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Catalytic Asymmetric Addition of Dialkylzinc to 3,4-Dihydroisoquinoline *N*-Oxides Utilizing Tartaric Acid Ester as a Chiral Auxiliary

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The catalytic asymmetric addition of dialkylzinc to a carbon–nitrogen double bond in 3,4-dihydroisoquinoline *N*-oxides was achieved by utilizing a catalytic amount of 2-magnesium 3-zinc salt of dicyclopentyl (*R*,*R*)-tartrate to afford (*S*)-1-alkyl-2-hydroxy-1,2,3,4-tetrahydroisoquinolines. In order to realize higher enantioselectivity, it was crucial to add the nitrones slowly into dialkylzinc in the presence of a catalytic amount of the 2-magnesium 3-zinc salt of (*R*,*R*)-tartrate.

The asymmetric nucleophilic addition of organometallic reagents to a carbon–nitrogen double bond provides an attractive direct route toward the optically active amines, which are the key intermediates for the synthesis of nitrogen-containing pharmaceutical and agrochemical substances. Due to the poor electrophilicity of the imino group compared with carbonyl compounds, only a limited number of catalytic reactions have been reported.[1] Among the imino functions, nitrone might be suitable as the substrate because it possesses an electronegative oxygen, which is coordinatable to metals and polarizes a carbon–nitrogen double bond effectively to enhance the electrophilic reactivity.[2,3] We have studied the asymmetric addition of organometallics to nitrones possessing the 3,4-dihydroisoquinoline skeleton using Chirald® as a chiral auxiliary.[4] However, the method still has problems for practical use, especially regarding the availability of chiral auxiliaries and the enantioselectivity. Among many chiral auxiliaries, tartaric acid ester is one of the most attractive candidates, because both of its enantiomers are readily available.[5,6] Herein, we wish to describe a new asymmetric addition of dialkylzinc to 3,4-dihydroisoquinoline *N*-oxide derivatives utilizing a catalytic amount of tartaric acid ester as an external chiral auxiliary.[7]

First, the addition reaction of diethylzinc to 3,4-dihydroisoquinoline *N*-oxide (**1a**) in the presence of a 0.2 molar amount of bis(ethylzinc) salt **2a**, derived in situ from diisopropyl (*R*,*R*)-tartrate ((*R*,*R*)-DIPT) and diethylzinc,[5i] was examined in CH_2Cl_2 at 25 °C. As shown in Table 1 (Eq. 1), the corresponding hydroxylamine **3a** was obtained in 61%

Table 1. Asymmetric Addition of Diethylzinc to the Nitrone **1a** Using the Salt **2** Derived from (*R*,*R*)-Tartaric Acid Esters[a)]

Entry	**2**				Et_2Zn/molar amounts	Yield of **3a**/%	ee[b)] %
	R^1	M^1	M^2				
1	Isopropyl	ZnEt	ZnEt	**a**	2.0	61	3
2		MgBr	MgBr	**b**	2.0	62	43
3		MgBr	ZnEt	**c**	2.0	98	51
4		MgBr	ZnEt	**c**	2.8	91	65
5		MgBr	ZnEt	**c**	3.8	86	61
6		MgBr	ZnMe	**d**	2.8	86	72
7	Methyl	MgBr	ZnEt	**e**	2.8	96	3
8	Ethyl	MgBr	ZnEt	**f**	2.8	90	40
9	1-Ethylpropyl	MgBr	ZnEt	**g**	2.8	88	56
10	Cyclobutyl	MgBr	ZnEt	**h**	2.8	91	51
11	Cyclopentyl	MgBr	ZnEt	**i**	2.8	94	74
12		MgBr	ZnMe	**j**	2.8	89	82
13	Cyclohexyl	MgBr	ZnEt	**k**	2.8	89	71
14	Cycloheptyl	MgBr	ZnEt	**l**	2.8	94	71
15	*t*-Butyl	MgBr	ZnEt	**m**	2.8	72	34

a) The reaction times were 14—22 h, except for Entry 5 (7 h). b) The optical yields were determined by an HPLC analysis (Daicel Chiralcel OD-H).

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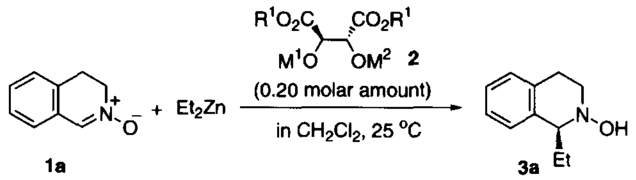
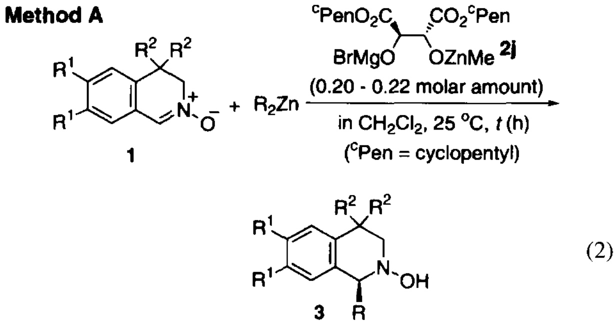
yield, but its optical yield was disappointedly low (Entry 1). On the contrary, the bis(bromomagnesium) salt **2b** was more effective to give optically active (*S*)-hydroxylamine **3a** (Entry 2). 2-Bromomagnesium 3-ethylzinc salt **2c** realized a higher enantioselection (Entry 3).[8] Using 2.8 molar amounts of diethylzinc, the optical yield was further improved up to 65% ee (Entries 4, 5).



(1)

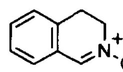
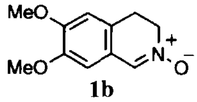
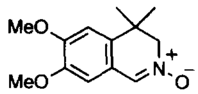
Next, the influence of the ester group in 2-bromomagnesium 3-ethylzinc salt **2** (M^1 = MgBr, M^2 = ZnEt) was investigated. The use of the esters, derived from primary alcohols, afforded product **3a** with lower selectivities (Entries 7, 8). In the case of the *t*-butyl ester, the enantioselectivity was also lower than that in the case of the isopropyl ester (Entry 15). The ester derived from acyclic secondary alcohol, 3-pentanol was less effective than the isopropyl ester (Entry 9). Among the esters of cyclic secondary alcohols examined, cyclopentyl ester was found to be the best choice (Entries 10, 11, 13, 14). Furthermore, using methylzinc salt instead of ethylzinc salt, alkylation proceeded more selectively (Entries 6, 12).[9] Especially, 2-bromomagnesium 3-methylzinc salt **2j**, derived from dicyclopentyl (*R*,*R*)-tartrate ((*R*,*R*)-DCPT), realized the highest selectivity of 82% ee.

Then, the asymmetric addition reaction of dialkylzinc to several 3,4-dihydroisoquinoline *N*-oxides **1a**—**c** was carried out in the presence of 2-bromomagnesium 3-methylzinc salt **2j** derived from (*R*,*R*)-DCPT (Method A, Eq. 2). As listed in Table 2,[10] the corresponding optically active (*S*)-hydroxylamines **3a**—**i** could be obtained with enantioselectivity up to 94% ee.



(2)

Table 2. Asymmetric Addition of Dialkylzinc to the Nitrones **1** (Method A)

Entry	Nitrones	R_2Zn	*t*/h	**3**	Yield/%	ee/%[a)]
1[b)]	 **1a**	Et_2Zn	18	**a**	89	82
2[b)]		Me_2Zn	19	**b**	84	63
3[b)]		$^nPr_2Zn$	22	**c**	85	77
4[c)]	 **1b**	Et_2Zn	19	**d**	90	83
5[c)]		Me_2Zn	19	**e**	90	64
6[c)]		$^nPr_2Zn$	23	**f**	78	76
7[c)]	 **1c**	Et_2Zn	19	**g**	93	94
8[c)]		Me_2Zn	19	**h**	95	85
9[c)]		$^nPr_2Zn$	18	**i**	90	88

a) Determined in a similar manner as that described in Table 3. b) 0.20 molar amount of **2j** was used. c) 0.22 molar amount of **2j** was used.

In order to reveal the stereochemical course of this nucleophilic addition, the relationship between the amount of dialkylzinc (*n* molar amounts) and the optical purity of the product was investigated in the presence of a stoichiometric amount of 2-magnesium 3-zinc salt of the tartrate (Fig. 1, Eq. 3). When **1a** was reacted with only 2-bromomagnesium 3-ethylzinc salt **2c** (*n* = 0), the reaction was sluggish and the opposite (*R*)-enantiomer **3a** was obtained in 19% yield with a selectivity of 62% ee by a *re*-facial attack. To the contrary, the (*S*)-enantiomer of **3a** was selectively obtained by a treatment with excess amounts of diethylzinc (*n*>ca. 2.0) in good yields. These results suggested that, in the catalytic nucleophilic addition reaction of diethylzinc, the ethyl group predominantly transferred not from ethyl group

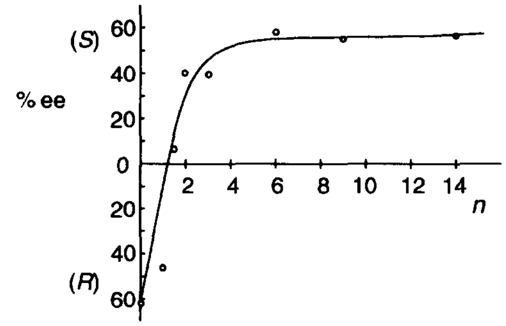
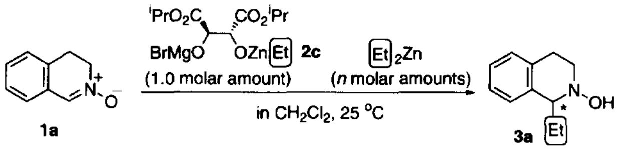


Fig. 1. Relationship between the molar amounts of Et_2Zn and the optical yield.



(3)

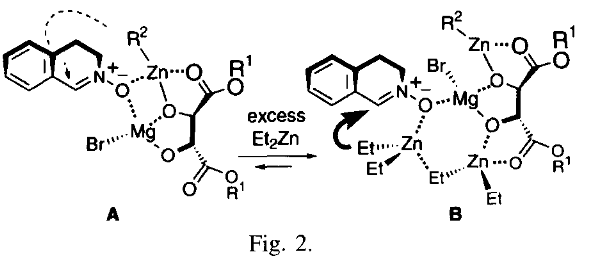
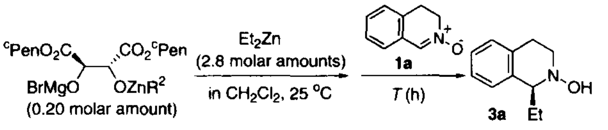


Fig. 2.

in zinc salt of tartrate (Fig. 2, **A** (R^2 = Et)), but from the diethylzinc associated with **2** to the nitrone, whose oxygen might coordinate to more Lewis acidic magnesium (Fig. 2, **B** (R^2 = Et)).[11,12] When methylzinc salt, **2d** or **2j**, was used for the addition reaction of diethylzinc, only the ethyl group in diethylzinc transferred with higher enantioselectivity, due to the less reactive methylzinc moiety[11a] (Fig. 2 (R^2 = Me)). The effect of the ester group in **2** is not yet clear, but probably the complex **B** exists in the aggregated form, and its structure might influence the enantioselectivity.

The fact that the enantioselectivity was enhanced in the presence of excess dialkylzinc prompted us to examine the reverse addition of nitrone to a mixture of a catalytic amount of magnesium zinc salt and excess amounts of dialkylzinc. Actually, according to this procedure, higher enantioselectivity was achieved (Eq. 4). The influence of the alkyl group in zinc salt of tartrate on the enantioselectivity was scarcely observed. Finally, the slow addition of nitrone **1a** realized an enantioselectivity of 90% ee.

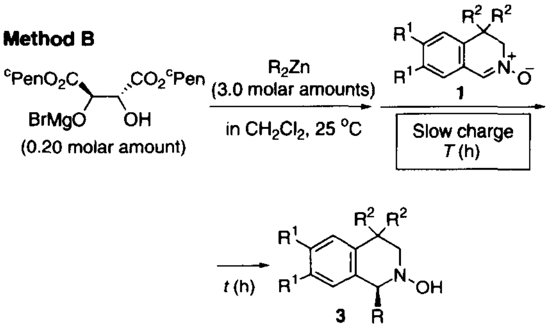


R^2	T	Yield	ee
R^2 = Et	T = 0 h	91% yield	83% ee
R^2 = Me	T = 0 h	83% yield	83% ee
R^2 = Et	T = 1.5 h	88% yield	90% ee

(4)

A catalytic asymmetric addition of dialkylzinc to several nitrones **1** was carried out to afford the corresponding optically active hydroxylamines **3** with high enantioselectivity up to 95% ee (Method B, Table 3, Eq. 5).

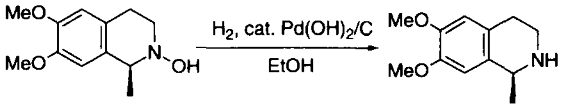
The stereochemistry of the newly formed chiral center in **3e** was determined to be *S* by conversion to salsolidine, a potent inhibitor of human monoamine oxidases;[13] i.e., the reduction of the hydroxylamine **3e** (>99% ee) purified by



(5)

HPLC using an optically active column gave salsolidine ($[\alpha]_D^{25}$ −56° (*c* 0.06, EtOH)) in 91% yield, whose configuration was confirmed to be *S* by a comparison of its specific rotation with that reported for (*S*)-salsolidine (lit,[14] $[\alpha]_D^{22}$ −59.5° (*c* 4.39, EtOH)).[15] The stereochemical course for the other addition of dialkylzincs to the nitrones **1** was also assumed to be from the *si* face of the carbon–nitrogen double bond of the nitrones **1**.[16]

As described above, the present method provides a new entry for the catalytic asymmetric addition of organometallics to the carbon–nitrogen double bond of nitrones utilizing a catalytic amount of tartaric acid ester as a chiral auxiliary. Since (*R*,*R*)- and (*S*,*S*)-tartaric acid esters are readily available, this method is a practical and useful way to prepare both enantiomers of 1-alkyltetrahydroisoquinolines, which are the key intermediates for chiral isoquinoline alkaloids.[17]

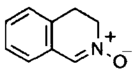
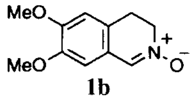
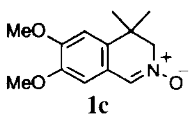


3e (*S*)-(−)-Salsolidine (6)

Experimental

All of the melting points were determined with a micro melting-

Table 3. Catalytic Asymmetric Addition of Dialkylzinc to Nitrones **1** by Slow Addition Method (Method B)

Entry	Nitrones	R_2Zn	T/h	t/h	3	Yield/%	ee/%	$[\alpha]_D^{25}$ in MeOH (c)
1	 **1a**	Et_2Zn	1.5	22	**a**	88	90[a)]	−59° (0.82)
2		Me_2Zn	5.5	10	**b**	93	82[a)]	−58° (0.78)
3		$^nPr_2Zn$	8	2	**c**	80	85[a)]	−36° (0.80)
4	 **1b**	Et_2Zn	3	3	**d**	99	92[a)]	−51° (1.23)
5		Me_2Zn	14	6	**e**	90	86[a)]	−43° (1.05)
6		$^nPr_2Zn$	3	2	**f**	80	86[a)]	−36° (1.05)
7	 **1c**	Et_2Zn	2	4	**g**	97	93[a)]	−51° (1.28)
8		Me_2Zn	6	3	**h**	85	95[a)]	−29° (0.74)
9		$^nPr_2Zn$	3	4	**i**	68	85[b)]	−32° (0.66)

a) Optical yields were determined by HPLC analysis (Daicel Chiralcel OD-H). b) Optical yield was determined by ^{1}H NMR analysis of the corresponding (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid ester derivative.

point apparatus (Yanagimoto-Seisakusho) and were uncorrected. The ^{1}H NMR spectra were recorded on a JEOL JNM-GX 400, a JEOL Lambda 400, and a JEOL Lambda 300 spectrometers with tetramethylsilane as an internal standard. The IR spectra were measured with a JASCO FT/IR-230 spectrometer. The MS and HRMS spectra were measured with a JEOL SX-102A mass spectrometer. The specific optical rotations were recorded on a JASCO DIP-370 spectrometer. All of the solvents were distilled and stored over drying agents. Flash column chromatography and thin-layer chromatography (TLC) were performed on Cica–Merck's silica gel 60 (No. 9835-5B) and Merck's silica gel 60 PF_{254} (Art. 7749), respectively.

Nitrones **1a**,[18] **1b**, and **1c** were prepared by oxidation of the corresponding tetrahydroisoquinolines.[18] The representative procedure is described for **1c** in the following. 6,7-Dimethoxy-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline was prepared starting from (3,4-dimethoxyphenyl)acetonitrile, as described below.

6,7-Dimethoxy-3,4-dihydroisoquinoline *N*-Oxide (1b): Mp 191.5 °C (from EtOH); IR (KBr) 3073, 3032, 2997, 2932, 2865, 2836, 1598, 1562, 1519, 1466, 1448, 1414, 1370, 1336, 1284, 1231, 1203, 1165, 1126, 1054, 1034, 1015, 985, 949, 891, 873, 788 $\mathrm{cm^{-1}}$; ^{1}H NMR ($CDCl_3$, 400 MHz) $\delta = 3.09$ (2H, t, $J = 7.94$ Hz), 3.85 (3H, s), 3.88 (3H, s), 3.99—4.04 (2H, m), 6.58 (1H, s), 6.67 (1H, s), 7.58 (1H, s). Found: C, 63.74; H, 6.37; N, 6.75%. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76%.

6,7-Dimethoxy-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline: To a THF (80 ml) solution of lithium diisopropylamide (90 mmol), which was prepared from diisopropylamine (11.8 ml, 90 mmol) and butyllithium (90 mmol, 58 ml of 1.55 M (1 M = 1 mol $\mathrm{dm^{-3}}$) solution in hexane), was added a THF (20 ml) solution of (3,4-dimethoxyphenyl)acetonitrile (5.316 g, 30 mmol) at −78 °C under a nitrogen atmosphere; the mixture was stirred for 30 min at that temperature. Then methyl iodide (5.6 ml, 90 mmol) was added to the mixture. After stirring for 1 h at −78 °C, the reaction mixture was quenched with sat. aqueous NH_4Cl and extracted with ethyl acetate three times. The combined extracts were washed with brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure to give the crude 2-(3,4-dimethoxyphenyl)-2-methylpropiononitrile (6.650 g). A THF (20 ml) solution of the crude product was added to a suspension of lithium aluminum hydride (2.277 g, 60 mmol) in THF (40 ml) at 0 °C under a nitrogen atmosphere, followed by refluxing for 4 h. After quenching with sat. aqueous Na_2SO_4 (17 ml), the precipitate was filtered off and washed with THF. The combined filtrates were condensed in vacuo to give the crude 2-(3,4-dimethoxyphenyl)-2-methylpropylamine (7.205 g). Next, it was treated with paraformaldehyde (1.135 g, 37.8 mmol) in formic acid (30 ml) at 40 °C for 24 h.[19] After cooling to room temperature, the reaction mixture was made basic by the addition of 30% aqueous NaOH and extracted several times with ethyl acetate. The combined extracts were dried over Na_2SO_4, and condensed under reduced pressure. The residue was purified by flash column chromatography (SiO_2, ethyl acetate/MeOH = 2/1—1/2, v/v) to give 6,7-dimethoxy-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline in 53% yield (3.315 g). An oil; MS *m/z* 221 (M^+; 56.52%), 220 (32.89), 204 (12.93), 192 (100.00), 177 (17.26), 165 (11.01), 149 (7.54), 91 (4.96); IR (neat) 3319, 2953, 2855, 1610, 1512, 1464, 1401, 1388, 1352, 1306, 1266, 1225, 1187, 1158, 1125, 1071, 1028, 857, 768, 732 $\mathrm{cm^{-1}}$; ^{1}H NMR ($CDCl_3$) $\delta = 1.27$ (6H, s), 2.86 (2H, s), 2.96 (1H, br), 3.83 (3H, s), 3.87 (3H, s), 3.95 (2H, s), 6.47 (1H, s), 6.80 (1H, s).

6,7-Dimethoxy-4,4-dimethyl-3,4-dihydroisoquinoline *N*-Oxide (1c): To a MeOH (50 ml) solution of 6,7-dimethoxy-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline (4.408 g, 20.8 mmol) prepared as mentioned above and Na_2WO_4 (0.275 g, 0.833 mmol) was dropwise added 30% aqueous H_2O_2 (6.24 ml, 62.4 mmol) at 0 °C; the mixture was stirred for 3 h at room temperature.[18] After most of the MeOH was evaporated in vacuo, brine (50 ml) was added and the mixture was extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and condensed under reduced pressure. The residue was purified by flash column chromatography (SiO_2, ethyl acetate/MeOH = 10/1, v/v) to give **1c** in 62% yield (3.066 g). Mp 135 °C (from EtOH); IR (KBr) 3061, 3004, 2961, 2836, 1598, 1516, 1469, 1409, 1354, 1291, 1228, 1211, 1175, 1080, 1034, 999, 937, 902, 854, 836, 778, 686 $\mathrm{cm^{-1}}$; ^{1}H NMR ($CDCl_3$, 400 MHz) $\delta = 1.35$ (6H, s), 3.792 (1H, s), 3.794 (1H, s), 3.89 (3H, s), 3.94 (3H, s), 6.64 (1H, s), 6.84 (1H, s), 7.70 (1H, s). Found: C, 66.36; H, 7.36; N, 5.95%. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95%.

Dimethyl, diethyl, and diisopropyl (*R*,*R*)-tartrates were commercially available and used after recrystallization or distillation. Di-*t*-butyl (*R*,*R*)-tartrate was synthesized from (2*R*,3*R*)-2,3-diacetoxybutanedioic acid.[20] Dicyclohexyl (*R*,*R*)-tartrate was prepared from (*R*,*R*)-tartaric acid and cyclohexanol.[5a] In a similar manner, other tartaric acid esters were prepared from (*R*,*R*)-tartaric acid and the corresponding alcohols.[5a,5f]

Bis(1-ethylpropyl) (*R*,*R*)-Tartrate: An oil; $[\alpha]_{\mathrm{D}}^{25}$ +15° (*c* 0.75, EtOH); MS *m/z* 290 (M^+; 0.24%), 191 (12.11), 175 (89.36), 146 (37.32), 129 (13.07), 105 (78.41), 89 (27.60), 76 (51.99), 71 (100.00), 60 (17.53), 59 (26.46), 55 (13.05); IR (neat) 3495, 2970, 2941, 2881, 1740, 1461, 1386, 1262, 1127, 1091, 1049, 1033, 997, 947, 903, 715 $\mathrm{cm^{-1}}$; ^{1}H NMR ($CDCl_3/CCl_4 = 1/3$, 400 MHz) $\delta = 0.94$ (12H, t, $J = 7.32$ Hz), 1.55—1.68 (8H, m), 3.10 (2H, brs), 4.43 (2H, s), 4.85—4.92 (2H, m).

Dicyclobutyl (*R*,*R*)-Tartrate: Mp 62—62.5 °C (from hexane/Et_2O); $[\alpha]_{\mathrm{D}}^{25}$ +18° (*c* 0.21, EtOH); IR (KBr) 3498, 3454, 2987, 2947, 2871, 1745, 1708, 1409, 1340, 1305, 1274, 1244, 1198, 1131, 1095, 948, 903, 818, 705 $\mathrm{cm^{-1}}$; ^{1}H NMR ($CDCl_3$, 300 MHz) $\delta = 1.57$—1.73 (2H, m), 1.79—1.90 (2H, m), 2.07—2.21 (4H, m), 2.35—2.45 (4H, m), 3.40 (2H, d, $J = 6.79$ Hz), 4.51 (2H, d, $J = 6.79$ Hz), 5.05—5.15 (2H, m). Found: C, 55.86; H, 7.01%. Calcd for $C_{12}H_{18}O_6$: C, 55.81; H, 7.03%.

Dicyclopentyl (*R*,*R*)-Tartrate: An oil; $[\alpha]_{\mathrm{D}}^{25}$ +24° (*c* 1.03, MeOH); MS *m/z* 287 (M^++1; 0.11%), 286 (M^+; 0.12), 201 (0.97), 185 (0.70), 173 (40.30), 144 (57.48), 127 (11.38), 105 (100.00), 89 (43.04), 86 (19.76), 85 (10.12), 77 (16.78), 76 (84.13), 69 (98.60), 68 (24.23), 67 (22.58), 60 (15.73), 57 (20.91); IR (neat) 3487, 2963, 2874, 1740, 1438, 1362, 1322, 1263, 1165, 1128, 1090, 1034, 957, 902, 834 $\mathrm{cm^{-1}}$; ^{1}H NMR ($CDCl_3$, 300 MHz) $\delta = 1.60$—1.96 (16H, m), 3.00 (2H, s), 4.45 (2H, s), 5.30—5.35 (2H, m).

Dicycloheptyl (*R*,*R*)-Tartrate: An oil; $[\alpha]_{\mathrm{D}}^{25}$ +11° (*c* 1.01, EtOH); MS *m/z* 342 (M^+; 0.18%), 246 (1.46), 201 (5.81), 172 (30.72), 151 (13.62), 114 (8.85), 113 (10.80), 98 (17.66), 97 (99.65), 96 (38.56), 89 (30.93), 81 (14.98), 76 (37.92), 55 (100.00); IR (neat) 3487, 2927, 2859, 1739, 1461, 1373, 1260, 1127, 1090, 1013, 998, 965, 884, 823, 789, 739, 710 $\mathrm{cm^{-1}}$; ^{1}H NMR ($CDCl_3$, 400 MHz) $\delta = 1.44$—1.77 (20H, m), 1.89—2.00 (4H, m), 2.94 (2H, brs), 4.47 (2H, s), 5.06—5.13 (2H, m).

A Representative Procedure for Asymmetric Addition of Dialkylzinc to Nitrones 1 (Method A, Table 2, Entry 7):[10] To a CH_2Cl_2 (3 ml) solution of (*R*,*R*)-DCPT (30 mg, 0.10 mmol) was added butylmagnesium bromide (0.11 mmol, 0.19 ml of 0.58 M solution in THF) at 0 °C under an argon atmosphere; the mixture was stirred for 10 min. To the solution, dimethylzinc (0.11 mmol, 0.11 ml of 1.00 M solution in hexane) was added and the mixture was stirred for 1 h. A CH_2Cl_2 (3 ml) solution of 6,7-dimethoxy-4,4-dimethyl-3,4-dihydroisoquinoline *N*-oxide (**1c**) (108 mg, 0.46 mmol) was added, followed by the addition of diethylzinc (1.48 mmol, 1.48 ml of 1.00 M solution in hexane) at 0 °C after 10 min; the resulting solution was stirred for 19 h at 25 °C. The reaction was quenched by the addition of sat. aqueous NH_4Cl, and the precipitate was filtered off. After the filtrate was extracted with CH_2Cl_2, the combined extracts were dried over Na_2SO_4 and condensed under reduced pressure. The residue was purified by TLC (SiO_2, hexane/Et_2O = 1/1, v/v) to give the corresponding hydroxylamine **3g** (113 mg, 93%) with the selectivity of 94% ee.

A Representative Procedure for Asymmetric Addition of Dialkylzinc to Nitrones 1 (Method B, Table 3, Entry 7): To a CH_2Cl_2 (2 ml) solution of (*R*,*R*)-DCPT (30 mg, 0.10 mmol) was added butylmagnesium bromide (0.10 mmol, 0.21 ml of 0.49 M solution in THF) at 0 °C under an argon atmosphere; the mixture was stirred for 10 min. To the solution, diethylzinc (1.57 mmol, 1.57 ml of 1.00 M solution in hexane) was added and the mixture was stirred for 10 min. A CH_2Cl_2 (3 ml) solution of 6,7-dimethoxy-4,4-dimethyl-3,4-dihydroisoquinoline *N*-oxide (**1c**) (123 mg, 0.52 mmol) was added dropwise over a period of 2 h using a mechanical syringe at 25 °C; the resulting solution was stirred for 4 h at that temperature. The reaction was quenched by addition of sat. aqueous NH_4Cl and the precipitate was filtered off. After the filtrate was extracted with CH_2Cl_2, the combined extracts were dried over Na_2SO_4 and condensed under reduced pressure. The residue was purified by TLC (SiO_2, hexane/Et_2O = 1/1, v/v) to give the corresponding hydroxylamine **3g** (135 mg, 97%) with the selectivity of 93% ee.

The physical and spectral data of the addition products **3a**—**i** are given in the following.

1-Ethyl-2-hydroxy-1,2,3,4-tetrahydroisoquinoline (3a): Mp 76 °C (from ethyl acetate/hexane); IR (KBr) 3221, 2965, 2842, 1578, 1495, 1452, 1424, 1378, 1354, 1321, 1274, 1125, 1102, 1046, 964, 933, 870, 842, 748 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.91 (3H, t, J = 7.32 Hz), 1.83—1.88 (1H, m), 2.02—2.12 (1H, m), 2.85—3.00 (2H, m), 3.10—3.17 (1H, m), 3.36—3.42 (1H, m), 3.92 (1H, t, J = 5.18 Hz), 7.00—7.12 (4H, m), 7.98 (1H, br). Found: C, 74.46; H, 8.76; N, 7.85%. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90%.

2-Hydroxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (3b): Mp 71—72 °C (from ethyl acetate/hexane); IR (KBr) 3221, 2932, 2843, 1577, 1494, 1469, 1451, 1426, 1373, 1353, 1307, 1277, 1227, 1123, 1095, 1042, 953, 863, 824, 768, 738 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.55 (3H, d, J = 6.40 Hz), 2.84—2.94 (1H, m), 2.98—3.14 (2H, m), 3.39—3.48 (1H, m), 3.92 (1H, br), 7.00—7.12 (4H, m), 7.95 (1H, br). Found: C, 73.83; H, 8.10; N, 8.71%. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.51%.

2-Hydroxy-1-propyl-1,2,3,4-tetrahydroisoquinoline (3c): An oil; MS *m*/*z* 191 (M$^+$; 0.47%), 172 (19.30), 158 (14.44), 156 (13.16), 148 (41.85), 145 (46.51), 144 (22.57), 143 (50.22), 132 (100.00), 130 (27.83), 115 (21.53), 103 (9.13); IR (neat) 3231, 3062, 3021, 2956, 2871, 1582, 1493, 1454, 1378, 1355, 1320, 1274, 1197, 1123, 1041, 968, 901, 866, 823, 743, 687 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.94 (3H, t, J = 7.34 Hz), 1.26—1.58 (2H, m), 1.71—1.92 (2H, m), 2.75—2.88 (1H, m), 2.95—3.09, (1H, m), 3.17—3.24 (1H, m), 3.37—3.45 (1H, m), 4.01 (1H, t, J = 5.69 Hz), 7.02—7.05 (4H, m), 8.36 (1H, br).

1-Ethyl-2-hydroxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (3d): Mp 139—140 °C (from ethyl acetate/hexane); IR (KBr) 3204, 2963, 2891, 2850, 1613, 1515, 1462, 1363, 1327, 1309, 1254, 1222, 1205, 1132, 1093, 1039, 1011, 964, 935, 867, 813, 783, 714 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.92 (3H, t, J = 7.32 Hz), 1.75—1.81 (1H, m), 1.98—2.03 (1H, m), 2.78—2.88 (2H, m), 3.08—3.14 (1H, m), 3.36 (1H, dt, J = 11.90, 5.80 Hz), 3.82—3.86 (1H, m), 3.82 (3H, s), 3.83 (3H, s), 6.51 (1H, s), 6.55 (1H, s), 7.01 (1H, br). Found: C, 65.61; H, 8.27; N, 5.85%. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90%.

2-Hydroxy-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (3e): Mp 109—110 °C (from ethyl acetate/hexane); IR (KBr) 3204, 2982, 2962, 2916, 2830, 1610, 1511, 1468, 1443, 1362, 1331, 1293, 1254, 1226, 1209, 1134, 1093, 1068, 1011, 966, 948, 856, 785 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.55 (3H, d, J = 6.60 Hz), 2.89—3.19 (3H, m), 3.39—3.49 (1H, m), 3.82—3.87 (1H, m), 3.83 (3H, s), 3.85 (3H, s), 6.56 (1H, s), 6.63 (1H, s), 8.63 (1H, br). Found: C, 64.56; H, 7.82; N, 6.26%. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27%.

2-Hydroxy-6,7-dimethoxy-1-propyl-1,2,3,4-tetrahydroisoquinoline (3f): Mp 93—94 °C (from ethyl acetate/hexane); IR (KBr) 3251, 2959, 2849, 1609, 1517, 1458, 1358, 1255, 1215, 1134, 1093, 1015, 962, 852, 796, 762 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.95 (3H, t, J = 7.34 Hz), 1.33—1.64 (2H, m), 1.66—1.93 (2H, m), 2.71—2.84 (1H, m), 2.86—2.98 (1H, m), 3.18 (1H, dt, J = 12.29, 5.87 Hz), 3.39 (1H, dt, J = 12.29, 6.05 Hz), 3.84 (3H, s), 3.85 (3H, s), 3.92 (1H, t, J = 5.50 Hz), 6.03 (1H, br), 6.57 (1H, s), 6.60 (1H, s). Found: C, 66.76; H, 8.24; N, 5.57%. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57%.

1-Ethyl-2-hydroxy-6,7-dimethoxy-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline (3g): Mp 139—140 °C (from ethyl acetate/hexane); IR (KBr) 3227, 2952, 2829, 1612, 1518, 1465, 1399, 1355, 1317, 1256, 1224, 1200, 1164, 1139, 1075, 1043, 998, 982, 933, 916, 863, 840, 823, 782 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.78 (3H, t, J = 7.33 Hz), 1.27 (3H, s), 1.32 (3H, s), 1.84—1.95 (1H, m), 2.14—2.26 (1H, m), 2.80 (1H, d, J = 10.37 Hz), 3.07 (1H, d, J = 10.37 Hz), 3.74—3.78 (1H, m), 3.81 (3H, s), 3.83 (3H, s), 5.50 (1H, brs), 6.54 (1H, s), 6.65 (1H, s). Found: C, 67.81; H, 9.03; N, 5.26%. Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28%.

2-Hydroxy-6,7-dimethoxy-1,4,4-trimethyl-1,2,3,4-tetrahydroisoquinoline (3h): Mp 115.5—116.5 °C (from ethyl acetate/hexane); MS *m*/*z* 251 (M$^+$; 30.08%), 236 (100.00), 220 (27.73), 206 (8.04), 204 (8.08), 191 (9.99), 160 (3.09), 88 (6.88); HRMS Found: *m*/*z* 251.1523. Calcd for $C_{14}H_{21}NO_3$: M, 251.1521. IR (KBr) 3234, 2958, 2835, 1613, 1518, 1460, 1396, 1359, 1319, 1298, 1281, 1255, 1227, 1173, 1145, 1066, 1042, 1013, 917, 856, 810, 750, 664 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.30 (3H, s), 1.38 (3H, s), 1.61 (3H, br), 2.86 (1H, d, J = 10.49 Hz), 3.19 (1H, d, J = 10.49 Hz), 3.77 (1H, br), 3.86 (3H, s), 3.87 (3H, s), 6.64 (1H, s), 6.73 (1H, s), 7.66 (1H, brs).

2-Hydroxy-6,7-dimethoxy-4,4-dimethyl-1-propyl-1,2,3,4-tetrahydroisoquinoline (3i): Mp 116.5—117 °C (from ethyl acetate/hexane); IR (KBr) 3255, 2961, 2836, 2821, 2803, 1608, 1510, 1466, 1398, 1352, 1317, 1254, 1222, 1197, 1168, 1140, 1073, 1048, 869, 812, 768 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.92 (3H, t, J = 7.32 Hz), 1.11—1.26 (1H, m), 1.30 (3H, s), 1.34 (3H, s), 1.38—1.52 (1H, m), 1.79—1.98 (1H, m), 2.00—2.24 (1H, m), 2.87 (1H, d, J = 10.49 Hz), 3.13 (1H, d, J = 10.49 Hz), 3.83—3.89 (1H, m), 3.85 (3H, s), 3.87 (3H, s), 6.32 (1H, br), 6.61 (1H, s), 6.73 (1H, s). Found: C, 68.61; H, 9.09; N, 4.91%. Calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01%.

(*S*)-Salsolidine: To an EtOH (2 ml) solution of (*S*)-2-hydroxy-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (**3e**) (19 mg, 0.09 mmol) (>99% ee), which was purified by HPLC using an optically active column (Daicel Chiralcel OD-H, hexane/EtOH = 30/1, v/v), was added 20% Pd(OH)$_2$/C (21 mg); the suspension was stirred at room temperature for 3 h under hydrogen at atmospheric pressure. After the filtration of the catalyst, the filtrate was condensed under reduced pressure and the residue was purified by short-column chromatography (SiO$_2$, ethyl acetate/MeOH = 1/1—0/1) to afford (*S*)-salsolidine (16 mg, 91%). $[\alpha]^{25}_{\mathrm{D}}$ $-56°$ (c 0.06, EtOH) [lit,[14] $[\alpha]^{22}_{\mathrm{D}}$ $-59.5°$ (c 4.39, EtOH)]. IR (neat) 3314, 2932, 2832, 1610, 1512, 1464, 1405, 1371, 1354, 1326, 1293, 1256, 1223, 1125, 1069, 1030, 998, 857, 791, 684 cm^{-1}; MS *m*/*z* 207 (M$^+$; 33.38%), 206 (30.60), 193 (30.10), 192 (100.00), 177 (7.10), 176 (13.39), 148 (4.07); ^{1}H NMR (CDCl$_3$, 400 MHz) δ = 1.44 (3H, d, J = 6.59 Hz), 2.03 (1H, brs), 2.62—2.69 (1H, m), 2.76—2.83 (1H, m), 2.96—3.03 (1H, m), 3.25 (1H, dt, J = 12.69, 5.12 Hz), 3.849 (3H, s), 3.853 (3H, s), 4.05 (1H, q, J = 6.59 Hz), 6.57 (1H, s), 6.62 (1H, s).

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