Enantioselective Mannich-Type Reactions Using a Novel Chiral Zirconium Catalyst for the Synthesis of Optically Active β-Amino Acid Derivatives

Haruro Ishitani, Masaharu Ueno, and Shū Kobayashi*

Contribution from the Graduate School of Pharmaceutical Sciences, The University of Tokyo, CREST, Japan Science and Technology Corporation (JST), Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Received May 12, 2000

Abstract: Catalytic enantioselective Mannich-type reactions of silyl enol ethers with aldimines have been successfully performed using a novel chiral zirconium catalyst prepared from zirconium(IV) *tert*-butoxide ($Zr(O^tBu)_4$), 2 equiv of (*R*)-6,6′-dibromo-1,1′-bi-2-naphthol ((*R*)-6,6′-Br_2BINOL), and *N*-methylimidazole. The use of aldimines having N-substituted hydroxyphenyl moieties is essential for obtaining high selectivities, and the N-substituted groups were converted to free amines using oxidative cleavage. Aldimines derived from aromatic aldehydes as well as heterocyclic and aliphatic aldehydes reacted with silyl enol ethers smoothly to afford the corresponding β-amino acid derivatives in high yields and high enantioselectivities. Several NMR experiments have been conducted to clarify the structure of the chiral Zr catalyst and also the catalytic cycle of this asymmetric reaction. Finally, a new BINOL derivative, (*R*)-6,6′-bis(trifluoromethyl)-1,1′-bi-2-naphthol ((*R*)-6,6′-$(CF_3)_2$BINOL), has been prepared. It was shown that the turnover of the catalyst using this novel ligand was improved, and high levels of yields and selectivities were obtained in the presence of a small amount of the zirconium catalyst.

Introduction

Asymmetric Mannich-type reactions of aldimines with enolate components are one of the most important carbon−carbon bond-forming reactions in organic synthesis. The reactions provide useful routes for the synthesis of chiral β-amino ketones or esters (Mannich bases), which are versatile chiral building blocks for the synthesis of many nitrogen-containing biologically important compounds including β-amino acids and β-lactams.[1] While several asymmetric Mannich-type reactions using stoichiometric amounts of chiral sources have already been reported,[2,3] very little is known concerning catalytic asymmetric versions.[4] This is in contrast to the recent progress achieved in catalytic enantioselective aldol reactions of aldehydes with enolate components, especially silyl enolates (Mukaiyama aldol reactions).[5] While chiral Lewis acids have played leading roles in these reactions, it is assumed that most Lewis acids would be trapped by basic nitrogen atoms of the starting materials and/or products in Mannich-type reactions and that truly catalytic reactions would be difficult to perform. In 1997, we reported the first example of truly catalytic enantioselective Mannich-type reactions of aldimines with silyl enolates using a novel zirconium catalyst[6] and now in this article describe full details including the general idea, catalyst structure, reaction mechanism, and scope of these reactions. A novel efficient catalyst which attains high turnover of the catalyst in this reaction is also reported.

Results and Discussion

To achieve truly efficient catalytic enantioselective Mannich-type reactions of aldimines with silyl enolates, it was thought that the choice of metals of Lewis acid catalysts was one of the

(1) Kleinman, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Chapter 2.3, Vol. 2, p 893.

(2) Diastereoselective asymmetric Mannich-type reactions. For example: (a) Fujisawa, T.; Kooriyama, Y.; Shimizu, M. *Tetrahedron Lett.* **1996**, *37*, 3881. (b) Arend, M. Risch, N. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2861. (c) Matsumura, Y. Tomita, T. *Tetrahedron Lett.* **1994**, *35*, 3737. (d) Page, P. C. B.; Allin, S. M.; Collington, E. W.; Carr, R. A. E. *J. Org. Chem.* **1993**, *58*, 6902. (e) Frauenrath, H.; Arenz, T.; Raabe, G.; Zorn, M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 83. (f) Nolen, E. G.; Aliocco, A.; Broody, M.; Zuppa, A. *Tetrahedron Lett.* **1991**, *32*, 73. (g) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215. (h) Katritzky, A. R.; Harris, P. A. *Tetrahedron* **1990**, *46*, 987. (i) Kunz, H.; Pfrengle, W. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1067. (j) Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, *30*, 5603. (k) Gennari, C.; Venturini, I.; Gislon, G.; Schimperna, G. *Tetrahedron Lett.* **1987**, *28*, 227. (l) Broadley, K.; Davies, S. G. *Tetrahedron Lett.* **1984**, *25*, 1743. (m) Seebach, D.; Betschart, C.; Schiess, M. *Helv. Chim. Acta* **1984**, *67*, 1593.

(3) For enantioselectve Mannich-type reactions using stoichiometric amounts of chiral sources: (a) Corey, E. J.; Decicco, C. P.; Newbold, R. C. *Tetrahedron Lett.* **1991**, *39*, 5287. (b) Ishihara, K.; Miyata, M.; Hattori, K.; Tada, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 10520. (c) Enders, D.; Ward, D.; Adam, J.; Raabe, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 981. See also: Risch, N.; Esser, A. *Liebigs Ann. Chem.* **1992**, 233.

(4) Quite recently, several catalytic enantioselective Mannich-type reactions have been reported: (a) Fujieda, H.; Kanai, M.; Kambara, T.; Iida, A.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2060. (b) Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 2474. (c) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548. (d) Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 5450. (e) Yamasaki, S.; Iida, T.; Shibasaki, M. *Tetrahedron* **1999**, *55*, 8857. (f) Yamada, K.-I.; Harwood, S. J.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3504. (g) Kambara, T.; Tomioka, K. *Chem. Pharm. Bull.* **1999**, *47*, 720.

(5) For review articles of this topic: (a) Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto Y., Eds.; Springer: Heidelgerg, 1999. Vol. 3, p 998. (b) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095. (c) Groger, H.; Vogel, E. M.; Shibasaki, M. *Chem. Eur. J.* **1998**, *4*, 1137. (d) Nelson, S. G. *Tetrahedron: Asym.* **1998**, *9*, 357. (e) Bach, T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 417.

(6) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 7153.

10.1021/ja001642p CCC: $19.00
Published on Web 08/11/2000

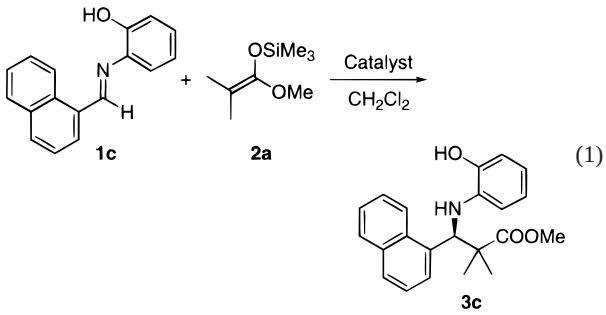
Table 1. Effect of Zirconium Compounds (Eq 1)[a]

	catalyst					
entry	precursor	ligand	base	time/h	yield/%	ee/%
1	$ZrCl_4$	**4a**[b]	^{n}BuLi[c]	30	trace	
2	$Zr(OTf)_4$	**4a**[b]	^{n}BuLi[c]	16	quant	2
3	$Zr(O^iPr)_4$	**4a**[b]		30	quant	2
4	$Zr(O^tBu)_4$	**4a**[b]		30	quant	9
5	$Zr(O^tBu)_4$	**4a**[c]		30	quant	38

[a] The reaction was carried out using 10 mol % of Zr at −45 °C. [b]10 mol %. [c]20 mol %.

most important keys. After careful examination of various metals, we decided to use zirconium(IV) as a metal center.[7,8] Another difficulty is the rather flexible aldimine−chiral Lewis acid complexes which often have several stable conformers (including the *E*/*Z* isomers of aldimines),[9] while aldehyde−chiral Lewis acid complexes are believed to be rigid.[10] Therefore, in the addition to aldimines activated by chiral Lewis acids, many transition states would exist to decrease selectivities. To address these issues, we planned to utilize a bidentate chelation (vide infra).[11]

We selected the aldimine **1c**, and first, the reaction with silyl enolate **2a** was investigated. The effect of zirconium compounds is shown in Table 1. In the presence of a zirconium compound prepared from zirconium(IV) chloride ($ZrCl_4$) and lithiated (*R*)-1,1′-bi-2-naphthol ((*R*)-BINOL), the reaction of **1c** with **2a** proceeded sluggishly (entry 1). The zirconium compound derived from zirconium(IV) triflate ($Zr(OTf)_4$)/lithiated (*R*)-BINOL or zirconium(IV) isopropoxide ($Zr(O^iPr)_4$) or zirconium(IV) *tert*-butoxide ($Zr(O^tBu)_4$)/(*R*)-BINOL catalyzed the reaction, but almost no chiral induction was obtained (entries 2−4). On the other hand, moderate selectivity was observed when the catalyst was prepared from $Zr(O^tBu)_4$ (10 mol %) and 2 equiv of (*R*)-BINOL (20 mol %) (entry 5).[12,13]



(1)

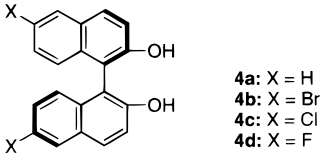
While a homogeneous solution was formed by combining $Zr(O^tBu)_4$ and (*R*)-BINOL in dichloromethane, precipitates appeared after 20 min. We thought that this result indicated formation of an oligomeric or a polymeric structure of the catalyst which might lead to the low selectivities in the Mannich reactions. To address this problem, several additives were examined (Table 2).[14] It was found that imidazole derivatives gave promising results.[15] While 45% ee of the product was obtained by using *N*-methylimidazole (NMI) as an additive at 0 °C, higher enantiomeric excess was observed when the reaction was carried out at −15 °C (entries 2 and 3). It was also revealed that 1,2-dimethylimidazole (DMI) was an effective additive and that the corresponding product was obtained in the same level of enantioselectivity, while the yield was decreased. To improve the yield and enantioselectivity of the reaction, several conditions were further examined. It was exciting to find that the enantiomeric excess was dramatically increased to 90% when the catalyst was prepared using (*R*)-6,6′-dibromo-BINOL (**4b**; 6,6′-Br_2BINOL; see Chart 1).[16] The same levels of the yields and selectivities were obtained when (*R*)-6,6′-dichloro-BINOL (**4c**) or (*R*)-6,6′- difluoro-BINOL (**4d**) was employed (entries 11 and 12). It was revealed later that the effect of the substituents at the 6,6′-positions of BINOL was a key to obtain high levels of yields, selectivities, and, particularly, turnover of the catalyst. These results will be discussed in the last part of this paper. On the other hand, high enantioselectivities were still obtained when the catalyst loading

Table 2. Effect of Several Reaction Parameters (Eq 1)

	catalyst[a]						
entry	mol % [Zr][b]	ligand	additive[c]	temp/°C	time/h	yield/%	ee/%
1	20	**4a**	DTBP	0	16	quant	30
2	20	**4a**	NMI	0	16	quant	45
3	20	**4a**	NMI	−15	16	80	70
4	10	**4a**	NMI	−15	30	quant	49
5	10	**4a**	NMI	−45	30	quant	58
6	20	**4a**	2-MI	0	16	37	51
7	20	**4a**	DMI	0	16	63	68
8	20	**4a**	DMI	−15	16	47	70
9	20	**4b**	NMI	−15	16	73	90
10	10	**4b**	NMI	−45	16	quant	92
11	10	**4c**	NMI	−45	16	98	93
12	10	**4d**	NMI	−45	16	90	87
13	5	**4b**	NMI	−45	16	69	95
14	5	**4b**	DMI	−15	16	quant	91
15[d]	2	**4b**	NMI	−45	30	75	86

[a] [Zr]/ligand/additive = 1/2.2/1.2. [b]$Zr(O^tBu)_4$. [c]DTBP, 2,6-di-*tert*-butylpyridine; NMI, *N*-methylimidazole; 2-MI, 2-methylimidazole; DMI, 1,2-dimethylimidazole. [d][Zr]/ligand/additive = 1/2.2/3.

Chart 1



(7) Rare earths are also promising candidates for the catalytic activation of aldimines. See: (a) Kobayashi, S.; Araki, M.; Ishitani, H.; Nagayama, S.; Hachiya, I. *Synlett* **1995**, 233. (b) Kobayashi, S.; Araki, M.; Yasuda, M. *Tetrahedron Lett.* **1995**, *36*, 5773.

(8) Different types of chiral zirconium catalysts that are effective in ring-opening reactions of epoxides, Diels−Alder reactions, and polymerization, etc., were reported: (a) Nugent, W. A. *J. Am. Chem. Soc.* **1992**, *114*, 2768. (b) Bedeschi, P.; Casolari, S.; Costa, A. L.; Tagliavini, E.; Umani-Ronchi, A. *Tetrahedron Lett.* **1995**, *36*, 7897. (c) Hoveyda, A. H.; Morken, J. P. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1262, and references therein.

(9) (a) McCarty, C. G. *The Chemistry of the Carbon−Nitrogen Double Bond*, Patai, S., Ed.; John Wiley & Sons: New York, 1970; Chapter 9. (b) Biørgo, J.; Boyd, D. R.; Watson, C. G.; Jennings, W. B. *J. Chem. Soc., Perkin Trans. 2* **1974**, 757.

(10) (a) Corey, E. J.; Rohde, J. J.; Fischer, A.; Azimioara, M. D. *Tetrahedron Lett.* **1997**, *38*, 33. (b) Corey, E. J.; Rohde, J. J. *Tetrahedron Lett.* **1997**, *38*, 38. (c) Corey, E. J.; Barnes-Seeman, D.; Lee, T. W. *Tetrahedron Lett.* **1997**, *38*, 1699.

(11) Ishitani, H.; Kobayashi, S. *Tetrahedron Lett.* **1996**, 37, 7357.

(12) Catalytic enantioselective allylation of aldehydes using a zirconium/BINOL (1/1) catalyst was reported: (a) Bedeshi, P.; Casolari, S.; Costa, A. L.; Tagliavini, E.; Umani-Ronchi, A. *Tetrahedron Lett.* **1995**, *36*, 7897. (b) Yu, C.-M.; Yoon, S.-K.; Choi, H.-S.; Baek, K. *J. Chem. Soc., Chem. Commun.* **1997**, 763.

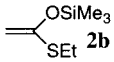
(13) The catalyst was prepared without removing ^{t}BuOH.

(14) About 20 additives were examined.

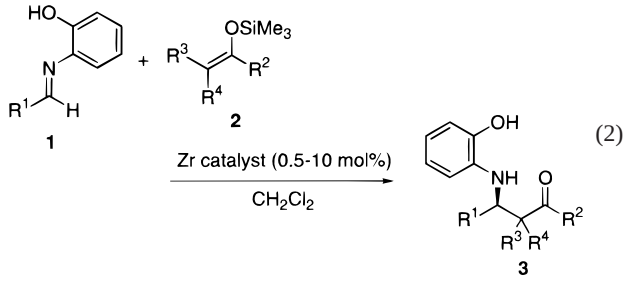
(15) We expected the imidazole derivatives coordinated the zirconium to form a monomeric structure.

(16) For the use of 6,6′-dibromo-1,1′-bi-2-naphthol, see: (a) Terada, M.; Motoyama, Y.; Mikami, K. *Tetrahedron Lett.* **1994**, *35*, 6693. (b) Sasai, H.; Tokunaga, T.; Watanabe, S.; Suzuki, T.; Itoh, N.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 7388.

Table 3. Catalytic Enantioselective Mannich-Type Reactions Using Ciral Ligand **4b** (Eq 2)[a]

entry	Imine; R^1	silyl enolate	catalyst /mol%	product	yield /%	ee /%
1	Ph (**1a**)	**2a**	10	**3a**	70	87
2	*p*-Cl-Ph (**1b**)	**2a**	5	**3b**	86	83
3	1-naphthyl (**1c**)	**2a**	10	**3c**	quant	92
4	Ph (**1a**)	 **2b**	10	**3d**	78	88
5	*p*-Cl-Ph (**1b**)	**2b**	10	**3e**	88	86
6	1-naphthyl (**1c**)	**2b**	5	**3f**	quant	>98
7	2-furyl (**1d**)	**2b**	10	**3g**	89	89
8	*c*-C_6H_{11} (**1e**)[b]	**2b**	10	**3h**	45	80
9	*i*-C_4H_9 (**1f**)[c]	**2b**	10	**3i**	47	80

[a] [Zr]/**4b**/additive = 1/2.2/1.2, −45 °C, 16 h. [b]The aldimine prepared from cyclohexanecarboxaldehyde and 2-amino-*m*-cresol was used. When the reaction was carried out at −23 °C, 71% yield and 71% ee were obtained. [c]The aldimine prepared from isovaleraldehyde and 2-amino-*m*-cresol was used.



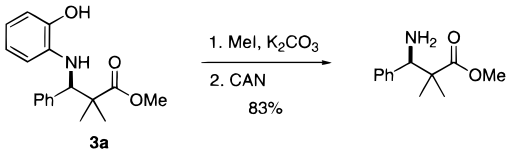
(2)

was reduced to 2−10 mol %. Although the yield was decreased when 5 mol % of the chiral catalyst including NMI was used at −45 °C (entry 13), both yield and enantioselectivity attained a satisfactory level by using DMI instead of NMI at −15 °C (entry 14).[17] It should be noted that the same high level of enantiomeric excess was obtained when 2 mol % of the chiral catalyst was employed (entry 15).

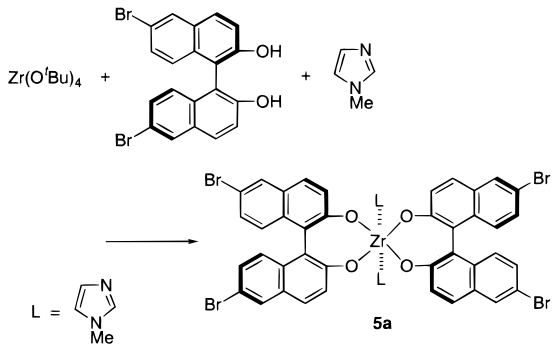
At this stage, several control experiments were performed. When Zr(O^{n}Pr)$_4$ or Zr(O^{i}Pr)$_4$[18] was used instead of Zr(O^{t}Bu)$_4$ in the reaction of **1c** with **2a** under the same reaction conditions shown in Table 2, entry 10, high yields and selectivities were also obtained (Zr(O^{n}Pr)$_4$ (10 mol %), 88% yield, 93% ee; Zr(O^{i}Pr)$_4$ (10 mol %), quantitative, 88% ee). On the other hand, it was revealed that the hydroxyphenyl group in **1c** was essential to obtain high selectivity. While **1c** was treated with **2a** under the conditions shown in Table 2, entry 10, to afford the corresponding adduct (**3c**) quantitatively with 92% ee, almost no chiral induction (<5% ee) was obtained when the aldimine prepared from 1-naphthylaldehyde and aniline or 1-naphthylaldehyde and 2-methoxyaniline was used under the same reaction conditions.

Other aldimines and silyl enolates were tested, and the results are summarized in Table 3. Not only aldimines derived from aromatic aldehydes but also aldimines derived from heterocyclic aldehydes worked well in this reaction, and good to high yields and enantiomeric excesses were obtained. Similar high levels of enantiomeric excess were also obtained when the silyl enol ether **2b** derived from *S*-ethyl thioacetate was used. While aldimines derived from aliphatic aldehydes such as cyclohexanecarboxaldehyde were known to be unstable, they worked efficiently when 2-aminophenol was substituted with 2-amino-*m*-cresol (entry 8). It is noteworthy that the use of 2-amino-*m*-cresol was effective not only in stabilizing the aldimine but also in obtaining high stereoselectivity. Namely, only poor chiral induction was observed when the aldimine derived from cyclohexanecarboxaldehyde and 2-aminophenol was used (less than 10% ee); however, the enantiomeric excess was greatly improved when the aldimine derived from 2-amino-*m*-cresol was employed. The methyl group of 2-amino-*m*-cresol would prevent *E*/*Z* isomerization of the aldimine−Lewis acid complex due to the steric repulsion between the cyclohexyl and methyl groups. Similarly, a high level of enantioselectivity was observed in the reaction of isovaleraldehyde (entry 9).

Scheme 1. Conversion to β-Amino Ester



Scheme 2. Formation of a Novel Zirconium Catalyst



The N-substituent of the product was easily removed according to Scheme 1. Thus, methylation of the phenolic OH of product **3a** using methyl iodide and potassium bicarbonate and deprotection using cerium ammonium nitrate (CAN) gave the β-amino ester.[19] The absolute configuration assignment was made by comparison of the optical rotation of the amino ester with that in the literature.[20]

Structure of the Chiral Catalyst. NMR experiments were performed to clarify the structure of the chiral zirconium catalyst. The catalyst was prepared from 1 equiv of Zr(O^{t}Bu)$_4$, 2 equiv of (*R*)-6,6′-Br$_2$BINOL, and 2 equiv of NMI in benzene-d_6. After stirring at room temperature for 1 h, the solvent was removed and ^{1}H and ^{13}C NMR were measured in dichloromethane-d_2. The ^{1}H and ^{13}C NMR spectra of the isolated catalyst[21] and (*R*)-6,6′-Br$_2$-BINOL indicated that the molar ratio of Zr, (*R*)-6,6′-Br$_2$BINOL, and NMI in the catalyst was 1:2:2.[22] Both ^{1}H and ^{13}C NMR spectra revealed that the four naphthalene rings of the zirconium catalyst were equivalent. In addition, the ^{13}C NMR chemical shift of phenolic carbons appeared at 159.6 ppm as a single peak, while the chemical shift of the phenolic carbon of free (*R*)-6,6′-Br$_2$BINOL appeared at 152.7 ppm. These peaks indicated that Zr−O−Ar moieties existed in the zirconium catalyst and that the catalyst had a highly symmetrical form. From these spectra, the structure of the catalyst was tentatively

(17) The same level of enantiomeric excess was obtained when the reaction was performed at −78 °C.

(18) Zr(O^{n}Pr)$_4$ and Zr(O^{i}Pr)$_4$ are less expensive than Zr(O^{t}Bu)$_4$.

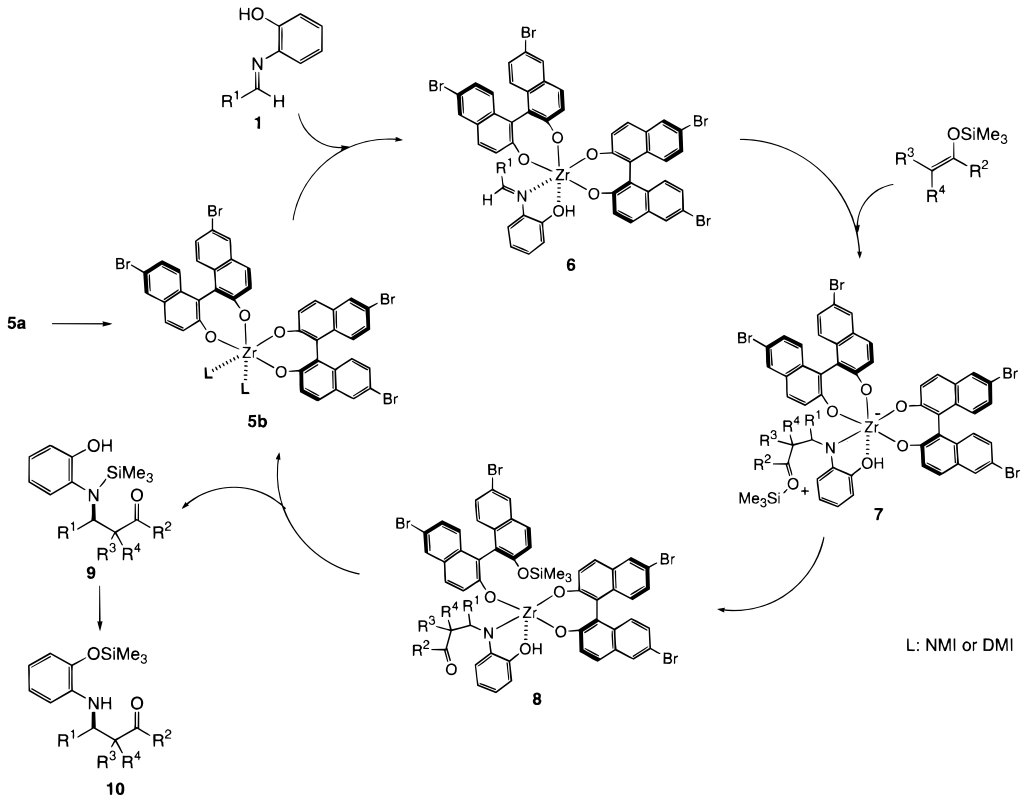
(19) Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765.

(20) Kunz, H.; Schanzenbach, D. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1068.

(21) The same levels of reactivity and selectivity were observed when using the isolated catalyst. The reaction of **1c** with **2a** gave **3c** quantitatively in 90% ee (Cf. Table 3, entry 3.).

(22) See Supporting Information.

Scheme 3. Assumed Catalytic Cycle of the Mannich-Type Reaction

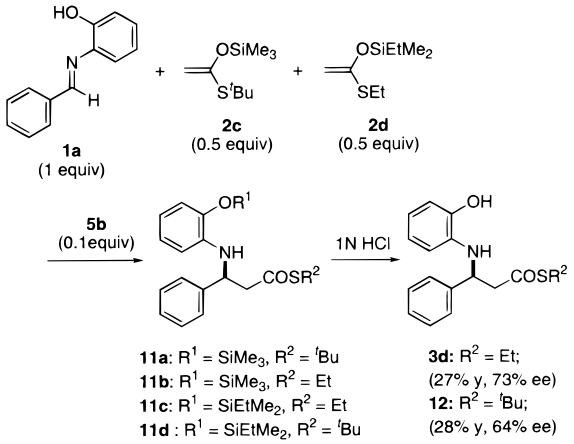


determined to be **5a** as shown in Scheme 2. Two (*R*)- 6,6′-Br_2-BINOLs locate at equatorial positions around the zirconium, and two NMIs coordinate at the axial positions. The highly symmetrical structure is one of the characteristics of this catalyst.

Catalytic Cycle. An assumed catalytic cycle of this Mannich-type reaction is shown in Scheme 3. The key is assumed to be isomerization of the zirconium catalyst from **5a** to **5b** when aldimines coordinate the zirconium.[23] As mentioned above, highly symmetrical structure **5a** was suggested from the NMR experiments. On the other hand, the bidentate coordination of aldimines to the zirconium was proved to be essential, since almost no chiral induction was observed when the aldimines derived from aniline or 2-methoxyaniline were used. For the bidentate coordination, one of the four equatorial Zr−O bonds had to flip to form an axial Zr−O bond. The zirconium catalyst **5b** coordinates to aldimine **1** to form zirconium complex **6**.[24−26] A silyl enol ether attacks the aldimine to produce **7** first, and then **8**, whose trimethylsilylated oxygen atom attacks the zirconium center to afford the product (**9** first and then **10**) along with regeneration of the catalyst **5b**. The product was obtained as a trimethylsilylated form without the acidic workup.

The catalytic cycle was supported by the following experiments. We first performed silyl crossover experiments (Scheme 4).[27] In the presence of chiral zirconium catalyst **5** (10 mol %), aldimine **1a** (1.0 equiv) was treated with the trimethylsilyl enol ether of *S-tert*-butyl thioacetate (**2c**, 0.5 equiv) and the ethyldimethylsilyl enol ether of *S*-ethyl thioacetate (**2d**, 0.5 equiv). The reaction was first monitored by GC/MS analysis; however, it was revealed that the expected products (**11a**−**d**) were not stable under the analysis conditions. We then decided to use ^{13}C NMR analysis. The ^{13}C NMR spectra of **11a**−**d** and that of the reaction mixture revealed that four products (**11a**−**d**) were observed in the mixture. In addition, it was confirmed that no silyl scrambling in the starting materials and the products occurred under the reaction conditions. These results indicated that intermolecular silyl scrambling occurred during the Mannich-type reaction process and that an intermediate such as **7** would exist during the reaction course. Since species such as **7** are expected to catalyze achiral Mannich-type reactions[28] and

Scheme 4. Crossover Experiments



(23) A direct pathway from **5a** to **6** may be possible.

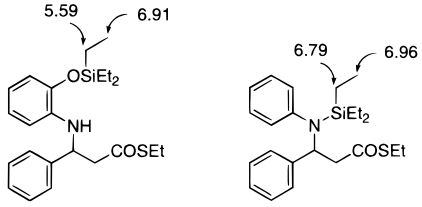
(24) We assume that this flipping leads to two isomeric structures. See also: Ishitani, H.; Kitazawa, T.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40*, 2161.

(25) We performed NMR studies concerning the mixture of the zirconium catalyst and an aldimine. ^1H and ^{13}C NMR spectra of the mixture were almost the same as those of **5a** at both room temperature and −30 °C. We assume that coordination of NMI to the zirconium is stronger than that of the aldimine to the zirconium

(26) For the structure of **6**, another form where the imino phenol deprotonates and one of the BINOL ligands protonates may be possible.

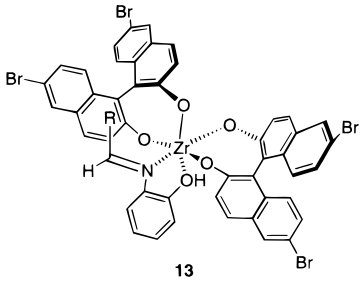
(27) For silyl crossover experiments in aldol reactions, see: (a) Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc*. **1994**, *116*, 4077. (b) Carreira, E. M.; Singer, R. A. *Tetrahedron Lett*. **1994**, *35*, 4323. (c) Denmark, S. E.; Chen, C.-T. *Tetrahedron Lett*. **1994**, *35*, 4327. (d) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc*. **1999**, *121*, 669.

Chart 2. ^{13}C NMR Chemical Shifts (ppm)



high enantioselectivity is obtained in the present zirconium-catalyzed asymmetric Mannich-type reactions, the life of **7** is assumed to be very short. It is noted that the silyl scrambling occurred during such short period. For isolation, **11a**−**d** were converted to β-amino thioesters **3d** and **12** by acidic workup. In addition, formation of N-silylated adduct **9** was also confirmed by ^{13}C NMR analysis. While formation of **9** was not detected in the reaction of **1a** with **2b** under the standard reaction conditions, the N-triethylsilylated adduct was observed by NMR analyses when the Mannich-type reaction of **1a** with 1-ethylthio-1-triethylsiloxyethene was performed under the same reaction conditions. That is, two signals at 6.76 and 6.98 ppm were observed in the ^{13}C NMR spectra of the Mannich-type adduct prepared from **1a** and 1-ethylthio-1-triethylsiloxyethene using the chiral zirconium catalyst. The signals correspond to those of the N-triethylsilylated adduct (Chart 2). These results indicate that **9** is an intermediate from **8** to **10** and that the rate of the silyl migration from **9** to **10** is influenced by steric bulkyness of the silyl groups.

As for the sense of enantioselection, we postulated stereochemical model **13** shown in Figure 1. In **13**, the *re* face was shielded by one of the naphthyl rings, and silyl enolates were expected to attack to the *si* face of aldimines.[29]

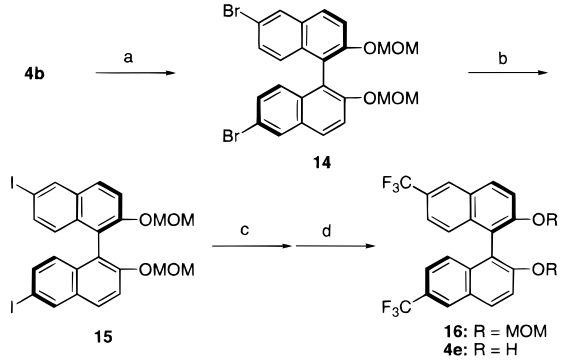


13

Figure 1. Assumed stereochemical model.

Turnover Improvement. While highly selective catalytic asymmeric Mannich-type reactions have been developed, turnover of the Zr catalyst was less than 20 in most cases. When 1 mol % of Zr catalyst **5** was used in the reaction of aldimine **1c** with silyl enolate **2a**, lower yield and selectivity were obtained. To improve the low turnover of the catalyst, we searched for more efficient ligands in this reaction. In the previous investigations, introduction of two halogen atoms at the 6,6′-positions of BINOLs was effective to improve not only selectivities but also turnover of the catalyst. It was assumed that Lewis acidity of the zirconium was increased by introducing the electron-withdrawing groups at the 6,6′-positions of BINOLs. As one of the strongest electron-withdrawing groups, we chose the trifluoromethyl group, and a novel BINOL derivative, (*R*)-6,6′-bis(trifluoromethyl)-1,1′-bi-2-naphthol ((*R*)-6,6′-$(CF_3)_2$BINOL, **4e**), was designed. Synthesis of 6,6′-$(CF_3)_2$BINOL (**4e**) was performed according to Scheme 5. 6,6′-Br_2BINOL (**3b**) was converted to its methoxymethyl (MOM) ether **(14)**, whose bromine groups at the 6,6′-positions were converted first to iodo groups (**15**) using I_2 and then to trifluoromethyl groups (**16**) using $CuCF_3$ in *N*-methylpyrrolidin-2-one (NMP).[30] After deprotection of the MOM groups, 6,6′-$(CF_3)_2$BINOL (**4e**) was isolated as white crystals.

Scheme 5. Preparation of 6,6′-CF_3BINOL (**4e**)[a]



[a] Conditions: (a) NaH, MOMCl/THF (98%). (b) BuLi, I_2/THF−Et_2O. (c) $CuCF_3$/NMP. (d) HCl/MeOH.

Table 4. Catalytic Enantioselective Mannich-Type Reactions Using Chiral Ligand **4e** (Eq 2)[a]

entry	imine; R^1	silyl enolate	catalyst/ mol %	product	yield/%	ee/%
1	Ph (**1a**)	**2a**	2	**3a**	quant	87
2	*p*-Cl−Ph (**1b**)	**2a**	2	**3b**	quant	83
3	Ph (**1a**)	**2b**	2	**3d**	quant	92
4	Ph (**1a**)	**2b**	0.5	**3d**	78	96
5	*p*-Cl−Ph (**1b**)	**2b**	2	**3e**	97	84
6	*i*-C_4H_9 (**1f**)[b]	**2b**	5	**3i**	65	83

[a] [Zr]/**4e**/additive = 1/2.2/1.2−78 °C, 16 h. [b]The aldimine prepared from isovaleraldehyde and 2-amino-*m*-cresol was used.

The reaction of **1a** with **2b** was performed using a zirconium catalyst prepared from $Zr(O^tBu)_4$, 6,6′-$(CF_3)_2$BINOL (**4e**), and NMI. It was revealed that in the presence of 2 mol % of the chiral zirconium catalyst, **1a** reacted with **2b** in dichloromethane at −78 °C to afford the corresponding Mannich-type adduct quantitatively in 92% ee. It was exciting to note that the reaction also proceeded smoothly in the presence of 0.5 mol % of the catalyst and the enantiomeric excess of the adduct was 96%. Other substrates were tested, and the results are summarized in Table 4. In the reactions of aldimines derived from aromatic aldehydes, the desired Mannich-type reactions proceeded cleanly to afford the corresponding adducts in high yields with high enantiomeric excesses in the presence of 2 mol % of the chiral zirconium catalyst. Also in the reaction of the aldimine derived from an aliphatic aldehyde, the yield and enantiomeric excess were improved even though 5 mol % of the catalyst was loaded.

Conclusion. A novel chiral zirconium catalyst has been developed and successfully used in enantioselective Mannich-

(28) (a) Colvin, E. W.; McGarry, D.; Nugent, M. J. *Tetrahedron* **1988**, *44*, 4157. A similar species is known to catalyze aldol reactions of silyl enol ethers with aldehydes. (b) Kobayashi, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 297. (c) Kobayashi, S.; Uchiro, H.; Fujishita, Y.; Shiina, I.; Mukaiyama, T. *J. Am. Chem. Soc.* **1991**, *113*, 4247. See also ref 27b.

(29) Preliminary experiments suggested that the reaction proceeded via acyclic transition states. When **1c** was treated with (*Z*)-1-ethyldimethylsiloxy-1-methoxy-1-propene in the presence of the zirconium catalyst (10 mol %) in dichloromethane at −78 °C, the desired anti adduct was predominantly obtained in good enantiomeric excess (syn/anti = 20/80, 78% ee (anti)). On the other hand, the same anti adduct was obtained preferentially (syn/anti = 16/84, 52% ee (anti) when (*E*)-1-ethyldimethylsiloxy-1-methoxy-1-propene was used under the same reaction conditions.

(30) (a) Carr, G. E.; Chambers, R. D.; Holmes, T. F. *J. Chem. Soc., Perkin Trans. 1*. **1988**, 921. See also: (b) Burton, D. J.; Wiemers, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 5014. (c) Wiemers, D. M.; Burton, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 832.

type reactions of silyl enol ethers with aldimines. The catalyst was prepared by mixing $Zr(O^tBu)_4$, a BINOL derivative, and NMI, and its symmetrical structure was revealed by NMR analyses. While it has been known that catalytic activation of aldimines is difficult compared to that of aldehydes, the use of the zirconium complex was shown to be the key to completing the catalytic cycle of the Mannich-type reactions. In addition, a novel BINOL derivative, (*R*)-$(CF_3)_2$BINOL, was prepared, and a high level of turnover of this Mannich-type reaction has been achieved. This new ligand will be applied to other BINOL-based chiral catalysts to enable versatile catalytic asymmetric synthesis.

Experimental Section

Typical Experimental Procedure for Asymmetric Reaction Using a Chiral Zirconium Catalyst. A typical experimental procedure is described for the reaction of aldimine **1c** with ketene silyl acetal **2a**. To $Zr(O^tBu)_4$ (0.04 mmol) in dichloromethane (0.25 mL) was added 6,6′-dibromo-1,1′-bi-2-naphthol (**4b**, 0.088 mmol) in dichloromethane (0.5 mL) and *N*-methylimidazole (0.048 mmol) in dichloromethane (0.25 mL) at room temperature. The mixture was stirred for 1 h at the same temperature and cooled to −45 °C. Dichloromethane solutions (0.75 mL) of **1c** (0.8 mmol) and **2a** (0.96 mmol) were successively added. The mixture was stirred for 10 h, and saturated $NaHCO_3$ was added to quench the reaction. The aqueous layer was extracted with dichloromethane, and the crude adduct was treated with THF−1 N HCl (10:1) at 0 °C for 30 min. Water was added, and the resulting mixture was neutralized. The aqueous layer was extracted with ethyl acetate, and the combined organic layer was dried. After filtration and evaporation under reduced pressure, the crude product was chromatographed on silica gel to give the desired adduct **3c** in a quantitative yield. The optical purity was determined by HPLC analysis using a chiral column (see below). Several products were fully characterized, and the optical purities were determined after methylation of phenolic OH group.

(*R*)-Methyl 2,2′-dimethyl-3-(2-hydroxyphenyl)amino-3-phenylpropionate (3a): $[\alpha]^{24}_D$ +1.4 (*c* 1.15, $CHCl_3$) (87% ee). Mp 112.5−114 °C. IR (KBr) 3401, 1709, 1611, 1514, 1453, 1391 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.21 (s, 3H), 1.24 (s, 3H), 3.68 (s, 3H), 4.57 (s, 1H), 6.36−6.76 (m, 4H), 7.21−7.28 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 19.9, 24.2, 47.3, 52.3, 64.3, 113.2, 114.1, 117.6, 120.8, 127.3, 127.9, 128.3, 135.6, 138.9, 144.0, 178.0. HPLC Daicel Chiralpak AD, hexane/^{i}PrOH = 9/1, flow rate 1.0 mL/min: t_R = 9.3 min (3*R*), t_R = 16.0 min (3*S*). Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.28; H, 7.20; N, 4.62. HRMS Calcd for $C_{18}H_{21}NO_3$ (M^+) 299.1522, found 299.1497.

Removal of the N-Protecting Group. 3a (0.4 mmol), a CH_3I−acetone (1:5) solution (5 mL), and K_2CO_3 (299 mg) were combined at room temperature. After the mixture was stirred for 8 h, NH_4Cl (aq) was added to quench the reaction. After the usual workup, methyl 3-[(2′-methoxyphenyl)amino]-2,2-dimethyl-3-phenylpropionate was obtained quantitatively. Oxidative cleavage using CAN was performed according to the literature method.[19] The absolute configuration assignment was made by comparison of the optical rotation of N-free amino ester with that in the literature.[20]

(*R*)-Methyl 3-amino-2,2-dimethyl-3-phenylpropionate: ^1H NMR ($CDCl_3$) δ 1.20 (s, 3H), 1.25 (s, 3H), 3.65 (s, 3H), 3.87 (br s, 1H), 7.23−7.35 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 20.6, 24.1, 52.0, 55.6, 127.3, 127.7, 127.9, 128.3, 176.9. (Hydrochloride) $[\alpha]_D^{26}$ +34.6 (*c* 0.17, 1 N HCl) (lit.[20] $[\alpha]_D^{23}$ −32.8 (*c* 1.1, 1 N HCl)).

(*R*)-6,6′-Dibromo-2,2′-di(methoxymethyl)oxy-1,1′-binaphthyl (14). To a suspension of sodium hydride (60%; 6.8 g, 170 mmol) in THF (100 mL) was added (*R*)-6,6′-dibromo-2,2′-dihydroxy-1,1′-binaphthyl (15.1 g, 34 mmol) in THF (200 mL). The resulting solution was stirred at room temperature for 30 min, and then chloromethyl methyl ether (6.5 mL, 85 mmol) in THF (10 mL) was added. The mixture was stirred for 2 h and was carefully quenched with MeOH and water. The aqueous layer was extracted with Et_2O, and the combined organic layer was washed with water, saturated aqueous $NaHCO_3$, and brine and then dried over Na_2SO_4. Pure **14** was obtained after recrystallization from CH_2Cl_2−hexane almost quantitatively (95%): Mp 135−136 °C. IR (KBr) 2961, 2899, 1589, 1498, 1244, 1050, 1062, 1024 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.16 (s, 6H), 4.98 (d, 2H, *J* = 6.8 Hz), 5.09 (d, 2H, *J* = 6.8 Hz), 6.98 (d, 2H, *J* = 9.0 Hz), 7.29 (dd, 2H, *J* = 2.2, 9.1 Hz), 7.60 (d, 2H, *J* = 9.0 Hz), 7.87 (d, 2H, *J* = 9.0 Hz), 8.04 (d, 2H, *J* = 1.8 Hz). ^{13}C NMR ($CDCl_3$) δ 55.9, 95.0, 118.0, 118.0, 120.7, 127.1, 128.7, 129.7, 129.9, 130.8, 132.4, 152.9. Anal. Calcd for $C_{24}H_{20}Br_2O_4$: C, 54.16; H, 3.79. found: C, 54.07; H, 3.88.

(*R*)-6,6′-Diiodo-2,2-di(methoxymethyl)oxy-1,1′-binaphthyl (15):[31] To a solution of (*R*)-6,6′-dibromo-2,2′-di(methoxymethyl)oxy-1,1′-binaphthyl (**14**, 8.0 g, 15 mmol) in THF (80 mL) was added a hexane solution of *n*-BuLi (1.6 M; 28 mL, 45 mmol) at −78 °C under argon. The reaction mixture was stirred for 30 min, and then a solution of iodine (11.4 g) in THF (10 mL) was added. The reaction mixture was allowed to warm to room temperature over 12 h and quenched with water. The resulting mixture was treated with aqueous 10% $NaHSO_3$ to destroy excess iodine. After being stirred for 1 h, the organic layer was washed with saturated aqueous $NaHCO_3$, water, and brine and dried over Na_2SO_4. After evaporation of the solvents, the residue was purified by silica gel column chromatography (hexane/AcOEt = 9/1) and recrystallization from CH_2Cl_2−hexane to afford **15** (7.4 g (79%)): Mp 123−124 °C. IR (KBr) 2954, 2897, 1577, 1493, 1241, 1149, 1022 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.17 (s, 6H), 4.99 (d, 2H, *J* = 6.8 Hz), 5.09 (d, 2H, *J* = 6.8 Hz), 6.84 (d, 2H, *J* = 8.8 Hz), 7.45 (dd, 2H, *J* = 1.8, 8.8 Hz), 7.58 (d, 2H, *J* = 9.0 Hz), 7.84 (d, 2H, *J* = 9.2 Hz), 8.27 (d, 2H, *J* = 1.8 Hz). ^{13}C NMR ($CDCl_3$) δ 56.0, 95.0, 117.8, 120.6, 127.1, 127.1, 128.6, 131.5, 131.5, 134.9, 136.6, 153.1. Anal. Calcd for $C_{24}H_{20}I_2O_4$: C, 46.03; H, 3.44. Found: C, 46.19; H, 3.45.

(*R*)-6,6′-Bis(trifluoromethyl)-2,2-dihydroxy-1,1′-binaphthyl (6-$(CF_3)_2$BINOL, 4e). A mixture of sodium trifluoroacetate (435 mg, 3.2 mmol), copper(I) iodide (609 mg, 3.2 mmol), **15** (250 mg, 0.4 mmol)), and *N*-methylpyrrolidin-2-one (8.0 mL) was stirred under argon at 160−180 °C for 8 h. After cooling, the reaction mixture was diluted with AcOEt and water and filtered on a Celite pad. The aqueous layer was extracted with AcOEt, and the combined organic layer was washed with water and brine and dried over Na_2SO_4. After evaporation of the solvents, the residue was purified by flash column chromatography on silica gel (hexane/CH_2Cl_2 = 1/1) and the product was dissolved in CH_2Cl_2 (1.0 mL). To this solution was added saturated HCl methanolic solution (1.0 mL) at 0 °C for 30 min. The resulting solution was diluted with water and extracted with CH_2Cl_2. The combined organic layer was washed with water and aqueous saturated $NaHCO_3$ and dried over Na_2SO_4. After evaporation of the solvents, the residue was purified by flash column chromatography on silica gel (hexane/Et_2O = 2/1) to afford **4e** (140 mg (83%)): $[\alpha]^{22}_D$ −36.1 (*c* 1.10, $CHCl_3$). Mp 111−112 °C. IR (KBr) 3465, 3038, 1633, 1311, 1198, 1152 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.14 (s, 2H), 7.19 (d, 2H, *J* = 8.8 Hz), 7.49 (dd, 2H, *J* = 1.8, 8.8 Hz), 7.50 (d, 2H, *J* = 9.0 Hz), 8.11 (d, 2H, *J* = 9.0 Hz), 8.22 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 110.5, 119.3, 123.4 (q, *J* = 3.1 Hz), 125.0, 126.1, 126.3 (q, *J* = 4.4 Hz), 126.5, 128.3, 132.7, 134.9, 154.5. ^{19}F NMR ($CDCl_3$) δ −142.4 (s, relative to CF_3COOH). HPLC, Daicel Chiralpak AD, hexane/^{i}PrOH = 9/1, flow rate 1.0 mL/min: t_R = 10.2 min (*R*) t_R = 25.9 min (*S*). HRMS, Calcd for $C_{22}H_{12}F_6O_2$ (M^+) 422.0741, found 422.0740.

NMR Experiments of the Chiral Zirconium Catalyst. To a C_6D_6 (0.5 mL) solution of 6-BrBINOL (0.24 mmol) and *N*-methylimidazole (0.24 mmol) was added a C_6D_6 (0.5 mL) solution of $Zr(O^tBu)_4$ (0.12 mmol) at room temperature. The resulting solution was stirred for 1 h at this temperature, then evaporated and dried under reduced pressure at 50 °C for 3 h. The sample for the NMR experiment was prepared using CD_2Cl_2 as a solvent. ^1H and ^{13}C NMR (CD_2Cl_2) data are shown in Supporting Information.

Silicon Crossover Experiment. To a CH_2Cl_2 solution (0.5 mL) of the chiral zirconium catalyst (0.033 mmol), which was prepared as described above, aldimine **1a** in CH_2Cl_2 (0.5 mL) and silyl enol ether **2c** and **2d** in CH_2Cl_2 (0.5 mL) were successively added at −45 °C. After 8 h, saturated aqueous $NaHCO_3$ was added to quench the reaction.

(31) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 and dried over Na_2SO_4. After concentration, the crude product was dissolved in CD_2Cl_2 and used for the NMR experiment.[32,33] tHE usual workup after treatment of 1 N HCl in THF gave the corresponding β-amino ester. **3d:** 27%, 73% ee; **12:** 28%, 64% ee.

Acknowledgment. This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan. M.U. thanks the JSPS fellowship for Japanese Junior Scientists.

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

(33) The NMR spectra are shown in Supporting Information.

Supporting Information Available: Experimental details and ^1H and ^{13}C NMR spectra of the catalyst and the crossover experiments and products (PDF). This material is available free of charge via the Internet at hppt://pubs.acs.org.

JA001642P