for example by Mandai et al. for the preparation of protected (*E*)-4-hydroxy-4-methyl-1-pentenyl iodide,[131] and was a key reaction for the regioselective preparation of segment **136** by Nicolaou et al. as part of their strategy toward the total synthesis of rapamycin (Scheme 35).[132]



Scheme 35

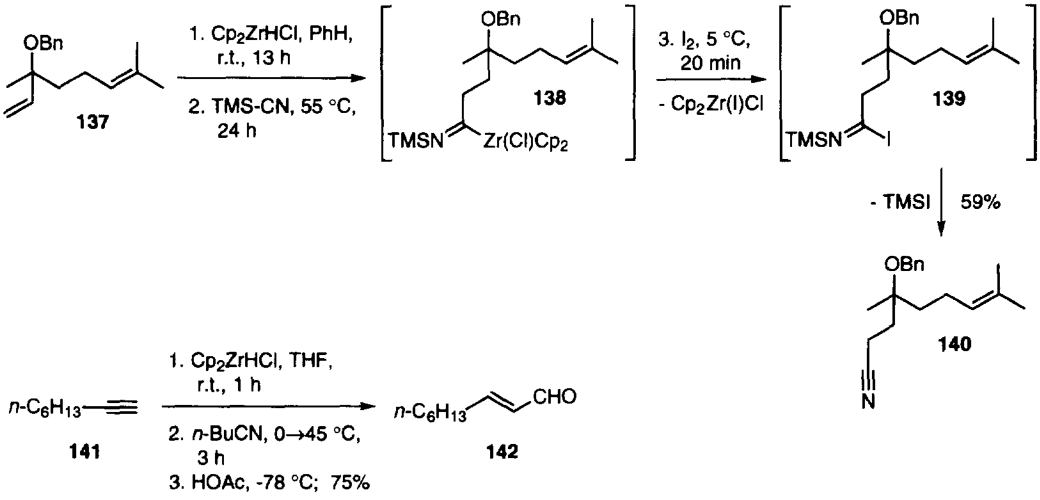
The reaction of homoallylic zirconocenes with halogen sources can lead to cyclization to give cyclopropanes.[78]

6. Oxidation and Hydrogenation

The oxidation of alkylchlorozirconocenes with basic H_2O_2, *t*-BuOOH, peracids, CrO_2Cl_2, MoOPh, or O_2 leads to alcohols in modest yields.[1,133] Stoichiometric TEMPO can also be used for this conversion.[134] The stereorandom reaction with molecular oxygen appears to produce alkylperoxide complexes that are rapidly decomposed by reaction with remaining alkylzirconocene under retention of configuration. Accordingly, alcohol formation occurs with ca. 50% racemization (from O_2 reaction) and 50% retention (from peroxide substitution) of configuration.[1,133] Hydrohafniation-oxidation has been used in cases where hydroboration failed.[49] The oxidation of alkenylchlorozirconocenes with O_2 or peroxides, however, does not give the expected carbonyl compounds.[1] Similarly, the catalytic hydrogenation of organozirconocenes is not a very clean reaction and requires high temperatures.[135,136]

7. Carbon Monoxide and Isonitrile Insertion into Organozirconocenes

Dicyclopentadienylzirconium alkenyl chlorides do not generally undergo carbon-carbon bond forming reactions, except with CO[78,97,137] and isonitriles[138,139,140,141,142] via insertion into the C-Zr bond. Both alkyl- and alkenylzirconocene chlorides are readily carbonylated with retention of configuration using carbon monoxide. The acylzirconocene chlorides thus obtained can be converted into aldehydes, carboxylic acids, esters, and acyl bromides by treatment with dilute HCl, $NaOH/H_2O_2$, $Br_2/MeOH$, and NBS, respectively.[78,97] Insertion of isonitriles into alkylzirconocenes produces iminoacyls which can be converted to imidoyl iodides by treatment with iodine. Decomposition of the imidoyl iodide leads to a nitrile in what amounts to an overall alkene hydrocyanation sequence (Scheme 36).[140] Alternatively, as reported by Negishi and coworkers, treatment of the iminoacyl complex with dilute acid provides a reliable route for the one-pot conversion of alkynes and alkenes into one-carbon homologated aldehydes (Scheme 36).[139]

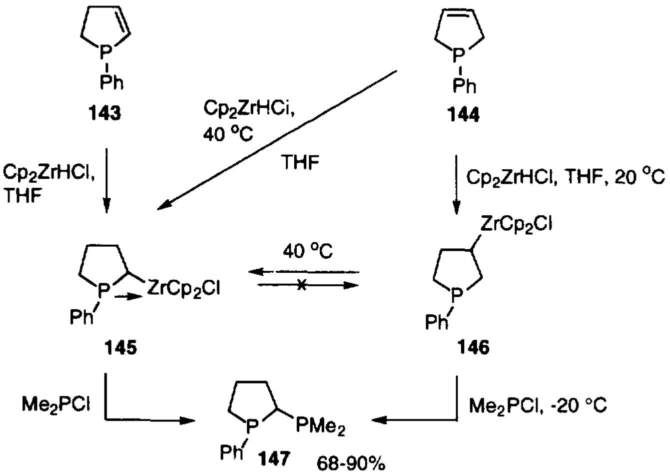


Scheme 36

The Negishi protocol has been used by Wipf and Xu for the preparation of a γ,δ-unsaturated aldehyde on route to curacin A (Scheme 17).[82]

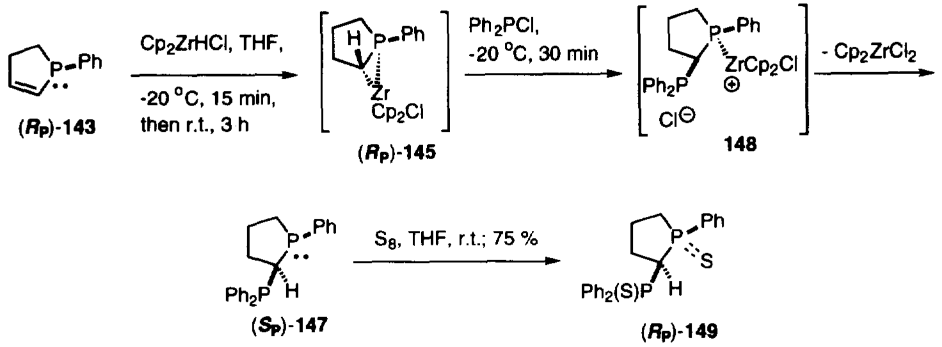
8. Conversion of Organozirconocenes to Organophosphorus, -selenium and -tellurium Compounds, and Amines

As mentioned previously, hydrozirconation of carbon-carbon multiple bonds leads generally to *cis*-addition products in which the zirconium moiety is linked to the less hindered carbon atom. Zablocka et al. published the first example of a regio- and diastereoselective preparation of both α- and β-zirconated products of dihydrophospholes. Hydrozirconation of the dihydrophosphole **143** with Cp_2ZrHCl at 40 °C afforded quantitatively the stable α-substituted phospholane **145** (Scheme 37). The exclusive formation of this regioisomer is most likely due to the coordination of zirconium to the phosphane group, which provided extra stabilization for the α-metalated phospholane. Hydrozirconation of the isomeric dihydrophosphole **144** at room temperature gave regioselectively the β-zirconated phospholane **146**. Increasing the temperature to 40 °C subsequently afforded the thermodynamically more stable product **145**. Somewhat surprisingly, treatment of either the organozirconium complex **145** or **146** with chlorophosphanes gave rise to the same diphosphane **147**.[143]



Scheme 37

Further investigations by Zablocka et al. have demonstrated the feasibility of an inversion of configuration at carbon during the electrophilic cleavage of the Zr-C bond of the α-zirconated phospholane **145**. In the presence of a strong phosphorus-zirconium interaction, the formation of a cationic zirconium, resulting from backside electrophilic cleavage with inversion at carbon, was postulated (Scheme 38).[144] The 1,1-diphosphine **147** was isolated in the form of the optically active diphosphine disulfide; addition of sulfur on phosphine occurred with retention of configuration. The authors concluded that the stereochemistry of the cleavage reaction depended on the availability of a vacant orbital on the metal. In the 18-electron complex **145**, a closed transition state would not be possible, and backside attack with inversion at carbon was favored.



Scheme 38

The reaction of alkenylchlorobis(cyclopentadienyl)zirconium(IV) complexes with phenyltellurenyl iodide and arylselenenyl bromides has been used for the preparation of vinylic tellurides and selenides.[72,145,146,147] Similarly, treatment of alkylzirconocenes with *O*-(mesitylsulfonyl)hydroxylamine leads to primary alkyl amines.[148] Other heteroatom electrophiles such as SO_2 and NO tend to attack both the Zr-C σ- and the cyclopentadienyl-Zr bonds.[149,150,151]

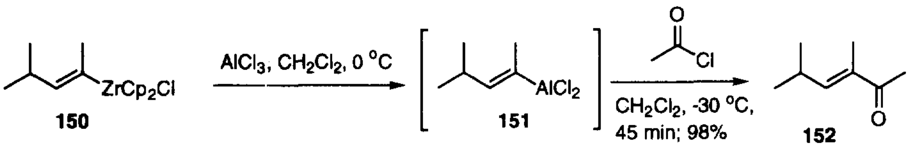
9. Transmetalation of Organozirconocenes

In spite of the substantial polarization of the zirconium-carbon bond reflected by the electronegativity of zirconium in the range of 1.2 to 1.3 on the Pauling scale, the organometallic chemistry of zirconocenes would be limited as a consequence of the steric shielding effect of the cyclopentadienyl ligands if it were not for the ease of transmetalation reactions of these complexes. Especially alkenyl zirconocenes participate in a wide range of ligand transfer reactions, and transmetalation from alanes, for example, is also a method for the preparation of zirconium organometallics. The transfer of alkyl ligands from zirconocenes is more difficult and requires extensive optimization of reaction conditions. Both processes are, unfortunately, mechanistically obscure, and much of the progress in synthetic applications in this area is based on empirical trials. However, the *in situ* transfer of organic substituents from zirconium to other metals opens unique manifolds for consecutive reaction processes that rapidly increase the structural complexity of the substrate and the usefulness of the overall process.

A. Zirconium→Aluminum

Organochlorobis(cyclopentadienyl)zirconium(IV) complexes can be used as precursors of alanes, which find broad use in organic synthesis.[1] Transmetalation reactions from zirconium to aluminum were first reported by Schwartz and Carr in 1977.[152] This group showed that simple mixing of Cp_2ZrRCl with $AlCl_3$ rapidly yielded the corresponding organoaluminum dichlorides (Scheme 39).

Subsequent acylation with acetyl chloride provided the α,β-unsaturated ketone **152** in high yield. Without transmetalation to aluminum, alkenylzirconocenes cannot be acylated with acid chlorides.[25] For the mechanism of the transmetalation from Zr to Al, a transition state involving a transition metal - main group metal complex containing a bridging alkyl (or vinylic) group was suggested.[107,152] Ligand transfer occurs with retention of configuration.[107]



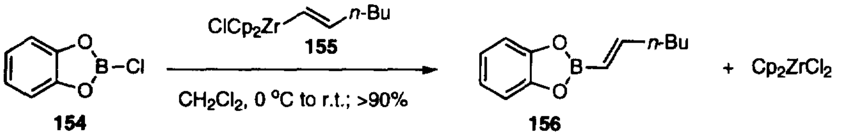
Scheme 39

The equilibrium in the transmetalation reaction depends strongly on the difference in the electronegativity of the two metals; however, even organic transformations that are seemingly contra-thermodynamic can be effected by judicious choice of metal ligands and selective trapping of one species.[153] A trialkylalane will transfer a ligand to Cp_2ZrCl_2, whereas the direction of transmetalation will be opposite from an alkenyl zirconocene to R_2AlCl.[107] Conversion of an alane to an ate complex with BuLi will increase its tendency to donate a ligand to zirconium.[154]

Negishi et al. developed a new method for the stereo- and regioselective synthesis of trisubstituted olefins via carbometalation of alkynes with organoalane-zirconocene dichloride complexes.[155] Terminal and internal triple bonds can be stereoselectively carbometalated. The formation of an organozirconium species was proposed, which rapidly exchanges the alkyl group with alkylalanes.[156] The actual mechanism of the Cp_2ZrCl_2-assisted carboalumination, and if indeed organozirconocenes are directly involved in this process, is still not clear.[157] Recently, an extension of this methodology to the zirconium-catalyzed alkylalumination of monosubstituted alkenes was reported.[158]

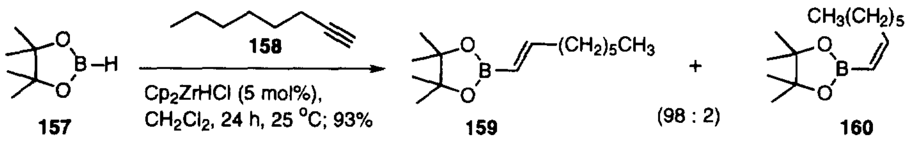
B. Zirconium→Boron

Caulton first reported the methyl group transfer from dimethylzirconocene to $BH_3 \cdot THF$, resulting in a mixture of methylboranes.[159] Subsequently, Fagan et al. published the synthesis of substituted boroles from the corresponding zirconium metallacycles,[160] and Fryzuk and coworkers synthesized substituted dienes *via* hydrozirconation of 1,3-enynes and transmetalation to diphenylbromoborane.[161] More recently, Cole and coworkers have investigated the migration of alkyl groups and 1-alkenyl groups from zirconium to various, structurally different boron compounds. Thus, they demonstrated that simple 1-hexenyl groups readily transmetalate to chloro- and bromoboranes in nonpolar solvents to give regio- and stereochemically pure 1-alkenylboranes (Scheme 40).[162,163,164]



Scheme 40

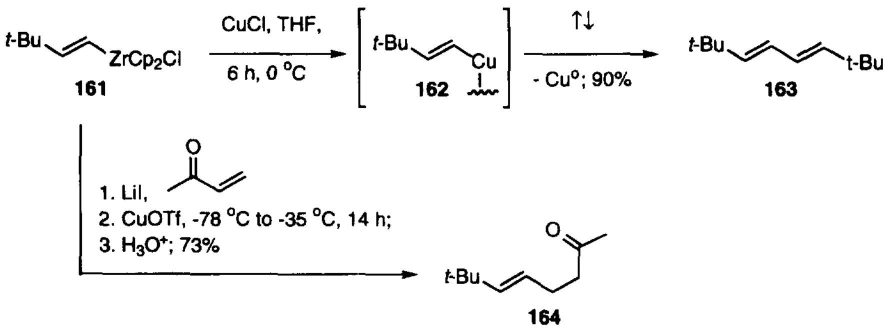
Further studies by Cole examined alkyldihaloboranes and dialkylhaloboranes for transmetalation of alkenyl- and alkylzirconocenes.[165] *n*-Octyldibromoborane reacted with one equivalent of 1-hexylzirconocene chloride to yield the dialkylbromoborane in 80% conversion within 2 h.[166] In an extension of this methodology, Srebnik et al. presented a Cp_2ZrHCl-catalyzed hydroboration of terminal and internal alkynes with pinacolborane (PBH) with excellent syn-selectivity and regioselectivity (Scheme 41).[167] Addition of 1-octyne to a solution of PBH containing 5 mol% Cp_2ZrHCl afforded vinyl borane **159** in 93% yield after stirring for 24 h at room temperature. The proposed mechanism included the initial hydrozirconation of the alkyne to give the alkenylzirconocene chloride, followed by vinyl-hydride exchange to give the product **159** under regeneration of Cp_2ZrHCl.



Scheme 41

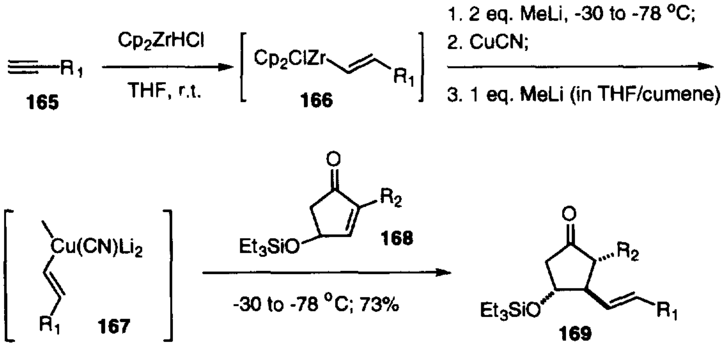
C. Zirconium→Copper

Transmetalation of organic ligands from zirconium to copper has become a very intensely researched process due to the wide application of organocopper reagents in synthetic chemistry.[168,169] The first example of a successful transfer of vinyl groups from zirconocene to copper(I) salts was reported by Schwartz and coworkers in 1977.[170] Thermal decomposition of the yellow-green copper complexes **162**, obtained by addition of CuCl to the alkenyl zirconocene **161**, led to the formation of a copper mirror and the (*E,E*)-diene **163** in 90% yield (Scheme 42). *In situ* conversion of the alkenyl organometallic intermediates to the corresponding ate complexes with LiI allowed conjugate addition reactions to α,β-unsaturated ketones. However, in these procedures, stoichiometric amounts of copper(I) salts were necessary, and alkyl groups did not transmetalate at a synthetically useful rate.[170]



Scheme 42

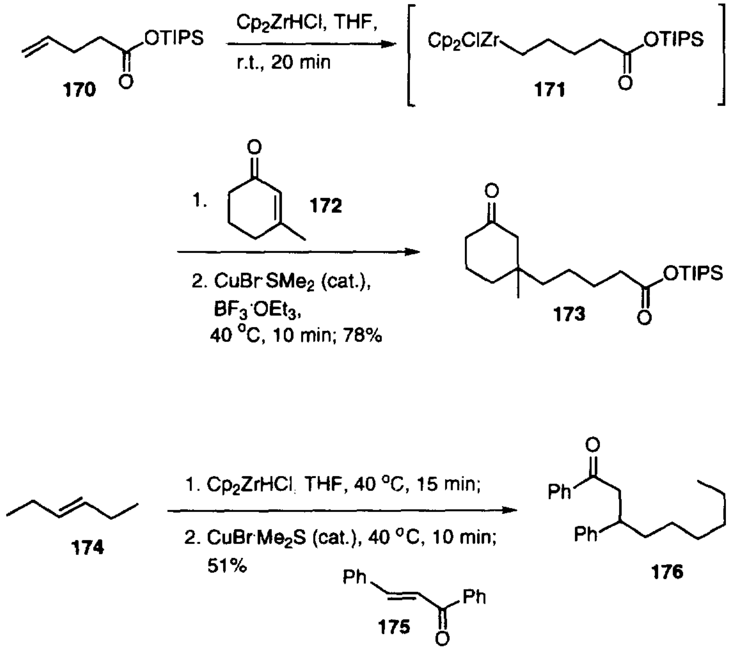
Subsequent to the pioneering studies of Schwartz and coworkers on Zr-Cu transmetalation,[171] many modified transmetalation reactions between organozirconium species and copper(I) salts have been reported.[168] An improved route to vinylic cuprates from monosubstituted acetylenes via a vinylzirconate intermediate was developed by Lipshutz and Ellsworth using dilithium cyanodimethylcuprate, $Me_2Cu(CN)Li_2$, as a catalyst [$Me_2Cu(CN)Li_2$ was prepared from 2 equiv of MeLi and CuCN in THF at -78 °C; transmetalation with Me_2CuLi was not successful].[172] The extension of this methodology by the Lipshutz group led to the synthesis of vinylic lithiocuprates containing internal electrophiles and the development of a short, efficient prostaglandin synthesis from alkyne precursors and functionalized cyclopentenones, *e. g.* for PGE_1,[55] and misoprostol.[173,174] Hydrozirconation of 4-methyl-4-[(trimethylsilyl)oxy]-1-octyne **165** with Schwartz reagent to give the alkenylzirconium intermediate, followed by addition of 2 equivalents of *n*-BuLi or MeLi and sequential addition of 1 equivalent each of copper cyanide and methyllithium gave the cyanocuprate. Subsequent treatment with (+/-)-methyl 7-[5-oxo-3-[(triethylsilyl)oxy]-1-cyclopenten-1-yl]heptanoate (**168**) yielded protected misoprostol **169** in 73% yield (Scheme 43).



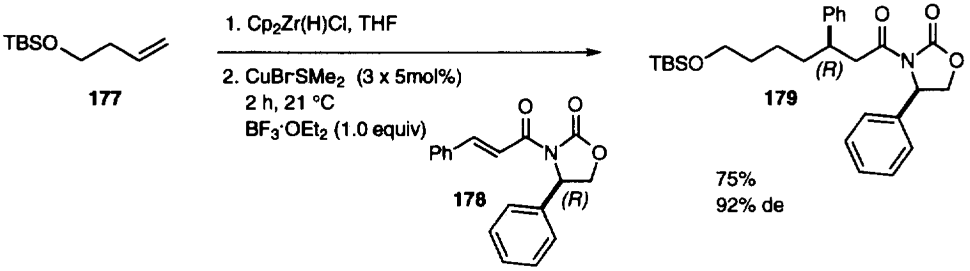
$R_1 = CH_2C(CH_3)(OTMS)\text{-}C_4H_9$
$R_2 = (CH_2)_6CO_2CH_3$

Scheme 43

Wipf and Smitrovich reported the first example for the use of alkyl zirconocenes and catalytic copper(I) salts for conjugate addition reactions in 1991.[62] Independently, this process was also investigated by Venanzi and Lehman.[175] Besides CuBr·SMe_2, other Cu(I) and Cu(II) salts such as CuBr, CuI, CuCN, $Cu(acac)_2$, $(C_4H_9C_2)CuCNLi_2$, and $Cu(OTf)_2$ catalyzed the 1,4-addition of functionalized zirconocene to alkenones (Scheme 44).[43,62,153] In contrast to most recently reported transmetalation protocols for cuprates that involve the transfer of kinetically labile alkenyl groups,[168] this methodology allows alkyl transfer via relatively stable, easily accessible zirconocene derivatives. The tendency of alkyl zirconium complexes to migrate along a linear chain toward the sterically least hindered position via insertion - β-hydride elimination reactions can be used to prepare primary organometallics from internal alkenes or mixtures of isomers. Primary, secondary, and functionalized alkyl groups can be transferred. Conjugate additions to enones and vinyl sulfones occur readily, whereas α,β-unsaturated aldehydes lead to mixtures of 1,2- and 1,4-addition products and α,β-unsaturated alkyl esters do not react.[43] In an asymmetric variant of this method, alkyl groups can be added to acyl oxazolidinone **178** with >90% de (Scheme 45).[176]



Scheme 44



Scheme 45

Mechanistically, the copper-catalyzed addition of alkylzirconocenes to enones proved to have distinctively different features than the analogous process involving alkenylzirconocenes:[43]

- The yield depended significantly on the presence of ionic impurities in the Schwartz reagent: Both alkali cations and halide anions inhibited the formation of the conjugate addition product. LiCl, NaI, $MgBr_2$ and $ZnCl_2$, for instance, were not tolerated. Since these compounds are side products of the *in situ* preparation of Schwartz reagent with $LiEt_3BH$[39] and *t*-BuMgCl,[38] or were added to facilitate ligand transfer from alkenylzirconocenes,[170] these protocols are not useful for hydrozirconation/copper-catalyzed conjugate addition sequences.
- The concentration of the reactants, especially enone and alkylzirconocene, is an important parameter in the copper-catalyzed conjugate addition. Desirable concentrations of the reactants are >0.5 M. Kinetics and NMR investigations indicate that the formation of an enone-zirconocene-copper complex is crucial for conjugate addition to occur.
- Et_3B and $Al(OEt)_3$ led to an enhanced activity, but optimal conditions were achieved in the presence of 1 equiv of the strongly Lewis-acidic BF_3-etherate.

Based on these observations, it can be hypothesized that for alkenylzirconocenes, the organic ligand is actually transferred to Cu(I) presumably via ate complex **181** (Figure 7). The organocopper species **182** is then responsible for further addition to α,β-unsaturated ketones. Alkenyl groups are better bridging ligands and are therefore exchanged more readily between metals.[177] The alkylzirconocene species **183** probably does not undergo the analogous exchange reaction with copper(I) alone or in the presence of alkali halides. Product formation occurs via the π-complex **185** between copper(I), enone, and zirconocene. The formation of this complex is disrupted by the presence of alkali halides whereas Lewis acids facilitate the breakdown of **185** to give product enolate. Further mechanistic studies are needed to clarify the order of events in these conjugate additions and elucidate the actual structure of the enone-metal complex. The formation of copper(0) mirror during the reaction highlights the possibility of redox-based side reactions. However, the absence of typical alkenes and alkane disproportionation products of organocopper reagents supports the hypothesis that no actual transmetalation occurs prior to product formation.

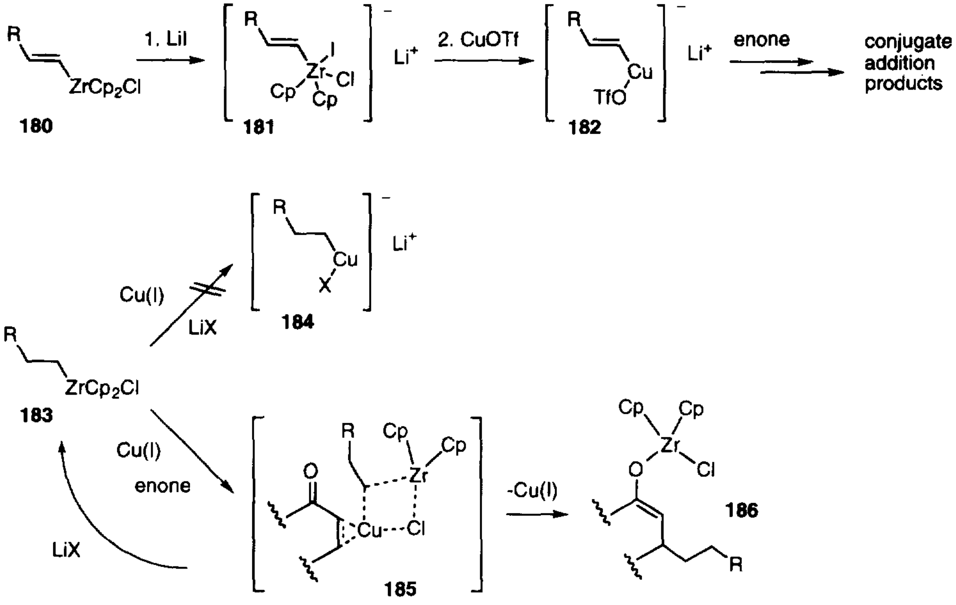
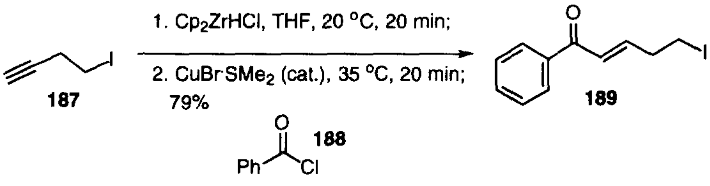


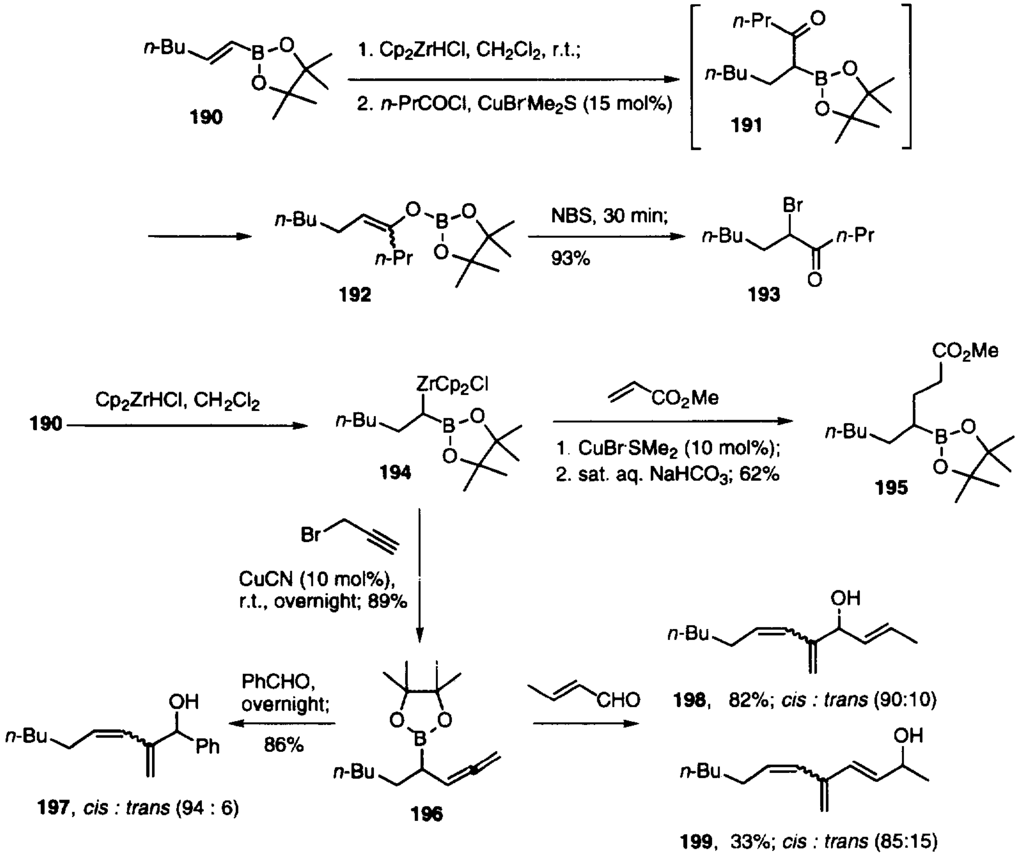
Figure 7

Wipf and Xu have developed a selective, one-pot synthesis of ketones from acid halides and alkenes or alkynes based on the hydrozirconation-copper(I)-catalyzed addition methodology.[74] Addition of aryl, alkyl, functionalized or sterically hindered acid chlorides and catalytic amounts of CuBr·SMe$_2$ to alkyl- and alkenyl zirconocenes provided the corresponding ketones in moderate to high yields even in the presence of very labile functionality (Scheme 46). No overaddition of the organometallic reagent, a side reaction that is typical for ketone synthesis from acid halides, was observed.[74,178]



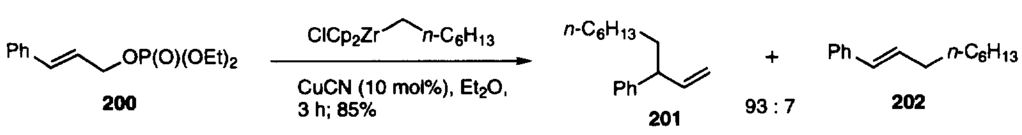
Scheme 46

This methodology was used by Srebnik and Zheng for the synthesis of enol borates from *gem*-borazirconocene alkanes and their regioselective conversion to α-bromo ketones (Scheme 47).[179] In the presence of copper(I)-salts,[84,85,105] *gem*-borazirconocenes also added across Michael acceptors (methyl acrylate) to afford 1,4-addition product **195**, whereas treatment with propargyl bromide yielded the α-allenic boronic ester **196**. Subsequent addition of benzaldehyde to the boryl allene **196** afforded the corresponding 1,3-dienyl allylic alcohol **197**, whereas addition of an α,β-unsaturated aldehyde such as crotonaldehyde led to trienes **198** or **199**, depending on the reaction conditions.[123,180,181]



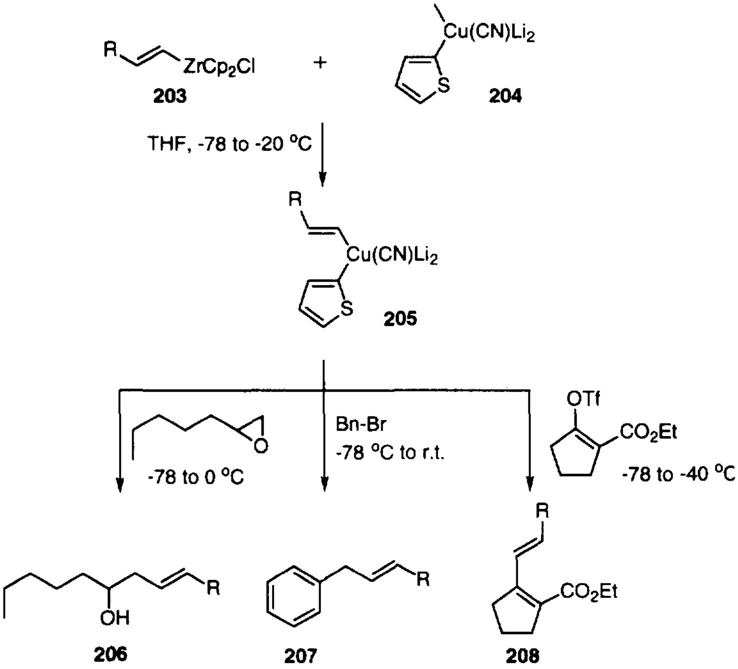
Scheme 47

Copper-catalyzed allylic substitution reactions of alkylchlorobis(cyclopentadienyl)zirconium(IV) complexes were investigated by Venanzi and Lipshutz.[175,182] The S_N2-substitution of allylic halides and phosphates occurred in good yields and provided terminal olefins as the major isomers (Scheme 48).



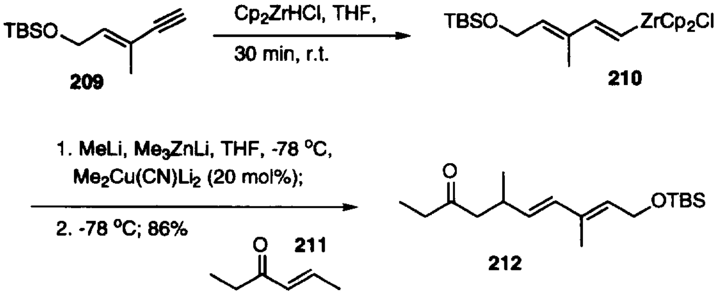
Scheme 48

Epoxide openings and substitution of benzylic halides and vinyl triflates can be performed with organozirconocenes and copper complexes with non-transferable ligands such as thienyl cuprates Me(2-Th)Cu(CN)Li_2, since the methyl substituent of mixed cuprates MeRCu(CN)Li_2 is preferentially transferred from copper to the electrophile (Scheme 49).[183] Addition to unactivated primary halides required the use of the presumed mixed metal cuprate Me(2-Th)Cu(CN)LiMgCl.

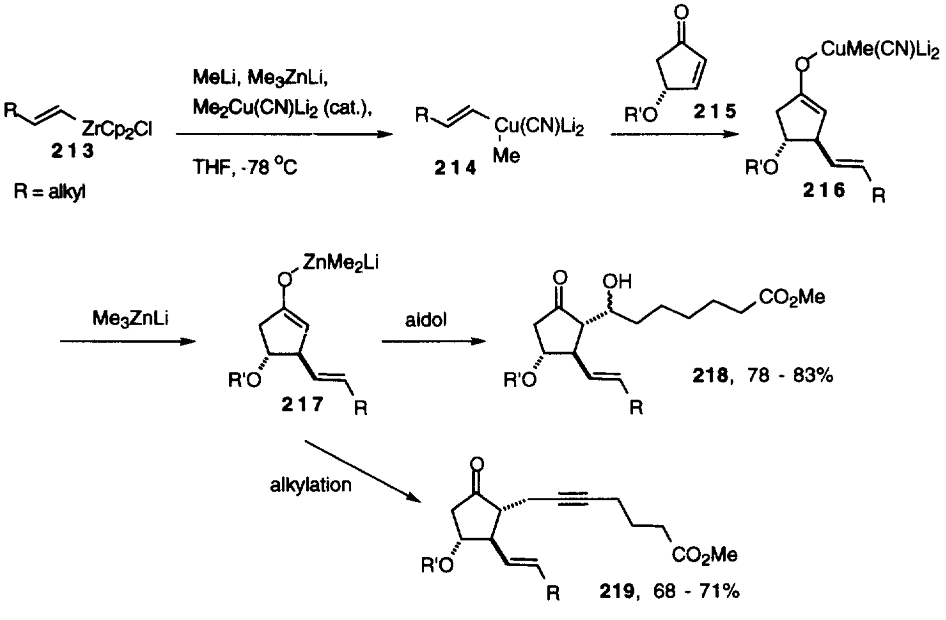


Scheme 49

To circumvent the use of stoichiometric copper reagents and organolithiums in this scheme, Lipshutz and Wood developed a cyanocuprate-catalyzed 1,4-addition of vinylic zirconocenes using a zincate as an organolithium "shuttle" (Scheme 50).[184] A 3-component coupling (3-CC) version of this process included the regeneration of the cyanocuprate ($Me_2Cu(CN)Li_2$) with methyl anions provided from the zincate (Me_3ZnLi) (Scheme 51).[112,185] The zincate transported the elements of MeLi to copper(I). MeLi itself, or any hard carbanionic equivalents, could not be tolerated by the starting material. Attempts to use the zincate without cuprate to effect both the transmetalation and the subsequent Michael addition were not successful.



Scheme 50



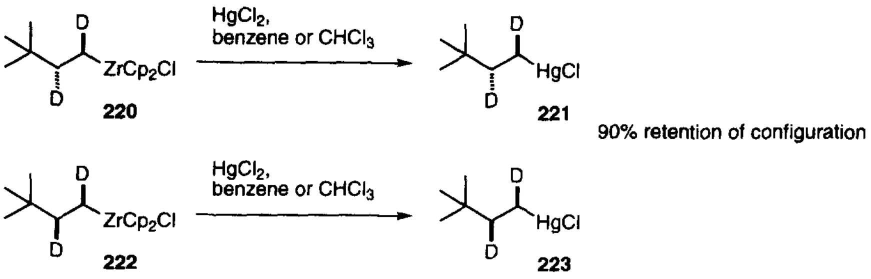
Scheme 51

Using spectroscopic evidence, a catalytic cycle for the cyanocuprate-catalyzed 3-component couplings was proposed.[186] The zincate Me_3ZnLi in the reaction mixture serves to transmetalate the initially formed copper enolate **216**, thereby regenerating the catalyst. This ligand-exchange leads to the production of the reactive zinc enolate **217**, which can undergo further C-C bond constructions, such as aldol and alkylation reactions leading to **218** and **219**.[187]

Catalytic copper(I) is also useful for the functionalization of zirconacyclopentenes.[188,189,7d]

D. Zirconium→Mercury

Erythro- and *threo-* alkylzirconocenes **220** and **222** were transmetalated by Budnik and Kochi to the mercury derivatives **221** and **223** with 90% retention of configuration (Scheme 52).[190]



Scheme 52

E. Zirconium→Nickel

Nickel-catalyzed conjugate addition of alkenylzirconocenes is a useful transformation for prostaglandin synthesis.[191] In the presence of catalytic amounts of Ni(acac)$_2$, rapid enone addition is achieved with terminal alkenylzirconocenes (Scheme 53).[192] Organometallics derived from internal alkynes give only modest yields, and no examples using alkylzirconocenes have been reported. Reduction of Ni(acac)$_2$ with one equivalent of DIBAL-H prior to reaction appears to give improved yields.[61,193] A one-electron transfer mechanism was proposed for these reactions (Figure 8).[194,195]

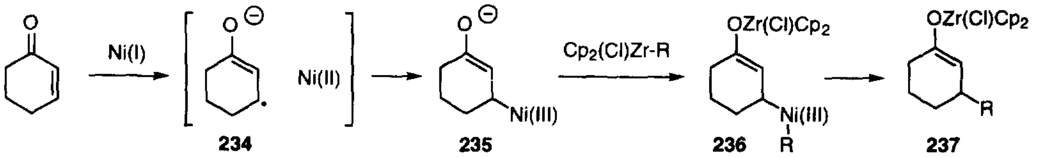
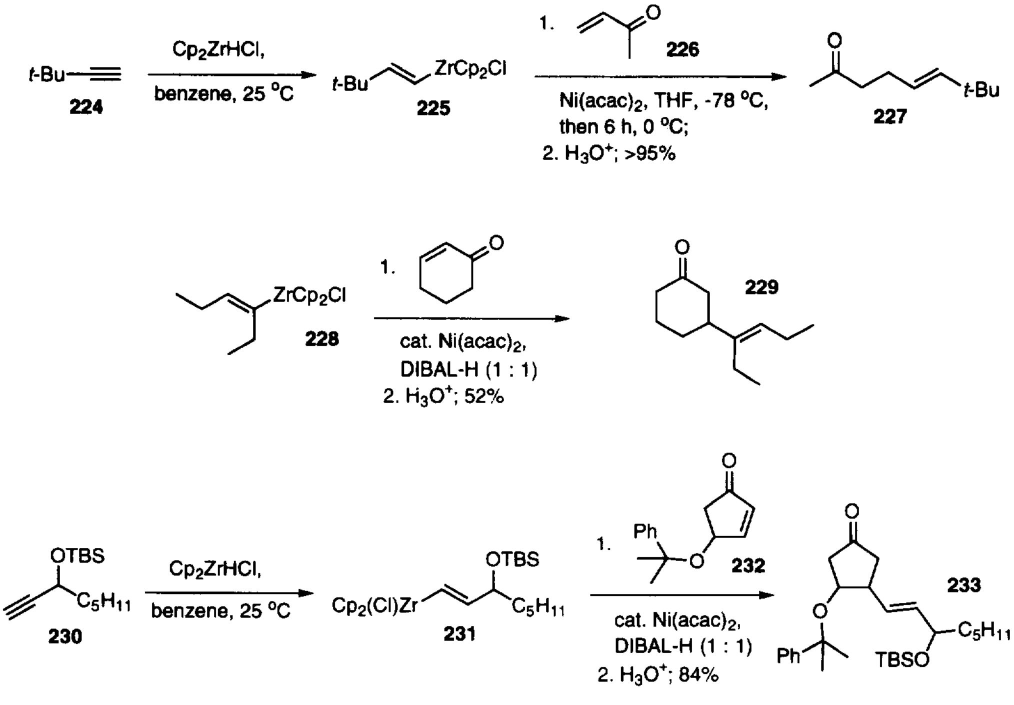
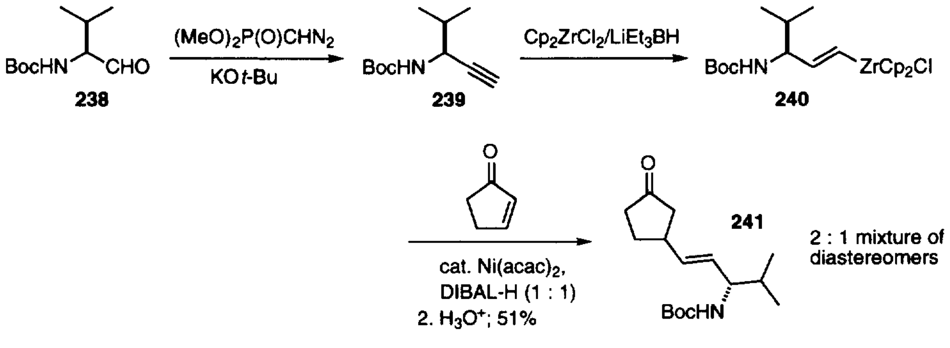


Figure 8



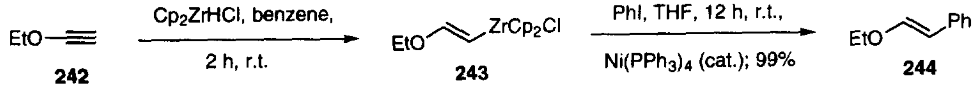
Scheme 53

Hauske et al. applied a Ni(II)-catalyzed conjugate addition to both cyclic and acyclic Michael acceptors in their investigations to convert amino aldehydes directly into substituted chiral allyl amines via the intermediacy of propargylic amines. Propargylic amine, prepared in one step from the amino aldehyde by exposure to dimethyl diazophosphonate, underwent hydrozirconation to the *trans* vinyl zirconium intermediate. Subsequent Ni(II)-catalyzed conjugate addition led to the desired chain-extended ketone **241** (Scheme 54).[196] This group also reported the synthesis of novel FKBP inhibitors by this methodology.[197]



Scheme 54

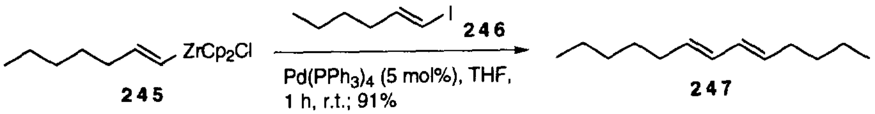
Negishi et al. discovered the nickel-catalyzed coupling of aryl halides and alkenylzirconium reagents. Arylnickel(II) species were formed by oxidative addition of halides to *in situ* generated $Ni(PPh_3)_4$ (Scheme 55). The transmetalation of internal alkenyl units proceeded very slowly in this cross-coupling process.[198,199] Addition of $ZnCl_2$ facilitated coupling with di- and trisubstituted alkenylzirconocenes.[200]



Scheme 55

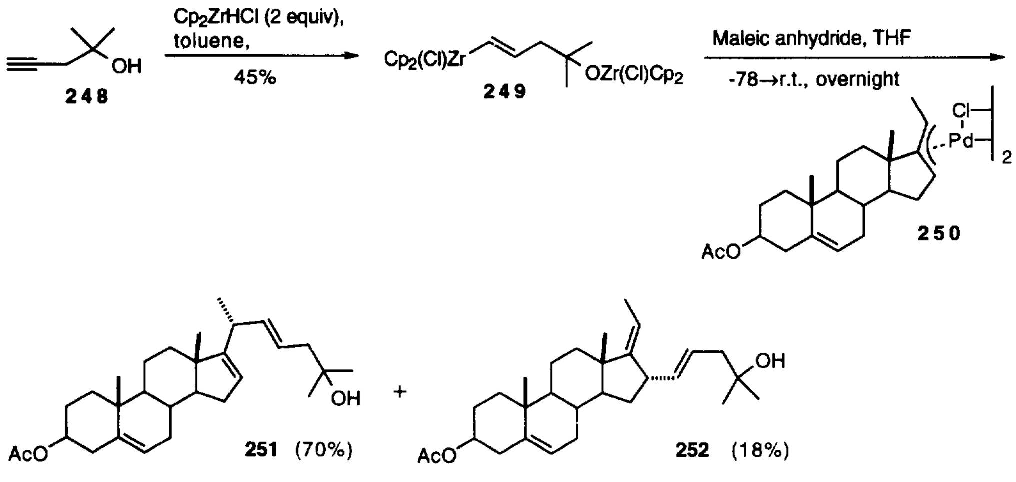
F. Zirconium→Palladium

The first observation of a Zr-Pd-transmetalation in alkene homocoupling reactions was reported by Schwartz et al. in 1977.[128] Negishi and coworkers investigated the palladium(0)-catalyzed regio- and stereoselective synthesis of conjugated dienes from alkenylzirconocenes and alkenyl halides (Scheme 56).[199,201] This method was also applied for the preparation of (*E*)-5-alkenyl-2'-deoxyuridines.[202] The Pd-catalyzed coupling reaction of alkenyl- and arylzirconium compounds with allylic halides, acetates, and alcohol derivatives containing $OAlR_2$, $OPO(OR_2)$, and $OSiR_3$ groups gave the corresponding cross-coupled products in the following order of reactivity: halogen, OAc > $OAlR_2$ > $OPO(OR)_2$ > $OSiR_3$.[203,204]



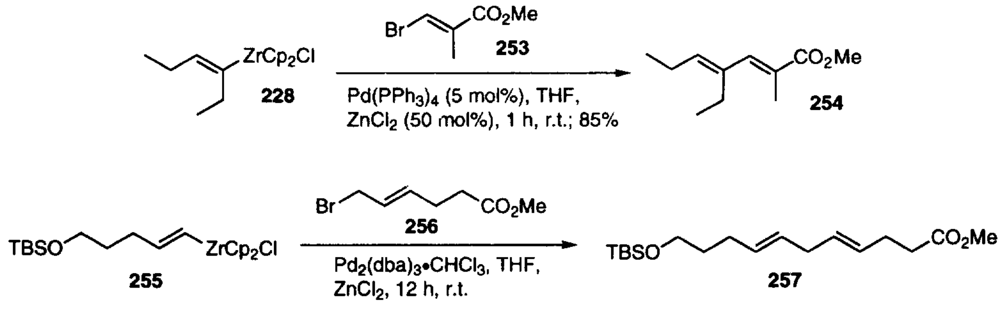
Scheme 56

Schwartz and coworkers described the reactions between (π-allylic)Pd(II) halide species and alkenylzirconium complexes which gave rise to 1,4-dienes in high yield. This methodology was used for the synthesis of 25-hydroxycholesterol and (20*R*)-cholestan-3-one (Scheme 57).[205,206] Palladium was replaced with retention of configuration. The use of additives such as maleic anhydride had a profound effect on the regiochemistry of the couplings.[207,208]



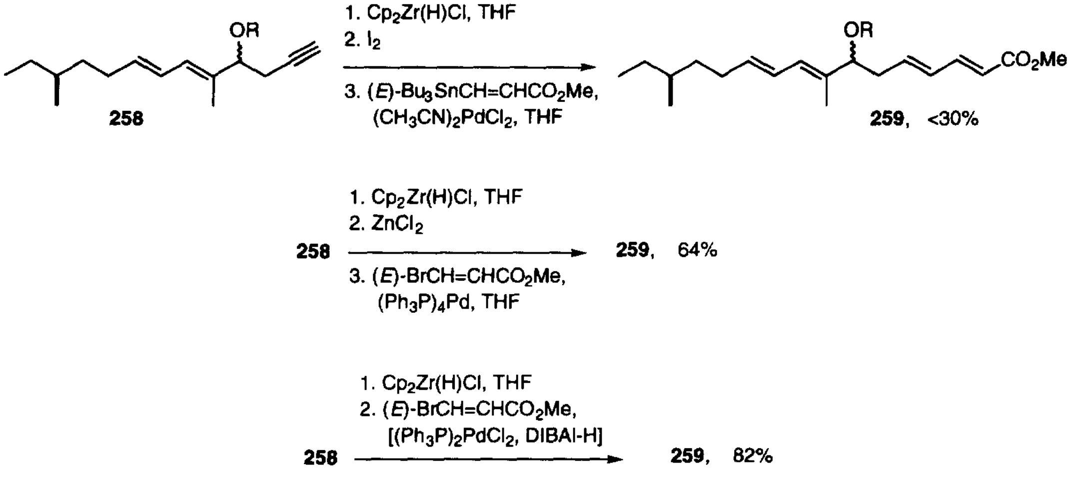
Scheme 57

In the palladium-catalyzed coupling of vinyl halides, the use of disubstituted and trisubstituted alkenylzirconocenes is unsatisfactory due to a slow Zr→Pd transmetalation. Negishi and coworkers discovered that the kinetics of this step can be improved by the addition of $ZnCl_2$ which has an electronegativity between Zr and Pd and low steric requirements. The use of 0.5 equiv of the $ZnCl_2$ "shuttle" induced the formation of **254** in 85% yield after 1 h at room temperature, whereas <2% product was formed in the absence of $ZnCl_2$ (Scheme 58).[200] In model studies toward the synthesis of hennoxazole A, this method was used for the formation of 1,4-diene **257** from zirconocene **255** and the π-allyl palladium complex derived from **256**.[209,210]



Scheme 58

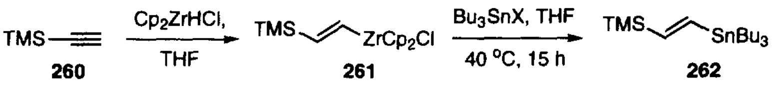
A nice comparison of the efficiency of various Zr→Pd transmetalation protocols was recently reported by Barrett et al.[211] Conversion of the alkenylzirconocene obtained *in situ* by hydrozirconation of alkyne **258** to the vinyl iodide, followed by Stille coupling gave the desired dienoate **259** in <30% yield (Scheme 59). In contrast, transmetalation to zinc chloride or direct use of the vinyl zirconocene, followed by palladium-catalyzed addition to bromoacrylate, increased the yield to 64% and 82%, respectively. This efficient synthesis of the sensitive tetraene ester **259** was an important step toward the total synthesis of papulacandin D by these authors.



Scheme 59

G. Zirconium→Tin

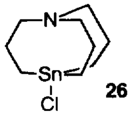
Conversion of organozirconocenes to stannanes has not yet been extensively investigated. A Zr→Sn-transmetalation was used for the synthesis of *n*-octyltin(IV) trichloride. $[(\eta^5\text{-}C_5H_5)_2Zr(n\text{-}Oct)Cl]$, prepared *in situ* from 1-, 2-, or 3-octene and Cp_2ZrHCl, reacted with stannic chloride in moderate yields to give *n*-$C_8H_{17}SnCl_3$.[212] Fryzuk et al. prepared 1,3-dienylstannanes by the selective hydrozirconation of 1,3-enynes and transmetalation with tributyltin chloride.[213] Recently, Kim and Kim developed a new efficient procedure for the synthesis of simple and bicyclic organostannanes by transmetalation of organozirconocenes with organotin alkoxides (Scheme 60). The hydrozirconation product of trimethylsilyl acetylene reacted very effectively with tributyltin ethoxide, whereas the transmetalation with tributyltin chloride, bis(tributyltin) oxide, tributyltin thiophenoxide or *N,N*-diethyltributylstannazane was very slow.[214]



X = Cl (24%); X = NEt_2 (36%); X = SPh (5%); X = $OSnBu_3$ (8%); X = OEt (85%)

Scheme 60

Hydrozirconation of triallylamine followed by *in situ* metal exchange with $SnCl_4$ was used by Vedejs et al. for the preparation of the 1-aza-5-stannabicycloundecane **263** (Figure 9).[215] This compound was subsequently applied as an internally activated stannane for palladium-catalyzed cross-coupling reactions.

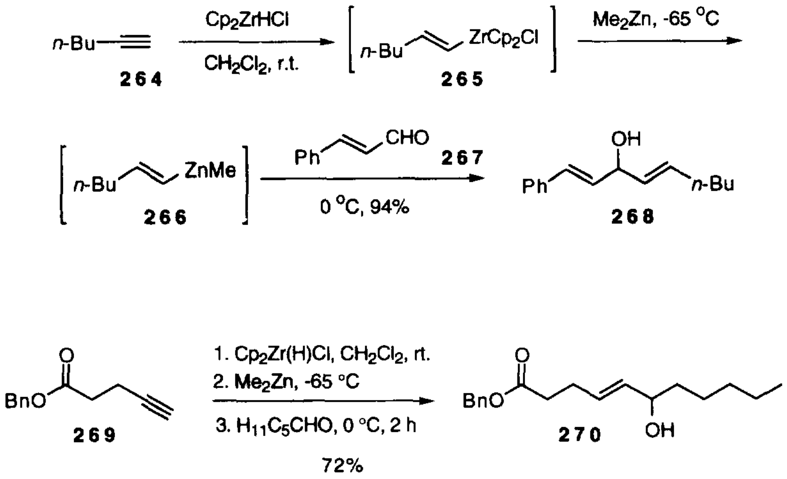


263

Figure 9

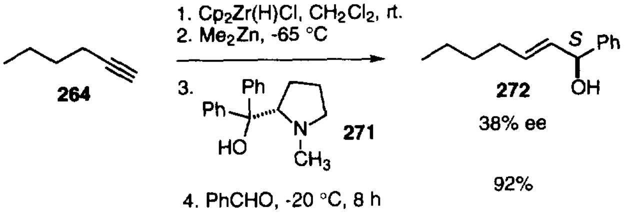
H. Zirconium→Zinc

The first indications of the feasibility of zirconocene-zinc ligand exchange reactions were revealed by Negishi and coworkers who found that many of the Pd- or Ni-catalyzed reactions of alkenylaluminum or -zirconium compounds with alkenyl, aryl, or alkynyl halides could be significantly accelerated by the addition of $ZnCl_2$.[200] An organozinc species was postulated as an intermediate, and Hartner and Schwartz were indeed able to prepare dineohexenylzinc from the corresponding chrorozirconocene.[106] A synthetically useful variant of this transmetalation reaction was reported by Wipf and Xu in 1994.[216,217] Transmetalation of alkenyl zirconocenes to the corresponding organozinc compounds occurred rapidly and at low temperatures in the presence of commercially available dimethyl- or diethylzinc (Scheme 61). Subsequent addition of aldehydes provided an *in situ* protocol for the conversion of alkynes into allylic alcohols.



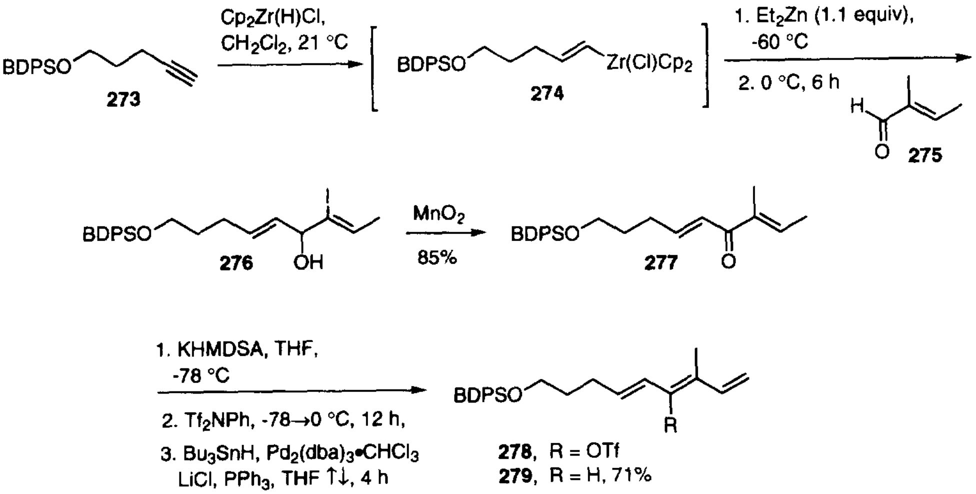
Scheme 61

In the presence of 8 mol% of chiral amino alcohol **271**, this process led to the formation of optically active allylic alcohol **272** (Scheme 62).[216] The unexpectedly low level of enantiomeric excess for the product (38% ee) is probably due to the presence of zirconocene complex that catalyzes the racemic addition reaction.



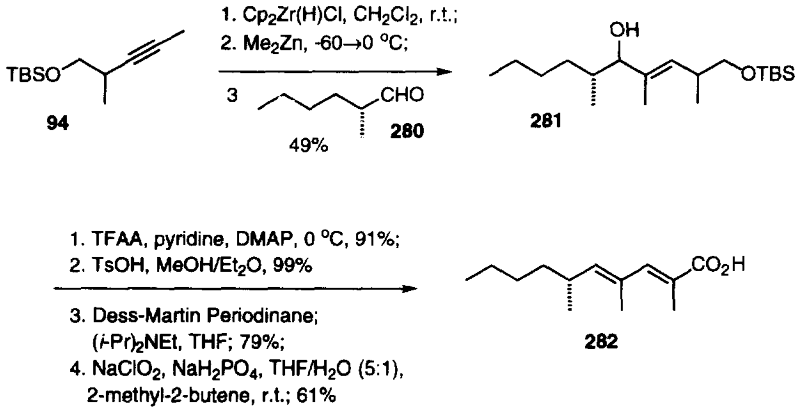
Scheme 62

The zirconium→zinc transmetalation combines the ease of preparation of functionalized organometallics from alkynes via hydrozirconation with the broad range of reactivity of organozinc reagents[218] and is therefore an attractive protocol in natural product total synthesis. For the synthesis of the curacin A segment **279**, Wipf and Xu performed a hydrozirconation of alkyne **273** followed by addition of the *in situ* obtained organozinc reagent to aldehyde **275** (Scheme 63).[82] The cross-conjugated dienone **277** was obtained in 85% yield after oxidation of bis-allylic alcohol **276** with manganese dioxide. Regio- and stereoselective enolization of the dienone, followed by Stille-reduction of the enoltriflate **278** gave triene **279** en route to curacin A.



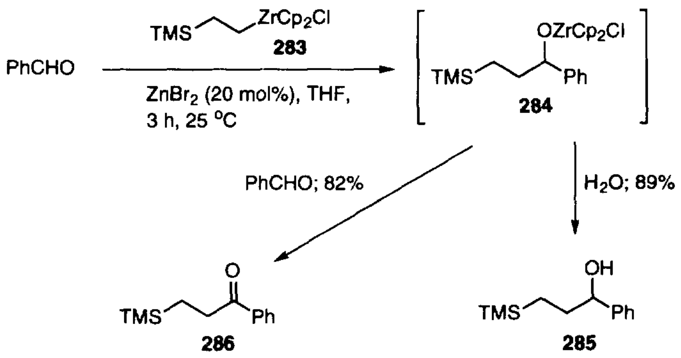
Scheme 63

Another application of this methodology was used for the preparation of the C_{13}-side chain of the antibiotic manumycin (Scheme 64).[219] A key step was the hydrozirconation of the TBS-protected alkyne **94**, followed by an *in situ* Zr→Zn-transmetalation and addition to (*R*)-2-methyl-hexanal. After trifluoroacetylation of the allylic alcohol, the silyl ether was converted to the carboxylic acid under elimination of the trifluoroacetate and formation of the conjugated diene moiety to give **282**.



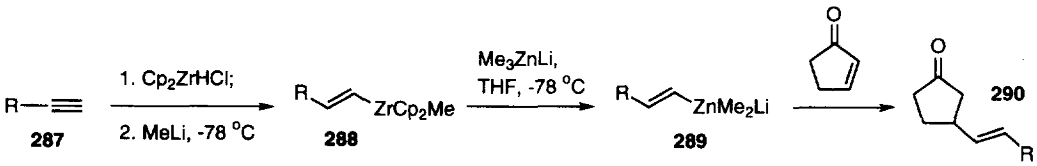
Scheme 64

Zheng and Srebnik have recently reported the acceleration of the 1,2-addition of alkyl- and alkenylzirconocene chlorides to aliphatic and aromatic aldehydes by catalytic amounts of $ZnBr_2$.[220] $ZnCl_2$ was found to be ineffective in dilute solutions, but could also catalyze the reaction, though less efficiently than $ZnBr_2$, in more concentrated mixtures. Treatment of the alkylzirconocene chloride **283** with benzaldehyde in the presence of catalytic amounts of $ZnBr_2$ afforded after aqueous workup the secondary alcohol **285** or the Oppenauer oxidation product **286**, depending on the ratio of reagents to benzaldehyde (Scheme 65).



Scheme 65

Lipshutz and Wood reported a related process involving the use of a mixed zincate in the transmetalation of an intermediate vinyl zirconocene, but the yields were highly variable and dependent on the nature of the R substituent in the 1-alkyne **287** (Scheme 66).[221]

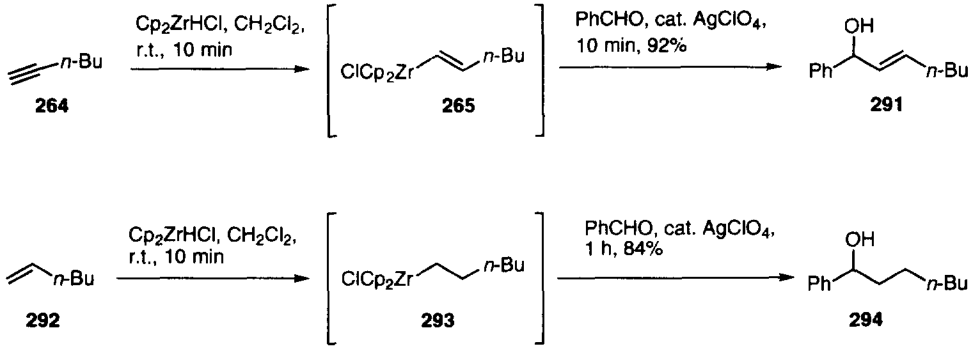


Scheme 66

It can be expected that further advances, especially in the asymmetric catalysis of the nucleophilic addition, will continue to broaden the scope of the zirconium-zinc transmetalation.

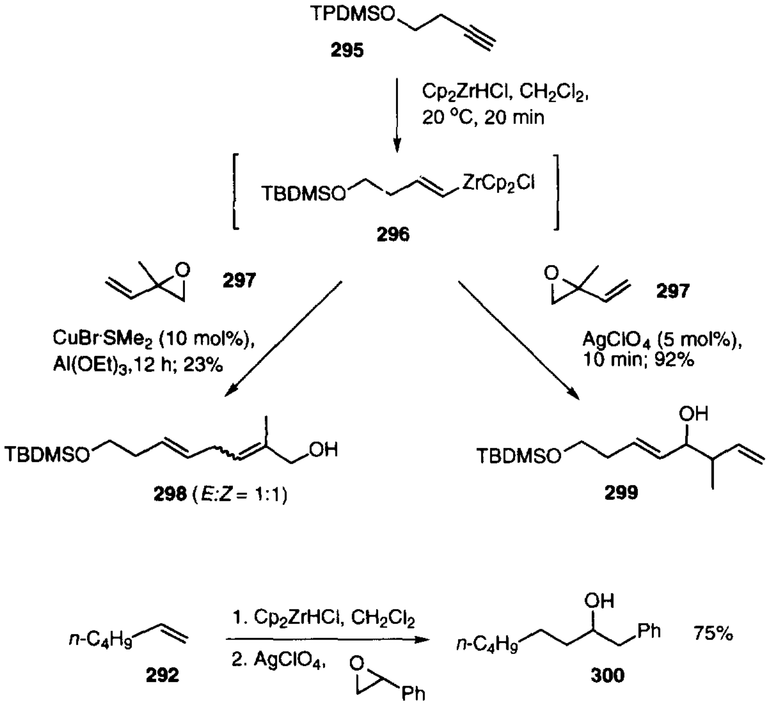
10. Cationic Zirconocene Complexes

The use of cationic zirconocenes as Ziegler-Natta polymerization catalysts abounds,[8,9,10] but there are still surprisingly few applications of cationic organometallics derived from organochlorobis(cyclopentadienyl)zirconium(IV) complexes.[222,223] In 1988, Suzuki et al. observed an acceleration effect in the C-glycosidation of phenols by treatment of glycosyl fluorides with a mixture of Cp_2MCl_2 (M = Ti, Zr, Hf) and $AgClO_4$.[224,225,226] In this process, the initially formed O-glycoside rearranged to the C-congener. Further studies of this group demonstrated the remarkable rate acceleration effect of $AgClO_4$ on the Grignard-type addition of alkenyl- and alkylzirconocenes to aldehydes, offering a new possibility for C-C bond formation (Scheme 67).[227]



Scheme 67

Wipf and Xu reported a highly efficient tandem epoxide rearrangement-carbonyl addition sequence with alkyl- and alkenylzirconocenes. Whereas the copper(I)-catalyzed addition of *in situ* prepared (*E*)-[*tert*-butyl-dimethylsilyl)oxy]zirconocene **296** in the presence of Al(OEt)$_3$ to the vinyl epoxide **297** resulted in a 23% yield of a 1:1 (*E*) : (*Z*) mixture of diene **298**, the addition of 5 mol% of AgClO$_4$ to a mixture of zirconocene **296** and epoxide **297** led to a rapid conversion to the secondary alcohol **299** in 92% yield (Scheme 68).[228] Key features of this new methodology are (1) a rapid opening of the epoxide ring followed by a [1,2]-hydride shift in the presence of *in situ* prepared cationic organozirconocene complexes; (2) C,C-bond formation via transfer of the alkenyl or alkyl ligand from the zirconocene to the aldehyde intermediate; (3) the use of highly functionalized (ester, alkene, silyl ether) Lewis acid-sensitive substrates and catalytic amounts of Ag(I) salt (Figure 10). The cationic zirconocene complex **302** is regenerated by chloride abstraction from **301** by alkoxy zirconocene **307** at the completion of a catalytic cycle.



Scheme 68

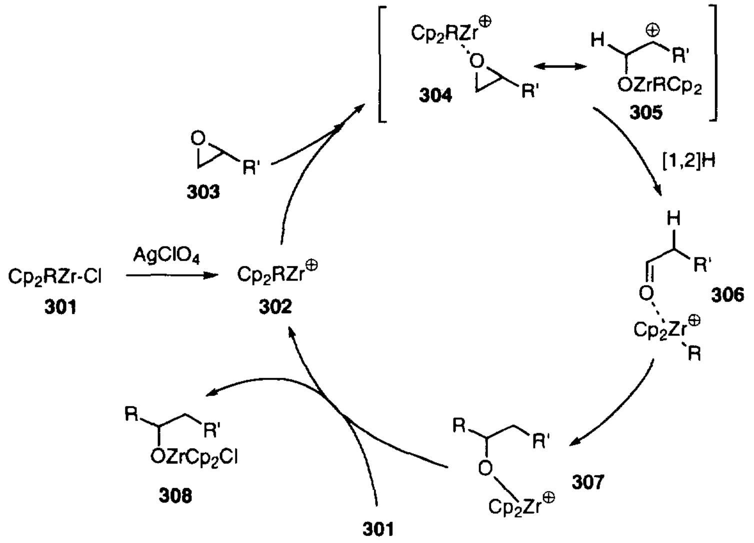
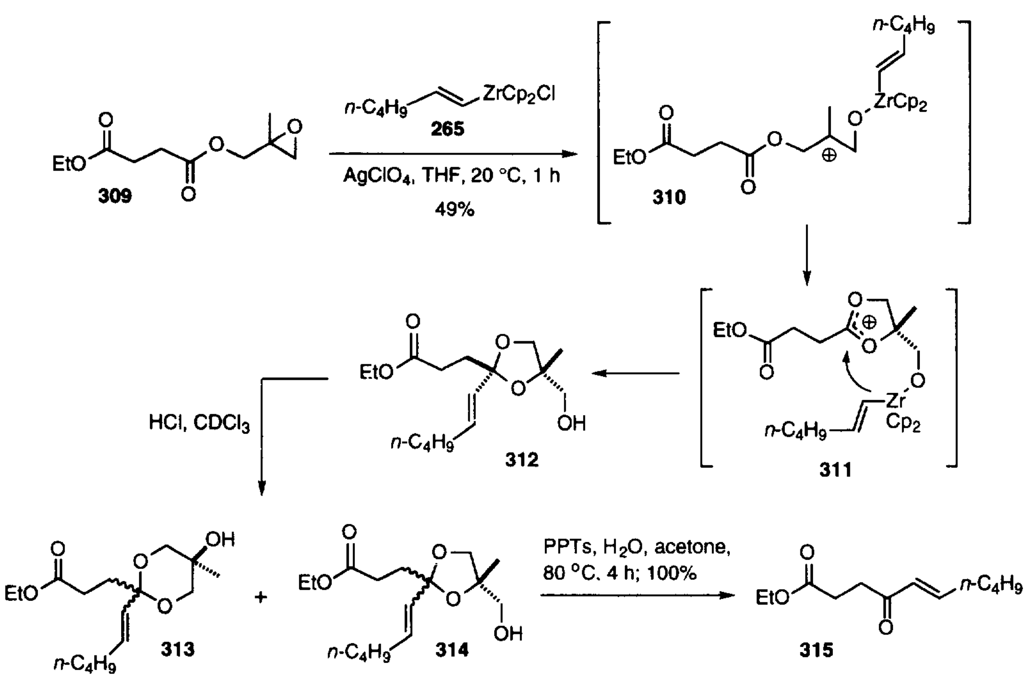


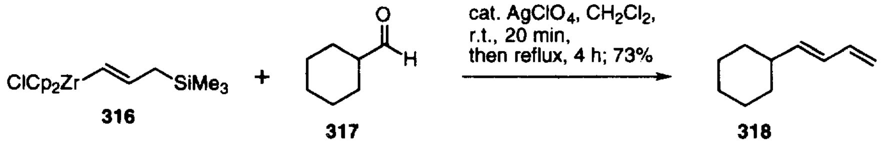
Figure 10

Intramolecular neighboring group participation of a Lewis-basic moiety attached to the epoxide can be used to suppress the [1,2]-hydrogen shift. Treatment of epoxy ester **309** with hexenyl zirconocene **265** in the presence of 5 mol% of silver perchlorate led to the isolation of acetal **312** in 49% yield (Scheme 69).[229] Only a single isomer was formed as a consequence of the suprafacial transfer of the alkenyl ligand in the dialkoxycarbenium intermediate **311**. Acetal **312** represents the kinetic product since treatment with small amounts of HCl in the NMR tube led to an approximately equimolar mixture of five- and six-membered acetals **313** and **314** with no diastereocontrol. Upon hydrolysis, keto ester **315** was isolated quantitatively. The overall transformation from diester **309** to ketoester **315** including the alkyne hydrozirconation can be performed in one pot and represents a chemoselective nucleophilic ester addition of an organometallic reagent that is free from subsequent carbonyl addition products. The intermediate dialkoxycarbenium ion **311** can also be used as a reactive Diels-Alder dienophile in substrates with an α,β-unsaturated epoxy ester moiety.[230]



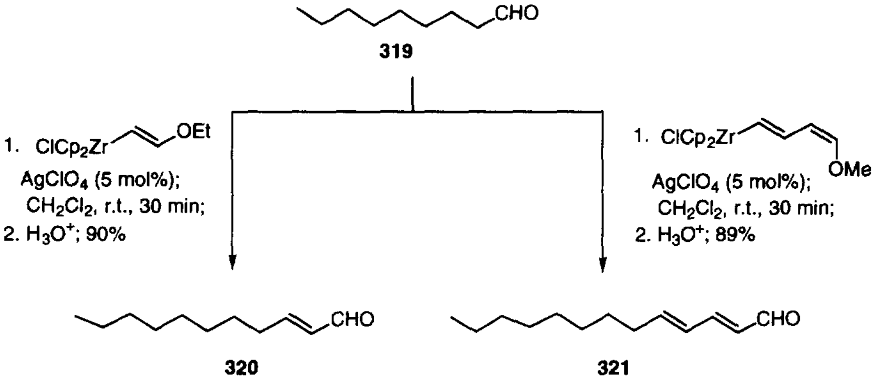
Scheme 69

Maeta and Suzuki described a new method for 1,3-diene synthesis based on a three-carbon elongation of aldehydes with *in situ* prepared cationic zirconocenes.[231] 3-Trimethylsilyl-1-propenylzirconocene chloride, generated from 3-trimethylsilyl-1-propyne and Cp_2ZrHCl, reacted with aldehyde in the presence of catalytic amounts of $AgClO_4$, and subsequent 1,4-elimination gave 1,3-dienes with excellent (*E*)-selectivities (Scheme 70).



Scheme 70

In a variant of this process, two- and four-carbon homologation of aldehydes was achieved by $AgClO_4$-catalyzed addition of alkoxyalkenylzirconocene chloride.[232] Treatment of 1-ethoxyacetylene or (*Z*)-1-methoxy-1-buten-3-yne with Cp_2ZrHCl, followed by addition of aldehyde and catalytic amounts of $AgClO_4$ afforded the corresponding (*E*)-unsaturated aldehydes **320** or **321** after acid hydrolysis (Scheme 71). More recently Suzuki and coworkers reported that $AgAsF_6$ serves as a safe and often more efficient alternative to the potentially explosive $AgClO_4$.[233]



Scheme 71

11. Concluding Remarks

Since the preparation of the first organochlorobis(cyclopentadienyl)zirconium(IV) complex by Wailes, Weigold and Bell 25 years ago,[234] the application of these organometallics for carbon-carbon and carbon-heteroatom bond formations has become an integral part of synthetic strategy and tactics. Nonetheless, we hope it becomes clear from this review that the chemistry of organozirconocenes is very much an emerging field, with many opportunities for further expansion into uncharted territory. The use of zirconium complexes in asymmetric or even diastereocontrolled transformations has just begun, and many more manifolds are open for transmetalation schemes and for the direct functionalization of organic molecules. A deeper understanding of reaction mechanisms ranging from hydrozirconation to ligand transfer reactions is clearly necessary and will assist in the development of catalytic processes that can take advantage of more elaborate zirconium complexes. As the widespread use of palladium complexes has shown, the fine-tuning of ligands can lead to considerable variation in reactivity and scope.[235] Therefore, the versatility that the parent organochlorobis(cyclopentadienyl)zirconium(IV) complexes have already demonstrated is quite remarkable.

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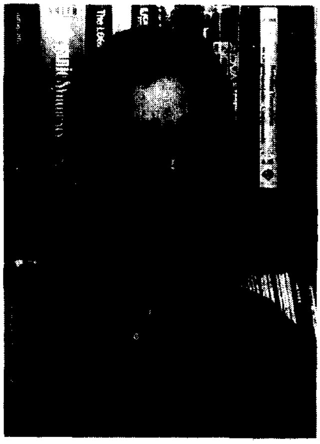
Biographical Sketch



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