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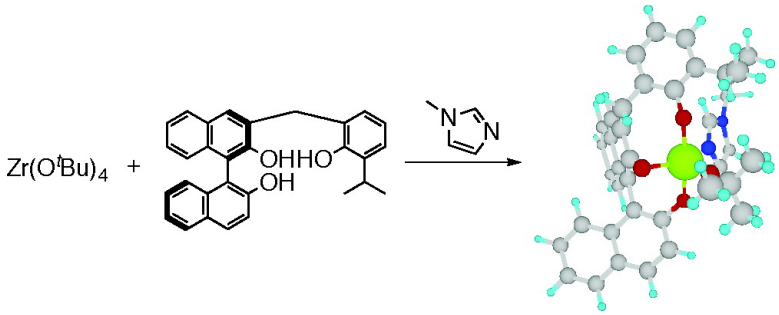

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Chiral Zirconium Catalysts Using Multidentate BINOL Derivatives for Catalytic Enantioselective Mannich-Type Reactions; Ligand Optimization and Approaches to Elucidation of the Catalyst Structure

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Abstract: Catalytic enantioselective Mannich-type reactions of silicon enolates with aldimines were investigated using chiral zirconium catalysts prepared from $Zr(O^tBu)_4$, *N*-methylimidazole, and newly designed multidentate BINOL derivatives. These new multidentate BINOL ligands were designed on the basis of an assumed transition state structure of a chiral zirconium catalyst derived from two molecules of (*R*)-6,6′-Br_2−BINOL. Not only tetradentate BINOL **4** but also tridentate BINOL derivatives were found to be effective, and high enantioselectivities were attained. In a structural study of the most effective zirconium complex prepared from tridentate ligand **6e**, several NMR experiments and DFT calculations were carried out. Consequently, the structure of an active catalyst and plausible mechanism of asymmetric induction were elucidated.

Introduction

Development of chiral catalysts for asymmetric reactions is one of the most fundamental missions in organic synthesis.[1] Among them, chiral Lewis acids are known to be useful catalysts for several reactions, and many combinations of metals and chiral ligands have been widely explored.[2] BINOL derivatives are often employed as chiral sources for catalysts and offer promising possibilities for modification and derivatization; accordingly many BINOL derivatives have been investigated.[3] Recently, multidentate BINOL derivatives have also been designed for the establishment of precise asymmetric environments thus achieving high enantioselectivity.[4]

Catalytic asymmetric reactions of imines are of great interest because of their potential usefulness for the synthesis of nitrogen-containing natural products.[5] We have already reported catalytic asymmetric Mannich-type reactions of imines prepared from aldehydes and 2-aminophenol using a chiral zirconium complex prepared from zirconium (IV) *tert*-butoxide and (*R*)-6,6′-disubstituted-1,1′-bi-2-naphthols.[6] It has also been shown that these catalytic systems were potent synthetic tools for the preparation of optically active β-amino acids and their derivatives.[7] For example, a synthesis of (2*R*,3*S*)-3-phenylisoserine·hydrochloride, which is a precursor of the C-13 side chain of paclitaxel, was demonstrated using (*S*)-6,6′-Br_2−BINOL as shown in Scheme 1.[8]

In these reactions the chiral zirconium catalyst formed C_2 symmetric structures consisting of 1 equiv of Zr and 2 equiv of (*R*)- or (*S*)-6,6′-Br_2-BINOL and more than 2 equiv of DMI or NMI in which all oxygen atoms of the BINOLs were oriented equatorial, as confirmed by NMR analyses. DMI or NMI plays important roles for dissociation of the monometallic Zr−BINOL complex from the oligomeric species and regulation of a structure of the Zr complex. In fact, almost no asymmetric

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(5) Reviews: (a) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (b) Denmark, S. E.; Nicaise, O. J.-C. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Ed.; Springer, Berlin, 1999; p 923. (c) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044. (d) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; VCH: Weinheim, 1997. (e) Kleinman, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Chapter 2.3, Vol. 2, p 893.
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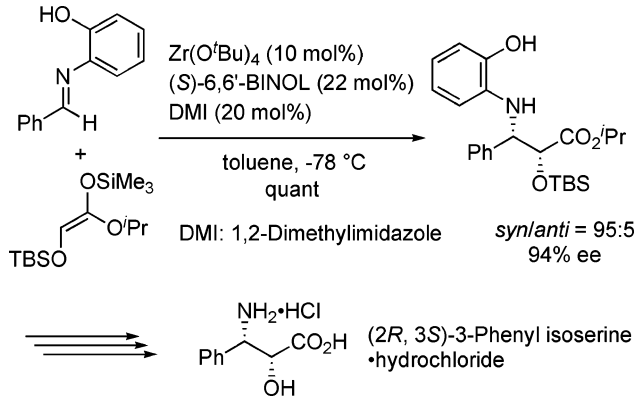
10.1021/ja053524d CCC: $30.25

Scheme 1. Synthesis of (2*R*,3*S*)-3-Phenylisoserine·Hydrochloride Using a Chiral Zirconium Catalyst



induction was observed without DMI or NMI.[5a] It was assumed that flipping of one of the four Zr−O bonds from an equatorial to an apical position occurred when a bidentate imine coordinated; a stereochemical model is shown in Figure 1. Further, the enantioselectivity observed could be explained by assuming a transition state derived from flipping A, in which the *si*-face of the imine was shielded effectively by a naphthalene ring of the BINOL; however, a transition state from flipping B would lead to a less selective reaction. Therefore, we thought that suppression of flipping B would be a way to improve the enantioselectivity. The most promising strategy to control the flipping is fixation of the two BINOLs by a spacer, that is, design of a novel tetradentate BINOL derivative.

Herein we describe the design and optimization of multidentate BINOL ligands, scope of the reactions, NMR experiments, and DFT calculations on the catalyst. The assumed structure of an active catalyst and a plausible mechanism of asymmetric induction are also proposed.

Results and Discussion

We designed tetradentate (*R*)-(*R*)-bis-BINOL-methane (BBM),[9] in which two BINOL molecules in the assumed flipped structure

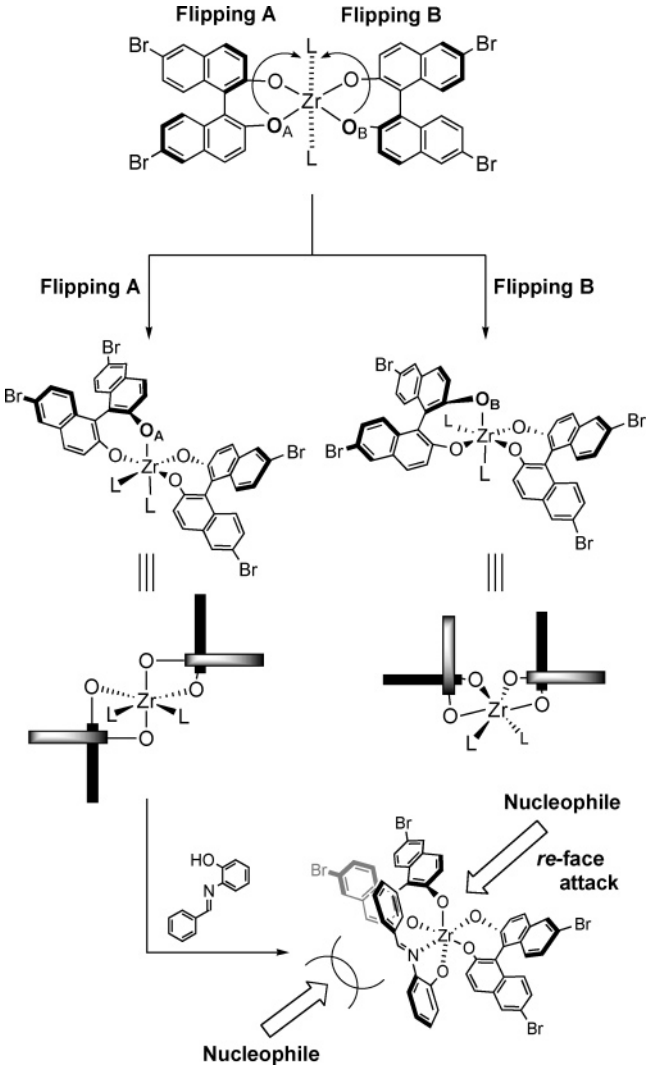


Figure 1. Structure of a chiral zirconium complex of bis(*R*)-6,6-Br_2−BINOL and assumed stereochemical model.

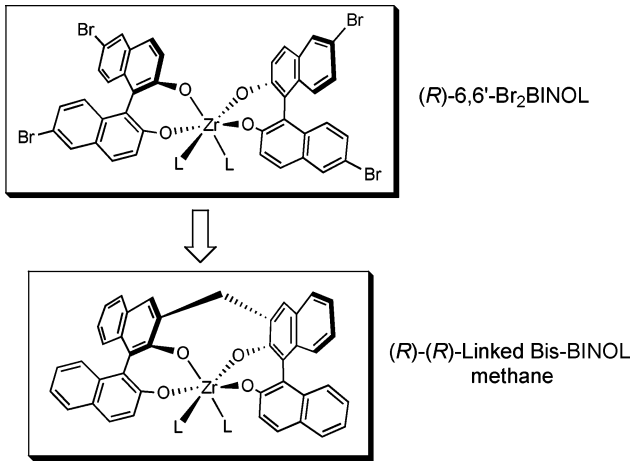


Figure 2. Design of a linked bis-BINOL ligand.

of the zirconium catalyst prepared from (*R*)-6,6′-Br_2−BINOL were connected with a C_1 spacer (Figure 2). BBM and analogues were synthesized as shown in Scheme 2.[9a] Ortho-lithiation of (*R*)-MOM-BINOL was carried out using Snieckus' method,[10] and then the arylaldehyde derivatives were treated to afford the

(7) Recently, several direct asymmetric Mannich-type reactions have been reported. For direct Mannich-type reactions, see reviews: (a) Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102. For recent examples, see also: (b) Cobb, A. J. L.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84. (c) Notz, W.; Watanabe, S.; Chowdari, N. S.; Zhong, G.; Betancort, J. M.; Tanaka, F.; Barbas, C. F., III *Adv. Synth. Catal.* **2004**, *346*, 1131. (d) Ibrahem, I.; Casas, J.; Córdova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 6528. (e) Zhuang, W.; Saaby, S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4476. (f) Matsunaga, S.; Yoshida, T.; Morimoto, H.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8777. (g) Hayashi, Y.; Tsuboi, W.; Ashimine, I.; Urushima, T.; Shoji, M.; Sakai, K. *Angew. Chem.* **2003**, *115*, 3805; *Angew. Chem., Int. Ed.* **2003**, *42*, 3677. (h) Hayashi, Y.; Tsuboi, W.; Shoji, M.; Suzuki, N. *J. Am. Chem. Soc.* **2003**, *125*, 11208. (i) Matsunaga, S.; Kumagai, N.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 4712. (j) Watanabe, S.; Córdova, A.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2002**, *4*, 4519. (k) Córdova, A.; Barbas, C. F., III. *Tetrahedron Lett.* **2002**, *43*, 7749. (l) Córdova, A.; Watanabe, S.; Tanaka, F.; Notz, W.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1866. (m) Córdova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1842. (n) List, B.; Porjaliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827. (o) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336. For examples using modified esters, see: (p) Bernardi, L.; Gothelf, A. S.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 2583. (q) Marigo, M.; Kjærsgaard, A.; Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Chem.—Eur. J.* **2003**, *9*, 2359. (r) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356 and references therein.

(8) Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431.

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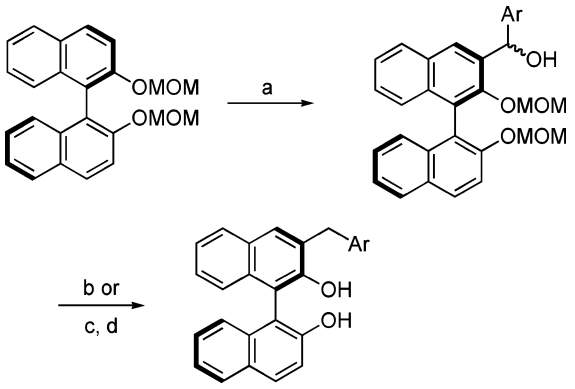
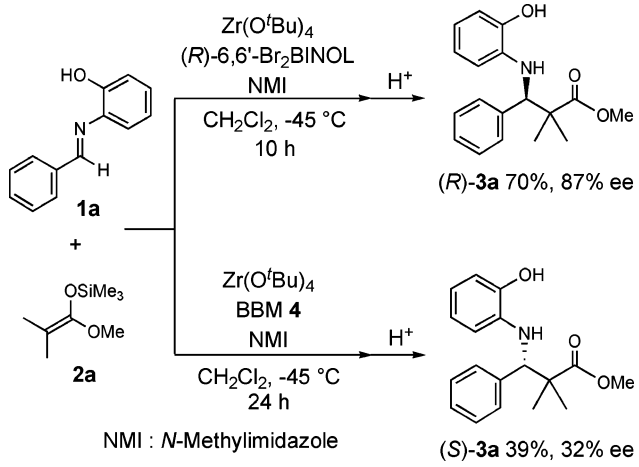
(10) Cox, P. J.; Wang, W.; Snieckus, V. *Tetrahedron Lett.* **1992**, *33*, 2253.

Scheme 2. Synthesis of Multidentate BINOL Derivatives[a]



[a] Conditions: (a) BuLi/TMEDA/Et_2O or ^{t}BuLi/Et_2O then ArCHO. (b) $NaBH_4$/TFA/CH_2Cl_2. (c) HCl/MeOH. (d) $Et_3SiH/BF_3{\cdot}Et_2O/CH_2Cl_2$.

Scheme 3. Stereoselection of the Chiral Zirconium Catalysts



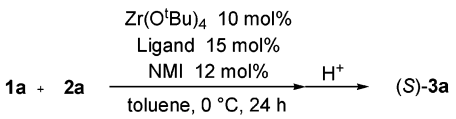
corresponding diarylmethanols.[11] Deprotection of the MOM groups and reduction of the dibenzylic position gave multidentate BINOL analogues.

We then performed the Mannich-type reaction of imine **1a** with ketene silyl acetal **2a** using a Zr catalyst prepared from BBM **4**. The reaction proceeded but more slowly when compared with that using the Zr catalyst prepared from (*R*)-6,6′-Br_2−BINOL. In addition, unexpectedly, (*S*)-**3a** was obtained by using the catalyst derived from BBM, while (*R*)-**3a** was obtained when (*R*)-6,6′-Br_2−BINOL was employed.[9a] That implies the structure of the catalyst formed by BBM **4** is completely different from the proposed structure in Figure 2, and the nucleophile attacked the opposite π-face of the imine when the catalyst prepared from **4** was used (Scheme 3). These unexpected results, in contrast to our initial transition state model, led us to conduct further investigations to clarify the origin of this unique phenomenon.

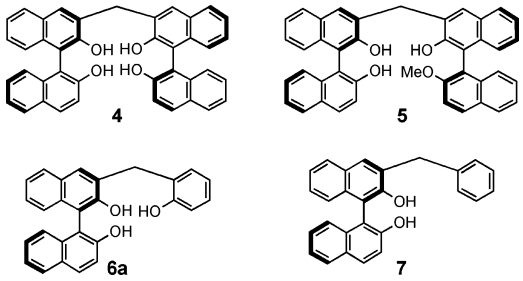
To clarify the structure of the chiral zirconium complex prepared from Zr(O^{t}Bu)$_4$, NMI, and BBM **4**, several NMR experiments were conducted. However, ^{1}H and ^{13}C NMR spectra of the complex were very complicated. It was assumed that the complexes of zirconium and the linked bis-BINOL derivative formed oligomeric structures, in contrast to the structure of the zirconium catalyst prepared from Zr(O^{t}Bu)$_4$, 6,6′-Br_2−BINOL, and NMI.[12] On the other hand, the Mannich-type adduct was

(11) Diarylmethanols were also prepared by reactions of (*R*)-3-CHO-MOM-BINOL with ArLi or ArMgX.

Table 1. Investigation of BBM **4** Analogues



Entry	Ligand	Yield/%	ee/%
1	**4**	82	94
2	**5**	67	74
3	**6a**	74	69
4	**7**	66	47



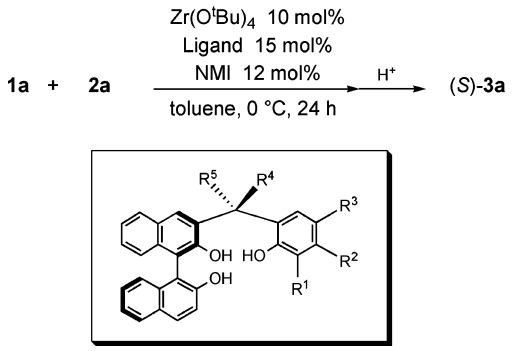
obtained in 82% yield with 94% ee when the reaction was conducted in toluene at 0 °C. Further, when an *O*-methylated BBM **5** was used as a chiral ligand in the Zr-catalyzed Mannich-type reaction, the desired adduct was obtained in 67% yield with 74% ee (Table 1, entry 2). This result revealed that all hydroxyl groups of tetradentate ligand **4** might not participate in the establishment of an effective asymmetric environment and that tridentate BINOL ligands might be efficient. We then synthesized and employed a simplified tridentate BINOL derivative **6a** in the Mannich-type reaction. The desired reaction proceeded smoothly, and the product was obtained in 74% yield with 69% ee (entry 3). When bidentate benzyl analogue **7** was employed, the yield and the enantiomeric excess decreased (entry 4).

We then searched for more effective ligands for zirconium catalysts by screening simplified tridentate BINOL derivatives. It was assumed that sterically demanding groups at the ortho position of the phenol moiety are necessary to achieve high enantioselectivity in tridentate BINOL derivatives, since the steric bulk of the phenol moiety is lower than that of linked bis-BINOL **4**. Moreover, electron-withdrawing substituents might be effective to increase the Lewis acidity of the catalyst. We have already reported that turnover numbers of related catalytic zirconium systems were much improved by introduction of electron-withdrawing groups at the 6,6′-positions of the binaphthyl ring systems due to enhanced Lewis acidity of the metal.[12] Based on these considerations, we prepared several tridentate BINOL derivatives and used them as ligands in the Zr-catalyzed Mannich-type reaction of aldimine **1a** with ketene silyl acetal **2a**. The results are summarized in Table 2.

In the presence of 10 mol % of a zirconium catalyst, which was prepared from Zr(O^{t}Bu)$_4$, 1.5 equiv of (*R*)-**6**, and 1.2 equiv of NMI, the desired reactions proceeded smoothly in toluene at 0 °C in almost all cases. In these tridentate ligands,

(12) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc*. **2000**, *122*, 8180.

Table 2. Screening of Tridentate BINOL Derivatives



entry	ligand	R^1	R^2	R^3	R^4	R^5	yield/%	ee/%
1	**6b**	CF_3	H	H	H	H	92	74
2	**6c**	Me	H	H	H	H	85	78
3	**6d**	Et	H	H	H	H	87	84
4	**6e**	*i*-Pr	H	H	H	H	92	87
5	**6f**	*t*-Bu	H	H	H	H	80	30
6	**6g**	Ph	H	H	H	H	79	30
7	**6h**	H	CF_3	H	H	H	80	75
8	**6i**	H	H	Ph	H	H	74	54
9	**6j**	*i*-Pr	H	H	OMe	H	46	15
10	**6k**	*i*-Pr	H	H	H	OMe	93	86

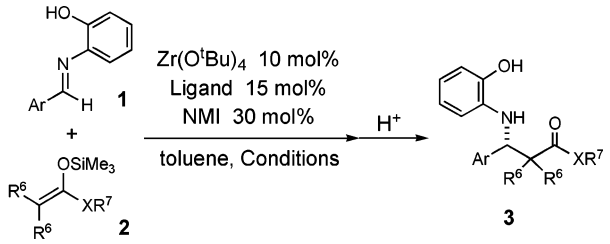
introduction of an electron-withdrawing group was not so effective for improving the reactivity (entries 1 and 7). On the other hand, it was found that the R^1 group had an important influence on the enantioselectivity and that a suitably sized substituent R^1 was required. Precisely, the size of the R^1 correlates with enantioselectivity for smaller groups (entries 2, 3, and 4), yet when R^1 is too bulky enantioselectivity is decreased (entries 5 and 6). The highest enantioselectivity was obtained when **6e** ($R^1 = {}^i$Pr) was employed (entry 4).[13] Further, the substituent of the methylene position was found to play an important role on the enantioselectivity (**6j** vs **6k**). While **6k** gave high enantioselectivity, **6j** showed only 15% ee. In the case of **6j**, it seemed that the methoxy group of the benzylic position was too close to the activated aldimine in a transition state (vide infra).

Next, we investigated the Mannich-type reactions of other aldimines with silicon enolates using chiral zirconium catalysts prepared from linked bis-BINOL methane **4** and tridentate BINOL derivative **6e**. The results are summarized in Table 3.

Imines derived from aromatic aldehydes having electron-donating and electron-withdrawing groups worked well to afford the desired Mannich-type adducts and high enantioselectivities. Similar high levels of enantioselectivity were obtained when the silicon enolates **2b** derived from ethyl isobutyrate and **2c** from *S*-ethyl thioacetate were used (entries 4 and 5). The catalyst prepared from **6e** showed much higher activity than that prepared from **4**, and the reactions proceeded at lower temperature using tridentate ligand **6e** (entry 1 vs 2). The imines prepared from sterically hindered aldehydes such as *o*-tolyl and 1- or 2-naphthylaldehydes, and those prepared from heterocyclic aldehydes also gave the products in high enantioselectivities. Moreover, it was also found that the reactions were slightly accelerated in the presence of a small amount of phenol (entries 7, 9, and 21). In these cases, phenol served as a proton source in the reaction; no alkoxide exchange with phenol occurred on the Zr catalyst.[14]

(13) Very recently we reported the chiral niobium catalyst using tridentate BINOL derivative **6e** for the Mannich-type reaction: Kobayashi, S.; Arai, K.; Shimizu, H.; Ihori, Y.; Ishitani, H.; Yamashita, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 761.

Table 3. Catalytic Asymmetric Mannich-Type Reactions

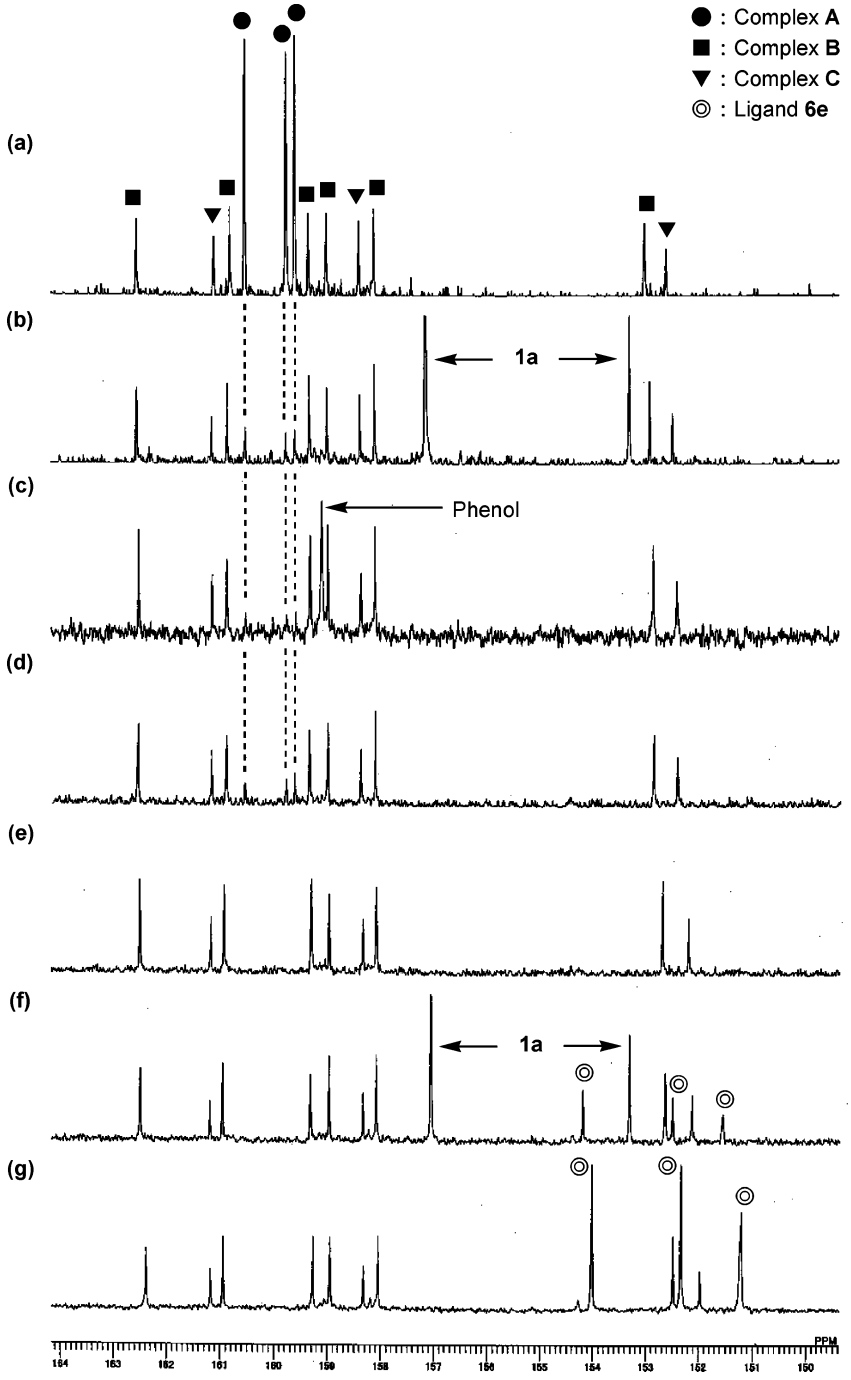


entry	imine	silicon enolate	ligand	conditions	yield/%	ee/%
1	**1a**	**2a**	**4**	0 °C, 24 h	82	94
2	**1a**	**2a**	**6e**	-15 °C, 20 h	95	94
3[a]	**1a**	**2a**	**6e**	rt., 16 h	92	91
4	**1a**	OSiMe3 OEt **2b**	**6e**	-15 °C, 20 h	70	93
5	**1a**	OSiMe3 SEt **2c**	**4**	-45 °C, 24 h	72	82
6	*p*-ClC_6H_4 (**1b**)	**2a**	**4**	0 °C, 24 h	72	85
7[b]	**1b**	**2a**	**6e**	-20 °C, 20 h	79	90
8	*m*-ClC_6H_4 (**1c**)	**2a**	**6e**	-40 °C, 3h -20 °C, 45h	98	92
9[b]	*p*-$MeOC_6H_4$ (**1d**)	**2a**	**4**	0 °C, 24 h	52	85
10	*o*-tol (**1e**)	**2a**	**4**	0 °C, 24 h	41	87
11	**1e**	**2c**	**4**	-45 °C, 44 h	53	90
12	*p*-tol (**1f**)	**2a**	**6e**	-40 °C, 3h -20 °C, 45h	89	93
13	*p*-$CF_3C_6H_4$ (**1g**)	**2a**	**6e**	-40 °C, 3h -20 °C, 45h	quant.	86
14	1-naphthyl (**1h**)	**2a**	**4**	0 °C, 24 h	70	85
15	**1h**	**2a**	**6e**	-40 °C, 44 h	55	92
16	2-naphthyl (**1i**)	**2a**	**4**	0 °C, 24 h	71	77
17	**1i**	**2c**	**4**	-45 °C, 44 h	56	94
18	2-furyl (**1j**)	**2a**	**4**	0 °C, 24 h	98	88
19	**1j**	**2a**	**6e**	-20 °C, 20 h	82	92
20	3-furyl (**1k**)	**2a**	**6e**	-44 °C, 44h	90	89
21[b]	2-thienyl (**1l**)	**2a**	**4**	0 °C, 24 h	40	90
22	3-thienyl (**1m**)	**2a**	**6e**	-40 °C, 3h -20 °C, 45h	96	92

[a] Benzene was used as a solvent instead of toluene. [b] PhOH (10 mol %) was added to the catalyst.

NMR Experiments. NMR experiments were performed to identify the nature of chiral zirconium catalyst. The complexes were prepared from 1 equiv of $Zr(O^tBu)_4$, 3 equiv of NMI and 1.0, 1.5, 2.0, and 3.0 equiv of **6e** in benzene-d_6. After being stirred at room temperature for 1 h, ^{1}H and ^{13}C NMR were measured. Independently, we prepared the same catalysts and

(14) The ^{13}C NMR signal of the phenolic carbon of phenol appeared at 156.2 ppm in benzene-d_6. When phenol was added to the Zr catalyst (Table 4, entry 3), it appeared at 159.1 ppm.



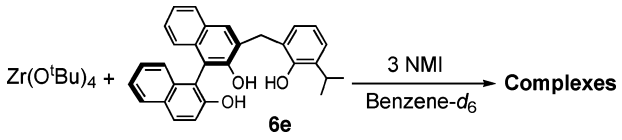
(a): $Zr(O^tBu)_4$: NMI : **6e** = 1:3:1. (b) $Zr(O^tBu)_4$: NMI : **6e** : **1a**= 1:3:1:1. (c) $Zr(O^tBu)_4$: NMI : **6e** : phenol = 1:3:1:1. (d) $Zr(O^tBu)_4$: NMI : **6e** = 1:3:1.5. (e) $Zr(O^tBu)_4$: NMI : **6e** = 1:3:2. (f) $Zr(O^tBu)_4$: NMI : **6e** : 1a = 1:3:1:1. (g) $Zr(O^tBu)_4$: NMI : **6e** = 1:3:3.

Figure 3. ^{13}C NMR spectra of chiral zirconium complexes.

conducted the reaction of **1a** with **2a** in benzene at room temperature. The results are shown in Table 4 and Figure 3.

In the case of using 1.0 equiv of **6e**, ^1H and ^{13}C NMR spectra showed the generation of three components (**A**, **B**, and **C**), and the molar ratio of these complexes was 3.4:1.2:1.0. Both ^1H and ^{13}C NMR spectra revealed that complex **A** held a unique **6e**. The ^{13}C NMR signals of phenolic carbons appeared at 159.6, 159.8, and 160.5 ppm, while the signals of the phenolic carbons of free **6e** appeared at 151.2, 152.3, and 154.0 ppm. These peaks indicated that three Zr−O−Ar moieties existed in the complex **A**; in addition, complex **A** was found to contain 1 equiv of NMI. In the case of using 1.5 equiv of **6e**, complex **B** was produced predominantly, and the molar ratio of complexes **A**, **B**, **C** was 0.21:1.2:1.0. It was found that the complex **B** held **6e** of two descriptions and that ^{13}C NMR signals of the phenolic carbons appeared at 152.5, 158.0, 158.9, 159.3, 160.9, and 162.4 ppm. These peaks indicated that five Zr−O−Ar moieties existed and that one hydroxyl group of the sidearm remained free in the complex **B**. On the other hand, when more than 2.0 equiv of the ligand were used, complex **A** was not detected. The NMR

Table 4. NMR Experiments of the Chiral Zirconium Complex of **6e**



entry	ligand (equiv)	**A**:**B**:**C**	yield/%[a]	ee/%[a]
1	1.0	3.4:1.2:1.0	94	92
2[b]	1.0	0.38:1.2:1.0		
3[c]	1.0	0.26:1.2:1.0	88	91
4	1.5	0.21:1.2:1.0	92	91
5	2.0	0.0:1.4:1.0	95	93
6[b]	2.0	0.0:1.4:1.0		
7	3.0	0.0:1.3:1.0	65	91

[a] The reactions of **1a** with **2a** were performed using the corresponding catalyst. [b] 1 equiv of **1a** was added. [c] 1 equiv of PhOH was added.

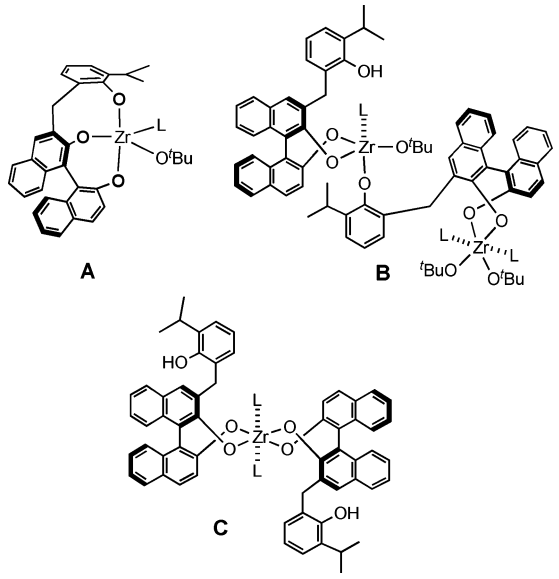


Figure 4. Assumed structures of the chiral zirconium complexes **A**−**C**.

spectra revealed that the complex **C** held a unique **6e** and that ^{13}C NMR signals of phenolic carbons appeared at 151.9, 158.3, and 161.2 ppm. These peaks indicated that two Zr−O−Ar moieties existed in complex **C**. Complex **C** was considered to be a 1:2 complex of Zr and **6e** with a highly symmetrical structure, although it was formed in the presence of a large excess of ligand **6e**. The assumed structures of complexes **A**−**C** are shown in Figure 4.

When 1 equiv of imine **1a** was added to the catalyst prepared from 1 equiv of **6e**, formation of a new complex consisting of the catalyst and the imine was not observed in the NMR spectra. However, the molar ratio of complexes **A**, **B**, and **C** changed to 0.38:1.2:1.0 (Table 4, entry 1 vs 2); that is, the ratio of complex **A** was decreased.[15] A similar tendency was observed when 1 equiv of phenol was added (entry 1 vs 3). When using 2 equiv of **6e**, the molar ratio of complexes **A**, **B**, and **C** did not change (entry 5 vs 6). It was assumed that a phenolic proton promoted a transformation of complex **A** into a new species (vide infra). It is interesting that, although Mannich-type reactions proceeded using these catalysts, the ratio of these

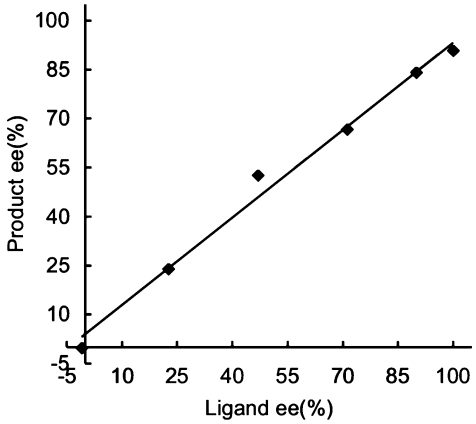


Figure 5. Correlation between ee of ligand **6e** and ee of the product.

complexes scarcely influenced enantioselectivities (entries 1, 3, 4, 5, and 6). Only when 3 equiv of **6e** were used did the reaction rate decreased slightly (entry 7).

We also investigated on a nonlinear effect to further elucidate the actual catalyst structure.[16] The correlation between the ee of the ligand **6e** and the ee of the product was carefully examined, and it was concluded that no nonlinear effect was observed in the reaction of **1a** with **2a**, as shown in Figure 5. The result may suggest that the dimeric complex (**B** or **C**) having two ligands is not an active catalyst species.

We assumed that complex **C** was inert as an active catalyst due to steric hindrance. It would be difficult for the complex **C** to activate an imine via bidentate coordination, because complex **C** could not flip like 6,6′-Br$_2$−BINOL due to the bulky substituent at the 3-position of BINOL. Since the structure of the complex **B** is rather flexible regarding the methylene groups at the benzylic positions, the remarkable effect of a methoxy group at the benzylic positions shown in Table 2, entry 9 vs 10 may not be explained by assuming complex **B** as an active catalyst. Moreover, it was also suggested that the complex **A** was not an active catalyst, because high enantioselectivity was obtained in the absence of complex **A** (Table 4, entries 5 and 7).

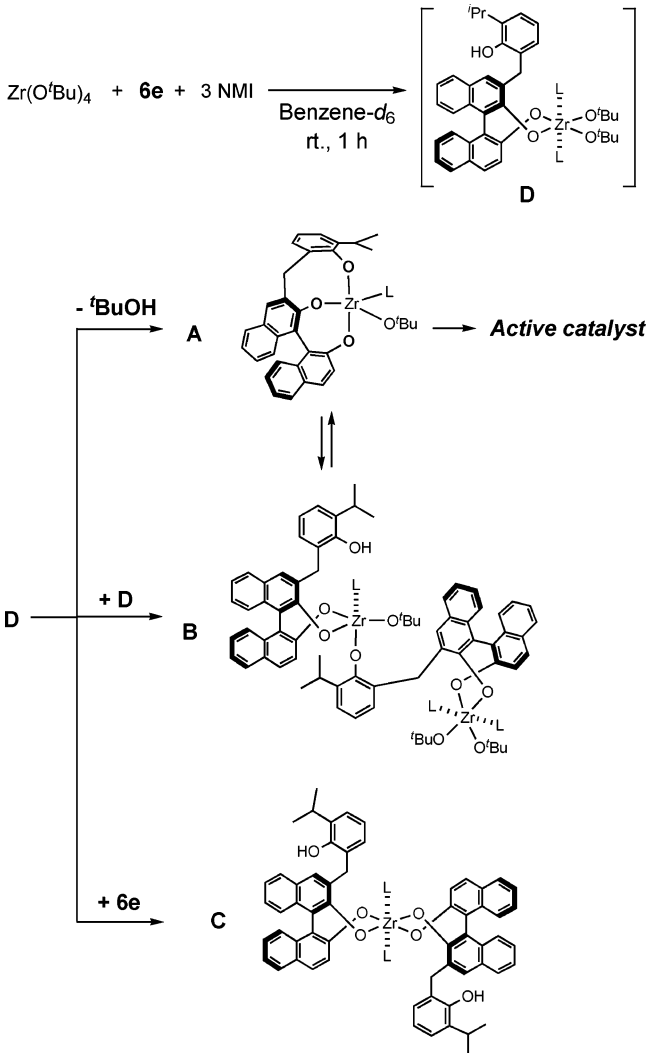
We proposed a plausible mechanism of the complex formation as shown in Scheme 4. Complexes **A**, **B**, and **C** were assumed to be generated from common intermediate **D**. Complex **A** was formed by an intramolecular reaction of **D**. Complex **B** was produced by an intermolecular reaction between two molecules of **D**. Further, complex **C** was formed by an intermolecular reaction of **D** with free **6e**. Consequently, we considered that complex **A** was a precursor of an active catalyst and that the formation of the active catalyst was accelerated by addition of a proton source like imine **1a** or phenol. It was assumed that the active catalyst was generated from complex **A** and existed as a transient species or in very small amounts in the reaction system, which were not detected by our NMR analyses. Complex **B** might serve as a precursor of **A**, thus, also a precursor of the active catalyst.[17] Complex **C** might be inert as a precursor due to stable bidentate coordination of the ligands.

(15) When ^{1}H NMR of complexes (a) and (c) in Figure 3 were measured in the presence of hexamethylbenzene as an internal standard, it was observed that the amount of complex **A** was decreased alone. The amounts of complex **B** and **C** did not change at all in these cases.

(16) (a) Kagan, H. B. *Synlett* **2001**, 888. (b) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2923.

(17) It was observed that a quantity of complex **B** decreased as the Mannich-type reaction proceeded, confirmed by other ^{1}H NMR experiments.

Scheme 4. Formation and Assumed Structures of the Chiral Zirconium Complexes with **6e**



DFT Calculations. To obtain further structural information about the active catalyst, we performed calculations on complex **A**; all calculations were carried out using TITAN molecular modeling package.[18] DFT calculations were done using JAGUAR quantum chemistry software[19] including TITAN. All starting geometries for DFT calculations were searched for beforehand by molecular mechanics (Monte Carlo method) using Merck's MMFF94 force field.[20] The basis set used for geometry optimization is LACVP** which is a basis set of double-ζ quality incorporating an effective core potential of Hay and Wadt[21] for the Zr and using the 6-31G** basis set for the other atoms. We employed the B3LYP functional,[22] Becke's three-parameter hybrid functional[23] for the exchange-correlation energy combined with the Lee−Yang−Parr correlation functional.[24] Molecular mechanics calculations extracted seven conformers with lower energies for complex **A**. Then, these conformers were calculated by the DFT method as mentioned above and were shown in Figure 6.

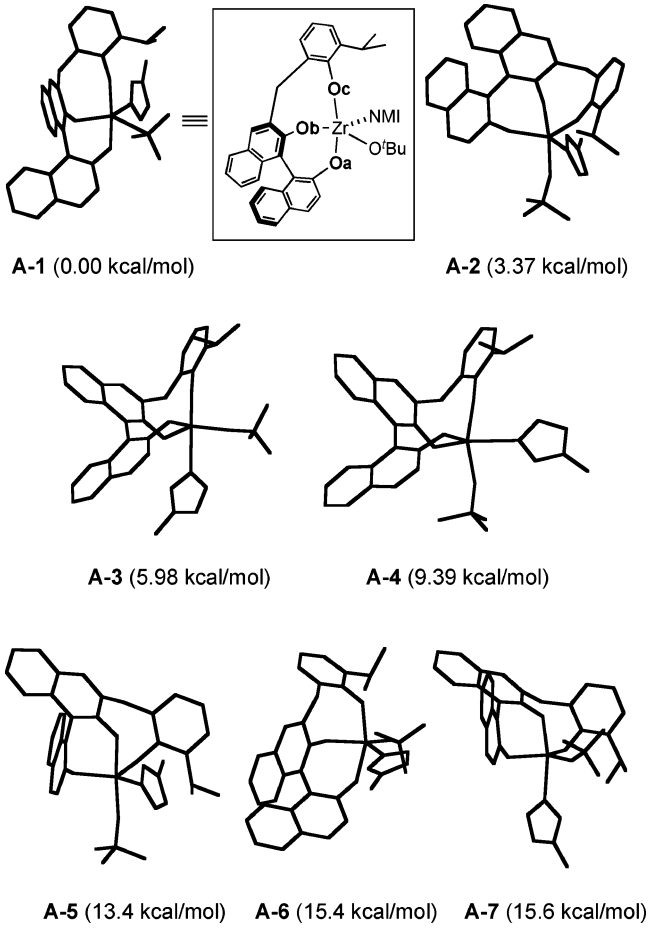


Figure 6. Calculated structures and relative energies of complex **A**.

The zirconium atom possessed a trigonal bipyramidal structure in all conformers; it turned out that conformer **A-1** had the lowest energy among all of them. In complex **A-1**, two oxygen atoms (Oa and Oc) were oriented in apical positions, while one oxygen atom (Ob), *tert*-butoxide, and NMI were in equatorial positions. However, since NMI was assumed to be eliminated from this complex by steric repulsion, the structure of the zirconium turns into a tetrahedron, which seemed to be coordinated by other ligands easily. Considering these results, the imine might coordinate to this tetrahedral zirconium complex and to be activated toward a nucleophilic attack of the ketene silyl acetal; namely, the tetrahedral zirconium complex (**E**) seemed to be an active catalyst. A stable structure of the tetrahedral complex **E** was also estimated by the DFT calculation (Figure 7).

It is noted that the calculated structure of **6e** in the complex **E** was similar to that in the complex **A-1.** Therefore, transformation of complex **A** to complex **E** and its reverse reaction would occur smoothly. The calculated structure of complex **E** also indicated that an imine could approach the zirconium atom from the opposite side to the Oa−Zr bond due to the steric hindrance. Based on these results, the assumed transition state model is shown in Figure 8. The complex of the active catalyst and the imine was similar to the structure shown in Scheme 5.

(18) *TITAN*, version 1.0; Wavefunction, Inc., Schrödinger, Inc., 1999.
(19) *JAGUAR*, version 3.5; Schrödinger, Inc., 1998.
(20) Halgren, T. A. *J. Comput. Chem*. **1996**, *17*, 490.
(21) (a) Hay, P. J.; Wadt, W. R. *J. Chem. Phys*. **1985**, *82*, 270. (b) Wadt, W. R.; Hay, P. J. *J. Chem. Phys*. **1985**, *82*, 284. (c) Hay, P. J.; Wadt, W. R. *J. Chem. Phys*. **1985**, *82*, 299.
(22) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem*. **1994**, *98*, 11623.
(23) (a) Becke, A. D. *J. Chem. Phys*. **1992**, *96*, 2155−2166. (b) Becke, A. D. *J. Chem. Phys*. **1993**, *98*, 1372. (c) Becke, A. D. *J. Chem. Phys*. **1993**, *98*, 5648.
(24) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev*. **1988**, *B41*, 785.

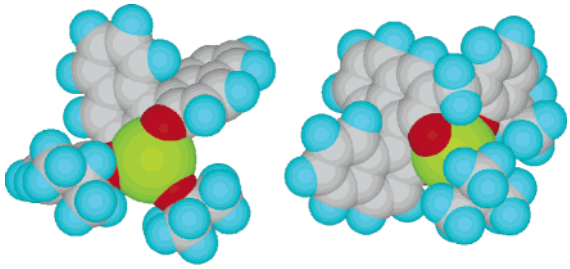


Figure 7. Calculated structures of tetrahedral complex **E**.

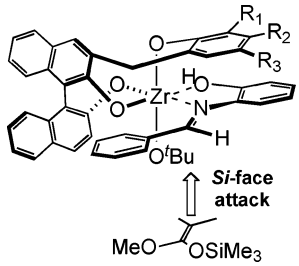
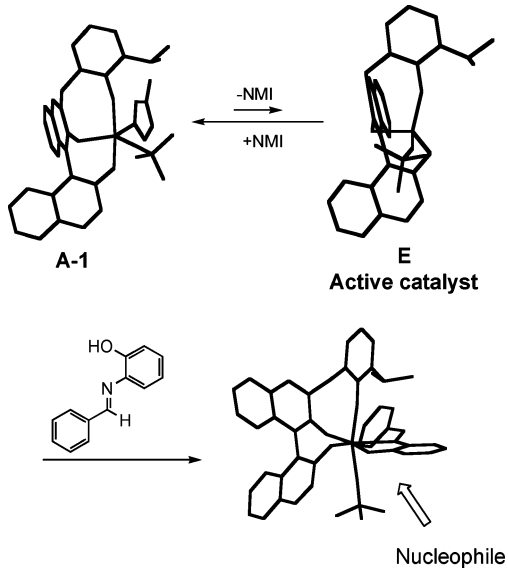


Figure 8. Assumed transition state model.

Scheme 5. Assumed Mechanism of the Exchange of NMI for Imine



Unfortunately, the SCF convergence was unsuccessful for this complex.

In the model, the *re* face of the imine is shielded from nucleophiles by the phenoxy sidearm of **6e**. As mentioned in Table 2, entries 9 and 10, stereochemistry of a methoxy substituent on the dibenzylic position of **6e** gave a significant effect on the enantioselection of the reaction. In the case using **6k**, the enantioselectivity was not affected; however, a significant decrease of enantiomeric excess was observed using **6j** as a ligand. These results can be clearly explained from the transition state model in Figure 8.

Since the methoxy group of **6j** has an apparent steric repulsion with the imine in the model, the complex seems to be unstable. In contrast, the methoxy group in the complex prepared from **6k** has a lesser steric effect in the model. Linked bis-BINOL methane derivatives **4** would also behave as tridentate BINOL **6e**, and identical stereoselectivity was observed between them.

Conclusion

Asymmetric catalysts with chiral zirconium complexes prepared from multidentate BINOL derivatives were investigated in Mannich-type reactions of aldimines with silicon enolates. An initial ligand design as the transition state mimic led to an unexpected inversion of the absolute configuration of the Mannich adducts. Optimized zirconium catalysts using multidentate BINOL derivatives, linked bis-BINOL or tridentate BINOL derivatives, showed high enantioselectivities. The structure of the chiral zirconium complex prepared from $Zr(O^tBu)_4$, a tridentate BINOL derivative and NMI, was investigated, and more than three kinds of complexes were observed by NMR analyses. DFT calculations revealed the stable structure of complex **A** and predicted an active tetrahedral species (complex **E**). A mechanism of the asymmetric induction was proposed, and a clear explanation of the ligand effect was obtained.

At the starting point of this study, the well-designed tetradentate BINOL derivative, BBM, was thought to work well in our assumed transition state of the Mannich-type reaction. However, the nature of the zirconium complexes was beyond our knowledge and gave us unexpected and interesting results. We believe that this new finding could lead to new effective design of chiral zirconium catalysts.

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Supporting Information Available: Experimental details and physical data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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