A New Chiral BLA Promoter for Asymmetric Aza Diels−Alder and Aldol-Type Reactions of Imines

Kazuaki Ishihara,† Mayumi Miyata,† Kouji Hattori,† Toshiji Tada,‡ and Hisashi Yamamoto*,†

Contribution from the School of Engineering, Nagoya University, Chikusa, Nagoya 464-01, Japan, and Fujisawa Pharmaceutical Company, Ltd., Kashima, Yodogawa-ku, Osaka 532, Japan

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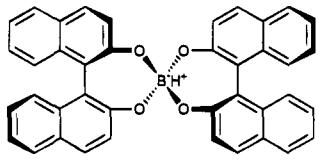
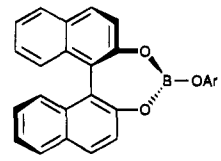
Abstract: A new type of chiral promoter for double asymmetric inductions of aza Diels−Alder and aldol-type reactions of imines is prepared from trialkyl borates ($B(OMe)_3$ or $B(OPh)_3$) and optically pure binaphthol; X-ray analysis of the boron complex demonstrates that it exists as a Brønsted acid-assisted chiral Lewis acid (BLA). The aldol-type reactions of a number of *N*-benzhydrylimines derived from aromatic aldehydes with the ketene silyl acetal derived from *tert*-butyl acetate mediated by the chiral BLA afford β-amino acid esters with high enantioselectivity. The solution conformations of the BLA·imine complexes have been studied using ^1H NMR analysis and difference NOE measurements. The absolute configurations of the adducts can be understood in terms of a rational model involving an intramolecular hydrogen binding interaction *via* a Brønsted acid.

Introduction

We recently described the first application of a Brønsted acid-assisted chiral Lewis acid (BLA) to the catalytic asymmetric Diels−Alder reaction between α-substituted α,β-enals and dienes.[1] As a consequence of our continuing interest in BLA, we have been exploring the potential utility of chiral Lewis acid−Brønsted acid combined systems for several Lewis acid-promoted reactions. The purpose of this article is to report the BLA **1** prepared from a 1:2 molar ratio mixture of a trialkyl



BLA ((*R*)-1)



(*R*)-2 (2a: Ar=Ph)

borate and optically pure binaphthol,[2] which is an attractive chiral promoter for asymmetric aza Diels−Alder[3] and aldol-type[4] reactions of imines. As another study relative to our present interest in BLA, we have recently described chiral boron complex **2** prepared from a 1:1 molar ratio of a triaryl borate and binaphthol as an efficient promoter for the above double asymmetric reactions of imines.[5,6]

Results and Discussion

The chiral BLA **1** was conveniently prepared *in situ* simply by mixing a 1:2 molar ratio of triphenyl borate and optically pure binaphthol in dichloromethane at ambient temperature for 1 h (method A). Also, a phenol-free solution of **1** was prepared by the reaction of $B(OMe)_3$ (1 equiv) with (*R*)-binaphthol (2 equiv) in dichloromethane at reflux with removal of methanol (4 Å molecular sieves in a Soxhlet thimble) for 2~3 h (method B);[1] the ^1H NMR spectrum of a colorless solution of **1** in CD_2Cl_2 after addition of D_2O showed no peak for methanol. A colorless crystal of (*S*)-**1** was obtained after two recrystallizations from a dichloromethane−hexane bilayer: $[\alpha]^{23}_D = -36.9°$ (*c* 0.27, THF); MS (FAB) *m/e* 580 (M^+). Anal. Calcd for $C_{40}H_{25}O_4B$: C, 82.77; H, 4.34. Found: C, 82.65; H, 4.78. Also, its molecular weight (MW 561.8), found cryoscopically in benzene, corresponds closely with the value (MW 580.45) calculated for a monomeric species.[7]

The complexes of **1** and chiral imines derived from an aldehyde and α-methylbenzylamine were bright yellow in color. Although attempted crystallizations of the (*R*)-**1**·(*S*)-benzylidene-α-methylbenzylamine (**1·3**) complex were unsuccessful, crystals of (*S*)-**1**·(*S*)-**3**·PhOH·CH_2Cl_2 for X-ray diffraction were obtained from a dichloromethane−hexane bilayer at 25 °C. This crystal is stable even at 25 °C and can be readily handled in air. X-ray analysis revealed that **1** was a monomeric ate complex structure

† Nagoya University.
‡ Fujisawa Pharmaceutical Co., Ltd.
* To whom correspondence should be addressed.
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(1) Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 1561.

(2) For references on the chiral borate reagent using binaphthol, see: (a) Kelly, T. R.; Whiting, A.; Chandrakumar, N. S. *J. Am. Chem. Soc.* **1986**, *108*, 3510. (b) Kaufmann, D.; Boese, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 545.

(3) For references on the diastereoselective aza Diels-Alder reaction of chiral imines, see: (a) Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768. (b) Midland, M. M.; McLoughlin, J. I. *Tetrahedron Lett.* **1988**, *29*, 4653. (c) Pfrengle, W.; Kunz, H. *J. Org. Chem.* **1989**, *54*, 4261. (d) Waldmann, H.; Braun, M.; Drager, M. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1468. (e) Midland, M. M.; Koops, R. W. *J. Org. Chem.* **1992**, *57*, 1158.

(4) For reviews on the diastereoselective aldol-type reaction of chiral imines, see: (a) Kleinnman, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: New York, 1991; Vol. 2, Chapter 4.1. (b) Hart, D. J.; Ha, D.-C. *Chem. Rev.* **1989**, *89*, 1447.

(5) For references on the diastereoselective aldol-type reaction of imines mediated by **2**, see: (a) Hattori, K.; Miyata, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 1151. (b) Hattori, K.; Yamamoto, H. *Synlett* **1993**, 239. (c) Hattori, K.; Yamamoto, H. *BioMed. Chem. Lett.* **1993**, *3*, 2337.

(6) For references on the diastereoselective aza Diels−Alder reaction of imines mediated by **2**, see: (a) Hattori, K.; Yamamoto, H. *J. Org. Chem.* **1992**, *57*, 3264. (b) Hattori, K.; Yamamoto, H. *Synlett* **1993**, 129. (c) Hattori, K.; Yamamoto, H. *Tetrahedron* **1993**, *49*, 1749.

(7) The solution of **1** in benzene, prepared *in situ* by a reaction of $B(OMe)_3$ and (*R*)-binaphthol in benzene at reflux with removal of methanol (4 Å molecular sieves in a Soxhlet thimble), was used directly for the molecular weight measurement by a cryoscopic method. The aldol-type reactions mediated by the (*R*)-**1** prepared *in* benzene and the (*R*)-**1** prepared by method B gave the same results.

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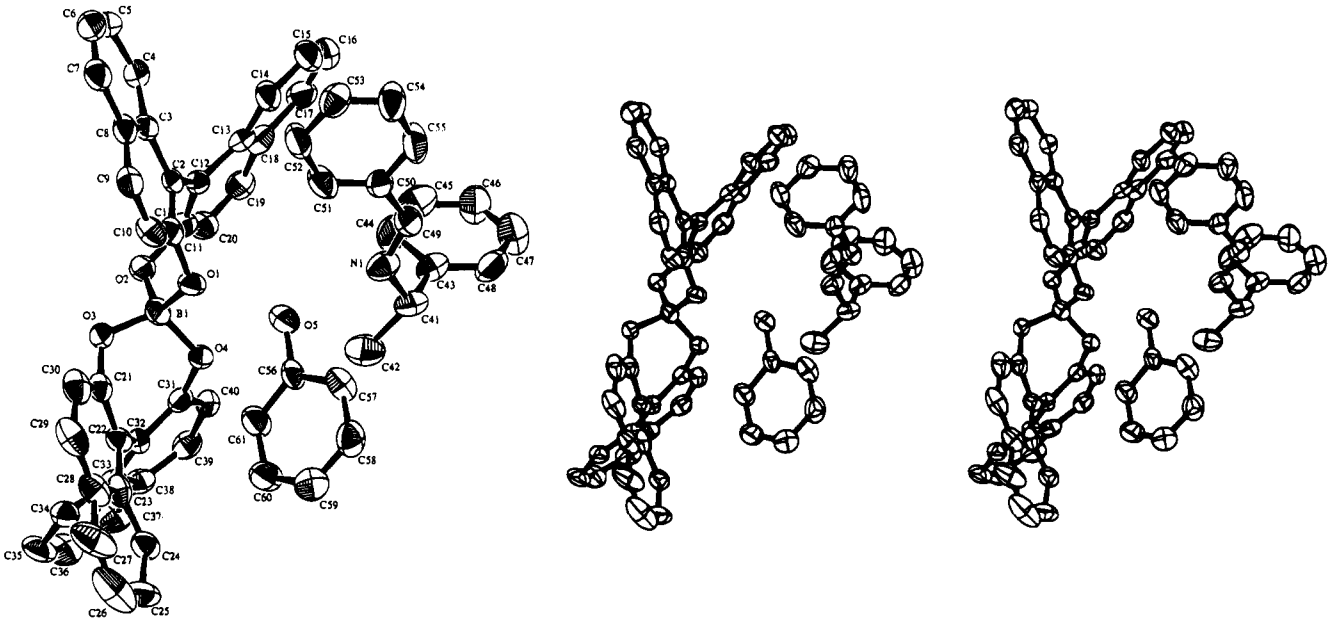
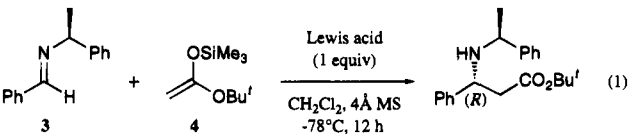


Figure 1. ORTEP diagram of (*S*)-**1**·(*S*)-**3**·PhOH·CH_2Cl_2 (CH_2Cl_2 is excluded from the figure).

and that this crystal was composed of a 1:1:1 molar ratio mixture of (*S*)-**1**, PhOH, and (*S*)-**3**, as shown in Figure 1. These three compounds in a crystal unit were jointed by two Brønsted acid–base coordinate bonds of a proton of (*S*)-**1** with an oxygen of PhOH and a proton of PhOH with a nitrogen of (*S*)-**3**.[8]

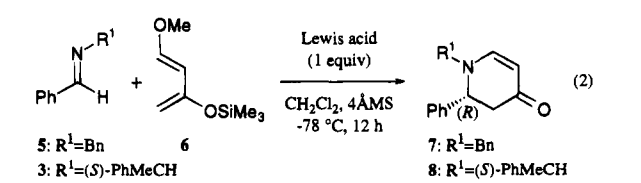
The use of **1** in the double stereodifferentiation[5] of aldol-type reactions of chiral imines led to striking success (eq 1).



(1)

Reaction of (*S*)-**3** with trimethylsilyl ketene acetal **4** derived from *tert*-butyl acetate in the presence of (*R*)-**1** (1 equiv; method A) at −78 °C for 12 h provided the corresponding aldol-type adduct (63% yield) with 94% de. The use of **1** prepared by method B gave similar results. Phenol included in the reaction mixture did not influence the reactivity or the diastereoselectivity. The aldol-type reaction using yellow crystals of (*R*)-**1**·(*S*)-**3**·PhOH[9] proceeded with unprecedented (>99.5:0.5) diastereoselectivity (method C). In general, **1** is a more efficient chiral Lewis acid promoter than **2a**.[5] Some examples are listed in Table 1.[10]

The aza Diels–Alder reaction[6] of benzylidenebenzylamine (**5**) with Danishefsky diene **6** in the presence of (*R*)-**1** (1 equiv) gave a 78% yield of (*R*)-*N*-benzyl-2,3-dihydro-2-phenyl-4-pyridone (**7**) with an ee of 86% (eq 2). Furthermore, when **3**



(2)

was employed as chiral imine in the reaction with **6** in the presence of (*R*)-**1** (1 equiv), a 64% yield of the aza Diels–Alder adduct **8** with a de of 99% was obtained after a reaction time of 12 h at −78 °C. These results clearly indicate double stereodifferentiation of the aza Diels–Alder reaction. In the procedure of method C, this cycloaddition proceeded with extraordinary (>99.5:0.5) diastereoselectivity. Examples are listed in Table 2.[10]

On the basis of the above results, we also developed the first method for the enantioselective synthesis of chiral β-amino acid esters from *achiral* imines and ketene silyl acetals using chiral BLA.[11]

As a first step, we studied the *N*-substituent-dependent enantioselectivity of the BLA **1**-promoted (1 equiv; method B) aldol-type reaction of imines (1 equiv) derived from benzaldehyde and several amines with **4** (2 equiv) in dichloromethane at −78 °C. The results of these experiments are summarized in Table 3. The enantioselectivity of the aldol-type reaction was dramatically increased by using instead sterically bulky *N*-substituents. The condensation of the imine **9** derived from benzhydrylamine occurred with high enantioselectivity (90% ee). Further, the best result (96% ee) was achieved by using a mixture of a 1:1 volumetric ratio of toluene and dichloromethane as solvents.

The enantioselective aldol-type reaction of a variety of *N*-benzhydrylimines with **4** by (*R*)-**1** under optimum conditions is summarized in Table 4. Excellent enantioselectivities (95% ee or better) were achieved in the reactions of aromatic aldehyde-derived imines. Unfortunately, the enantioselectivities were low in the cases of the condensations of aliphatic aldehyde-derived imines ($R^1 = C_3H_7$: 59% yield, 56% ee). The removal of the *N*-benzhydryl protecting group from β-aryl-β-amino acid esters was easily proceeded by catalytic hydrogenation (10% Pd/C, H_2, MeOH). In general, benzylamino compounds are debenzylated by hydrogenolysis over palladium on carbon in the order of *N*-substituent $Ph_2CH \gg PhCH_2 > PhMeCH > PhCHCH_2CO_2t\text{-}Bu$.[12]

Thus, we have defined *a new method for the synthesis of β-aryl-β-amino acids in enantiomerically pure form*, which are important fragments of spermine alkaloids.[13] For instance, (*S*)-

(8) According to X-ray analysis, it was clear that (*S*)-**1**, PhOH, and (*S*)-**3** in the crystal unit were joined by two hydrogen bonds. Nevertheless, exact positions of the hydrogen bridges could not be determined.

(9) This crystal was prepared by addition of (*S*)-**3** to a solution of (*R*)-**1** (method A) and subsequent crystallization from a dichloromethane–hexane bilayer. The component ratio was determined by ^1H NMR analysis.

(10) Binaphthol can be recovered in >95% yield.

(11) For the first example of the enantioselective synthesis of chiral β-amino acid esters from achiral imines and esters, see: Corey, E. J.; Decicco, C. P.; Newbold, R. C. *Tetrahedron Lett.* **1991**, *32*, 5287.

Table 1. Double Asymmetric Induction of the Aldol-Type Reaction of (*S*)-**3** with **4** (Eq 1)

Lewis acid	preparation method[a]	yield[b] (%)	de[c] (%)
(*R*)-**1**	A	63	94 (*R*)
(*S*)-**1**	A	18	66 (*R*)
(*R*)-**1**	B	63	95 (*R*)
(*S*)-**1**	B	54	74 (*R*)
(*R*)-**1**	C	65	>99 (*R*)
(*S*)-**1**	C	64	62 (*R*)
(*R*)-**2a**		59	92 (*R*)[d]
(*S*)-**2a**		56	74 (*R*)[d]
$B(OPh)_3$		67	78 (*R*)

[a] See text. [b] Isolated yield by column chromatography. [c] Determined by HPLC analysis. Absolute configurations of β-positions of aldol adducts are indicated. [d] See ref 5a.

Table 2. Asymmetric Aza Diels–Alder Reaction (Eq 2)

imine	Lewis acid	preparation method[a]	yield[b] (%)	de[c] (%)
5	(*R*)-**1**	B	78	86 (*R*)[d]
	(*R*)-**2**		75	82 (*R*)[d,e]
3	(*R*)-**1**	B	64	99 (*R*)
	(*S*)-**1**	B	49	83 (*R*)
	(*R*)-**1**	C	64	>99 (*R*)
	(*S*)-**1**	C	49	84 (*R*)
	(*R*)-**2a**		61	98 (*R*)[e]
	(*S*)-**2a**		30	86 (*R*)[e]
	$B(OPh)_3$		57	92 (*R*)[e]

[a] See text. [b] Isolated yield by column chromatography. [c] Determined by HPLC analysis. Absolute configurations of 2-positions of Diels-Alder adducts are indicated. [d] Enantiomeric excess value. [e] See ref 6c.

Table 3. *N*-Substituent Effect (R^1) on the Aldol-Type Reaction of Imines ((*E*)-PhCH=NR^1) with **4** by (*R*)-**1**

N-substituent (R^1)	Ph	Bn	1-naphthylmethyl	Ph_2CH	(*S*)-PhMeCH
ee or de (%)	<5	29 (*R*)	46	90 (*R*)	95 (*R*)

Table 4. Enantioselective Aldol-Type Reaction of *N*-Benzhydrylimines ((*E*)-R^2CH=NCHPh_2) with **4** by (*R*)-**1**[a]

entry	R^2	yield (%)[b]	ee (%)[c]
1	C_6H_5	58	96 (*R*)
2	*p*-MeC_6H_4	35	97
3	*p*-ClC_6H_4	45	98
4	*p*-$AcOC_6H_4$	52	98
5	2,4-$Cl_2C_6H_3$	49	95
6	2-naphthyl	43	96

[a] See typical procedure (Experimental Section). [b] Isolated yield by column chromatography. [c] Determined by HPLC analysis. Absolute configurations of β-positions of aldol adducts are indicated.

β-phenyl-β-alanine derivatives (entry 1) are optically active units of (*S*)-dihydroperiphylline,[14] (*S*)-celacinnine,[15] and (*S*)-verbascenine.[16]

Finally, we studied the solution conformations of the uncomplexed (*S*)-**3** and the complex (*R*)-**1**·(*S*)-**3** using ^{1}H NMR analysis and difference NOE measurements to understand the stereochemical outcome of the above reactions. Irradiation of H^a in the complex in CD_2Cl_2 at −60 °C resulted in a weak NOE (5%) to CH^c_3 and no NOE to H^b (Figure 2).[17] At this time, the imine proton H^a was strongly deshielded by the phenyl ring of the *N*-substituent and the naphthyl ring of (*R*)-**1**, while H^b and H^c were weakly shielded by the naphthyl ring of (*R*)-**1**: chemical shifts for H^a, H^b, and H^c for the uncomplexed (*S*)-**3** were δ 8.39, 4.50, and 1.52, respectively, while chemical shifts for H^a, H^b, and H^c for the uncomplexed (*S*)-**3** were δ 12.65, 3.50, and 1.22, respectively. These results indicate that the phenyl group of the *N*-substituent is close to H^a.[17] Thus, the absolute configuration of the adducts can be understood in terms of a rational model **10** involving an intramolecular hydrogen binding interaction *via* a Brønsted acid (Figure 2). Although there is no evidence that the hydrogen bonded structure exists, this hypothetical interaction would cause the Lewis acidity of boron and the π-basicity of the naphthoxy moiety to increase and the transition state assembly would be stabilized.[1] In the complex **10**, the 2-hydroxynaphthyl group fixed by the intramolecular hydrogen bond would effectively block the *si* face of the (*E*)-imine **3**[18] complexed with (*R*)-**1** and the nucleophile would approach the *re* face. On the other hand, although the ^{1}H NMR assignment of complex (*R*)-**1**·**9** was not clear, the absolute enantioselectivity in the aldol-type reaction of *N*-benzhydrylimine can be understood by a similar mechanistic model.

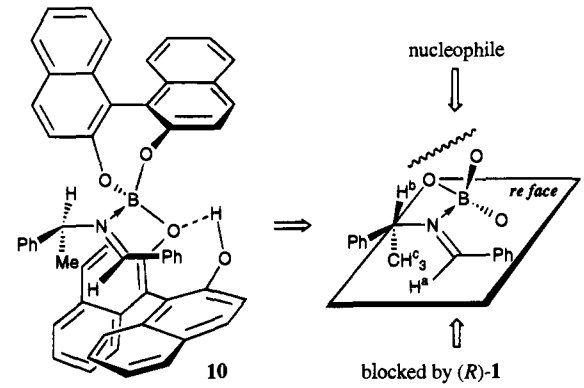


Figure 2. Matched pair complex (*R*)-**1**·(*S*)-**3**.

Conclusion

A new concept for the design of an enantioselective Lewis acid has been supported by experiments which demonstrate that it is a very practical and promising methodology for enantioselective synthesis of optically pure amino compounds. We believe that the experimental results outlined above will stimulate further exciting advances for the BLA system and offer essential information on the direction of future design of catalytic asymmetric reactions of imines by chiral Lewis acids.

Experimental Section

General Procedure. Infrared (IR) spectra were recorded on a Shimazu FT-IR 8100 spectrometer. ^{1}H NMR spectra were measured on a Varian Gemini-200 or Gemini-300 spectrometer. High-performance liquid chromatography (HPLC) was done with a Shimazu 6A or 9A instrument using 4.6 mm × 25 cm Daicel CHIRALCEL OD, OD-H, OJ, AD, and AS. Optical rotations were measured on a JASCO DIP-140 digital polarimeter. Melting points were determined using a Yanaco MP-J3. All experiments were carried out under an atmosphere of dry argon. For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF^{254}, 0.25 mm)

(12) The order of the reactivity in the hydrogenolysis was determined by control experiments using *N*-benzhydrylheptylamine, *N*-benzylheptylamine, *N*-(α-phenylethyl)heptylamine, and *tert*-butyl 3-(α-phenylethyl)-amino-3-phenylpropionate as starting substrates.

(13) For a review, see: Wasserman, H. H.; Wu, J. S. *Heterocycles* **1982**, *17*, 581.

(14) Kaseda, T.; Kikuchi, T.; Kibayashi, C. *Tetrahedron Lett.* **1989**, *30*, 4539 and references therein.

(15) Seguineau, C.; Richomme, P.; Pusset, J. *Helv. Chim. Acta* **1992**, *75*, 2283 and references therein.

(16) Fiedler, W. J.; Hesse, M. *Helv. Chim. Acta* **1993**, *76*, 1511 and references therein.

(17) In NOE experiments of uncomplexed **3** in CD_2Cl_2 at −78 °C, irradiation of H^a resulted in a strong NOE (25%) for H^b and a weak NOE (4%) for CH^c_3. These results indicate that H^b is close to H^a.

(18) The preferred (*E*) geometry of **3** could clearly be demonstrated by ^{1}H NMR analysis and NOE experiments on the complex.

were used. The products were purified by preparative column chromatography on silica gel (E. Merck 9385). Microanalyses were accomplished at the School of Agriculture, Nagoya University.

In experiments requiring dry solvents, ether and tetrahydrofuran (THF) were purchased from Aldrich Chemical Co. as "anhydrous" and stored over 4 Å molecular sieves. Benzene, hexane, and toluene were dried over sodium metal. Methylene chloride was freshly distilled from calcium hydride. Trimethyl borate was distilled from sodium metal under argon. Other simple chemicals were purchased and used as such.

Preparation of Imines. A mixture of amine (10 mmol), aldehyde (10 mmol), and $MgSO_4$ (3 g) in benzene (10 mL) was stirred at room temperature for several hours. The reaction mixture was filtered, and the fitrate was concentrated. The residue was distilled under reduced pressure, or the solid was washed with hexane.

(*S*)-(+)-*N*-Benzylidene-α-methylbenzylamine (3):[19] bp 135 °C (5 Torr); $[\alpha]^{24}_D$ +73.3° (*c* 1.6, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.60 (d, *J* = 6.6 Hz, 3H, CH_3), 4.54 (q, *J* = 6.6 Hz, 1H, NCH), 7.20−7.50 (m, 8H, Ph), 7.70−7.85 (m, 2H, Ph), 8.38 (s, 1H, N=CH); IR (neat) 1646, 1493, 1451, 1379, 754, 695 cm^{-1}.

***N*-Benzylidenebenzylamine (5)**:[20] bp 126 °C (5 Torr); ^1H NMR ($CDCl_3$) δ 4.83 (d, *J* = 1.3 Hz, 2H, NCH_2), 7.30−7.45 (m, 8H, Ph), 7.79 (dd, *J* = 2.3, 6.0 Hz, 2H, Ph), 8.40 (s, 1H, N=CH); IR (liquid film) 1646, 1497, 1453, 1026, 752, 695 cm^{-1}.

***N*-Benzylideneaniline**:[21] ^1H NMR ($CDCl_3$) δ 7.20−7.50 (m, 8H, Ph), 7.90−7.95 (m, 2H, Ph), 8.47 (s, 1H, N=CH); IR (liquid film) 1628, 1592, 1578, 1451, 1368, 1194, 1173, 1073, 976, 907, 758, 695 cm^{-1}.

***N*-Benzylidene-1-naphthylmethylamine**: mp 51−52 °C; ^1H NMR ($CDCl_3$) δ 5.26 (d, *J* = 1.4 Hz, 2H, NCH_2), 7.40−7.60 (m, 7H, Ar), 7.80−8.00 (m, 4H, Ar), 8.10−8.15 (m, 1H, Ar), 8.38 (d, *J* = 1.4 Hz, 1H, N=CH); IR (liquid film) 1646, 1597, 1580, 1510, 1451, 1308, 793, 756, 693 cm^{-1}. Anal. Calcd for $C_{18}H_{15}N$: C, 88.13; H, 6.16; N, 5.71. Found: C, 88.09; H, 6.10; N, 5.71.

***N*-Benzylidenebenzhydrylamine (9)**:[22,24] mp 90−92 °C; ^1H NMR ($CDCl_3$) δ 5.60 (s, 1H, Ph_2CH), 7.20−7.50 (m, 13H, Ar), 7.80−7.90 (m, 2H, Ar), 8.43 (s, 1H, N=CH); IR (liquid film) 1638, 1599, 1493, 1381, 1022, 756, 742, 696 cm^{-1}.

***N*-(4-Methylbenzylidene)benzhydrylamine**:[23] mp 73−74 °C; ^1H NMR ($CDCl_3$) δ 2.37 (s, 3H, CH_3), 5.58 (s, 1H, Ph_2CH), 7.20−7.50 (3, 12H, Ar), 8.38 (s, 1H, N=CH); IR (liquid film) 1640, 1491, 1453, 812, 698 cm^{-1}.

***N*-(4-Chlorobenzylidene)benzhydrylamine**:[24] mp 77−78 °C; ^1H NMR ($CDCl_3$) δ 5.60 (s, 1H, Ph_2CH), 7.20−7.50 (m, 12H, Ar), 7.80 (s, 1H, Ar), 8.39 (s, 1H, N=CH); IR (liquid film) 1644, 1595, 1491, 1453, 1086, 820, 745, 700 cm^{-1}.

***N*-(4-Acetoxybenzylidene)benzhydrylamine**: mp 127−128 °C; ^1H NMR ($CDCl_3$) δ 2.31 (s, 3H, CH_3O), 5.70 (s, 1H, Ph_2CH), 7.10−7.40 (m, 12H, Ar), 7.87 (d, *J* = 8.5 Hz, 2H, Ar), 8.40 (s, 1H, N=CH); IR (KBr) 1757, 1647, 1491, 1121, 1188, 1154 cm^{-1}. Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.15; H, 5.67; N, 4.28.

***N*-(2,4-Dichlorobenzylidene)benzhydrylamine**: mp 101−102 °C; ^1H NMR ($CDCl_3$) δ 5.65 (s, 1H, Ph_2CH), 7.20−7.40 (m, 12H, Ar), 8.21 (d, *J* = 8.4 Hz, 1H, Ar), 8.82 (s, 1H, N=CH); IR (liquid film) 1634, 1586, 1495, 1470, 1379, 1100, 831, 758, 698 cm^{-1}. Anal. Calcd for $C_{20}H_{15}C_{12}N$: C, 70.60; H, 4.44; N, 4.12. Found: C, 70.59; H, 4.40; N, 4.18.

***N*-2-Naphthylidenebenzhydrylamine**:[24] mp 151−152 °C; ^1H NMR ($CDCl_3$) δ 5.68 (s, 1H, Ph_2CH), 7.20−7.55 (m, 12H, Ar), 7.80−7.95 (m, 3H, Ar), 8.09 (s, 1H, Ar), 8.18 (dd, *J* = 1.6, 8.5 Hz, 1H, Ar), 8.58 (s, 1H, N=CH); IR (liquid film) 1636, 1491, 1451, 828, 756, 698 cm^{-1}.

Preparation of 1-*tert*-Butoxy-1-((trimethylsilyl)oxy)ethylene (4).[25] A solution of lithium diisopropylamide (LDA) (24 mmol) in THF (40 mL) was cooled to −78 °C, and *tert*-butyl acetate (2.7 mL, 20 mmol) was added dropwise over a few minutes. The solution was stirred for 1 h at that temperature, and then chlorotrimethylsilane (TMSCl) (2.8 mL, 22 mmol) was added. This mixture was allowed to warm to room temperature over several hours. The white solid, which was generated from the resulting suspension, was removed by a Celite filter, and the filtrate was concentrated *in vacuo*. The residue was distilled under reduced pressure: ^1H NMR ($CDCl_3$) δ 0.23 (s, 9H, $Si(CH_3)_3$), 1.35 (s, 9H, *t*-Bu), 3.42 (d, *J* = 1.8 Hz, 1H, C*H*H), 3.44 (d, *J* = 1.8 Hz, 1H, CH*H*).

Preparation of Crystals of (*S*)-1. A dry 50 mL round-bottom flask fitted with a stirbar and a 10 mL pressure-equalized addition funnel (containing a cotton plug and ca. 4 g of 4 Å molecular sieves (pellets) and functioning as a Soxhlet extractor) surmounted by a reflux condenser was charged with (*S*)-binaphthol (600 mg, 2.01 mmol), trimethyl borate (1.19 mL, 0.89 M solution in dichloromethane, 1.06 mmol), and dichloromethane (25 mL). An argon atmosphere was secured, and the solution was brought to reflux (bath temperature 50~60 °C). After 2.5 h, the reaction mixture was cooled to 25 °C and the colorless solution was concentrated *in vacuo*. A colorless crystal of (*S*)-**1** was obtained after two recrystallizations from a dichloromethane (5 mL)−hexane (5 mL) bilayer of the crude residue.

Typical Procedures A, B, and C for the Generation of Chiral BLA 1. Method A. To a suspension of powdered 4 Å molecular sieves (1 g) in dichloromethane (10 mL) were added (*R*)-binaphthol (100 mg, 0.35 mmol) and $B(OPh)_3$ (101 mg, 0.35 mmol) at room temperature under argon atmosphere, and the mixture was stirred for 1 h. Molecular sieves (4 Å) were added as a drying agent.

Method B. A dry 25 mL round-bottom flask fitted with a stirbar and a 10 mL pressure-equalized addition funnel (containing a cotton plug and ca. 4 g of 4 Å molecular sieves (pellets) and functioning as a Soxhlet extractor) surmounted by a reflux condenser was charged with (*R*)-binaphthol (200 mg, 0.70 mmol), trimethyl borate (3.5 mL, 0.1 M solution in dichloromethane, 0.35 mmol), and dichloromethane (3 mL). An argon atmosphere was secured, and the solution was brought to reflux (bath temperature 50~60 °C). After 2~3 h, the reaction mixture was cooled to 25 °C and the addition funnel and condenser were quickly removed and replaced with a septum.

Method C. To the mixture of (*R*)-binaphthol (100 mg, 0.35 mmol) and $B(OPh)_3$ (101 mg, 0.35 mmol) was added dichloromethane (10 mL) at room temperature under an argon atmosphere. After the solution was stirred for 1 h, (*S*)-**3** (73 mg, 0.35 mmol) was added at room temperature and the color of the mixture changed to yellow. Yellow crystals of (*R*)-**1**·(*S*)-**3**·PhOH were produced by adding hexane (10 mL) to the yellow solution of (*R*)-**1** (crystallization from a dichloromethane−hexane bilayer).

Diastereoselective Aza Diels−Alder and Aldol-Type Reactions of Chiral Imine 3 Promoted by Chiral BLA 1 (Tables 1 and 2). These reactions were carried out using **1** in place of **2** according to the procedure in the literature.[5a,6c]

Typical Procedure for Enantioselective Aldol-Type Reaction of *N*-Benzhydrylimines ((*E*)-R^2CH=NCHPh$_2$) with 4 by (*R*)-1 (Table 4). To the white precipitate of (*R*)-**1** in dichloromethane (3 mL), which was prepared by method B, were added 2 mL of dichloromethane, 5 mL of toluene, and the corresponding *N*-benzhydrylimine (0.35 mmol) at 0 °C, and the yellow suspension was stirred at 0 °C for 10 min. After the suspension was cooled to −78 °C, **4** (2 equiv) was added dropwise. After being stirred for 20 h, the solution was washed with water and saturated $NaHCO_3$ and then dried over $MgSO_4$. Evaporation of the solvent and purification by column chromatography on silica gel gave the corresponding product.

***tert*-Butyl 3-(Benzhydrylamino)-3-phenylpropionate** (R^2 = Ph, entry 1): ^1H NMR ($CDCl_3$) δ 1.39 (s, 9H, *t*-Bu), 2.53 (dd, *J* = 5.6, 14.6 Hz, 1H, C*H*H), 2.66 (dd, *J* = 8.6, 14.6 Hz, 1H, CH*H*), 3.97 (dd, *J* = 5.6, 8.6 Hz, 1H, PhC*H*), 4.58 (s, 1H, Ph_2CH), 7.10−7.40 (m, 15H, 3Ph); IR (liquid film) 1721, 1493, 1455, 1370, 1152, 702 cm^{-1}; HPLC (column OD-H, hexane:*i*-PrOH = 100:1, 0.5 mL/min) major isomer t_R = 10.1 min, minor isomer t_R = 12.1 min. Anal. Calcd for $C_{26}H_{29}NO_2$: C, 80.59; H, 7.54; N, 3.61. Found: C, 80.51; H, 7.76; N, 3.52.

***tert*-Butyl 3-(Benzhydrylamino)-3-*p*-tolylpropionate** (R^2 = *p*-MeC_6H_4, entry 2): ^1H NMR ($CDCl_3$) δ 1.40 (s, 9H, *t*-Bu), 2.35 (s,

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3H, *p*-C*H*$_3$C$_6$H$_4$), 2.50 (dd, J = 5.8 Hz, 14.6 Hz, 1H, C*H*H), 2.61 (dd, J = 8.8, 14.6 Hz, 1H, CH*H*), 3.92 (dd, J = 5.8, 8.8 Hz, 1H, *p*-MeC$_6$H$_4$C*H*), 4.56 (s, 1H, Ph$_2$C*H*), 7.10−7.40 (m, 14H, Ar); IR (liquid film) 1725, 1493, 1455, 1368, 1256, 1152, 758, 702 cm^{-1}; HPLC (column OD-H, hexane:*i*-PrOH = 200:1, 0.5 mL/min) major isomer t_R = 26.6 min, minor isomer t_R = 25.6 min. Anal. Calcd for $C_{27}H_{31}NO_2$: C, 80.76; H, 7.78; N, 3.49. Found: C, 80.71; H, 8.03; N, 3.42.

***tert*-Butyl 3-(Benzhydrylamino)-3-(*p*-chlorophenyl)propionate** (R^2 = *p*-ClC$_6$H$_4$, entry 3): ^{1}H NMR (CDCl$_3$) δ 1.38 (s, 9H, *t*-Bu), 2.49 (dd, J = 5.8, 14.8 Hz, 1H, C*H*H), 2.61 (dd, J = 8.6, 14.8 Hz, 1H, CH*H*), 3.93 (dd, J = 5.8, 8.6 Hz, 1H, *p*-ClC$_6$H$_4$C*H*), 4.52 (s, 1H, Ph$_2$C*H*), 7.10−7.40 (m, 14H, Ar); IR (liquid film) 1725, 1493, 1455, 1368, 1150, 702 cm^{-1}; HPLC (column OD-H, hexane:*i*-PrOH = 100:1, 0.5 mL/min) major isomer t_R = 11.0 min, minor isomer t_R = 9.8 min. Anal. Calcd for $C_{26}H_{28}ClNO_2$: C, 74.01; H, 6.69; N, 3.32. Found: C, 74.00; H, 6.87; N, 3.09.

***tert*-Butyl 3-(Benzhydrylamino)-3-(*p*-acetoxyphenyl)propionate** (R^2 = *p*-AcOC$_6$H$_4$, entry 4): ^{1}H NMR (CDCl$_3$) δ 1.38 (s, 9H, *t*-Bu), 2.30 (s, 3H, Ac), 2.50 (dd, J = 5.2, 14.6 Hz, 1H, C*H*H), 2.61 (dd, J = 8.8, 14.6 Hz, 1H, CH*H*), 3.96 (dd, J = 5.2, 8.8 Hz, 1H, *p*-AcOCH$_4$C*H*), 4.56 (s, 1H, Ph$_2$C*H*), 7.10−7.40 (m, 14H, Ar); IR (liquid film) 2982, 2930, 1765, 1721, 1705, 1601, 1370, 1198, 1156, 1015, 912, 739, 704 cm^{-1}; HPLC (column OD-H, hexane:*i*-PrOH = 10:1, 0.5 mL/min) major isomer t_R = 23.5 min, minor isomer t_R = 17.2 min. Anal. Calcd for $C_{28}H_{31}NO_4$: C, 75.48; H, 7.01; N, 3.14. Found: C, 75.26; H, 6.93; N, 3.21.

***tert*-Butyl 3(Benzhydrylamino)-3-(2,4-dichlorophenyl)propionate** (R^2 = 2,4-Cl$_2$C$_6$H$_3$, entry 5): mp 77−79 °C; ^{1}H NMR (CDCl$_3$) δ 1.39 (s, 9H, *t*-Bu), 2.54−2.58 (m, 2H, CH$_2$), 4.40 (dd, J = 9.0, 12.0 Hz, 1H, 2,4-Cl$_2$C$_6$H$_3$C*H*), 4.53 (s, 1H, Ph$_2$C*H*), 7.10−7.40 (m, 13H, Ar); IR (liquid film) 1725, 1588, 1493, 1471, 1368, 1256, 1154, 1102, 758, 700 cm^{-1}; HPLC (column AD, hexane:*i*-PrOH = 200:1, 0.5 mL/min) major isomer t_R = 14.2 min, minor isomer t_R = 23.5 min. Anal. Calcd for $C_{26}H_{27}Cl_2NO_2$: C, 68.42; H, 5.96; N, 3.07. Found: C, 68.50; H, 6.03; N, 2.95.

***tert*-Butyl 3-(Benzhydrylamino)-3-2-naphthylpropionate** (R^2 = 2-naphthyl, entry 6): ^{1}H NMR (CDCl$_3$) δ 1.38 (s, 9H, *t*-Bu), 2.60 (dd, J = 5.6, 14.6 Hz, 1H, C*H*H), 2.72 (dd, J = 8.8, 14.6 Hz, 2H, CH*H*), 4.14 (dd, J = 5.6, 8.8 Hz, 1H, NpC*H*), 4.58 (s, 1H, Ph$_2$C*H*), 7.10−7.90 (m, 17H, Ar); IR (liquid film) 1725, 1493, 1455, 1368, 1150, 767, 702 cm^{-1}; HPLC (column AD, hexane:*i*-PrOH = 100:1, 1.0 mL/min) major isomer t_R = 7.8 min, minor isomer t_R = 14.1 min. Anal. Calcd for $C_{30}H_{31}NO_2$: C, 82.35; H, 7.14; N, 3.20. Found: C, 82.36; H, 7.45; N, 2.89.

Hydrogenation of (*R*)-(+)-*tert*-Butyl 3-(Benzhydrylamino)-3-phenylpropionate.[26] The corresponding β-amino acid ester (146.5 mg, 0.38 mmol) and a catalytic amount of palladium on carbon (10 mol %, 30 mg) were mixed in dry MeOH (10 mL) and stirred at room temperature under atmospheric pressure of H_2 for 14 h. The catalyst was removed by filtration through a Celite pad, and the filtrate was concentrated. Purification by column chromatography on silica gel gave β-phenyl-β-alanine *tert*-butyl ester (69.8 mg) in 83% yield: $[\alpha]^{23}_D$ +22.4° (*c* 1.05, CHCl$_3$); ^{1}H NMR (CDCl$_3$) δ 1.42 (s, 9H, *t*-Bu), 1.82 (br, 2H, NH$_2$), 2.59 (d, J = 6.9 Hz, 2H, CH$_2$CO), 4.38 (t, J = 6.9 Hz, PhC*H*), 7.2−7.4 (m, 5H, Ph); IR (liquid film) 2979, 2926, 1725, 1455, 1368, 1150, 700 cm^{-1}.

NMR Studies. 500 MHz ^{1}H NMR spectra were obtained on a Varian VXR 500 spectrometer. Chemical shifts of ^{1}H NMR are expressed in parts per million downfield relative to internal dichloromethane-d_2 (δ = 5.28). Dichloromethane-d_2 was freshly distilled from CaH$_2$ prior to use.

General Procedure for the Preparation of the NMR Sample of the Uncomplexed Imine (*S*)-3. (*S*)-**3** (0.05 mmol) and 2.0 mL of dichloromethane-d_2 were cooled to −78 °C and then placed in the probe of the precooled NMR (−78 °C), and ^{1}H NMR spectra were recorded and 1D difference NOE experiments were performed.

(*S*)-Benzylidene-α-methylbenzylamine (3): ^{1}H NMR (CD$_2$Cl$_2$, −78 °C) δ 1.52 (d, J = 7.0 Hz, 3H, CH$_3$), 4.50 (q, J = 7.0 Hz, 1H, CH$_3$C*H*), 7.20−7.44 (m, 8H, Ar), 7.75 (d, J = 4.5 Hz, 2H, Ar), 8.39 (s, 1H, N=CH).

General Procedure for the Preparation of the NMR Sample of Complex (*R*)-1·(*S*)-3. To the white precipitate of (*R*)-**1** (0.25 mmol) in dichloromethane-d_2 (3 mL), which was prepared by method B, were added dichloromethane-d_2 (2 mL) and the corresponding imine (0.23 mmol) at 25 °C, and the yellow suspension was stirred at 25 °C for 10 min. A 0.6 mL sample of the yellow complex solution was added to an oven-dried 5 mm NMR tube under Ar atmosphere by syringe. Then the sample tube was placed in the probe of the precooled NMR (−60 °C), and ^{1}H NMR spectra were recorded and 1D difference NOE experiments were performed.

Complex (*R*)-1·(*S*)-3: ^{1}H NMR (CD$_2$Cl$_2$, −60 °C) δ 1.22 (d, J = 1.0 Hz, 3H, CH$_3$), 3.50 (br, 1H, C*H*CH$_3$), 6.50−8.40 (m, 24H (for **1**) + 10H (for **3**)), 12.65 (br, 1H, CH=N).

X-ray Crystallographic Data: empirical formula $C_{62}H_{46}BCl_2NO_5$ (966.77); space group $P2_1$, a = 9.830(2) Å, b = 19.701(2) Å, c = 13.075(1) Å, β = 97.73(1)°, V = 2508.9(5) Å^3; Z = 2; d_{calcd} = 1.280 g/cm^3; λ(Cu Kα) = 1.541 78 Å. A total of 3348 ($F_o > 3\sigma(F_o)$) reflections were used for structure factor calculation. The final refinement converged to R = 0.080 and R_w = 0.067. Data for crystallographic analysis were measured on an RIGAKU AFC-5R diffractometer using Cu Kα radiation and ω−2θ scans. Structures were solved by direct methods with SAPI-91 and refined by least squares using the full matrix. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Analytical Research Laboratories, Fujisawa Pharmaceutical Co., Ltd.

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Supplementary Material Available: ORTEP diagrams and a listing of complete crystallographic data for (*S*)-**1**·(*S*)-**3**·PhOH·CH$_2$Cl$_2$ (7 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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