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Multi Component Reaction

Synthesis of Cyclohexanol Derivatives by Zirconocene-Mediated Ring-Contraction Reactions of Seven-Membered Cyclic Enol Ethers**

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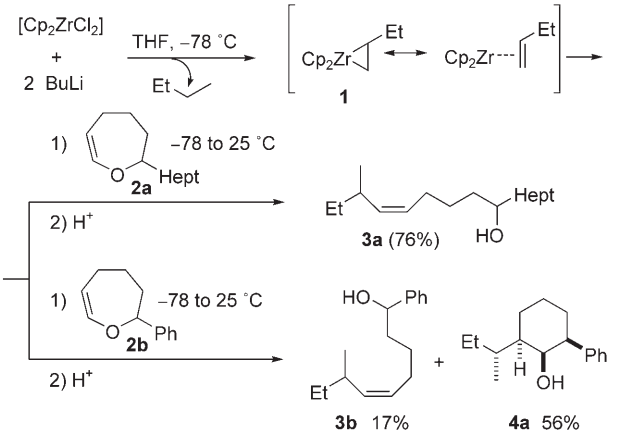
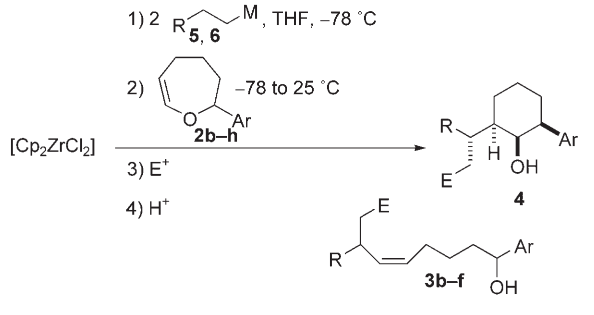
Alkene–zirconocene complexes are excellent reagents for carbon–carbon cross-coupling reactions with a great variety of unsaturated substrates.[1] Among these processes, the reaction with heterosubstituted alkenes leads to a wide range of compounds that are not easily available by other methods.[2] During our recent studies of the reaction between organozirconium complexes and enol ethers,[3,4] we found that alkene–zirconocene complexes react with five-, and six-membered cyclic enol ethers.[3b] In light of these results we decided to investigate the reaction with seven-membered cyclic enol ethers. We report herein an unprecedented zirconocene-mediated ring contraction of seven-membered cyclic enol ethers which allows an easy and diastereoselective synthesis of cyclohexanol derivatives.

Our initial experiments were performed with seven-membered cyclic enol ethers **2a**,**b** (Scheme 1). Thus, zirconocene dichloride was treated with two equivalents of butyllithium in THF at −78 °C to generate the alkene–zirconocene complex **1**.[5] Subsequently **1** was treated with cyclic enol ether **2a** in situ and then warmed to room temperature. Hydrolysis of the reaction mixture gave the alkenol derivative **3a**, which was isolated in 76 % yield.[6] The formation of compound **3a** is easily explained by an insertion/β-elimination process similar to that observed for five-membered cyclic enol ethers.[3b] In an attempt to further investigate the scope of this process, we performed an experiment with the phenyl-substituted enol ether **2b** under the same conditions. To our surprise, this reaction mainly led to the cyclohexanol derivative **4a** (56 % yield) as a single diastereoisomer. The expected alkenol **3b** could also be isolated as a minor product of the reaction (17 %).[6] The formation of cyclohexanol **4a** involves an unprecedented ring contraction of the initial seven-membered cyclic enol ether. At this point, it seemed clear that the presence of an aromatic group at the 7-position of the initial enol ether **2b** must have some influence on the process by directing the reaction towards the formation of the cyclohexanol derivative **4a**.



Scheme 1. Reaction of alkene–zirconocene complexes **1** with seven-membered cyclic enol ethers **2a**,**b**.

The scope of this new reaction was studied by performing a set of experiments with the enol ethers **2b**–**h**, all of which contain an aryl group at the appropriate position, as starting materials (Scheme 2 and Table 1). These experiments were performed by consecutive reaction of zirconocene dichloride with two equivalents of the corresponding organolithium **5** or Grignard reagent **6** in THF at −78 °C, subsequent treatment with cyclic enol ether **2b**–**h**, warming to room temperature, addition of the electrophile, and then hydrolysis. It is



Scheme 2. Zirconocene-mediated coupling reaction of organometallic compounds **5** (M = Li) and **6** (M = MgBr), aryl-substituted enol ethers **2b**–**h**, and electrophiles (see Table 1 for R, Ar, and E).

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Table 1: Cyclohexanol (**4**) or alkenol derivatives (**3**) obtained from the zirconocene-mediated coupling reaction of organometallic compounds **5** and **6**, aryl-substituted enol ethers **2b–h**, and electrophiles E^+.

5 or 6	R	2	Ar	E^+	Product (yield [%])[a]
5a	Et	**2b**	Ph	H_2O (H)	**3b** (17), **4a** (56)
5a	Et	**2b**	Ph	allyl chloride (allyl)[b]	**3c** (15), **4b** (54)
6a	H	**2b**	Ph	H_2O (H)	**3d** (19), **4c** (56)
5a	Et	**2c**	3-$MeOC_6H_4$	H_2O (H)	**3e** (41), **4d** (45)
5a	Et	**2d**	4-MeC_6H_4	H_2O (H)	**3f** (32), **4e** (39)
5a	Et	**2e**	4-ClC_6H_4	D_2O (D)	**4f** (75)
5a	Et	**2f**	2,4-$Cl_2C_6H_3$	H_2O (H)	**4g** (86)
6b	Pent	**2f**	2,4-$Cl_2C_6H_3$	H_2O (H)	**4h** (70)
6a	H	**2f**	2,4-$Cl_2C_6H_3$	allyl chloride (allyl)[b]	**4i** (72)
6c	Me	**2f**	2,4-$Cl_2C_6H_3$	H_2O (H)	**4j** (79)
5a	Et	**2g**	2,3,6-$Cl_3C_6H_2$	H_2O (H)	**4k** (78)
6c	Me	**2g**	2,3,6-$Cl_3C_6H_2$	allyl chloride (allyl)[b]	**4l** (75)
5a	Et	**2h**	4-FC_6H_4	H_2O (H)	**4m** (76)
6c	Me	**2h**	4-FC_6H_4	H_2O (H)	**4n** (77)

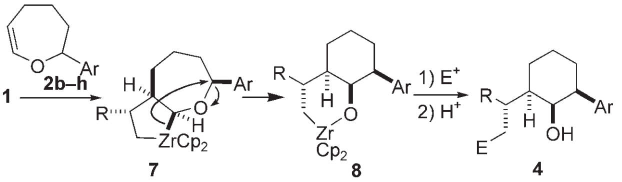
[a] Yield of isolated product based on **2**. [b] CuCl (5 mol%) and LiCl (1 equiv) were also added. After 1 h at 25 °C the reaction mixture was stirred at 50 °C for 6 h.

important to note the simplicity of the procedure—all the reagents are added sequentially in a one-pot reaction. Cyclohexanol derivatives **4** were isolated as the major or only reaction product and as a single diastereoisomer in all cases.[7]

A careful examination of the results given in Table 1 allows some interesting features of the process to be identified. First of all, it seems clear that formation of cyclohexanol derivatives **4** is influenced by the electronic nature of the aryl substituent of the starting enol ether **2**. Thus, with the phenyl-substituted enol ether **2b** the reaction mainly gives the corresponding cyclohexanol derivatives **4a–c**, although small amounts of the alkenol derivatives **3b–d** are also formed. In all these examples the ratio of **3** to **4** is approximately 1:3. Higher amounts of the corresponding alkenol derivatives **3** are obtained when electron-donating groups are introduced onto the aromatic ring of the starting enol ether (**2c**,**d**; **3**/**4** ≈ 1:1). Formation of **3** can be avoided by using enol ethers containing an aryl group substituted with electron-withdrawing groups (**2e–h**). Only the formation of the corresponding cyclohexanol derivatives **4**, which were isolated in high yield and as single diastereoisomers, was observed in all cases.

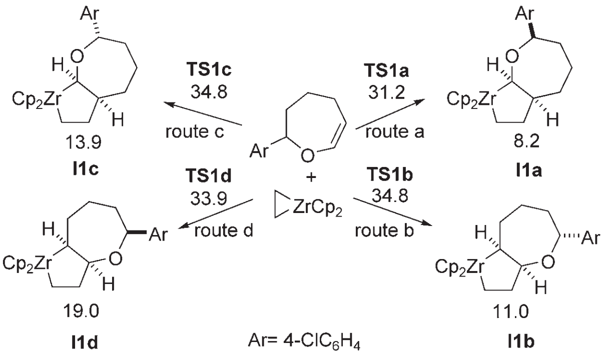
Several organolithium (**5**) or Grignard (**6**) reagents were used without major problems. As for the electrophile added in the last step of the reaction, functionalization by addition of carbon electrophiles such as allyl chloride is also noteworthy.

A plausible mechanism for the reaction of alkene–zirconocene complexes **1** with aryl-substituted seven-membered cyclic enol ethers **2** to give the cyclohexanol derivatives **4** is outlined in Scheme 3. Thus, a doubly regioselective insertion reaction of alkene–zirconocene complex **1** and enol ether **2** generates the bicyclic derivative **7**, which evolves through an intramolecular migratory insertion process to give **8**.[8] This process supposes a formal ring contraction of the initial seven-membered cyclic enol ether.[9] Reaction of **8** with the corresponding electrophile (E^+) and subsequent hydrolysis furnishes the cyclohexanol derivatives **4**. Interestingly, to justify the high stereocontrol observed in the formation of **4** (four new chiral centers are formed in a selective way) we should suppose an initial approximation of the zirconocene complex **1** to the double bond of the enol ether **2** (to form **7**) from the face where the aryl group is placed.



Scheme 3. Proposed mechanism for the formation of compounds **4**.

To gain further insight into the mechanism of formation of **4** we decided to study the reaction between **1** and **2** by means of DFT (density functional theory) computations at the B3LYP/6-31G* level using the Stuttgart/Dresden effective core potential for Zr, and taking into account the effect of THF solvent by the PCM method (see Supporting Information for further details). The Gibbs free-energies in solution reported herein are relative to the separate reactants. We first investigated the insertion of the seven-membered cyclic enol ether into the Zr–C bond. This insertion process, which is the rate-determining step for the reaction according to our theoretical results, can take place in four different ways (routes a–d in Scheme 4) depending on the approach of the alkene–zirconocene complex relative to the aryl substituent on the ether and on the location of the Zr atom with respect to the O atom. As shown in Scheme 4, the most favorable pathway corresponds to the insertion resulting from approach of the alkene–zirconocene complex to the double bond of the enol ether from the face where the aryl substituent is placed to form intermediate **I1a** (8.2 kcal mol^{-1}), where the Zr atom lies close to the O atom (route a). This insertion proceeds via the transition state **TS1a** with an energy barrier of 31.2 kcal mol^{-1}.



Scheme 4. Gibbs free-energy barriers (kcal mol^{-1}) for the four different modes of insertion of the seven-membered cyclic ether into the Zr–C bond of the alkene–zirconocene complex in THF solution, as obtained by DFT calculations.

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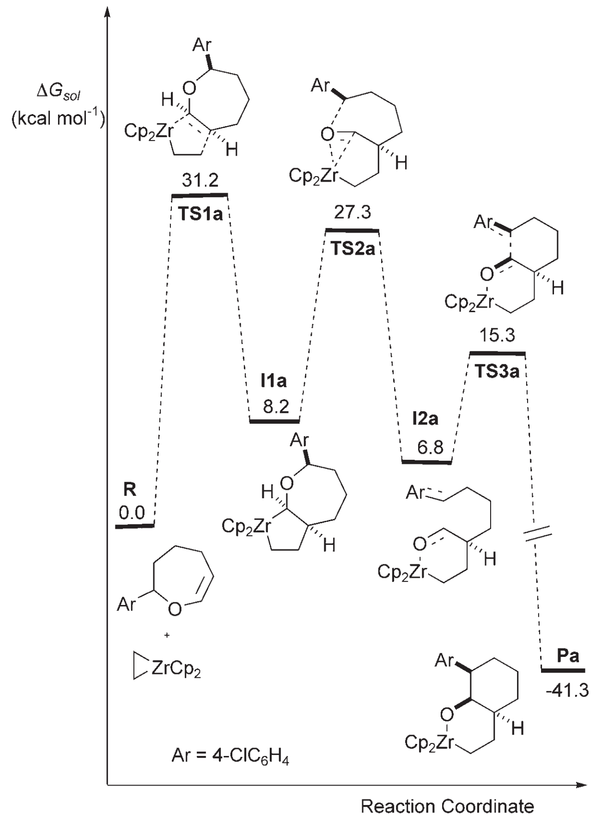

Figure 1. Gibbs free-energy profile in solution (kcal mol^{-1}) for the most favorable insertion of the cyclic ether into the Zr–C bond (route a in Scheme 4).

As can be seen in Figure 1, intermediate **I1a** (analogous to **7** in Scheme 3) can evolve via **TS2a** (27.3 kcal mol^{-1}) by homolytic rupture of the Zr–C bond close to the O atom and the O–C(Ar) bond and simultaneous formation of a Zr–O bond to give intermediate **I2a** (6.8 kcal mol^{-1}). This intermediate has a biradical character with the unpaired electrons mainly located at C(O) (spin density $= +0.6$) and C(Ar) (spin density $= -0.7$). The existence of this intermediate as a minimum on the potential energy surface of the system is possible because of the effective delocalization of the unpaired electrons owing to the polarizability of the Zr–O bond and the aryl substituent. Intermediate **I2a** then evolves via transition state **TS3a** (15.3 kcal mol^{-1}) by forming a bond between the two carbon atoms with radical character to yield the final product **Pa** (analogous to **8** in Scheme 3; -41.3 kcal mol^{-1}). Consequently, our calculations predict that the reaction between **1** and **2** yields **Pa** (**8**) as the only product, which is in agreement with the experimental results. Two stereogenic centers are formed in the last step of the mechanism (from **I2a** to **Pa**), therefore we decided to check the possibility of forming the other diastereoisomer by calculating the energy required for rotation around the C(aryl)–C bond. We found that the energy barrier for this step (10.6 kcal mol^{-1}) is higher than the energy required for the direct reaction to form **Pa** via **TS3a** (8.5 kcal mol^{-1}).

In conclusion, we have described an unprecedented one-pot, three-component, zirconocene-mediated coupling reaction of alkyllithiums or Grignard reagents, seven-membered enol ethers, and an electrophile. This reaction allows the straightforward synthesis of highly functionalized cyclohexanol derivatives in high yield and as single diastereoisomers from simple starting materials. Up to three new carbon-carbon bonds and four new stereogenic centers are formed in this process. In a formal sense, the global process could be considered as an unprecedented ring-contraction reaction of the initial seven-membered cyclic enol ether. From a mechanistic point of view it is a new reaction pathway in the field of organozirconium chemistry, the mechanism of which is supported by calculations.

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