Synthetic Methods

Reaction of Alkene–Zirconocene Complexes and Cyclic Enol Ethers through New Reaction Pathways**

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In recent years there has been increasing interest in the use of organozirconocene complexes in organic and organometallic chemistry because of their unique ability to promote uncommon transformations.[1] In this context, the discovery by Negishi et al. of a convenient method for the generation of low-valent zirconocene species was considered to be a crucial achievement.[2] Thus, the butene–zirconocene complex **1** (Negishi reagent) has been shown to be an excellent reagent for carbon–carbon coupling reactions involving different unsaturated substrates.[3] Some years ago, we initiated a program for developing new reactions using organozirconocene complexes[4] and became interested in the reaction of alkyne– and imine–zirconocene[5,6] complexes with enol ethers. In closely related work, Marek and co-workers reported the generation of vinyl–zirconium derivatives from the reaction of acyclic enol ethers and the Negishi reagent.[7] Initially, this transformation was thought to proceed through a formal exchange of the olefinic ligand to generate a new alkene–zirconocene complex followed by β-elimination of the alkoxide.[7] Further investigations by Marek and co-workers seem to indicate that this reaction occurs through a carbometalative ring-expansion that generates the zirconacyclopentane intermediate **I** followed by an elimination reaction (Scheme 1).[8] Unfortunately, the intermediate **I** could not be trapped. Herein, we report our preliminary results on the reaction of cyclic enol ethers and alkene–zirconocene complexes to yield new functionalized molecules arising from unprecedented reaction pathways that involve the coupling of enol ethers and alkene–zirconocene complexes.

Our investigations began by studying the reaction of several alkene–zirconocene complexes **2** and five-membered cyclic enol ethers **3**. Thus, [Cp_2ZrCl_2] was treated with two equivalents of an organolithium compound **4** in THF at −78 °C to generate the corresponding alkene–zirconocene complex **2**. In situ treatment of **2** with the corresponding cyclic enol ether **3** was followed by heating to room temperature

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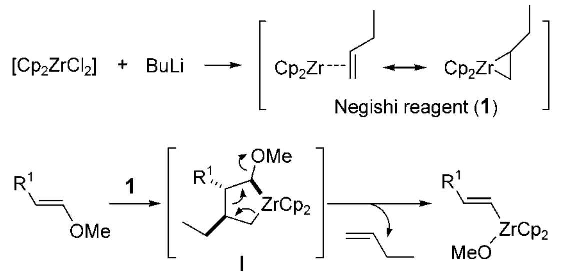
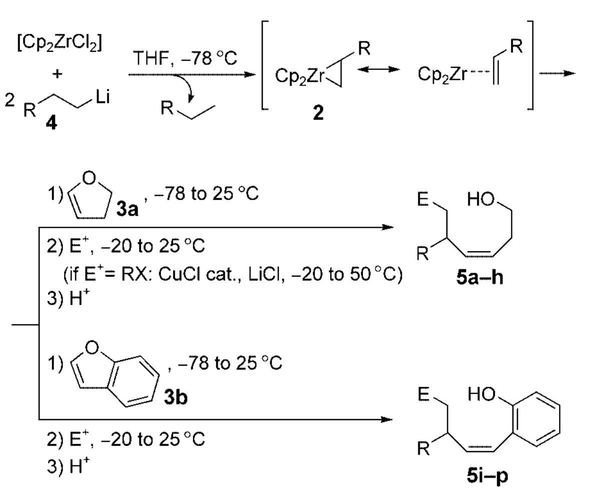


Scheme 1. Negishi reagent **1** and Marek's synthesis of vinyl–zirconocene complexes from acyclic enol ethers. Cp = cyclopentadienyl.

and further treatment with an electrophile. After hydrolysis, the new alcohol or phenol derivatives **5** was formed in high yield and as single *Z* diastereoisomers in all cases (Scheme 2 and Table 1). Of particular interest are compounds functionalized with carbon electrophiles (**5d** and **5e**) and assembled in a one-pot, three-component coupling reaction. To our surprise, none of the expected compounds arising from a mechanism analogous to that described by Marek and co-workers[7] for acyclic enol ethers were formed.

The unusual insertion process described above prompted us to investigate the reaction of alkene–zirconocene complexes **2** and the six-membered cyclic enol ether **6**. When these experiments were performed under the same conditions as those previously described, we obtained cyclobutane derivatives **7** in high yields and as single diastereoisomers in all cases (Scheme 3 and Table 2).[9] Surprisingly, the expected olefins analogous to **5** were not observed. It was also possible in this case that the resulting cyclobutane derivative had been functionalized by carbon electrophiles (**7c**) in a one-pot,



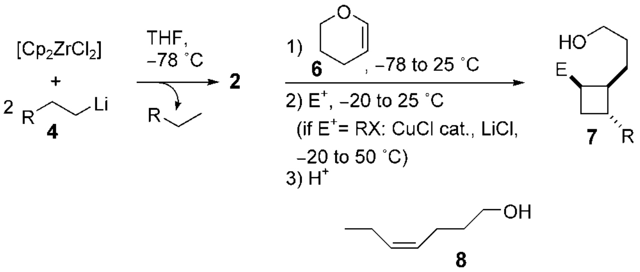
Scheme 2. Zirconium-mediated reaction of alkyllithium compounds **4** and five-membered cyclic enol ethers **3** to give alkenol derivatives **5**.

three-component coupling reaction. Moreover, these unexpected results indicate that, as far as we know, it is the first time a six-membered enol ether participates in a coupling reaction with zirconocene complexes.[10]

Table 1: Alkenol derivatives **5** from the zirconium-mediated reaction of alkyllithium derivatives **4** and enol ether **3**.

Alkyllithium	R[a]	Enol ether	E$^+$	E	Product	Yield [%][b]
4a	Et	**3a**	H_2O	H	**5a**	80
4a	Et	**3a**	D_2O	D	**5b**	81
4a	Et	**3a**	I_2	I	**5c**	75
4a	Et	**3a**	$CH_2{=}CHCH_2Cl$[c]	allyl	**5d**	82
4a	Et	**3a**	$PhCH_2Br$[d]	Bn	**5e**	68
4b	Pent	**3a**	H_2O	H	**5f**	78
4b	Pent	**3a**	I_2	I	**5g**	76
4c	Me	**3a**	I_2	I	**5h**	70
4a	Et	**3b**	H_2O	H	**5i**	85
4a	Et	**3b**	D_2O	D	**5j**	81
4a	Et	**3b**	I_2	I	**5k**	72
4b	Pent	**3b**	D_2O	D	**5l**	82
4b	Pent	**3b**	I_2	I	**5m**	73
4c	Me	**3b**	I_2	I	**5n**	78
4d	H	**3b**	H_2O	H	**5o**	82
4d	H	**3b**	I_2	I	**5p**	70

[a] Pent = pentyl. [b] Based on starting enol ether **3**. [c] CuCl (5 mol%) and LiCl (1 equiv) are also added. After 1 h at 25 °C, the reaction was stirred at 50 °C for 6 h. [d] CuCl (10 mol%) and LiCl (1 equiv) are also added. After 1 h at 25 °C, the reaction was stirred at 50 °C for 6 h.



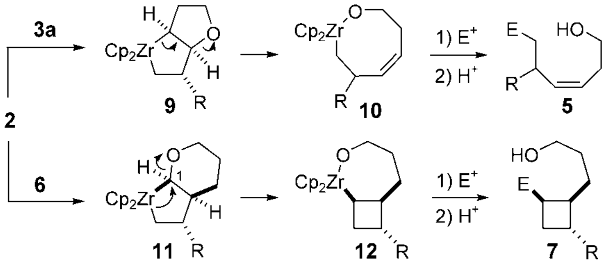
Scheme 3. Zirconium-mediated reaction of alkyllithium compounds **4** and six-membered cyclic enol ether **6** to give cyclobutane derivatives **7**.

We propose the mechanism depicted in Scheme 4 to explain the formation of compounds **5** and **7**. Initially, the double bond of the enol ether **3a** is inserted between the secondary carbon atom and the zirconium center of zirconacyclopropane (**2**) to generate the bicyclic intermediate **9**. β-Elimination of the alkoxy group from **9** results in the formation of oxazirconacyclooctene derivative **10**. After the hydrolysis step, the final addition of the electrophile leads to the *Z*-alkene derivative **5**. It is important to note that this process is doubly regioselective. On one hand, the insertion only occurs at the Zr–C bond of **2**, which implies the more substituted carbon atom is attacked,[3d] while conversely, the reaction is also regioselective with respect to the enol ether **3a**: the double bond is orientated during the insertion step so that the oxygen atom is far away from the zirconocene moiety. Moreover, we believe that the *Z* stereochemistry of **5** is fixed by the *cis* geometry of the bicyclic derivative **9** and the subsequent *anti*-periplanar elimination. The formation of

Table 2: Cyclobutane derivatives **7** from the zirconium-mediated reaction of alkyllithium derivatives **4** and enol ethers **6**.

Alkyllithium	R	E^+	E	Product	Yield [%][a]
4a	Et	H_2O	H	**7a**	69
4a	Et	D_2O	D	**7b**	63
4a	Et	$CH_2{=}CHCH_2Cl$[b]	allyl	**7c**	53
4b	Pent	H_2O	H	**7d**	70
4c	Me	D_2O	D	**7e**	60
4d	H	H_2O	H	**7f**	66[c]

[a] Based on the amount of starting $[Cp_2ZrCl_2]$. Very small amounts (<5%) of the corresponding compounds analogous to **8** were detected in the crude pruduct of the reactions. [b] CuCl (5 mol%) and LiCl (1 equiv) are also added. After 1 h at 25°C, the reaction was stirred at 50°C for 6 h. [c] The total yield corresponded to an approximately 1:1 inseparable mixture of **7f** and alkenol **8**. Pure **7f** (33% yield) was obtained after treating the mixture of **7f** and **8** with bromine and further purification.



Scheme 4. Proposed mechanism for the formation of compounds **5** and **7**.

phenol derivatives **5i–p** from enol ether **3b** follows a similar pathway.

Moreover, the generation of cyclobutane derivatives **7** from the six-membered enol ether **6** can be explained by insertion of the double bond of this enol ether into **2** to produce the bicyclic intermediate **11**. An intramolecular migratory insertion process[11] generates intermediate **12**, which after reaction with an electrophile and hydrolysis affords cyclobutane derivatives **7**.[9] As before, this insertion process is regioselective with respect to **2**, with the reaction occurring at the more substituted Zr–C bond.[3d] The reaction is also regioselective with respect to the enol ether **6** since the double bond of this enol ether is oriented so that the oxygen atom is close to the zirconocene moiety.

The coupling products obtained firmly support the carbometalative ring-expansion mechanism tentatively formulated by Marek and co-workers for the reaction of the Negishi reagent and acyclic enol ethers to give vinyl–zirconocene complexes.[7,8] In fact, intermediate **11** is analogous to **I** (see Scheme 1). However, in our case the elimination reaction leading to the vinyl–zirconocene complexes (see Scheme 1) does not proceed and instead an intramolecular migratory insertion process furnishes the cyclobutane derivatives **7**. According to model proposed by Marek and coworkers for the formation of (*E*)-vinylzirconocenes,[8] an isomerization at C1 in **11** should occur before the elimination step. We believe that in our case this process is not favored because of the rigidity of the bicyclic intermediate **11**, and hence the intramolecular migratory insertion process is preferred.

Another surprising feature of these reactions is that the orientation adopted by the enol ether during the insertion process depends on the size of the enol ether ring. Although a more detailed study is required, we believe that the orientation adopted by the five-membered enol ether **3** is governed by electronic effects.[12] However, steric effects probably play an important role in the opposite orientation adopted by the pyran derivatives **6** during the insertion process. In fact, it has been observed that the reaction of **6** and the sterically less-demanding zirconacyclopropane **2** (R = H) (derived from the reaction of EtLi and zirconocene dichloride) leads to an approximately 1:1 mixture of the cyclobutyl derivative **7f** and the alkene derivative **8** (Scheme 3 and Table 2). The formation of compound **8** could be explained by a mechanism analogous to that described for the formation of **5** (Scheme 4) where pyran **6** is oriented during the insertion step in a way that is analogous to that adopted by the furans **3**.

In summary, we have described the first coupling reaction of cyclic enol ethers and alkene–zirconocene complexes. The reactions described here follow different pathways compared to previously reported results for acyclic enol ethers. The reaction has been shown to be dependent on the ring size of the enol ether, and thus, for five-membered enol ethers, the reaction leads to alcohols or phenols containing a *Z* double bond through an insertion/β-elimination process, while the reaction with six-membered enol ethers generates cyclobutane derivatives through an unprecedented insertion/intramolecular migratory insertion reaction. Moreover, these results firmly support the carbometalative ring-expansion mechanism tentatively proposed by Marek and co-workers for related reactions.

Besides the important mechanistic aspects described, this work is expected to have wide application in synthetic organic chemistry since highly functionalized compounds can be readily obtained from simple starting materials. Further detailed investigations into the synthetic and mechanistic aspects of these reactions, including experimental and theoretical calculations, are underway.[13]

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Keywords: insertion · organometallic reagents · small ring systems · synthetic methods · zirconium

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[9] The relative configuration of the chiral centers has been unequivocally ascertained by NMR spectroscopic analysis (including HMQC, HMBC, COSY, and NOESY experiments).

[10] 3,4-Dihydro-2*H*-pyran (**6**) does not react with alkyne–zirconocene complexes; see ref. [5c].

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[12] The polarization of the carbon–zirconium bond of the zirconacyclopropane **2** and the carbon–carbon double bond of the enol ethers clearly support the formation of intermediate **9**; see refs. [5b and 6].

[13] Iodo derivatives, such as **5n**, could be precursors of interesting 1-benzoxepin derivatives (for example the fungal metabolite pterulone). Also the cyclobutane derivatives **7** have pleasant odor properties with potential application.