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Medium-Sized Carbocycles by a Zirconocene-Catalyzed Tandem Formal Ring Expansion–Magnesation Reaction of Alkenyl-Substituted Cyclic Enol Ethers

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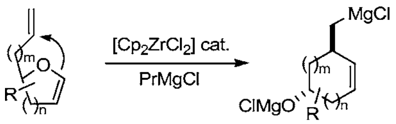
ABSTRACT



A new regio- and stereoselective zirconocene-catalyzed reaction for the synthesis of medium-sized rings is described. The global reaction supposes a formal ring expansion of a cyclic enol ether to give a functionalized carbocycle.

The increasing interest in the development of new methods for the generation of medium-sized carbocycles lies in both the pharmacological applications of many of these cores and the difficulty of their syntheses.[1] Transition-metal-mediated strategies that form new C−C bonds are outstanding methods in the construction of these medium-sized rings.[2] During the last years, we have been involved in the study of the reaction of organozirconium complexes and enol ethers.[3,4] In this context, we are especially interested in the development of new zirconium-catalyzed C−C bond forming reactions.[5] On the basis of our findings in this field,[6] it was tempting to design a zirconium-based approach directed toward those attractive synthetic targets. Thus, we hypothesized that the in situ generated Negishi zirconocene equivalent ("ZrCp$_2$") would tend to react with enol ethers **1** generating a new

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[1] (a) Faulkner, D. J. *Nat. Prod. Rep.* **1984**, *1*, 251−280. (b) Faulkner, D. J. *Nat. Prod. Rep.* **1984**, *1*, 551−598. (c) Faulkner, D. J. *Nat. Prod. Rep.* **1986**, *3*, 1−33. (d) Faulkner, D. J. *Nat. Prod. Rep.* **1987**, *4*, 539−576. (e) Faulkner, D. J. *Nat. Prod. Rep.* **1988**, *5*, 613−663. (f) Oishi, T.; Ohtsuka, Y. *Studies in Natural Products Chemistry*; Rahman, A., Ed.; Elsevier: Amsterdam, 1989; p 73. (g) Moody, C. J. *Studies in Natural Products Chemistry*; Rahman, A., Ed.; Elsevier: Amsterdam, 1992; p 201.

[2] For some leading reviews, see: (a) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, 48, 5757−5821. (b) Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15−44. (c) Rousseau, G.; *Tetrahedron* **1995**, *51*, 2777−2849. (d) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881−930. (e) Yet, L. *Chem. Rev.* **2000**, *100*, 2963−3008.

[3] (a) Barluenga, J.; Fernández, A.; Álvarez-Rodrigo, L.; Rodríguez, F.; Fañanás, F. J. *Synlett* **2005**, 2513−2515. (b) Barluenga, J.; Álvarez-Rodrigo, L.; Rodríguez, F.; Fañanás, F. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3932−3935. (c) Barluenga, J.; Rodríguez, F.; Álvarez-Rodrigo, L.; Zapico, J. M.; Fañanás, F. J. *Chem.−Eur. J.* **2004**, *10*, 109−116. (d) Barluenga, J.; Rodríguez, F.; Álvarez-Rodrigo, L.; Fañanás, F. J. *Chem.−Eur. J.* **2004**, *10*, 101−108.

[4] In this context, the impressive work developed by I. Marek and co-workers should be noted (see: Chinkov, N.; Marek, I. In *New Aspects of Zirconium Containing Organic Compounds, Topics In Organomet. Chem.*; Marek, I., Ed.; Springer: Berlin, 2005; Vol. 10). For a review, see: Chinkov, N.; Chechik, H.; Majumdar, S.; Liard, A.; Marek, I. *Synthesis* **2002**, 2473−2483. Also, for a recent interesting cyclization reaction of enol ether derivatives mediated by zirconium complexes, see: Owen, D. R.; Whitby, R. J. *Synthesis* **2005**, 2061−2074.

[5] For some recent papers, see: (a) Tan, Z.; Negishi, E. *Angew. Chem., Int. Ed.* **2004**, *43*, 2911−2914. (b) Negishi, E.; Tan, Z.; Liang, B.; Novak, T. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5782−5787. (c) Huo, S.; Shi, J.; Negishi, E. *Angew. Chem., Int. Ed.* **2002**, *41*, 2141−2143. (d) Cesati, R. R., III.; de Armas, J.; Hoveyda, A. H. *Org. Lett.* **2002**, *4*, 395−398. (e) de Armas, J.; Hoveyda, A. H. *Org. Lett.* **2001**, *3*, 2097−2100. (f) de Armas, J.; Kolis, S. P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 5977−5983. (g) Hoveyda, A. H. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; WILEY-VCH: Weinheim, 2002; p 180. (h) Uesaka, N.; Mori, M.; Okamura, K.; Date, T. *J. Org. Chem.* **1994**, *59*, 4542−4547.

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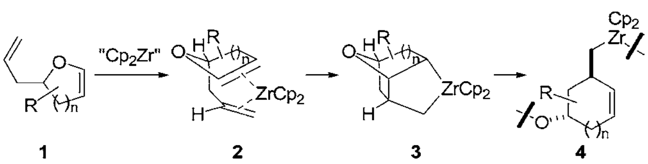
zirconocene complex **2**. The subsequent cyclometalation reaction would afford the tricyclic complex **3**, whose evolution through a well-known elimination of the β-alkoxy group may furnish the complex **4** (Scheme 1).

Scheme 1. Proposal for the Intramolecular Zirconocene-Mediated Reaction of Alkenyl-Substituted Cyclic Enol Ethers **1**



This substrate-directed strategy shows great potential to enable the efficient construction of complex medium-sized carbocycles from a simple heterocycle. The final goal of our investigations was the development of a catalytic method, and herein we describe our results in this field.

To test the proposal depicted in Scheme 1, we examined the reactivity of the 1-allyl-1*H*-isochromene **1a** in cocyclization/elimination reactions mediated by zirconium. Thus, cyclic enol ether **1a** was treated with the reactive low-valent (1-butene)zirconocene species, generated following Negishi's method by mixing zirconocene dichloride with 2 equiv of butyllithium in THF at −78 °C.[7] The reaction was warmed to 0 °C, and after 1 h, an electrophile was added. The typical workup and purification steps allowed the isolation of the cycloheptenol derivatives **5** in high yield and as single diastereoisomers in all cases (Scheme 2 and Table 1, entries 1−3).[8] With the support of these results, it could be inferred that an elongation of the chain connecting the alkene and the dihydropyran moieties would provide a viable and easy pathway for the synthesis of eight-membered rings, which still remains a significant synthetic challenge. Thus, we settled on using the homoallyl-substituted analogue **1b** as the most suitable substrate on which to test the reaction. The cyclization/elimination process occurred as expected to provide exclusively the eight-membered carbocycles **6** in high yield and as unique diastereoisomers (Scheme 2 and Table 1, entries 4−7).

Scheme 2. Zirconocene-Mediated Reaction of Cyclic Enol Ethers **1a**,**b**

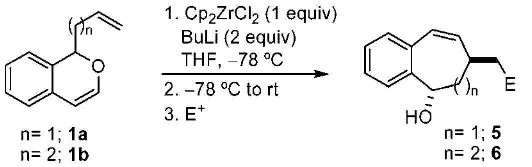


Table 1. Seven- and Eight-Membered Carbocycles **5** and **6** from the Zirconocene-Mediated Reaction of Cyclic Enol Ethers **1a**,**b**

entry	1	*n*	E$^+$ (E)	product (yield %)[a]
1	**1a**[b]	1	H_2O (H)	**5a** (89)
2	**1a**[b]	1	D_2O (D)	**5b** (76)
3	**1a**[b]	1	I_2 (I)	**5c** (72)
4	**1b**[c]	2	H_2O (H)	**6a** (68)
5	**1b**[c]	2	D_2O (D)	**6b** (65)
6	**1b**[c]	2	I_2 (I)	**6c** (56)
7	**1b**[c]	2	$CH_2{=}HCH_2Cl$ ($CH_2{=}CHCH_2$)[d]	**6d** (71)

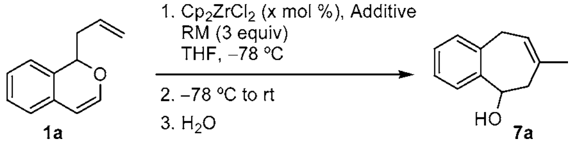
[a] Isolated yield based on starting **1**. [b] Optimized reaction conditions: 0 °C, 1 h. [c] Optimized reaction conditions: 20 °C, 4 h. [d] CuCl (5 mol %) was also added. After 1 h at 20 °C, the reaction was stirred at 50 °C for 2 h.

At this stage, our results in the zirconocene-mediated reaction of 2-alkenyl-substituted cyclic enol ethers **1** have resulted in a mild method for the regio- and diastereoselective synthesis of seven- and eight-membered carbocycles, and therefore, we focused our studies on the development of a catalytic version.

On the basis of the strategy designed, we speculated that under catalytic conditions the reaction of the intermediate **4** with an excess of an organometallic reagent (organolithium or Grignard) could proceed through a double transmetalation reaction so as to afford a new organometallic reagent, while regenerating the zirconium catalyst.

The feasibility of this project was first tested on the model substrate **1a**. Thereby, a set of reactions were run using different organometallic reagents while varying the zirconocene dichloride loading (Table 2).

Table 2. Zirconocene-Catalyzed Reaction of Cyclic Enol Ether **1a**



entry	RM	*x* (mol %)	additive	**7a** (yield %)[a]
1	BuLi	25−50	–	–[b]
2	EtMgBr	25−50	–	–[b]
3	PrMgCl	50	–	61
4	PrMgCl	25	–	42
5	PrMgCl	15	PPh_3[c]	74

[a] Isolated yield based on starting **1a**. [b] Complex mixture of unidentified products. [c] 30 mol % of PPh_3 was used.

In consonance with our related findings in this field,[6] the best results were found by using propylmagnesium chloride as the organometallic counterpart in the presence of a

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(6) Barluenga, J.; Álvarez-Rodrigo, L.; Rodríguez, F.; Fañanás, F. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6362−6365.

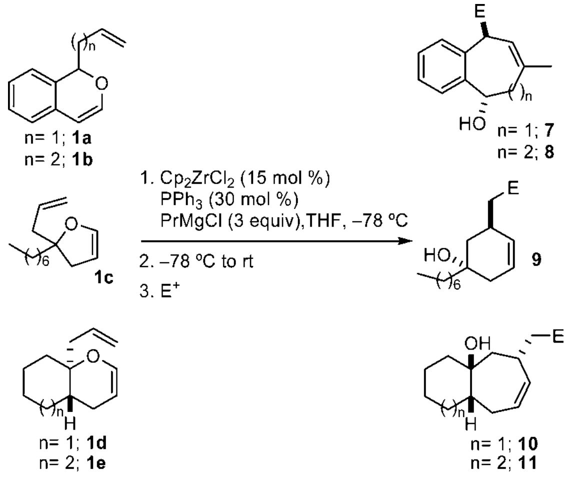
(7) Negishi, E.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829−2832.

(8) The structures and relative configuration were unequivocally determined by NMR experiments (COSY, HMQC, HMBC, and NOESY).

catalytic amount of PPh_3 (entry 5). So, under the optimal reaction conditions (15 mol % of Cp_2ZrCl_2 and 30 mol % of PPh_3), starting enol ether **1a** was completely transformed into the seven-membered ring derivative **7a** (positional isomer of cycloheptenol **5a**) after 12 h at room temperature in THF (74% yield of isolated product).

To explore the scope of this catalytic reaction, three different starting cyclic enol ether patterns (**1a**,**b**, **1c**, and **1d**,**e**) were chosen. Also, a range of electrophiles were used to amplify the overall utility of this catalytic method. As shown in Table 3, functionalized six-, seven-, and eight-membered carbocycles were easily obtained.

Table 3. Medium-Sized Carbocycles **7**−**11** from the Zirconocene-Catalyzed Reaction of Cyclic Enol Ethers **1a**−**e**



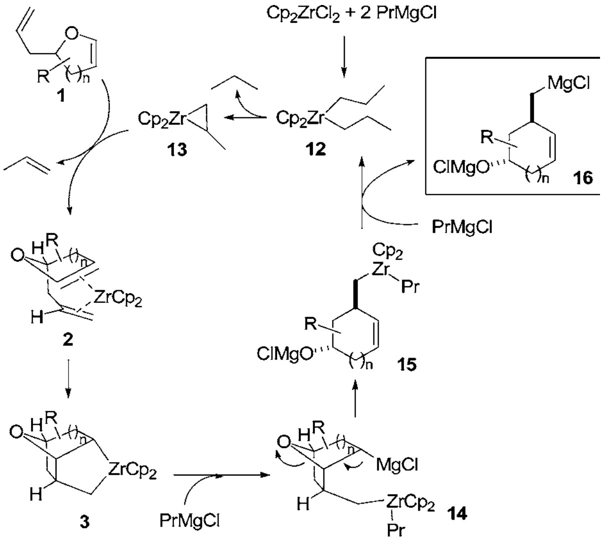
entry	1	*n*	E^+ (E)	product (yield %)[a]
1	**1a**	1	H_2O (H)	**7a** (74)
2	**1a**	1	$CH_2{=}HCH_2Cl$ ($CH_2{=}CHCH_2$)[b]	**7b** (61)
3	**1b**	2	H_2O (H)	**8a** (56)
4	**1c**	–	H_2O (H)	**9a** (56)
5	**1c**	–	D_2O (D)	**9b** (53)
6	**1c**	–	$CH_2{=}C(CH_3)CH_2Cl$ [$CH_2{=}C(CH_3)CH_2$][b]	**9c** (48)
7	**1d**[c]	1	H_2O (H)	**10a**[d] (53)
8	**1e**[c]	2	H_2O (H)	**11a**[d] (60)
9	**1e**[c]	2	$CH_2{=}CHCH_2Cl$ ($CH_2{=}CHCH_2$)[b]	**11b**[d] (55)

[a] Isolated yield based on starting **1**. [b] CuCl (5 mol %) was also added. After 1 h at 25 °C, the reaction was stirred at 50 °C for 2 h. [c] The catalyst loading could be lowered to 10 mol % of Cp_2ZrCl_2 and 20 mol % of PPh_3. [d] Also, 20−25% of the diene derivative, containing an exocyclic double bond, was isolated (see Supporting Information).

It is important to note that the carbocycles **7** and **8** obtained under catalytic conditions are the formal isomerized derivatives of the carbocycles **5** and **6** obtained under stoichiometric conditions. Thus, the stoichiometric and catalytic versions of these reactions allow access to different functionalized carbocycles in a totally diastereoselective way. Functionalization with carbon electrophiles (entries 2, 6, and 9) deserves special attention because three new C−C bonds are formed.[8]

A careful examination of the proposed mechanistic pathway for these reactions allows discussing some interesting features of the process, as well as finding an explanation for the excellent diastereocontrol observed. The common mechanistic proposal for reactions with substrates **1a**−**e** is depicted in Scheme 3, though on the model of enol ether **1** to simplify.

Scheme 3. Catalytic Cycle Proposed for the Isomerization−Ring Expansion−Magnesation Reaction of Cyclic Enol Ethers **1**



As shown in Scheme 3, the in situ formed low-valent zirconocene species **13** could coordinate to both of the double bonds of the substrate **1**, generating a π-complex **2** that is in equilibrium with the corresponding zirconatricycle **3**. The most remarkable feature is the regio- and diastereoselective formation of the zirconatricycle intermediate **3**, through a carbozirconation reaction. The process is regioselective not only with respect to the enol ether that is inserted placing the oxygen atom far away from the zirconocene moiety[9] but also with respect to the alkene moiety, because only the internal carbon atom of the initial alkene forms a new carbon−carbon bond with the enol ether. Addition of PrMgCl to **3** followed by Mg−Zr exchange affords the bimetallic species **14** which after Mg−alkoxide elimination gives rise to intermediate **15**.[10] Under catalytic conditions, and as a consequence of the excess of alkylmagnesium chloride, the intermediate **15** could experience a new zirconium−magnesium exchange, leading to the regeneration of the catalytic species **12**, accompanied by the formation of a new organometallic compound **16** with a diverse reactivity profile.

As discussed before, in the case of substrates **1a**,**b**, a double bond isomerization is observed. Formation of these products could be explained through a dehydrozirconation reaction on the corresponding intermediate **15a**,**b** followed

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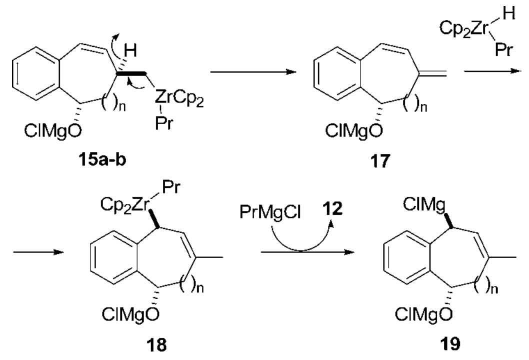
(9) It should be noted that the outcome of the intramolecular reaction of an alkene−zirconocene complex and a six-membered cyclic enol ether is different from the intermolecular version of the reaction; see ref 3b.

(10) Although a Zr−alkoxide elimination reaction could be proposed on intermediate **3**, this option would afford a constrained bicyclic oxazirconocene complex. For this reason, an initial Mg−Zr exchange is proposed as the most likely step. Support for this mechanism may be found in the work developed by Hoveyda et al. See ref 5g.

Scheme 4. Proposed Mechanism for the Formation of Grignard Reagents **19**, Precursors of Compounds **7** and **8**



by a formal 1,4-hydrozirconation reaction[11] to generate the stable benzylic zirconocene complex **18** (Scheme 4).[12] As illustrated, a final zirconium−magnesium exchange would deliver the corresponding Grignard reagent **19**, regenerating the catalytic species **12** as discussed before. The final reaction of Grignard reagents **19** with electrophiles renders the final products **7** and **8**.[13]

In summary, we have described a new zirconocene-catalyzed reaction for the synthesis of medium-sized rings. These transformations furnish products with exquisite levels of regio- and stereoselection as a function of the highly ordered transition-state geometries they spring from. The high complexity accomplished in the final products should be remarked upon in addition to the very straightforward experimental procedure. The products obtained by these methods would be otherwise significantly more difficult to access, particularly in a diastereoselective fashion. The global reaction supposes a formal ring expansion of a cyclic enol ether to give a functionalized carbocycle.

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Supporting Information Available: Experimental procedures and characterization data for compounds. Copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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[11] Mechanistic hypotheses for isomerization sequences in zirconocene complexes have been reported. See: (a) Chinkov, N.; Majumdar, S.; Marek, I. *J. Am. Chem. Soc.* **2002**, *124*, 10282−10283. (b) Chinkov, N.; Majumdar, S.; Marek, I. *J. Am. Chem. Soc.* **2003**, *125*, 13258−13264. (c) Chinkov, N.; Levin, A.; Marek, I. *Angew. Chem., Int. Ed.* **2006**, *45*, 465−468.

[12] (a) Ikeuchi, Y.; Taguchi, T.; Hanzawa, Y. *J. Org. Chem.* **2005**, *70*, 756−759. (b) Ikeuchi, Y.; Taguchi, T.; Hanzawa, Y. *J. Org. Chem.* **2005**, *70*, 4354−4359.

[13] Formation of products **7** and **8** as single diastereoisomers is surprising as it is known that benzylic organomagnesium species such as **19** are not configurationally stable.