DOI: 10.1002/ejoc.200700939

Cross-Coupling–Elimination Reactions Mediated or Catalyzed by Zirconium Complexes: A Valuable Tool in Organic Synthesis

Francisco J. Fañanás*[a] and Félix Rodríguez*[a]

Keywords: Cross-coupling / Elimination / Insertion / Migratory insertion / Zirconium

The tandem zirconocene-mediated or -catalyzed cross-coupling–elimination reaction provides an efficient and versatile procedure for the construction of scaffolds that in many cases are difficult to access by traditional organic chemistry. In general, this process supposes the reaction of two unsaturated molecules. One of them is coordinated to the zirconocene and the other one contains a heteroatom at an appropriate position for the subsequent elimination process. In this Microreview we discuss the concept of this useful approach focussing on the reactivity of alkyne-, aryne-, alkene- and iminezirconocene complexes towards alkenes containing a heteroatom functionality at the allylic or vinylic position. Some examples of heteroatom-substituted alkynes are also covered.

1. Introduction

The activation of an unsaturated molecule on coordination to a metal is a fundamental process in organometallic chemistry, both conceptually and in synthetic applications. Of all the metals that can be used to effect this activation, the use of zirconium complexes has rapidly increased in the last few decades.[1] This special interest in organozirconium compounds is mainly due to their dual behaviour which combines typical transition-metal reactions and classical carbanion chemistry. The great majority of organozirconium complexes used in organic synthesis are zirconocene derivatives (Cp_2Zr). So, the first synthesis of Cp_2ZrCl_2 by Wilkinson and Birmingham, reported in 1954,[2] could be considered as the birth of organozirconium chemistry. One of the first applications of zirconocene complexes was as polymerization catalysts and even at present the largest use of these complexes is the industrial polymerization of unsaturated molecules.[3] However, the use of organozirconium compounds in the synthesis of fine chemicals started in 1970 with the preparation by Wailes and Weigold of zirconocene hydrochloride.[4] In extensive work in the mid-1970s, Schwartz developed the hydrozirconation reaction which can be considered as the first synthetically useful application of zirconocene complexes in organic chemistry.[5]

[a] Instituto Universitario de Química Organometálica "Enrique Moles", Unidad Asociada al C.S.I.C., Universidad de Oviedo, c/ Julián Clavería 8, 33006 Oviedo, Spain
Fax: +34-985103446
E-mail: fjfv@uniovi.es

Francisco J. Fañanás was born in 1952 in Huesca, Spain. He received his B.Sc. degree from the University of Zaragoza in 1974 and his Ph.D. in chemistry in 1979 from the University of Oviedo under the supervision of Professor Barluenga and Professor Yus. He was a post-doctoral fellow in the laboratory of Professor H. Hoberg at the Max Planck Institut für Kohlenforschung, Mülheim a.d. Ruhr, Germany, from 1982 to 1984 working on nickel chemistry. In 1985 he joined the Instituto Nacional del Carbón in Oviedo as a Research Assistant. Thereafter, in 1987, he joined the Organic Department at the University of Oviedo as an Associate Professor becoming Full Professor in 2005. Professor Fañanás is co-author of more than 90 scientific articles, monographs and book chapters. His research interest is focused on organic synthesis mediated by the transition metals of groups 4 and 6.

Félix Rodríguez was born in Jarrio (Asturias, Spain). After his undergraduate education in chemistry at the University of Oviedo he joined the research group of Professor Barluenga where he worked in the field of organometallic chemistry using Fischer carbene complexes. In 1998 he received his Ph.D. and then moved to the University of Cambridge for a postdoctoral stay (1999–2001) as a Marie Curie fellow under the supervision of Professor Steven V. Ley. During this time he was involved in several projects including the development of synthetic methodologies in the field of butane 2,3-diacetal (BDA) chemistry, the total synthesis of a number of natural products and the development of new strategies for the parallel synthesis of small-molecule libraries. In 2002 he returned to the University of Oviedo and currently he is supported by a Ramón y Cajal contract. His research interest is focused on the use of transition-metal complexes in organic synthesis (particularly group 4 and 6 organometallic compounds) and the design of new catalytic processes.

Systematic investigations in the late 1970s and 1980s developed by Negishi further expanded the synthetic scope of these complexes.[6] Since then, the interest in organozirconium chemistry has greatly increased due to the unique ability of these complexes to promote uncommon transformations.[7]

The zirconocene unit (Cp_2Zr) is an unstable 14-electron species which is generated in situ in most cases from Cp_2ZrCl_2 by reduction with Mg and $HgCl_2$[8] or by treatment with two equivalents of an organolithium or Grignard reagent (Negishi's procedure).[9] The reaction of zirconocene with unsaturated molecules gives rise to the corresponding 16-electron unsaturated molecule–zirconocene complex. As shown in Figure 1 the most common complexes of this kind are the alkyne- (**1**), alkene- (**2**) and iminezirconocene complexes **3**. These complexes may be best viewed as resonance hybrids between these species **1**–**3** and the corresponding three-membered zirconacycle species **4** (Figure 1).

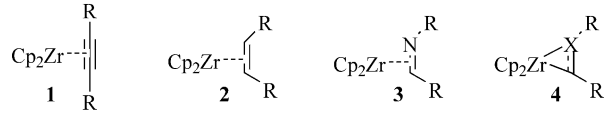
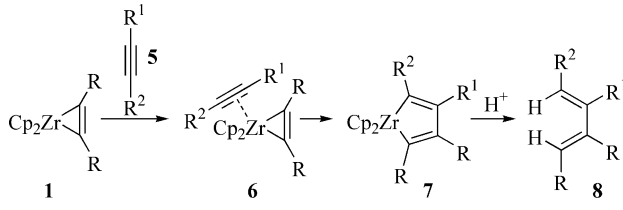


Figure 1. Unsaturated molecule–zirconocene complexes.

The most typical reactivity of the zirconocene complexes **1**–**3** is shown in the example in Scheme 1. Thus, the 16-electron alkynezirconocene complex **1** (represented as its zirconacyclopropene resonance form) tends to react with another unsaturated molecule such as the new alkyne **5** to give the 18-electron complex **6**. The subsequent cyclometallation reaction furnishes the corresponding zirconacyclopentadiene derivative **7**. Although these complexes may react with many electrophiles, the simplest reaction they undergo is hydrolysis to give the corresponding butadiene derivative **8**. Following the same strategy zirconocene complexes **1**–**3** react with unsaturated molecules (alkynes, alkenes, allenes, etc.) to give the corresponding zirconacycle derivative analogous to **7** which can be further transformed into an organic molecule by treatment with electrophiles.



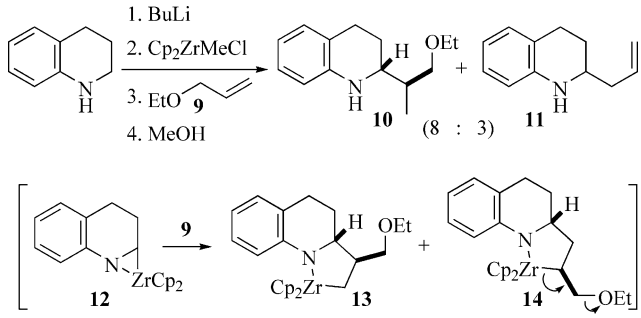
Scheme 1. An example of the typical reactivity of zirconocene complexes. Insertion of alkynes into alkynezirconocene complexes.

In this review article we will focus on the reaction of zirconocene complexes **1**–**3** and alkenes or alkynes which contain in their structures an appropriate functionality that may act as a leaving group at some point of the reaction (mainly we will refer to the reactivity of allylic and vinylic ethers or halides). As we will discuss, in general, these processes initiate further reaction pathways analogous to that described in Scheme 1. However, the presence of a heteroatom at an appropriate position confers particular features to the mechanisms of the reactions and then interesting and, in many cases, unexpected products are obtained.

2. Reaction of Allylic-Functionalized Alkenes and Zirconocene Complexes

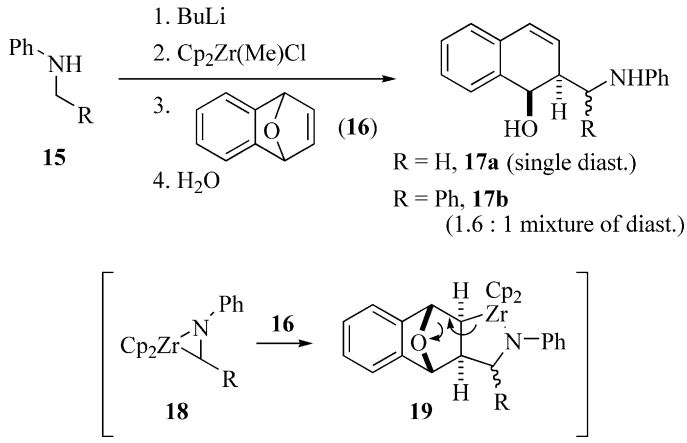
2.1 Iminezirconocene Complexes: Reaction with Allyl Ethers

In a paper that appeared in 1990, Whitby and co-workers reported a single example of the reaction of the η^2-imine complex **12**, derived from tetrahydroquinoline, and allyl ethyl ether **9** to give a mixture of the amino ether **10** and the homoallylamine **11** in an 8:3 ratio (Scheme 2).[10] The formation of these two products is explained by the initial formation of the η^2-imine complex **12** through a well-established cyclometallation reaction.[11] Insertion of the double bond of enol ether **9** takes place regioselectively at the zirconium–carbon bond of **12**. However, this insertion process leads to the two regioisomers **13** and **14** depending on the orientation of the allyl ether **9** during the insertion step (Scheme 2). The hydrolysis of intermediate **13** generates amino ether **10**. On the other hand, intermediate **14** evolves through a process of β-elimination of the alkoxy group to give, after hydrolysis, the homoallylamine **11**.



Scheme 2. Reaction of an iminezirconocene complex and allyl ethyl ether.

This reaction was further studied in our group by using different amines as starting materials.[12] Similarly to the above-commented single example reported by Whitby and co-workers, regioisomeric mixtures of the corresponding amino ether and the homoallylamine derivatives are obtained in different ratios depending on the structure of the initial amine. However, a unique regioisomer is obtained when the symmetric allylic ether **16** is used. Thus, the reaction of amines **15** with butyllithium and chloro(methyl)-zirconocene to generate the η^2-imine complex **18** followed by treatment with 1,4-dihydro-1,4-epoxynaphthalene (**16**) leads to the formation of amino alcohols **17a**,**b** in high yields (Scheme 3). Interestingly, compound **17a** is obtained as a single diastereoisomer whereas **17b** is isolated as a 1.6:1 mixture of two diastereoisomers. The formation of products **17** is easily understood by regioselective insertion of the double bond of enol ether **16** into the zirconium–carbon



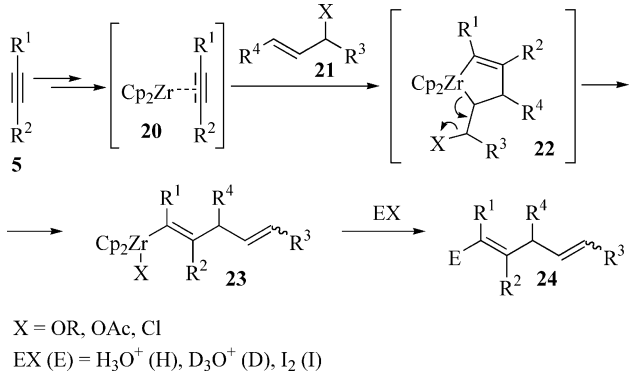
Scheme 3. Reaction of iminezirconocene complexes and 1,4-dihydro-1,4-epoxynaphthalene.

bond of **18** to form the zirconaazacyclopentane derivative **19**. This intermediate suffers β-elimination of the alkoxy group to finally generate compounds **17**.

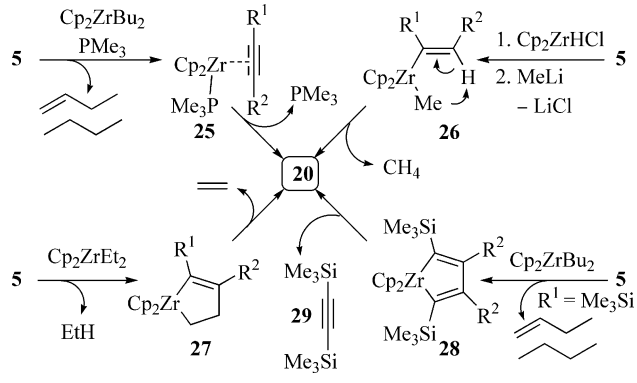
2.2 Alkynezirconocene Complexes: Reaction with Allylic-Functionalized Olefins

Takahashi and co-workers have extensively studied the reactivity of alkynezirconocene complexes **20** towards allylic compounds **21** (allyl ethers, allylic halides and allylic acetates) (Scheme 4).[13] This reaction leads to the formation of 1,4-diene derivatives **23** through a process that globally can be considered as an allylzirconation of the initial alkyne **5**. Further reaction of organometallic compounds **23** with appropriate electrophiles affords the corresponding organic substrate **24**. The mechanism that explains the formation of these products implies the insertion of the alkene **21** into the alkynezirconocene complex **20** to afford intermediate **22**. This reaction is totally regioselective with respect to the alkene **21** as the double bond of theses allylic compounds is oriented during the insertion process so that the substituent (X group) is close to the zirconocene moiety. Finally, β-elimination reaction in **22** results in the formation of the alkenylzirconocene complex **23**.

Interestingly, the authors developed several methods to access the alkynezirconocene complexes **20** from the alkynes **5** (Scheme 5). The first method supposes the treatment of alkyne **5** with the Negishi reagent (Cp_2ZrBu_2) in the presence of a stabilizing compound such as a phosphane to generate the complex **25**, precursor of **20**. For terminal alkynes, this method is not appropriate and so, in these cases, complexes **20** were obtained by hydrozirconation of the alkynes **5** followed by methylation with MeLi to give **26**. The final β-hydrogen abstraction gives rise to the desired complex **20**. Alternatively, the reaction of alkynes **5** with Cp_2ZrEt_2 affords the relatively stable zirconacyclopentene derivatives **27** which behave like the alkynezirconocene complexes **20**. Thus, in the presence of an unsaturated molecule such as **21** (see Scheme 4) these complexes **27** react to produce intermediates **22** releasing a molecule of ethene. Finally, the authors have also found that zirconacyclopentadiene derivatives **28** with α-trimethylsilyl groups could also formally be considered as equivalents of the corresponding alkynezirconocene complex **20** (Scheme 5). So, complexes **28** react with alkenes **21** (see Scheme 4) to afford intermediate **22** releasing a molecule of bis(trimethylsilyl)acetylene **29**.

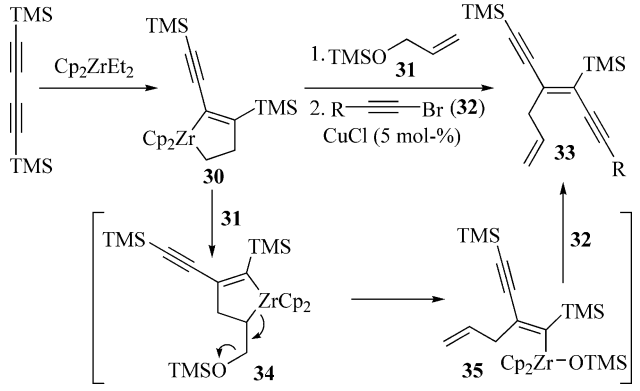


Scheme 4. Cross-coupling reaction of alkynes and allylic-functionalized alkenes mediated by zirconocene.



Scheme 5. Methods for the preparation of alkynezirconocene complexes.

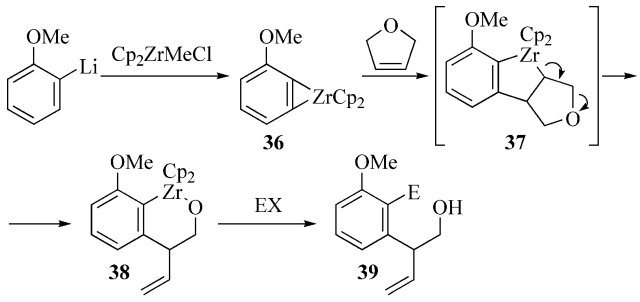
The allylzirconation reaction of triple bonds described above has recently been applied by Liu and Gao in the synthesis of the *trans*-enediyne derivatives **33** (Scheme 6).[14] The treatment of bis(trimethylsilyl)butadiyne with $Cp_2Zr(CH_2{=}CH_2)$, generated in situ from Cp_2ZrEt_2, leads to the formation of the zirconacycle **30**. In the presence of an excess of allyloxytrimethylsilane, the alkenylzirconocene derivative **35** is formed through intermediate **34**. The insertion process is doubly regioselective: insertion occurs by locating the silyl group at the α-position of the zirconacycle intermediate **34**. Also, the double bond of the allyl ether **31** is oriented during the insertion step such that the alkoxymethyl substituent is close to the zirconocene moiety. β-Elimination of the alkoxy group from **34** results in the formation of intermediate **35**. Further reaction of **35** with alkynyl bromides **32** in the presence of a catalytic amount of CuCl (5 mol-%) affords the final *trans*-enediyne derivatives **33**. Remarkably, all of the sequence shown in Scheme 6 can be performed in a one-pot procedure, without isolation of any intermediate, providing a valuable method for the stereoselective synthesis of interesting enediyne derivatives.



Scheme 6. Synthesis of enediyne derivatives mediated by zirconocene.

2.3 Arynezirconocene Complexes: Reaction with Allyl Ethers

Arynezirconocene complexes may be considered as a particular type of alkynezirconocene complex. Cuny and Buchwald have shown that these kinds of zirconocene complexes can effect the ring-opening of cyclic allylic ethers to produce homoallylic alcohols (Scheme 7).[15] Arynezirconocene complexes are readily available by reaction of the corresponding aryllithium derivative and methylzirconocene chloride. Thus, for example, the reaction of 2-methoxyphenyllithium and methylzirconocene chloride affords the zirconocene 3-methoxybenzene complex **36**. The reaction of this complex with 2,5-dihydrofuran leads to the regioselective formation of intermediate **37** (the insertion of the allylic ether occurs at the zirconium–carbon bond of **36** farthest from the methoxy group). The subsequent β-alkoxide elimination reaction in **37** gives the cyclic zirconocene complex **38**. Final reaction with appropriate electrophiles produces the functionalized homoallylic alcohols **39**. The global process supposes a ring-opening reaction of the initial cyclic allyl ether.

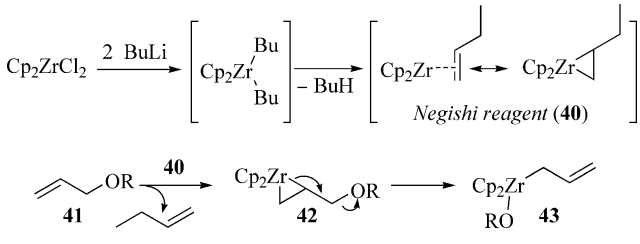


EX (E) = MeOH (H), I_2 (I)

Scheme 7. Reaction of an arynezirconocene complex and 2,5-dihydrofuran.

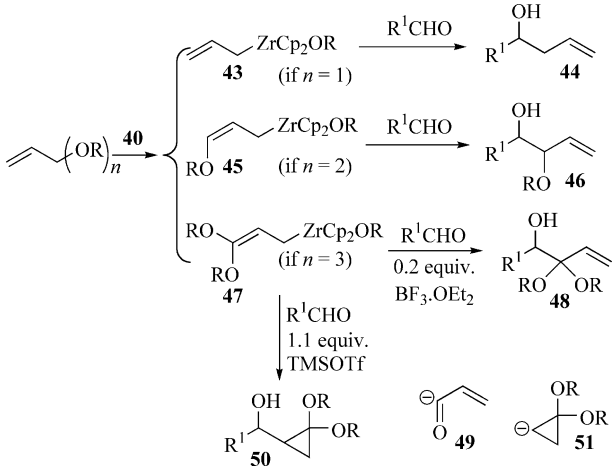
2.4 Alkenezirconocene Complexes in Stoichiometric Processes: Reaction with Allylic and Propargylic Ethers

The discovery of the butenezirconocene complex **40** as a zirconocene equivalent ("Cp_2Zr") is considered to be a crucial achievement in the chemistry of zirconium.[9] This complex can be easily generated in situ by warming a solution of Cp_2ZrBu_2, derived from the reaction of Cp_2ZrCl_2 with 2 equiv. of butyllithium. The studies performed by Negishi and co-workers on the bicyclization reactions of diallyl ether by using this reagent led to the accidental discovery of the formation of the allylzirconocene species.[16] This reaction was widely studied by Taguchi and co-workers.[17] Thus, it has been demonstrated that treatment of allyl ethers **41** with the Negishi reagent (note that this complex is a simple alkenezirconocene complex) leads to the formation of the allylic zirconocene species **43** (Scheme 8). This reaction proceeds through an initial ligand-exchange process that produces intermediate **42** releasing a molecule of butene. The subsequent β-alkoxy group elimination reaction leads to the corresponding zirconocene complexes **43** (Scheme 8). It is important to remark that in these reactions the alkene coming from the initial alkenezirconocene complex (Negishi reagent) is not incorporated into the final product as it is released in the initial ligand-exchange reaction.



Scheme 8. Allylzirconocene complexes from the reaction of allyl ethers and the Negishi reagent.

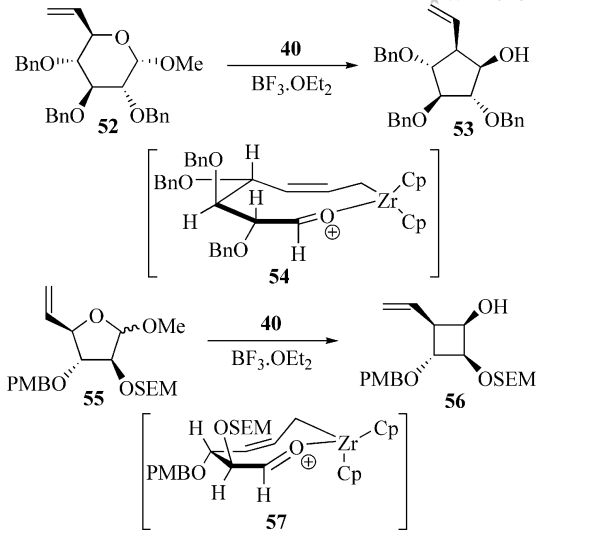
Following this strategy it is also possible to access functionalized γ-alkoxyallylic zirconium species **45**[18] and the γ,γ-dialkoxyallylic zirconium species **47**[19] (Scheme 9). The allylic organometallic compounds **43**, **45** and **47** react with carbonyl compounds to give the corresponding allylic alcohols **44**, **46**, and **48**, respectively. In this context, the reactivity of the γ,γ-dialkoxyallylic zirconocene complexes **47** deserves some comment. These complexes react with aldehydes at the γ-position of the zirconium in the presence of 0.2 equiv. of a Lewis acid to give the expected alcohol **48**. Therefore, the zirconium species **47** functions as the acryloyl anion equivalent **49**. On the other hand, the reaction of complexes **47** with an aldehyde in the presence of more than a stoichiometric amount of a Lewis acid produces the *gem*-dialkoxycyclopropane derivatives **50** in a reaction in which **47** operates as the dialkoxycyclopropyl anion equivalent **51**.[20]



Scheme 9. Synthesis and reactivity of allylzirconocene complexes.

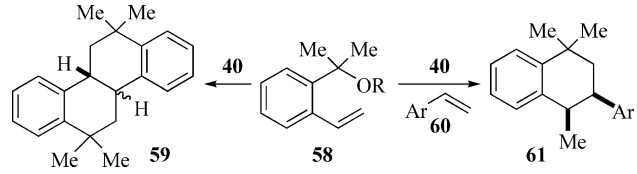
In a clever extrapolation of these reactions, Taguchi[21] and Paquette[22] and their co-workers demonstrated that 5-vinylpyranosides and 4-vinylfuranosides, exemplified by **52** and **55**, are cleanly and efficiently transformed under treatment with the in situ formed Negishi reagent **40** and boron trifluoride etherate into vinylcyclopentanol **53** or vinylcyclobutanol **56** (Scheme 10). The high stereoselectivity of these processes is attributed to non-bonded interactions that favour intermediates **54** and **57**. These neat transformations can be considered as zirconium-mediated ring-contraction reactions that transform heterocycles (the sugar derivatives) into carbocycles.

The extensive studies on the reactivity of allylic systems and alkenezirconocene complexes led Hanzawa and coworkers to evaluate the reactivity of the aromatic π-conjugated system of styrene derivatives **58** which bear an olefin and an alkoxy leaving group (Scheme 11).[23] Thus, the reaction of these styrene derivatives **58** with the Negishi reagent **40** produces the tetracyclic compound **59** through a formal dimerization process. However, in the presence of an excess of styrene derivatives **60**, the heterocoupling product **61** is



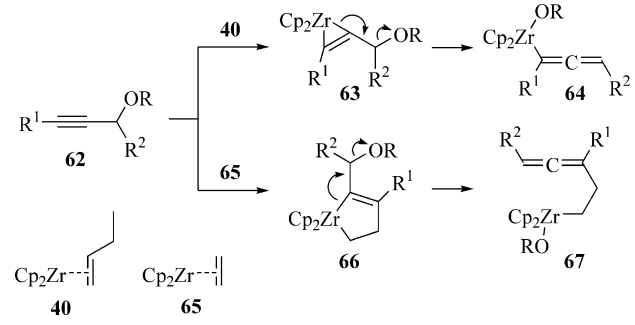
Scheme 10. Zirconium-mediated ring-contraction reactions: from sugars to carbocycles.

obtained with high regio- and stereoselectivity. The precise reaction mechanisms for the formation of these products have yet to be elucidated.



Scheme 11. Reaction of styrene derivatives and the Negishi reagent.

Propargylic ethers **62** react with in-situ-formed butenezirconocene complex **40** (Negishi reagent) in a similar way to that described for allyl ethers (see Scheme 8).[17] So, an initial ligand exchange process leads to intermediate **63** releasing a molecule of butene (Scheme 12). The subsequent β-alkoxy elimination reaction gives the allenylzirconocene derivatives **64**. It is interesting to note the different reaction profile depending on the nature of the alkenylzirconocene complex that is treated with the propargyl ethers **62**. As already mentioned, when the butenezirconocene complex is used, allenylzirconocene complex **64** is formed. In this reac-



Scheme 12. Allene derivatives from the reaction of propargylic ethers and alkenezirconocene complexes.

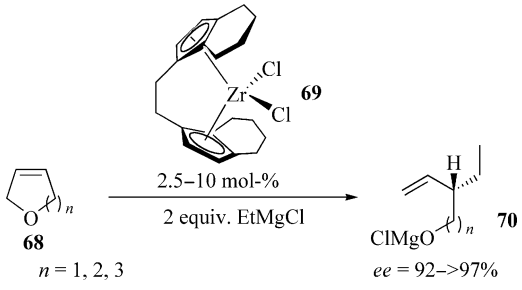
tion the butene moiety of **40** is not incorporated into the final product **64**. However, when the ethenezirconocene complex **65** is used,[24] an initial insertion reaction leads to the zirconacyclopentene derivative **66**. This complex evolves through a β-alkoxy elimination reaction to give the new zirconocene complex **67**. As shown, the product **67** incorporates into its structure the ethene moiety coming from the complex **65** (Scheme 12).

2.5 Alkenezirconocene Complexes as Catalysts in the Reaction with Allyl Ethers

Apart from polymerization reactions there are not many processes catalyzed by zirconocene complexes. This could be due to the fact that in general it is more difficult to develop catalytic reactions with high turnover numbers with early transition metals such as zirconium than it is with late transition metals such as palladium. However, some of the most interesting catalytic processes in the field of organozirconium chemistry make use of alkenes with a leaving group at the allylic position (usually allyl ethers). The most representative reactions of this kind are summarized in the next sections.

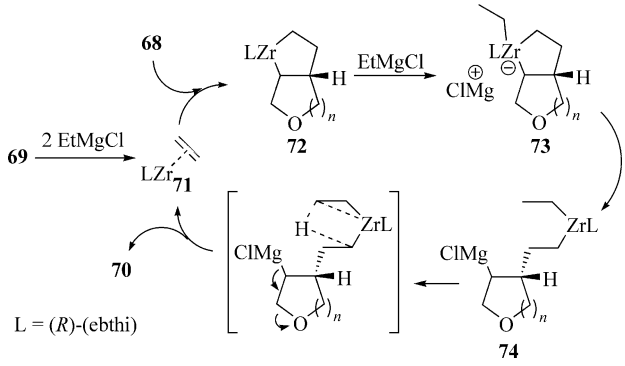
2.5.1 Intermolecular Catalytic Alkylations

Hoveyda and co-workers have reported an interesting asymmetric zirconium-catalyzed carbomagnesation reaction of cyclic allylic ethers which affords lineal alcohols with exceptional levels of regio- and enantioselectivity.[25] As illustrated in Scheme 13, in the presence of 2.5–10 mol-% of non-racemic ethylene[bis(tetrahydroindenyl)]zirconium dichloride [(ebthi)$_2$ZrCl$_2$] **69** and excess ethylmagnesium chloride as the alkylating agent, five-, six- and seven-membered cyclic allyl ethers **68** undergo facile asymmetric ethylmagnesation to give the lineal alkenol derivatives **70**.



Scheme 13. Asymmetric zirconium-catalyzed carbomagnesation reactions of cyclic allylic ethers.

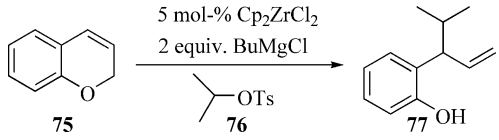
In the catalytic cycle proposed,[26] the asymmetric carbomagnesation is initiated by the formation of the chiral ethene–(*R*)-(ebthi)zirconocene complex **71** upon reaction of the initial zirconium dichloride complex **69** with ethylmagnesium chloride (Scheme 14). Coupling of the chiral complex **71** with cyclic allyl ethers **68** leads to the metallacyclopentane intermediate **72**. Reaction of this complex with ethylmagnesium chloride affords the zirconate **73**, which undergoes zirconium–magnesium exchange to yield intermediate **74**. Subsequent β-hydride abstraction accompanied by intramolecular magnesium alkoxide elimination leads to the release of the carbomagnesation product **70** and regeneration of the chiral catalytic species **71**. Detailed studies indicate that zirconacyclopentane intermediates such as **72** do not undergo spontaneous elimination to give the corresponding zirconocene alkoxide, so zirconium–magnesium exchange is likely to be a prerequisite for the alkoxide elimination and formation of the terminal alkene.



Scheme 14. Mechanism of the zirconium-catalyzed carbomagnesation reaction of cyclic allylic ethers.

Hoveyda and co-workers have used this stereoselective ethylmagnesation reaction as the key step in the synthesis of the antifungal agent fluvirucin.[27] Also, in a wise extension of this protocol, the same group has developed a method for the kinetic resolution of cyclic allylic ethers.[28]

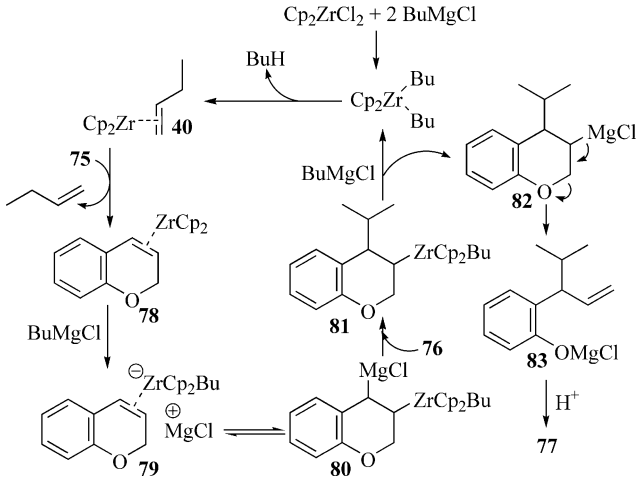
Despite the demonstrated utility of this catalytic carbomagnesation in stereoselective synthesis, a notable shortcoming of the process is that alkyl Grignard reagents other than ethylmagnesium halides are less efficient or fail to participate in the reaction. To overcome this limitation, Hoveyda and co-workers have developed a new zirconium-catalyzed electrophilic alkylation reaction of allylic ethers. In this process various electrophiles are used in the presence of a Grignard reagent and 5–10 mol-% of zirconocene dichloride.[29] For example, treatment of chromene (**75**) (an allylic ether) with 2 equiv. of butylmagnesium chloride and isopropyl tosylate (**76**) in the presence of 5 mol-% of zirconocene dichloride affords the phenol derivative **77** (Scheme 15). At this point it is important to compare this reaction with the carbomagnesation reaction shown in Scheme 13. The main difference is that in one case the alkylating agent is a nucleophile (EtMgCl, see Scheme 13) and in the other case the alkylating agent is an electrophile (the tosylate, Scheme 15).



Scheme 15. Zirconium-catalyzed electrophilic alkylation reaction of cyclic allylic ethers.

The mechanism that explains the zirconium-catalyzed electrophilic alkylation reaction is shown in Scheme 16. First, as discussed before (see Scheme 8), a mixture of bu-

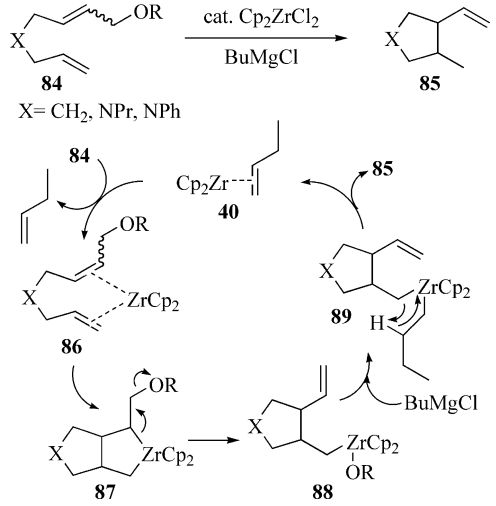
tylmagnesium chloride and zirconocene dichloride produces the Negishi reagent **40**. In the presence of chromene (**75**), a ligand-exchange reaction to give complex **78** is proposed. In the presence of an excess of butylmagnesium chloride the zirconate intermediate **79** is formed. These species may be in equilibrium with the bimetallic complex **80**, which in the presence of the alkylating agent **76** gives the new zirconocene complex **81**. Further reaction with butylmagnesium chloride regenerates the zirconium catalytic species releasing the organomagnesium intermediate **82** which, after a β-alkoxy elimination reaction and hydrolysis, leads to the final products **77**.



Scheme 16. Mechanism of the zirconium-catalyzed electrophilic alkylation reaction of cyclic allylic ethers.

2.5.2 Intramolecular Catalytic Alkylations: Coupling–Elimination Processes

In 1994 Waymouth and Takahashi and co-workers independently reported a similar zirconocene-catalyzed intramolecular cyclization reaction of 1,6-dienes **84** bearing a terminal double bond and an allylic ether moiety that gives the products **85** (Scheme 17).[30] The reaction proceeds



Scheme 17. Zirconocene-catalyzed intramolecular cyclization reaction of 1,6-dienes containing an allylic ether.

through the initial formation of the Negishi reagent **40** by the reaction of zirconocene dichloride with 2 equiv. of butylmagnesium chloride as discussed above (Scheme 8). Further ligand-exchange reaction furnishes intermediate **86** which cyclizes to form the bicyclic complex **87**. The subsequent β-alkoxy elimination accounts for the vinyl functionality in intermediate **88**. In the presence of butylmagnesium chloride this intermediate evolves to give the new zirconocene complex **89** through a simple ligand exchange. Finally, a β-hydrogen abstraction reaction leads to the product **85** and regeneration of the catalytic species **40**.

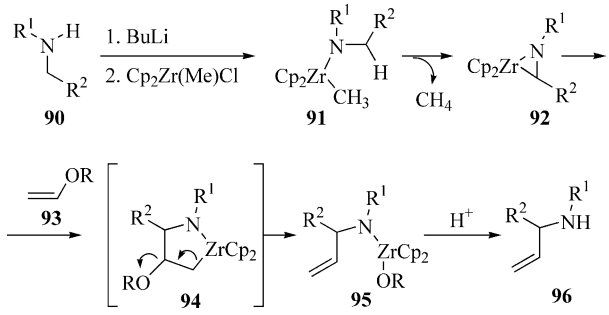
The asymmetric version of this reaction has been developed by Hoveyda and co-workers.[31] Depending on the structure of the substrate diene, exceptional levels of diastereoselectivity and enantioselectivity are attained.

The coupling-elimination reaction shown in Scheme 17 has been applied as the key reaction in the synthesis of some interesting natural products.[32]

3. Reaction of Vinylic-Functionalized Alkenes and Zirconocene Complexes

3.1 Iminezirconocene Complexes: Reaction with Enol Ethers

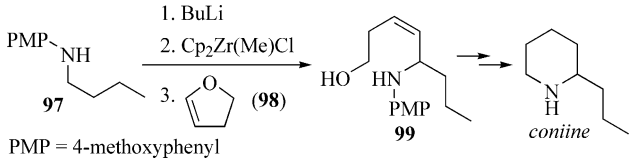
As previously discussed (see section 2.1), iminezirconocene complexes **92** are easily obtained from the reaction of amines **90** with butyllithium and chloro(methyl)zirconocene (Scheme 18). This process affords in first place the methylzirconocene amide **91** which evolves through β-abstraction of hydrogen to give iminezirconocene complexes **92** and a molecule of methane.[11] Reaction of these complexes with enol ethers **93** leads, after hydrolysis, to the formation of the new allylamines **96**.[12] This reaction is thought to proceed through the regioselective insertion of the double bond of the enol ether **93** into the zirconium–carbon bond of **92**. Moreover, the insertion of enol ether **93** occurs with the appropriate orientation to furnish the zirconaazacyclopentane **94**. β-Elimination of the alkoxy group leads to the zirconocene complex **95** which after hydrolysis afford allylamines **96**.



Scheme 18. Reaction of iminezirconocene complexes and enol ethers.

Interestingly, when 2,3-dihydrofuran (**98**) is used as the starting enol ether, amino alcohol derivatives such as **99** containing a *Z* double bond in their structure are easily

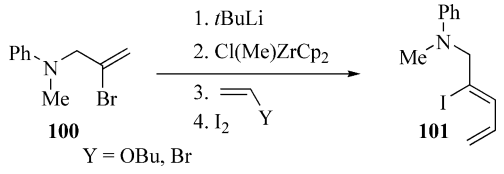
isolated. Conventional modification of these amino alcohols allows the straightforward synthesis of 2-substituted piperidines. By applying this method, a formal total synthesis of the alkaloid coniine was easily achieved from the protected butylamine **97** (Scheme 19).[12]



Scheme 19. Zirconocene-mediated synthesis of piperidine derivatives: synthesis of coniine.

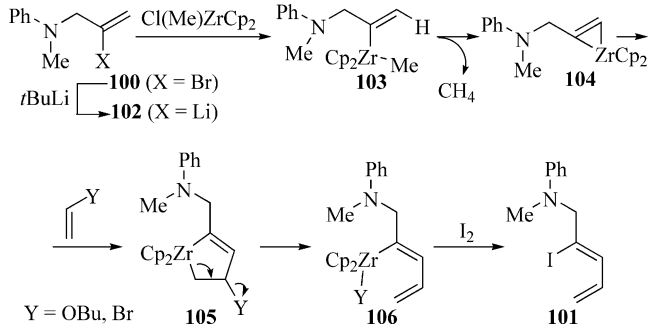
3.2 Alkynezirconocene Complexes. Reaction with Heterosubstituted Alkenes and Alkynes

The first reported example of the reaction of an alkynezirconocene complex and heterosubstituted olefins was published in 1995 by Barluenga et al.[33] In this reaction the treatment of *N*-(2-bromoallyl)-*N*-methylaniline (**100**) with *tert*-butyllithium followed by the addition of chloro(methyl)zirconocene and further reaction with butyl vinyl ether or vinyl bromide gives, after treatment with iodine, the 1,3-butadiene **101** (Scheme 20).



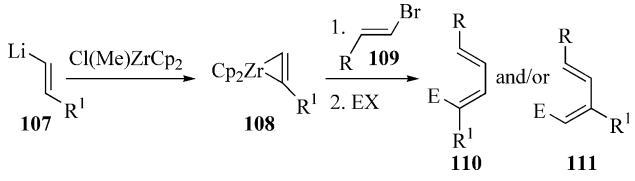
Scheme 20. Synthesis of 1,3-butadiene derivatives from bromoalkenes and heterosubstituted alkenes.

The mechanism of this process implies the initial formation of the organolithium compound **102** by treatment of the bromide **100** with *tert*-butyllithium (Scheme 21). This organolithium **102** reacts with zirconocene methyl chloride to give the methyl(vinyl)zirconocene complex **103**. Subsequent β-abstraction of hydrogen leads to the zirconacyclopropene derivative **104** releasing a molecule of methane. The insertion of the double bond of the vinyl ether or vinyl bromide takes place regioselectively at the less hindered zirconium–carbon bond of **104** leading to intermediate **105**. Moreover, this reaction is also regioselective with respect to the enol ether (or vinyl bromide): the double bond is oriented during the insertion step so that the oxygen (or bromine) atom is far away from the zirconocene moiety. β-Elimination reaction in **105** results in the formation of the dienylzirconocene derivative **106**. Finally, the reaction with an electrophile (iodine in this case) leads to the final product **101** (Scheme 21).



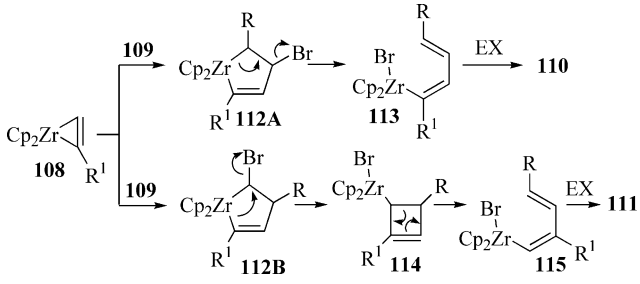
Scheme 21. Mechanism of the reaction of bromoalkenes and heterosubstituted alkenes mediated by zirconocene.

These initial studies were followed by a deeper investigation into the reaction of alkynezirconocene complexes and alkenyl bromides.[34] These studies demonstrated a more complex process than that described in Scheme 21. Thus, it was shown that the reaction of alkynezirconocene complexes **108**, which are obtained by the reaction of alkenyllithium compounds **107** and zirconocene methyl chloride, with alkenyl bromides **109** gives dienes **110** and/or **111** depending on the structure of both the starting alkenyllithium derivative **107** and the alkenyl bromide **109** (Scheme 22). Interestingly, when alkyl-substituted vinyl bromides are used, the reaction exclusively leads to dienes **111**.



Scheme 22. Different 1,3-butadiene derivatives from the reaction of alkynezirconocene complexes and bromoalkenes.

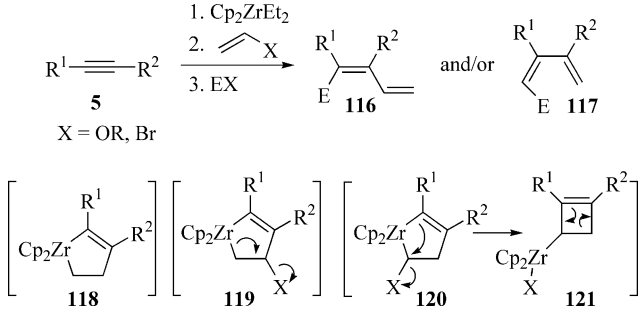
The formation of dienes **110** and **111** can be explained by the mechanism shown in Scheme 23. First, the reaction of organolithium compound **107** with zirconocene methyl chloride generates the zirconacyclopropene complex **108** through a ligand-exchange reaction followed by β-abstraction of hydrogen. Insertion of the double bond of the alkenyl bromide **109** takes place regioselectively at the less hindered zirconium–carbon bond of **108**. However, depending on the orientation of the vinyl bromide during the insertion step, two different zirconacyclopentene derivatives, **112A** or



Scheme 23. Mechanisms of the reaction of alkynezirconocene complexes and bromoalkenes.

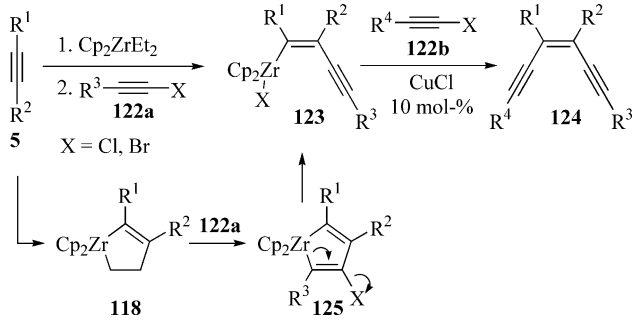
112B, can be obtained. Intermediate **112A** evolves through β-elimination of the bromine to give the dienylzirconocene complex **113**, which gives diene **110** after reaction with an electrophile. Note that this mechanism is analogous to that described for the reaction of alkynezirconocene complexes with butyl vinyl ether or vinyl bromide (see Scheme 20 and Scheme 21). On the other hand, the formation of dienes **111** from intermediate **112B** can be understood through an intramolecular migratory insertion process which affords cyclobutenezirconocene complex **114**. Thermal cleavage of the cyclobutene complex gives dienylzirconocene complex **115** which, after reaction with an electrophile, furnishes diene **111**. Experimental support for this mechanism was found by the isolation, under appropriate reaction conditions, of several cyclobutenes derived from complex **114**.[34]

Takahashi and co-workers have also been involved in the study of the reaction of alkynezirconocene complexes and heterosubstituted alkenes (enol ethers and alkenyl halides).[35] This work differs from that developed by Barluenga and co-workers described above in the method used for the generation of the alkynezirconocene complex. As shown in Scheme 24, treatment of alkynes **5** with diethylzirconocene and further reaction with an enol ether (or vinyl bromide) leads, after reaction with an electrophile, to dienes **116** (or a mixture of dienes **116** and **117** when vinyl bromide is used). In this case, the reaction evolves through the initial in situ transformation of Cp_2ZrEt_2 into $Cp_2Zr(CH_2{=}CH_2)$. In the presence of alkynes **5**, an insertion reaction occurs to give zirconacyclopentene derivatives **118**. The ethylene moiety of **118** is easily replaced by unsaturated compounds such as enol ethers or vinyl bromide to give the new zirconacyclopentene derivatives **119** or **120** depending on the orientation of the double bond during the insertion process. A β-elimination reaction in **119** leads to dienes **116** and an intramolecular migratory insertion reaction in **120** leads to dienes **117** through cyclobutane derivatives **121** (Scheme 24).



Scheme 24. Coupling reaction of alkynes and enol ethers or bromoalkenes mediated by zirconocene.

As an extension of this work, Takahashi and co-workers have developed an interesting alkynylzirconation reaction of alkynes through the reaction of an alkyne **5** with diethylzirconocene and an alkynyl halide **122a** (Scheme 25).[36] The reaction follows a mechanism analogous to those previously described which implies the formation of a zirconacyclopentadiene derivative **125** with a halogen at the β-position followed by β-halogen elimination to give metallated enyne derivatives **123**. Compounds **123** react with different electrophiles (H_2O, I_2, allyl chloride, benzoyl chloride, etc.) to give the corresponding functionalized enyne derivatives. An attractive application of this method is the one-pot synthesis of (*Z*)-enediynes **124** by treatment of the intermediate zirconocene complex **123** with a second alkynyl halide **122b** in the presence of a catalytic amount of CuCl (Scheme 25).

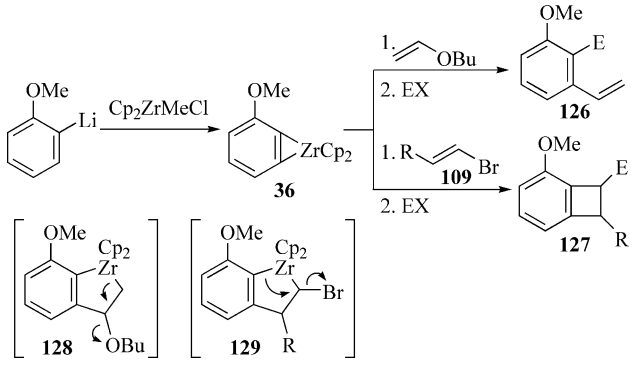


Scheme 25. Coupling reaction of alkynes and alkynyl halydes mediated by zirconocene: synthesis of (*Z*)-enediynes.

3.3 Arynezirconocene Complexes: Reaction with Heterosubstituted Alkenes

In the course of the studies carried out by Barluenga et al. on the reactivity of zirconocene complexes and heterosubstituted alkenes, we have found that arynezirconocene complexes exemplified by **36** react with butyl vinyl ether to give the styrene derivatives **126** as single regioisomers (Scheme 26).[37] This process supposes an easy functionalization of the aromatic ring by the selective introduction of a vinyl moiety and an electrophile at two adjacent positions of the initial aromatic ring. The reaction proceeds by the formation of the intermediate **128** which evolves through β-alkoxy elimination. This process is doubly regioselective: insertion occurs at the zirconium–carbon bond of **36** that is farthest from the methoxy group and the double bond of the enol ether is oriented during the insertion step so that the oxygen atom is far away from the zirconocene moiety. This reaction has been extended to the use of different aryllithiums and enol ethers as starting materials. Particularly interesting is the employ of cyclic enol ethers since functionalized (*Z*)-alkenol derivatives are easily obtained.

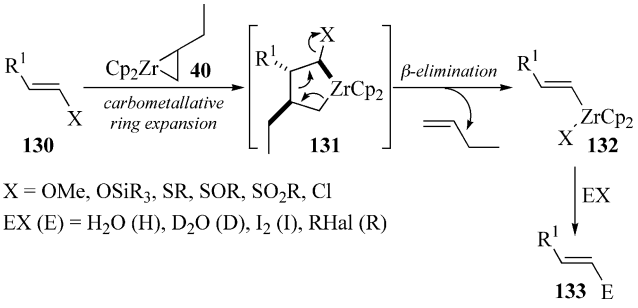
Interestingly, when this reaction is performed with alkenyl bromides **109** instead of enol ethers, cyclobutabenzene derivatives such as **127** are isolated in a totally regio- and diastereoselective way (Scheme 26).[38] Again, the process supposes an easy functionalization of two adjacent positions in the starting aryllithium. In this case, the reaction proceeds through the regioselective formation of intermediate **129** which evolves, as in some other cases described before, through an intramolecular migratory insertion process to give the cyclobutabenzene derivatives **127**.



Scheme 26. Reaction of arynezirconocene complexes and heterosubstituted alkenes.

3.4 Alkenezirconocene Complexes: Reaction with Heterosubstituted Alkenes and Alkynes

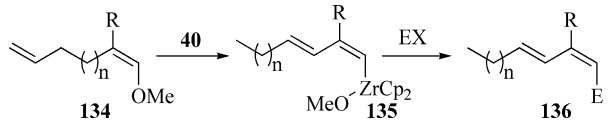
Marek and co-workers have been involved for a few years in a comprehensive study of the reaction of heterosubstituted alkenes **130** and alkenezirconocene complexes (in particular the Negishi reagent **40**). As shown in Scheme 27 the reaction of the Negishi reagent **40** with vinyl alkoxides,[39] sulfides, sulfoxides, sulfones[40] or chlorides[41] and also with silyl-[42] or tosyloxydienes[43] supposes a straightforward method for the preparation of alkenylzirconocene complexes such as **132**. Initially, this interesting transformation was thought to proceed through a formal exchange of the olefinic ligand to generate a new alkenezirconocene complex followed by β-elimination of the alkoxide.[7g] Further investigations in this field seem to indicate that this reaction occurs through a carbometallative ring-expansion, which generates the intermediate **131**, followed by an elimination reaction.[44]



Scheme 27. Alkenylzirconocene complexes from heterosubstituted alkenes and the Negishi reagent.

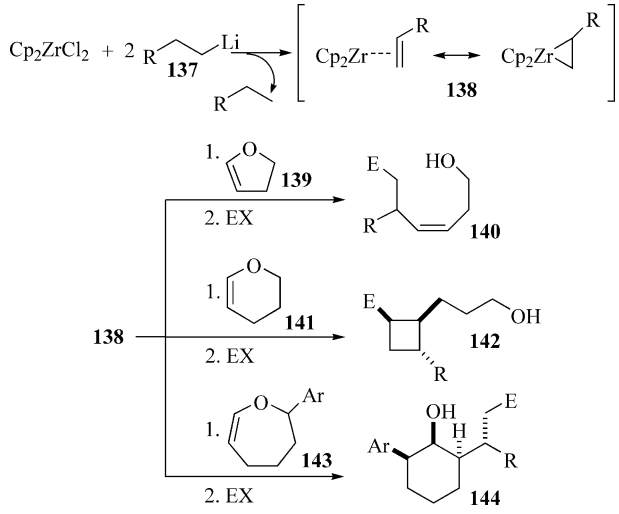
Alkenylzirconocene complexes **132** react with electrophiles to afford the new functionalized alkenes **133** (Scheme 27). So, globally the process from alkenes **130** to alkenes **133** supposes a formal substitution reaction of the heteroatom of **130** by the corresponding electrophile. Although conventional electrophiles such as water, deuterium oxide or iodine may be used, more appealing is the transmetallation of zirconium to copper, zinc or palladium in order to perform carbon–carbon couplings.

Marek and co-workers have also developed a reaction for the synthesis of dienylzirconocene complexes **135** from non-conjugated unsaturated enol ethers **134** (Scheme 28).[45] This methodology is based on a tandem allylic C–H bond activation–elimination sequence. As expected, the reaction of organometallic compounds **135** with appropriate electrophiles, like those shown in Scheme 27, leads to functionalized dienes **136** (Scheme 28).



Scheme 28. Dienylzirconocene complexes from non-conjugated unsaturated enol ethers.

Totally different reaction pathways were found by Barluenga and co-workers when cyclic enol ethers were used.[46] Thus, the reaction of alkenezirconocene complexes **138**, generated by the reaction of zirconocene dichloride and 2 equiv. of alkyllithium compounds **137**, with five-membered cyclic enol ether **139** and further reaction with an electrophile furnishes the new alcohol derivatives **140** in high yields. When the same reaction is performed using the six-membered cyclic enol ether **141**, cyclobutane derivatives **142** are isolated in high yields and as unique diastereoisomers. Finally, the reaction of alkenezirconocene complex **138** and seven-membered cyclic enol ethers **143** leads to the formation of cyclohexane derivatives **144** in high yields and as single diastereoisomers (Scheme 29).

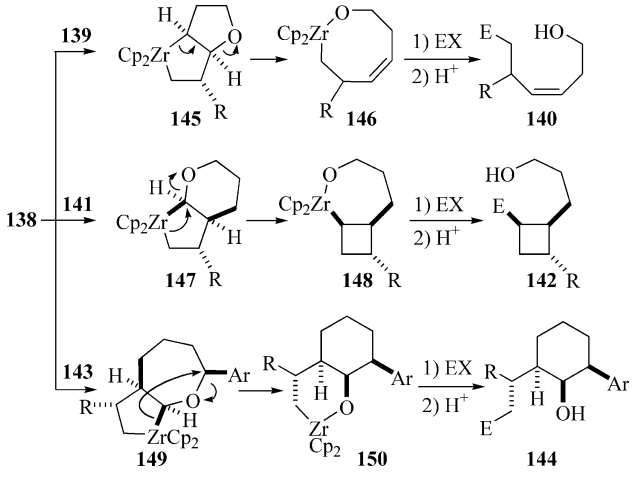


Scheme 29. Reactions of alkenezirconocene complexes and cyclic enol ethers.

It is interesting to note the different behaviour of cyclic enol ethers (**139**, **141** or **143** in Scheme 29) and acyclic enol ethers (see Scheme 27) when they react with alkenezirconocene complexes (**40** or **138**). Thus, with acyclic enol ethers, no incorporation of the alkene moiety of the starting zirconocene complex is observed in the final product (see Scheme 27). Formally, in these cases, the process supposes a simple substitution of the alkoxy group of the enol ether by the zirconocene group. On the other hand, the reaction with cyclic enol ethers leads to products **140**, **142** or **144**

that incorporate into their structures the alkene from the zirconocene complex **138** (Scheme 29).

The mechanism that explains the formation of compounds **140**, **142** and **144** is shown in Scheme 30. For the formation of alcohols **140**, an initial insertion of the double bond of enol ether **139** into the zirconium–secondary carbon bond of zirconacyclopropane **138** to generate the bicyclic intermediate **145** is considered. This intermediate evolves through a β-elimination of the alkoxy group to form the oxazirconacyclooctene derivative **146**. The final addition of the electrophile leads, after hydrolysis, to the (*Z*)-alkene derivatives **140**. It is important to remark that this process is doubly regioselective. On one hand, the insertion only occurs at the Zr–C bond of **138** which implies the more substituted carbon is attacked, while conversely, the reaction is also regioselective with respect to the enol ether **139**: the double bond is orientated during the insertion step with the oxygen atom far away from the zirconocene moiety (Scheme 30).

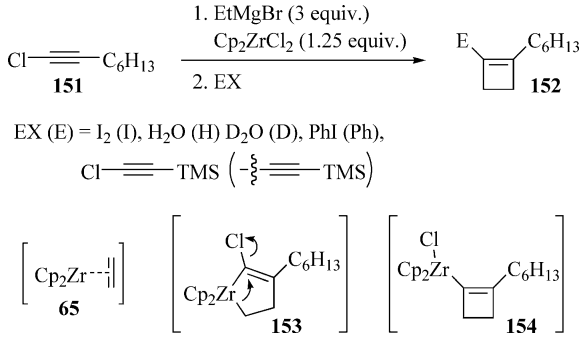


Scheme 30. Mechanisms of the reactions of alkene-zirconocene complexes and cyclic enol ethers.

The generation of cyclobutane derivatives **142** from the six-membered enol ether **141** can be explained by an insertion of the double bond of this enol ether into **138** to produce the bicyclic intermediate **147**. An intramolecular migratory insertion process generates intermediate **148** which, after reaction with an electrophile and hydrolysis, affords cyclobutane derivatives **142**. Again, the insertion process is regioselective with respect to the zirconacyclopropane **138** with the reaction occurring at the more substituted Zr–C bond. The reaction is also regioselective with respect to the enol ether **141** since the double bond of this enol ether is orientated so that the oxygen atom is close to the zirconocene moiety (note that the orientation of the enol ether is the contrary to that observed for five-membered enol ethers) (Scheme 30).

A plausible mechanism for the reaction of in situ formed alkenezirconocene complexes **138** and aryl-substituted seven-membered cyclic enol ethers **143** implies, again, a doubly regioselective insertion reaction to generate the bicyclic derivative **149**. This intermediate evolves through an intramolecular migratory insertion process to give **150**. This process supposes a formal ring-contraction of the initial seven-membered cyclic enol ether. At this point it is important to note the different evolution of the relatively similar intermediates **147** and **149**. Although in both cases an intramolecular migratory insertion reaction is proposed, note that the carbon–zirconium and carbon–oxygen bonds implied in this process are not the same. Reaction of intermediate **150** with the corresponding electrophile and hydrolysis furnishes the cyclohexanol derivatives **144**. Interestingly, in order to justify the high stereocontrol observed in the formation of **144** (four new chiral centres are formed in a selective way) it is supposed that the zirconocene complex **138** approaches the double bond of the enol ether **143** (to form **149**) from the same face as that on which the aryl group is placed (Scheme 30). The mechanism of this unusual transformation is supported by theoretical calculations.[46b]

Cyclobutene derivatives have also been obtained by Takahashi and co-workers in the zirconocene-mediated or -catalyzed reaction of ethylmagnesium bromide and alkynyl halides.[47] So, for example, reaction of alkynyl chloride **151** with ethylmagnesium bromide and zirconocene dichloride furnishes different cyclobutene derivatives **152** depending on the electrophile used in the last step of the reaction (Scheme 31). This reaction proceeds through the initial formation of ethenezirconocene complex **65** that reacts by insertion of the alkyne **151** to give the α-halozirconacyclopentene intermediate **153**. An intramolecular migratory insertion reaction accounts for the formation of the cyclobutane derivative **154**. The final reaction with the electrophile accounts for the formation of products **152** (Scheme 31).

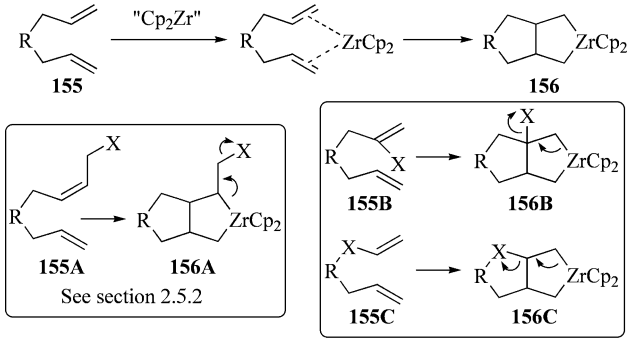


Scheme 31. Cyclobutene derivatives from alkynyl chlorides and in situ formed alkenezirconocene complexes.

3.5 Intramolecular Reactions of Alkenezirconocene Complexes and Heterosubstituted Alkenes

It is well known that the reaction of 1,6-dienes **155** with a zirconocene equivalent furnishes the corresponding zirconabicycle **156** (Scheme 32).[48] When this zirconabicycle intermediate contains a β-leaving group it evolves, through an elimination reaction, to provide in a very simple way interesting structures that in many cases are difficult to obtain by traditional procedures. The β-leaving group (see **156A**) may come from a 1,6-diene **155A** with a heteroatom

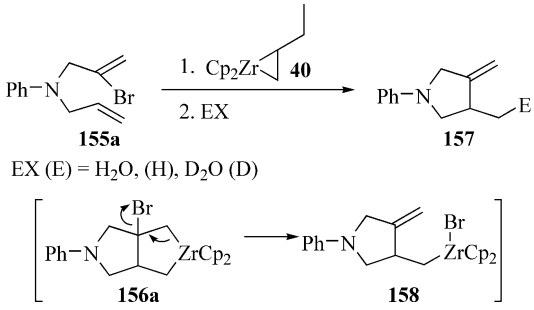
at an allylic position. The reactivity of this kind of diene has already been discussed in Section 2.5.2 of this review. Alternatively, the β-leaving group (see **156B** and **156C**) may come from 1,6-diene **155B** or **155C** with a heteroatom at a vinylic position. These possibilities will be analyzed in the next sections.



Scheme 32. Reactivity of different 1,6-diene derivatives and zirconocene.

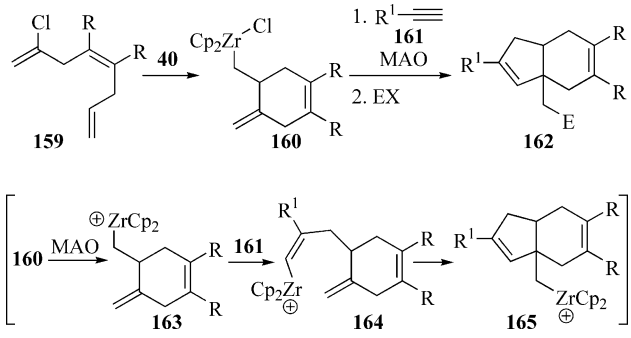
3.5.1 Stoichiometric Reactions: Zirconocene-Mediated Cyclization–Elimination Reactions

We have already discussed in Section 2.5.2 how Waymouth and co-workers have developed a catalytic cyclization–elimination reaction of dienes that contain a leaving group (methoxy group) at an allylic position. In an extension of this work, in 1997 the same group published a related reaction that involved the use of dienes containing a leaving group (bromine) at a vinylic position (general structure similar to **155B** in Scheme 32).[49] Thus, for example, reaction of bromodiene **155a** with the Negishi reagent **40** as the zirconocene equivalent, followed by treatment with an electrophile, gives the pyrrolidine derivative **157** (Scheme 33). The reaction implies the formation of intermediate **156a** which evolves through a β-bromo elimination reaction to give the new zirconocene complex **158**. Reaction of this intermediate with the electrophile leads to the corresponding product **157**.



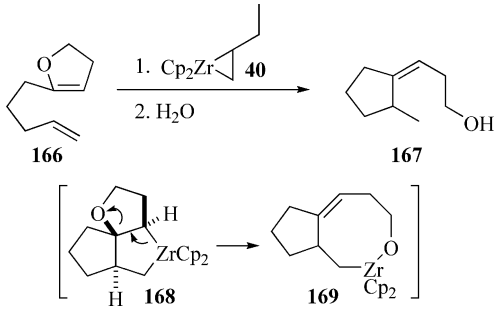
Scheme 33. Cyclization–elimination reactions of 1,6-diene derivatives containing a vinylic bromine atom.

Takahashi and co-workers have developed a similar reaction employing 1,7-dienes **159** (Scheme 34).[50] Interestingly, these authors found that the (cycloalkenyl)alkyl zirconium compounds obtained in the first step of the reaction evolve in the presence of methylaluminoxane (MAO) and an alkyne **161** to give the tetrahydroindene derivatives **162**. The mechanism for the formation of zirconocene complexes **160** is similar to that described in Scheme 33. To explain the transformation of these intermediates into the final products **162** the authors propose the sequence shown in Scheme 34. Thus, in the presence of MAO complexes **160** are transformed into the cationic species **163**. Insertion of the alkyne **161** into the Zr–C(sp^3) bond of **163** gives complexes **164**. A second insertion reaction of the *exo*-methylene moiety into the Zr–C(sp^2) bond affords intermediates **165** which by reaction with an appropriate electrophile furnish the products **162** (Scheme 34).



Scheme 34. Cyclization–elimination reactions of 1,7-diene derivatives: synthesis of tetrahydroindene derivatives.

Owen and Whitby have also reported the cyclization–elimination reaction of 2-heterosubstituted 1,6-dienes and 1,6-enynes in which the heteroatom (β-leaving group) may not be only a halogen atom but also an alkoxy group.[51] In the example shown in Scheme 35, the dihydrofuran derivative **166** reacts with the Negishi reagent to give after hydrolysis the cyclopentane derivative **167** bearing an exocyclic double bond and an alcohol functionality. This reaction proceeds through the formation of intermediate **168** that evolves through β-alkoxy elimination to give complex **169**. The final hydrolysis step accounts for the formation of products **167** (Scheme 35).



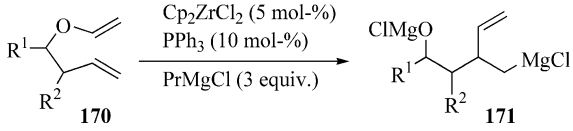
Scheme 35. Cyclization–elimination reaction of 2-alkoxy-substituted 1,6-diene derivatives.

3.5.2 Catalytic Reactions: Zirconocene-Catalyzed Cyclization–Elimination Reactions

All the intramolecular reactions commented upon in the last section involved the use of stoichiometric amounts of

zirconium complexes and a starting diene derivative in which the leaving group is not part of the linking chain (general structure **155B** in Scheme 32). As part of our ongoing studies in this field, we became interested in the reactivity of dienes such as **155C** (see Scheme 32) in which the leaving group is part of the chain.[52] Our final goal was the development of new reactions that use only catalytic amounts of zirconium complexes.

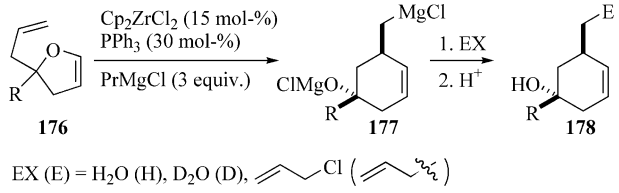
In this context, we have developed a new zirconocene-catalyzed isomerization–magnesation reaction of readily available alkene-substituted enol ethers **170** (Scheme 36).[53] Thus, the treatment of starting enol ethers **170** with 3 equiv. of propylmagnesium chloride in the presence of 5 mol-% of zirconocene dichloride and 10 mol-% of triphenylphosphane leads to the formation of the Grignard reagents **171**. These organomagnesium reagents react with typical electrophiles to give the corresponding alkenol derivative. It is interesting to note that the global process shown in Scheme 36 could be considered as a vinylmagnesation of a terminal alkene which is rather a difficult challenge.



Scheme 36. Zirconocene-catalyzed isomerization–magnesation reaction of alkene-substituted enol ethers.

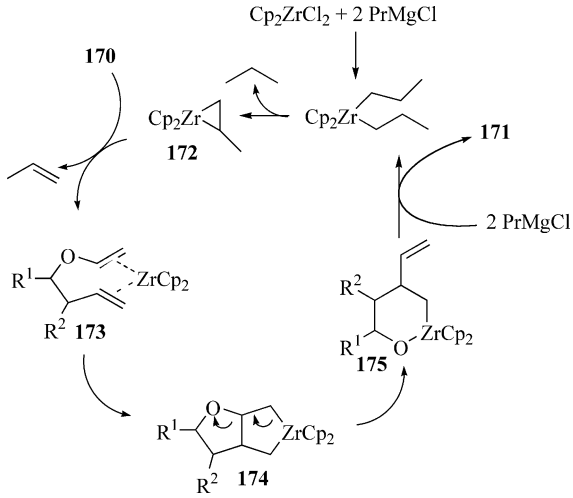
The mechanism proposed for this catalytic reaction is shown in Scheme 37. Initially, the zirconocene dichloride reacts with 2 equiv. of propylmagnesium chloride to form the corresponding dipropylzirconocene complex which further evolves, as described by Negishi, to give the propene-zirconocene complex **172** by losing a molecule of propane. This 14-electron complex reacts in the presence of the alkene-substituted enol ether **170** through a ligand-exchange process releasing a molecule of propene and forming the 18-electron zirconocene complex **173**. A carbocyclization reaction furnishes the bicyclic complex **174**. Subsequent Zr-alkoxide elimination affords the intermediate **175**. Finally, a double magnesium–zirconium exchange gives the final organomagnesium compound **171** regenerating the dipropylzirconocene complex which initiates a new catalytic cycle.

An interesting extension of this new catalytic method is the synthesis of six-, seven- and eight-membered carbocycles from cyclic enol ethers (Scheme 38).[54] For example, when the allyl-substituted dihydrofuran derivatives **176** are treated with 3 equiv. of propylmagnesium chloride in the presence of 15 mol-% of zirconocene dichloride and 30 mol-% of triphenylphosphane, the Grignard reagents **177** are obtained. Further treatment of these organomagnesium reagents with electrophiles affords the cyclohexenol derivatives **178** as single diastereoisomers. The global process supposes a formal ring-expansion of a cyclic enol ether to give a functionalized carbocycle.

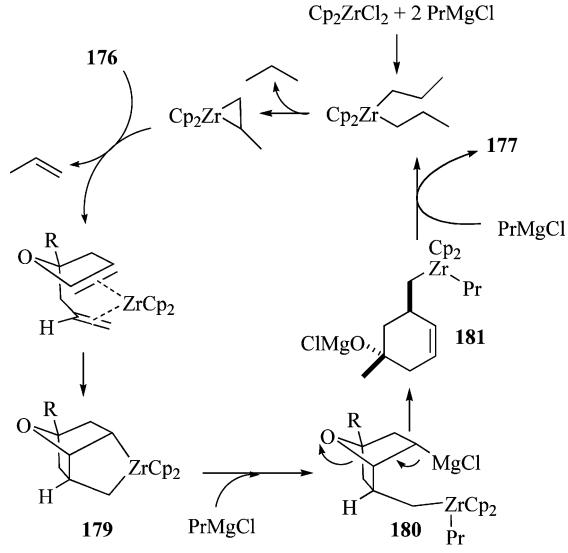


Scheme 38. Zirconocene-catalyzed formal ring-expansion reaction of cyclic enol ethers to give functionalized carbocycles.

Although the mechanism of this transformation is in many aspects similar to that described in Scheme 37, some features should be noted (Scheme 39). Thus, the first steps of the catalytic cycle leading to intermediate **179** are the same as those previously discussed. At this point, although a Zr-alkoxide elimination reaction could be proposed, this option would afford a very constrained bicyclic oxazirconocene complex. For this reason, an initial Mg–Zr exchange to give the bimetallic species **180** is proposed as the most likely step. Subsequent Mg-alkoxide elimination leads to in-



Scheme 37. Mechanism of the zirconocene-catalyzed isomerization–magnesation reaction of enol ethers.



Scheme 39. Mechanism of the formal zirconocene-catalyzed ring-expansion reaction of cyclic enol ethers.

termediate **181**. Under the catalytic conditions, and as a consequence of an excess of propylmagnesium chloride, the intermediate **181** may experience a new zirconium–magnesium exchange, affording the Grignard reagent **177** and regenerating the catalytic species.

4. Summary and Outlook

As shown in this review, the tandem zirconium-mediated or -catalyzed cross-coupling–elimination reaction is a powerful tool in organic chemistry for accessing complex structures in a straightforward manner from, in general, readily available starting materials. Although much progress has been made in this area in recent years, many challenges remain to be addressed. In particular, the development of catalytic versions of some of the reported reactions should be accompanied by asymmetric versions of these processes. Another exciting area in which this chemistry should find application in the future is the synthesis of natural products or their analogues. At the moment it is difficult to find in the literature synthetic applications of the organozirconium chemistry perhaps due to the inability of organic chemists to adapt their thinking to the sometimes rather difficult pathways of organozirconium chemistry. However, owing to the impressive opportunities that this chemistry allows, future exciting developments in this field can be expected.

Acknowledgments

We gratefully acknowledge the Ministerio de Educación y Ciencia (MEC) for financial support of our research. F. R. also thanks the Fondo Social Europeo (Ramón y Cajal contract). We are also indebted to all our collaborators and in particular to Professor José Barluenga for his helpful assistance.

[1] a) I. Marek (Ed.), *New Aspects of Zirconium Containing Organic Compounds, Topics in Organometallic Chemistry*, vol. 10, Springer, Berlin, **2005**; b) I. Marek (Ed.), *Titanium and Zirconium in Organic Synthesis*, Wiley-VCH, Weinheim, **2002**.

[2] G. Wilkinson, J. M. Birmingham, *J. Am. Chem. Soc.* **1954**, *76*, 4281–4284.

[3] For recent reviews see, for example: a) H. G. Alt, A. Köpll, *Chem. Rev.* **2000**, *100*, 1205–1221; b) G. W. Coates, *Chem. Rev.* **2000**, *100*, 1223–1252.

[4] a) P. C. Wailes, H. Weigold, *J. Organomet. Chem.* **1970**, *24*, 405–411; b) see also: P. C. Wailes, H. Weigold, *J. Organomet. Chem.* **1971**, *27*, 373–378.

[5] a) D. W. Hart, J. Schwartz, *J. Am. Chem. Soc.* **1974**, *96*, 8115; b) D. W. Hart, T. F. Blackburn, J. Schwartz, *J. Am. Chem. Soc.* **1975**, *97*, 679–680; c) C. A. Bertelo, J. Schwartz, *J. Am. Chem. Soc.* **1976**, *98*, 262–264; d) J. Schwartz, J. A. Labinger, *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 333.

[6] E. Negishi, T. Takahashi, *Acc. Chem. Res.* **1994**, *27*, 124–130, and references therein.

[7] For some reviews on different uses of organozirconium reagents, see: a) Y. Hanzawa, H. Ito, T. Taguchi, *Synlett* **1995**, 299–305; b) A. Ohff, S. Pulst, C. Lefeber, N. Peulecke, P. Arndt, V. V. Burkalov, U. Rosenthal, *Synlett* **1996**, 111–118; c) E. Negishi, D. Y. Kondakov, *Chem. Soc. Rev.* **1996**, *25*, 417–426; d) S. F. Fillery, G. J. Gordon, T. Luker, R. J. Whitby, *Pure Appl. Chem.* **1997**, *69*, 633–638; e) N. Avarvari, P. Rosa, F. Mathey, P. Le Floch, *J. Organomet. Chem.* **1998**, *567*, 151–155; f) T. Takahashi, M. Kotora, R. Hara, Z. Xi, *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2591–2602; g) A. Liard, J. Kaftanov, H. Chechik, S. Farhat, N. Morlender-Vais, C. Averbuj, I. Marek, *J. Organomet. Chem.* **2001**, *624*, 26–33; h) E. Negishi, *Pure Appl. Chem.* **2001**, *73*, 239–242; i) I. Bytschkov, S. Doye, *Eur. J. Org. Chem.* **2003**, 935–946; j) J. Barluenga, F. Rodríguez, L. Álvarez-Rodrigo, F. J. Fañanás, *Chem. Soc. Rev.* **2005**, *34*, 762–768; k) I. Marek, N. Chinkov, A. Levin, *Synlett* **2006**, 501–514; l) U. Rosenthal, V. V. Burlakov, M. A. Bach, T. Beweries, *Chem. Soc. Rev.* **2007**, *36*, 719–728.

[8] S. Thanedar, M. F. Farona, *J. Organomet. Chem.* **1982**, *235*, 65–68.

[9] E. Negishi, F. E. Cederbaum, T. Takahashi, *Tetrahedron Lett.* **1986**, *27*, 2829–2832.

[10] N. Coles, R. J. Whitby, J. Blagg, *Synlett* **1990**, 271–272.

[11] N. Coles, M. C. J. Harris, R. J. Whitby, J. Blagg, *Organometallics* **1994**, *13*, 190–199.

[12] J. Barluenga, F. Rodríguez, L. Álvarez-Rodrigo, J. M. Zapico, F. J. Fañanás, *Chem. Eur. J.* **2004**, *10*, 109–116.

[13] a) T. Takahashi, N. Suzuki, M. Kageyama, D. Y. Kondakov, R. Hara, *Tetrahedron Lett.* **1993**, *34*, 4811–4814; b) N. Suzuki, D. Y. Kondakov, M. Kageyama, M. Kotora, R. Hara, T. Takahashi, *Tetrahedron* **1995**, *51*, 4519–4540.

[14] Y. Liu, H. Gao, *Org. Lett.* **2006**, *8*, 309–311.

[15] G. D. Cuny, S. L. Buchwald, *Organometallics* **1991**, *10*, 363–365.

[16] C. J. Rousset, D. R. Swanson, F. Lamaty, E. Negishi, *Tetrahedron Lett.* **1989**, *30*, 5105–5108.

[17] a) H. Ito, T. Nakamura, T. Taguchi, Y. Hanzawa, *Tetrahedron* **1995**, *51*, 4507–4518. See also ref.[7a].

[18] H. Ito, T. Taguchi, Y. Hanzawa, *Tetrahedron Lett.* **1992**, *33*, 7873–7876.

[19] a) H. Ito, T. Taguchi, *Tetrahedron Lett.* **1997**, *38*, 5829–5830; b) H. Ito, H. Kuroi, H. Ding, T. Taguchi, *J. Am. Chem. Soc.* **1998**, *120*, 6623–6624; c) H. Ito, A. Sato, T. Taguchi, *Tetrahedron Lett.* **1999**, *40*, 3217–3220; d) H. Ito, A. Sato, T. Kusanagi, T. Taguchi, *Tetrahedron Lett.* **1999**, *40*, 3397–3398; e) A. Sato, H. Ito, T. Taguchi, *J. Org. Chem.* **2000**, *65*, 918–921; f) A. Sato, H. Ito, Y. Yamaguchi, T. Taguchi, *Tetrahedron Lett.* **2000**, *41*, 10239–10243.

[20] H. Ito, A. Sato, T. Taguchi, *Tetrahedron* **2005**, *61*, 10868–10879.

[21] H. Ito, Y. Motoki, T. Taguchi, Y. Hanzawa, *J. Am. Chem. Soc.* **1993**, *115*, 8835–8836. See also ref.[7a].

[22] For an excellent review on the investigations of Paquette and co-workers on this subject and also on the synthetic applications, see: L. A. Paquette, *J. Organomet. Chem.* **2006**, *691*, 2083–2088.

[23] Y. Ikeuchi, T. Taguchi, Y. Hanzawa, *J. Org. Chem.* **2005**, *70*, 4354–4359.

[24] T. Takahashi, R. Hara, S. Huo, Y. Ura, M. P. Leese, N. Suzuki, *Tetrahedron Lett.* **1997**, *38*, 8723–8726.

[25] a) J. P. Morken, M. T. Didiuk, A. H. Hoveyda, *J. Am. Chem. Soc.* **1993**, *115*, 6997–6998; for a non-asymmetric version of this reaction, see: b) N. Suzuki, D. Y. Kondakov, T. Takahashi, *J. Am. Chem. Soc.* **1993**, *115*, 8485–8486; for some interesting reports on zirconocene-catalyzed carbomagnesiation reactions, see: c) T. Takahashi, T. Seki, Y. Nitto, M. Saburi, C. J. Rousset, E. Negishi, *J. Am. Chem. Soc.* **1991**, *113*, 6266–6268; d) K. S. Knight, R. M. Waymouth, *J. Am. Chem. Soc.* **1991**, *113*, 6268–6270; e) D. P. Lewis, P. M. Muller, R. J. Whitby, R. V. H. Jones, *Tetrahedron Lett.* **1991**, *32*, 6797; f) R. Fischer, D. Walther, P. Gebhardt, H. Görls, *Organometallics* **2000**, *19*, 2532–2540.

[26] a) A. H. Hoveyda, J. P. Morken, *J. Org. Chem.* **1993**, *58*, 4237–4244; b) M. T. Didiuk, C. W. Johannes, J. P. Morken, A. H. Hoveyda, *J. Am. Chem. Soc.* **1995**, *117*, 7097–7104.

[27] Z. Xu, C. W. Johannes, A. F. Houri, D. S. La, D. A. Cogan, G. E. Hofilena, A. H. Hoveyda, *J. Am. Chem. Soc.* **1997**, *119*, 10302–10316.

[28] a) J. P. Morken, M. T. Didiuk, M. S. Vissier, A. H. Hoveyda, *J. Am. Chem. Soc.* **1994**, *116*, 3123–3124; b) M. S. Visser, A. H. Hoveyda, *Tetrahedron* **1995**, *51*, 4383–4394; c) J. P. A. Harrity, M. S. Visser, J. D. Gleason, A. H. Hoveyda, *J. Am. Chem. Soc.* **1997**, *119*, 1488–1489; d) N. M. Heron, J. A. Adams, A. H. Hoveyda, *J. Am. Chem. Soc.* **1997**, *119*, 6205–6206; e) J. P. A. Harrity, D. S. La, D. R. Cefalo, M. S. Visser, A. H. Hoveyda, *J. Am. Chem. Soc.* **1998**, *120*, 2343–2351; f) C. W. Johannes, M. S. Visser, G. S. Weatherhead, A. H. Hoveyda, *J. Am. Chem. Soc.* **1998**, *120*, 8340–8347; g) J. A. Adams, J. G. Ford, P. J. Stamatos, A. H. Hoveyda, *J. Org. Chem.* **1999**, *64*, 9690–9696; see also: h) L. Bell, R. J. Whitby, R. V. H. Jones, M. C. H. Standen, *Tetrahedron Lett.* **1996**, *37*, 7139–7142.

[29] J. de Armas, S. P. Kolis, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 5977–5983.

[30] a) K. Knight, R. M. Waymouth, *Organometallics* **1994**, *13*, 2575–2577; b) T. Takahashi, D. Y. Kondakov, N. Suzuki, *Organometallics* **1994**, *13*, 3411–3412.

[31] S. J. Degrado, J. A. Adams, A. H. Hoveyda, *Inorg. Chim. Acta* **2003**, *345*, 261–267.

[32] For example, see: a) A. D. Campbell, T. M. Raynham, R. J. K. Taylor, *J. Chem. Soc. Perkin Trans. 1* **2000**, 3194–3204; b) P. Herrmann, M. Kotora, *Tetrahedron Lett.* **2007**, *48*, 3209–3212.

[33] J. Barluenga, R. Sanz, F. J. Fañanás, *Z. Naturforsch., Teil B* **1995**, *50*, 312–314.

[34] J. Barluenga, F. Rodríguez, L. Álvarez-Rodrigo, F. J. Fañanás, *Chem. Eur. J.* **2004**, *10*, 101–108.

[35] a) T. Takahashi, D. Y. Kondakov, Z. Xi, N. Suzuki, *J. Am. Chem. Soc.* **1995**, *117*, 5871–5872; b) T. Takahashi, Z. Xi, R. Fischer, S. Huo, C. Xi, K. Nakajima, *J. Am. Chem. Soc.* **1997**, *119*, 4561–4562.

[36] Y. Liu, Z. Zhong, K. Nakajima, T. Takahashi, *J. Org. Chem.* **2002**, *67*, 7451–7456.

[37] J. Barluenga, A. Fernández, L. Álvarez-Rodrigo, F. Rodríguez, F. J. Fañanás, *Synlett* **2005**, 2513–2515.

[38] J. Barluenga, J. Calleja, L. Álvarez-Rodrigo, F. Rodríguez, F. J. Fañanás, manuscript submitted.

[39] A. Liard, I. Marek, *J. Org. Chem.* **2000**, *65*, 7218–7220.

[40] a) S. Farhat, I. Marek, *Angew. Chem. Int. Ed.* **2002**, *41*, 1410–1413; b) S. Farhat, I. Zouev, I. Marek, *Tetrahedron* **2004**, *60*, 13291337.

[41] T. Takahashi, M. Kotora, R. Fischer, Y. Nishihara, K. Nakajima, *J. Am. Chem. Soc.* **1995**, *117*, 11039–11040.

[42] B. Ganchegui, P. Bertus, J. Szymoniak, *Synlett* **2001**, 123–125.

[43] M. Fujiwara, J. Ichikawa, T. Okauchi, T. Minami, *Tetrahedron Lett.* **1999**, *40*, 7261–7265.

[44] N. Chinkov, H. Chechik, S. Majumdar, A. Liard, I. Marek, *Synthesis* **2002**, 2473–2483.

[45] a) N. Chinkov, S. Majumdar, I. Marek, *J. Am. Chem. Soc.* **2002**, *124*, 10282–10283; b) N. Chinkov, S. Majumdar, I. Marek, *J. Am. Chem. Soc.* **2003**, *125*, 13258–13264; see also ref.[7k].

[46] a) J. Barluenga, L. Álvarez-Rodrigo, F. Rodríguez, F. J. Fañanás, *Angew. Chem. Int. Ed.* **2004**, *43*, 3932–3935; b) J. Barluenga, L. Álvarez-Rodrigo, F. Rodríguez, F. J. Fañanás, T. L. Sordo, P. Campomanes, *Angew. Chem. Int. Ed.* **2007**, *46*, 2607–2609.

[47] K. Kasai, Y. Liu, R. Hara, T. Takahashi, *Chem. Commun.* **1998**, 1989–1990.

[48] C. J. Rousset, D. R. Swanson, F. Lamaty, E. Negishi, *Tetrahedron Lett.* **1989**, *30*, 5105–5108.

[49] D. B. Millward, R. M. Waymouth, *Organometallics* **1997**, *16*, 1153–1158.

[50] M. Kotora, G. Gao, Z. Li, Z. Xi, T. Takahashi, *Tetrahedron Lett.* **2000**, *41*, 7905–7909.

[51] D. R. Owen, R. J. Whitby, *Synthesis* **2005**, 2061–2074.

[52] For a titanium-mediated reaction with this kind of diene, see: R. Nakajima, H. Urabe, F. Sato, *Chem. Lett.* **2002**, 4–5.

[53] J. Barluenga, L. Álvarez-Rodrigo, F. Rodríguez, F. J. Fañanás, *Angew. Chem. Int. Ed.* **2006**, *45*, 6362–6365.

[54] J. Barluenga, L. Álvarez-Rodrigo, F. Rodríguez, F. J. Fañanás, *Org. Lett.* **2007**, *9*, 3081–3084.

Received: October 2, 2007
Published Online: January 3, 2008

