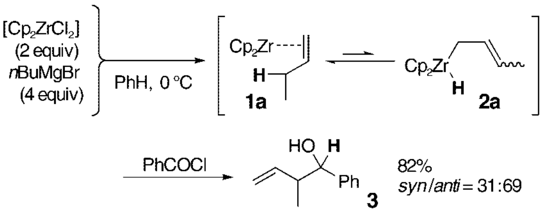
Tandem Reduction–Allylation

Highly Diastereoselective Tandem Reduction–Allylation Reactions of 1,4-Diketones with Zirconocene–Olefin Complexes**

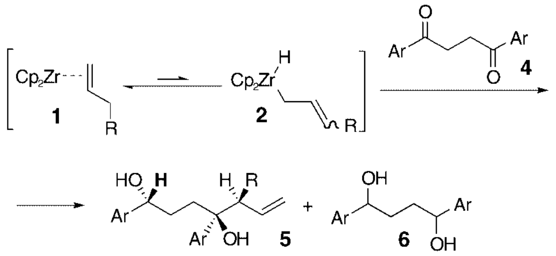
*Kazuya Fujita, Hiroshi Shinokubo, and Koichiro Oshima**

Since the development by Negishi et al. of a convenient method for the generation of low-valent zirconocene species,[1] the reaction of zirconocene–alkene complexes with a variety of unsaturated compounds has been regarded as a powerful tool for carbon–carbon bond-forming processes.[2] Recently, we found that [Cp_2Zr(1-alkene)] **1**, prepared at 0 °C in benzene, reacted with acid chlorides to provide homoallylic alcohols **3** (Scheme 1).[3] In this reaction, the [Cp_2Zr(alkene)] serves as a donor both of hydride and of an allyl group. We assume that an equilibrium exists between zirconocene–allyl–hydride complex **2a** and zirconocene–alkene complex **1a** through reversible allylic C–H bond cleavage of the coordinating alkene.[4] On the basis of this finding, we envisaged the application of [Cp_2Zr(alkene)] complexes as dual nucleophiles in reactions with diketones. We discovered that a tandem reduction–allylation reaction of 1,4-diketones takes place in the presence of a [Cp_2Zr(1-alkene)] complex with a high level of 1,4-diastereoselectivity. To our knowledge this is the first example of the 1,4-diastereoselective allylation of ketones.[5]



Scheme 1. Reaction of [Cp_2Zr(1-butene)] with benzoyl chloride.

The treatment of [Cp_2ZrCl_2] (2.0 equiv) with *n*PrMgBr (4.0 equiv) in benzene at 0 °C provided [Cp_2Zr(propene)] (**1b**, R = H). 1,4-Diketone **4a** (Ar = 3,5-$F_2(C_6H_3)$) was added to this mixture and the reduction of one carbonyl group and allylation at the other occurred to provide 1,4-diol **5a** in 64 % yield with excellent diastereoselectivity (Scheme 2, Table 1, entry 1). By-product **6a** was also obtained in 6 % yield.[6] The reaction of **1b** with other aromatic 1,4-diketones is summarized in Table 1 (entries 2–9).[7] Most of the reactions proceeded in satisfactory yields, although the use of electron-rich aromatic 1,4-diketones such as **4h** resulted in lower yields (Table 1, entry 8).[8] Ether and ester functionalities are also tolerated under the reaction conditions (e.g. Table 1, entry 9).



Scheme 2. Reaction of [Cp_2Zr(1-alkene)] complexes with 1,4-diketones.

Table 1: Conversion of 1,4-diketones into *anti* 1,4-diols.[a]

Entry	**4**	Ar	R	**5** (%Yield)	*anti*/*syn*	**6** (%Yield)
1[b]	**a**	3,5-$F_2(C_6H_3)$	H	**a** (64)	96:4	**a** (6)
2[b]	**b**	Ph	H	**b** (57)	94:6	**b** (18)
3[b]	**c**	3-$CF_3(C_6H_4)$	H	**c** (60)	92:8	**c** (11)
4[b]	**d**	4-$CF_3(C_6H_4)$	H	**d** (62)	92:8	**d** (16)
5[b]	**e**	4-Br(C_6H_4)	H	**e** (52)	> 99:1	**e** (13)
6[b]	**f**	4-Cl(C_6H_4)	H	**f** (60)	96:4	**f** (9)
7[b]	**g**	4-F(C_6H_4)	H	**g** (62)	96:4	**g** (7)
8[b]	**h**	4-MeO(C_6H_4)	H	**h** (29)	91:9	**h** (36)
9[b]	**i**	4-*t*BuO$_2$C(C_6H_4)	H	**i** (62)	97:3	**i** (13)
10[c]	**a**	3,5-$F_2(C_6H_3)$	Me	**j** (76)	97:3	**a** (5)
11[c]	**b**	Ph	Me	**k** (54)	95:5	**b** (17)
12[c]	**c**	3-$CF_3(C_6H_4)$	Me	**l** (78)	96:4	**c** (11)
13[c]	**d**	4-$CF_3(C_6H_4)$	Me	**m** (62)	92:8	**d** (16)
14[c]	**e**	4-Br(C_6H_4)	Me	**n** (70)	97:3	**e** (14)
15[c]	**f**	4-Cl(C_6H_4)	Me	**o** (81)	97:3	**f** (11)
16[c]	**g**	4-F(C_6H_4)	Me	**p** (62)	96:4	**g** (7)
17[d]	**a**	3,5-$F_2(C_6H_3)$	Et	**q** (66)	95:5	**a** (16)
18[e]	**a**	3,5-$F_2(C_6H_3)$	*n*Pr	**r** (59)	96:4	**a** (21)
19[f]	**a**	3,5-$F_2(C_6H_3)$	Ph	**s** (71)	> 99:1	**a** (6)

[a] Reaction conditions: [Cp_2ZrCl_2] (2.0 mmol), benzene (30 mL), Grignard reagent (1.0 M in THF, 4.0 mmol), 1,4-diketone (1.0 mmol), 0 °C. Grignard reagents used: [b] *n*PrMgBr. [c] *n*BuMgBr. [d] *n*PentMgBr. [e] *n*HexMgBr. [f] Ph($CH_2)_3$MgBr.

---

[*] Prof. Dr. K. Oshima, K. Fujita, Dr. H. Shinokubo
Department of Material Chemistry
Graduate School of Engineering, Kyoto University
Yoshida, Sakyo-ku, Kyoto 606-8501 (Japan)
Fax: (+81) 75-753-4863
E-mail: oshima@fm1.kuic.kyoto-u.ac.jp

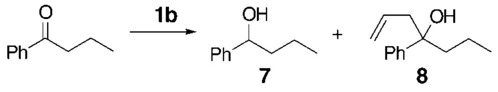
[**] This work was supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan. We thank Prof. Tamejiro Hiyama and Dr. Masaki Shimizu (Kyoto University) for X-ray crystallographic analysis. K.F. acknowledges the JSPS for financial support.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

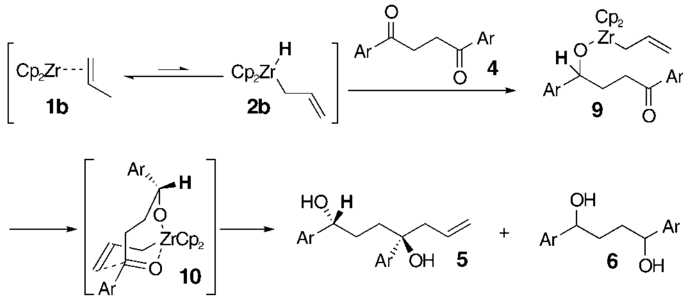
DOI: 10.1002/ange.200351480

Especially rewarding was the high level of *anti*/*syn* stereoselectivity displayed by the reaction (> 95:5 in most cases), with respect to the two OH-bearing carbon centers.[9] The relative 1,4-stereochemistry of the major isomer was assigned as *anti* based on the X-ray crystallographic analysis of **5e**.

To elucidate the order in which the nucleophilic attacks by hydride and the allyl group take place, we examined the reactivity of zirconocene complex **1b** toward phenyl propyl ketone (Scheme 3). Analysis of the crude mixture indicated predominant formation of **7** along with a trace amount of the allylated adduct **8**. This result clearly suggests that hydride transfer occurs prior to that of the allyl moiety.[10] Consequently, we propose the reaction mechanism depicted in Scheme 4 for the formation of the *anti* 1,4-diols. Thus, $[Cp_2Zr(propene)]$ (**1b**), through its equilibrium with **2b**, delivers hydride to one of the carbonyl carbon centers of a 1,4-diketone **4** to yield an allylzirconium alkoxide **9**. Subsequent intramolecular addition of the allyl group on zirconium to the other carbonyl carbon atom then takes place with the formation of an *anti* 1,4-diol **5**.



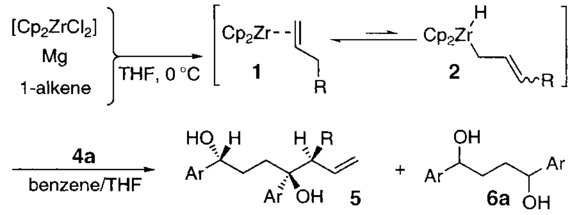
Scheme 3. Reaction of $[Cp_2Zr(propene)]$ with phenyl propyl ketone.



Scheme 4. Proposed reaction pathway.

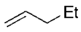
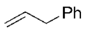
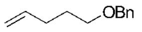
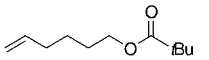
We next turned our attention to tandem reduction–3-alkenylation reactions with other 1-alkenes. The results are listed in Table 1 (entries 10–19). For example, the treatment of 1,4-diketone **4a** with $[Cp_2ZrCl_2]$ (2.0 equiv), after prior treatment of the latter with *n*BuMgBr (4.0 equiv), resulted in the formation of **5j** in 76% yield with excellent 1,4,5-diastereoselectivity (Table 1, entry 10). The alkenylation reactions proceeded with perfect 4,5-*syn* selectivity as well as with excellent 1,4-*anti* stereoselectivity.[11] The use of pentyl, hexyl, and 3-phenylpropyl Grignard reagents also allowed the formation of the corresponding homoallylic alcohols with excellent stereoselectivity (Table 1, entries 17, 18, and 19).

The preparation of the requisite Grignard reagents is laborious. It is known that a zirconocene–olefin complex can be prepared from $[Cp_2ZrCl_2]$ and Mg metal in the presence of the 1-alkene.[12] $[Cp_2Zr(1\text{-alkene})]$ complexes prepared in this way were also found to serve as dual nucleophiles, and the desired 1,4-diols were obtained in reasonable yields with excellent stereoselectivity (Scheme 5). Table 2 summarizes the reduction–3-alkenylation reactions of 1,4-diketone **4a** with several olefins. Ether and ester groups were tolerated under the reaction conditions (Table 2, entries 3 and 4). Thus, the reaction allows the facile preparation of various functionalized 1,4-diols.



Scheme 5. Preparation of zirconocene complexes with magnesium metal.

Table 2: Synthesis of *anti* 1,4-diols from 1-alkenes.[a]

Entry	Alkene	5	Yield [%]	1,4-*anti*/*syn*	Yield of **6a** [%]
1		**q**	68	96:4	9
2		**s**	53	>99:1	0
3		**t**	68	>99:1	0
4		**u**	44	>99:1	0

[a] Reaction conditions: $[Cp_2ZrCl_2]$ (3.0 mmol), Mg (4.5 mmol), alkene (6.0 mmol), 1,4-diketone (1.0 mmol), benzene/THF (25/5 mL), 0 °C.

In conclusion, we have disclosed a highly 1,4-stereoselective tandem reduction–3-alkenylation of 1,4-diketones with zirconocene–alkene complexes. Reduction of one of the carbonyl groups, followed by intramolecular transfer of the allyl group, enables excellent levels of diastereocontrol of three stereocenters. Investigations into the further utility of zirconocene–alkene complexes as dual nucleophiles is currently underway in our laboratory.

Experimental Section

*n*PrMgBr (1.0 M in THF, 4.0 mL, 4.0 mmol) was added dropwise to a mixture of $[Cp_2ZrCl_2]$ (585 mg, 2.0 mmol) in benzene (30 mL) at 0 °C. The resulting viscous black suspension was stirred for 30 min at 0 °C, then a solution of **4a** (310 mg, 1.0 mmol) in benzene (2 mL) was added. The reaction mixture was stirred for a further 5 h at 0 °C, then was poured into aqueous HCl. This mixture was extracted with hexane/ethyl acetate, and the organic extracts were dried and concentrated. Purification on silica gel provided **5a** (228 mg, 0.64 mmol) in 64% yield.

Received: March 25, 2003 [Z51480]

Keywords: allylation · C-H activation · domino reactions · reduction · zirconium

[1] E.-I. Negishi, F. E. Cederbaum, T. Takahashi, *Tetrahedron Lett.* **1986**, *27*, 2829.

[2] For leading reviews, see: a) E.-I. Negishi, T. Takahashi, *Acc. Chem. Res.* **1994**, *27*, 124; b) E.-I. Negishi, D. Y. Kondakov, *Chem. Soc. Rev.* **1996**, *25*, 417; c) E.-I. Negishi, T. Takahashi, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 755; d) T. Takahashi, M. Kotora, R. Hara, Z. Xi, *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2591.

[3] K. Fujita, H. Yorimitsu, H. Shinokubo, K. Oshima, *J. Am. Chem. Soc.* **2001**, *123*, 12115.

[4] It has been shown that zirconocene–olefin complex **1** and allyl–zirconocene–hydride complex **2** are in an equilibrium that is significantly shifted toward **1**: V. K. Dioumaev, J. F. Harrod, *Organometallics* **1997**, *16*, 1452; see also: E.-I. Negishi, J. P. Maya, D. Choueiry, *Tetrahedron* **1995**, *51*, 4447.

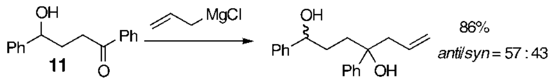
[5] The 1,4-diastereoselective methylation of γ-alkoxy aldehydes has been reported: a) M. T. Reetz, K. Kesseler, S. Schmidtberger, B. Wenderoth, R. Steinbach, *Angew. Chem.* **1983**, *95*, 1007; *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 989; b) M. T. Reetz, *Angew. Chem.* **1984**, *96*, 542; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 556.

[6] ^{13}C NMR spectroscopic analysis indicated that 1,4-diol **6a** had formed as a mixture of isomers. We assume that **6** resulted from the intermolecular reduction of intermediate **9** by zirconocene hydride **2b**. The formation of double reduction product **6** is suppressed by conducting the reaction under high dilution conditions.

[7] When 1,5-diketones or 1,6-diketones were used in place of 1,4-diketones, trace amounts of the expected products were isolated along with products of double reduction. Nucleophilic addition reactions did not occur with 1,3-diketones because of enolization of these substrates.

[8] In contrast to aromatic 1,4-diketones, the reaction of 5,8-dodecadione with **1b** afforded the desired adduct in only 15 % yield.

[9] The reaction of γ-hydroxyketone **11** with allylmagnesium chloride exhibited no diastereoselectivity.



[10] This order of sequential nucleophilic attack was also found in the reaction of zirconocene–alkene complex **1** with acid chlorides; see reference [3].

[11] The relative 4,5-configuration of the diols was assigned by comparison of their spectral data with those reported for analogues; see: Y. Kataoka, I. Makihara, T. Yamagata, K. Tani, *Organometallics* **1997**, *16*, 4788.

[12] a) E.-I. Negishi, S. J. Holmes, J. M. Tour, J. A. Miller, *J. Am. Chem. Soc.* **1985**, *107*, 2568; b) K. Miura, M. Funatsu, H. Saito, H. Ito, A. Hosomi, *Tetrahedron Lett.* **1996**, *37*, 9059; c) S. Thanedar, M. F. Farona, *J. Organomet. Chem.* **1982**, *235*, 65.