Titanium 3,3'-Modified-Biphenolate Complexes Atropisomerically Controlled by TADDOLs: Novel Chiral Lewis Acid Catalysts for Asymmetric Methylation with an Achiral Methyl-Titanium Reagent

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Received 26 July 2001

Abstract: Chiral Ti complexes, which are constituted of 3,3'-modified-biphenolate (BIPOLate) ligands atropisomerically controlled by (*R*)-TADDOLs, are shown to be novel chiral Lewis acid catalysts for the methylation reaction of aldehydes with an achiral methyl-titanium reagent. Thus, the chiral 3,3'-modified BIPOLate/TADDOLate-Ti complexes give enhanced enantioselectivities up to 100% enantiomeric excess.

Key words: asymmetric methylation, atropisomer, chiral Lewis acid catalyst, chiral titanium complex, 3,3'-modified biphenols

Development of an asymmetric catalyst is of central importance in modern synthetic and pharmaceutical chemistry,[1] wherein the design of a chiral ligand is the key to increase the catalyst activity from an achiral pre-catalyst and, hence, to induce chirality in a product („ligand accelerated catalysis"[2]). In homogeneous asymmetric catalysis, Sharpless et al. have emphasized the significance of „chiral ligand acceleration". An asymmetric catalyst is formed from an achiral „pre-catalyst" via ligand exchange with an added chiral ligand (Figure 1). In heterogeneous asymmetric catalysis, the term „chiral modification"[3] is coined for the process of modifying an achiral heterogeneous catalyst, particularly on the surface with a „chiral modifier", namely a „chiral ligand" (Figure 1). The asymmetric catalysts thus prepared can be further evolved into highly activated catalysts by association with chiral activators (Figure 1).[4] The term „asymmetric activation" may be proposed for this process in an analogy to the activation process of an achiral reagent or catalyst to provide an activated but achiral one.

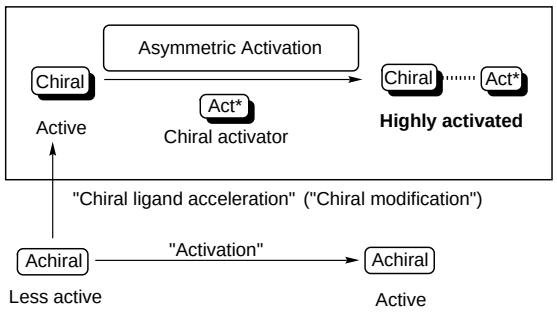
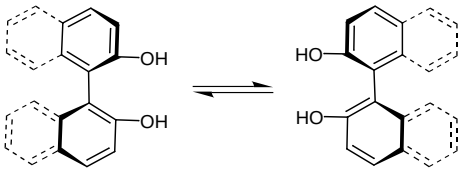


Figure 1 Asymmetric activation

In order to obtain the enantiopure forms of *atropos*,[5] for example binaphthol (BINOL), ligands, asymmetric synthesis or resolution is required. By contrast, the *tropos*[5] biphenol (BIPOL) counterparts (Figure 2) can, in principle, be used without their asymmetric synthesis or resolution, because they can be controlled in enantio-enriched forms, after complexation with a chiral activator 1) to control the chirality through epimerization and 2) to increase the catalyst activity of the complex („asymmetric activation").[4]



BIPOL : Tropos

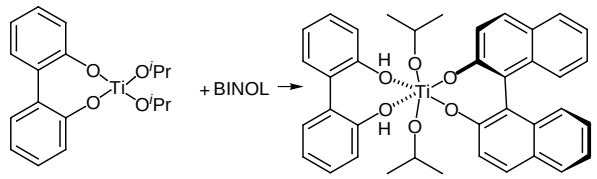
BINOL : Atropos

Figure 2 *Tropos or Atropos*

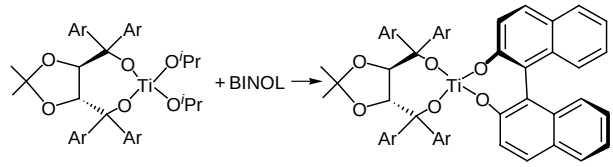
However, in an ene reaction, we have already examined a combination of BIPOLate-Ti complex with *atropos* BINOL to control the chirality of the *tropos* BIPOL ligand and to increase the catalytic activity of the BIPOLate-Ti complex but eventually observed a ligand exchange reaction of BIPOL with BINOL (Scheme 1).[6] Furthermore, we have reported that TADDOLate-Ti complexes exhibit a higher catalytic activity and enatioselectivity through asymmetric activation with BINOL (Scheme 2).[7] Therefore, we examine the Lewis acid catalysis by a titanium complex (**1**) consisting of *tropos* and sterically demanding BIPOL with substituents at the 3,3'-position in a combination of TADDOLs to control the chirality of the BIPOL ligand (Scheme 3) in the methylation reaction with achiral methyl-titanium complex as a nucleophilic and sterically demanding methylating reagent. Herein, we report that the dynamic chirality control of the BIPOL ligands gives highly enantiomerically pure methylcarbinols of great synthetic use by the molecular design of 3,3'-substituted BIPOL.

Synlett 2001, No. 12, 30 11 2001. Article Identifier:
1437-2096,E;2001,0,12,1889,1892,ftx,en;Y14501ST.pdf.

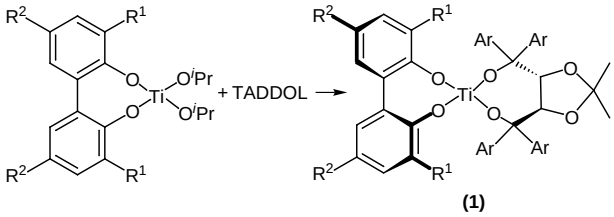
ISSN 0936-5214



Scheme 1

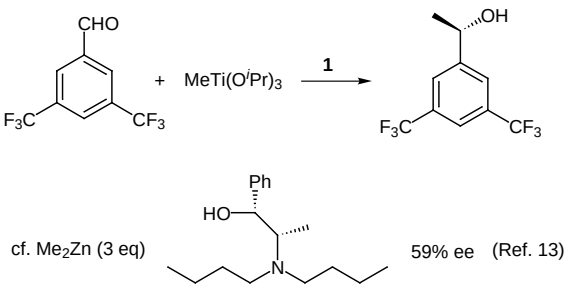


Scheme 2



Scheme 3

In catalytic asymmetric carbon-carbon bond forming reactions, highly promising candidates for the asymmetric catalysts[8] are Lewis acidic metal complexes bearing chiral and non-racemic ligands. For example, catalytic asymmetric alkylation with diethylzinc reagent has been successfully reported, using chiral aminoalcohol–zinc catalysts by Oguni,[9] Soai,[10] Noyori,[11] and Knochel.[12] In sharp contrast, only low levels of enantioselectivity (up to 59% ee)[13] were obtained in the methylation reaction with dimethylzinc even by using similar aminoalcohol–zinc catalysts (Scheme 4), presumably because of low steric demand of dimethylzinc reagent. Thus, we developed chiral BIPOLate/TADDOLate-Ti catalysts (**1**) to give enhanced enantioselectivities up to 100% ee, in a combination with a highly nucleophilic but sterically demanding achiral methyl-titanium reagent.



Scheme 4

The BIPOLate/TADDOLate-Ti catalysts (**1**) were prepared in the following manner: Treatment of $Ti(O^iPr)_4$ and (*R*)-BIPOL in toluene for 1 hour gave $Ti(O^iPr)_2$(BIPOLato)$_2$.[6] $Ti(O^iPr)_2(BIPOLato)_2$ was, upon addition of TADDOL, found to be transformed to Ti(BIPOLato)(TADDOLato) (**1**).

We have thus examined the methylation reaction with achiral methyltitanium triisopropoxide. It is generally difficult to carry out these methylation reactions in a catalytic manner, because of the high nucleophilicity of the achiral methylation reagent. In this paradox, however, these reactions were found to be catalyzed effectively by the use of only 10 mol% of the titanium catalysts (**1**) to give the methylcarbinol in good isolated yields but in moderate enantioselectivities at –78 to –35 °C (Table 1).

Table 1 Catalysis by BINOLate/TADDOLate-Ti Complex **1a**[a]

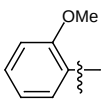
Entry	Temp (°C)	Yield (%)	Enantioselectivity (% ee)
1	0	79	45
2	–70 to –35	60	73
3	–70 to –35	18	66

[a] Catalyzed by 3 mol% of **1a** (R^1=R^2=H)

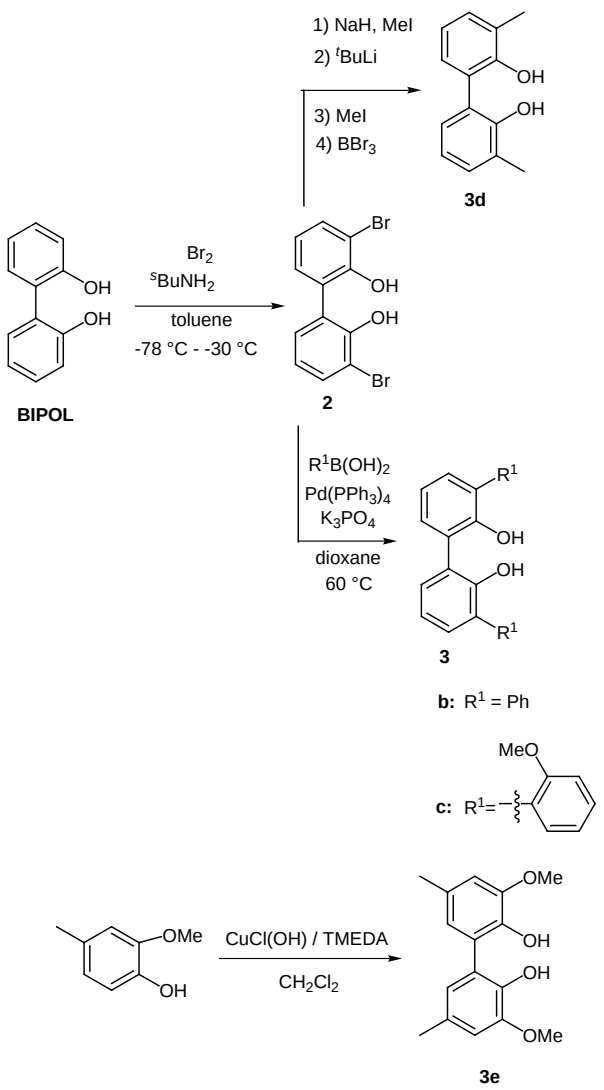
We have thus designed modified BIPOLate/TADDOLate-Ti complexes by the introduction of sterically demanding substituents at the 3,3'-positions, which closely locate toward the chiral TADDOLate ligands (Table 2). Preparation of the 3,3'-substituted BIPOLs is as follows: Commercially available BIPOL was transformed to bromide **2** with *sec*-Bu_2NH_2 and Br_2. The Suzuki coupling[9] of **2** with phenylboronic acid afforded 3,3'-diphenyl BIPOLs **3b**,**c** (Scheme 5). 3,3'-Dimethyl BIPOL **3d** was prepared by methylation. 3,3'-Dimethoxy BIPOL **3e** was prepared by oxidative coupling with CuCl(OH)/TMEDA.

As expected, the introduction of sterically bulky 3,3'-substituents leads to the increase in enantioselectivity except for the phenylated ones (**1b** and **1c**) (Table 2). Particularly, 3,3'-dimethoxy derivative (**1e**) gave virtually complete enantioselectivity (100% ee) in sharp contrast to the mod-

Table 2 3,3'-Modified BIPOLate/TADDOLate-Ti Complexes **1**[a]

1	R^1	R^2	Yield (%)	Enantioselectivity (% ee)
1b	Ph	H	36	69
1c		H	40	65
1d	Me	H	56	88
1e	MeO	Me	60	100

[a] Conditions: toluene, 12 hours, –78 to –35 °C.



Scheme 5

erate enantioselectivity obtained with the *o*-methoxyphenyl derivative (**1c**).

Molecular mechanics calculations of the two diastereomeric Ti(3,3'-$(MeO)_2$-BIPOLato)(TADDOLato) showed that the (*R*)/(*R*)-diastereomer is more stable than the (*R*)/(*S*)-one by 3.6 kcal/mol (Figure 3). In the transition states, methylating reagent would approach preferentially from the *Si*-face of an aldehyde affording the (*S*)-product because the access to the *Si*-face is directed by the chelating 3,3'-methoxy-substituents. Furthermore, the access to the *Re*-face of aldehyde leading to the (*R*)-product is sterically disfavored by the bulky 3,3'-substituents (Figure 4).

We have thus reported the titanium complexes bearing 3,3'-modified BIPOL ligands atropisomerically controlled by (*R*)-TADDOL as a novel and highly enantioselective Lewis acid catalyst. Further works along this line are now under progress.

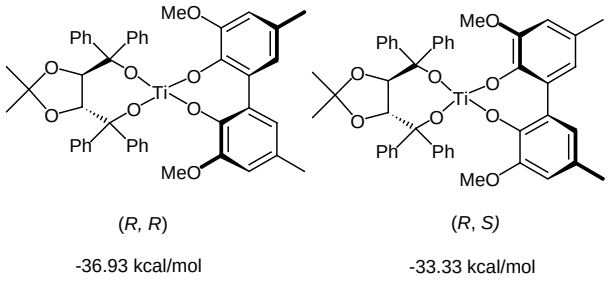


Figure 3 MM2 Calculation

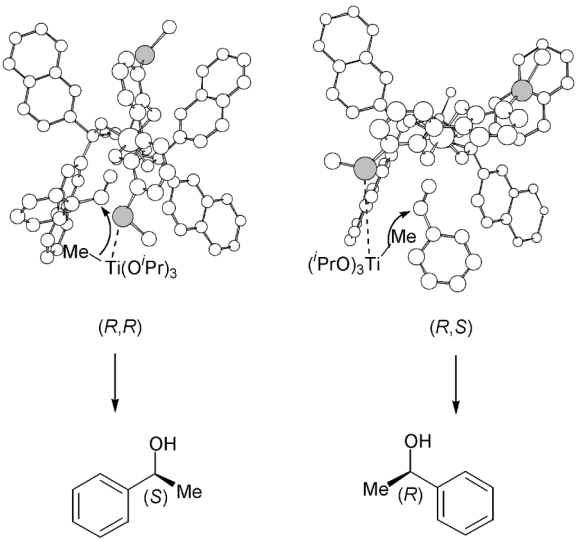


Figure 4 *Si*- vs. *Re*-Face Approach (CF3 have been omitted for clarity)

References

(1) (a) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*, Vol. 1-3; Springer: Berlin, **1999**. (b) *Transition Metals for Organic Synthesis*; Beller, M.; Bolm, C., Eds.; VCH: Weinheim, **1998**. (c) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, **1994**. (d) Brunner, H.; Zettlmeier, W. *Handbook of Enantioselective Catalysis*; VCH: Weinheim, **1993**. (e) *Catalytic Asymmetric Synthesis*, Vol. I and II; Ojima, I., Ed.; VCH: New York, **1993, 2000**. (f) Kagan, H. B. *Comprehensive Organic Chemistry*, Vol. 8; Pergamon: Oxford, **1992**. (g) *Asymmetric Catalysis*; Bosnich, B., Ed.; Martinus Nijhoff Publishers: Dordrecht, **1986**.

(2) Reviews: (a) Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059. (b) Jacobsen, E. N.; Marko, I.; France, M. B.; Svendsen, J. S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 737. (c) Jacobsen, E. N.; Marko, I.; France, M. B.; Svendsen, J. S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968.

(3) (a) Reviews: Blaser, H.-U.; Muller, M. *Enantioselective Catalysis by Chiral Solids: Approaches and Results in Heterogeneous Catalysis and Fine Chemicals II*; Guisnet, M.; Barrault, J.; Bouchoule, C.; Duprez, D.; Perot, G.; Maurel, M.; Montassier, C., Eds.; Elsevier: Amsterdam, **1991**. (b) Blaser, H.-U. *Tetrahedron: Asymmetry* **1991**, *2*, 843. (c) Garland, M.; Blaser, H. U. *J. Am. Chem. Soc.* **1990**, *112*, 7048. (d) Margitfalvi, J. L.; Marti, P.; Baiker, A.; Botz, L.; Sticher, O. *Catal. Lett.* **1990**, *6*, 281.

(4) Mikami, K.; Terada, M.; Korenaga, T.; Matsumoto, Y.; Ueki, M.; Angelaud, R. *Angew. Chem. Int. Ed.* **2000**, *39*, 9000.
(5) In Greek, not (*a*) turn (*tropos*), our review: Mikami, K.; Aikawa, K.; Yusa, Y.; Jodry, J. *Synlett* in press.
(6) Mikami, K.; Matsukawa, S. *Nature* **1997**, *385*, 613.
(7) (a) Mikami, K.; Matsukawa, S.; Volk, T.; Terada, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *109*, 2936. (b) Mikami, K.; Matsukawa, S.; Volk, T.; Terada, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2768.
(8) Reviews: (a) *Lewis Acids in Organic Synthesis*, Vol. 1 and 2; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, **2000**. (b) Dias, L. C. *J. Braz. Chem. Soc.* **1997**, *8*, 289. (c) Santelli, M.; Pons, J.-M. *Lewis Acid and Selectivity in Organic Synthesis*; CRC Press: New York, **1996**. (d) Mikami, K.; Nakai, T. *Asymmetric Lewis Acid Catalysts*, Vol. 124; Kagaku Zoukan, Kagaku Dojin: Tokyo, **1995**, 177. (e) Oh, T.; Reilly, M. *Org. Prep. Proced. Int.* **1994**, *26*, 129. (f) Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763. (g) Narasaka, K. *Synthesis* **1991**, 1. (h) Shanbayati, S.; Schreiber, S. L. In *Comprehensive Organic Synthesis*, Vol. 1; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, **1991**, 283. (i) *Selectivities in Lewis Acid Promoted Reactions*; Schinzer, D., Ed.; Kluwer Academic Publishers: Dordrecht, **1988**. (j) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer: Berlin, **1986**.
(9) Oguni, N.; Matsuda, Y.; Kaneko, T. *J. Am. Chem. Soc.* **1988**, *110*, 7877.
(10) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833.
(11) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49.
(12) Knochel, P. In *Comprehensive Organic Synthesis.*, Vol. 1; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, **1991**, 211.
(13) Hayase, T.; Sugiyama, T.; Suzuki, M.; Sibata, T.; Soai, K. *J. Fluorine Chem.* **1997**, *84*, 1.