Diastereoselective Inter- and Intramolecular Pinacol Coupling of Aldehydes Promoted by Monomeric Titanocene(III) Complex Cp_2TiPh

Yoshihiko Yamamoto,[†] Reiko Hattori,[†] Takeyuki Miwa,[†] Yu-ichiro Nakagai,[†] Takateru Kubota,[‡] Chiyo Yamamoto,[‡] Yoshio Okamoto,[‡] and Kenji Itoh*[,†]

Department of Molecular Design and Engineering, and Department of Applied Chemistry, Graduate School of Engineering, Nagoya University, Chikusa, Nagoya 464-8603, Japan

Itohk@apchem.nagoya-u.ac.jp

Received December 26, 2000

A monomeric titanocene(III) derivative, Cp_2TiPh, effectively promoted the pinacol coupling of both an aromatic aldehyde, benzaldehyde, and an aliphatic aldehyde, 3-phenylpropionaldehyde. The same reactive complex was successfully generated by a catalytic amount of a precursor, Cp_2Ti-(Ph)Cl, and its stoichiometric amount of Zn. The Cp_2TiPh-catalyzed pinacol coupling of benzaldehyde derivatives and aliphatic aldehydes afforded the corresponding 1,2-diols in high yields with moderate to good *threo*-selectivity. On the other hand, Cp_2TiPh-catalyzed pinacol cyclization of dials gave cyclic 1,2-diols with excellent diastereoselectivity. The extension of this protocol to chiral dials demonstrated that the phenyltitanium complex catalytically transmitted an axial chirality or a central chirality of the starting dials to the central chirality of the resultant 1,2-diols.

Introduction

The reductive couplings of carbonyl compounds have found extensive use in organic synthesis.[1] In particular, a *threo*-selective pinacol coupling has received much attention because enatiomerically pure *threo*-diols can be used for asymmetric syntheses.[2,3] In addition, the pinacol coupling has been employed as a key step in the syntheses of natural products and pharmaceuticals.[4] For these purposes, stoichiometric reactions have so far been used, however, catalytic methods are highly desirable from both an atom-economical and environmental points of view. Although many catalytic methods have recently been developed,[5−8] few of them provided a satisfactory yield and a diastereoselectivity for a wide range of aldehydes. With this in mind, we investigated the catalyzed inter- and intramolecular pinacol couplings using Cp_2TiPh.[9]

* To whom correspondence should be addressed. Fax: +81-52-789-3205.

[†] Department of Molecular Design and Enginerring, and Department of Applied Chemistry.

[‡] Department of Applied Chemistry.

(1) For recent reviews of reductive carbonyl coupling, see: (a) McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513. (b) Robertson, G. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 3, p 563. (c) Dushin, R. G. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 12, p 1071. (d) Fürstner, A.; Bogdanovic *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2443. (e) Gansäuer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771.

(2) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; John Wiley & Sons: New York, 1995.

(3) Altenbach, H.-J. In Chiral Cyclic Acetals in Synthesis. *Organic Synthesis Highlights*; Mulzer, J., Altenbach, H.-J., Braun, M., Krohn, K., Reissig, H.-U., Eds.; John Wiley & Sons: Weinheim, 1991; p. 19.

(4) For recent examples, see: (a) McMurry, J. E.; Dushin, R. G. *J. Am. Chem. Soc.* **1990**, *112*, 6942. (b) Dauben, W. G.; Wang, T. Z.; Stephene, R. W. *Tetrahedron Lett.* **1990**, *31*, 2393. (c) Kammermeier, B.; Beck, G.; Jacobi, D.; Jendralla, H. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 685. (d) Nicolaou, K. C.; Liu, J. J.; Yang, Z.; Ueno, H.; Sorensen, E. J.; Claiborne, C. F.; Guy, R. K.; Hwang, C. K.; Nakada, M.; Nantermet, P. G. *J. Am. Chem. Soc.* **1995**, *117*, 634. (e) Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Nantermet, P. G.; Claiborne, C. F.; Renauld, J.; Guy, R. K.; Shibayama, K. *J. Am. Chem. Soc.* **1995**, *117*, 645. (f) Kitamura, M.; Ohmori, K.; Kawase, T.; Suzuki, K. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1229.

(5) Samarium- and Cerium-catalyzed reactions: (a) Léonard, E.; Dunach, E.; Périchon, J. *J. Chem. Soc., Chem. Commun.* **1989**, 276. (b) Nomura, R.; Matsuno, T.; Endo, T. *J. Am. Chem. Soc.* **1996**, *118*, 11666. (c) Groth, U.; Jeske, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 574.

(6) Titanium-catalyzed reactions: (a) Zhang, Y.; Liu, T. *Synth. Commun.* **1988**, *18*, 2173. (b) Gansäuer, A. *Chem. Commun.* **1997**, 457. (c) Gansäuer, A. *Synlett* **1997**, 363. (d) Gansäuer, A.; Bauer, D. *J. Org. Chem.* **1998**, *63*, 2070. (e) Gansäuer, A.; Moschioni, M.; Bauer, D. *Eur. J. Org. Chem.* **1998**, *1923*, 3. (f) Gansäuer, A.; Bauer, D. *Eur. J. Org. Chem.* **1998**, *2673*, 3. (g) Hirao, T.; Hatano, B.; Asahara, M.; Muguruma, Y.; Ogawa, A. *Tetrahedron Lett.* **1998**, *39*, 5247. (h) Lipski, T. A.; Hilfiker, M. A.; Nelson, S. G. *J. Org. Chem.* **1997**, *62*, 4566. (i) Bandini, M.; Cozzi, P. G.; Morganti, S.; Umani-Ronchi, A. *Tetrahedron Lett.* **1999**, *40*, 1997. (j) Annunziata, R.; Benaglia, M.; Cinquini, M.; Raimondi, L. *Eur. J. Org. Chem.* **1999**, *3369*, 9.

(7) Vanadium-catalyzed reactions: (a) Hirao, T.; Hasegawa, T.; Muguruma, Y.; Ikeda, I. *J. Org. Chem.* **1996**, *61*, 366. (b) Hirao, T.; Asahara, M.; Muguruma, Y.; Ogawa, A. *J. Org. Chem.* **1998**, *63*, 2812.

(8) Chromium-catalyzed reaction: Boland, W.; Svatos, A. *Synlett* **1998**, 549.

(9) Yamamoto, Y.; Hattori, R.; Itoh, K. *Chem. Commun.* **1999**, 825.

(10) (a) Dan, Y.; Geise, H. J. *J. Organomet. Chem.* **1991**, *405*, 1. (b) Spencer, R. P.; Schwartz, J. *J. Org. Chem.* **1997**, *62*, 4204. (c) Spencer, R. P.; Schwartz, J. *Tetrahedron* **2000**, *56*, 2103.

(11) (a)Handa, Y.; Inanaga, J. *Tetrahedron Lett.* **1987**, *28*, 5717. (b) Schobert, R. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 855. (c) Barden, M. C.; Schwartz, J. *J. Am. Chem. Soc.* **1996**, *118*, 5484.

(12) (a) Nugent, W. A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1988**, *110*, 8561. (b) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1989**, *111*, 4525. (c) RajanBabu, T. V.; Nugent, W. A.; Beattie, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 6408. (d) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986. (e) Merlic, C. A.; Xu, D. *J. Am. Chem. Soc.* **1991**, *113*, 9855. (f) Yadav, J. S.; Srinivas, D. *Chem. Lett.* **1997**, 905. (g) Chakraborty, T. K.; Dutta, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1257. (h) Maiti, G.; Roy, S. C. *J. Chem. Soc., Perkin Trans. 1* **1996**, 403. (i) Mandal, P. K.; Maiti, G.; Roy, S. C. *J. Org. Chem.* **1998**, *63*, 2829. (j) Mandal, P. K.; Roy, S. C. *Tetrahedon Lett.* **1999**, *55*, 11395. (k) Gansäuer, A.; Pierobon, M.; Bluhm, H. *Angew. Chem. Int. Ed.* **1998**, *37*, 101. (l) Gansäuer, A.; Bluhm, H.; Pierobon, M. *J. Am. Chem. Soc.* **1998**, *120*, 12849. (m) Gansäuer, A.; Lauterbach, T.; Bluhm, H.; Noltemeyer, M. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2909. (n) Fernández-Mateos, A.; de la Nava, E. M.; Coca, G. P.; Silvo, A. R.; González, R. R. *Org. Lett.* **1999**, *1*, 607.

(13) (a) Barber, W. A. *Inorg. Synth.* **1960**, *6*, 27. (b) Reid, A. F.; Wailes, P. C. *Aust. J. Chem.* **1966**, *19*, 309. (c) Manzer, L. *Inorg. Synth.* **1982**, *21*, 84.

10.1021/jo001781p CCC: $20.00
Published on Web 05/03/2001

In this context, titanocene(III) chloride, "Cp_2TiCl", has received much attention as an efficient one-electron reducing reagent in organic synthesis.[10−12] Titanocene chloride is obtained as a chlorine bridged dimer **1** by the reaction of titanium trichloride with cyclopentadienides.[13] Alternatively, titanocene chloride can be readily generated by the in-situ reduction of commercially available titanocene dichloride (Cp_2TiCl_2) with a variety of reducing agents, including metals (Be, Mn, and Zn) and Grignard reagents.[14] In such cases, trinuclear complexes **2** are formed by clustering of the resultant titanocene(III) chloride and the metal salts MCl_2.[15] Therefore, the coexisting metal ion could dramatically alter the reactivity of this reagent. Accordingly, the diastereoselectivity in the pinacol coupling of benzaldehyde strongly depends on the reducing agent for titanocene dichloride.[11a] On the other hand, Teuben has reported the synthesis of titanocene(III) derivatives involving a σ-bonded aryl group, Cp_2TiAr (**3**), which proved to be paramagnetic and monomeric both in solid state and in solutions.[16] Such a monomeric nature of the phenyltitanocene complex might cause a different reducing ability. In fact, we have previously found that Cp_2TiPh effectively promoted the reductive intramolecular coupling of ketonitriles leading to α-hydroxycycloalkanones, although the parent Cp_2TiCl did not promote the ketonitrile cyclization.[17] It is reasonable to expect that the phenyltitanium complex acts as an excellent promoter for pinacol coupling. Focusing our attention to the monomeric complex Cp_2TiPh, we have started our study on the inter- and intramolecular reductive coupling of aromatic and aliphatic aldehydes.

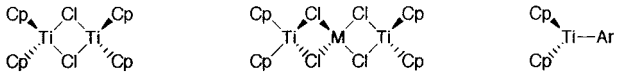
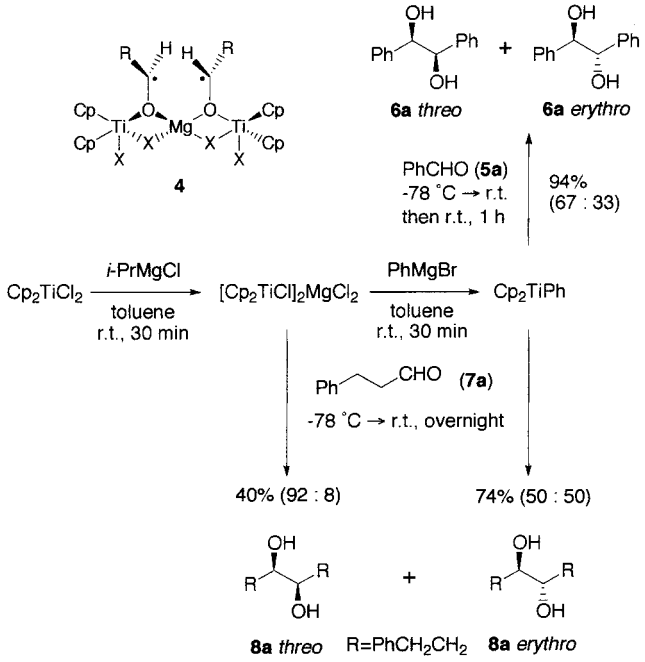


Figure 1.

Scheme 1



Results and Discussion

Stoichiometric Reductive Coupling of Aromatic and Aliphatic Aldehydes with Titanocene(III) Reagents. Prior to the investigation of the Cp_2TiPh-catalyzed coupling, we first examined the reactivity difference between "Cp_2TiCl" and Cp_2TiPh in stoichiometric pinacol couplings of some aldehydes. In 1987, Inanaga et al. reported that a titanium(III) reagent generated in situ by reduction of Cp_2TiCl_2 with *sec*-BuMgCl in THF promotes the highly *threo*-selective pinacol coupling of aromatic and α,β-unsaturated aldehydes in moderate to high yields.[11a] According to their claim, the presence of MgX_2 is essential for the high *threo*-selectivity, and they proposed that the pinacol coupling proceeds via trimetallic intermediates **4**, in which R groups are arranged anti to each other to afford the *threo*-diols (Scheme 1). A trimetallic complex, $[Cp_2Ti(\mu\text{-}Cl)_2]Mg(THF)_2$, has been characterized by X-ray crystallography, which was consistent with Inanaga's mechanism.[15b] In accordance with these studies, the treatment of Cp_2TiCl_2 with *i*-PrMgCl in THF followed by the addition of benzaldehyde **5a** to afford hydrobenzoin **6a** (46% yield) with the diastereomeric ratio of *threo*/*erythro* = 97:3. The diastereoselectivity was slightly higher in toluene (*threo*/*erythro* = 99:1). On the other hand, Cp_2TiPh, generated by the treatment of Cp_2TiCl_2 with *i*-PrMgCl followed by PhMgBr in toluene, converted **5a** into **6a** with lower diastereomeric ratio of *threo*/*erythro* = 67:33 albeit in higher yield (94%). Similarly, an aliphatic aldehyde, 3-phenylpropionaldehyde (**7a**), was treated with the toluene solution of $[Cp_2TiCl]_2MgCl_2$ to afford a coupling product **8a** in 40% yield with high diastereomeric ratio (*threo*/*erythro* = 92:8). The yield was raised to 74% by use of Cp_2TiPh, however, no diastereoselectivity was observed.

From the above results, we can conclude that the monomeric nature of Cp_2TiPh render high reducing ability to the complex at the expense of diastereoselectivity under stoichiometric conditions.

(14) Coutts, R. S. P.; Wailes, P. C. *Adv. Organomet. Chem.* **1970**, *9*, 153.
(15) (a) Sekutowski, D. G.; Stucky, G. D. *Inorg. Chem.* **1975**, *14*, 2192. (b) Stephan, D. W. *Organometallics* **1992**, *11*, 996.
(16) (a) Teuben, J. H.; de Liefde Meijer, H. J. *Recl. Trav. Chim. Pays-Bas* **1971**, *90*, 360. (b) Teuben, J. H.; de Liefde Meijer, H. J. *J. Organomet. Chem.* **1972**, *46*, 313.
(17) (a) Yamamoto, Y.; Matsumi, D.; Itoh, K. *Chem. Commun.* **1998**, 875. (b) Yamamoto, Y.; Matsumi, D.; Hattori, R.; Itoh, K. *J. Org. Chem.* **1999**, *64*, 3224.
(18) Waters, J. A.; Mortimer, G. A. *J. Organomet. Chem.* **1970**, *22*, 417.
(19) For the reductive coupling of benzaldehyde with Zn, see: So, J.-H.; Park, M.-K.; Boudjouk, P. *J. Org. Chem.* **1988**, *53*, 5871.
(20) (a) Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 1, Chapter 4. (b) Surzur, J.-M. In *Reactive Intermediates*, Abramovitch, R. A., Ed.; Plenum Press: New York, 1982; Vol. 2, Chapter 3. (c) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, Chapters 4.2.2 and 4.2.3.
(21) (a) Ikeda, T.; Yue, S.; Hutchinson, C. R. *J. Org. Chem.* **1985**, *50*, 5193. (b) Fevig, T. L.; Elliott, R. L.; Curran, D. P. *J. Am. Chem. Soc.* **1988**, *110*, 5064. (c) Fox, D. P.; Little, R. D.; Baizer, M. M. *J. Org. Chem.* **1985**, *50*, 2202. (d) Little, R. D.; Fox, D. P.; Hijfte, L. V.; Dannecker, R.; Sowell, G.; Wolin, R. L.; Moëns, L.; Baizer, M. *J. Org. Chem.* **1988**, *53*, 7. (e) Fukuzawa, S.; Iida, M.; Nakanishi, A.; Fujinaki, T.; Sakai, S. *J. Chem. Soc., Chem. Commun.* **1987**, 920. (f) Enholm, E. J.; Trivellas, A. *Tetrahedron Lett.* **1989**, *30*, 1063.
(22) Stoichiometric titanium-induced intramolecular pinacol couplings of dials have been reported, see: McMurry, J. E.; Rico, J. G. *Tetrahedron Lett.* **1989**, *30*, 1169.
(23) Chiara, J. L.; Cabri, W.; Hanessian, S. *Tetrahedron Lett.* **1991**, *32*, 1125.

Scheme 2

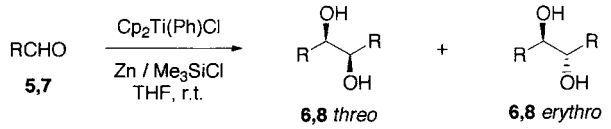


Table 1. $Cp_2Ti(Ph)Cl$-Catalyzed Pinacol Coupling of PhCHO 5a[a]

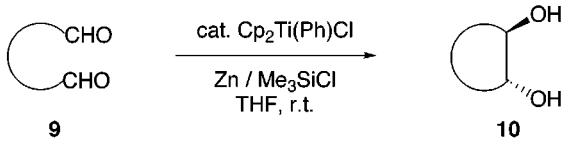
entry	cat. (mol %)	concentrated (M)	time	yield (%)	*threo/erythro*[b]
1	3	0.6	30 min	53	45:55
2	3	0.3	45 min	72	62:38
3	3	0.2	1 h	79	70:30
4	3	0.12	70 min	88	71:29 (75:25)[c]
5	0	0.12	70 min	7[d]	50:50

[a] Benzaldehyde was treated with $Cp_2Ti(Ph)Cl$ in the presence of Zn (1 equiv) and Me_3SiCl (1.5 equiv) in THF at room temperature. [b] Ratios determined by ^1H NMR analysis of isolated **6a**. [c] Ratios determined by ^1H NMR analysis of the crude reaction mixture after hydrolysis. [d] Benzyl alcohol was also isolated in 13% yield.

Cp_2TiPh-Catalyzed Intermolecular Pinacol Coupling of Aromatic and Aliphatic Aldehydes. The phenyltitanium(III) reagent was readily prepared in situ by the reduction of Cp_2TiCl_2 with *i*-PrMgCl followed by addition of PhMgBr. The same reactive species may alternatively be generated by reducing $Cp_2Ti(Ph)Cl$[18] with Zn powder. If this is realized, $Cp_2Ti(Ph)Cl$ should catalyze the pinacol coupling in the presence of a stoichiometric amount of Zn. In fact, the stoichiometric reaction using equimolar amounts of $Cp_2Ti(Ph)Cl$ and Zn promoted the desired reductive coupling of **5a** to give **6a** in 99% yield. It is noteworthy that *threo*-stereoselectivity (84:16) was better than that observed with the phenyltitanium complex prepared in situ from Cp_2TiCl_2 and Grignard reagents. The catalytic reaction was carried out as follows; a THF (2 mL) solution of benzaldehyde **5a** (3 mmol) and Me_3SiCl (1.5 equiv) was added to a mixture of 3 mol % $Cp_2Ti(Ph)Cl$ and Zn (1 equiv) in THF (3 mL) and the mixture was stirred for 30 min at ambient temperature. Usual workup and chromatographic separation gave **6a** in 53% yield without diastereoselection (Scheme 2, R = Ph; Table 1, entry 1). The yield and the diastereoselectivity were extensively improved under lower concentration conditions (entries 2−4). In the 0.12 M solution, **6a** was obtained in 88% yield with the diastereomeric ratio of *threo/erythro* = 71:29 (entry 4). The importance of the titanium catalyst was well illustrated by the fact that **6a** was obtained only in 7% yield together with benzyl alcohol (13%) as a simple reduction product in the absence of the catalyst (entry 5).[19]

Under the optimized reaction conditions, variously substituted benzaldehydes were then subjected to the present catalyzed reductive coupling. Whereas both *p*- and *o*-tolylaldehyde gave corresponding hydrobenzoin derivatives **5b** and **5c** in high yields, the latter slightly decreased the diastereoselectivity (Table 2, entries 1 and 2). Neither an electron-donating substituent (MeO-) nor an electron-withdrawing one (Cl-) affect the yields and diastereoselectivities (entries 3 and 4). In contrast to the above benzaldehyde derivatives, acid-sensitive furfural **5f** unfortunately gave complex mixtures. To improve the reaction conditions applicable to acid-sensitive aldehydes, Me_3SiCl was replaced by collidine hydrochloride, which was successfully employed in the Ti(III)-catalyzed ring-opening of acid-sensitive epoxides.[12k−m] In the presence of collidine hydrochloride, furfural **5f** was reduced at ambient temperature for 4 h using 10 mol % catalyst to furnish the desired diol **6f** in 54% yield (entry 5). It is noteworthy that the diastereomeric ratio was much higher (*threo/erythro* = 90:10) than those observed in the reduction of benzaldehyde derivatives (Tables 1 and 2). In the reaction of **5a**, the *threo*-selectivity was also improved (*threo/erythro* = 90:10) by using the collidine salt with molecular sieves.

Scheme 3



We next examined the pinacol coupling of less reactive aliphatic aldehydes. 3-Phenylpropionaldehyde (**7a**) was reacted under 0.2 M concentration for 18 h to give the diol **8a** in 80% yield with the diastereomeric ratio of *threo/erythro* = 64:36 (Table 2, entry 6). The reactivities of aliphatic aldehydes were considerably influenced by a substituent α to the formyl group. Cyclohexanecarboxyaldehyde (**7b**) having a secondary carbon center at the α-position gave a coupling product **8b** in 50% yield with the similar diastereoselectivity with **8a** (entry 7), whereas pivalaldehyde (**7c**), having a tertiary carbon center at the α-position, hardly reacted under the present conditions (entry 8). The 5-*exo*-*trig*-cyclization of 5-hexenyl radicals has found extensive use in the construction of five membered carbocycles.[20] 5-Hexenals, especially with an activated olefin appendage, are potential precursors of substituted cyclopentanols.[21] The Cp_2TiPh-catalyzed reduction of **7d**, however, gave a pinacol coupling product **8d** in 54% yield as a sole identifiable product (entry 9). This is in striking contrast to the stoichiometric reduction of **7d** with SmI_2 gave the expected 5-*exo*-cyclization product.[21f]

$Cp_2Ti(Ar)Cl$-Catalyzed Intramolecular Pinacol Coupling of Dials. The catalytic intramolecular pinacol couplings have received less attention compared to the intermolecular couplings of monoaldehydes.[22] On the basis of the above results, our new catalytic system was next applied to the intramolecular reductive coupling of dials (Scheme 3, Table 3). In the presence of 6 mol % $Cp_2Ti(Ph)Cl$, a 1,5-dial **9a** was reduced at ambient temperature for 38 h to afford the desired diol **10a** in 40% yield with an excellent *trans*-selectivity (*trans/cis* = 99:1). It is noteworthy that this high *trans*-stereoselectivity is in striking contrast to the *cis*-selectivity observed in the known methods using stoichiometric amount of SmI_2[23] or $TiCl_3(THF)_3$/*t*-BuOH catalyst.[6f] In a similar manner, 10 mol % of the catalyst selectively converted a 1,6-dial **9b** into a *trans*-cyclohexanediol **10b** in a higher yield (60%). The yield was improved up to 74% using a stoichiometric amount of the titanium reagent at 0 °C for 1 h. Moreover, a 1,6-dial **9c** having a bulky tertiary butyl group at the 3-position gave only a single stereoisomer **10c** in 52% yield. The relative configuration of the all three stereogenic centers in **10c** were completely controlled. The stereochemistry of **10c** was determined by comparison of its spectral data with those reported.[24]

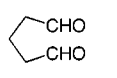
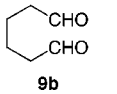
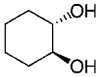
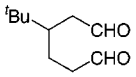
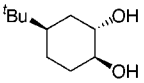
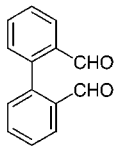
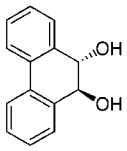
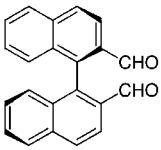
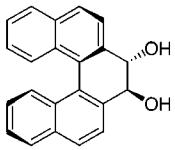
(24) Trainor, R. W.; Deacon, G. B.; Jackson, W. R.; Giunta, N. *Aust. J. Chem.* **1992**, *45*, 1265.

Table 2. $Cp_2Ti(Ph)Cl$-Catalyzed Pinacol Coupling of Aromatic Aldehydes 5b−e and Aliphatic Aldehydes 7a−d[a]

entry	R	concentration (M)	time	yield (%)	*threo/erythro*[b]
1	*p*-$CH_3C_6H_4$ (**5b**)	0.12	2 h	96	74:26 (72:28)[c]
2	*o*-$CH_3C_6H_4$ (**5c**)	0.12	2.5 h	96	66:34 (66:34)[c]
3	*p*-$CH_3OC_6H_4$ (**5d**)	0.12	1 h	84	72:28 (73:27)[c]
4	*p*-ClC_6H_4 (**5e**)	0.12	1 h	90	75:25 (74:26)[c]
5	2-furyl (**5f**)[d]	0.12	4 h	54	90:10
6	$PhCH_2CH_2$ (**7a**)	0.2	18 h	80	64:36 (60:40)[c]
7	*c*-C_6H_{11} (**7b**)	0.2	24 h	50	70:30 (67:33)[c]
8	$(CH_3)_3C$ (**7c**)	0.2	24 h	trace	67:33
9	$PhCH{=}CH(CH_2)_3$ (**7d**)	0.2	20 h	54	66:34

[a] Aldehydes were treated with $Cp_2Ti(Ph)Cl$ (3 mol % or 10 mol % for entry 5) in the presence of Zn (1 equiv) and Me_3SiCl (1.5 equiv) in THF at room temperature. [b] Ratios determined by ^1H NMR analysis of isolated products. [c] Ratios determined by ^1H NMR analysis of the crude reaction mixture after hydrolysis. [d] Collidine hydrochloride were used instead of Me_3SiCl.

Table 3. Intramolecular Pinacol Coupling of Dials 9a−d,f Using $Cp_2Ti(Ph)Cl/Zn/Me_3SiCl$[a]

dial	cat. amount time	diol	yield[b]	*trans* : *cis*[c]
 **9a**	6 mol % 38 h	 **10a**	40%	99 : 1
 **9b**	10 mol % 14 h	 **10b**	60%	99 : 1
 **9c**	10 mol % 14 h	 **10c**	52%	100 : 0
 **9d**	6 mol % 14 h	 **10d**	70%	91 : 9
 **9f**	6 mol % 14 h	 **10f** 99.5 % *ee*	78%	100 : 0

[a] Conditions: $Cp_2Ti(Ph)Cl$, Zn (1 equiv), Me_3SiCl (1.5 equiv), THF (0.05 M), rt. [b] Isolated yields. [c] Ratios determined by ^1H NMR analysis of isolated products.

In the ^1H NMR spectra, the methyne protons α to the hydroxy groups have no $H_{ax}-H_{ax}$ or $H_{ax}-H_{eq}$ coupling with the coupling constants over 10 Hz, indicating that both are constrained to occupy the equatorial positions. Among the four isomers, **10c** is the only one having no axial methyne proton α to the hydroxy groups as shown in Figure 2. In addition, the ^{13}C NMR spectra and its melting point are in good agreement with the reported data.[24]

These results clearly indicate that the bulky Ti(IV) fragment surrounded by two cyclopentadienyl and one phenyl ligands cannot coordinate to the other carbonyl terminus, and cyclization must proceed via diradical intermediates such as **11**, in which two bulky $Cp_2(Ph)$-TiO moieties occupy axial positions to each other in order to reduce steric repulsion between them (Figure 2). This is in sharp contrast to the intramolecular coupling of **9b**

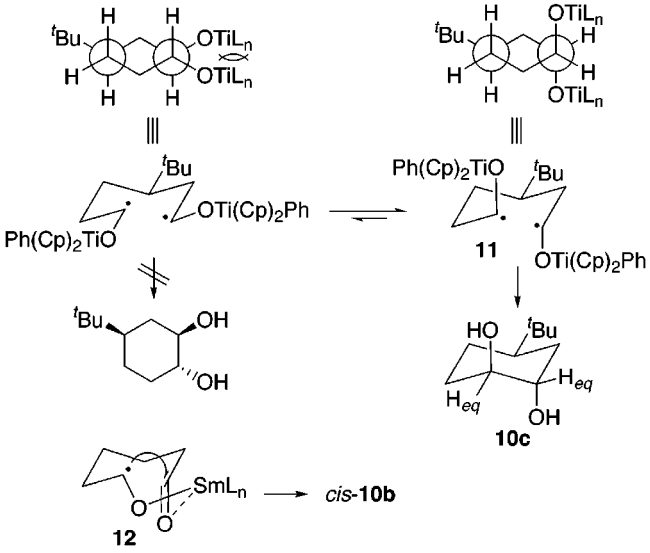


Figure 2.

promoted by SmI_2 affording *cis*-products via chelated intermediates such as **12** (Figure 2).[23]

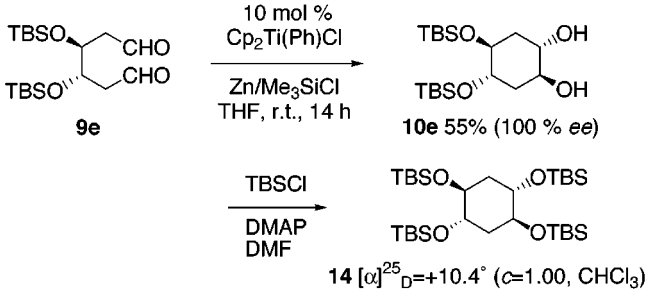
In general, aromatic aldehydes tend to give pinacol coupling products in higher yields than aliphatic aldehydes. Thus, the intramolecular coupling of an aromatic dial was expected to give the desired cyclization product in better yield. Such an intramolecular coupling of an aromatic dial was successfully realized by the catalytic reduction of a biphenylic dial **9d.** As expected, a tricyclic diol **10d**[25] was obtained in higher yield (70%) with the high *trans*-selectivity of *trans*/*cis* = 91:9 (Table 3). In contrast to aliphatic dials, biphenylic dials selectively give *trans*-diol products in stoichiometric reduction using various low-valent transition metals as shown by Suzuki and co-workers.[26a] In this situation, titanocene dichloride could be used as a catalyst precursor to afford the diol **10d** with excellent diastereoselectivity (*trans*/*cis* = 93:7), albeit in slightly lower yield (65%).

Chirality Transfer in Cp_2TiPh-Catalyzed Pinacol Cyclization. As shown above, the relative configuration of all three stereogenic centers was perfectly controlled in the cyclization of the dial **9c** having a tertiary butyl group at the 3-position. This result clearly suggests that a chiral center at β to the formyl group must control

(25) Lewis, D. A.; Armstrong, R. N. *Biochemistry* **1983**, *22*, 6297.

(26) (a) Ohmori, K.; Kitamura, M.; Suzuki, K. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1226. (b) Taniguchi, N.; Hata, T.; Uemura, M. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 1232. (c) Larsen, A. O.; Taylor, R. A.; White, P. S.; Gagné, M. R. *Organometallics* **1999**, *18*, 5157, and also, see; Neo, A. G.; Gref, A.; Riant, O. *Chem. Commun.* **1998**, 2353.

Scheme 4



the newly formed chiral centers of the diol moiety. Such a 1,3-asymmetric induction was demonstrated in the cyclization of an optically active dial **9e**, which was synthesized from (2*S*,3*S*)-1,2,3,4-diepoxybutane (see Experimental Section).[27] Under the same conditions in the case of **9b** with Cp_2TiPh, **9e** was reduced to give a diol product in 55% yield with 100% optical purity (Scheme 4). The obtained diol must be assigned to a C_2-symmetrical *trans*-diol **10e** or **13** rather than a less symmetrical *cis*-diol because only three sp^3 carbon peaks of the cyclohexane ring (δ 35.1, 71.5, and 71.7) were observed together with four sp^3 peaks of the *tert*-butyldimethylsilyl group (δ −4.8, −4.7, 17.9, and 25.8) in the ^{13}C NMR spectra. The measurement of the optical rotation after the protection of the free hydroxyl groups revealed that the resultant tetrasilyl ether is an optically active all-*trans*-tetraether **14** ($[\alpha]^{25}_D = +10.4$ °: $c = 1.00$, $CHCl_3$) rather than a *meso*-tetraether derived from **13**. Accordingly, the product obtained from **9e** was reasonably assigned to all-*trans*-substituted isomer **10e**.

Recently, some research groups have independently developed the pinacol cyclizations of chiral biphenylic dials using stoichiometric SmI_2.[26] Particularly, Suzuki has demonstrated that the axial chirality of the biaryl moiety can perfectly be transmitted to the central chirality of the *trans*-diol moiety of the cyclized product.[26a] In our hands, (*R*)-binaphthylic dial **9f** was *catalytically* converted into a (*S*,*S*)-diol **10f**[26a] as a single diastereomer in 78% yield with up to 99.5% optical purity (Table 3). Therefore, our catalytic system also proved to be effective for such a chirality transfer in biphenylic systems.

Conclusions

We have demonstrated that Cp_2TiPh is an effective pinacol coupling promoter. Under catalyzed conditions using $Cp_2Ti(Ph)Cl/Zn/Me_3SiCl$, the reductive coupling of aromatic aldehydes showed *threo*-selectivity ranging from *threo*/*erythro* = 66:34 to 75:25. The present method is also applicable to aliphatic aldehydes, but the diastereomeric ratios were lower than those for the aromatic aldehydes. In contrast, the extension of the present catalytic coupling to the intramolecular version of dials gave cyclic *trans*-1,2-diols with excellent diastereoselectivity, indicative of nonchelation intermediates being involved in the present reductive cyclization using the monomeric bulky titanium(III) reagent. In addition, significant 1,3-asymmetric inductions were achieved in the reductive cyclization of 1,6-dials possessing chiral centers β to the formyl groups. Accordingly, a C_2-chiral dial, 3,4-di(*tert*-butyldimethylsilyloxy)-1,6-dial, was converted into a naturally occurring tetrol derivative. In the cyclization of a binaphthyl dial, the excellent chirality transfer from the axial moiety to the diol moiety was also realized by our catalyst system.

Experimental Section

General. ^1H and ^{13}C NMR spectra were obtained at 300 and 75 MHz, respectively, for samples in $CDCl_3$ solution. Optical rotations were obtained on a digital polarimeter. HPLC analyses were performed on a Daicel Chiralpak AD column (0.46 mm, 25 cm) eluted with hexane/ethanol. Flash chromatography was performed using a silica gel column (Merck Silica gel 60) eluted with mixed solvents (hexane/AcOEt). Ether, THF, and toluene were distilled from CaH_2, degassed, and stored over Na. Cp_2TiCl_2 was purchased from Kanto Chemical Co., Inc. (2*S*,3*S*)-1,2,3,4-diepoxybutane was synthesized by the reported method.[27]

General Procedure for Cp_2TiPh-Mediated Reductive Coupling of Aldehydes. Stoichiometric Reaction (Method A). To a suspension of Cp_2TiCl_2 (747 mg, 3.0 mmol) in dry degassed toluene (10 mL) was added a solution of freshly prepared ^{i}PrMgCl [^{i}PrCl (259 mg, 3.3 mmol) and Mg (160 mg, 6.6 mmol)] in dry degassed ether (5 mL) under Ar atmosphere at room temperature. The reaction mixture was stirred for 30 min. To the resultant green solution a solution of freshly prepared PhMgBr [PhBr (471 mg, 3.0 mmol) and Mg (146 mg, 6.0 mmol)] in dry degassed ether (5 mmol) was added at room temperature, and the reaction mixture was stirred for further 30 min. To the obtained dark-green Cp_2TiPh solution benzaldehyde **5a** (212 mg, 2 mmol) was added at room temperature and the reaction mixture was stirred for 1 h. The reaction was quenched by 1 N HCl (10 mL) and the mixture was stirred for 30 min. The organic layer was separated and washed with brine (20 mL). The aqueous layer was extracted with ethyl acetate (20 mL × 3). The combined organic layer was dried with $MgSO_4$ and concentrated in vacuo. The crude mixture was purified by silica gel flash column chromatography (hexane−AcOEt 2:1) to give hydrobenzoin **6a** (206 mg, 96%) as white solids. The reactions of Cp_2TiPh with **7a** is performed in the same manner.

Stoichiometric Reaction (Method B). To a solution of $Cp_2Ti(Ph)Cl$ (291 mg, 1 mmol) and Zn (64 mg, 1 mmol) in dry degassed THF (7 mL) was added Me_3SiCl (0.19 mL, 1.5 mmol) and the solution was stirred for 1 h under Ar atmosphere at room temperature. To the resultant green solution benzaldehyde **5a** (106 mg, 1 mmol) was added at room temperature and the reaction mixture was stirred for 1 h. The standard workup as described above gave hydrobenzoin **6a** (105 mg, 99%).

Catalytic Reaction (Method A). To a solution of $Cp_2Ti(Ph)Cl$ (27 mg, 0.09 mmol) and Zn (196 mg, 3 mmol) in dry degassed THF (20 mL) was added a THF (5 mL) solution of an aldehyde (3 mmol) and Me_3SiCl (0.57 mL, 4.5 mmol), and the solution was stirred for the time specified in Tables 1 and 2 under Ar atmosphere at room temperature. The standard workup as described above gave a reductive coupling product except for **5d**. The reaction of **5d** was quenched by 10% K_2CO_3 (5 mL) and after concentration and the treatment with K_2CO_3 (50 mg, 0.3 mmol) in MeOH (6 mL) for 2 h, the above-described workup gave **6d**. The yields were summarized in Tables 1 and 2.

(Method B). To a solution of 2,4,6-collidine (1.5 mmol) in absolute methanol (0.2 mL) was added Me_3SiCl (0.38 mL, 3.0 mmol) at 0 °C. After stirring for 20 min at room temperature, the reaction mixture was concentrated under reduced pressure. To the solution of $Cp_2Ti(Ph)Cl$ (30 mg, 0.1 mmol), Zn (65 mg, 1 mmol), powdered molecular sieves 3 Å (200 mg), and the above preformed collidine salt in dry degassed THF (6.6 mL) was added a THF (1.7 mL) solution of **5a** (106 mg, 1 mmol), and the solution was stirred for 2 h under Ar atmosphere at room temperature. The standard workup as described above gave **6a** (94 mg, 87%).

(27) Seebach, D.; Kalinowski, H.-O.; Bastani, B.; Crass, G.; Daum, H.; Dörr, H.; DuPreez, N. P.; Ehrig, V.; Langer, W.; Nüssler, C.; Oei, H.-A.; Schmidt, M. *Helv. Chim. Acta* **1977**, *60*, 301.

Analytical Data for 8d. Solid (elution, hexane−AcOEt 4:1); IR ($CHCl_3$) 3579 (OH) 1598 (Ph) cm^{-1}; ^1H NMR δ 1.40−1.80 (8 H, m), 2.15−2.25 (4 H, m), 3.40−3.50 and 3.60−3.70 (1.32 and 0.68 H, respectively, m), 6.21 (2 H, dt, J = 16, 6.9 Hz), 6.39 (2 H, d, J = 16 Hz), 7.18−7.29 (10 H, m); ^{13}C NMR δ 25.4 and 25.7, 30.7, 32.9 and 33.1, 74.3 and 74.5, 125.9, 126.9, 128.5, 130.2, 130.4, 137.7; MS (FD) *m*/*z* (rel intensity) 350 (M^+, 67), 175 (100). Anal. Calcd for $C_{24}H_{30}O_2$: C, 82.24; H, 8.64. Found: C, 82.14; H, 8.74.

General Procedure for $Cp_2Ti(Ph)Cl$-Catalyzed Cyclization of Dials 9. To a solution of $Cp_2Ti(Ph)Cl$ (27 mg, 0.09 mmol for **9a**,**d**,**f** or 45 mg, 0.15 mmol for **9b**,**c**,**e**) and Zn (196 mg, 3 mmol) in dry degassed THF (25 mL) was added a THF (3.5 mL) solution of a dial (1.5 mmol) and Me_3SiCl (0.57 mL, 4.5 mmol) and the solution was stirred for 14 h (38 h for **10a**) under Ar atmosphere at room temperature. The standard workup as described above gave a reductive coupling product. The yields and diastereomeric ratios were summarized in Table 3.

Synthesis and Pinacol Cyclization of Chiral Dial 9e. To a 1 M solution of vinylmagnesium bromide in THF (80 mL, 80 mmol) was added CuI (15.2 g, 80 mmol) at −30 °C, and the mixture was stirred for 15 min. To the resultant yellow solution was added a solution of (2*S*,3*S*)-1,2,3,4-diepoxybutane (860 mg, 10 mmol) in THF (10 mL) at −30 °C. After stirring for 30 min, the reaction was quenched at room temperature by sat. NH_4Cl (30 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (10 mL × 3). The combined organic layer was dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (hexane−AcOEt 30:1) to give (4*S*,5*S*)-1,7-octadiene-4,5-diol (947 mg, 66%) as white solids: mp 41−42 °C; $[\alpha]^{25}_D$ = −49.0 ° (*c* = 0.30, MeOH); IR ($CHCl_3$) 3581 (OH), 1641 (C=C) cm^{-1}; ^1H NMR δ 2.17 (2 H, br s), 2.21−2.42 (4 H, m), 3.50−3.60 (2 H, m), 5.12−5.20 (4 H, m), 5.79−5.93 (2 H, m); ^{13}C NMR δ 38.3, 72.7, 118.1, 134.3; MS (FD) *m*/*z* (rel intensity) 142 (M^+, 19), 71 (100), 57 (34). Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.44; H, 10.07.

To a solution of the obtained diol (469 mg, 3.3 mmol), *tert*-butyldimethylsilyl chloride (1.63 g, 10.8 mmol), and *N*,*N*-(dimethylamino)pyridine (4.5 mg, 3.4 mmol) in dry DMF (20 mL) was added Et_3N (1.7 mL, 12.5 mmol), and the solution was stirred for 16 h at room temperature. The reaction mixture was poured onto ice water. The organic layer was separated and washed with brine (20 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL × 3). The combined organic layer was dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (hexane) to give (4*S*,5*S*)-4,5-di(*tert*-butyldimethylsilyloxy)-1,7-octadiene (1.07 g, 87%) as a colorless oil: $[\alpha]^{25}_D$ = −39.4 ° (*c* = 0.81, $CHCl_3$); IR ($CHCl_3$) 1630 (C=C), 1255 (Si−C) cm^{-1}; ^1H NMR δ 0.03 (12 H,s), 0.88 (18 H, s), 1.97−2.08 (2 H, m), 2.39−2.48 (2 H, m), 3.56−3.63 (2 H, m), 4.97−5.08 (4 H, m), 5.81 (2 H, ddt, J = 17.1, 9.9, 7.2 Hz); ^{13}C NMR δ −4.20, −4.23, 18.1, 25.9, 35.3, 75.4, 116.2, 136.9; MS (FD) *m*/*z* (rel intensity) 371 (M^+, 100). Anal. Calcd for $C_{20}H_{42}O_2Si_2$: C, 64.80; H,11.42. Found: C, 64.58; H, 11.65.

A solution of the obtained silyl ether (1.8 g, 5.0 mmol) in dry MeOH/CH_2Cl_2 (10 mL and 5 mL, respectively) was treated with an oxygen−ozone stream at −78 °C for 40 min. A slow nitrogen stream was then bubbled through the solution and dimethyl sulfide (1.1 mL, 15 mmol) was added. After strring for 1 h, the solution was allowed to come to room temperature and stirred for another 2 h. The solvent was removed under reduced pressure. The residue was washed with water and extracted with hexanes−Et_2O (v/v 1:1, 3 mL × 4). The organic layer was dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by bulb-to-bulb distillation (130 °C/1 mmHg) to give a dial **9e** (1.27 g, 68%) as a colorless oil: $[\alpha]^{25}_D$ = −34.4 ° (*c* = 0.90, $CHCl_3$); IR ($CHCl_3$) 1725 (C=O), 1257 (Si−C) cm^{-1}; ^1H NMR δ 0.06 (6 H,s), 0.09 (6 H, s), 0.84 (18 H, s), 2.46 (2 H, ddd, J = 16.2, 8.1, 2.7 Hz), 2.72 (2 H, ddd, J = 16.2, 3.3, 1.8 Hz), 4.25−4.32 (2 H, m), 9.78 (2 H, dd, J = 2.7, 1.8 Hz); ^{13}C NMR δ −4.7, −4.3, 17.9, 25.7, 45.6, 69.4, 200.5; MS (FD) *m*/*z* (rel intensity) 375 (M^+, 7), 317 (100). This compound is unstable and decomposed slowly even at −15 °C. Thus, elemental analysis was omitted.

The Cp_2TiPh-catalyzed cyclization of **9e** (374 mg, 1.0 mmol) was carried out as above. Chromatographic separation (elution, hexane−AcOEt 5:1) afforded **10e** (206 mg, 55%) as white solids: mp 143−144 °C; $[\alpha]^{25}_D$ = +6.82 ° (*c* = 0.91, MeOH); IR ($CHCl_3$) 3594 (OH) 1255 (Si−C) cm^{-1}; ^1H NMR δ 0.03 (6 H, s), 0.06 (6 H, s), 0.88 (18 H, s), 1.74−1.90 (4 H, m), 2.04 (2 H, br s), 3.68−3.79 (4 H, m); ^{13}C NMR δ −4.8, −4.7, 17.9, 25.8, 35.1, 71.4, 71.7; MS (FD) *m*/*z* (rel intensity) 377 (M^+, 100). Anal. Calcd for $C_{18}H_{40}O_4Si_2$: C, 57.40; H, 10.70. Found: C, 57.24; H, 10.86.

To a solution of the chiral diol **10e** (74 mg, 0.2 mmol), *tert*-butyldimethylsilyl chloride (82 mg, 0.55 mmol), and DMAP (20 mg, 0.17 mmol) in dry DMF (1 mL) was added Et_3N (0.08 mL, 0.6 mmol) at room temperature, and the solution was stirred for 17 h. The reaction mixture was poured onto ice water, and the organic layer was separated and washed with brine (20 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL × 3). The combined organic layer was dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography (hexane−AcOEt 100:1) to give tetra(silyloxy)cyclohexane **14** (99 mg, 82%) as white solids: mp 160−161 °C; $[\alpha]^{25}_D$ = +10.4 ° (*c* = 1.00, $CHCl_3$); IR ($CHCl_3$) 1255 (Si−C) cm^{-1}; ^1H NMR δ 0.04 (12 H,s), 0.06 (12 H, s), 0.89 (36 H, s), 1.71−1.76 (4 H, m), 3.66−3.70 (4 H, m); ^{13}C NMR δ −4.9, 18.1, 25.9, 37.0, 71.9; MS (FD) *m*/*z* (rel intensity) 548 ($M^+ - C_4H_9$, 100). Anal. Calcd for $C_{30}H_{68}O_4Si_4$: C, 59.54; H, 11.32. Found: C, 59.43; H, 11.43.

Acknowledgment. We gratefully acknowledge financial support (12450360 and 12875175) from the Ministry of Education, Science Sports and Culture, Japan.

JO001781P