Rearrangement

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Zirconocene-Catalyzed Reactions of Alkenyl-Substituted Enol Ethers**

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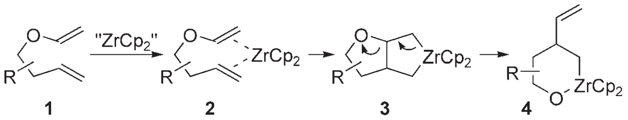
Organozirconocene complexes[1] have become very useful tools in organic chemistry since the pioneering works of Schwartz[2] and Negishi.[3] Despite the extensive advances in this area that have been accomplished in recent years, very few catalytic processes involving the use of zirconocene complexes have been described.[4] Particularly noteworthy are those catalytic carbometalative processes developed mainly by Negishi[5] and Hoveyda.[6] Some years ago, we initiated a study of new cross-coupling reactions between organozirconocene complexes and heterosubstituted alkenes (principally enol ethers).[7] In this context, the extensive work by Marek and co-workers should also be remarked upon.[8] In an attempt to further develop this interesting chemistry, we decided to investigate intramolecular versions of the reaction of alkene–zirconocene complexes and enol ethers (Scheme 1).[9] Thus, we envisioned that alkenyl-substituted enol ethers such as **1** could coordinate to a zirconocene complex generated in situ to give species **2**, which could react through a carbocyclization process to give **3**. These new complexes would evolve by a β-elimination of the alkoxy group to finally give **4,** which could be further functionalized by reaction with electrophiles. Thus, the general reaction from **1** to **4** would suppose an interesting isomerization–metalation



Scheme 1. Proposed intramolecular version of the reaction of alkene–zirconocene complexes and enol ethers. Cp = cyclopentadienyl.

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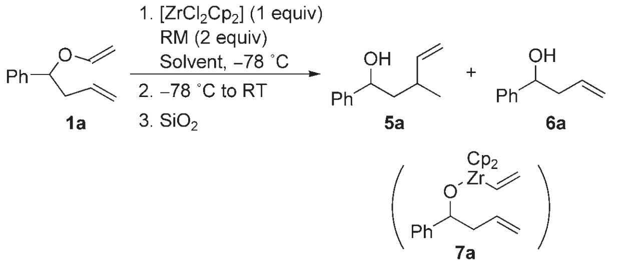
process. The final goal of our investigation was the development of a catalytic method, and herein we describe a new zirconocene-catalyzed isomerization–magnesation reaction of alkene-substituted enol ethers.

At the outset of this study, the reaction was tested with stoichiometric amounts of zirconocene dichloride. Thus, the reactive low-valent zirconocene species were generated by the method developed by Negishi by mixing zirconocene dichloride [$ZrCl_2Cp_2$] with two equivalents of a Grignard or an organolithium reagent. This reaction gives the corresponding alkene–zirconocene complex, which after a ligand exchange reaction would generate the necessary complex **2**. Initially, the reaction was studied on the model alkenyl-substituted enol ether **1a** (Scheme 2 and Table 1). Thus, **1a** was treated with one equivalent of [$ZrCl_2Cp_2$] and two equivalents of different Grignard or organolithium reagents at −78 °C. The reaction was allowed to reach room temperature and after 1 h was quenched with silica gel. Thus, the expected alkenol **5a**, which is formed by simple hydrolysis of the corresponding zirconium complex **4** (see Scheme 1), was obtained together with different amounts of alcohol **6a**. Formation of **6a** could be explained by following the mechanism proposed by Marek and co-workers for the synthesis of alkenyl–zirconium complexes from acyclic enol ethers.[8c,i] Thus, we suppose the generation of vinyl–zirconium complex **7a**, as the by-product **6a** and a molecule of ethene are generated after hydrolysis.



Scheme 2. Zirconocene-mediated reaction of enol ether **1a**.

Table 1: Products obtained from the zirconocene-mediated reaction of enol ether **1a** and different Grignard or organolithium reagents.

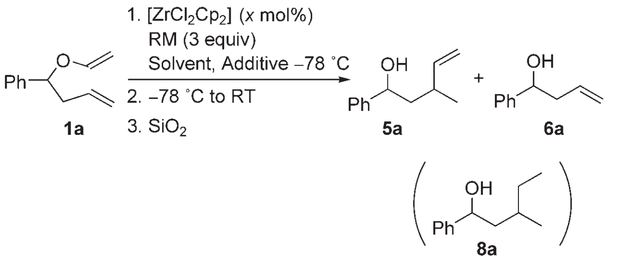
Entry	RM	Solvent	Product	Yield [%][a]	d.r. of **5a**[b]
1	EtMgBr	THF	**6a**	90	–
2	EtMgBr	Et_2O	**6a**	86	–
3	PrMgCl	THF	**5a**/**6a**	78/5	1:1
4	PrMgCl	Et_2O	**5a**/**6a**	66/5	1:1
5	BuLi	THF	**5a**	88	1:1
6	BuLi	Et_2O	**5a**	78	5:1[c]

[a] Yield based on starting material **1a**. [b] Determined by ^{1}H NMR spectroscopic analysis of the reaction crude product. [c] The major diastereoisomer was found to be the 1,3-*anti* isomer (see the Supporting Information).

As shown in Table 1, the formation of the desired compound **5a** or by-product **6a** was highly influenced by the structure of the Grignard or organolithium reagent used. Thus, we observed the exclusive formation of **6a** when ethylmagnesium bromide was used either in diethyl ether or THF (Table 1, entries 1 and 2). However, **5a** was obtained in 78 % yield as a 1:1 mixture of diastereoisomers when propylmagnesium chloride was used in THF. A small amount of **6a** was also isolated (5 % yield; Table 1, entry 3). Similar results, although with slightly lower yields, were obtained when this reaction was performed in diethyl ether (Table 1, entry 4). Finally, **5a** was obtained in 88 % yield (1:1 mixture of diastereoisomers) by using butyllithium (Table 1, entry 5). However, the selectivity of the reaction improved and a 5:1 mixture of diastereoisomers was obtained when the reaction was carried out in diethyl ether (78 % yield; Table 1, entry 6).[10] It is of note that formation of **6a** was completely suppressed by using butyllithium.

Once we had found the right conditions to direct the reaction to the isomerized compound **5a**, thus avoiding the formation of undesired **6a**, we decided to investigate the reaction under catalytic conditions with zirconium. We speculated that under catalytic conditions, the excess of organometallic reagents (Grignard or organolithium compounds) could react with intermediate **4** (see Scheme 1) through a double transmetalation reaction, thereby regenerating the catalytic zirconium species and forming a new organometallic reagent related to **4** (with magnesium or lithium instead of zirconium).

To find the optimum conditions, model compound **1a** was treated with an excess of the corresponding organometallic compound in the presence of catalytic amounts of commercially available zirconocene dichloride under various reaction conditions (Scheme 3 and Table 2). As the best results in the stoichiometric reactions were reached by using butyllithium, we started our catalytic studies with this organometallic



Scheme 3. Zirconocene-catalyzed reaction of enol ether **1a**.

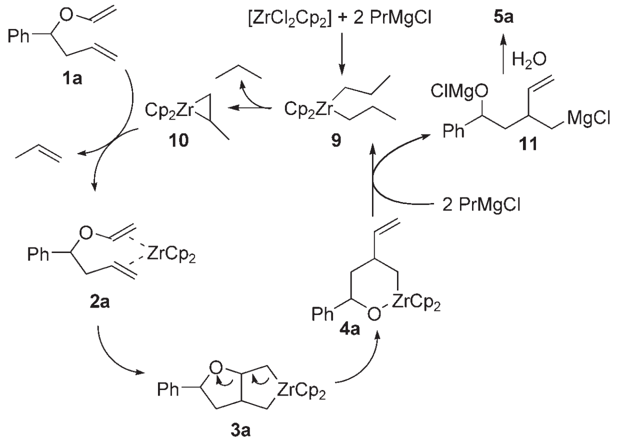
Table 2: Zirconocene-catalyzed reaction of enol ether **1a** and different Grignard or organolithium reagents.

Entry	RM	[$ZrCl_2Cp_2$] [mol %]	Solvent	Additive	Products	Yield [%][a]	d.r. of **5a**
1	BuLi	5–25	THF[b]	–	polymer	–	–
2	EtMgBr	25	THF[b]	–	**6a**/**8a**	25/66	–
3	EtMgBr	5	THF[b]	–	**6a**/**8a**	5/85	–
4	PrMgCl	15	Et_2O	–	**5a**/**6a**	63/12	2:1
5	PrMgCl	15	THF	–	**5a**/**6a**	76/15	1:1
6	PrMgCl	5	Et_2O	PPh_3[c]	**5a**	62	2:1
7	PrMgCl	5	THF	PPh_3[c]	**5a**	82	1:1

[a] Yield of the isolated products based on starting material **1a**. [b] Similar results were found when Et_2O was used as the solvent. [c] 10 mol % of PPh_3 was used.

reagent. However, we did not detect the formation of **5a** in any case attempted and mainly observed polymerization of the starting material (Table 2, entry 1). In consonance with the results of the stoichiometric reactions, by using ethylmagnesium bromide we observed the formation of **6a** along with different quantities of the new alcohol **8a**, depending on the amount of catalyst used (Table 2, entries 2 and 3). Formation of **8a** is easily explained by a simple zirconium-catalyzed carbomagnesiation of the double bond of **6a** and further hydrolysis. Fortunately, we observed the formation of the desired alkenol **5a** together with a small amount of **6a** (Table 2, entries 4 and 5) after only 1 h at room temperature when propylmagnesium chloride was employed in the presence of 20 mol % of $[ZrCl_2Cp_2]$. Both diethyl ether and THF were found to be appropriate solvents; however, a slightly higher diastereoselectivity was found in diethyl ether and higher yield in THF. The reaction times became longer when the amount of catalyst was lowered, and 24 h were required for complete conversion of the starting material when 5 mol % of $[ZrCl_2Cp_2]$ was used. We tried some reactions in the presence of an additive[11] in an attempt to totally avoid the formation of **6a** and to achieve complete conversions in shorter times. To our delight, under the optimal reaction conditions (5 mol % of $[ZrCl_2Cp_2]$, 10 mol % PPh_3), starting compound **1a** was completely transformed into isomerized alcohol **5a** after 8 h at room temperature in THF (82 % yield of the isolated product, 1:1 mixture of diastereoisomers; Table 2, entry 7). The formation of **6a** was not observed under these conditions. Again, slightly higher selectivity, although lower yield, was found when diethyl ether was used as the solvent (Table 2, entry 6).

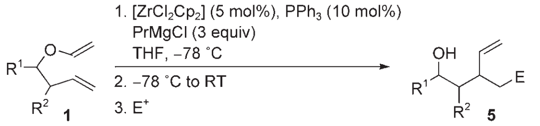
A proposed mechanism for the catalytic reaction is shown in Scheme 4. Initially, the zirconocene dichloride reacts with two equivalents of propylmagnesium chloride to form the corresponding dipropylzirconocene complex **9**, which further evolves, as described by Negishi, to give the propene–zirconocene complex **10** with the loss of a molecule of propane. This sixteen-electron complex reacts in the presence of the alkene-substituted enol ether **1a** through a ligand-exchange process, thus releasing a molecule of propene and forming the eighteen-electron zirconocene complex **2a**. A carbocyclization reaction furnishes the bicyclic complex **3a**. Subsequent elimination of zirconium alkoxide affords the intermediate **4a**.[12] Finally, a double magnesium–zirconium exchange gives the final organomagnesium compound **11** and regenerates the dipropylzirconocene complex **9**, which initiates a new catalytic cycle.[11]

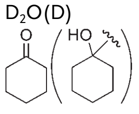
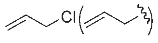
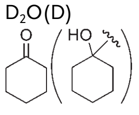


Scheme 4. Proposed mechanism for the zirconocene-catalyzed reaction of **1a**.

With an effective zirconocene-catalyzed reaction in hand, we investigated the scope of the process. Table 3 shows the results of the reactions performed under the optimized catalytic conditions previously found for **1a**. The reaction worked for a range of alkene-substituted enol ethers **1**, and the formed Grignard reagent could be trapped with different typical electrophiles for organomagnesium reagents. The final rearranged products **5** were isolated in high yield, but unfortunately the reaction gave mixtures of both possible diastereoisomers (d.r. ≈ 1:1, except for starting material **1e** d.r. = 14:1; however, the yield in this case was lower). Attempts to improve the selectivity by changing the reaction

Table 3: Zirconocene-catalyzed reaction of enol ethers **1** in the synthesis of functionalized alcohols **5**.

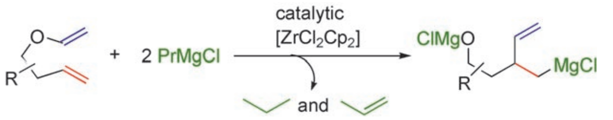


Entry	R^1	R^2	Starting diene	E^+(E)	Product	Yield [%][a]
1	Ph	H	**1a**	H_2O(H)	**5a**	82
2	Cy	H	**1b**	H_2O(H)	**5b**	93
3	Cy	H	**1b**	D_2O(D)	**5c**	85
4	Cy	H	**1b**		**5d**	56[b]
5	Cy	H	**1b**		**5e**	67
5	heptyl	H	**1c**	H_2O(H)	**5f**	94
6	heptyl	H	**1c**	D_2O(D)	**5g**	84
7	heptyl	H	**1c**		**5h**	64[b]
8	$Ph(CH_2)_2$	H	**1d**	H_2O(H)	**5i**	90
9	$Ph(CH_2)_2$	H	**1d**	D_2O(D)	**5j**	88
10	H	Ph	**1e**	H_2O(H)	**5k**	52[c]

[a] Yield of the isolated products based on starting material **1**; unless noted, an inseparable 1:1 mixture of the two possible diastereoisomers was obtained. [b] Both diastereoisomers from the 1:1 mixture were readily separated. [c] In this case, the formation of several other by-products was observed, and the major diastereoisomer was found to be (2*R**,3*R**)-3-methyl-2-phenyl-4-penten-1-ol (d.r. = 14:1; see the Supporting Information). E = electrophile.

conditions were unsuccessful until now. For this reason, current efforts are being directed to find the appropriate catalyst or reaction conditions to achieve higher selectivities.

In summary, we have developed a new zirconocene-catalyzed isomerization–magnesation reaction of readily available alkene-substituted enol ethers.[13] The net process supposes the migration of the vinyl moiety of the enol ether to the internal position of the initial alkene and the magnesation of the terminal carbon atom of that initial alkene moiety (Scheme 5). The global reaction may also be considered as an equivalent of the vinylmagnesation of terminal olefins, which is still a rather difficult challenge in the field of carbometallation of alkenes. This unprecedented process is one of the few examples of zirconocene-catalyzed reactions described in the literature. The reaction supposes a simple methodology to access to functionalized Grignard reagents which could find application in organic synthesis programs.



Scheme 5. General reaction of the zirconocene-catalyzed isomerization–magnesation process.

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Keywords: Grignard reagents · homogeneous catalysis · rearrangement · synthetic methods · zirconium

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[12] Alternatively, a similar mechanism that involves the formation of a zirconate species by addition of PrMgCl to **3a** followed by Mg–Zr exchange, elimination of Mg alkoxide, further reaction with another molecule of PrMgCl, and a second transmetalation step to form **11** and **9** might also be suggested; see ref. [6].

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