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REVIEW

Synthesis and Reactions of *gem*-Borazirconocenes

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INTRODUCTION

The aim of this research has been to develop methodologies for synthesizing *gem*-borazirconocene alkanes and alkenes (Fig. 1), and to explore their chemistry. These compounds have not been previously investigated. They offer the potential to synthesize new classes of organometallic reagents and a large variety of organic compounds in a highly stereoselective manner.

The carbon–boron bond in organoboranes undergoes a large variety of transformations, making these useful reagents in synthesis.[1] The chemistry of organozirconium reagents is also well known.[2] Cleavage of the carbon–zirconium bond occurs with various electrophiles, generally under mild conditions, to provide access to products not readily available by organoborane chemistry. The different reactivities of the carbon–boron and carbon–zirconium bonds towards electrophiles are perhaps a consequence of the different electronegativities of boron and zirconium. Also, one is a transition metal while the other has intriguing transition-metal-like chemistry.[3] Thus carbonylation of the carbon–zirconium bond[4] occurs at 25 °C and about 1 atm of CO while that of the carbon–boron bond requires elevated temperatures and high pressures.[5] On the other hand, oxidation of the carbon–boron bond appears to be a more facile process. It is thus reasonable to presume that a union of boronzirconium organic chemistry should be a synergistic processes, affording products and chemistry not attainable by each reagent itself.

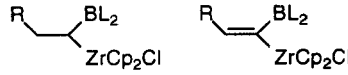

Figure 1 *gem*-Borazirconocenes.

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The impetus to the development of *gem*-bimetallics was initially to discover alkylidene transfer reagents like Tebbe's reagent.[6] Schwartz made bimetallic aluminum–zirconocene derivatives by hydrometallation of different vinyl metallic compounds.[7] Knochel has developed zinc–zirconium *gem*-bimetallics by hydrozirconation of vinylzincs and used them as alkylidene transfer reagents.[8] More recently, other *gem*-bimetallics have been developed with different reactivities of the two carbon–metal bonds. Thus, Normant has reported allylmetallation of vinyl metals to afford zinc–magnesium and zinc–lithium *gem*-bimetallics which can selectively react with different electrophiles such as $ClSnBu_3$, H_2O, etc.[9] However, selective and sequential cleavage of the two carbon–metal bonds with different electrophiles is the 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.[10] Lipshutz has developed reagents based on tin and zirconium through hydrozirconation of stannylacetylenes.[11] By selective cleavage of the carbon–zirconium bond with water, these reagents provide an efficient procedure for preparing *cis*-alkenylstannanes. Pelter has devised methods for preparation of *gem*-boralithio alkanes.[12] However, *gem*-boralithio alkanes require bulky boron ligands, such as mesityl, for stability.

PREPARATION

Both hydrozirconation and hydroboration reactions are well established, and widely applicable to a large variety of vinyl and acetylene deriva-

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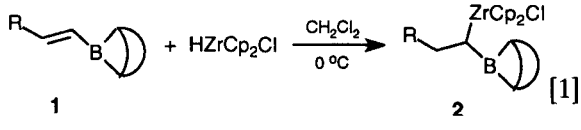
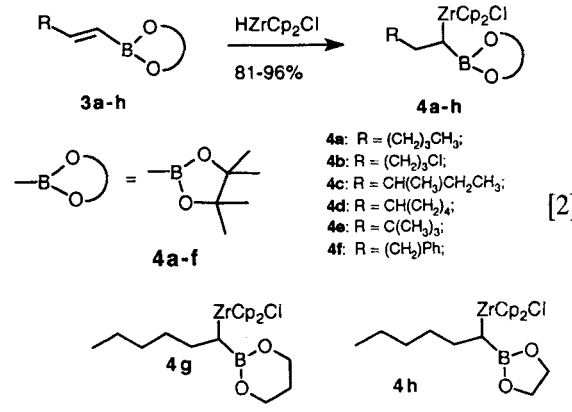
tives. Also, alkenylboranes and alkenylzirconium compounds are readily prepared. Therefore hydrometallation of the corresponding alkenylmetals should be a convenient method of preparing *gem*-borazirconocenes.[13] *gem*-Borazirconocene alkanes could be prepared by either hydrozirconation of alkenylboranes or hydroboration of alkenylzirconium compounds. Compared with alkenylzirconium compounds, alkenylboranes are more stable, and more easily stored. Furthermore, alkenylboranes allow for much broader scope in using boron ligands, such as various alkanes, diols and amino alcohols. This makes a large variety of alkenylboranes readily available. Therefore, we selected hydrozirconation of alkenylboranes as the procedure for preparing *gem*-borazirconocene alkanes. Initially, *B*-alkenylborabicyclo[3.3.1]nonanes (*B*-alkenyl-9-BBN) were chosen as the substrates for hydrozirconation. This is because the cyclononyl moiety in the alkenylborane derivatives is relatively nonreactive. 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 *B*-alkenyl-9-BBN derivatives **1** proceeded smoothly in dichloromethane, affording the expected *gem*-borazirconocenes **2** (Eqn [1]).[14]



1 2 [1]

R = n-butyl, 3-chloropropyl, cyclopentyl, 1-methylpropyl, t-butyl, 3-phenylpropyl, phenyl
Cp = cyclopentadienyl

These compounds proved to be unstable and difficult to characterize. We reasoned that the source of the instability may be the trialkylboron moiety. Boronates are more stable than trialkylboranes, since the lone-electron pairs on an oxygen atom can donate to the empty orbital of a boron atom. The corresponding *gem*-borazirconocenes should also be more stable. Thus, hydrozirconation of the alkenylboronic esters **3** afforded a clear yellow solution of the *gem*-borazirconocenes **4** (Eqn [2]).[15]

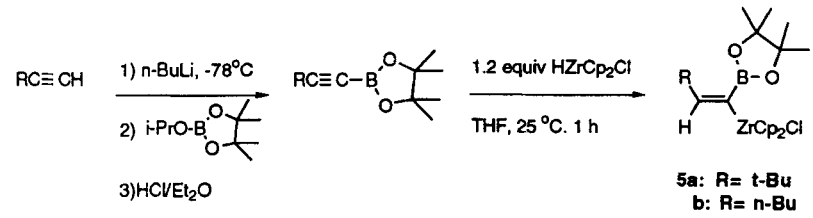


[2]

As expected, the compounds **4** 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.

We initially postulated that the driving force for placing Zr and B on the same carbon might be due to interactions between zirconium and oxygen or boron and chlorine atoms. However, the X-ray analysis of **4g** revealed that there are no intra- or inter-molecular interactions between zirconium, boron, chlorine or oxygen atoms.[16] Compound **4g** was also unambiguously characterized[16] by ^1H–^1H double quantum filtered COSY[17] and ^{13}C–^1H heteronuclear chemical shift correlation NMR[18] spectroscopy. The considerable differences in the chemical shifts of the diastereotopic Cp groups were found in both ^1H and ^{13}C NMR spectra. The NMR study accurately showed that the methine proton (δ 1.86 ppm) was attached to the α-carbon, and that two protons (δ 1.96, 1.39 ppm) 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.

We have also been investigating the synthesis and chemistry of a new class of *gem*-bimetalloalkenes based on dioxaborolanes and zirconocene.[19] the chemistry of C_{sp^2}–Zr and C_{sp^2}–B bonds differ considerably and should allow a sequential route to substituted alkenes. Furthermore, the cleavage of the C_{sp^2}–Zr and C_{sp^2}–B bonds generally occurs with retention of geometry.[1a,20] 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[11] and Knochel,[21] other mixed *gem*-bimetalloalkenes containing aluminum and



Scheme 1

zironium,[22] aluminum and hafnium,[23] gallium and zirconium,[24] tin and boron,[25] silicon and aluminum,[26] silicon and zirconium,[22] and silicon and tin,[27] have also been described.

As representatives of this class of compounds, we prepared one hindered and one nonhindered *gem*-borazirconocene alkene.[19] Their synthesis is outlined in Scheme 1. The 1-alkynyl dioxaborolanes were synthesized in high yield according to the method of Brown[28] by the reaction of 1-lithio acetylides with 2-isopropoxy-4,4,5,5,-tetramethyl-1,3,2-dioxaborolane[29] at −78 °C, followed by treatment with ethereal hydrogen chloride. Hydrozirconation of the 1-alkynyl dioxaborolanes with 1.2 equiv of zirconocene hydrochloride[30] afforded the desired products. In both cases the zirconium was placed on C1 (Scheme 1). The tert-butyl derivative **5a** was isolated as a pale greenish crystalline solid (81.5% yield).

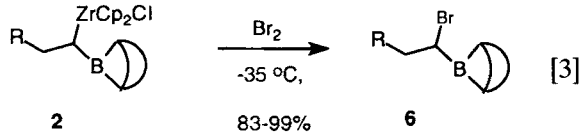
The X-ray analysis of **5a** confirmed the configuration of the four-coordinated zirconium complex, with two cyclopentadienyl rings, Cl and C_{sp^2} as four ligands. There are two molecules in the asymmetric part of the unit cell. Their configurations are identical, although the conformations differ in details. Compound **5a** was also unambiguously characterized by ^{1}H, ^{11}B, ^{13}C and ^{13}C–^{1}H heteronuclear chemical shift correlation NMR spectroscopy. The absence of CB_{pp}–π overlap in solution is indicated by the ^{11}B chemical shift ($\delta = 32.3$) since this is in the same region ($\delta = 31.1$) as the resonance for the corresponding boron–zirconium 1,1-dimetalloalkane, chlorobis(cyclopentadienyl) - [1 - (4,4,5,5 - tetra - methyl-1,3,2-dioxaborolane-2-yl)-3,3-dimethylbutyl]zirconium(IV).[16] Another interesting feature is the absence of the C-1 (the carbon bearing B and Zr) resonance in the ^{13}C NMR spectrum of a $CDCl_3$ solution. This is attributed to scalar ^{13}C spin–spin relaxation between (i) ^{13}C and ^{11}B, (ii) ^{13}C and ^{10}B, and (iii) ^{13}C and ^{91}Zr. Metals with abundant isotopes that have spin quantum numbers exceeding 1/2 can broaden ^{13}C resonances for directly attached (and sometimes remote) carbons in organometallic compounds.[31] In some cases where this scalar spin–spin relaxation occurs, ^{13}C signals may not be observed at all, such as for C-1 of **5a** in $CDCl_3$. However, in [D_8] THF at 25 °C, a resonance is visible for C-1 ($\delta = 187.8$, width at half-height $W_{1/2ht} = 145$ Hz) of **5a**. Upon lowering the temperature the linewidth of this resonance narrows ($W_{1/2ht} = 8$ Hz at −95 °C) but its shift is invariant. The magnitude of this shift is outside the normal range (80–145 ppm) for substituted alkenes not bonded to a metal through the alkenyl carbons. Since little difference is found for the ^{13}C chemical shifts of nonmetallated alkenyl carbons between *E* and *Z* isomers, it is instructive to compare these values in **5a** {δ(C-1) = 187.8, δ(C-2) = 120.5, [D_8]THF} and (*E*)-[1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)]-3,3-dimethylbutene [δ(C-1) = 112.1, δ(C-2) = 164, $CDCl_3$]. Here, substitution of H by $ZrCp_2Cl$ has deshielded C-1 by 75.7 ppm and shielded C-2 by 41.5 ppm. These effects are currently under investigation.

HALOGENATION

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 apparently more polar than the carbon–boron bond. As a result of this, 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,[32] while protonolysis[33] of organoboranes requires forcing conditions, typically at 120 °C. Therefore we reasoned that selective cleavage of the carbon–zirconium bond of borazirconium compounds should be readily attainable. From a mechanistic viewpoint, cleavage of the carbon–metal bond by halogenation may proceed with either retention

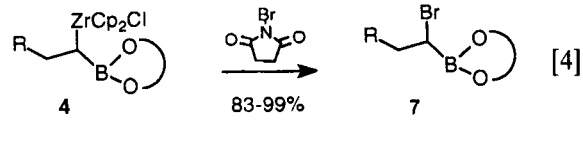
of configuration at carbon, or inversion, depending on the structures and reaction conditions.[34] Halogenation of organozirconium compounds was reported to proceed with retention of configuration.[35] On the other hand, the carbon–boron bond in organoboranes is quite inert to halogens.[36] Base is essential for the halogenolysis of organoboranes. The reaction proceeds by an S_E2 mechanism.[37] Since halogenolysis of organozirconium compounds is a very facile process, without any need of base, the carbon–boron bond in borazirconocene bimetallics should not be affected under the conditions in which the carbon–zirconium bond is cleaved.

The expected products, α-haloboranes, are generally stable. Although the boron–zirconium bimetallics **2** based on trialkylboranes are not stable, selective cleavage of their carbon–zirconium bonds did afford α-bromoboranes **6** (Eqn [3]).



2 83-99% **6** [3]

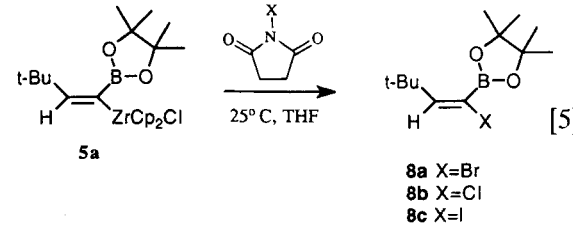
The use of *N*-bromosuccinimide resulted in very complex mixtures without the expected α-haloboranes. Apparently, the succinimide moiety may have acted as a base, and caused various side reactions.[38–40] However, α-haloboronic esters are much more stable than α-halotrialkylboranes. Our next effort was thus to investigate the halogenation of borazirconocene bimetallics **4** based on boronic esters. As expected, the reaction occurred very smoothly, affording α-bromoboronic esters **7** (Eqn [4]).[41]



4 83-99% **7** [4]

It should be pointed out that in contrast 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.[42] Therefore, the reaction of **4** 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-iodo-boronic esters with *N*-chlorosuccinimide and *N*-iodosuccinimide, respectively. α-Haloboronic esters have also been obtained by hydrogen halide additions to alkenyl boronic esters or borane additions to 1-alkenyl halides. However, the regioselectivities of these additions are not always satisfactory. For instance, the hydroboration of 1-chloro-1-butene with BH_3 gave an 85:15 mixture of α- and β-addition of the boron moiety.[43] To our knowledge, regioselective additions to vinyl halides by dibromoborane or catecholborane, which might provide convenient conversions to α-haloboronic esters, has not been reported, whereas dipropyl vinylboronate with hydrogen iodide gave a 60:40 ratio of α- and β-iodoboronic esters.[44] In contrast to these results, our novel method for preparation of α-haloboronic esters from alkenyl boronic esters has obvious advantages which include regiospecific selectivity, and conversion to α-chloro-, α-bromo- or α-iodo-boronic esters by corresponding *N*-halosuccinimides in a one-pot reaction. In addition to the above results, we found that the cleavage of the carbon–zirconium bond in **4a** by bromine in dichloromethane or iodine (neat) also worked well.

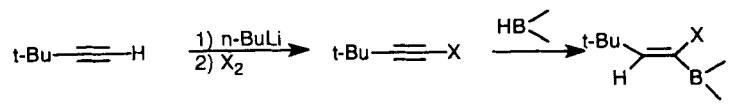
Vinylboronates generally are less reactive than vinylzirconocenes towards various electrophiles and therefore selective reaction of the latter should be possible. We have found that selective cleavage of the carbon–zirconium bond in **5a** by N-halosuccinimides provides (α-haloalkenyl)boronic esters **8** in excellent chemical yields and with complete regioselectivity (Eqn [5]).[19]



5a [5]

8a X=Br
8b X=Cl
8c X=I

This method provides a very useful class of boron intermediates for organic synthesis.[38] Moreover, using our method we can access *E*-(α-haloalkenyl)boronic esters. Consequently, our approach complements hydroboration of 1-haloalkynes that provides only the *Z*-isomer (Scheme 2).[45]



Scheme 2

DIASTEREOSELECTIVE HYDROZIRCONATION

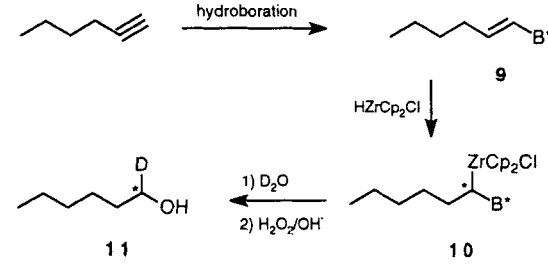
Although asymmetric synthesis is one of most interesting and challenging problems for organic chemists, no attention has been paid to asymmetric hydrozirconation. In our continuing studies on the synthesis and utility of *gem*-borazirconocenes, we decided to explore asymmetric hydrozirconation. Alkenylboron compounds, the substrates for hydrozirconation, have the obvious advantage of much latitude in using boron ligands. A large variety of optically active monoterpenes, 1,2-diols and amino alcohols are readily available, and 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. We anticipated a high degree of diastereoselectivity and therefore optical induction, based on the following considerations.

(1) The stereochemistry of protonolysis or deuterolysis of alkenylzirconium compounds has been reported to occur with retention of configuration.[4b,20] Electrophilic carbon–zirconium bond cleavage in alkylzirconium compounds has also been shown to occur with retention of the configuration at carbon.[20,35] It has been suggested that the cleavage process involves a closed transition state. Therefore, in the process of deuterolysis, the oxygen atom in deuterium oxide coordinates with the zirconium atom via its vacant low-lying valence orbital, and the deuterium facilitates frontside attack on the carbon–zirconium bond.

(2) Oxidation of organoboranes with hydrogen peroxide in basic conditions is believed to proceed with retention of the stereochemistry of the migrating group. Peroxide coordinates with the boron atom via its empty *p* orbital, followed by substituent migration from the boron to the oxygen atom. Essentially organoboranes can be converted into the corresponding alcohols with retention of configuration.[1]

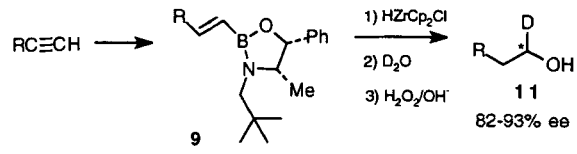
Therefore, treatment of the optically active *gem*-borazirconocene alkanes with deuterium oxide followed by alkaline oxidation should afford the corresponding optically active 1-deuterio primary alcohols. The enantiomeric excess of the resulting primary alcohols would represent the diastereoselectivity of the asymmetric hydrozirconation (Scheme 3).

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 (**9**) provided optically active 1,1-bimetallics, **10**. Selective cleavage of the carbon–zirconium bond in **10** with deuterium oxide, followed by alkaline oxidation of the carbon–boron bond, afforded the optically active 1-deuterio primary alcohols, **11**. Enantiometric excess (ee) was determined by ^{1}H-NMR analysis using an inverse gated decoupling sequence[46] on the MTPA esters. Monoterpene derivatives of alkenylboranes **9** did not undergo complete hydrozirconation. They gave low chemical yields and low incorporation of deuterium. The 1,2-diol and 1,2-amino alcohol derivatives of **9** hydrozirconated completely and provided alcohols in relatively high chemical yields and with high deuterium incorporation. Both classes of compounds did not give high diastereoselectivity. However, the alkenyl oxazaborolidines, in addition to providing products in high chemical yields and with excellent incorporation of deuterium, also gave the best diastereoselectivity. The (1*R*,2*S*)-ephedrine derivatives were superior to the diastereometric (1*R*,2*R*)-pseudoephedrine derivatives. The *N*-neopentyl



B*=boron with optically active ligand

Scheme 3



R: n-butyl, 3-chloropropyl, cyclopentyl, 3-phenylpropyl, t-butyl.

Scheme 4

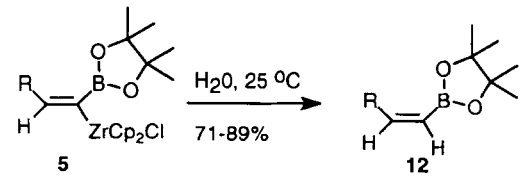
derivative was particularly outstanding (Scheme 4).[47]

The absolute configuration of optically active 1-deuterio-1-hexanol has been reported.[48] Thus by analyzing this known optically active alcohol, the absolute configuration of the 1,1-bimetallic reagent from which it was derived could be determined. Based on the data we obtained ($[\alpha]_D^{29} + 0.42$; $c = 34.0$, hexanes), the 1,1-bimetallic derived from 1-hexyne was assigned structure **10a** (Scheme 5).

Although the mechanism of this new type of asymmetric reaction is not yet understood, the assignment of structure **10a** is consistent with the approach of $HZrCp_2Cl$ from the less-hindered face of the double bond. The pseudoephedrine-derived reagents, whose double bond is more symmetrically disposed, gave lower selectivity in the hydrozirconation step.

HYDROLYSIS

As an example of selective reactivity of *gem*-borazirconocene alkenes, we examined their hydrolysis. The carbon–zirconium bond is more reactive than the carbon–boron bond towards various electrophiles, and we therefore expected hydrolysis to occur preferentially with cleavage of the former bond. Since hydrolysis of alkenylzirconocenes is known to proceed with retention of configuration,[2] a direct utility of **5** was the preparation of (*Z*)-1-alkenylboronates **12** (Eqn [6]).[49]

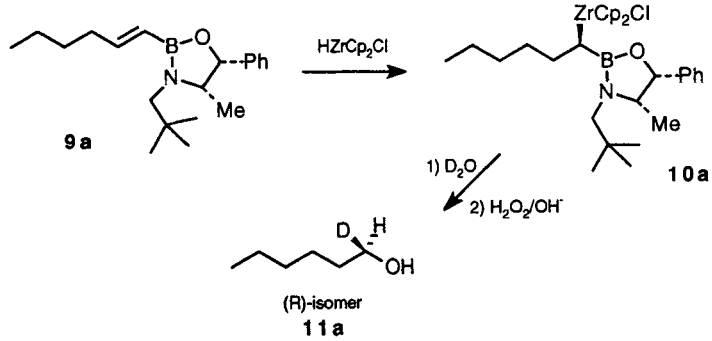


[6]

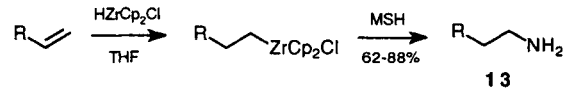
Though the *gem*-dimetalloalkenes can be isolated, in the present case it is not necessary. The desired (*Z*)-1-alkenylboronates can be obtained in a one-pot procedure by hydrozirconation followed by hydrolysis with excess H_2O. The reaction sequence is operationally simple and is compatible with various functional groups such as halides, acetals, silanes and silyloxy protecting groups.[49]

AMINATION

The purpose of this project was to find appropriate aminating reagents which could 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.[50] Previous routes[50a] to these compounds rely on hydroboration, homologation with chloromethyl-lithium, and coupling with lithium hexamethyldisilylamide [$LiN(SiMe_3)_2$]. Our newly developed *gem*-borazirconocene alkanes have the potential to provide a convenient and efficient alternative



Scheme 5



Scheme 6

approach to α-aminoboronic esters via selective cleavage of the carbon–zirconium bond with proper aminating reagents. In addition, amination of organozirconium compounds had never been explored. Thus, this study could also expand the scope of zirconium chemistry.

α-Aminoboronic esters have been synthesized principally according to Matteson's method.[50a] More recently, another access to α-aminoboronic esters has been reported,[51] based on lithiation and catalytic hydrogenation. This method, is limited however, to the preparation of the pyrrole-related compounds.

Since the conversion of organozirconium compounds to amines has never been reported, we initiated a program to explore the amination of organozirconocene chlorides. Of the various electrophilic aminating reagents available for reaction with organometallic compounds, we chose to try the *O*-sulfonylhydroxylamines. They are readily available from easily accessible starting materials in a number of high-yielding steps.[52,53] One reagent, *O*-mesitylsulfonyl hydroxylamine (MSH), has been shown to be superior to others in terms of solubility in organic solvents and reactivity as an electrophilic aminating reagent.[54] Our investigation of amination involved hydrozirconation of an alkene followed by reaction of the resulting alkylzirconocene chloride with MSH (Scheme 6).[35]

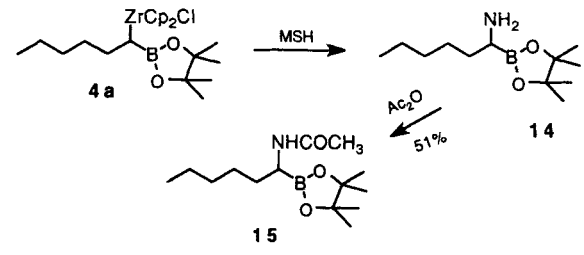
Styrene, however, gave two products (1-phenyl-1-ethylamine and 2-phenyl-1-ethylamine) in a 1:3 ratio,[55] which indicated that the hydrozirconation was not completely regioselective.[56] Since it is well known that hydrozirconation of trisubstituted alkenes places zirconium on the least hindered carbon of the chain by a process involving zirconium migration, this class of alkenes was not investigated.[2] 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 allylic rearrangement. Examination of its ^{1}H NMR spectrum revealed two nonequivalent methyl groups on a double bond. Amination 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 $RZrCp_2Cl$ transfers, and thus it is more efficient than the reactions involving R_3B reagents where one group is lost, or those involving R_2Zn reagents where yields are low and mixtures are usually obtained.[57]

After we successfully achieved amination of the alkylzirconocene chloride, we extended the reaction to borazirconocene 1,1-alkanes. In fact, amination of *gem*-borazirconocene alkanes with MSH has proven to be a facile process.[58] Thus, when MSH was added to the *gem*-bimetallics in THF at ambient temperature, the amination was completed in 20 min (Scheme 7).

Compound **14** was difficult to purify, and unstable, as described in the literature.[50] Therefore **14** was not isolated, but rather treated to yield its stable derivative **15**, pinacol 1-acetamido-1-hexylboronate. However, acylated derivative **15** could not be purified by column chromatography since it was destroyed by silica gel, and also partially decomposed on alumina. Fortunately, we found that it dissolves in basic aqueous solution (pH > 11), and can be extracted into ether when the pH of the aqueous layer is 5–6. Finally, pure **15** was obtained by repeated washing with weak acids and bases. It should be mentioned here that strong acidic solution, which also dissolves compound **14**, 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 be very useful as an alternative access to α-aminoboronic esters, an important class of inhibitors of serine proteases.

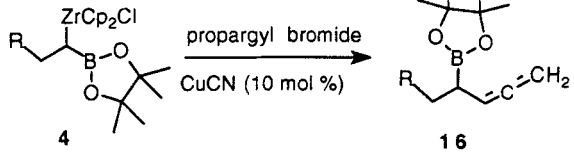
CARBON–CARBON BOND-FORMING REACTIONS

Since considerable steric crowding around the zirconium atom in organozirconium compounds decreases its nucleophilicity, direct carbon–carbon bond-forming reactions of organozirconocenes are limited to carbon monoxide insertions.[4] However, in the presence of catalytic



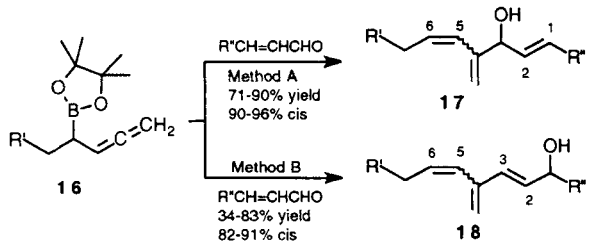
Scheme 7

amounts of other metals, organozirconocene compounds readily undergo carbon–carbon bond-forming reactions, including cross-coupling with organic halides,[59,60] alkene and alkyne insertion,[61] addition of cationic organozirconium complexes to oxiranes[62] and aldehydes[63] and conjugate addition to α,β-unsaturated ketones.[64,65] The use of organozirconium compounds as carbanion equivalents is greatly facilitated by transmetallations to the more reactive aluminum,[61] copper,[65] nickel,[59] and palladium[60] derivatives. Especially, copper-catalyzed carbon–carbon bond-forming reactions of alkyl- or alkenylzirconocene compounds have been intensively studied, and found considerable application in organic synthesis.[66] For carbon–carbon bond formation of *gem*-borazirconocene alkanes **4** we selected propargyl bromide as the electrophile since its cross-coupling with **4** provides access to α-allenic boronic esters, a new class of interesting boron compounds. Also, based on the literature, copper(I) was chosen as the catalyst for the carbon–carbon bond formation. α-Allenic boronic esters **16** were isolated in good yields.[67] No acetylenic by-products were detected. Presumably, the reaction proceeds by way of zirconium–copper exchange to give an organocuprate species which is the actual participant in the S_N2' reaction pathway.[68] The assignment of the allenic structure is in complete agreement with ^1H NMR and ^{13}C NMR chemical shifts reported in the literature.[69] The reaction works well for both hindered and nonhindered **4** (Eqn [7]).



[7]

α-Allenic boronic esters **16** are also allylboranes. Other allylboranes were found to undergo a very facile reaction with aldehydes to give homoallylic alcohols.[70] It was therefore natural to react compounds **16** with aldehydes. Addition of an α,β-unsaturated aldehyde to the isolated boryl allene affords **17** (Scheme 8).[67] Allylboration with **16** works exceedingly well for aromatic aldehydes, except for the reaction with *m*-hydroxybenzaldehyde. The low yield in the latter case may be due to the known sensitivity of

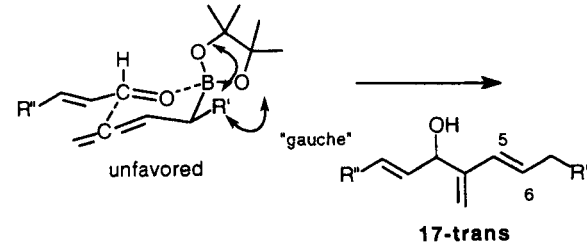


Scheme 8 *Method A*: after coupling **4** with propargyl bromide, the α-allenic boronates **16** were isolated and reacted with aldehydes. *Method B*: aldehydes were added *in situ* to the reaction of **4** and propargyl bromide, without isolating **16**.

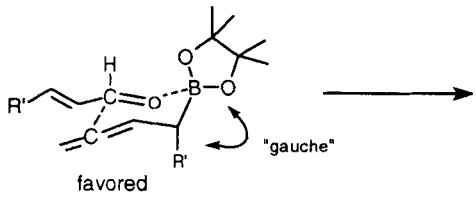
allylboranes to protic sources.[1c] Not only is the reaction slower for aliphatic aldehydes, but the yields are somewhat lower too. The predominant isomer of the newly formed double bond in all cases is the (*Z*)-isomer.

Addition of an α,β-unsaturated aldehyde to **16** leads to trienes **17** or **18**, depending on the reaction conditions (Scheme 8). The geometry of the newly formed double bond (C5–C6) in both **17** and **18** was predominantly *Z*. Two types of trienes were obtained, depending on the reaction conditions. Method A involves the reaction of isolated α-allenic boronates **16** with aldehydes under salt-free conditions, and provided trienes **17**. In method B, the α-allenic boronates were not isolated but prepared *in situ* and allowed to react with aldehydes to give the rearranged trienes **18**. The yields in method A were much better than those of method B.

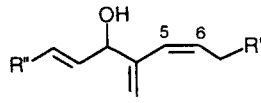
The assignment of structure **17** is again consistent with the postulated mechanism of the reaction.[71] The transition state leading to *trans*-(C5–C6) **17** places the R′ group in an equatorial position. Two unfavorable *gauche* interactions between the equatorial substituent and the bulky boron ring are introduced[72] (Eqn [8]). However, in the transition state leading to *cis*-**17**, with the R′ group in the axial position, only one *gauche* interaction is present. The latter is favored and good *cis* selectivity (9:1) is observed.



[8]



[9]

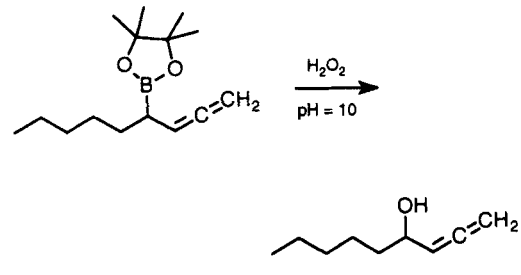


17-cis

The geometry of the newly formed double bond in **17** (C5–C6) was readily apparent from the ^{1}H NMR spectra. Since both the *cis* and *trans* diastereomers were detected in the reaction mixture, the vicinal coupling constants for each isomer could be determined after appropriate decoupling experiments. The *cis*-**17** isomer was assigned on the basis of its smaller coupling constant (*cis*, ~11.8 Hz; *trans*, ~17.1 Hz).[73] The C5–C6 double bond in **18** was assigned in an analogous manner. The *trans* geometry of the double bond of unsaturated aldehydes used in the allylboration was retained in the products **17** (C1–C2) and **18** (C2–C3).

We postulate that compounds **18** are obtained by allylic rearrangement of **17** facilitated by the presence of the various salts acting as Lewis acids. The mechanism of the rearrangement is not simple, however. When compounds **17** were treated with Lewis acids, i.e. $ZnCl_2$, complex reaction mixtures were observed, including **18**.

α-Allenic boronic esters **16** can be easily converted to α-allenic alcohols (useful intermediates in organic transformations[74] and constituents of numerous natural products[75] and biologically active molecules[76]) by controlled alkaline oxidation (Eqn [10]).

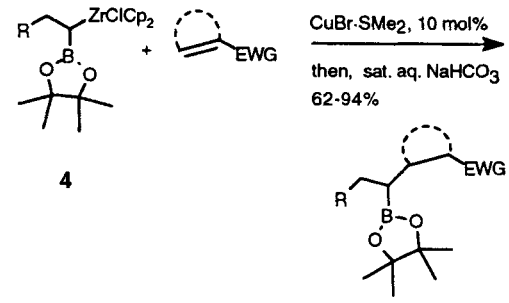


[10]

82%

The conjugate addition of zirconocene alkenes to enones in the presence of copper or nickel salts was first reported by Schwartz.[77] Bimetallics offer the possibility of multiple transformations. Specifically, bimetallics in which the reactivities of the carbon–metal bonds are sufficiently different make possible two sequential transformations, thereby greatly extending the utility of these kinds of reagents. In the case of zirconocenes, Lipshutz has prepared *gem*-stannazirconocene alkenes and reacted them with α,β-unsaturated enones.[78]

In our case, reaction of **4** (R = Me, nBu, 3-chloropropyl) with various Michael acceptors in the presence of $CuBr \cdot SMe_2$ (10 mol%) gave exclusively products of 1,4-addition, **19** (Eqn [11]).[79]

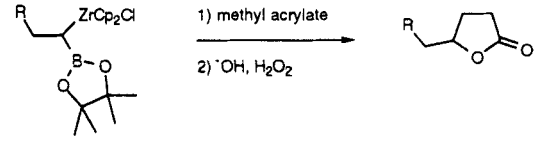


4

[11]

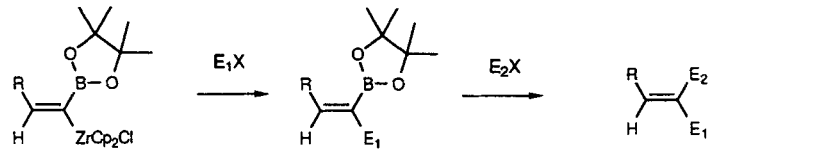
19

In each case it is the C–Zr bond that reacts to give, after aqueous work-up, the 1,4-addition product. The C–B bond is stable under the conditions of the reaction. Suitable substrates are α,β-unsaturated aldehydes, esters, ketones and nitriles. In general the yields are excellent. The somewhat lower yields with acrylonitrile and methyl acrylate are possibly due to competing polymerization reactions. Many of these boron-containing adducts would be very difficult or impossible to synthesize by other methods. In the case of the addition to methyl acrylate, oxidation of **4** followed by cyclization gave lactone **20** (Eqn [12]).



[12]

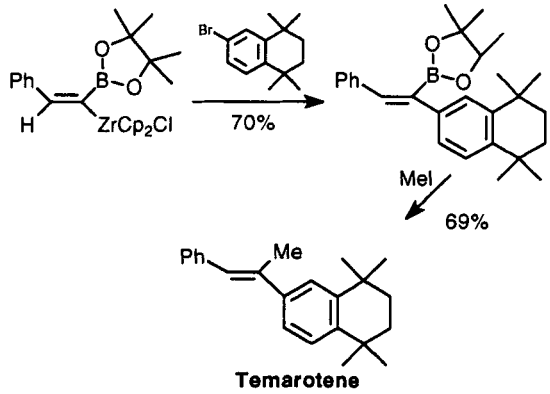
4 **20**



Scheme 9

Compounds **5** react with initial cleavage of the C–Zr bond, and undergo carbon–carbon bond formation with acid chlorides, allyl halides, α,β-unsaturated ketones, and vinyl and aryl halides [in the presence of copper(I) or palladium(0) catalysts] to give coupling products **21** in high yield. It is then possible to couple the C–B bond with a different alkyl, vinyl or aryl halide to provide **22**. In this manner it is possible to prepare isomeric alkenes from the same starting material by reversing the sequence of electrophiles. Thus reaction of **5b** (R = nBu) with 2-bromopropene followed by coupling with phenyl iodide provided **22a** (E_1 = propenyl, E_2 = phenyl). The same starting material, **5b** (R = nBu), leads to the isomeric product **22b** (E_1 = phenyl, E_2 = propenyl) by reversing the sequence of addition of electrophiles (Scheme 9)

Temarotene[80] is a retinoid[81] and is of interest because it shows no sign of hypervitaminosis A and it is not teratogenic, presumably due to lack of a polar group.[82] The published synthesis of temarotene-type compounds is long and leads to mixtures of isomers from which the desired product is isolated.[83,84] The synthesis of temarotene by our methodology is straightforward (Scheme 10).[85]



Scheme 10

CONCLUSION

gem-Borazirconocene alkanes and alkenes are unique reagents for preparing new classes of bimetallics. Sequential reactions of the Zr–C and the B–C bonds makes new classes of organoboranes available. Investigation of the chemistry of these interesting compounds is continuing, especially in the area of catalysis, selective reactions and coordination chemistry. Future publications are forthcoming.

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