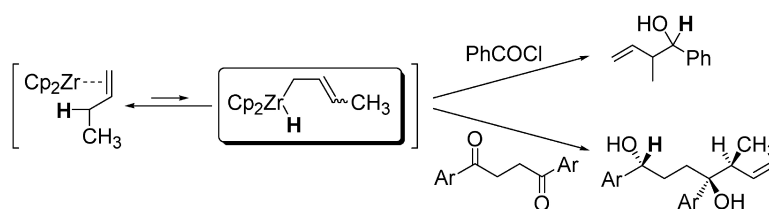Article

Transformation of Zirconocene–Olefin Complexes into Zirconocene Allyl Hydride and Their Use as Dual Nucleophilic Reagents: Reactions with Acid Chloride and 1,4-Diketone

Kazuya Fujita, Hideki Yorimitsu, Hiroshi Shinokubo, and Koichiro Oshima

More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

Transformation of Zirconocene−Olefin Complexes into Zirconocene Allyl Hydride and Their Use as Dual Nucleophilic Reagents: Reactions with Acid Chloride and 1,4-Diketone

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

Contribution from the Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyoto-daigaku Katsura, Nishikyo-ku, Kyoto 615-8510, Japan

Received February 13, 2004; E-mail: oshima@fm1.kuic.kyoto-u.ac.jp

Abstract: Zirconocene−olefin complexes $Cp_2Zr(H_2C=CHR)$, prepared in benzene−THF at 0 °C, react with acid chlorides to provide homoallylic alcohols. The key is an equilibrium between the zirconocene−olefin complexes and the corresponding zirconocene allyl hydride complexes via allylic C−H bond cleavage of the coordinating alkenes. Furthermore, the zirconocene−olefin complexes are also available for the reaction with 1,4-diketone to afford *anti*-1,4-diols with excellent diastereoselectivity. Thus, $Cp_2Zr(H_2C=CHR)$ serves as a donor of both hydride and an allylic group. These reactions also proceed efficiently by using zirconocene−olefin complexes, derived from Cp_2ZrCl_2, Mg metal, and 1-alkenes.

Introduction

Since the development of a convenient method for the generation of low-valent zirconocene species by Negishi et al.,[1] the reaction of zirconocene−olefin complexes $Cp_2Zr(H_2-C=CHR)$ (**1**) with a variety of unsaturated compounds has been regarded as a powerful tool for regioselective C−C bond formation reaction.[2] For example, **1** reacted with another alkene to afford zirconacyclopentane **2a** or **2b** and the substituted butane **3a** or **3b** after hydrolysis (Scheme 1).[3] In these reactions, the alkyl groups R and R′ were at the β positions of zirconacyclopentane with >98% regioselectivity, whereas the aryl group Ar was at the α position with >98% regioselectivity.

Additionally, coupling reaction with aldehyde or ketone afforded the corresponding saturated alcohol via an oxazirconacyclopentane intermediate (Scheme 2).[4] It is noteworthy that **6a** was obtained exclusively and that the regioisomer **6b** was not detected.

Aside from the reaction in Scheme 2, little is known about other polar addition reactions of zirconocene−olefin complexes. Thus, we felt that this area clearly deserved further exploration and set out to address the reaction of $Cp_2Zr(H_2C=CHEt)$ with acid halide. As a result, we found that $Cp_2Zr(H_2C=CHEt)$ (**1a**), prepared in benzene−THF at 0 °C, reacted with acid chloride to furnish homoallylic alcohol.[5] In this reaction, the key would
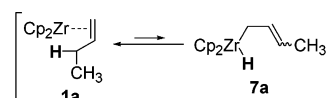
Scheme 1
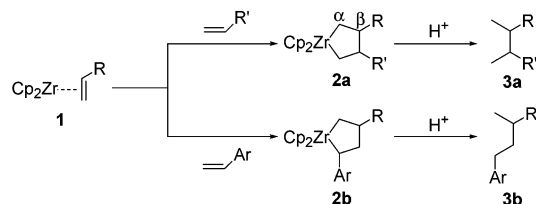
Scheme 2
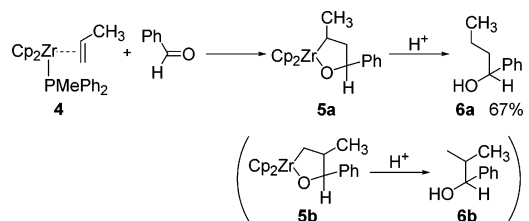
Scheme 3

be an equilibrium between the zirconocene−olefin complex **1a** and a zirconocene allyl hydride complex **7a** via allylic C−H bond cleavage of the coordinating alkene (Scheme 3).[6] We propose that hydride attack on benzoyl chloride should result in formation of benzaldehyde, which subsequently undergoes allylation to form the desired homoallylic alcohol. Namely, the zirconocene allyl hydride complex functions as the source of

(1) (a) Negishi, E.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829. (b) Negishi, E.; Holms, S. J.; Tour, J. M.; Miller, J. A.; Cederbaum, F. E.; Swanson, D. R.; Takahashi, T. *J. Am. Chem. Soc.* **1989**, *111*, 3336.
(2) For leading reviews, see: (a) Negishi, E.; Takahashi, T. *Acc. Chem. Res.* **1994**, *27*, 124. (b) Negishi, E.; Kondakov, D. Y. *Chem. Soc. Rev.* **1996**, *26*, 417. (c) Negishi, E.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 755. (d) Takahashi, T.; Kotora, M.; Hara, R.; Xi, Z. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2591.
(3) Swanson, D. R.; Rousset, C. J.; Negishi, E. *J. Org. Chem.* **1989**, *54*, 3521.
(4) (a) Takahashi, T.; Suzuki, N.; Hasegawa, M.; Nitto, Y.; Aoyagi, K.; Saburi, M. *Chem. Lett.* **1992**, 331. (b) Suzuki, N.; Rousset, C. J.; Aoyagi, K.; Kotora, M.; Takahashi, T. *J. Organomet. Chem.* **1994**, *473*, 117.
(5) (a) Fujita, K.; Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K. *J. Am. Chem. Soc.* **2001**, *123*, 12115. (b) Fujita, K.; Yorimitsu, H.; Oshima, K. *Chem. Rec.* **2004**, *4*, 110.
(6) Harrod has proved that **1a** and **7a** are in an equilibrium which is significantly shifted toward **1a**: Dioumaev, V. K.; Harrod, J. F. *Organometallics* **1997**, *16*, 1452. Also see, Negishi, E.; Maya, J. P.; Choueiry, D. *Tetrahedron* **1995**, *51*, 4447.

Scheme 4
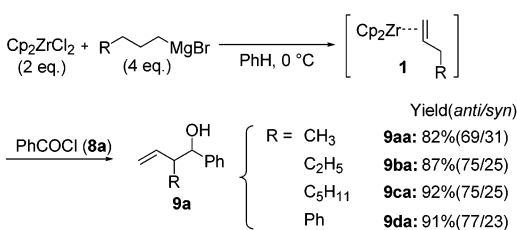
Table 1. Reaction of Zirconocene−1-Butene Complex with Various Acid Chlorides[a]

entry	R	product	yield/%	anti/syn
1	Ph	**9aa**	82	69:31
2	2-CH$_3$(C$_6$H$_4$)	**9ab**	63	71:29
3	4-Cl(C$_6$H$_4$)	**9ac**	67	67:33
4	furyl	**9ad**	60	58:42
5	4-CH$_3$O(C$_6$H$_4$)	**9ae**	22	64:36
6	4-CF$_3$(C$_6$H$_4$)	**9af**	65	62:38

[a] Cp$_2$ZrCl$_2$ (2.0 mmol), butylmagnesium bromide (1.0 M in THF, 4.0 mL, 4.0 mmol), acid chloride (1.0 mmol), and benzene (20 mL) were employed at 0 °C.

two different anion species, hydride and allylic anion. Although the existence of the zirconocene allyl hydride complex is known,[6] there are only a few reports dealing with the formation mechanism and no report on its application to organic synthesis. Herein we wish to describe the full details of application of the zirconocene allyl hydride complexes, tautomers of zirconocene−olefin complexes, as dual nucleophilic reagents.

Conversion of Acid Chloride into Homoallylic Alcohol. Cp$_2$ZrCl$_2$ (2 mmol) was treated with *n*-C$_4$H$_9$MgBr (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 (**8a**, 1 mmol) was added. The whole mixture was stirred for 3 h at 0 °C. Usual workup followed by silica gel column purification afforded **9aa** in 82% yield (Scheme 4).[7] Pentyl-, octyl-, and 3-phenylpropylmagnesium bromide, instead of butylmagnesium bromide, were also effective to yield the corresponding homoallylic alcohols. The use of benzene as a solvent would be crucial for the successful process. The use of THF as a solvent, instead of benzene, decreased the yield of **9**.

Reactions with other aromatic acid chlorides are summarized in Table 1. Most of the reactions proceeded smoothly to furnish the corresponding desired products in satisfactory yields with slight anti selectivity, although electron-rich acid chlorides such as **8e** resulted in lower yield (entry 5).

We are tempted to assume the reaction mechanism for the formation of homoallylic alcohol as depicted in Scheme 5. There exists an equilibrium between Cp$_2$Zr(H$_2$C=CHEt) (**1a**) and zirconocene crotyl hydride (**7a**, Cp$_2$Zr(crotyl)H) according to the literature of Harrod.[6,8] In this reaction, **7a** functions as the source of two different anion species, hydride and allyl anion,
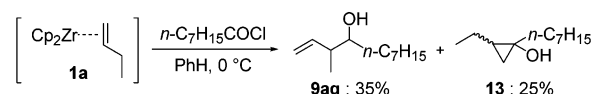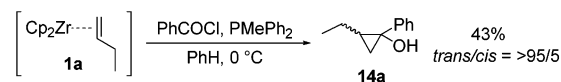
Scheme 5
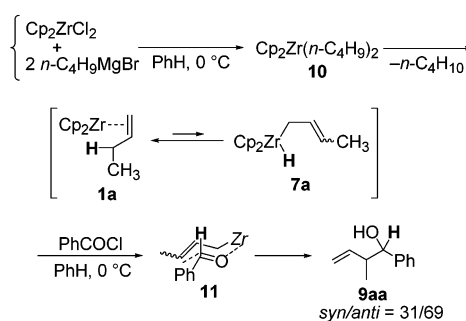
Scheme 6
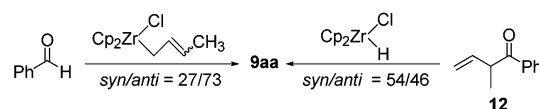
Scheme 7

Scheme 8

utilizing allylic C−H bond activation of 1-butene. Hydride attack on benzoyl chloride followed by allylation furnishes **9aa**. The following experiments suggest the order of the sequential nucleophilic attack (Scheme 6). Reaction of benzaldehyde with crotylzirconium reagent, prepared from Cp$_2$ZrCl$_2$ and crotyl Grignard reagent, yielded **9aa** with anti selectivity (syn/anti = 27:73). The selectivity was similar to that observed in the reaction in Scheme 4. On the other hand, treatment of ketone **12** with the Schwartz reagent led to slight syn selectivity.

In contrast to the reaction with aromatic acid chlorides, upon treatment of octanoyl chloride with **1a**, cyclopropanol **13** was obtained in 25% yield, in addition to **9ag** (Scheme 7). More interestingly, the presence of PMePh$_2$ in the reaction of benzoyl chloride gave rise to the formation of *trans*-**14a**[9] without contamination by **9aa** (Scheme 8). Coordination of PMePh$_2$ to the zirconium center would prevent the formation of zirconocene crotyl hydride.

Furthermore, we found that treatment of ester, instead of benzoyl chloride, with a zirconocene−olefin complex at 0 °C cleanly furnished 1,2-disubstituted cyclopropanol **14** in good yield (Scheme 9).[10] This cyclopropanol formation proceeded smoothly with aryl-, alkyl-, cycloalkyl-, and alkenylcarboxylates (Table 2). γ-Lactone **17** could also be easily transformed into

(7) Traces of benzyl alcohol and the saturated analogue of **9aa** were detectable byproducts in the crude oil. Other conceivable byproducts such as tertiary alcohol, generated via double allylation, were not observed at all.

(8) Photolysis of Fe(CO)$_4$(η²-CH$_2$=CHCH$_3$) resulted in similar rearrangement: Barnhart, T. M.; McMahon, R. J. *J. Am. Chem. Soc.* **1992**, *114*, 5434.

(9) The relative configurations "cis" and "trans" are assigned by the Cahn−Ingold−Prelog system throughout the present text.

(10) Titanium−alkene complexes induce formation of cyclopropanols: (a) Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1995**, *117*, 9919. (b) Lee, J.; Kang, C. H.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 291. (c) Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 4198. (d) Kasatkin, A.; Nakagawa, T.; Okamoto, S.; Sato, F. *J. Am. Chem. Soc.* **1995**, *117*, 3881. (e) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevski, D. A. *Synthesis* **1991**, 234. (f) Corey, E. J.; Rao, S. A.; Noe, M. C. *J. Am. Chem. Soc.* **1994**, *116*, 9345. (g) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789. Szymoniak also reported that the reaction of a zirconocene−ethylene complex with ester provided the corresponding cyclopropanol. (h) Gandon, V.; Bertus, P.; Szymoniak, J. *Eur. J. Org. Chem.* **2000**, *6*, 3713.
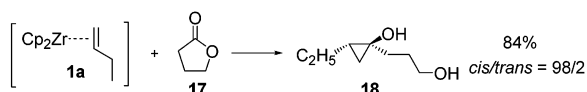
Scheme 9
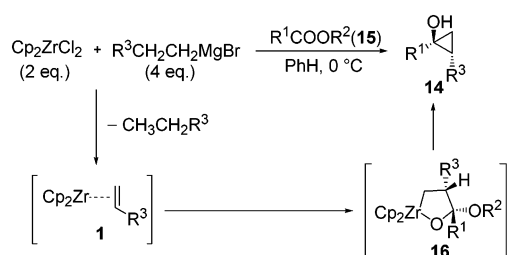
Table 2. Reaction of Zirconocene−Olefin Complex with Various Esters[a]

Entry	R^1	R^2	R^3	Product	Yield/%	*cis/trans*[b]
1	Ph	CH_3	C_2H_5	**14a**	91	90/10
2	Ph	i-C_3H_7	C_2H_5	**14a**	99	79/21
3	Ph	C_2H_5	CH_3[c]	**14b**	84	>99/1
4	n-C_8H_{17}	CH_3	C_2H_5	**14c**	82	>99/1
5	c-C_6H_{11}	CH_3	C_2H_5	**14d**	92	>99/1
6		CH_3	C_2H_5	**14e**	66	88/12

[a] Cp_2ZrCl_2 (2.0 mmol), butylmagnesium bromide (1.0 M in THF, 4.0 mL, 4.0 mmol), ester (1.0 mmol), and benzene (20 mL) were employed at 0 °C. [b] Reference 9. [c] Propylmagnesium bromide was used instead of butylmagnesium bromide.

Scheme 10

the corresponding diol **18** (Scheme 10).[11] It is worth noting that the products were formed with high trans diastereoselectivity. The stereochemistry of the product was confirmed by NOE study of **14b**. The trans stereoselectivity was also found in the reaction of titanium-catalyzed Kulinkovich hydroxycyclopropanation.[10e,f] This reaction would proceed via oxazirconacyclopentane **16** (Scheme 9).

Preparation of the requisite Grignard reagents is laborious. Next, we investigated direct preparation of Cp_2Zr(2-alkenyl)H from Cp_2ZrCl_2 and alkene. Zirconocene dichloride was treated with 2 equiv of cyclopentylmagnesium bromide in the presence of 3 equiv of 1-pentene in benzene at 0 °C for 30 min and at 25 °C for an additional 1 h (Scheme 11, Method A). Initially formed Cp_2Zr(cyclopentene) (**19**) was anticipated to undergo ligand exchange, forming Cp_2Zr(1-pentene).[12,13] This was indeed the case, and **9ba** was obtained in 76% yield upon treatment of benzoyl chloride with the reagent at 0 °C (Table 3, entry 1). Other alkenes could participate in the ligand exchange to furnish the corresponding homoallylic alcohols (Table 3, Method A).[14]

(11) Esposito, A.; Taddei, M. *J. Org. Chem.* **2000**, *65*, 9245. Two examples of the reductive coupling of lactone with terminal alkene according to the Kulinkovich protocol have been described in ref 10c.

(12) A similar ligand exchange reaction of a titanium reagent was reported: see ref 10c.

(13) It is possible that the zirconacyclopentanes resulting from addition of two alkenes to a zirconocene−olefin complex can be formed. However, we propose the zirconacyclopentane is also equilibrated with a zirconocene−olefin complex and zirconocene allyl hydride. See ref 3.

(14) The reaction in THF itself resulted in the diminished yields of **9**. For instance, **9ea** was obtained in 26% yield along with benzyl alcohol (17%).

Scheme 11
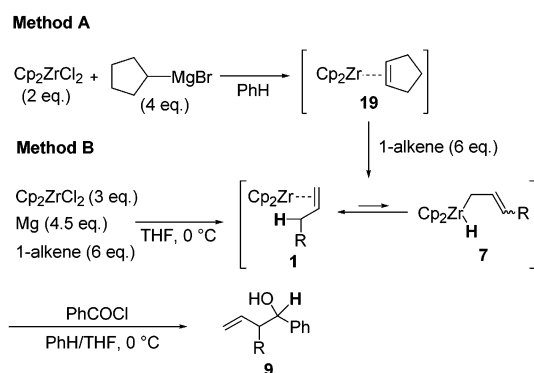
Method A

Method B

Table 3. Direct Synthesis of Homoallylic Alcohols from Alkenes[a]

Entry		Olefin	Method	Product	Yield/%	*anti/syn*
1	C_2H_5	**20b**	A	**9ba**	76	75/25
2		**20b**	B	**9ba**	77	77/23
3	n-C_5H_{11}	**20c**	B	**9ca**	62	74/26
4	Ph	**20d**	A	**9da**	65	76/24
5	n-C_3H_7	**20e**	A	**9ea**	74	80/20
6		**20e**	B	**9ea**	75	77/23
7	$SiPh_3$	**20f**	A	**9fa**	31	single
8	O~Ph	**20g**	A	**9ga**	32	77/23
9		**20g**	B	**9ga**	62	77/23
10		**20h**	A	**9ha**	52	-
11		**20h**	B	**9ha**	43	-
12	t-C_4H_9	**20i**	B	**9ia**	67	78/22
13	t-C_4H_9 / n-C_6H_{13}	**20j**	B	**9ja**	61	74/26

[a] Method A: Cp_2ZrCl_2 (2.0 mmol), cyclopentylmagnesium bromide (1.0 M in THF, 4.0 mL, 4.0 mmol), alkene (6.0 mmol), acid chloride (1.0 mmol), and benzene (20 mL) were employed. Method B: Cp_2ZrCl_2 (3.0 mmol), Mg (4.5 mmol), alkene (6.0 mmol), acid chloride (1.0 mmol), and benzene (25 mL) were employed.

Furthermore, reduction of Cp_2ZrCl_2 with Mg metal in the presence of alkene also provided the reagent **7**.[13,15] In this method, addition of benzene as a cosolvent prior to reaction with PhCOCl was crucial for the successful formation of homoallylic alcohols. Alcohol **9ba** was formed in 46% yield in the reaction without benzene. The results were comparable to those obtained by Method A (Table 3, 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.

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

Scheme 12

Scheme 13
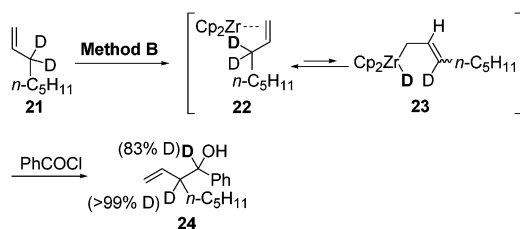
β-H abstraction

γ-H abstraction
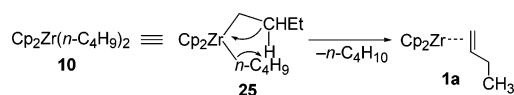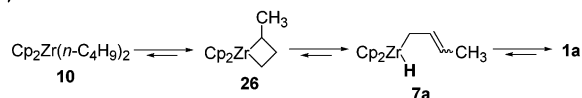
Scheme 14

Scheme 15

The allylic C−H bond cleavage as shown in Scheme 5 was further confirmed by employing 3,3-dideuterio-1-octene (**21**). Zirconium complex **23** was prepared from **21** by Method B, and benzoyl chloride was added to **23** to afford dideuterated homoallylic alcohol **24** (Scheme 12).

There is a controversy over the pathway of the conversion of dialkylzirconocene into the corresponding zirconocene−olefin complex (Scheme 13). The primary reaction of Cp$_2$ZrCl$_2$ and butyl Grignard reagent is simple and leads to the formation of Cp$_2$Zr(n-C$_4$H$_9$)$_2$ (**10**). Negishi et al. assumed that decomposition of dialkylzirconocene **10** occurs through β-H abstraction to form butane and **1a** (Scheme 13).[16] On the other hand, Harrod's group suggested that **10** decomposes via γ-H abstraction which leads to zirconacyclobutane **26**. Strained zirconacycle **26** rearranges to form zirconocene crotyl hydride (**7a**), which undergoes further rearrangement to produce **1a**.[6]

By taking advantage of the present reaction, we examined the following investigation to clarify the mechanism of the conversion of dialkylzirconocene into the zirconocene−olefin complex. Reaction of benzoyl chloride with dialkylzirconocene **28**, derived from Cp$_2$ZrCl$_2$ and 2,2-dideuteriooctylmagnesium bromide (**27**), yielded **31** (Scheme 14). Deuterium was incorporated perfectly at the internal olefinic position. We could not observe any deuterium of significance at other positions. The formation of **31** which possesses only one deuterium provides strong evidence for the β-H abstraction. If zirconacyclobutane **32** is formed through the γ-H abstraction, the products such as **34** and **37** would contain two deuteriums. In practice, neither of the products were detected. Thus, the result proves that this process cannot proceed via the γ-H abstraction.

We also tried subsequent examination to get further confidence. Zirconium complex **39** was also prepared from Cp$_2$ZrCl$_2$ and 3,3-dideuteriooctylmagnesium bromide (**38**), and benzoyl chloride was added to **39**. As expected, deuterium was incorporated at the allylic and benzylic positions (Scheme 15).[17]

Tandem Reduction−Allylation Reactions of 1,4-Diketones. As mentioned above, Cp$_2$Zr(H$_2$C=CHEt) serves as a donor of both hydride and an allyl group. On the basis of this finding,
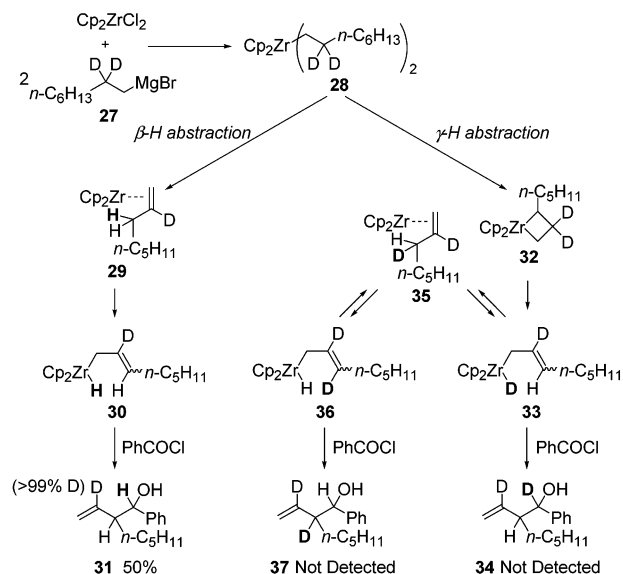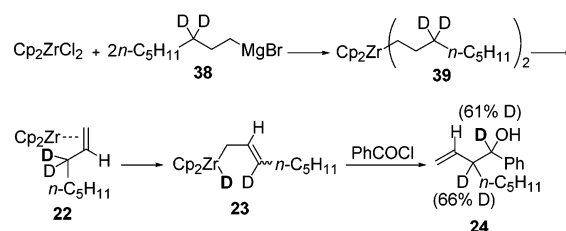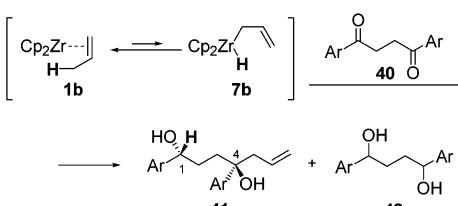
we attempted further application of a zirconocene−olefin complex as a dual nucleophilic reagent in reactions with various substrates bearing two electrophilic centers intramolecularly. As a result, we discovered that a tandem reduction−allylation reaction of 1,4-diketones takes place in the presence of a

(17) Deuterium was not completely incorporated at the allylic and benzylic positions in **24**. Additionally, the examination of the ^{1}H and ^{2}D NMR of the product **24** indicates that deuterium was also found at the methylene and methyl groups of the pentyl chain. This migration of deuterium can be explained by the following mechanism.
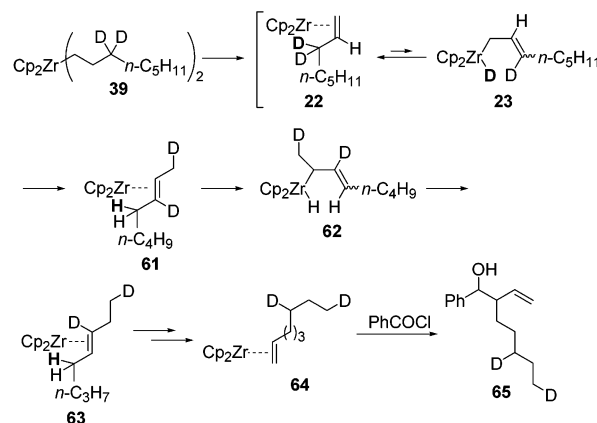
First, treatment of Cp$_2$ZrCl$_2$ and **38** forms zirconocene−olefin complex **22** through the β-H abstraction. Complex **22** is equilibrated with zirconocene allyl deuteride complex **23** via allylic C−D bond activation. It is assumed that **61** is then produced via reductive elimination, because the nucleophilicity of the deuteride in **23** is weaker than the hydride in zirconocene allyl hydride complex **7**, probably due to isotope effect. By a similar allylic C−H activation−reductive elimination sequence, **64** is finally formed. Complex **64** reacts with benzoyl chloride to provide homoallyl alcohol derivative **65**. Thus, the desired product **24** in which deuteriums are incorporated at the allylic and benzylic positions would be contaminated with **65**.

(16) (a) Negishi, E.; Swanson, D. R.; Takahashi, T. *J. Chem. Soc., Chem. Commun.* **1990**, 1254. (b) Negishi, E.; Holms, S. J.; Tour, J. M.; Miller, J. A.; Cederbaum, F. E.; Swanson, D. R.; Takahashi, T. *J. Am. Chem. Soc.* **1989**, *111*, 3336.

Table 4. Reduction−Allylation Reactions of 1,4-Diketones[a]

entry	40	Ar	product 41	yield/ %	anti/syn	42	yield/ %
1	40a	3,5-F$_2$(C$_6$H$_3$)	41a	64	96:4	42a	6
2	40b	Ph	41b	57	94:6	42b	18
3	40c	3-CF$_3$(C$_6$H$_4$)	41c	60	92:8	42c	11
4	40d	4-CF$_3$(C$_6$H$_4$)	41d	62	92:8	42d	16
5	40e	4-Br(C$_6$H$_4$)	41e	52	>99:1	42e	13
6	40f	4-Cl(C$_6$H$_4$)	41f	60	96:4	42f	9
7	40g	4-F(C$_6$H$_4$)	41g	62	96:4	42g	7
8	40h	4-MeO(C$_6$H$_4$)	41h	29	91:9	42h	36
9	40i	4-*t*-BuOCO(C$_6$H$_4$)	41i	62	97:3	42i	13

[a] Cp$_2$ZrCl$_2$ (2.0 mmol), propylmagnesium bromide (1.0 M in THF, 4.0 mL, 4.0 mmol), 1,4-diketone (1.0 mmol), and benzene (30 mL) were employed.
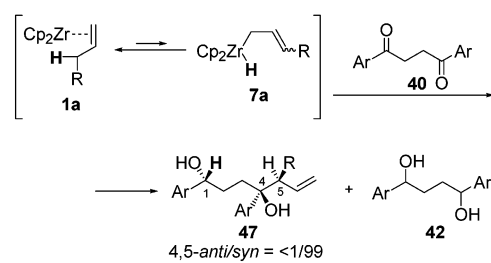
zirconocene−olefin complex with a high level of 1,4-diastereoselectivity.[18] To our knowledge, this is the first example of the 1,4-diastereoselective allylation of ketones.[19]

Treatment of Cp$_2$ZrCl$_2$ (2.0 mmol) with *n*-C$_3$H$_7$MgBr (1.0 M THF solution, 4.0 mL, 4.0 mmol) in benzene (30 mL) at 0 °C provided Cp$_2$Zr(propene) (**1b**). 1,4-Diketone **40a** (1.0 mmol) was added to this mixture, and the reduction of one carbonyl group and allylation at the other occurred to provide 1,4-diol **41a** in 64% yield with excellent diastereoselectivity. Byproduct **42a** was also obtained in 6% yield.[20] The reaction of **1b** with other aromatic 1,4-diketones is summarized in Table 4.[21] Most of the reactions proceeded in satisfactory yields, although the use of electron-rich aromatic 1,4-diketones such as **40h** resulted in lower yields (entry 8).[22] Ether and ester functionalities were also tolerated under the reaction conditions (entries 8 and 9).

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.[23] The relative 1,4-stereochemistry of the major isomer was assigned as anti based on the X-ray crystallographic analysis of **41e**.

To elucidate the order in which the nucleophilic attacks by hydride and the allyl group take place, we examined the

(18) Fujita, K.; Shinokubo, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 2550.

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

(20) ^{13}C NMR spectroscopic analysis indicated that 1,4-diol **42a** had formed as a mixture of isomers. We assume that **42** resulted from the intermolecular reduction of intermediate **45** by zirconocene hydride **7b**. The formation of double reduction product **42** was suppressed by conducting the reaction under high dilution conditions.

(21) 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.

(22) In contrast to aromatic 1,4-diketones, the reaction of 5,8-dodecanedione with **1b** afforded the desired adduct in only 15% yield.

(23) The reaction of γ-hydroxyketone **66** with allylmagnesium chloride exhibited no diastereoselectivity.
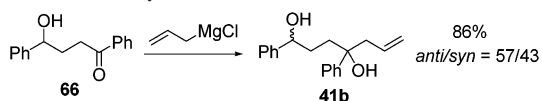
Scheme 16
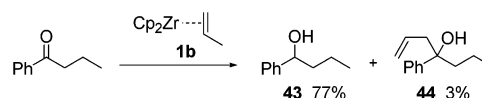
Scheme 17
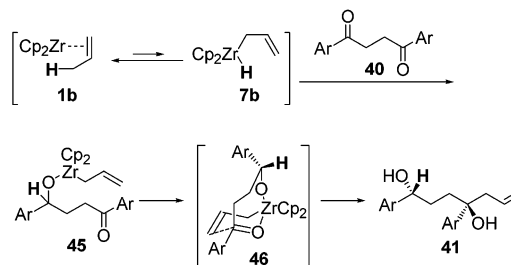
Table 5. Reduction−Crotylation Reactions of 1,4-Diketones[a]

4,5-*anti/syn* = <1/99

entry	40	Ar	R	product 47	yield/ %	1,4-anti/syn	42	yield/ %
1	40a	3,5-F$_2$(C$_6$H$_3$)	Me	47a	76	97:3	42a	5
2	40b	Ph	Me	47b	54	95:5	42b	17
3	40c	3-CF$_3$(C$_6$H$_4$)	Me	47c	78	96:4	42c	11
4	40d	4-CF$_3$(C$_6$H$_4$)	Me	47d	62	92:8	42d	16
5	40e	4-Br(C$_6$H$_4$)	Me	47e	70	97:3	42e	14
6	40f	4-Cl(C$_6$H$_4$)	Me	47f	81	97:3	42f	11
7	40g	4-F(C$_6$H$_4$)	Me	47g	62	96:4	42g	7
8	40a	3,5-F$_2$(C$_6$H$_3$)	Et	47h	66	95:5	42a	16
9	40a	3,5-F$_2$(C$_6$H$_3$)	*n*-C$_3$H$_7$	47i	59	96:4	42a	21
10	40a	3,5-F$_2$(C$_6$H$_3$)	Ph	47j	71	>99:1	42a	6

[a] Cp$_2$ZrCl$_2$ (2.0 mmol), butylmagnesium bromide (1.0 M in THF, 4.0 mL, 4.0 mmol), 1,4-diketone (1.0 mmol), and benzene (30 mL) were employed.

reactivity of zirconocene complex **1b** toward phenyl propyl ketone (Scheme 16). Analysis of the crude mixture indicated predominant formation of **43** along with a trace amount of the allylated adduct **44**.

This result clearly suggests that hydride transfer occurs prior to allyl transfer, which is the same order as the reaction with acid chloride. Consequently, we propose the reaction mechanism depicted in Scheme 17 for the formation of the *anti*-1,4-diols. Thus, Cp$_2$Zr(propene) (**1b**), through its equilibrium with **7b**, delivers hydride to one of the carbonyl carbon centers of 1,4-diketone **40** to yield allylzirconium alkoxide **45**. Subsequent intramolecular addition of the allyl group on zirconium then takes place to form *anti*-1,4-diol **41**.

We turned our attention to a tandem reduction−crotylation reaction. The results are listed in Table 5. For example, treatment of 1,4-diketone **40a** with **1a** (2.0 equiv) resulted in the formation of **47a** in 76% yield (entry 1). It deserves comment that the crotylation reaction proceeded with perfect 4,5-syn selectivity as well as with excellent 1,4-anti stereoselectivity.[24] The use of pentyl, hexyl, and 3-phenylpropyl Grignard reagents also allowed the formation of the corresponding homoallylic alcohols with excellent stereoselectivity (entries 8, 9, and 10).

Table 6. Synthesis of Anti 1,4-Diols from 1-Alkenes[a]

Entry	Alkene	Product 47	Yield/%	1,4-*anti/syn*	Yield of 42a (%)
1	$\diagdown\!\!\diagup$C$_2$H$_5$	**47h**	68	96/4	9
2	$\diagdown\!\!\diagup$Ph	**47j**	53	>99/1	0
3	$\diagdown\!\!\diagup$O$\diagdown$Ph	**47k**	68	>99/1	0
4	$\diagdown\!\!\diagup\diagdown\!\!\diagup$O—C(=O)—*t*-C$_4H_9$	**47l**	44	>99/1	0

a Cp$_2$ZrCl$_2$ (3.0 mmol), Mg (4.5 mmol), alkene (6.0 mmol), 1,4-diketone (1.0 mmol), and benzene/THF (25:5 mL) were employed.
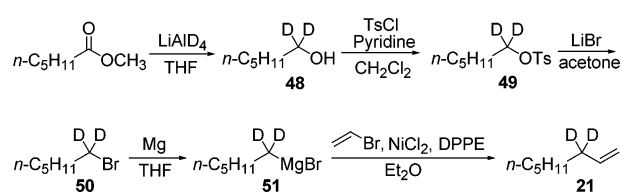
In this tandem reduction–allylation reaction, zirconocene–olefin complexes, derived from Cp$_2$ZrCl$_2$ and Mg metal in the presence of the 1-alkene, were also found to serve as dual nucleophilic reagents, and the desired 1,4-diols were obtained in reasonable yields with excellent stereoselectivity. Table 6 summarizes the reduction–allylation reactions of 1,4-diketone **40a** with several olefins. Advantageously, various functional groups such as ether and ester groups could survive under the reaction conditions (entries 3 and 4). Thus, the reaction allows facile preparation of various functionalized 1,4-diols.

Conclusion

In conclusion, we found that zirconocene–olefin complexes functioned as the source of two different anion species, hydride and allyl anion in the reaction with substrate bearing two electrophilic centers intramolecularly. The key intermediate is zirconocene allyl hydride, formed through reversible allylic C—H bond cleavage of the coordinating alkene of the zirconocene–olefin complex. The reaction with acid chloride afforded the corresponding homoallylic alcohol by sequential H/allyl attacks. Furthermore, in the reaction with 1,4-diketone, it was also found that the high level of stereoselectivity was displayed by utilizing the reagent. To date, zirconocene–olefin complexes have served only as precursors of various zirconacycles. Thus, the use of the dual nucleophilic reagent, zirconocene allyl hydride, will provide unprecedented synthetic routes to organic compounds.

General Procedure for Synthesis of Homoallylic Alcohol with Zirconocene Dichloride and a Grignard Reagent. Benzene (20 mL) was added to Cp$_2$ZrCl$_2$ (585 mg, 2.0 mmol) in a 50-mL reaction flask under argon. After the mixture was cooled to 0 °C in an ice/water bath, butylmagnesium bromide (4.0 mL, 1.0 M THF solution, 4.0 mmol) was added. The solution immediately turned into a viscous black suspension, and the resulting mixture was stirred for 30 min at 0 °C. Benzoyl chloride (141 mg, 1.0 mmol) was then added at 0 °C, and the mixture was stirred for another 3 h at 0 °C. The mixture was

(24) The relative 4,5-configuration of the diols was assigned by comparison of their spectral data with those reported for analogues. See: Kataoka, Y.; Makihara, I.; Yamagata, T.; Tani, K. *Organometallics* **1997**, *16*, 4788.
(25) Sui-Seng. C.; Soleihavoup, M.; Maurette, L.; Tedeschi, C.; Donnadieu, B.; Chauvin, R. *Eur. J. Org. Chem.* **2003**, *9*, 1641.

Scheme 18

poured into aqueous HCl (50 mL, 3 M) and extracted with hexane/ethyl acetate (5:1 = v/v%, 25 mL × 3). The combined organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude oil was purified on silica gel (hexane/ethyl acetate = 10:1) to furnish 2-methyl-1-phenyl-3-buten-1-ol (**9aa**, 133 mg, 0.82 mmol) in 82% yield.

General Procedure for Reaction of Zirconocene—Olefin Complex with Ester. To a solution of Cp$_2$ZrCl$_2$ (585 mg, 2.0 mmol) in benzene (20 mL), butylmagnesium bromide (4.0 mL, 1.0 M THF solution, 4.0 mmol) was added at 0 °C. After the mixture was stirred for 30 min at the same temperature, methyl benzoate (136 mg, 1.0 mmol) was then added dropwise to the resulting mixture at 0 °C. Then, the reaction mixture was stirred for another 3 h at 0 °C. Quenching the reaction with hydrochloric acid followed by extraction, concentration, and column purification yielded 2-ethyl-1-phenylcyclopropanol (**14a**, 148 mg, 0.91 mmol) in 91% yield.

Typical Procedure via Olefin Exchange (Method A). Cyclopentylmagnesium bromide (4.0 mL, 1.0 M THF solution, 4.0 mmol) was added to a solution of Cp$_2$ZrCl$_2$ (585 mg, 2.0 mmol) and 1-hexene (505 mg, 6.0 mmol) in benzene (20 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and then for an additional 1 h at 25 °C. Next, the resulting mixture was cooled to 0 °C again, and benzoyl chloride (141 mg, 1.0 mmol) was added. After being stirred for another 3 h at 0 °C, the mixture was poured into hydrochloric acid (50 mL, 3 M). Extraction with hexane/ethyl acetate (5:1 = v/v%, 25 mL × 3) followed by silica gel column purification afforded 1-phenyl-2-vinyl-1-pentanol (**9ea**, 141 mg, 0.74 mmol) in 74% yield.

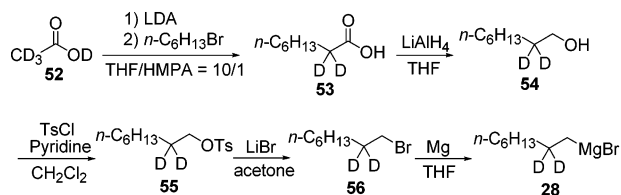**Procedure with Cp$_2$Zr(H$_2$C=CHR) Prepared from Olefin, Magnesium Metal, and Zirconocene Dichloride (Method B).** THF (1 mL) was added to Cp$_2$ZrCl$_2$ (877 mg, 3.0 mmol) and magnesium metal (109 mg, 4.5 mmol) in a 50-mL flask filled with argon. 1,2-Dibromoethane (85 mg, 0.45 mmol) was added to activate the magnesium metal, and the mixture was stirred for 15 min. After the solution was cooled to 0 °C, a solution of 1-pentene (421 mg, 6.0 mmol) in THF (4 mL) was added. The reaction mixture was stirred for 3 h at 0 °C to form the zirconocene—olefin complex. Benzene (25 mL) was then added as cosolvent, and benzoyl chloride (141 mg, 1.0 mmol) was dropped. The resulting mixture was stirred for 30 min at 0 °C. Quenching the reaction with hydrochloric acid followed by extraction, concentration, and silica gel column purification yielded 2-ethyl-1-phenyl-3-buten-1-ol (**9ba**, 136 mg, 0.77 mmol) in 77% yield as a colorless oil.

Preparation of 3,3-Dideuterio-1-octene (21). 3,3-Dideuterio-1-octene (**21**) was prepared as shown in Scheme 18. First, to a suspension of lithium aluminum deuteride (1.05 g, 25.0 mmol) in dry THF (10 mL) was added a solution of methyl hexanoate (6.51 g, 50.0 mmol) at 0 °C. The mixture was warmed to room
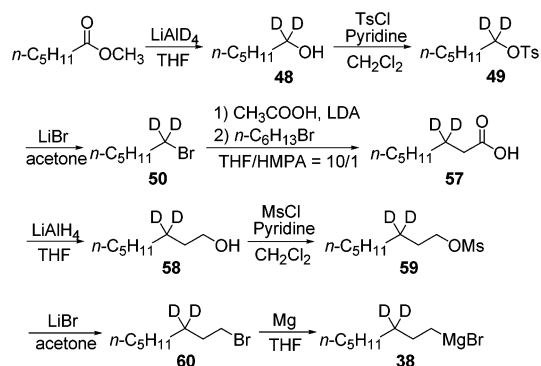
Scheme 19

temperature and then stirred for another 3 h at 25 °C. Quenching the reaction with aqueous HCl followed by extraction, concentration, and silica gel column purification yielded 1,1-dideuterio-1-hexanol (**48**, 4.81 g, 46.2 mmol) in 92% yield. Next, pyridine (5.14 g, 65.0 mmol) was added dropwise to a solution of 1,1-dideuterio-1-hexanol (**48**, 4.81 g, 46.2 mmol) and tosyl chloride (9.53 g, 50.0 mmol) in CH_2Cl_2 at room temperature. After being stirred for 24 h at the same temperature, the reaction mixture was poured into saturated NH_4Cl. Usual work up and column purification afforded 1,1-dideuteriohexyl tosylate (**49**, 10.3 g, 45.3 mmol) in 98% yield. LiBr (7.81 g, 90.0 mmol) was added to a solution of **49** (10.3 g, 45.3 mmol) in acetone at room temperature, and the resulting mixture was stirred for 12 h at 55 °C. Usual workup and purification by column chromatography on silica gel provided 1-bromo-1,1-dideuteriohexane (**50**, 7.27 g, 43.5 mmol) in 96% yield. Magnesium metal (0.73 g, 30.0 mmol) and THF (10 mL) were placed in a 50-mL reaction flask under argon. Alkyl bromide **50** (4.17 g, 25.0 mmol) in THF (2 mL) was added dropwise to the mixture at room temperature. The resulting mixture was stirred for 5 h at 25 °C, and alkylmagnesium bromide **51** was formed. Finally, alkyl-magnesium bromide **51** (4.0 mL, 1.0 M THF solution, 4.0 mmol) was added at 0 °C to a stirred mixture of $NiCl_2$ (0.03 g, 0.25 mmol), DPPP (0.03 g, 0.25 mmol), and vinyl bromide (2.67 g, 25.0 mmol) in Et_2O (15 mL). The mixture was stirred at 35 °C for 5 h. After the mixture was quenched with aqueous HCl, it was extracted with hexane/ethyl acetate (5:1 = v/v%, 25 mL × 3). The crude product was purified by silica gel column chromatography to afford 3,3-dideuterio-1-octene (**21**, 2.54 g, 22.3 mmol).

Synthesis of 2,2-Dideuteriooctylmagnesium Bromide (28). 2,2-Dideuteriooctylmagnesium bromide could be synthesized from acetic acid-d_4 (**52**) as shown in Scheme 19. Diisopropyl-amine (19.4 g, 192.0 mmol) and butyllithium (108 mL, 1.6 M hexane solution, 173 mmol) were mixed in THF (60 mL) under argon and were stirred for 30 min at 0 °C to form lithium diisopropylamide. The resulting mixture and HMPA (14 mL) were successively added to a solution of **52** (5.28 g, 80.0 mmol) in THF (10 mL) at −40 °C. After the mixture was warmed to 0 °C, hexyl bromide (14.0 g, 85.0 mmol) was added dropwise to the reaction mixture at the same temperature and the reaction temperature was gradually raised to ambient temperature. The mixture was stirred for another 5 h at 25 °C and poured into aqueous HCl (50 mL, 3 M) and extracted with hexane/ethyl acetate (1:1 = v/v%, 25 mL × 3). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude oil was purified on silica gel (hexane/ethyl acetate = 3:1) to furnish 2,2-dideuteriooctanoic acid (**53**, 6.55 g, 44.8 mmol) in 56% yield. As for the following procedure, a similar procedure described in Scheme 18 was used to afford 2,2-dideuteriooct-ylmagnesium bromide (**28**).

Preparation of 3,3-Dideuteriooctylmagnesium Bromide (38). By a similar procedure described above, 3,3-dideuterio-

Scheme 20

octylmagnesium bromide **38** can be prepared as shown in Scheme 20.

General Procedure for Synthesis of *anti*-1,4-Diol with Zirconocene Dichloride and Propylmagnesium Bromide. Benzene (30 mL) and Cp_2ZrCl_2 (585 mg, 2.0 mmol) were placed in a 50-mL reaction flask under argon. After the mixture was cooled to 0 °C in an ice/water bath, propylmagnesium bromide (4.0 mL, 1.0 M THF solution, 4.0 mmol) was added dropwise. The solution immediately turned into a viscous black suspension, and the resulting mixture was stirred for 30 min at 0 °C. A solution of 1,4-bis(3,5-difluorophenyl)-1,4-butanedione (**40a**, 310 mg, 1.0 mmol) in benzene (2 mL) was then added at 0 °C, and the mixture was stirred for another 5 h at 0 °C. The mixture was poured into aqueous HCl (50 mL, 3 M) and extracted with hexane/ethyl acetate (5:1, 25 mL × 3). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude oil was purified on silica gel (hexane/ethyl acetate = 10:1) to yield 1,4-bis(3,5-difluorophenyl)-6-heptene-1,4-diol (**41a**, 228 mg, 0.64 mmol) in 64% yield along with 6% yield of 1,4-bis(3,5-difluorophenyl)-1,4-butanediol (**42a**).

General Procedure with Butylmagnesium Bromide. But-ylmagnesium bromide (4.0 mL, 1.0 M THF solution, 4.0 mmol) was added dropwise to a solution of Cp_2ZrCl_2 (585 mg, 2.0 mmol) in benzene (20 mL) at 0 °C, and the mixture was stirred at the same temperature for 30 min. To the reaction mixture was added a solution of 1,4-bis(3,5-difluorophenyl)-1,4-butane-dione (**40a**, 310 mg, 1.0 mmol) at 0 °C. After being stirred for another 5 h at 0 °C, the mixture was poured into aqueous hydrochloric acid (50 mL, 3 M). Extraction with hexane/ethyl acetate (5:1, 25 mL × 3) followed by silica gel column purification afforded 1,4-bis(3,5-difluorophenyl)-5-methyl-6-heptene-1,4-diol (**47a**, 280 mg, 0.76 mmol) in 76% yield.

Synthesis of *anti*-1,4-Diols from 1-Alkenes. Magnesium turnings (109 mg, 4.5 mmol) in THF (1 mL) were treated with 1,2-dibromoethane (85 mg, 0.45 mmol). After the mixture was stirred for 15 min, 1-pentene (421 mg, 6.0 mmol) was introduced at ambient temperature. The mixture was cooled to 0 °C, and a solution of Cp_2ZrCl_2 (877 mg, 3.0 mmol) in THF (4 mL) was added. The reaction mixture was stirred for 3 h at 0 °C. Benzene (30 mL) was then added, and 1,4-bis(3,5-difluorophenyl)-1,4-butanedione (**40a**, 310 mg, 1.0 mmol) was dropped. The resulting mixture was stirred for 5 h at 0 °C. Quenching the reaction with aqueous hydrochloric acid followed by extraction, concentration, and silica gel column purification provided 1,4-bis(3,5-difluorophenyl)-5-ethyl-6-heptene-1,4-diol (**47h**, 259 mg, 0.68 mmol) in 68% yield as a colorless oil.

Supporting Information Available: Experimental details. This material is available free of charge via the Interent at http://pubs.acs.org.

JA049184Y