

## Access to functionalized cyclopropylcarbinyl compounds from homoallylic ethers via zirconocene intermediates

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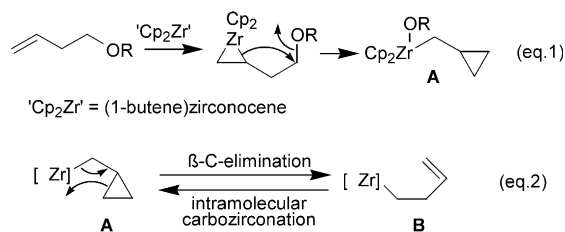
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**Abstract**—Cyclopropylcarbinylzirconium complexes were generated from homoallylic ethers and zirconocene ( $\text{Cp}_2\text{ZrCl}_2/2n\text{-BuLi}$ ). They underwent further in situ transformations that is, bromination–substitution, transmetallation–functionalization and insertion reactions to afford various cyclopropylcarbinyl derivatives. In contrast, ring-opening products could be selectively obtained by treating the zirconium complex with MeLi, prior to functionalization.  
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The synthetic methods employed for preparing cyclopropanes are typically based upon the direct cyclopropanation of alkenes.<sup>1</sup> However, in the last decade some new approaches to cyclopropanes have been developed. Among them, the Kulinkovich synthesis of cyclopropanols from esters and the de Meijere synthesis of tertiary cyclopropylamines from amides should be noticed.<sup>2</sup> We have recently reported zirconium- and titanium-mediated reactions that allow the preparation of primary cyclopropylamines from nitriles,<sup>3</sup> cyclopropanes from aldehydes and ketones,<sup>4</sup> as well as from allylic<sup>5</sup> and homoallylic<sup>6</sup> ethers. The last reaction is depicted in Scheme 1. It proceeds through the  $\gamma$ -elimination of the alkoxy group to afford the cyclopropylcarbinylzirconium intermediate **A** (Eq. 1). Cyclopropylcarbinyl–homoallyl rearrangement takes place occasionally (**A** predominant over **B**, Eq. 2), depending on the substrate structure.

We envisioned to explore in situ transformations from **A** with the aim of converting homoallylic ethers directly into cyclopropylcarbinyl derivatives. So far, a few synthetic applications of cyclopropylcarbinylmetal complexes ( $\text{M}=\text{Fe}$ ,  $\text{Co}$ ,  $\text{Pd}$ ,  $\text{Ni}$ ,  $\text{Rh}$ ,  $\text{Mn}$ ,  $\text{Pt}$ ) have been reported, dealing with ring-opening reactions.<sup>7</sup> Such reactions typically proceed via homolytic cleavage of



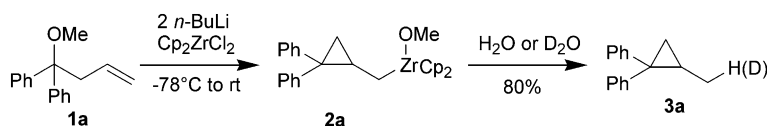
Scheme 1.

the metal–carbon bond, followed by a fast ring opening of the resulting cyclopropylcarbinyl radical.<sup>8</sup> We thought that non ring-opening transformations from **A** could be carried out, due to the unfavoured homolytic cleavage of the zirconium–carbon bond.<sup>9</sup> In order to test this hypothesis, we first reacted the homoallylic ether **1a** with (1-butene) $\text{ZrCp}_2$ , reformed in situ from  $\text{Cp}_2\text{ZrCl}_2$  and  $n\text{-BuLi}$ .<sup>10</sup> The exchange of 1-butene with **1a** followed by the  $\gamma$ -elimination of the OMe group led to the cyclopropylcarbinylzirconocene **2a**. The hydrolysis (deuterolysis) of **2a** afforded the cyclopropane **3a** ( $\text{X}=\text{H}$  or  $\text{D}$ ) in 80% isolated yield (Scheme 2).<sup>6</sup>

As expected, the zirconium complex **2a** underwent the bromolysis reaction without ring opening, thus confirming the heterolytic cleavage of the C–Zr bond in this reaction.<sup>11</sup> Thus, treatment of **2a** with NBS provided the cyclopropylcarbinyl bromide **4a** in 74% yield (NMR yield starting from the ether **1a**).<sup>12</sup> The bromide **4b** was obtained in the analogous manner

**Keywords:** Cyclopropylcarbinyl compounds; Homoallylic ethers; Zirconium.

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Scheme 2.

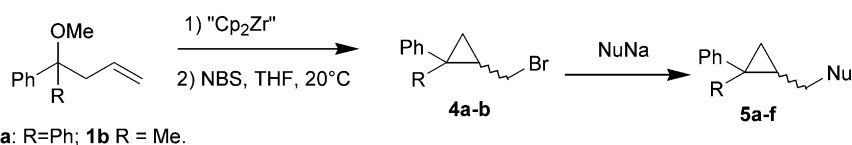
from **1b**. Although cyclopropylcarbinyl–homoallyl rearrangement has been demonstrated to operate starting from **1b**,<sup>6</sup> no acyclic olefinic bromide was obtained in this case. This might be rationalized by assuming that Curtin–Hammett conditions apply, in which more rapid bromonolysis takes place from **A** than from **B** (Scheme 1, Eq. 2).<sup>13</sup>

The cyclopropylcarbinyl bromides **4a–b** underwent subsequent displacement reactions with mild nonbasic nucleophiles. Carbon-, oxygen-, nitrogen- and sulfur-based nucleophilic reagents could be employed (Table 1). These reactions were performed under mild conditions to afford functionalized cyclopropanes **5a–f** in moderate to good yields.<sup>14</sup> A possible access to various functionalized cyclopropylcarbinyl derivatives from readily available homoallylic ethers should be synthetically useful.

Alkylzirconocenes are rather unreactive towards typical carbon-based electrophiles. However, by using these complexes, C–C bond constructions can be achieved through carbenoid insertion into the C–Zr bond,<sup>15</sup> or transmetalation to various metals.<sup>16</sup> We have noticed

that in our case, both insertion and transmetalation can be applied to transform cyclopropylcarbinylzirconocenes into functionalized cyclopropanes. Firstly, reaction of **2a** with BnNC was carried out in toluene at 40°C for 6 h. Hydrolysis of the reaction mixture and subsequent reduction of the resulting crude aldehyde afforded the alcohol **6** in 36% yield (starting from **1a**) (Scheme 3).<sup>17</sup> Secondly, transmetalation to copper using **2a** and a catalytic amount of Cu<sup>I</sup> allowed further acylation and allylation reactions.<sup>18</sup> In this way, ketone **7** and homoallylcyclopropane **8** were formed, the latter being accompanied by the ring-opening compound **9**. The transmetalation of **2a** using HgCl<sub>2</sub> was also performed to afford the mercury derivative **10** (Scheme 3) that can be isolated and characterized by NMR spectroscopy.

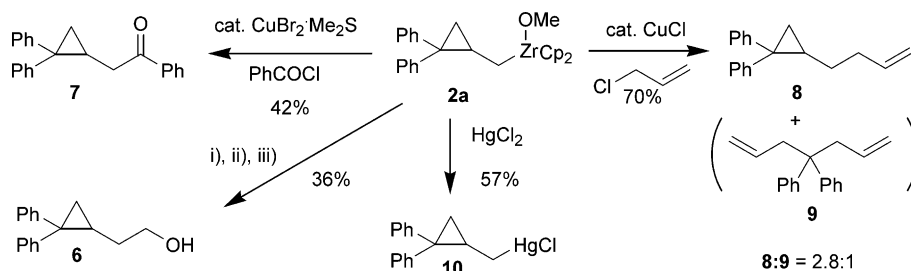
Finally, we tried to favour reactions with ring opening from the cyclopropylcarbinylzirconocene **2a**, and found that such reactions can be carried out by activating the complex with MeLi. Thus, treatment of **2a** with MeLi at low temperature and subsequent addition of PhCHO or PhCOCl afforded, respectively, the alcohol **11** and ketone **12** in moderate yields (Scheme 4). These

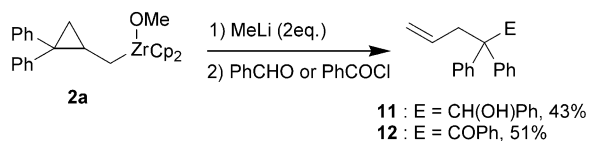
Table 1. Preparation of the bromides **4a–b** and their reactions with nucleophiles

**1a**: R=Ph; **1b** R = Me.

Entry	Ether	Nu	<b>5</b>	Yield, % ( <i>trans:cis</i> ) <sup>a</sup>
1	<b>1a</b>	N <sub>3</sub>	<b>5a</b>	60
2	<b>2b</b>	N <sub>3</sub>	<b>5b</b>	47 (1.6:1)
3	<b>1a</b>	CN	<b>5c</b>	68
4	<b>1a</b>	OPh	<b>5d</b>	24
5	<b>1a</b>	SO <sub>2</sub> Ph	<b>5e</b>	43
6	<b>2b</b>	SO <sub>2</sub> Ph	<b>5f</b>	33 (1.6:1)

<sup>a</sup> Isolated yields.

Scheme 3. Reagents and conditions: (i) BnNC; (ii) HCl (3N); (iii) NaBH<sub>4</sub>.



Scheme 4.

reactions possibly proceed through ring opening from an intermediate zirconium ate complex. They involve a substituted homoallyl anion equivalent and lead to the creation of a quaternary carbon centre.

In conclusion, we have generated cyclopropylcarbinyl-zirconocenes from homoallylic ethers and studied their in situ transformations into functionalized cyclopropylcarbinyl compounds. A remarkable feature of these reactions is that they occurred without ring opening. However, ring-opening products could be obtained selectively by treating the zirconium intermediate with MeLi prior to functionalization.

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- Similarly, the reaction of **2a** with I<sub>2</sub> gave the corresponding iodide; however, this compound appeared unstable.
- Starting from an homoallylic ether bearing two alkyl groups, complex reaction mixtures containing alkenes were obtained.
- Selected data for **5a**: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz): δ 1.31 (m, 2H), 1.88 (m, 1H), 2.98 (ABX system, 2H), 7.03–7.43 (m, 10H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 62.5 MHz): δ 17.7, 23.1, 34.6, 51.5, 125.1, 125.8, 126.7, 127.3, 127.5, 129.2, 139.3, 144.7.
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- Selected data for **6**: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz): δ 0.96 (m, 1H); 1.25 (m, 2H), 1.69 (m, 2H), 3.66 (td, J = 6.5, 2.0, Hz, 2H), 7.04–7.38 (m, 10H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 62.5 MHz): δ 20.8, 23.3, 34.5, 35.2, 63.2, 121.2, 126.9, 128.2, 128.7, 128.8, 131.0, 142.0, 147.6; HRMS: found 239.1426, calcd for C<sub>17</sub>H<sub>16</sub>O<sup>+</sup> 239.1436 (24, M+1).
- This result is noteworthy, since transmetalations are generally more difficult with alkyl- than with alkenylzirconocenes.