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Asymmetric 1,2-Addition of Organolithiums to Aldimines Catalyzed by Chiral Ligand

Isao Inoue,[a] Mitsuru Shindo,[b] Kenji Koga,[b] and Kiyoshi Tomioka[c]*

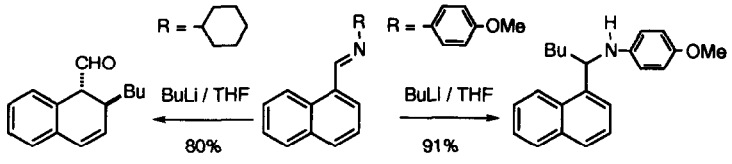
[a]Organic Chemistry Research Laboratory, Tanabe Seiyaku Co. Ltd., Toda, Saitama 335,
[b]Faculty of Pharmaceutical Sciences, University of Tokyo, Bunkyo-ku, Tokyo 113,
[c]The Institute of Scientific and Industrial Research, Osaka University, Ibaraki, Osaka 567, Japan

Abstract: An asymmetric 1,2-addition reaction of organolithiums with imines **3**, **7** was catalyzed by a 0.05-1.3 equivalent of a chiral amino ether **2** to provide the corresponding optically active amines **4**, **8**.

Asymmetric control in the addition of carbon nucleophiles to the imine function and its derivatives constitutes an important method for the preparation of optically active amines.[1] Although impressive progress has been made recently, these methods are limited to the auxiliary-based asymmetric induction by using chiral imines and hydrazones as chiral substrates.[2] External chiral ligand mediated enantioselective addition of organometallic reagents to imines has a high potential in the production of optically active amines.[3] As a research program aimed at the development of asymmetric reactions mediated by external chiral ligands,[4] we have already reported the first catalytic and stoichiometric asymmetric addition of organolithiums to imines derived from *p*-anisidine derivatives and aldehydes, giving the product amines in 90-48% ee.[5,6] We describe our further approach based on the method by using an external chiral ligand as an asymmetric catalyst.

SWITCH OF REGIOSELECTIVITY FROM 1,4- TO 1,2-ADDITION

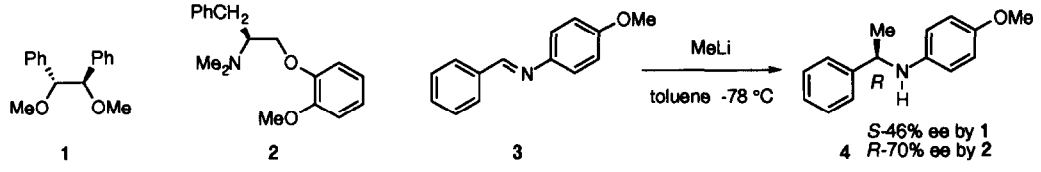
In the context of a related project directed toward the chiral ligand controlled enantioselective 1,4-addition reaction,[7] we observed a complete change of the reaction pattern from 1,4- to 1,2-addition by changing cyclohexylimine to arylimine of 1-naphthalenecarbaldehyde.[8]



On the basis of this interesting observation, we examined various possibilities for enantioselective 1,2-addition reactions of organolithiums with arylimines to provide optically active amines. We chose *p*-anisidine derivatives as arylamine part, expecting convenient oxidative removal of the 4-methoxyphenyl group to liberate a primary amine.[9] The imines were prepared in high yields by the condensation of the corresponding aldehydes with *p*-anisidine derivatives.

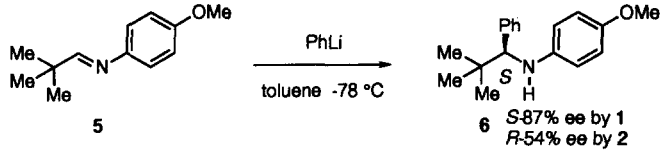
STOICHIOMETRIC ASYMMETRIC 1,2-ADDITION REACTION

We examined the reactions of methyllithium (low halide) with 4-methoxyphenylimine of benzaldehyde **3** by using stoichiometric amount of the chiral ligands **1**[7] and **2**[10]. In the absence of the ligand, the reaction in toluene at -78 °C does not proceed smoothly, affording 1,2-addition product dl-**4** in only 6% yield after 120 min (Table 1, entry 1). In the presence of the ligands, the reaction proceeded smoothly to afford, after 20 min, **4** in high yield. The ligands **1** and **2** provided *S*- and *R*-**4** in 46 and 70% enantiomeric excess (ee), respectively (entries 2 and 3). The ligands **1** and **2** were recovered quantitatively for reuse without any loss of enantiomeric purity.



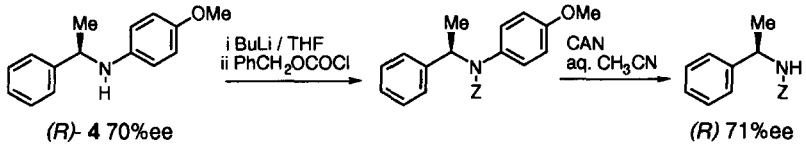
1 2 3 4

In the reaction of phenyllithium with the imine of pivalaldehyde **5**, **1** and **2** gave *S*- and *R*-**6** in 87 and 54% ee, respectively. These indicate that reactivity of methyllithium-ligand complex is higher than methyllithium and the enantioselectivity depends on the structure of the imine as well as that of the ligand.



5 6

The 4-methoxyphenyl group of the amine **4** or **6** was easily removed by a two-step sequence.[5] Treatment of the amine **4** or **6** with n-butyllithium followed by ZCl (benzyloxycarbonyl chloride)



(R)-**4** 70%ee *(R)* 71%ee

provided the Z-protected amine. Subsequent oxidative removal of the 4-methoxyphenyl group was carried out by CAN (ceric ammonium nitrate)[9] in aqueous acetonitrile to provide the Z-protected primary amine without significant loss of enantiomeric purity in good yield. The absolute configuration of the product was determined by using this two-step reaction.

CATALYTIC ASYMMETRIC 1,2-ADDITION REACTION

It thus seemed to us that the possibility of asymmetric C-C bond formation catalyzed by a substoichiometric amount of the chiral ligand deserved to be explored. This approach appeared particularly true because such a process would result in the catalytic asymmetric C-C bond formation in that versatile organolithiums are applicable as carbon nucleophiles.

Contrary to the stoichiometric asymmetric reaction that proceeded at -78 °C to provide **4** in 70% ee in 94% yield (Table 1, entry 3), the catalytic reaction in which a substoichiometric amount of **2** was used as a catalyst did not proceed smoothly at -78 °C, giving **4** in the yield corresponding to the amount of **2** used. Fortunately, the reaction of methyllithium with **3** at -42 °C was effected by the presence of 2.6 equivalent of **2** to give **4** in 66% ee (entry 6). The enantiomeric excess of **4** slightly decreased to 62, 58, and 47% as the amount of **2** decreased to 0.5, 0.2, and 0.1 equivalent, respectively (entries 7-9). However, 0.05 equivalent of **2** still exhibited remarkable catalytic effect on asymmetric induction to give **4** in 40% ee (entry 10). Asymmetric catalyst turnover number (CTN) was calculated to be 12 (entry 10, theoretical maximum CTN is 20 in the asymmetric induction) on the basis of 66% ee obtained in the stoichiometric reaction (2.6 equivalent of **2**).[11] However, the reaction proceeded even in the absence **2** at -42 °C for 3 h to give dl-**4** in 91% yield (entry 4).

Table 1. Catalytic Asymmetric 1,2-Addition of Methyllithium to **3** Producing **4** in Toluene[a]

entry	ligand	equiv[b]	temp/°C	time/min	ee/%(*RS*)[c]	yield/%[d]
1	none	0	-78	120		6
2	**1**	2.6	-78	20	46 *S*	90
3	**2**	2.6	-78	20	70 *R*	94
4	none		-42	180		91
5	none		-42	30		34
6	**2**	2.6	-42	20	66 *R*	95
7	**2**	0.5	-42	20	62 *R*	96
8	**2**	0.2	-42	60	58 *R*	85
9	**2**	0.1	-42	60	47 *R*	90
10	**2**	0.05	-42	180	40 *R*	96

a) Reaction was performed using 2 equiv. of MeLi (low halide, Aldrich) in toluene. b) Ligand equivalent to **3**. c) Determined by HPLC analysis using chiral column (Waters Optipak-XC, hexane-isopropanol = 9:1, 0.3 ml/min, 254 nm). d) Yields referred to isolated pure compounds.

Judging from these experimental results it may be supposed that the rate of reaction of methyllithium complexed with **2** overwhelmed that of the non-catalytic reaction. Furthermore, regeneration of the ligand 2-methyllithium complex takes place at the requisite temperature and makes the catalytic asymmetric reaction possible.

It is also important to note that low halide methyllithium is essential in the catalytic reaction. The reaction using methyllithium-lithium bromide complex (Aldrich) proceeded smoothly to afford the comparable ee and yield in the stoichiometric reaction. However, in the catalytic reaction in the presence of 0.2 equivalent of **2**, enantioselectivity decreased to 34%, probably due to some activation of methyllithium by lithium bromide.[4]

It is also noteworthy that, in the reaction of n-butyllithium, the choice of the reaction solvent is critical to realize the catalytic asymmetric induction (Table 2). Addition of n-butyllithium to **3** in diisopropyl ether provided *R*-product of 60% ee with regardless to the amount of **2** (2.6 and 0.3 equivalents, entries 6 and 7). However, significant decrease of enantioselectivity was observed in toluene (58 vs 25% ee, entries 1 and 2) and in ether (67 vs 45% ee, entries 4 and 5). A 0.05 equivalent of **2** in diisopropyl ether provided the addition product in 40% ee. A catalyst turnover number in the asymmetric induction was calculated to be 13 (theoretical maximum CTN is 20) (entry 8).[11]

Table 2. Asymmetric Addition of n-Butyllithium to **3** at -78 °C Catalyzed by **2**[a]

entry	solvent	equiv[b]	ee/%[c]	yield/%[d]
1	toluene	2.6	58	89
2	toluene	0.3	25	99
3	toluene-Et_2O (9:1)	0.3	40	93
4	Et_2O	2.6	67	88
5	Et_2O	0.3	45	90
6	iPr_2O	2.6	60	99
7	iPr_2O	0.3	60	99
8	iPr_2O	0.05	40	97

a) Reaction was performed using 2 equiv. of n-BuLi (hexane solution). b) Ligand equivalent to **3**. c) Determined by HPLC analysis using chiral column (Waters Optipak-TC, hexane-isopropanol = 9:1, 0.3 ml/min, 254 nm). d) Yields referred to isolated pure compounds.

CATALYTIC ASYMMETRIC 1,2-ADDITION REACTION OF ORGANOLITHIUMS WITH SOME IMINES

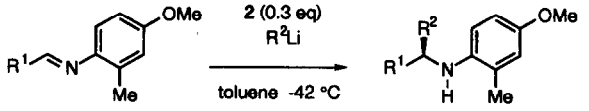
Since the reaction with the imine **7** derived from 4-methoxy-2-methylaniline provides the product **8** in up to 90% in the stoichiometric asymmetric reaction,[5] then we examined catalytic reaction using **7** as a substrate (Table 3).

The reaction of methyllithium with **7** in the presence of 0.3 equvalent of **2** proceeded smoothly to afford **8** in up to 66% ee. Addition of vinyllithium to **7** was also catalyzed by 0.3 equivalent of **2** to provide the product **7** in 66% ee (entry 3).

Remarkable catalytic asymmetric induction was also observed in the reactions of **7** derived from cinnamaldehyde, 1- and 2-naphthalenecarbaldehydes with methyl-, butyllithiums to provide the corresponding optically active amines **8**.

Enantioselectivity described here is moderate, however, we believe that further efforts aiming to clarify the catalytic mechanism of the reaction and to improve the enantioselectivity by developing more efficient chiral catalysts will open the new frontier of the catalytic asymmetric reactions in which organolithium can be used as a carbon nucleophile.

Table 3. Catalytic Asymmetric 1,2-Addition of Organolithiums to Imines **7** Producing **8**[a]



7 **8**

entry	R^1	R^{2b}	ee/%[c]	yield/%[d]
1	Ph	Me	(90)	(97)[e]
2	Ph	Me	66(77)	88(97)
3	Ph	CH_2=CH	66(70)	75(92)
4	PhCH=CH	Me	47(53)	84(90)
5	1-Naph	Me	60(72)	80(94)
6	2-Naph	Me	52(66)	81(96)
7	2-Naph	Bu	60(69)	86(88)[f]

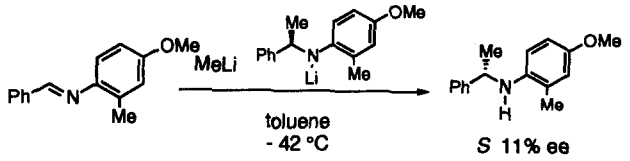
a) Reaction was performed by using 0.3 eq. of **2**. Numbers in parentheses represent the values obtained by using stoichiometric amount of **2**. b) MeLi (low halide) in ether (Aldrich), n-BuLi in hexane (Wako Pure Chemical Industries), PhLi in ether-cyclohexane (Aldrich) were used. Vinyllithium in ether was prepared from tetravinyltin and PhLi. c) Determined by HPLC analysis using chiral column (Waters Optipak-XC and -TC). d) Yields referred to isolated pure compounds. e) The reaction was performed at -100 °C. f) In ether.

PROBABLE CATALYTIC CYCLE OF THE REACTION

It is reasonable to predict that the major course of the reaction proceeds from the ligand-organolithium complex which has higher reactivity than organolithium itself in nonpolar hydrocarbon solvents or in other solvents with less coordinating ability. The ee observed in the reaction is the weighted sum of the catalytic and noncatalytic reactions.

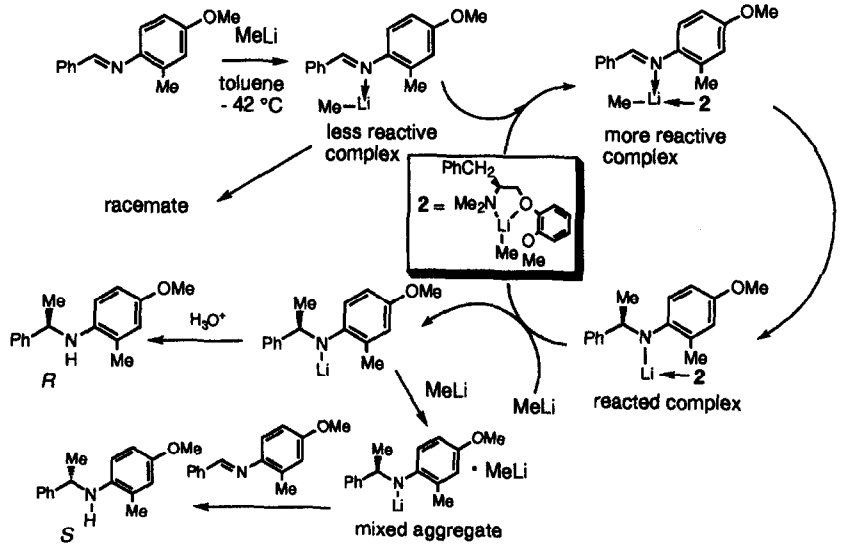
It is also important to note that the initial product in the reaction, lithium amide, also promotes the addition reaction by forming a mixed aggregate with organolithium. Thus, the reaction of methyllithium

with **7** (R^1=Ph) in the presence of the lithium amide of the optically pure *R*-**8** (R^1=Ph, R^2=Me) provided *S*-**8** (R^1=Ph, R^2=Me) in 11% ee.



Regeneration of the reactive ligand-organolithium complex, through ligand exchange from the reacted complex and methyllithium, is an essential step in the catalytic reaction.

Probable Catalytic Cycle Mediated by Chiral Ligand



Further studies toward development of much more effective ligand as a chiral catalyst are in progress in our laboratories.

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EXPERIMENTAL[13]

Preparation of the imines

***N*-Phenylmethylene-4-methoxybenzenamine** **3**: A mixture of *p*-anisidine (13.8 g, 0.112 mol) and benzaldehyde (10.4 ml, 0.102 mol) was stirred at 40 °C for 1 h and diluted with diethyl ether (200 ml). The solution was successively washed with 5% aq. AcOH, brine and then dried over K_2CO_3. Concentration

and following recrystallization from ethanol (35 ml) gave **3** (17.9 g, 83 %) as colorless leaflets of mp 70-72 °C.[14] IR (KBr): 3640, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.82 (3H, s), 6.91 (2H, d, J=9.2 Hz), 7.23 (2H, d, J=9.2 Hz), 7.3-7.5 (3H, m), 7.8-8.0 (2H, m), 8.47 (1H, s). MS *m/z*: 211 (M^+). Anal. Calcd for $C_{14}H_{13}NO$: C 79.60, H 6.20, N 6.63. Found: C 79.59, H 6.22, N 6.59.

***N*-(2,2-Dimethylpropylene)-4-methoxybenzenamine 5**: A mixture of *p*-anisidine (4.93 g, 0.04 mol) and pivalaldehyde (7.6 ml, 0.07 mol) in EtOH (40 ml) was stirred at 0 °C for 1.5 h and concentrated, and then diluted with benzene (50 ml). The solution was dried over KOH. Concentration and following distillation (bp 127 °C/10 mmHg) gave **5** (5.79 g, 76%) as colorless solid of mp 50-52 °C. IR ($CHCl_3$): 1645 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.17 (9H, s), 3.79 (3H, s), 6.85 and 7.00 (each 2H, d, J=9.0 Hz), 7.69 (1H, s). MS *m/z*: 191 (M^+). Anal. Calcd for $C_{12}H_{17}NO$: C 75.36, H 8.96, N 7.32. Found: C 75.15, H 8.83, N 7.42.

***N*-Phenylethenylmethylene-4-methoxy-2-methylbenzenamine 7 (R^1=PhCH=CH)**: A solution of 4-methoxy-2-methylaniline (1.51 g, 0.011 mol) and cinnamaldehyde (1.32 g, 0.01 mol) was stirred at 100 °C for 1.5 h and then diluted with diethyl ether (30 ml). The solution was successively washed with 5% aq. AcOH, brine and then dried over K_2CO_3. Concentration and following distillation (bp 190 °C/0.3 mmHg) gave **7** (2.13 g, 85 %) as a pale yellow oil which was solidified on standing, mp 65-69 °C. IR (Nujol): 1630, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.36 (3H, s), 3.79 (3H, s), 6.6-7.0 (3H, m), 7.1-7.6 (7H, m), 8.1-8.2 (1H, m). MS *m/z*: 250 (M^+). Anal. Calcd for $C_{17}H_{17}NO$: C 81.24, H 6.82, N 5.57. Found: C 81.16, H 6.77, N 5.46.

***N*-(1-Naphthalenylmethylene)-4-methoxy-2-methylbenzenamine 7 (R^1=1-Naph)**: Prepared in 91% from 4-methoxy-2-methylaniline and 1-naphthaldehyde by the same way as **7**. Pale yellow oil of bp 200 °C/0.3 mmHg. IR (film): 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.47 (3H, s), 3.83 (3H, s), 6.8-6.9 (2H, m), 7.04 (1H, d, J=8.9 Hz), 7.5-8.1 (6H, m), 9.00 (1H, s), 9.21 (1H, d, J=9.3 Hz). MS *m/z*: 275 (M^+). Anal. Calcd for $C_{19}H_{17}NO$: C 82.88, H 6.22, N 5.09. Found: C 82.72, H 6.21, N 4.96.

***N*-(2-Naphthalenylmethylene)-4-methoxy-2-methylbenzenamine 7 (R^1=2-Naph)**: Prepared in 73% from 4-methoxy-2-methylaniline and 2-naphthaldehyde by the same way as **7**. Pale yellow needles of mp 108-110 °C (hexane). IR (Nujol): 1620, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.43 (3H, s), 3.81 (3H, s), 6.7-7.1 (3H, m), 7.4-8.3 (7H, m), 8.53 (1H, s). MS *m/z*: 275 (M^+). Anal. Calcd for $C_{19}H_{17}NO$: C 82.88, H 6.22, N 5.09. Found: C 82.78, H 6.25, N 4.92.

Asymmetric alkylation of imines 3, 5, 7

***(R)*-*N*-(4-Methoxyphenyl)-α-methylbenzenemethanamine 4 (Table 1, entry 8)**: To a solution of **3** (317 mg, 1.5 mmol) and **2** (86 mg, 0.3 mmol) in toluene (30 ml) was added an ether solution of methyllithium (low halide, 1.36M, 2.2 ml, 3.0 mmol) at -78 °C over a period of 5 min. The mixture was stirred at -42 °C for 1 h and quenched with water (20 ml). The organic layer was separated and washed with brine and then dried over K_2CO_3. Concentration and following purification by silica gel column chromatography (hexane-ether (3:1)) followed by distillation (bp 200 °C/1.5 mmHg) gave *R*-**4** (289 mg, 85%) as a pale yellow oil. $[\alpha]_{365}^{20}$ +27.1 °(c 1.21, EtOH). IR ($CHCl_3$): 3420 cm^{-1}. ^{1}H-NMR ($CDCl_3$, TMS) δ: 1.49 (3H, d, J=6.8 Hz), 3.68 (3H, s), 4.39 (1H, q, J=6.8 Hz), 6.46 and 6.70 (each 2H, d, J=9.3 Hz), 7.1-7.5 (5H, m). MS *m/z*: 227 (M^+). Anal. Calcd for $C_{15}H_{17}NO$: C 79.26, H 7.54, N 6.16. Found: C 79.20, H 7.49, N 6.30.

Ee was determined by HPLC analysis to be 58% (Waters OptiPak TC, hexane-iPrOH (9:1), 0.25 ml/min, 23.6 min (minor enantiomer) : 25.6 min (major enantiomer)).

Further elution of column chromatography recovered **2** quantitatively.

(*S*)-*N*-(1-Phenyl-2,2-dimethylpropyl)-4-methoxybenzenamine 6: To a solution of **5** (191 mg, 1.0 mmol) and **1** (630 mg, 2.6 mmol) in toluene (20 ml) was added a solution of phenyllithium (1.76M, 1.14 ml, 2.0 mmol) at -23 °C over a period of 3 min. The mixture was stirred at -23 °C for 20 min and quenched with water (10 ml). The organic layer was separated and washed with brine and then dried over K_2CO_3. Concentration and following purification by silica gel column chromatography (benzene) followed by distillation (bp 230 °C/1.5 mmHg) gave *S*-**6** (228 mg, 85%) as a colorless oil. $[\alpha]_{435}^{20}$ -52.5 °(c 1.53, EtOH). IR ($CHCl_3$): 3440 cm^{-1}. ^{1}H-NMR ($CDCl_3$, TMS) δ: 0.98 (9H, s), 3.65 (3H, s), 3.96 (1H, s), 6.43 and 6.65 (each 2H, d, J=9.0 Hz), 7.1-7.4 (5H, m). MS *m/z*: 269 (M^+). Anal. Calcd for $C_{18}H_{23}NO$: C 80.25, H 8.61, N 5.20. Found: C 80.41, H 8.78, N 5.20.

Ee was determined by HPLC analysis to be 87% (Waters OptiPak XC, hexane-iPrOH (9:1), 0.1 ml/min, 43.3 min (minor enantiomer) : 46.3 min (major enantiomer)).

(*R*)-*N*-(4-Methoxyphenyl)-α-butylbenzenemethanamine (Table 2, entry 7): To a solution of **3** (133 mg, 0.63 mmol) and **2** (54 mg, 0.19 mmol) in iPr_2O (12.5 ml) was added a hexane solution of butyllithium (1.51M, 0.83 ml, 1.26 mmol) at -78 °C. The mixture was stirred at -78 °C for 1 h and quenched with water (10 ml). The organic layer was separated and washed with brine and then dried over K_2CO_3. Concentration and following purification by silica gel column chromatography (hexane-ether (3:1)) followed by distillation (bp 200 °C/2 mmHg) gave *R*-product (168 mg, 99%) as a pale yellow oil. $[\alpha]_{365}^{20}$ +92 °(c 1.21, EtOH). IR ($CHCl_3$): 3420 cm^{-1}. ^{1}H-NMR ($CDCl_3$, TMS) δ: 0.88 (3H, bt), 1.0-1.5 (4H, m), 1.7-1.8 (2H, m), 3.67 (3H, s), 4.21 (1H, t, J=6.6 Hz), 6.46 and 6.58 (each 2H, d, J=9.0 Hz), 7.2-7.4 (5H, m). MS *m/z*: 269 (M^+). Anal. Calcd for $C_{18}H_{23}NO$: C 80.25, H 8.61, N 5.20. Found: C 80.03, H 8.63, N 5.29.

Ee was determined by HPLC analysis to be 60% (Waters OptiPak TC, hexane-iPrOH (9:1), 0.25 ml/min, 19.8 min (major enantiomer) : 22.6 min (minor enantiomer)).

(*R*)-*N*-(4-Methoxy-2-methylphenyl)-α-ethenylbenzenemethanamine 8 (R^1=Ph, R^2=CH_2=CH) (Table 3, entry 3): Colorless oil of bp 150 °C/ mmHg. IR (neat): 3420, 1510 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.18 (3H, s), 3.60 (1H, bs), 3.70 (3H, s), 4.90 (1H, bd, J =5.8 Hz), 5.19 (1H, dt, J=9.7, 1.6 Hz), 5.24 (1H, dt, J=17.1, 1.6 Hz), 6.07 (1H, ddd, J=17.1, 9.7, 1.6 Hz), 6.43 (1H, d, J=8.6 Hz), 6.55 (1H, d, J=2.6 Hz), 6.6-6.7 (1H, m), 7.2-7.5 (5H, m). MS *m/z*: 253 (M^+). Anal. Calcd for C17H18NO: C 80.60, H 7.56, N 5.53. Found: C 80.46, H 7.59, N 5.78. $[\alpha]_D^{20}$ -7.0 °(c 1.30, $CHCl_3$). HPLC (Waters XC, hexane-iPrOH = 100:1, 0.5 ml/min, 16.4 min:19.9 min=83:17 (66 % ee)).

(*R*)-*N*-(3-Phenyl-1-methyl-2-propenyl)-4-methoxy-2-methylbenzeneamine 8 (R^1=PhCH=CH, R^2=Me) (Table 3, entry 4): Colorless oil of bp 170 °C/0.3 mmHg. IR (film): 3420, 1510 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, d, J=6.7 Hz), 2.17 (3H, s), 3.23 (1H, bs), 3.71 (3H, s), 6.20 (1H, dd, J=5.5, 16 Hz), 6.4-6.7 (5H, m), 7.1-7.4 (5H, m). MS *m/z*: 267 (M^+). Anal. Calcd for $C_{18}H_{21}NO$: C 80.86, H 7.92, N 5.24. Found: C 81.06, H 7.86, N 5.06. $[\alpha]_D^{20}$ +41.3 °(c 1.04, $CHCl_3$). HPLC (Waters XC, hexane-iPrOH = 100:1, 1.0 ml/min, 16.7 min:20.2 min=26.4:73.6 (47 % ee)).

(*R*)-*N*-(4-Methoxy-2-methylphenyl)-α-methyl-1-naphthalenemethanamine 8 (R^1=1-Naph, R^2=Me) (Table 3, entry 5): Colorless oil of bp 210 °C/0.3 mmHg. IR (film): 3440, 1510 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.67 (3H, d, J=6.7 Hz), 2.25 (3H, s), 3.65 (3H, s), 3.69 (1H, bs), 5.25 (1H, q, J=6.7 Hz), 6.16 (1H, d, J=8.7 Hz), 6.43 (1H, dd, J=8.7, 3.0 Hz), 6.70 (1H, d, J=3.0 Hz), 8.09-8.23 (1H, m). MS *m/z*: 291 (M^+). $[\alpha]_D^{20}$ -135.1 °(c 1.00, $CHCl_3$). HPLC (Waters XC, hexane-iPrOH (9:1), 0.3 ml/min, 19.0 min:25.7 min=80.4:19.6 (60 % ee)).

(*R*)-*N*-(4-Methoxy-2-methylphenyl)-α-methyl-2-naphthalenemethanamine 8 (R^1=2-Naph, R^2=Me) (Table 3, entry 6): Semisolid. IR (Nujol): 3380, 1510 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.60 (3H, d, J=6.7 Hz), 2.24 (3H, s), 3.64 (3H, s), 3.65 (1H, bs), 4.61 (1H, q, J=6.7 Hz), 6.32 (1H, d, J=8.6 Hz), 6.49 (1H, dd, J=8.6, 2.6 Hz), 6.69 (1H, d, J=2.6 Hz), 7.3-7.9 (7H, m). MS *m/z*: 291 (M^+). Anal. Calcd for $C_{20}H_{21}NO$: C 82.44, H 7.26, N 4.81. Found: C 82.30, H 7.31, N 4.82. $[\alpha]_D^{20}$ -19.1 °(c 0.95, $CHCl_3$). HPLC (Daicel OJ, hexane-EtOH (9:1), 1.0 ml/min, 21.8 min:24.7 min=24.76 (52 % ee)).

(*R*)-*N*-(4-Methoxy-2-methylphenyl)-α-butyl-2-naphthalenemethanamine 8 (R^1=2-Naph, R^2=Bu) (Table 3, entry 7): Pale yellow oil, IR (film): 3420, 1510 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.7-1.0 (3H, m), 1.1-1.6 (4H, m), 1.7-2.0 (2H, m), 2.24 (3H, s), 3.64 (3H, s), 3.70 (1H, bs), 4.22 (1H, t, J=6.6 Hz), 6.31 (1H, d, J=8.7 Hz), 6.48 (1H, dd, J=8.7, 2.6 Hz), 6.67 (1H, d, J=2.6 Hz), 7.3-7.9 (7H, m). MS *m/z*: 333 (M^+). Anal. Calcd for $C_{23}H_{27}NO$: C 82.84, H 8.16, N 4.20. Found: C 82.41, H 8.16, N 4.16. $[\alpha]_D^{20}$ -19.0 °(c 1.20, $CHCl_3$). HPLC (Waters TC, hexane-iPrOH (100:1), 0.3 ml/min, 25.9 min:29.7 min=84:16 (69 % ee)).

The reaction promoted by lithium amide of optically pure *R*-4: A ether solution of MeLi (1.35 ml, 2.1 mmol) was added to a solution of optically pure ***R*-4** (169 mg, 0.7 mmol) in toluene (14 ml) at -78 °C. The whole was stirred at -23 °C for 30 min. A solution of **3** (158 mg, 0.7 mmol) in toluene (3 ml) was added at -78 °C and the mixture was stirred at -42 °C for 3 h. The mixture was diluted with water (10 ml). The separated organic layer was washed with brine and then dried over K_2CO_3. Concentration and following column chromatography (SiO_2, hexane-Et_2O (3:1)) gave a pale yellow oil. Distillation provided the corresponding product (292 mg). Assuming a complete recovery of **4** added in the reaction, the yield of the methylation reaction is 73 %. Chiral HPLC analysis showed 53 % ee that corresponds to 11 % ee of the methylated product with *S*-absolute configuration.

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11. Catalyst turnover number (CTN) is calculated based on the equation: $CTN=ee_c\ yield_c / eq_c\ ee_s\ yield_s$ where ee_c, ee_s and $yield_c$, $yield_s$ represent %ee and %yield corresponding to catalytic and stoichiometric reaction, eq_c represents the molar equivalent of the catalyst to the imine.
12. We are also grateful to the Material Analysis Center of ISIR, Osaka University, for NMR measurements.
13. Melting points were measured using a Büchi 510 melting point apparatus and are not corrected. Optical rotations were taken with a Jasco DIP-181 polarimeter. IR spectra were taken with a Jasco infrared spectrometer model DS-402G. ^1H NMR spectra were taken with a JEOL GX-400 spectrometer at 400 MHz, a JNM-PS 100 spectrometer, a JEOL-FX 100 spectrometer at 100 MHz, or with a Hitachi R-90H spectrometer at 90 MHz. ^{13}C NMR spectra were taken with a JEOL GX-400 spectrometer at 100 MHz or a Hitachi R-90H spectrometer at 22.5 MHz. Chemical shift values are expressed in ppm relative to internal tetramethylsilane. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; m, multiplet. MS were taken with a JEOL-01, SG-2 mass spectrometer or a JEOL DX-300 mass spectrometer.
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