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Phenylenebis(ethynyl)-Tethered Bis-BINOL Ligands for Enantioselective Catalyst Based on Dimeric Ti(IV) Aggregate

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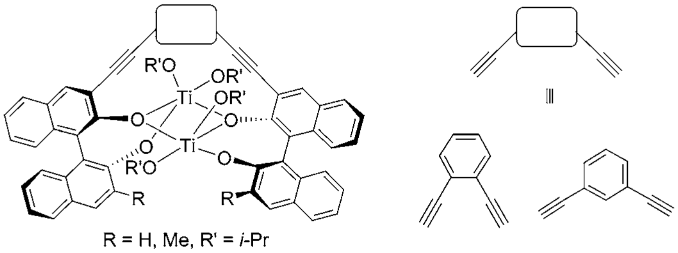
ABSTRACT



Bis-BINOLs 7a–c in which two BINOL units are tethered by phenylenebis(ethynyl) groups react with titanium tetraisopropoxide (2 equiv) to form intramolecular dimeric titanium(IV) aggregates 2a–c. Of these, 2a,b with an *o*-phenylenebis(ethynyl) tether are stable in the presence of excess titanium tetraisopropoxide. Complex 2a exhibits a relatively high enantioselectivity in asymmetric addition of diethylzinc to an aldehyde.

Titanium complexes of 1,1′-bi-2-naphthol (BINOL) and its derivatives have been employed as enantioselective catalysts in a number of useful asymmetric processes.[1] Despite their importance in asymmetric catalysis, there is little information regarding the structures of these titanium complexes.[2,3] Of these, (BINOLate)Ti(O-*i*-Pr)$_2$ and their derivatives are relatively well-characterized. The solid-state structure of trimeric aggregate [(BINOLate)Ti(O-*i*-Pr)$_2$]$_3$, with one six-coordinate and two five-coordinate titanium centers, has been established by X-ray crystallography.[4] However, its structure in solution remains elusive owing to the kinetic lability of titanium alkoxide ligands. Moreover, the aggregation phenomenon hampered the identification of an active catalyst structure in the enantioselective reactions.[5]

Introduction of a proper tether between two BINOLate-Ti units would stabilize a dimeric aggregate structure, allowing us to study the enantioselectivity of the dimeric form. Such a bis-BINOLate-Ti$_2$ complex would also serve as a starting point for the development of well-characterized dimeric titanium(IV) aggregate based chiral Lewis acid catalysts.[6]

Herein, we wish to report the preparation and characterization of intramolecular dimeric aggregates **2a**−**c**, as well as

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[1] (a) Rosini, C.; Franzini, L.; Raffaelli, A.; Salvadori, P. *Synthesis* **1992**, 503. (b) Mikami, K. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley and Sons: New York, 1995; Vol. 1, p 397. (c) Pu, L. *Chem. Rev.* **1998**, *98*, 2405. (d) Mikami, K.; Nakai, T. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed., John Wiley and Sons: New York, 2000; p 543.

[2] (a) Boyle, T. J.; Barnes, D. L.; Heppert, J. A.; Morales, L.; Takusagawa, F. *Organometallics* **1992**, *11*, 1112. (b) Boyle, T. J.; Eilerts, N. W.; Heppert, J. A.; Takusagawa, F. *Organometallics* **1994**, *13*, 2218.

[3] (a) Terada, M.; Matsumoto, Y.; Nakamura, Y.; Mikami, K. *Inorg. Chim. Acta* **1999**, *296*, 267. (b) Mikami, K.; Ueki, M.; Matsumoto, Y.; Terada, M. *Chirality* **2001**, *13*, 541.

[4] Baisells, J.; Davis, T. J.; Carroll, P.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10336.

[5] A detailed study on the catalyst structure in the BINOLate-titanium complex catalyzed asymmetric addition of diorganozincs to aldehydes has been reported recently; see ref 4.

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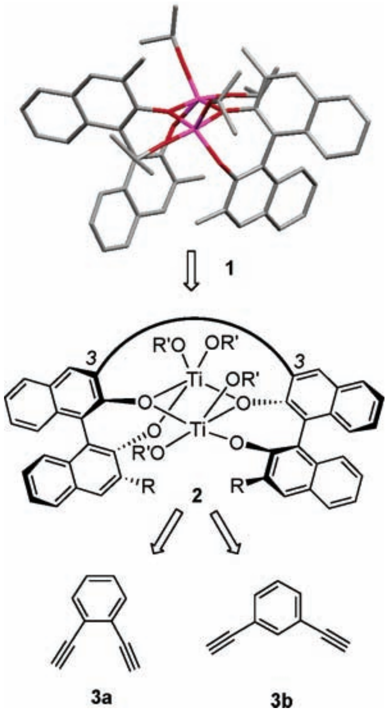
the application of complex **2a** as a catalyst to asymmetric addition of diethylzinc to an aldehyde.

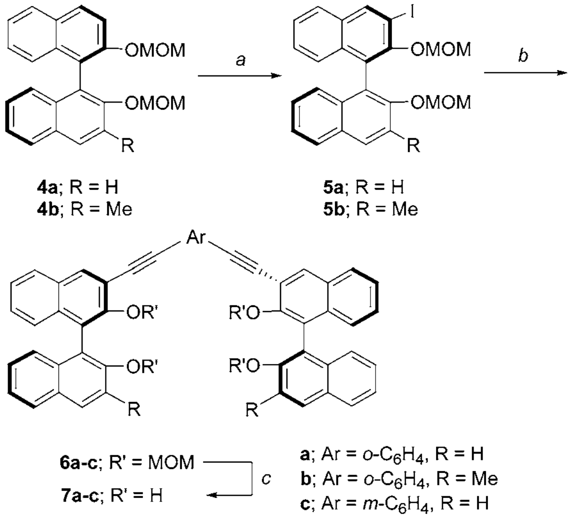
For the molecular design of bis-BINOL ligands appropriate to a titanium(IV) dimeric aggregate, we started from the X-ray structure of $[(3,3'\text{-Me}_2\text{BINOLate})\text{Ti}(\text{O-}i\text{-Pr})_2]_2$ (**1**) reported by Heppert et al. (Scheme 1).[2b] The structure suggested that linkage of the two BINOLate units at the 3-positions is promising as shown in structure **2**. We chose *o*- and *m*-phenylenebis(ethynyl) groups **3a,b** as tethers because of their rigid structure, as well as the sterically less demanding character of the ethynyl moiety.

Scheme 1. Molecular Design for Bis-BINOL Ligands



Phenylenebis(ethynyl)-tethered bis-BINOLs **7a**−**c** were prepared in a convergent manner by a three-component coupling reaction under Sonogashira reaction conditions (Scheme 2).[7] Thus, directed lithiation of (*R*)-BINOL derivative **4a** with *t*-BuLi in THF followed by treatment with I_2 gave iodide **5a** in 71% yield. Reaction of **5a** (2 equiv) and *o*-diethynylbenzene in benzene and Et_3N in the presence of $Pd(PPh_3)_4$ (10 mol %) and CuI (20 mol %) afforded the corresponding three-component coupling product **6a** (79%), which was then hydrolyzed under acidic conditions to give *o*-bis-BINOL **7a** in 91% yield. *o*-Bis-MeBINOL **7b** was synthesized from **4b**[8] in 52% overall yields via a route similar to that for **7a**. Three-component coupling reaction of **5a** (2 equiv) and *m*-diethynylbenzene gave **6c** in 91% yield. Treatment of **6c** with concentrated HCl gave a complex product mixture, probably as a result of the instability of the *m*-phenylenebis(ethynyl) moiety under acidic conditions. Deprotection of the MOM groups was successfully accomplished with Me_3SiBr[9] to furnish *m*-bis-BINOL **7c** in 77% yield.

Scheme 2. Preparation of Bis-BINOLs **7a**−**c**[a]



[a] Conditions: (*a*) (1) *t*-BuLi, THF, (2) I_2; (*b*) *o*- or *m*-$(HC{\equiv}C)_2$-C_6H_4, $Pd(PPh_3)_4$, CuI, Et_3N, benzene, 60 °C; (*c*) for **6a**,**b**, concentrated HCl, MeOH−$CHCl_3$, 70 °C; For **6c**, Me_3SiBr, CH_2Cl_2, room temperature.

o-Bis-BINOL **1a** was treated with titanium tetraisopropoxide (2 equiv) in CH_2Cl_2 at room temperature, and the resulting orange solution was concentrated in vacuo. At 25 °C in $CDCl_3$, the ^1H and ^{13}C NMR spectra of the residue showed sharp signals that are consistent with the formation of *o*-bis-BINOLate-Ti_2 **2a** of C_2-symmetric intramolecular dimeric aggregate structure **2A**.[10] Thus, for example, H_a and $H_{a'}$ protons appear as a singlet (2H) at δ 8.20 (Figure 1a). The spectrum shows two *i*-PrO methyne resonances (2H each) at δ 4.09 and 4.64 and four diastereomeric *i*-PrO

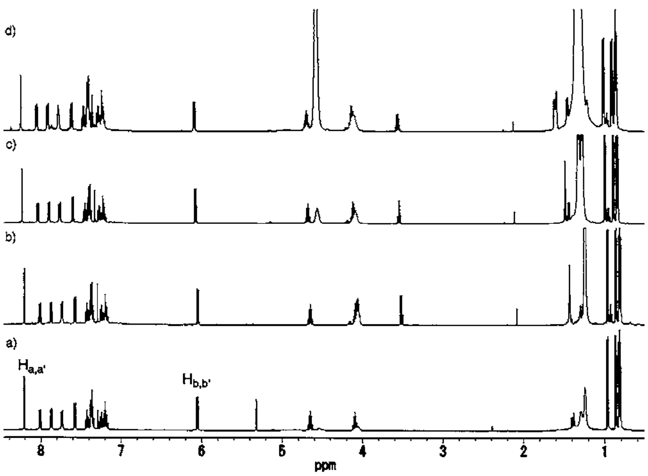
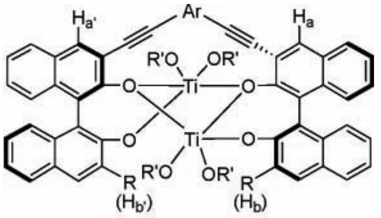
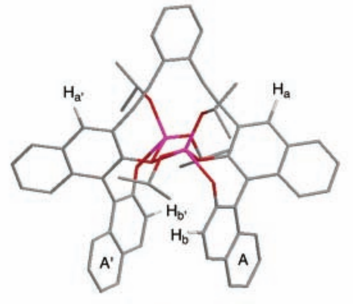


Figure 1. ^1H NMR spectra of *o*-bis-BINOLate-Ti_2 **2a** (0.06 M) in $CDCl_3$. (a) After removal of *i*-PrOH. (b−d) Titration of **7a** by titanium tetraisopropoxide for the ratio 1:2 (b), 1:4 (c), and 1:12 (d).

methyl doublets at δ 0.80, 0.81, 0.85, and 0.96. Notably, H_b and $H_{b'}$ protons of **2a** resonate at higher field at δ 6.04 (d, 2H). The high field shift of H_b proton can be rationalized by the shielding influence from the naphthalene ring A′.



2a; Ar = *o*-C_6H_4, R = H, R' = *i*-Pr
2b; Ar = *o*-C_6H_4, R = Me, R' = *i*-Pr
2c; Ar = *m*-C_6H_4, R = H, R' = *i*-Pr



2A

The ^1H NMR spectrum of a $CDCl_3$ solution of bis-BINOL **7a** and titanium tetraisopropoxide (2 equiv) also showed a set of resonances derived from **2a** and free *i*-PrOH (Figure 1b). In the presence of titanium tetraisopropoxide, (BINOLate)Ti(O-*i*-Pr)$_2$ is known to form intermolecular aggregate (BINOLate)Ti_2(O-*i*-Pr)$_6$.[11,2] In contrast to this, the ^1H NMR signals of complex **2a** were invariant with up to 10 equiv excess of titanium tetraisopropoxide (Figure 1c,d). These observations clearly show the stabilization of the dimeric aggregation form by introduction of the *o*-phenylenebis(ethynyl) tether.

By treatment with titanium tetraisopropoxide (2 equiv) and removal of *i*-PrOH in vacuo, *o*-bis-MeBINOL **7b** and *m*-bis-BINOL **7c** also afforded the corresponding intramolecular dimeric complexes **2b** and **2c**, respectively.[12] For **2b**, behavior in the ^1H NMR titration experiment was almost similar to that for **2a** except that even a 1:1 mixture of **7b** and titanium tetraisopropoxide showed the formation of **2b** together with a free ligand **7b** (Figure 2). In comparison with **2a**,**b**, *m*-bis-BINOLate-Ti_2 complex **2c** is prone to intermolecular aggregation with excess titanium tetraisopropoxide. In a similar NMR titration experiment by 4 equiv of titanium tetraisopropoxide (Figure 3b), **2c** was partially converted to a complex that could be assigned as *m*-bis-BINOLateTi$_4$(O-*i*-Pr)$_{10}$. This complex became a main component in the presence of 12 equiv total of titanium tetraisopropoxide (Figure 3c).

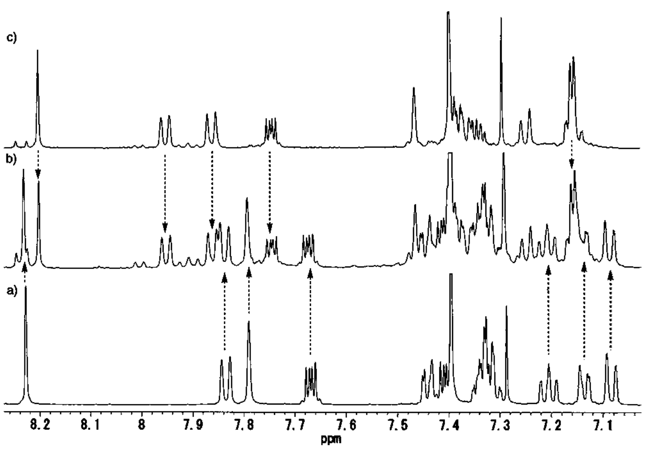


Figure 2. ^1H NMR titration of *o*-bis-MeBINOL **7b** (0.03 M) in $CDCl_3$ by titanium tetraisopropoxide for the ratio 1:0 (a), 1:1 (b), and 1:2 (c).

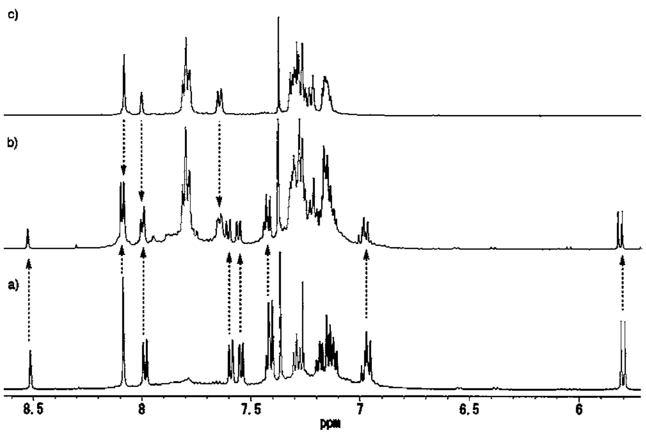


Figure 3. ^1H NMR titration of *m*-bis-BINOL **7c** (0.06 M) in $CDCl_3$ by titanium tetraisopropoxide for the ratio 1:2 (a), 1:4 (b), and 1:12 (c).

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(6) For structurally related bis-BINOLs and their use as ligands for chiral catalysts, see: (a) Vogl, E. M.; Matsunaga, S.; Kanai, M.; Iida, T.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 7917. (b) Ishitani, H.; Kitazawa, T.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40*, 2161. (c) Matsunaga, S.; Das, J.; Roels, J.; Vogl, E. M.; Yamamoto, N.; Iida, T.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 2252. (d) Matsunaga, S.; Kumagai, N.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 4712. (e) Kumagai, N.; Matsunaga, S.; Kinoshita, T.; Harada, S.; Okada, S.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2169 and references therein. (f) Sekiguti, T.; Iizuka, Y.; Takizawa, S.; Jayaprakash, D.; Arai, T.; Sasai, H. *Org. Lett.* **2003**, *5*, 2647.

(7) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (b) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J.; Eds.; Wiley-VCH: Weinheim, Germany, 1998; p 203.

(8) Compound **4b** was prepared in 76% yield from **4a** by successive treatment with *t*-BuLi and MeI.

(9) Huffman, J. W.; Zhang, X.; Wu, M.-J.; Joyner, H. H.; Pennington, W. T. *J. Org. Chem.* **1991**, *56*, 1481.

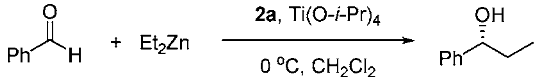
(10) Molecular modeling and energy minimization were conducted using AM1 (AM1-d parameters for Ti) method within CAChe 5.04 package (Fujitsu L.T.D., 2003).

(11) Mori, M.; Nakai, T. *Tetrahedron Lett.* **1997**, *38*, 6233.

(12) High field shifts of a methyl singlet (δ 1.13) and a $H_{b(b')}$ doublet (δ 5.82) were observed for **2b** and **2c**, respectively. See Supporting Information.

o-Bis-BINOLate-Ti_2 complex **2a** as a catalyst was examined in prototypical diethylzinc addition to benzaldehyde (eq 1, Table 1).[4,11,13,14] According to the reaction conditions reported for (BINOLate)Ti(O-*i*-Pr)$_2$,[11,13] reactions were carried out by using 2 equiv of diethylzinc in CH_2Cl_2 at 0 °C for 19 h in the presence of excess titanium tetraisopropoxide. With a catalyst load of 10 mol %, **2a** exhibited high enantioselectivity comparable to that reported for (BINOLate)Ti(O-*i*-Pr)$_2$ (entry 4).[11,13,15] Even at 2 mol % catalyst loading, the reaction proceeded smoothly with slightly diminished enantioselectivity (entry 5). In the previously reported asymmetric alkylation reactions, more than 1 equiv of titanium tetraisopropoxide was usually employed for obtaining high turnover frequencies and high enantioselectivity. The use of a reduced amount of titanium tetraisopropoxide, as low as 0.2 equiv, in the reaction catalyzed by **2a** turned out to give similar level of selectivity (entry 3).

Table 1. *o*-Bis-BINOLate-Ti_2 (**2a**)-Catalyzed Asymmetric Addition of Et_2Zn to Benzaldehyde



(1)

entry	**2a** (mol %)	Ti(O-*i*-Pr)$_4$ (equiv)	conversion[a] (%)	ee[b] (%)
1	20	0.8	>98	85
2	20	0.4	>98	84
3	20	0.2	>98	87
4	10	0.9	>98	88
5	2	1.0	>98	81

[a] Determined by GC. [b] Determined by HPLC using a Chiralcel OD column.

In summary, we have demonstrated that phenylenebis(ethynyl)-tethered bis-BINOLs **7a−c** form intramolecular dimeric aggregates **2a−c**, whose solution structures were characterized by NMR spectroscopy. *o*-Bis-BINOLate-Ti_2 **2a** exhibited high enantioselectivity in asymmetric ethylation of benzaldehyde even at low catalyst load and in the presence of a small excess of titanium tetraisopropoxide.

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Supporting Information Available: Experimental procedures and characterization data for compounds **2a−c**, **6a−c**, and **7a−c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Zhang, F.-Y.; Yip, C.-W.; Cao, R.; Chan, A. S. *Tetrahedron: Asymmetry*, **1997**, *8*, 585.

(14) (a) Zhang, F.-Y.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 3651. (b) Hu, Q.-S.; Pugh, V.; Sabat, M.; Pu, L. *J. Org. Chem.* **1999**, *64*, 7528. (c) Shen, X.; Guo, H.; Ding, K. *Tetrahedron: Asymmetry* **2000**, *11*, 4321. (d) Lipshutz, B. H.; Shin, Y.-J. *Tetrahedron Lett.* **2000**, *41*, 9515. (e) Chen, Y.; Yekta, S.; Martyn, J. P.; Zheng, J.; Yudin, A. K. *Org. Lett.* **2000**, *2*, 3433. (f) Yang, X.-W.; Sheng, J.-H.; Da, C.-S.; Wang, H.-S.; Su, W.; Wang, R.; Chan, A. S. C. *J. Org. Chem.* **2000**, *65*, 295. (g) Nakamura, Y.; Takeuchi, S.; Ohgo, Y.; Curran, D. P. *Tetrahedron Lett.* **2000**, *41*, 57. (h) Jayaprakash, D.; Sasai, H. *Tetrahedron: Asymmetry* **2001**, *12*, 2589.

(15) Under similar conditions, reaction catalyzed by **2b** and **2c** afforded the product of 20% ee (20% conversion) and 85% ee (>98% conversion), respectively.