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Asymmetric Aza-Diels-Alder Reaction: Enantio- and Diastereoselective Reaction of Imine Mediated by Chiral Lewis Acid

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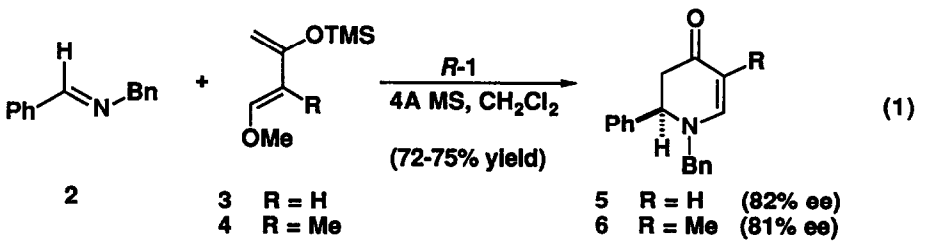
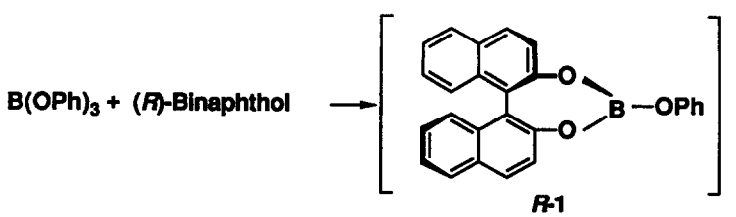
Abstract: An efficient asymmetric aza-Diels-Alder reaction using chiral boron mediator is developed. The key to its success is the use of the chiral boron complex prepared *in situ* from (*R*)- or (*S*)- binaphthol and $B(OPh)_3$. The enantiomeric reaction of prochiral imine affords products of up to 90% ee. The double asymmetric induction of chiral imine using α-benzylamine as a chiral auxiliary is achieved with almost complete diastereoselectivity for both aliphatic and aromatic aldimines. This method is applied to the efficient synthesis anabasine and coniine of piperidine alkaloides.

Impressive progress has recently been made on asymmetric reactions which attained the synthesis of various optically active compounds with high optical purity. The development of chiral Lewis acid catalyst is one of the most challenging and formidable fields in organic synthesis.[1] The catalytic asymmetric reaction of *imine*, however, which has a wide variety of possibilities for the synthesis of β-lactam and many biologically active products,[2] has never been developed to a useful level. In this paper, we describe an asymmetric aza-Diels-Alder reaction of imine (eq. 1) catalyzed by an *in situ* generated chiral boron complex of type **1**.[3] The method is successful with both aromatic and aliphatic aldimines and affords products of high enantiomeric purity.



2 **3** R = H, **4** R = Me → **5** R = H (82% ee), **6** R = Me (81% ee) (1)

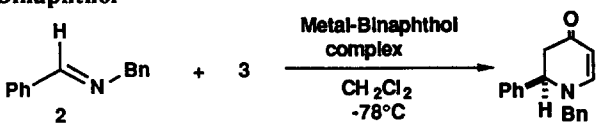


R-1

The chiral boron complex ***R*-1** was prepared *in situ* simply by mixing a 1:1 molar ratio of optically active binaphthol and triphenyl borate in CH_2Cl_2 at ambient temperature for 1 h. The aza-Diels-Alder reaction of aldimine **2** with Danishefsky diene **3**[4] was promoted by this catalyst solution in the presence of molecular sieves 4A[5] at -78°C for several hours. After the usual workup, purification by column chromatography furnished the cyclo-adduct **5** in 75% yield. Product enantiomer ratio was determined to be 82% ee by HPLC analysis using a chiral column, and absolute configuration was ascertained to be *R* after converting to the known 2(*R*)-phenylpiperidine.[6]

The unique feature of the binaphthol-triphenylborate as chiral Lewis acid was clarified after extensive study. As a ligand we focused our study on a binaphthol, which has already been established as a highly potent chiral ligand and both enantiomers of which have been utilized in a variety of asymmetric reactions.[7] Some results are shown in Table 1. The boron complex of binaphthol was found to be an effective catalyst to activate imine, and attained a moderate level of induction (entries 1-4). As the source of boron reagent, triaryl borate has high ability in both reactivity and enantioselectivity (entries 1, 5-7) and the use of a structurally more bulky aryloxy reagent slightly improved the optical yield (entries 7-9).

Table 1. Asymmetric Aza-Diels-Alder Reaction Mediated by Various Metal Complex of Binaphthol[a]



entry	Mediator Metal	yield (%)[b]	ee (%)[c]
1	BH_3	62	72
2	$TiCl_2(O^iPr)_2$	20	17
3	Me_3Al	15	12
4[d]	Me_2Zn	0	-
5	$PhB(OH)_2$	15	30
6	$B(OMe)_3$	42	72
7	$B(OPh)_3$	75	82
8	B(O-2-Tolyl)$_3$	76	84
9	B(O-3,5-Xylyl)$_3$	75	86

[a] All reactions were carried out in the same manner as described for the reaction **2** and **3** mediated by ***R*-1** except using mediator metal and (*R*)-binaphthol. [b] Yield of product was determined after isolation by column chromatography. [c] The % ee was determined by HPLC using a chiral column. [d] Binaphthol-Zn complex was prepared at -78°C.

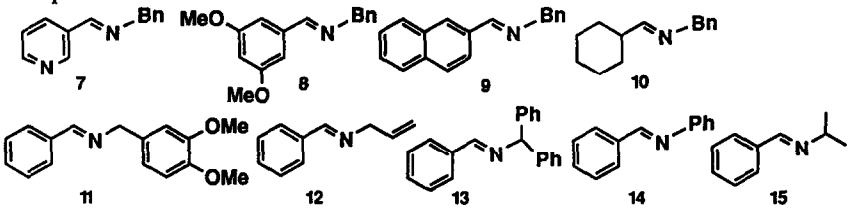
The present method is applicable to a variety of aldimines to provide the Diels-Alder adduct in high enantiomeric purity (Table 2). Since both (*R*)- and (*S*)-binaphthol are commercially available in optically pure

form, the present asymmetric process allows the synthesis of both enantiomers of dihydropyridone derivatives (entries 1,2). The choice of solvent is crucial for high optical yields, as the reactions of entries 3-5 were found to be much more efficient in methylene chloride than in other solvents: in tetrahydrofuran (22% ee), in propionitrile (22% ee), and in toluene (74% ee). Generally, benzyl type substituted imine is preferable to other substitutions (entries 12-15).

Table 2. Asymmetric Aza-Diels-Alder Reaction with Different Imines[a]

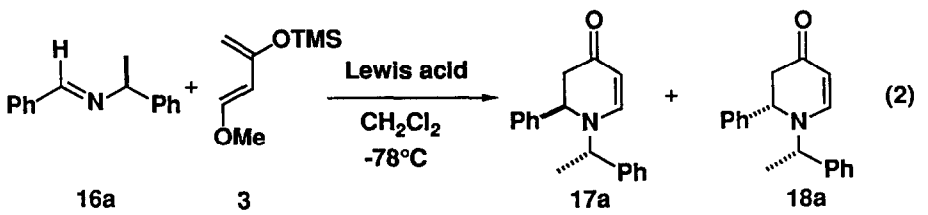
entry	imine[b]	diene	yield (%)[c]	ee (%)[d]
1	**2**	**3**	75	82
2[e]			72	82
3[f]			22	22
4[g]			38	22
5[h]			15	74
6		**4**	72	81
7	**7**	**3**	71	90
8	**8**	**3**	89	74
9	**9**	**3**	83	84
10	**10**	**3**	45	76
11		**4**	35	78
12	**11**	**3**	73	85
13	**12**	**3**	97	70
14	**13**	**3**	0	-
15	**14**	**3**	77	24
16	**15**	**3**	13	4

[a] Unless otherwise specified, reactions were carried out in dichloromethane using 1 eq. of *R*-**1** and 1.2 eq. of the diene for 5 h. [b] Structures **7-15** are given below. [c] Yield was determined after isolation by column chromatography. [d] The % ee was determined by HPLC using a chiral culumn. [e] (*S*)-Binaphthol was used. [f] Tetrahydrofuran was used as a solvent. [g] Propionitrile was used as a solvent. [h] Toluene was used as a solvent.



Next, we turned to an investigation of diastereofacial selectivity with the imine containing a chiral auxiliary in aza-Diels-Alder reaction.[8] In a preliminary work, Grieco[8a] demonstrated aza-Diels-Alder reaction of chiral iminium salts using α-methylbenzylamine as an auxiliary, and the resulting stereoselectivity was moderate (ratio of 4:1). Recently, several inactivated imines having chiral auxiliaries have been developed in aza-Diels-Alder reaction with Danishefsky diene. For example, Waldman[8b] utilized amino acids for chiral auxiliary and Kunz[8c] or Midland[8d] effectively utilized other auxiliaries including sugar or α-aldehyde for this

type of reaction. These auxiliaries have thus been demonstrated to be quite useful for the diastereoselective condensation, however, there have been certain practical *difficulties in preparing and/or removing* their auxiliaries. The possibility of a simple α-methylbenzylamine auxiliary is appealing since this functional group is *easy to prepare and to remove* in aza-Diels-Alder reaction. As indicated in Table 3 which summarizes some of our results; a series of Lewis acid mediators were utilized and good to excellent diastereoselectivities were obtained using boron, zinc, or titanium reagent. The assignment of the absolute configuration of **17a** was determined by X-ray structural analysis. As shown in Table 4, we immediately found that excellent diastereoselectivity was realized with a reagent derived from triphenyl borate and biphenol of related derivatives. The use of too more structurally bulky aryloxy reagents reduced asymmetric induction.



16a 3 17a 18a (2)

Table 3. Aza-Diels-Alder Reaction Mediated by Lewis Acids[a]

Lewis Acid (equiv)	Yield (%)[b]	**17a:18a**[c]
BF_3•OEt_2 (1.0)	63	85:15
BF_3•OEt_2 (1.5)	41	94:6
$B(OPh)_3$ (1.5)	61	96:4
$EtAlCl_2$ (1.5)	16	77:23
$MeAl(OPh)_2$ (1.5)	23	90:10
$ZnCl_2$ (1.5)	75	96:4
$TiCl_4$ (1.0)	7	87:13
$TiCl_2(O^iPr)_2$ (1.5)	56	95:5

[a] Reaction was carried out in CH_2Cl_2 at -78°C for 8 h. [b] Isolated yield by column chromatography. [c] Determined by HPLC.

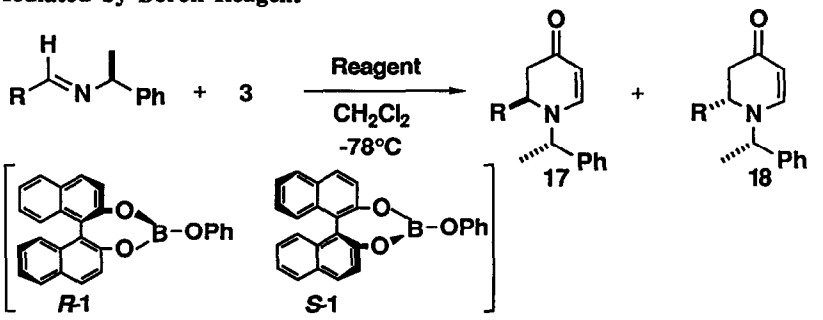
Table 4. Aza-Diels-Alder Reaction Mediated by Various Boron Complexes[a]

Boron complex		Yield (%)	**17a:18a**
$B(OPh)_3$	- Catechol	53	94:6
BH_3	- Biphenol	38	90:10
$B(OMe)_3$	- Biphenol	38	87:13
$B(OPh)_3$	- Biphenol	55	98:2
B(O-2-Tolyl)$_3$	- Biphenol	62	98:2
B(O-*2,3,5*-Mesityl)$_3$	- Biphenol	50	92:8
B(O-*2,4,6*-Mesityl)$_3$	- Biphenol	0	-
$B(OPh)_3$	- Terphenol[b]	69	98:2

[a] Reaction was carried out in CH_2Cl_2 at -78°C for several hours. For typical procedure see experimental section. [b] *2,2':6',2"*-trihydroxyterphenyl.

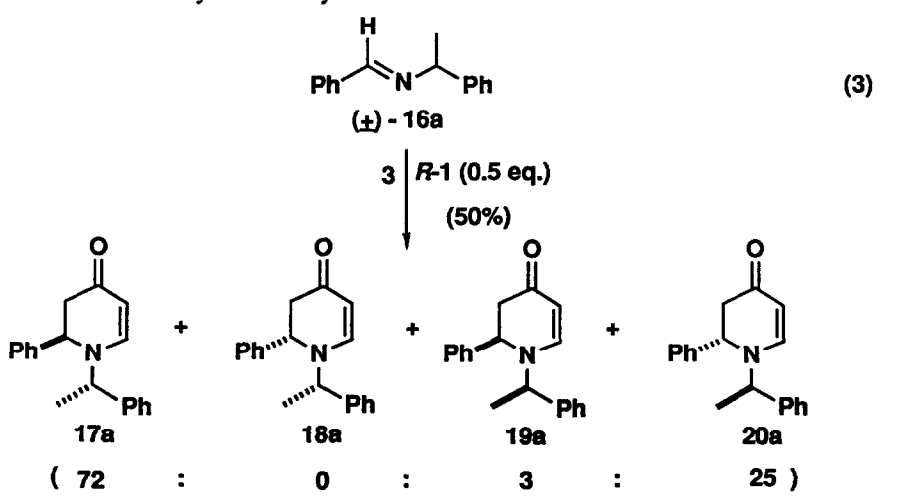
As a logical extension of this work, we examined the combined use of chiral auxiliary and chiral mediator, ***R*-1** or ***S*-1**, for this reaction: application of concept of double asymmetric induction. The effectiveness of this method is apparent from the results summarized in Table 5. Under optimum conditions with better matching pair, almost complete diastereoselectivities were obtained for a variety of aldimines. Furthermore, the reactions were faster with the matching pair than with the mismatching pair. This phenomenon was actually confirmed that the chiral catalyst discriminated to some extent between the racemic imines of **(+)-16a** and **(-)-16a** to accomplish the effective kinetic resolution (eq 3).

Table 5. Double Asymmetric Induction of Aza-Diels-Alder Reaction Mediated by Boron Reagent[a]



Imine: R	Boron Mediator (1equiv)	Yield (%)[b]	17:18[c]
16a: Phenyl	$B(OPh)_3$	57	96:4
	R-1	61	99:1
	S-1	30	93:7
16b: 3-Pyridyl	$B(OPh)_3$	53	89:11
	R-1	63	99:1
	S-1	35	86:14
16c: *c*-Hexyl	$B(OPh)_3$	40	90:10
	R-1	31	99:1
	S-1	20	89:11
16d: *n*-Propyl	$B(OPh)_3$	59	91:9
	R-1	49	95:5
	S-1	31	91:9

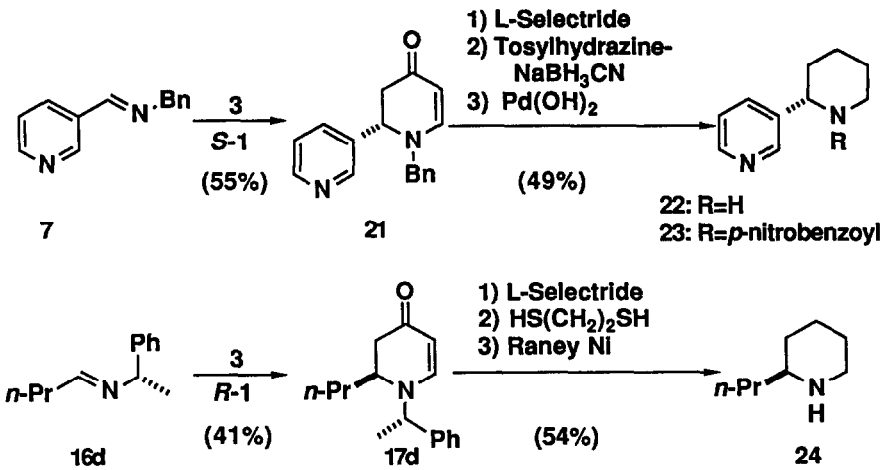
[a] Reaction was carried out at -78°C for several hours. For typical experimental procedure see for experimental section. [b] Isolated yield by column chromatography. [c] Determined by HPLC analysis.



(3)

Lastly, the practical advantage of this method is illustrated by the synthesis of piperidine alkaloids (-)-anabasine[9] and (+)-coniine[10] (Scheme 1). A mixture of 3-pyridyl aldimine **7** and diene **3** was exposed at -78°C with the chiral boron mediator derived from (*S*)-binaphthol to obtain dihydropyridone **21**. After recrystallization from ether, **21** was essentially optically pure, mp 92°C (55 % yield from **7**). Reduction of adduct **21** with L-selectride at -78°C afforded quantitatively the conjugate reduction product, which was converted to the corresponding anabasine derivative by tosylhydrazone formation followed by sodium cyanoborohydride reduction. Removal of benzyl group with palladium catalyst gave (-)-anabasine **22** (49% overall yield from **21**). The absolute configuration was confirmed by transformation to *p*-nitrobenzoate **23**. In contrast, the pure diastereomer **17d** was obtained in 41% yield after isolation by column chromatography. The compound **17d** was reduced with L-selectride in the same manner. After thioketalization, treatment with Raney nickel resulted in simultaneous desulfurization and the removal of benzyl group to give (+)-coniine **24** (54% overall yield from **17d**).

Scheme 1



Thus the present method provides high enantio- and diastereoselective reaction for a variety of aldimines. Both enantiomers of binaphthol as a chiral ligand are commercially available and easily recovered upon workup, making the method especially attractive for large-scale synthesis. These results clearly indicate the practical value of this methodology.

Experimental section

General. Infrared (IR) spectra were recorded on a Hitachi 260-10 or Shimadzu FTIR-8100 spectrometer. ^{1}H-NMR spectra were measured on a Varian Gemini-200 spectrometer. High-performance liquid chromatography (HPLC) analysis was carried out on a Shimadzu LC-6A instrument with a SPD-6A UV detector. Optical rotations were measured on a JASCO DIP-140 digital polarimeter. All experiments were performed under an atmosphere of dry argon unless otherwise specified. The products were purified by preparative column chromatography on silica gel E. Merck 9385. Elemental analysis, mass spectra, and X-ray analysis were performed at the analysis laboratories of Fujisawa Pharmaceutical Co..

Methylene chloride was stored over 4A MS. (*R*)- and (*S*)-1,1'-Bi-2-naphthol were purchased from Wako Pure Chemical Industries LTD. Triphenyl borate was purchased from Tokyo Kasei Co., LTD. Benzylideneaniline (**14**) was purchased from Aldrich. Other simple chemicals were purchased and used as such.

Preparation of aldimines. Aldimines were obtained in the usual manner by treatment of aldehyde and amine with $MgSO_4$ in benzene at room temperature for 1 h.[2] The crude aldimines were purified by distillation except **8**, **9**, **11**, **13**, and **16b** were directly subjected for the next step without purification.

Benzylidenebenzylamine (2): Bp 126°C (5 mmHg); ^{1}H NMR ($CDCl_3$) δ 4.82 (2H, s), 7.18-7.49 (8H, m), 7.73-7.82 (2H, m), 8.39 (1H, s); IR (neat) 1645 cm^{-1}.

3-Pyridylmethylidenebenzylamine (7): Bp 154°C (5.5 mmHg); ^{1}H NMR ($CDCl_3$) δ 4.86 (2H, s), 7.2-7.5 (5H, m), 8.18 (1H, d, J = 8.0 Hz), 8.44 (1H, s), 8.66 (1H, m), 8.90 (1H, d, J = 2.0 Hz); IR (neat) 1650 cm^{-1}.

3,5-Dimethoxybenzylidenebenzylamine (8): ^{1}H NMR ($CDCl_3$) δ 3.83 (6H, s), 4.83 (2H, s), 6.51 (1H, m), 6.95 (2H, d, J = 2.2 Hz), 7.2-7.4 (5H, m), 8.31 (1H, s); IR (neat) 1660 cm^{-1}.

2-Naphthylmethylidenebenzylamine (9): ^{1}H NMR ($CDCl_3$) δ 4.87 (2H, s), 7.2-7.7 (7H, m), 7.8-8.1 (5H, m), 8.54 (1H, s); IR (neat) 1650 cm^{-1}.

***c*-Hexylmethylidenebenzylamine (10):** Bp 127°C (4 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.1–1.4 (5H, m), 1.5-1.9 (5H, m), 2.10-2.30 (1H, m), 4.52 (2H, s),7.14-7.85 (5H, m), 7.63 (1H, d, J = 6.5 Hz); IR (neat) 1675 cm^{-1}.

Benzylidene-3,4-dimethoxybenzylamine (11): ^{1}H NMR ($CDCl_3$) δ 3.88 (3H, s), 3.90 (3H, s), 4.78 (2H, s), 6.85-6.95 (2H, m), 7.35-7.50 (4H, m), 7.75-7.85 (2H, m), 8.40 (1H, s); IR (neat) 1660 cm^{-1}.

Benzylideneallylamine (12): Bp 86°C (7 mmHg); ^{1}H NMR ($CDCl_3$) δ 4.26 (2H, m), 5.1-5.4 (2H, m), 5.9-6.3 (1H, m), 7.3-7.5 (3H, m), 7.7-7.9 (2H, m), 8.30 (1H, s); IR (neat) 1645 cm^{-1}.

Benzylidenebenzhydrylamine (13): ^{1}H NMR ($CDCl_3$) δ 5.60 (1H, s), 7.2-7.6 (13H, m), 7.8-7.9 (2H, m), 8.43 (1H, s); IR (neat) 1645 cm^{-1}.

Benzylidene-*iso*-propylamine (15): Bp 71°C (10 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.23 (6H, s), 3.50 (1H, s), 7.2-7.9 (5H, m), 8.29 (1H, s); IR (neat) 1650 cm^{-1}.

(*S*)-Benzylidene-α-methylbenzylamine (16a): Bp 135°C (5 mmHg); $[\alpha]_D^{24}$ +73.3° (*c* 1.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.60 (3H, d, J = 6.6Hz), 4.54 (1H, q, J = 6.6Hz), 7.2-7.5 (8H, m), 7.7-7.85 (2H, m), 8.38 (1H, s); IR (neat) 1640 cm^{-1}.

(*S*)-3-Pyridylmethylidene-α-methylbenzylamine (16b): $[\alpha]_D^{24}$ +65.6° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) d 1.61 (3H, d, J = 6.6 Hz), 4.87 (1H, q, J = 6.6 Hz), 7.32 (6H, m), 8.19 (1H, m), 8.42 (1H, m), 8.65 (1H, m), 8.89 (1H, br.s); IR (neat) 1647 cm^{-1}.

(*S*)-*c*-Hexylmethylidene-α-methylbenzylamine (16c): Bp 130°C (4 mmHg); $[\alpha]_D^{24}$ -55.1° (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.2–1.5 (4H, m), 1.48 (3H, d, J = 6.8 Hz), 1.6-2.0 (6H, m), 2.1-2.4 (1H, m), 4.25 (1H, q, J = 6.8 Hz), 7.2-7.4 (5H, m), 7.59 (1H, d, J = 5.6 Hz); IR (neat) 1680 cm^{-1}

(*S*)-*n*-Butylidene-α-methylbenzylamine (16d): Bp 101°C (5 mmHg); $[\alpha]_D^{24}$ -79.6° (*c* 2.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, J = 7.4 Hz), 1.48 (3H, t, J = 6.8 Hz), 1.50 (2H, m), 2.24 (2H, m), 4.25 (1H, q, J = 6.8 Hz), 7.1-7.4 (5H, m), 7.73 (1H, t, J = 6.2 Hz); IR (neat) 1668 cm^{-1}.

General method for Aza-Diels-Alder reaction with chiral boron reagent 1. To a suspension of powdered 4A molecular sieves (1.0 g) in CH_2Cl_2 (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. After stirring for 1 h, the mixture was cooled to 0°C, then a solution of imine **2** (68 mg, 0.35 mmol) in CH_2Cl_2 (1 mL) was added. After stirring for 10 min at the same temperature, the mixture was cooled to -78°C, and a solution of diene **3** (0.084 mL, 0.42 mmol) in CH_2Cl_2 (1 mL) was added dropwise. After stirring for 5 h, the solution was washed with water and saturated $NaHCO_3$, and then dried over $MgSO_4$. Evaporation of solvent and purification by column chromatography on silica gel gave dihydropyridone **5** in 75% yield. Reactions with other aldimines were also carried out in the similar manner.

N-Benzyl-2,3-dihydro-2-phenyl-4-pyridone (5): $[\alpha]_D^{24}$ -4.7° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.66 (1H, dd, *J* = 19, 8.0 Hz), 2.81 (1H, dd, *J* = 19, 7.2 Hz), 4.08, 4.33 (2H, ABq, *J* = 15 Hz), 4.48 (1H, dd, *J* = 8.0, 7.2 Hz), 5.07 (1H, d, *J* = 7.6 Hz), 7.10 (1H, d, *J* = 7.6 Hz), 7.17-7.40 (10H, m); IR (neat) 1640 cm^{-1}; LCMS for $C_{18}H_{17}N_1O_1$, 264 (M+1); Anal. Calcd: C, 82.10, H, 6.51, N, 5.32. Found; C, 82.13, H, 6.51, N, 5.28; HPLC (DAICEL CHIRALCEL OD, 25cm x 0.46cm I.D., rate 1.0 ml/min, Hex/IPA = 8/2) 18.6 min (91%) 20.9 min (9%);

N-Benzyl-2,3-dihydro-5-methyl-2-phenyl-4-pyridone (6): $[\alpha]_D^{24}$ +25.6° (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.73 (3H, s), 2.60 (1H, dd, *J* = 19, 9.0 Hz), 2.76 (1H, dd, *J* = 19, 7.0 Hz), 4.02, 4.26 (2H, ABq, *J* = 15 Hz), 4.42 (1H, dd, *J* = 9.0, 7.0 Hz), 7.0-7.4 (11H, m); IR (neat) 1640 cm^{-1}; LCMS for $C_{19}H_{19}N_1O_1$, 278 (M+1); Anal. Calcd: C, 82.28, H, 6.90, N, 5.05. Found; C, 81.80, H, 7.33, N, 4.89; HPLC (DAICEL CHIRALCEL OD, 25cm x 0.46cm I.D., rate 1.0 ml/min, Hex/IPA = 9/1) 17.1 min (90.5 %) 20.3 min (9.5 %).

N-Benzyl-2,3-dihydro-2-(3-pyridyl)-4-pyridone (21): $[\alpha]_D^{24}$ -39.4° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.61 (1H, dd, *J* = 15, 7.0 Hz), 2.90 (1H, dd, *J* = 15, 7.4 Hz), 4.12, 4.43 (2H, ABq, *J* = 15 Hz), 4.54 (1H, t, *J* = 7.0 Hz), 5.12 (1H, d, *J* = 7.6 Hz), 7.1-7.5 (7H, m), 7.65 (1H, d, *J* = 8 Hz), 8.45 (1H, d, *J* = 2 Hz), 8.58 (1H, d, *J* = 5 Hz); IR (nujol) 1640 cm^{-1}; LCMS for $C_{17}H_{16}N_2O_1$, 265 (M+1); Anal. Calcd: C, 77.25, H, 6.10, N, 10.60. Found; C, 76.74, H, 6.07, N, 10.39; HPLC (DAICEL CHIRALCEL OD, 25cm x 0.46cm I.D., rate 1.0 ml/min, Hex/IPA = 6/4) 14.3 min (95 %) 21.3 min (5 %).

N-Benzyl-2,3-dihydro-2-(3,5-dimethoxyphenyl)-4-pyridone: $[\alpha]_D^{24}$ - 28.9° (*c* 3.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.68 (1H, dd, *J* = 18, 8.0 Hz), 2.81 (1H, dd, *J* = 18, 7.2 Hz), 3.76 (6H, s), 4.15, 4.37 (2H, ABq, *J* = 15 Hz), 4.43 (1H, t, *J* = 7.5 Hz), 5.08 (1H, d, *J* = 7.6 Hz), 7.1-7.4 (9H, m); IR (neat) 1650 cm^{-1}; HRMS, calcd for $C_{20}H_{22}N_1O_3$, 324.1600. found, 324.1606; HPLC (DAICEL CHIRALCEL OD, 25cm x 0.46cm I.D., rate 1.0 ml/min, Hex/IPA = 8/2) 21.9 min (13 %) 28.2 min (87 %).

N-Benzyl-2,3-dihydro-2-(2-naphthyl)-4-pyridone: $[\alpha]_D^{24}$ -38.2° (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.81 (1H, dd, *J* = 16, 6.8 Hz), 2.89 (1H, dd, *J* = 16, 6.0 Hz), 4.14, 4.39 (2H, ABq, *J* = 14 Hz), 4.68 (1H, t, *J* = 6.5 Hz), 5.14 (1H, d, *J* = 7.8 Hz), 7.1-7.7 (10H, m), 7.8-8.0 (3H, m); IR (neat) 1640 cm^{-1}; LCMS for $C_{22}H_{19}N_1O_1$, 314 (M+1); Anal. Calcd: C, 84.32, H, 6.11, N, 4.47. Found; C, 84.29, H, 6.07, N, 4.45; HPLC (DAICEL CHIRALCEL AD, 25cm x 0.46cm I.D., rate 1.0 ml/min, Hex/IPA = 9/1) 22.7 min (92 %) 28.1 min (8 %).

N-Benzyl-2,3-dihydro-2-(*c*-hexyl)-4-pyridone: $[\alpha]_D^{24}$ +206.8° (*c* 1.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.9-1.8 (5H, m), 1.5-2.1 (6H, m), 2.12 (1H, dd, *J* = 14, 7.6 Hz), 2.38 (1H, dd, *J* = 14, 4.0 Hz),

3.20 (1H, m), 4.40 (2H, ABq, J = 14 Hz), 4.87 (1H, d, J = 7.4 Hz), 7.09 (1H, d, J = 7.4 Hz), 7.17-7.43 (5H, m); IR (neat) 1640 cm^{-1}; HRMS calcd for $C_{18}H_{24}N_1O_1$, 270.1858. found, 270.1852; HPLC (DAICEL CHIRALCEL AD, 25cm x 0.46cm I.D., rate 1.0 ml/min, Hex/IPA = 9/1) 16.9 min (12 %) 17.6 min (88 %).

N-Benzyl-2,3-dihydro-2-(*c*-hexyl)-5-methyl-4-pyridone: $[\alpha]_D^{24}$ +224.5° (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.80-1.30 (4H, m), 1.5- 2.0 (7H, m), 1.65 (3H, s), 2.39 (1H, dd, J = 17, 3.6 Hz), 2.59 (1H, dd, J = 17, 7.4 Hz), 3.14 (1H, m), 4.30, 4.41 (2H, ABq, J = 15 Hz), 6.97 (1H, s), 7.2-7.4 (5H, m); IR (neat) 1645 cm^{-1}; LCMS for $C_{19}H_{25}N_1O_1$, 284 (M+1); HPLC (DAICEL CHIRALCEL AD, 25cm x 0.46cm I.D., rate 0.6 ml/min, Hex/IPA = 19/1) 23.6 min (11 %) 25.6 min (89 %).

2,3-Dihydro-N-(3,4-dimethoxybenzyl)-2-phenyl-4-pyridone: $[\alpha]_D^{24}$ +51.2° (*c* 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.65 (1H, dd, J = 18, 8.0 Hz), 2.81 (1H, dd, J = 18, 8.0 Hz), 3.80 (3H, s), 3.86 (3H, s), 4.06, 4.29 (2H, ABq, J = 15 Hz), 4.48 (1H, t, J = 8.0 Hz), 5.06 (1H, d, J = 8.0 Hz), 6.81 (1H, d, J = 8.0 Hz), 7.2-7.6 (8H, m); IR (neat) 1650 cm^{-1}; HRMS calcd for $C_{20}H_{22}N_1O_3$, 324.1600. found 324.1605; HPLC (DAICEL CHIRALCEL OD, 25cm x 0.46cm I.D., rate 0.6 ml/min, Hex/IPA = 6/4) 29.9 min (92.5 %) 32.9 min (7.5 %).

N-Allyl-2,3-dihydro-2-phenyl-4-pyridone: $[\alpha]_D^{24}$ -187.7° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.6- 3.0 (2H, m), 3.5-3.9 (2H, m), 4.63 (1H, t, J = 7.2 Hz), 5.0-5.3 (3H, m), 5.6-5.9 (1H, m), 7.2-7.5 (6H, m); IR (neat) 1637 cm^{-1}; LCMS for $C_{14}H_{15}N_1O_1$, 214 (M+1); HPLC (DAICEL CHIRALCEL OD, 25cm x 0.46cm I.D., rate 1.0 ml/min, Hex/IPA = 8/2) 11.35 min (85 %) 13.66 min (15 %).

2,3-Dihydro-N-phenyl-2-phenyl-4-pyridone: $[\alpha]_D^{24}$ -93.7° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.85 (1H, dd, J = 3.6, 14 Hz), 3.29 (1H, dd, J = 7.2, 14 Hz), 5.2-5.4 (1H, m), 5.27 (1H, d, J = 6.8 Hz), 6.9-7.4 (9H, m), 7.65 (1H, d, J = 6.8 Hz); IR (neat) 1650 cm^{-1}; LCMS for $C_{17}H_{15}N_1O_1$, 250 (M+1); HPLC (DAICEL CHIRALCEL OD, 25cm x 0.46cm I.D., rate 1.0 ml/min, Hex/IPA = 8/2) 24.1 min (62 %) 29.3 min (38 %).

2,3-Dihydro-N-*iso*-propyl-2-phenyl-4-pyridone: $[\alpha]_D^{24}$ +5.6° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.10 (3H, d, J = 6.6 Hz), 1.22 (3H, d, J = 6.6 Hz), 2.5-2.9 (2H, m), 3.32 (1H, m), 4.61 (1H, t, J = 7.0 Hz), 5.06 (1H, d, J = 7.6Hz), 7.2-7.6 (6H, m); IR (neat) 1640 cm^{-1}; HPLC (DAICEL CHIRALCEL OD, 25cm x 0.46cm I.D., rate 1.5 ml/min, Hex/IPA = 8/2) 5.57 min (52 %) 7.55 min (48 %).

General method for Aza-Diels-Alder reaction of chiral imine with boron reagent. To a suspension of powdered 4A molecular sieves (1.0 g) in CH_2Cl_2 (10 mL) were added biphenol or related derivatives (0.35 mmol) and $B(OPh)_3$ (101 mg, 0.35 mmol) at room temperature under argon. After stirring for 1 h, the mixture was cooled to 0°C, then a solution of imine **16a** (73 mg, 0.35 mmol) in CH_2Cl_2 (1 mL) was added. After stirring for 10 min at the same temperature, the mixture was cooled to -78°C, and a solution of diene **3** (0.084 mL, 0.42 mmol) in CH_2Cl_2 (1 mL) was added dropwise. After stirring at the same temperature for several hours, the solution was washed with water and saturated $NaHCO_3$, and then dried over $MgSO_4$. Evaporation of solvent and purification by column chromatography on silica gel gave a mixture of dihydropyridones **17a** and **18a**.

(2*R*)-2,3-Dihydro-N-(*S*)-α-methylbenzyl-2-phenyl-4-pyridone (17a): (17a:18a=99:1) Mp 76°C; $[\alpha]_D^{24}$ -181.7° (*c* 1.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.46 (3H, d, J = 7.0 Hz), 2.63-2.88 (2H, m), 4.43 (1H, q, J = 7.0 Hz), 4.70 (1H, dd, J = 6.6, 8.8 Hz), 5.04 (1H, d, J = 6.0 Hz), 7.06 (1H, d, J = 6.0

Hz), 7.23-7.55 (10H, m); IR (neat) 1650 cm^{-1}; FABMS for $C_{19}H_{17}N_1O_1$, 278 (M+1); Anal. Calcd: C, 82.28, H, 6.90, N, 5.05 Found; C, 81.98, H, 7.11, N, 4.98.

(2*R*)-2,3-Dihydro-N-(*S*)-α-methylbenzyl-2-(3-pyridyl)-4-pyridone (17b): (17b:18b=99:1) $[\alpha]_D^{24}$ -75.0° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.51 (3H, d, *J* = 7 Hz), 2.58 (1H, dd, *J* = 6.4, 16 Hz), 2.93 (1H, dd, *J* = 7.0, 16 Hz), 4.51 (1H, q, *J* = 7.0 Hz), 4.73 (1H, t, *J* = 7.0 Hz), 5.08 (1H, d, *J* = 7.5 Hz), 7.10-7.55 (7H, m), 7.72-7.81 (1H, d, *J* = 6.0 Hz), 8.57-8.68 (2H, m); IR (neat) 1637 cm^{-1}; HRMS calcd for $C_{18}H_{19}N_2O_1$, 279.1497. found, 279.1496.

(2*R*)-2,3-Dihydro-2-*c*-hexyl-N-(*S*)-α-methylbenzyl-4-pyridone (17c): (17c:18c=99:1) $[\alpha]_D^{24}$ +38.0° (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.9–1.4 (4H, m), 1.5-2.0 (7H, m), 2.42 (1H, dd, *J* = 1.6, 16 Hz), 2.67 (1H, dd, *J* = 8.0, 16 Hz), 3.33-3.48 (1H, m), 4.52 (1H, q, *J* = 7.0 Hz), 4.75 (1H, d, *J* = 7.5 Hz), 6.81 (1H, d, *J* = 7.5 Hz), 7.26-7.60 (5H,m); IR (neat) 1660 cm^{-1}; FABMS for $C_{19}H_{25}N_1O_1$, 284 (M+1).

(2*S*)-2,3-Dihydro-N-(*S*)-α-methylbenzyl-2-*n*-propyl-4-pyridone (17d): (17d:18d=95:5) $[\alpha]_D^{24}$ +163.1° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.92 (3H, t, *J* = 7.0 Hz), 1.2-2.1 (4H, m), 2.32 (1H, dd, *J* = 3.0, 18 Hz), 2.69 (1H, dd, *J* = 8.0, 18 Hz), 3.50-3.65 (1H, m), 4.57 (1H, q, *J* = 7.0 Hz), 4.87 (1H, d, *J* = 7.5 Hz), 6.90 (1H,d, *J* = 7.5 Hz), 7.2-7.6 (5H, m); IR (neat) 1638 cm^{-1}; LCMS for $C_{16}H_{21}N_1O_1$, 244 (M+1); Anal. Calcd: C, 78.97, H, 8.70, N, 5.76. Found; C, 78.98, H, 8.70, N, 5.64.

Kinetic resolution of ±16: The reaction of **±16** (73 mg, 0.35 mmol) and **3** (0.084mL, 0.42 mL) was carried out in the above same manner except $B(OPh)_3$ (51 mg, 0.175 mmol) and *R*-binaphthol (50 mg, 0.175 mmol) were used. (50% yield) Ratio of products was determined by HPLC (DAICEL CHIRALCEL OD, 25cm x 0.46cm I.D., rate 0.6 ml/min, Hex/IPA = 8/2) **17a**: 22.77 min 72%, **18a**: 19.01 min 0%, **19a**: 21.10 min 3%, **20a**: 31.38 min 25%

Determination of the absolute configuration of the dihydropyridone 5: To a solution of **5** (350 mg, 82% ee, determined by HPLC) in THF (10 mL) was dropwise added L-selectride (1M, 2.0mL) at -78°C under argon. After being stirred for 1 h at the same temperature, the solution was quenched with water, diluted with AcOEt. The mixture was washed with saturated aq. $NaHCO_3$ and brine, and dried over $MgSO_4$. The crude material after concentration was purified by column chromatography on silica gel (AcOEt/hexane) to give (2*R*)-N-benzyl-2-phenyl-4-piperidinone (331 mg, 93% yield): $[\alpha]_D^{24}$ +45.1° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.30 (2H, m), 2.62 (2H, m), 2.90, 3.81 (2H, ABq, *J* = 14 Hz), 3.20 (1H, m), 3.58 (1H, m), 4.12 (1H, m), 7.2-7.5 (10H, m); IR (neat) 1728 cm^{-1}; LCMS for $C_{18}H_{19}N_1O_1$, 266 (M+1).

To a solution of the resulting ketone (200 mg) in DMF (3 mL) and Sulfolane (3 mL) were added tosylhydrazine (200 mg), *p*-toluenesulfonic acid (20 mg) and $NaBH_3CN$ (250 mg) under argon. After being stirred for 1 h at 100°C, the solution was diluted with AcOEt. The mixture was washed with saturated aq. $NaHCO_3$ and brine, and dried over $MgSO_4$. The crude material was purified by column chromatography on silica gel (AcOEt/hexane) to give (2*R*)-N-benzyl-2-phenylpiperidine (105 mg, 55% yield): $[\alpha]_D^{24}$ +44.7° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.2–2.0 (7H, m), 2.80, 3.79 (2H, ABq, *J* = 14 Hz), 2.99 (1H, dt, *J* = 12, 6.0 Hz), 3.12 (1H, dd, *J* = 12, 4.0 Hz), 7.2-7.6 (10H, m); IR (neat) 1454, 1100, 760, 740, 700 cm^{-1}; LCMS for $C_{18}H_{21}N_1$, 252 (M+1).

To a solution of the piperidine (35 mg) in MeOH (10 mL) was added $Pd(OH)_2$ (10 mg) and stirred for 1 h under H_2 atmospher at room temperature. After filtration, solvent was removed *in vacuo* to give **(2*R*)-**

phenylpiperidine (19 mg, 85% yield): $[\alpha]_D^{24}$ +27.6° (*c* 1.0, MeOH), (lit.[6] $[\alpha]_D$ +35.3°, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.6–2.0 (6H, m), 2.79 (1H, dt, *J* = 14, 6.0 Hz), 3.18 (1H, br. d, *J* = 14, Hz), 3.62 (1H, dd, *J* = 10, 2.6 Hz), 7.2-7.5 (5H, m); IR (neat) 3200 cm^{-1}; LCMS for $C_{11}H_{15}N_1$, 162 (M+1).

Synthesis of (-)-anabasine (22): The reaction was carried out in the same manner except (*S*)-binaphthol was used.

(2*S*)-N-Benzyl-2,3-dihydro-2-(3-pyridyl)-4-pyridone (21): The obtained solid (240 mg) by column chromatography was purified by recrystallization from ether (5mL) to leave a colorless solid (195 mg, 81% yield): $[\alpha]_D^{24}$ +44.9° (*c* 1.0, $CHCl_3$); mp 92°C; HPLC (column OD, 25cm x 0.46cm I.D., rate 1.0 ml/min, Hex/IPA = 6/4) 14.3 min (1 %) 21.3 min (99 %).

(2*S*)-N-Benzyl-2-(3-pyridyl)-4-piperidinone: (99% yield) $[\alpha]_D^{24}$ -37.0° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.3–2.8 (5H, m), 3.04, 3.80 (2H, ABq, *J* = 14 Hz), 3.25 (1H, m), 3.71 (1H, dd, *J* = 12, 5.5 Hz), 7.2-7.4 (6H, m), 7.85(1H, m), 8.59 (1H, dd, *J* = 6.0, 1.8 Hz), 8.71 (1H, d, *J* = 1.8 Hz); IR (neat) 1725 cm^{-1}; LCMS for $C_{17}H_{18}N_2O_1$, 267 (M+1).

(2*S*)-N-Benzyl-2-(3-pyridyl)piperidine: (69% yield) $[\alpha]_D^{24}$ -43.6° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.2–2.0 (7H, m), 2.82, 3.70 (2H, ABq, *J* = 13 Hz), 2.99 (1H, br. d, *J* = 11 Hz), 3.19 (1H, dd, *J* = 11, 3.0 Hz), 7.15-7.40 (6H, m), 7.85 (1H, m), 8.49 (1H, m), 8.65 (1H, d, *J* = 2.0 Hz); IR (neat) 1425, 1420, 1300, 1150 cm^{-1}; LCMS for $C_{17}H_{20}N_2$, 253 (M+1).

(-)-Anabasine (22): (72 % yield) $[\alpha]_D^{24}$ -41.5° (*c* 1.0, benzene); ^{1}H NMR (CD_3OD) δ 2.78 (1H, m), 3.18 (1H, m), 3.60 (1H, m), 7.2-7.3 (1H, m), 7.69 (1H, br. d, *J* = 8.0 Hz), 8.50 (1H, dd, *J* = 1.6, 4.5 Hz), 8.59 (1H, d, *J* = 1.6 Hz); IR (neat) 3300 cm^{-1}; LCMS for $C_{10}H_{14}N_2$, 163 (M+1).

To a solution of (-)-anabasine (10 mg) in THF (5 mL) were added Et_3N (0.02 mL) and 4-nitrobenzoyl chloride (40 mg) under argon at 0°C. After being stirred for 1 h, the solution was quenched with water. The reaction mixture was diluted with AcOEt, washed with saturated aq. $NaHCO_3$ and brine, and dried over $MgSO_4$. The crude material was purified by column chromatography on silica gel (AcOEt/hexane) to give **(2*S*)-N-(4-nitrobenzoyl)-2-(3-pyridyl)piperidine (23)** (52% yield): $[\alpha]_D^{24}$ -130.4° (*c* 0.4, MeOH) (lit.[9] $[\alpha]_D^{15}$-130.0°, *c* 3.0, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.5–1.9 (6H, m), 2.05 (1H, m), 2.48 (1H, m), 2.97 (1H, m), 7.36 (1H, m), 7.60 (1H, m), 7.63 (2H, d, *J* = 8.6 Hz), 8.30 (2H, d, *J* = 8.6 Hz), 8.50 (2H, m); IR (nujol) 1640 cm^{-1}; LCMS for $C_{17}H_{17}N_3O_3$, 312 (M+1).

Synthesis of (+)-coniine (24)

The Diels-Alder reaction of **16d** was carried out in the same manner with ***R*-1** to give the mixturer (**17d**:**18d**=95:5). The mixture was purified by culumn chromatography to give pure **17d** (41% yield from **16d**, **17d**:**18d**=99:1).

(2*S*)-N-(*S*)-α-Methylbenzyl-2-propyl-4-piperidinone : The reaction was carried out in the same manner. (93% yield) $[\alpha]_D^{24}$ -20.2° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.86 (3H, t, *J* = 7.4 Hz), 1.36 (3H, d, *J* = 6.6 Hz), 1.2-1.6 (4H, m), 2.1-2.5 (3H, m), 2.62 (1H, m), 2.91 (2H, m), 3.19 (1H, m), 3.99 (1H, q, *J* = 6.6 Hz), 7.2-7.5 (5H, m); IR (neat) 1716 cm^{-1}; LCMS for $C_{16}H_{23}N_1O_1$, 246 (M+1).

(2*S*)-4-(1,3-Dithiolane-2-yl)-N-(*S*)-α-methylbenzyl-2-propylpiperidine: To a solution of piperidinone (100 mg) in CH_2Cl_2 (5 mL) were added ethanedithiol (0.10 mL) and BF_3·OEt_2 (0.30 mL) at 0°C. After stirring for 24 h at the room temperature, the mixture was diluted with AcOEt, washed with 1N-NaOH and brine, and dried over $MgSO_4$. The crude material was purified by column chromatography on silica gel

(benzene) to give piperidine (100 mg) in 76% yield. $[\alpha]_D^{24}$ +55.1° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.92 (3H, t, *J* = 7.2 Hz), 1.28 (3H, d, *J* = 6.8 Hz), 1.3-1.8 (4H, m), 1.91 (2H, m), 2.11 (2 H, m), 2.2- 2.5 (2H, m), 2.71 (1H, m), 3.28 (4H, m), 4.29 (1H, q, *J* = 6.8 Hz), 7.2-7.5 (5H, m); IR (neat) 1493, 1446, 1385, 1151, 1100, 910, 770, 727, 700 cm^{-1}; LCMS for $C_{18}H_{27}N_1S_2$, 322 (M+1).

(+)-Coniine (24): To a solution of piperidine (140 mg) in ethanol (20 mL) was added Raney Ni (about 1 g) and stirred for 2 h under reflux. After filtration, the solvent was removed *in vacuo*. The obtained oil was dissolved in a mixture of ether and 1N-HCl. After the aquous layer was adjusted to pH 12 with 1N-NaOH, the mixture was extracted with $CHCl_3$ in three times. The gathered organic layer was dried over $MgSO_4$, and concentrated to give coniine (42 mg) in 76 %. $[\alpha]_D^{24}$ +8.0° (*c* 1.0, EtOH) (lit.[10] $[\alpha]_D$ +8.1°, *c* 1.62, EtOH); ^1H NMR ($CDCl_3$) δ 0.88 (3H, t, *J* = 7.0 Hz)), 1.2-1.9 (10H, m), 2.69 (2H, m), 3.28 (1H, m).

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References and Notes

(1) Review: (a) Morrison, J. D. *Asymmetric Synthesis*; Academic Press: New York, 1984; Vol. 3B. (b) Bosnich, B. *Asymmetric Catalysis*; Martinus Nijhoff Publishers: Dordrecht, 1986. (c) Narasaka, K. *Synthesis*, **1991**,1.

(2) Review: (a) Boger, D. L.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: New York, 1987. (b) Kileinman, E. F. In Trost, B. M.; Fleming, I.; Heathcock, C. H. Ed. Comprehensive Organic Synthesis, Vol.2, Chapter 4.1., Pergamon Press, 1991. (c) Hart, D. J.; Ha, D.-C. *Chem. Rev.*, **1989**, *89*, 1447. For more recent work, see: Comines, D. L.; Goehring, R. R.; Joseph, S. P.; O'Connor, S. *J. Org. Chem.*, **1990**, *55*, 2574. Bailey, P. D.; Brown, G. R.; Korber, F.; Reed, A.; Wilson, R. D. *Tetrahedron: Asymmetry*, **1991**, *2*, 1263. van der Steen, F. H.; Kleijn, H.; Britovsek, G. J. P.; Jactrzebbski, J. T. B. H.; van Koten, G. *J. Org. Chem.*, **1992**, *57*, 3906 and references cited therein.

(3) Yamamoto, H.; Hattori, K. *J. Org. Chem.*, **1992**, *57*, 3264.

(4) Danishefsky, S.; Kervin, J., Jr. *Tetrahedron Lett.*, **1982**, *23*, 3739.

(5) Presence of MS 4A has no effect on the % ee, however, increases the yield of products.

(6) Vetuschi, C.; Ottolino, A.; Tortorella, V. *Gazzetta Chimica Italiana*, **1975**, *105*, 935.

(7) Review: Rosini, C.; Franzini, L.; Raffaelli, A.; Salvadori, P. *Synthesis*, **1992**, 503.

(8) (a) Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.*, **1985**, *107*, 1768. (b) Waldmann, H.; Braun, M.; Dräger, M. *Angew Chem. Int. Ed. Engl.*, **1990**, *29*, 1468. Waldmann, H.; Braun, M.; Weymann, M.; Gewehr, M. *SYNLETT*, **1991**, 881. Waldmann, H.; Braun, M.; Dräger, M. *Tetrahedron: Asymmetry*, **1991**, *2*, 1231. Waldmann, H.; Braun, M. *J. Org. Chem.*, **1992**, *57*, 4444. (c) Pfrengle, W.; Kunz, H. *J. Org. Chem.*, **1989**, *54*, 4261. (d) Midland, M. M.; McLoughlin, J. I. *Tetrahedron Lett.*, **1988**, *29*, 4653. Midland, M. M.; Koops, R. W. *J. Org. Chem.*, **1992**, *57*, 1158.

(9) Späth, E.; Kesztler, F. *Chem. Ber.*, **1937**, 70, 704; Solt, M. L.; Dawson, R. F.; Christman, D. R. *Plant Physiol*, **1960**, 35, 887; Lukes, R.; Arojan, A. A.; Kovár, J.; Bláha, K. *Coll. Czech. Chem. Commun.*, **1982**, 27, 751.

(10) Tallent, W. H.; Horning, E. C. *J. Am. Chem Soc.*, **1956**, *78*, 4467. Guerrier, L.; Royer, J.; Grierson, D. S.; Husson, H.-P. *J. Am. Chem. Soc.*, **1983**, *105*, 7754.