

Conversion of Acid Chloride into Homoallylic Alcohol via Allylic C–H Bond Activation of Alkene with a Zirconocene Complex

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Zirconocene–alkene complexes [Cp₂Zr(alkene)], generated *in situ* by thermolysis of dialkylzirconocene, have been widely used in organic synthesis. The complexes are transformed into zirconacycles via oxidative coupling with another carbon–carbon multiple bond.¹ Additionally, coupling reaction with aldehydes or ketones affords the corresponding saturated alcohols via the oxazirconacyclopentane intermediate.² However, reaction of Cp₂Zr(alkene) with acid halide has not been explored. During the course of our study on reactions mediated by zirconocene complexes,³ we found that Cp₂Zr(alkene) **1**, prepared at 0 °C, reacted with acid chloride **2** to give homoallylic alcohol **3**. The formation of the alcohol apparently involved allylic C–H bond activation of the coordinating alkene. Here we wish to disclose our preliminary result of study on this reaction.

Cp₂ZrCl₂ (2 mmol) was treated with *n*-BuMgBr (1 M THF solution, 4 mL, 4 mmol) in benzene (20 mL) with cooling in an ice/water bath. After the reaction mixture was stirred at 0 °C for 30 min, benzoyl chloride (**2a**, 1 mmol) was added. The whole mixture was stirred for 3 h at 0 °C. Usual workup followed by silica gel column purification afforded **3aa** in 82% yield (Scheme 1).⁴ Pentyl-, octyl-, and 3-phenylpropylmagnesium bromide, instead of butylmagnesium bromide, were also effective to yield the corresponding homoallylic alcohols.⁵

Reaction with other aromatic acid chlorides is summarized in Table 1. Most of the reactions proceeded in satisfactory yields, although electron-rich acid chlorides such as **2e** resulted in lower yields. In contrast to the reaction with aromatic acid chloride, upon treatment of octanoyl chloride with **1a**, cyclopropanol **4** was obtained in 25% yield, in addition to **3ag** (Scheme 2).⁶ More interestingly, reaction with methyl benzoate, instead of benzoyl chloride, cleanly furnished cyclopropanol **5** in 85% yield. It is also worth noting that addition of PPh₂Me as an additive to the reaction of **2a** gave rise to formation of **5** without contamination of **3aa**.

(1) (a) Negishi, E.; Takahashi, T. *Acc. Chem. Res.* **1994**, *27*, 124–130. (b) Negishi, E.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 755–769. (c) Takahashi, T.; Kotora, M.; Hara, R.; Xi, Z. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2591–2602.

(2) (a) Takahashi, T.; Suzuki, N.; Hasegawa, M.; Nitto, Y.; Aoyagi, K.; Saburi, M. *Chem. Lett.* **1992**, 331–334. (b) Suzuki, N.; Rousset, C. J.; Aoyagi, K.; Kotora, M.; Takahashi, T. *J. Organomet. Chem.* **1994**, *473*, 117–128.

(3) Fujita, K.; Nakamura, T.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2001**, *123*, 3137–3138.

(4) Traces of benzyl alcohol and the saturated analogue of **3aa** were detectable byproducts in the crude oil. Other conceivable byproducts such as tertiary alcohol, generated via double allylation, were not observed at all.

(5) The use of THF as a solvent, instead of benzene, decreased the yield of **3** (**3aa**: 80%, **3da**: 76%).

(6) Titanium–alkene complexes effected formation of cyclopropanols: (a) Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1995**, *117*, 9919–9920. (b) Kasatkin, A.; Nakagawa, T.; Okamoto, S.; Sato, F. *J. Am. Chem. Soc.* **1995**, *117*, 3881–3882. (c) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevski, D. A. *Synthesis* **1991**, 234. (d) Corey, E. J.; Rao, S. A.; Noe, M. C. *J. Am. Chem. Soc.* **1994**, *116*, 9345–9346. (e) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789–2834.

Scheme 1

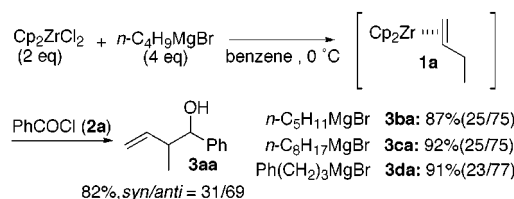
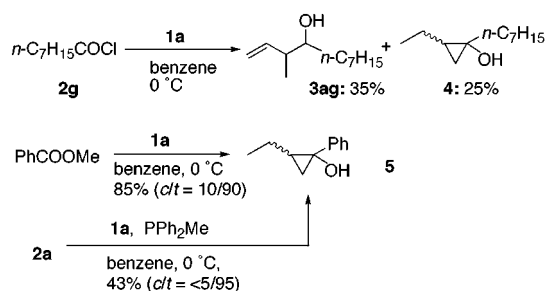


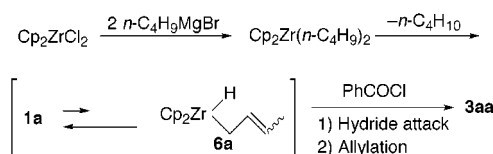
Table 1. Reaction of **1a** with Various Acid Chlorides

R	yield/% (syn/anti)
2-CH ₃ -C ₆ H ₄	3ab : 63 (29/71)
4-Cl-C ₆ H ₄	3ac : 67 (33/67)
2-Furyl	3ad : 60 (42/58)
4-CH ₃ O-C ₆ H ₄	3ae : 22 (36/64)
4-CF ₃ -C ₆ H ₄	3af : 65 (38/62)

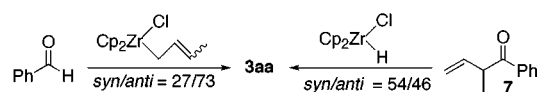
Scheme 2



Scheme 3



Scheme 4



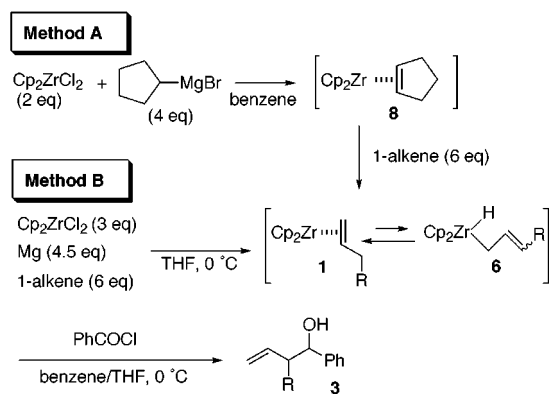
We are tempted to assume the reaction mechanism for the formation of homoallylic alcohol as depicted in Scheme 3. There exists an equilibrium between Cp₂Zr(1-butene) and zirconocene crotyl hydride [**6a**, Cp₂Zr(crotyl)H] according to the literature of Harrod.^{7,8} Hydride attack on benzoyl chloride followed by allylation furnishes **3aa**. The following experiments suggest the order of the sequential nucleophilic attack (Scheme 4). Reaction of benzaldehyde with the crotylzirconium reagent, prepared from Cp₂ZrCl₂ and a crotyl Grignard reagent, yielded **3aa** with anti selectivity (syn/anti = 27/73). The selectivity was similar to that observed in the reaction in Scheme 1. On the other hand, treatment of ketone **7** with Schwartz reagent led to a slight syn selectivity.

Preparations of the requisite Grignard reagents are laborious. Next, we investigated direct preparation of Cp₂Zr(2-alkenyl)H from Cp₂ZrCl₂ and alkene. Zirconocene dichloride (2 mmol) was treated with cyclopentylmagnesium bromide (4 mmol) in the

(7) Dioumaev, V. K.; Harrod, J. F. *Organometallics* **1997**, *16*, 1452–1464. Also see, Negishi, E.; Maye, J. P.; Chouery, D. *Tetrahedron* **1995**, *51*, 4447–4462.

(8) Photolysis of Fe(CO)₅(η²-CH₂=CHCH₃) resulted in similar rearrangement: Barnhart, T. M.; McMahon, R. J. *J. Am. Chem. Soc.* **1992**, *114*, 5434–5435.

Scheme 5

**Table 2.** Direct Synthesis of Homoallylic Alcohols from Alkenes

$\text{CH}_2=\text{CH}-\text{CH}_2-\text{R}$ **12** $\xrightarrow[\text{Method A or B}]{\text{PhCOCl}}$ $\text{CH}_2=\text{CH}-\text{CH}(\text{OH})-\text{CH}_2-\text{R}$ **3**

entry	$\text{CH}_2=\text{CH}-\text{R}$	Method	yield/% (syn/anti)
1	$\text{CH}_2=\text{CH}-\text{C}_2\text{H}_5$	12b A	3ba : 76%(25/75)
2	$\text{CH}_2=\text{CH}-\text{C}_2\text{H}_5$	12b B	3ba : 77%(23/77)
3	$\text{CH}_2=\text{CH}-n\text{-C}_5\text{H}_{11}$	12c B	3ca : 62%(26/74)
4	$\text{CH}_2=\text{CH}-\text{Ph}$	12d A	3da : 65%(24/76)
5	$\text{CH}_2=\text{CH}-n\text{-C}_3\text{H}_7$	12e A	3ea : 74%(20/80)
6	$\text{CH}_2=\text{CH}-n\text{-C}_3\text{H}_7$	12e B	3ea : 75%(23/77)
7	$\text{CH}_2=\text{CH}-\text{SiPh}_3$	12f A	3fa : 31%(single)
8	$\text{CH}_2=\text{CH}-\text{CH}_2-\text{CH}_2-\text{O}-\text{Ph}$	12g A	3ga : 32%(23/77)
9	$\text{CH}_2=\text{CH}-\text{CH}_2-\text{CH}_2-\text{O}-\text{Ph}$	12g B	3ga : 62%(23/77)
10	$\text{CH}_2=\text{CH}-\text{C}_6\text{H}_{11}$	12h A	3ha : 52%
11	$\text{CH}_2=\text{CH}-\text{C}_6\text{H}_{11}$	12h B	3ha : 43%
12	$\text{CH}_2=\text{CH}-\text{CH}_2-\text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{C}_4\text{H}_9$	12i B	3ia : 67%(22/78)
13	$\text{CH}_2=\text{CH}-\text{CH}_2-\text{CH}_2-\text{N}(\text{C}_6\text{H}_{13})-\text{C}(=\text{O})-\text{C}_4\text{H}_9$	12j B	3ja : 61%(26/74)

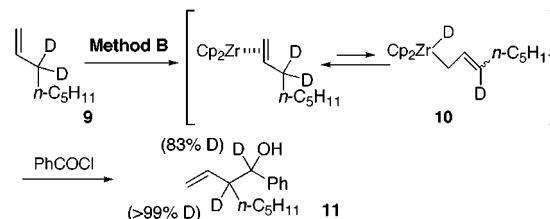
presence of 1-pentene (6 mmol) in benzene (20 mL) at 0 °C for 30 min and at 25 °C for an additional 1 h (Scheme 5, Method A). Initially formed $\text{Cp}_2\text{Zr}(\text{cyclopentene})$ **8** was anticipated to undergo ligand exchange, forming $\text{Cp}_2\text{Zr}(\text{1-pentene})$.⁹ This was indeed the case, and **3ba** was obtained in 76% yield upon treatment of benzoyl chloride with the reagent at 0 °C (Table 2, entry 1). Other alkenes could participate in the ligand exchange to furnish the corresponding homoallylic alcohols (Table 2, Method A).¹⁰

Furthermore, reduction of Cp_2ZrCl_2 with Mg metal in the presence of alkene also provided the reagent **6**.¹¹ In this method, addition of benzene as a cosolvent prior to reaction with PhCOCl

(9) A similar ligand exchange reaction of a titanium reagent was reported: Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 4198–4199. Also see ref 6a.

(10) The reaction in THF itself resulted in the diminished yields of **3**. For instance, **3ea** was obtained in 26% yield along with benzyl alcohol (17%).

Scheme 6



is again crucial for the successful formation of homoallylic alcohols. Alcohol **3ba** was formed in 46% yield in the reaction without benzene. The results were comparable to those obtained by Method A (Table 2, Method B). Advantageously, ester and amide moieties could survive under the reaction conditions (entries 12 and 13). Alkenes are much more readily available than the corresponding allylic magnesium reagents. Thus, this method promises rapid synthesis of a wide spectrum of homoallylic alcohols.

The allylic C–H bond cleavage as shown in Scheme 3 was further confirmed by employing 3,3-dideuterio-1-octene (**9**). Zirconium complex **10** was prepared from **9** by Method B, and benzoyl chloride was added to **10** to afford deuterated homoallylic alcohol **11** (Scheme 6).

In summary, we have found a new divergent route to homoallylic alcohols, utilizing the allylic C–H bond activation of alkenes. Reaction of an allylic halide/metal or an allylic metal with aldehyde is a standard procedure to obtain homoallylic alcohol. Direct formation of allylic metals from alkenes employs highly basic and nucleophilic organolithium reagents.¹² As far as zirconium compounds are concerned, allylic zirconium reagents have been prepared from low-valent zirconocene and alkenes that have good leaving groups such as alkoxide at the allylic position.¹³ In contrast, the present methodology requires easy-handling and readily available alkenes, instead of reactive allylic halides, and saves tasks in preparing allylic halides. The $\text{Cp}_2\text{Zr}(\text{alkene})$ -mediated allylation offers mild and efficient synthesis of homoallylic alcohols. Moreover, this reaction will develop novel utility of the $\text{Cp}_2\text{Zr}(\text{alkene})$ reagent.

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Supporting Information Available: Experimental details and characterization data (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(11) (a) Miura, K.; Funatsu, M.; Saito, H.; Ito, H.; Hosomi, A. *Tetrahedron Lett.* **1996**, *37*, 9059–9062. (b) Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, J. A. *J. Am. Chem. Soc.* **1985**, *107*, 2568–2569. (c) Thanedar, S.; Faron, M. F. *J. Organomet. Chem.* **1982**, *235*, 65–68.

(12) From simple alkene: (a) Heus-Kloos, Y. A.; de Jong, R. L. P.; Verkruisje, H. D.; Brandsma, L.; Julia, S. *Synthesis* **1985**, 958–959. (b) Akiyama, S.; Hooz, J. *Tetrahedron Lett.* **1973**, *14*, 4115–4118. From alkene having a metal-directing group: (c) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282–2316. (d) Prasad, K. R. K.; Hoppe, D. *Synlett* **2000**, 1067–1069. (e) Pippel, D. J.; Weisenberger, G. A.; Faibish, N. C.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 4919–4927.

(13) (a) Ito, H.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **1992**, *33*, 1295–1298. (b) Ito, H.; Nakamura, T.; Taguchi, T.; Hanzawa, Y. *Tetrahedron* **1995**, *51*, 4507–4518. (c) Hanzawa, Y.; Ito, H.; Taguchi, T. *Synlett* **1995**, 299–305. (d) Ito, H.; Kuroi, H.; Ding, H.; Taguchi, T. *J. Am. Chem. Soc.* **1998**, *120*, 6623–6624. (e) Rousset, C. J.; Swanson, D. R.; Lamaty, F.; Negishi, E. *Tetrahedron Lett.* **1989**, *30*, 5105–5108.