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Tetrahedron
Tetrahedron 60 (2004) 1269–1279

Tetrahedron report number 668

Selective carbon–carbon bond formations with alkenylzirconocenes

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Received 10 November 2003

Contents

1. Introduction

The efficient assembly of complex molecules requires methods that link functionalized segments by selective carbon–carbon bond formations. In this context, the chemistry of organozirconocenes has made great advances since the preparation of the first zirconocene, Cp_2ZrBr_2 in 1953.[1–3] This Report summarizes recent developments of the use of alkenylzirconocene complexes in organic synthesis in an attempt to highlight the continued potential for new reaction discovery that transmetalation reactions hold.

2. Preparation of alkenylzirconocenes

The major, but not sole, access to alkenylzirconocene intermediates is through the hydrozirconation of alkynes with the Schwartz reagent, $Cp_2Zr(H)Cl$.[4a] Kinetically and thermodynamically favored *syn*-addition of this complex onto a terminal or internal alkyne followed by in situ treatment with electrophilic reagents affords di- or trisubstituted *trans*-alkenes in high stereochemical purity.[4b] For unsymmetrical internal alkynes, the process can lead to mixtures with preference of the isomer derived from a geminal juxtaposition of Zr-species and the sterically less demanding substituent.[4c] Excess of $Cp_2Zr(H)Cl$ and moderate heating are known to isomerize the intermediate adducts and improve the regioselectivity in most cases.[4d] In general, the functional group compatibility of the process is limited by the oxophilic, hard Lewis acid character of the Schwartz reagent. Epoxides, isonitriles, aldehydes, ketones, nitriles, amides, enones, and reactive esters can be reduced competitively with the alkyne moiety and should be avoided. Among the tolerated functional groups are silyl, *t*-butyl or even benzyl esters and ethers, carbamates, sulfonamides, and most simple ethers as well as alkenes if 1 equiv. or less of $Cp_2Zr(H)Cl$ is utilized.[5]

An alternative, rapidly evolving access to alkenylzirconocene complexes is offered by the formal insertion of $Cp_2Zr(II)$ into sp^2 carbon–halogen as well as carbon–sulfur bonds;[6] the functional group tolerance and synthetic scope in C,C-bond formations of this process remains to be fully elucidated.

3. Zirconium→Zn transmetalations

The use of $ZnCl_2$ for acceleration of Pd- and Ni-catalyzed cross-coupling of alkenyl aluminum and zirconium compounds with alkenyl, aryl or alkynyl halides was first

Keywords: Alkenylzirconocenes; Transmetalation; Organic synthesis.
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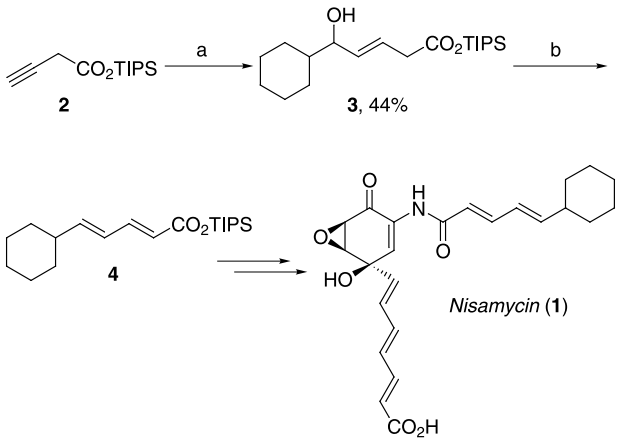
0040–4020/$ - see front matter
doi:10.1016/j.tet.2003.12.018

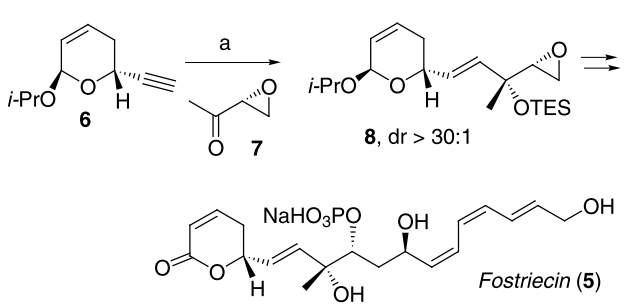
reported by Negishi et al. (vide infra).[7] Wipf and Xu[8] observed that the transmetalation of alkenylzirconocene to the corresponding organozinc compounds occurred rapidly and at low temperatures in the presence of dimethyl- or diethylzinc. Subsequent addition of aldehydes to the reaction mixture afforded allylic alcohols in high yields. In the presence of chiral amino alcohol or amino thiol catalysts, high enantioselectivities were obtained.[8,9]

The high diastereo- and enantioselectivity of the C,C-bond formation contributes greatly to the synthetic versatility of the Zr→Zn transmetalation process.[10] Several natural product total syntheses have used this methodology as a key step in the construction of allylic alcohol moieties, and it has also been applied to the preparation of polyene segments in (+)-curacin A and in the manumycin family.[11,12] Wipf and Coish reported the synthesis of (±)-nisamycin **1**[11c] from alkyne **2**, which was hydrozirconated, transmetalated to the corresponding alkenylzinc intermediate and added to aldehyde, affording **3** in 44% yield (Scheme 1). The newly formed allylic alcohol **3** was subsequently dehydrated to produce the (*E*)-diene **4**.



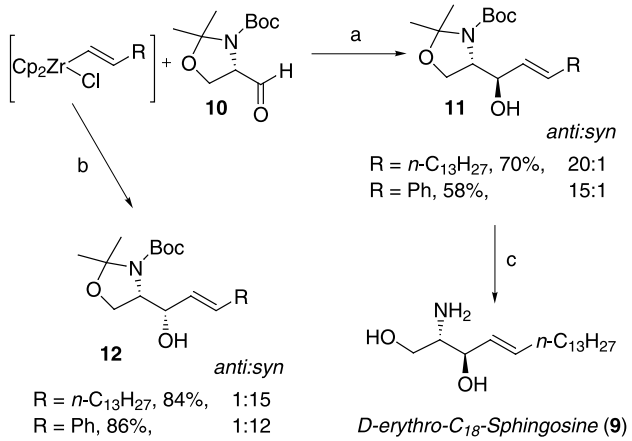
Scheme 1. Dehydration of the allylic alcohol moiety for the construction of the (*E*)-diene side chain of nisamycin: (a) Cp_2ZrHCl, Me_2Zn, *c*-$C_6H_{11}CHO$; (b) (i) CF_3CO-imidazole, THF, pyr., −10 to 10 °C, 1 h; (ii) *i*-Pr_2NEt, rt, 5 h.

An interesting diastereoselective version of the Zr→Zn transmetalation was reported by Jacobsen and Chavez in the synthesis of fostriecin **5** (Scheme 2).[13] After hydrozirconation of alkyne **6**, the alkenylzinc intermediate added diastereoselectively in a 1,2-fashion to the chiral epoxyketone **7**. Protection of the tertiary alcohol provided **8** in 45% yield and >30:1 diastereoselectivity.



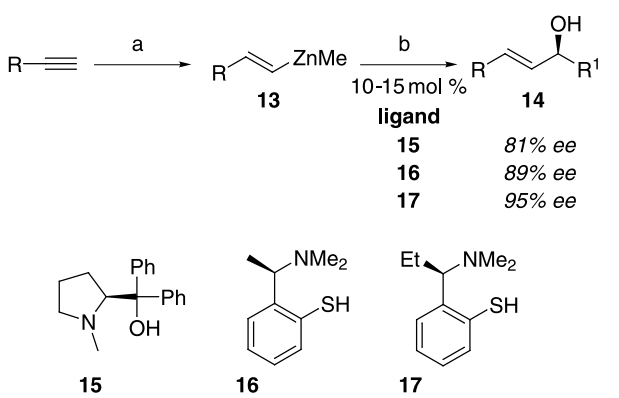
Scheme 2. Diastereoselective 1,2-addition to a chiral epoxyketone: (a) (i) Cp_2ZrHCl, CH_2Cl_2; (ii) Me_2Zn; (iii) **7**; (iv) TES–Cl, imidazole, DMF.

An efficient stereodivergent synthesis of D-*erythro*-C_{18}-sphingosine **9** has been reported by Murakami and Furusawa, who explored the enantioselective addition of alkenylzirconocenes to the L-serine-derived chiral aldehyde **10**.[14] Additives such as Ag[15] and Zn salts were used as catalysts, and the combination of Wipf's[8] and Srebnik's[16] Zr→Zn transmetalation conditions was found to allow a tuning of *anti*/*syn*-selectivity. In fact, the *anti*-selective formation of product **11** in THF at room temperature was due to the presence of catalytic zinc dibromide.[16] Mild acidic hydrolysis afforded the sphingosine **9**. The use of an equimolar amount of Et_2Zn in CH_2Cl_2,[8] at a temperature range from −30 to 0 °C, led to the formation of the *syn*-addition products **12** (Scheme 3).



Scheme 3. Reaction conditions determine the diastereoselectivity in the synthesis of D-*erythro*-C_{18}-sphingosine: (a) $ZnBr_2$, (25–50 mol%), THF, rt; (b) **10**, Et_2Zn, CH_2Cl_2, −30–0 °C; (c) aq. AcOH, 50 °C.

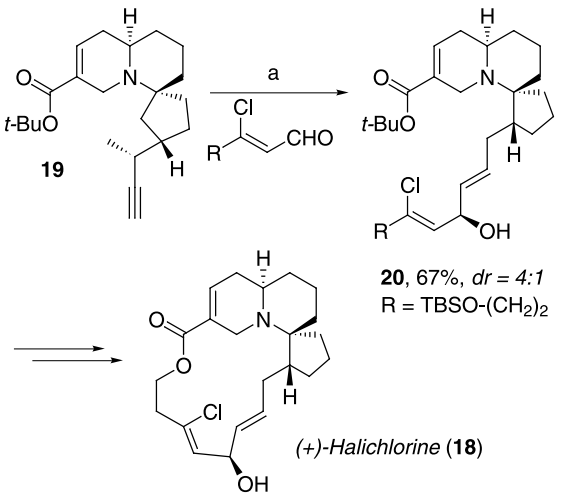
Despite its versatility, the enantioselective protocol for the Zr→Zn transmetalation–aldehyde addition is still being refined. In their first report on this subject, Wipf and Xu did not obtain a satisfactory enantiomeric excess of allylic alcohols when 8 mol% of ligand **15** were used (Scheme 4).[8] The main reason for the low ee of 38% was attributed to the presence of stoichiometric zirconocene complex catalyzing the formation of racemic product. The competitive aldehyde



Scheme 4. Chiral ligand effects in the catalytic asymmetric addition to aldehydes: (a) (i) Cp_2ZrHCl, CH_2Cl_2, 22 °C; (ii) Me_2Zn, −78 °C, toluene; (b) R^1CHO, −30 °C.

addition kinetics are a result of the presence of two Lewis-acidic metals in the Zr→Zn transmetalation mixture. In subsequent work, Wipf and co-workers achieved significant ee improvements by the use of larger amounts of ligand **15** and lower reaction temperatures.[9,17] In addition, amino thiols proved to be superior ligands, most likely due to the higher thiophilicity of zinc versus zirconium (Scheme 4).[9] Treatment of organozinc **13** with 10 mol% of ligand **16** followed by warming from −78 to −30 °C afforded allylic alcohol **14** in 89% ee. Moreover, amino thiol **17** afforded addition product **14** in 95% ee.

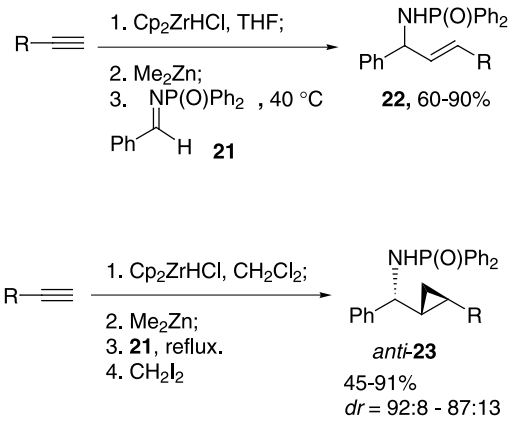
The enantioselective procedure using 10 mol% of ligand **15** was applied by Danishefsky et al. at a late stage of the total synthesis of (+)-halichlorine (**18**, Scheme 5),[18] when the advanced intermediate **19** proved to be too sensitive for classical Horner–Wadsworth–Emmons chain extension conditions.



Scheme 5. Asymmetric Zr→Zn chemistry in a key step of the total synthesis of halichlorine: (a) (i) Cp_2ZrHCl, CH_2Cl_2; (ii) Me_2Zn, heptane; (iii) 10 mol% of ligand **15**, −30 °C.

Aldimines are less reactive towards nucleophiles than carbonyl compounds due to their diminished double bond polarization and softer Lewis basicity at the nitrogen atom. However, with proper activation, organometallic reagents can readily be added in a 1,2-fashion. Stimulated by the results obtained in the use of Zr→Zn transmetalation conditions for allylic alcohol formation,[17] Wipf et al. investigated the corresponding addition to aldimines.[19] After hydrozirconation of 1-hexyne in CH_2Cl_2, (R=C_4H_9, Scheme 6), in situ transmetalation with Me_2Zn and addition to *N*-diphenylphosphinoylimine **21** produced the expected allylic amine **22**, but also revealed an efficient three-component condensation that furnished the *anti*-*C*-cyclopropylalkylamine **23** in 58% yield, after heating for 16 h. A switch of the reaction solvent from CH_2Cl_2 to THF afforded the corresponding allylic amide **22** as the sole product.

Further reaction optimization revealed the scope and provided support for a reaction mechanism in these solvent-dependent conversions.[2k,20] The production of **22** was improved when THF was substituted with toluene at room temperature. Functional group tolerance at the alkyne

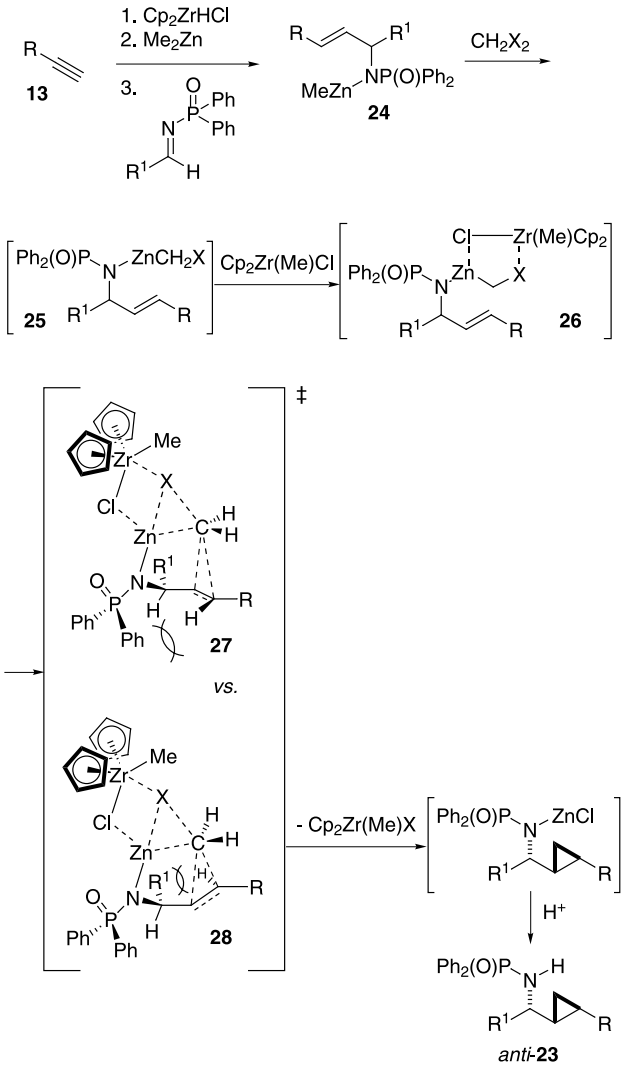


Scheme 6. New solvent-dependent routes for allylic amine and cyclopropylalkylamine preparation.

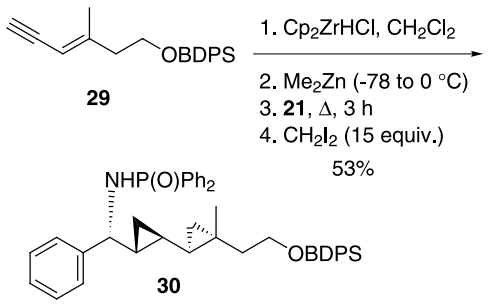
moiety included silyl ethers and silyl esters, sulfonamides and carbamates. Electron-donating aryl substituents on the imine, though, significantly reduced the amount of the isolated amide. Sterically very hindered alkynes proved to be unreactive towards addition, although internal alkynes such as 3-hexyne worked well. It is also noteworthy that *N*-tosylalkylimines and *N*-tosylbenzaldimines were converted to the allylic sulfonamides.

The scope for the cyclopropanation pathway is nearly the same as for the allylic amine formation, except that both electron-donating and electron-deficient substrates worked well and that the presence of bulky substituents on the imine aryl group reduced the diastereoselectivity. The three-component condensation represents the first example of a preparative cyclopropanation reaction in which CH_2Cl_2 serves as the carbene source; the activation of C–Cl bonds poses a considerable kinetic and thermodynamic barrier that is apparently overcome by the concerted action of alkyl zinc and zirconocene species. As expected, addition of CH_2Br_2 and CH_2I_2 further accelerated the cyclopropanation process, and in the general protocol the conversion was completed by adding upto 5 equiv. of CH_2I_2 at room temperature subsequent to the addition of **21** (Scheme 6).

The proposed mechanism for this reaction was based on experimental observations such as the formation of the metalated aldimine addition product as a precursor to the cyclopropane (Scheme 7). In general, *syn*-diastereomers are formed by directed Simmons–Smith-type cyclopropanations of allylic alcohols;[21] in contrast, the *anti*-selectivity confirmed by X-ray structure analysis of *C*-cyclopropylalkylamines **23** was remarkable, and the presence of zirconocene complex proved to be crucial for an efficient cyclopropanation and high *anti*-diastereomeric ratios. It was proposed that the zinc species in the N-metalated allylic amide intermediate **24**, derived from the addition of the Zr→Zn transmetalation intermediate **13** to the aldimine, inserted into a dihalomethane carbon–halogen bond to provide intermediate **25**, a process that is most likely favorably assisted by the nitrogen ligand on the zinc, the zirconocene complex or both.[21b,22a] Subsequently, the $Cp_2Zr(Me)Cl$ complex, originating from the transmetalation step, could act as a Lewis acid activator for zinc

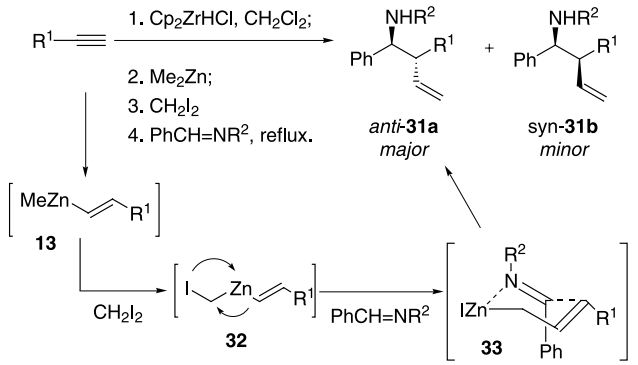


Scheme 7. Mechanistic hypothesis for *C*-cyclopropylalkylamine formation in the Zr→Zn transmetalation–imine addition.



Scheme 8. One-pot conversion of enynes to dicyclopropylalkylamines.

In yet another variant of the three-component coupling of aldimines, diiodomethane and alkenylzirconocenes, Wipf and Kendall observed that the sequence of addition of reactants strongly influences product formation.[23a] When CH_2I_2 was added prior to the imine, the homoallylic amine **31** was obtained in good yield favoring the *anti*-isomer **31a** (Scheme 9).



Scheme 9. Homoallylic amines **31** formed via a 1,2-shift of the organozinc intermediate.

carbenoid formation through complexation of the halomethyl zinc halogen, as represented in complex **26**. *syn*- and *anti*-Product formation can be derived from the two possible transition states **27** and **28**, respectively. The former minimizes 1,3-allylic strain, but suffers from a large steric interaction between the bulky *N*-diphenylphosphinoyl group and the alkene moiety. In contrast, the favored transition state **28** mimimizes diphenylphosphinoyl–alkene interactions, while at the same time suffering from 1,3-allylic strain. The relative configuration of the major product, *anti*-**23**, is in agreement with the trends observed for the cyclopropanation of allylic ethers.

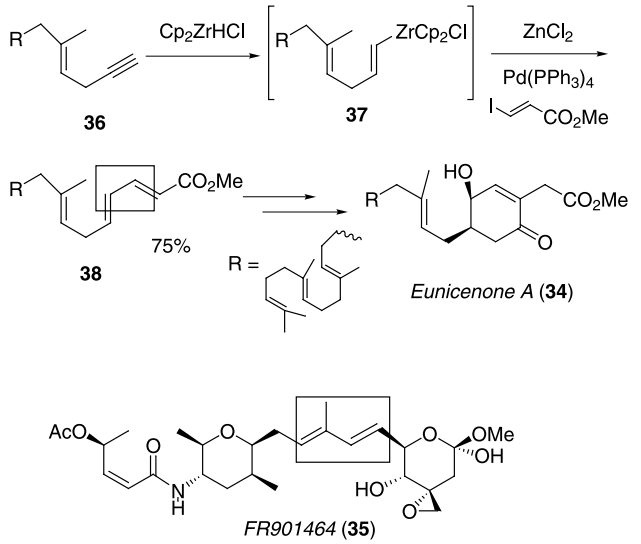
An important extension of this new methodology was accomplished by the conversion of enyne **29** to dicyclopropane **30** (Scheme 8).[20] A single diastereomer was observed and five new C,C-bonds were formed in this cascade reaction. Multistep pathways are traditionally required to accomplish the formation of products of this type. The structure assignment was again based on an X-ray analysis of a desilylated derivative of **30**.

The proposed mechanism was rationalized in terms of a [1,2]-shift in **32**, which is derived from the reaction of **13** with CH_2I_2. 'Homologation' of a metal carbenoid into an alkenyl–metal bond is a known but still mostly unexplored process.[24] The resulting allylic zinc species adds to the aldimine in the chair-like transition state **33** which explains the *anti*-configuration preference. This mechanism is in agreement with the experimental observation that internal alkynes or bulky imine substituents erode the *anti*-selectivity, probably due to steric interactions between the pseudoaxial substituents.

Although many synthetic and mechanistic aspects of the Zr→Zn transmetalation chemistry still need to be further elucidated, the formation of multiple reaction products with different carbon connectivities and cyclopropane rings depending on rather subtle aspects of solvent composition and order of addition is intriguing. As a recent communication on the formation of bicyclo[1.1.0]butanes and *C*,*C*-dicyclopropylmethylamines demonstrates,[23b] the potential of this methodology to serve as a novel, direct route to structurally diverse compounds is far from being exhausted.

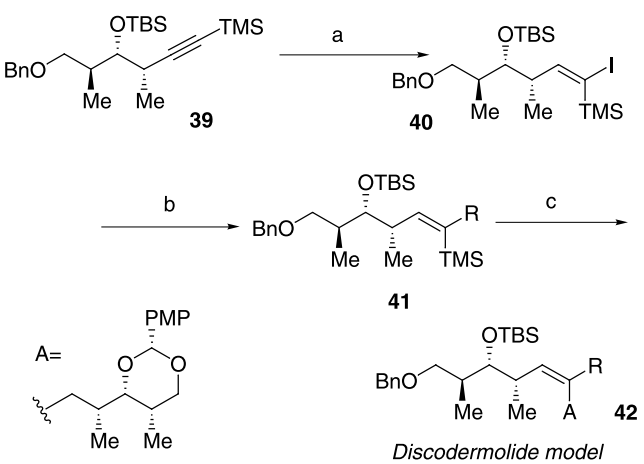
4. The zirconium→Zn→Pd transmetalation sequence

The use of $ZnCl_2$ as a 'shuttle' to facilitate the palladium-catalyzed cross-couplings of organozirconocenes for C,C-bond formations has been further explored lately and has now become a versatile tool in synthesis.[7,25] The versatility of this process was demonstrated by the syntheses of complex molecules such as eunicenone A **34**,[26] pitiamide A[27] and 'FR901464' **35**[28] (Scheme 10).



Scheme 10. Use of $ZnCl_2$ to facilitate cross-couplings of organozirconcenes.

As an example of this sequence, hydrozirconation of alkyne **36** provided the alkenylzirconocene **37** which, however, was unreactive toward direct Zr→Pd exchange reactions. Transmetalation to the less sterically demanding zinc species solved this problem and accelerated the palladium heterocoupling with organohalides. Coupling product **38** was obtained in 75% yield after treatment of **37** with stoichiometric amounts of $ZnCl_2$ in the presence of the vinyl iodide and catalytic $Pd(PPh_3)_4$.



Scheme 11. Synthesis of a discodermolide model: (a) (i) Cp_2ZrHCl, THF, 55 °C; (ii) I_2, THF; (b) RZnCl, $Pd(PPh_3)_4$, THF; (c) (i) I_2, CH_2Cl_2; (ii) *t*-BuLi, $ZnCl_2$, $Pd(PPh_3)_4$, A–I.

Panek et al. preferred to use a Zr→Zn→Pd transmetalation sequence via an intermediate vinyl iodide[2f,3f] in the development of a flexible route to discodermolide and callystatin A (Scheme 11).[29a] Hydrozirconation of the silyl acetylene **39**,[30] followed by iodination, produced **40** in 88% yield. Subsequent palladium cross-coupling with Grignard-derived zinc chlorides produced **41**. Iododesilylation and a second cross-coupling afforded trisubstituted olefin **42**. The same strategy was also applied to the synthesis of the side chain amino acid in microcystin[25] and (−)-motuporin.[29b]

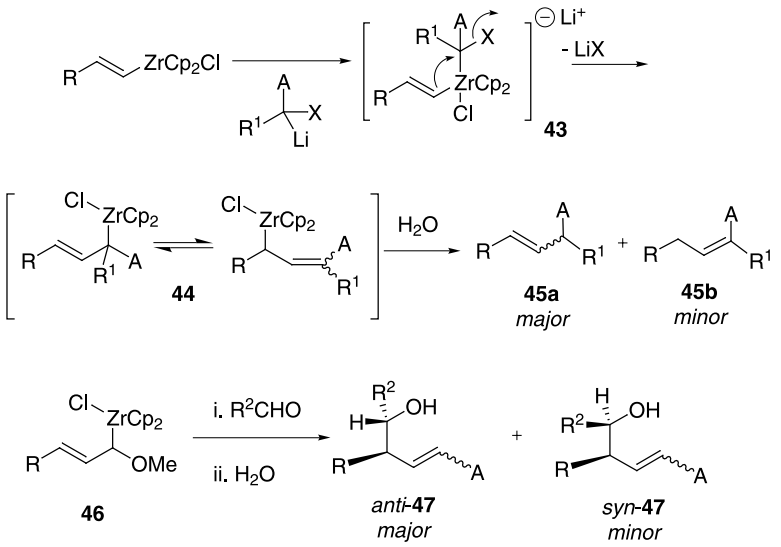
5. Lithium carbenoid insertions via the 1,2-metalate rearrangement

The insertion of lithium carbenoids into metal–carbon bonds via a 1,2-metalate rearrangement is still a rarely applied process.[31] However, this is an interesting and potentially powerful strategy since the product retains the organometallic functionality of the starting material. Whitby and Kasatkin described the use of this reaction for the convergent formation of allylzirconium compounds,[32] whose synthetic importance is based on their high reactivity toward electrophiles. The lithium carbenoid, RC(A)LiX, adds to the alkenylzirconocene, forming the complex **43**; subsequent 1,2-rearrangement leads to the allylic- and homoallylic zirconocenes as major and minor intermediates, respectively, with ratios of quenched **45a/45b** >80:20 (Scheme 12). Generally, deprotonation of the lithium carbenoid precursor is performed in situ with the addition of LiTMP (lithium 2,2,6,6-tetramethylpiperidide) in THF at −100 °C to a solution of an alkenylzirconocene and RC(A)HX and affords, after hydrolysis, product **45a** almost exclusively. The scope of these reactions includes A=ether, cyano, sulfonyl, MOM, TMS or phosphonate groups, and the leaving group X can be Cl or $PhSO_2$. Aldehydes were also used as electrophiles to trap the allylic zirconocene intermediate **46**, followed by hydrolysis to give the *anti*-homoallylic alcohol **47** in good yields and excellent diastereoselectivity.

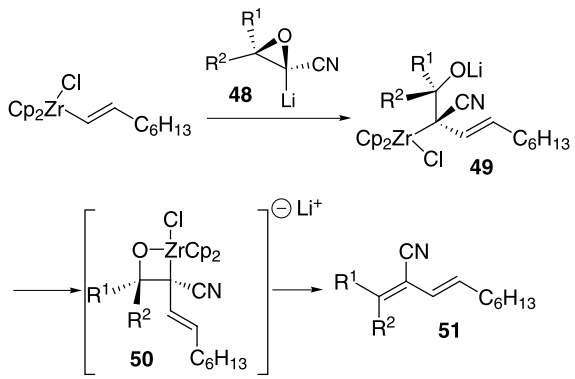
Another variant of this method is the formation of lithium carbenoids from α,β-epoxynitriles **48**, affording (*E*)-2-cyano-1,3-dienes **51** in moderate to good yields (Scheme 13).[33] A reasonable mechanism for this transformation includes epoxide opening by 1,2-migration of the alkenyl fragment, producing **49**. *syn*-β-Elimination of the zirconium alkoxide in complex **50** leads to the observed products.

The process of carbenoid insertion represents an interesting alternative to the usual methods of allyl organometallic formation, such as oxidative addition or transmetalation of species formed from allyl halides. Allyl alcohol derivatives can be used as precursors if low-valent metal complexes such as Cp_2Zr(1-butene) and $(i\text{-PrO})_2Ti$(propene) are employed.[34] Allenes can similarly be hydrozirconated to afford allylzirconocene reagents for organic synthesis.[35]

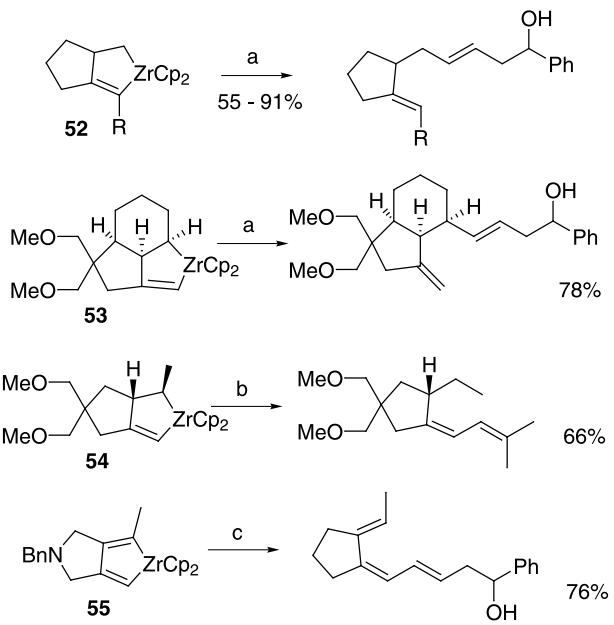
Whitby et al. studied the regiochemistry of carbenoid insertion into unsymmetrical alkenylzirconacycles (Scheme 14).[36] Alkenylzirconocenes **52**, **53**, **54** and **55** were obtained by cyclometalations of terminal alkynes with



Scheme 12. Lithium carbenoid insertion into an alkenylzirconocene intermediate.



Scheme 13. 1,2-Metalate rearrangement in the synthesis of dienyl nitriles.



Scheme 14. (a) (i) CH_2=CH–C(H)LiCl, (ii) PhCHO, $BF_3{\cdot}Et_2O$, (iii) $NaHCO_3$; (b) (i) CH_2=C(Me)–C(H)LiCl, (ii) AcOH; (c) (i) 5 equiv. of CH_2=CH–C(H)LiCl, (ii) PhCHO, $BF_3{\cdot}Et_2O$, (iii) $NaHCO_3$.

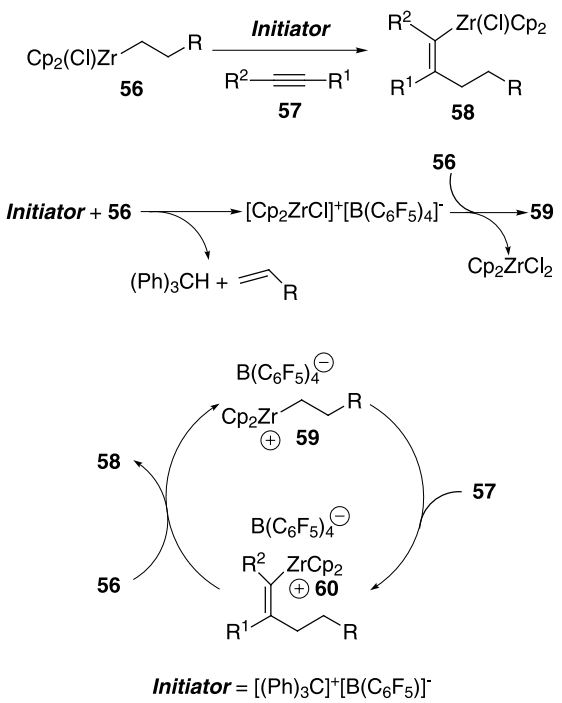
Negishi's reagent.[37] In all cases represented by **52**, the process was completely regioselective, with the insertion occurring into the alkyl–zirconocene bond, which is less sterically hindered than the alkenyl–Zr bond that bears an R substituent. Explanations for exceptions to this rule were much more complicated, as in the case of **53**, in which the insertion occurred at the more congested site, the alkyl–Zr bond. Only in one case, for the cyclic **54**, insertion into the alkenylzirconocene bond was observed. In the cyclopentadienezirconocene **55**, the less substituted site underwent preferential insertion.

HOMO–LUMO calculations were used to explain exceptions to the rule as in **53** and **54**. In **54**, these calculations indicated that the methyl group at the alkyl site was in the same plane of the LUMO, complicating the approach of the carbenoid species. In **52** and **53**, it was shown that the alkyl site groups were pointing well away from the plane of the LUMO, thereby favoring lateral attack on this site. However, steric hindrance in **53** was too high to be ignored and an electrophilic attack mechanism, with a substantial positive charge on the carbenoid species, might be responsible for the unexpected regioselectivity result.

6. Regioselective alkylzirconation of internal alkynes

Suzuki et al. reported the alkylation of unsymmetrical internal alkynes **57** in the presence of $[(Ph)_3C]^+[(C_6F_5)_4B]^-$ as initiator, with the in situ generated alkylzirconocene **56** to produce the tetrasubstituted alkenylzirconocene intermediate **58** (Scheme 15).[38] The regiocontrolled formation of tri- or tetrasubstituted alkenes can be achieved by hydrometalation, followed by proper coupling, or by carbometalation of internal alkynes.[39] The latter procedure has limitations because of reactivity, regioselectivity and side reaction problems deriving from β-hydride transfer when alkyl metals are employed.[40]

The alkyl transfer occurred selectively at the more sterically hindered carbon of the triple bond in excellent yield. The

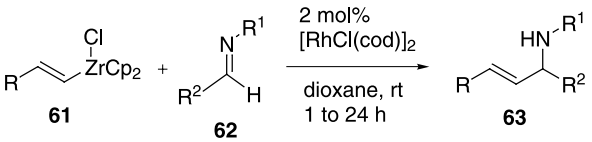


Scheme 15. Alkylzirconation of internal alkynes initiated by $[(Ph)_3C]^+$-$[(C_6F_5)_4B]^-$.

same trend was observed whether the alkynes were diphenyl or dialkyl-substituted, provided the sterics of the two alkyl groups were sufficiently different. The reaction is initiated by the action of a catalytic amount of $[(Ph)_3C]^+[(C_6F_5)_4B]^-$ on **56** to generate a $[Cp_2ZrCl]^+$ species, which reacts with **56** to form **59**. This mechanism was supported by the detection of $(Ph)_3CH$ derived from β-H abstraction of the trityl portion of the initiator. The cationic **59** activated the alkyne **57**, enabling the alkyl transfer to afford the alkenylzirconocene **60**, followed by chloride transfer with **56** to result in **58**.

7. Rh(I)-Catalyzed additions to aldimines

The problem of the inherently low reactivity of organozirconocene compounds towards addition to bulky electrophiles such as aldimines can also be addressed by a rhodium-catalyzed process. Hanzawa et al. presented the first example of a catalytic addition of alkenylzirconocenes to aldimine derivatives.[41] Rh-catalyzed additions of other organometallic reagents to aldehydes, imines or α,β-unsaturated carbonyl compounds are well known and developed.[42] The addition of organozirconocene **61** to the aldimine **62**, catalyzed by 2 mol% of $[RhCl(cod)]_2$, afforded allylic amines **63** in good yields (Scheme 16). This addition requires the use of *N*-activating groups such as $-PO(OEt)_2$ and −COOMe or −Ts groups. Alkyl, ether and phenyl

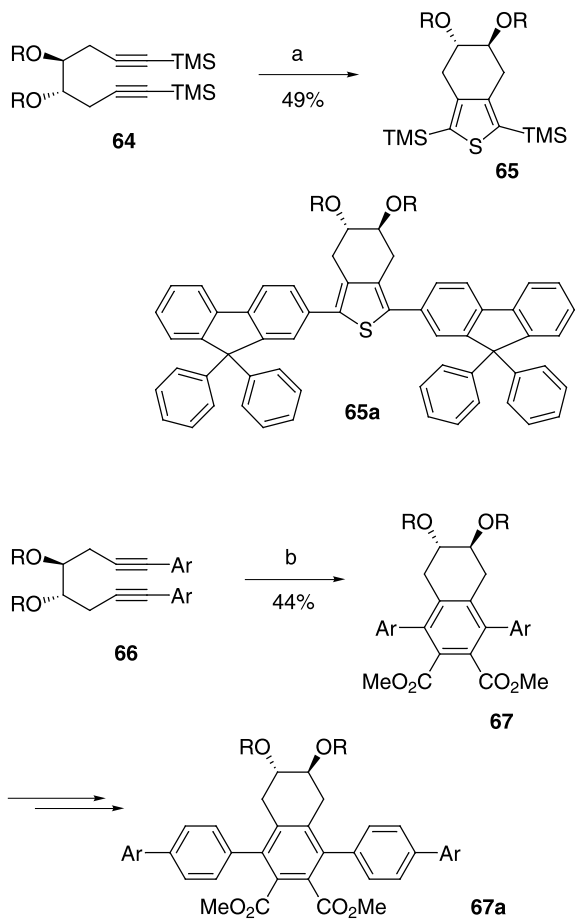


Scheme 16. Rhodium-catalyzed addition of alkenylzirconocenes to aldimines.

substituents at the alkyne were well tolerated, even though internal alkenylziconocenes required longer reaction times. The nature of R^2 had little effect on the reaction rate and product yield. Monodentate or bidentate phosphine ligands only retarded the reaction, and heating had to be applied to accelerate the process. Alkylzirconocene chloride did not react under any conditions tried. The transmetalation of an alkyl ligand from a zirconocene to other metals is more difficult than the corresponding alkenyl transfer, and few examples are known.[2f] The interesting rhodium-catalyzed process is still being further optimized, and the authors are working on its extension to aldehydes and α,β-unsaturated carbonyl compounds. Much of the future practical significance of this process will depend on the development of a catalytic asymmetric variant and the use of a cheaper transition metal catalyst.

8. Zr-Promoted cyclizations of diynes

This process generates synthetic intermediates containing cycloalkenylzirconocene units, which can be transformed into a variety of targets such as thiophenes, phospholes, germoles and highly functionalized benzene derivatives.[43] The utility of these products is most relevant for the material science field.



Scheme 17. (a) (i) Cp_2ZrCl_2, *n*-BuLi, (ii) S_2Cl_2; (b) (i) Cp_2ZrCl_2, *n*-BuLi, (ii) CuCl, DMAD.

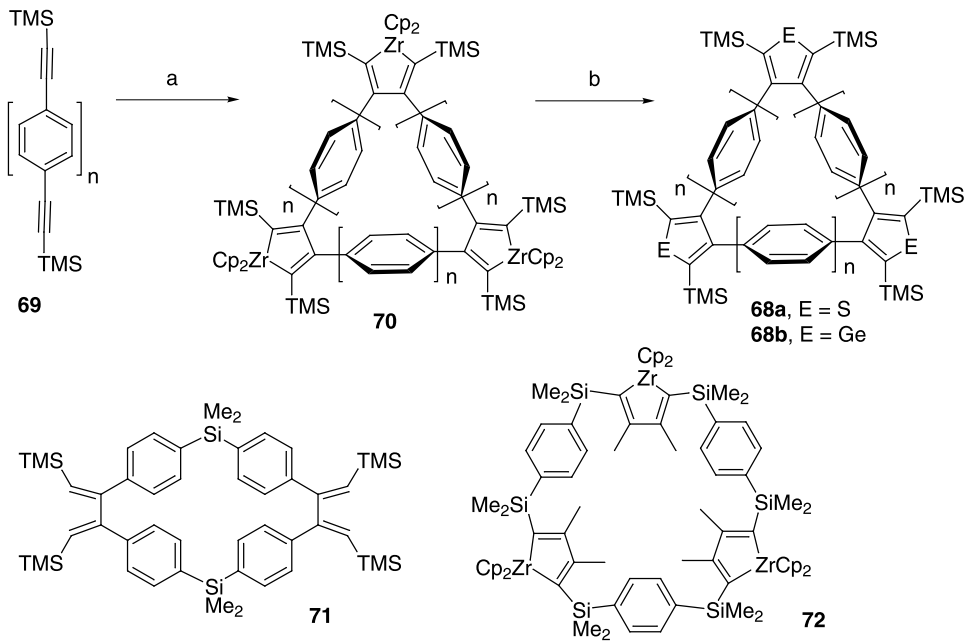
Chemical transformations of this type illustrate new options for efficiently tuning the electronic and optical properties of extended π-systems. Wong and Chen applied the Zr-promoted cyclization of diynes to introduce side chains in C_2-chiral molecules as precursors for new conjugated materials.[44] The tartaric acid derived diyne **64** was treated with in situ prepared Negishi reagent[37] to form a cyclopentadienylzirconocene, which could be quenched with S_2Cl_2 to afford the new C_2-symmetrical, chiral thiophene **65** (Scheme 17). In the same fashion, the zirconacyclopentadiene derived from **66** was converted to the diester **67** in the presence of CuCl and dimethyl acetylenecarboxylate (DMAD). Compounds **65a** and **67a**, obtained after further transformations of **65** and **67**, respectively, showed interesting optical properties.

Tilley et al. have synthesized the unusual triangular germole and thiophene macromolecules **68a** and **68b** by zirconocene-promoted cyclization of diynes (Scheme 18).[45] As a consequence of the exterior functional groups, such structures serve as building blocks (tectons) for designed crystal lattices and discrete supramolecular assemblies. Their synthesis is always a difficult problem because of the high-dilution conditions and exhaustive separations necessary to remove oligomeric products. In this context, the zirconocene coupling reactions served as a promoter of high yielding macrocyclizations. The linear diynes of variable lengths **69** were treated in a 1:1 proportion with in situ prepared Negishi reagent, initially at −78 °C and then heated to 65 °C to generate the corresponding Zr-containing macrocycles **70**. All reactions could be quenched with mild acidic solutions to yield the demetalated version of **70**. Many of the methods of carrying out electrophilic substitutions on zirconacyclopentadienes are not suitable for this target structure because of the presence of TMS groups. The zirconocene promoted coupling of diynes **69**, bearing silyl substituents, allows the control of regiochemistry.[2i,4d,46] In addition, the TMS substituent α to the zirconocene prevents most substitution reactions at zirconium, due to steric hindrance. However, reactions with S_2Cl_2 and $GeCl_4$ have been shown to be feasible and high yielding, affording **68a** and **68b**, respectively.

When the diynes used for the zirconocene coupling were not linear, other interesting classes of macrocycles could be generated, as represented by **71** and **72**, which have the potential for new optical applications.

9. Conclusion

The range of synthetic preparations and applications of alkenylzirconocene species continues to expand rapidly even 50 years after the discovery of the first zirconocene. In particular, new C,C-bond forming methods involving unprecedented organozirconium and -zinc chemistry provide a fertile ground for the development of new efficient cascade reactions and diversity-oriented synthesis. Carbon–heteroatom bond formations are of significant utility for materials chemistry. Important building blocks have been constructed through the simple elaboration of alkenylzirconocenes with proper electrophiles such as sulfonyl chlorides and dialkyl chlorophosphates, which afford (*E*)-disubstituted vinyl sulfones[47] and arylvinylphosphonates, respectively.[48] Kinetic versus thermodynamic control in the hydrozirconation of alkynes and the effect of functional groups on the control of the regioselectivity of hydrozirconation are still areas of investigation. The recent hydrozirconation of alkynyl sulfoxides and sulfones,[49] or the treatment of acetylenic tellurides with Cp_2ZrHCl to afford geminal bimetalloalkenes[50] are noteworthy due to their simplicity and effectiveness. Finally, the zirconocene-mediated activation of a C–F bond in the generation and cross-coupling reaction of 1-fluorovinylzirconocenes[51] is another good example of the seemingly limitless synthetic opportunities in zirconocene chemistry.



Scheme 18. (a) Cp_2ZrCl_2, 2 equiv. *n*BuLi, THF, −78 °C; (b) E_xCl_n=S_2Cl_2 or $GeCl_4$.

Acknowledgements

P.W. thanks the National Science Foundation (CHE-0078944) for support. R.L.N. acknowledges the Brazilian governmental agency Conselho Nacional de Pesquisa e Desenvolvimento Científico (CNPq) for a postdoctoral fellowship.

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Ruth L. Nunes was born in Recife, Brazil, in 1971. She obtained her Chemistry Bachelor degree in 1993 at the Federal University of Pernambuco, Brazil. In 2000, she graduated with a Doctor in Science degree in natural products synthesis from the research group of Dr. Lothar W. Bieber. In 2001, she joined Dr. Peter Wipf's group at the University of Pittsburgh as a postdoctoral fellow, where she was involved in the investigation of the water/zirconium-accelerated carboalumination of alkynes and combinatorial chemistry solid phase synthesis projects. In 2003, she started her position as a development researcher at the Federal University of Pernambuco, working with new sulfoxide, ketoester and oxirane ligands for the synthesis of photo- and electro-luminescence devices.