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Enantioselective Reaction of An Imine with Methyllithium Catalyzed by A Chiral Ligand

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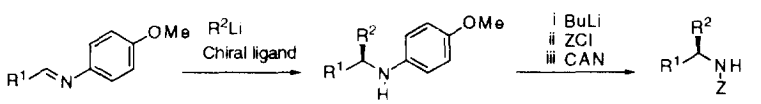
Abstract: Enantioselective reaction of benzaldehyde 4-anisidineimine **1** with methyllithium in toluene was mediated by a series of chiral aminoethers **3-11** to give the corresponding amine **2** in good to moderate ee. The chiral tridentate aminoethers **7-11** are superior to the bidentate ligands **3-6**. Lithium bromide affects significantly the enantioselectivity in the catalytic reaction, but not in the stoichiometric reaction.

It is highly promising that catalytic asymmetric control in a carbon-carbon bond forming reaction of a powerful carbonucleophile would provide a versatile synthetic tool.[1] We have been engaged in this area[2] and reported the first catalytic asymmetric addition reaction of organolithiums with imines to give β-substituted aldehydes in 99-80% ee[3] or chiral amines in 90-48% ee.[4] The external chiral ligand mediated enantioselective addition of organometallic reagents to imines has a high potential in the production of optically active amines as shown in Scheme 1. We describe herein our further approach toward structure-enantioselectivity relationships of the chiral ligand.[5]

Scheme 1

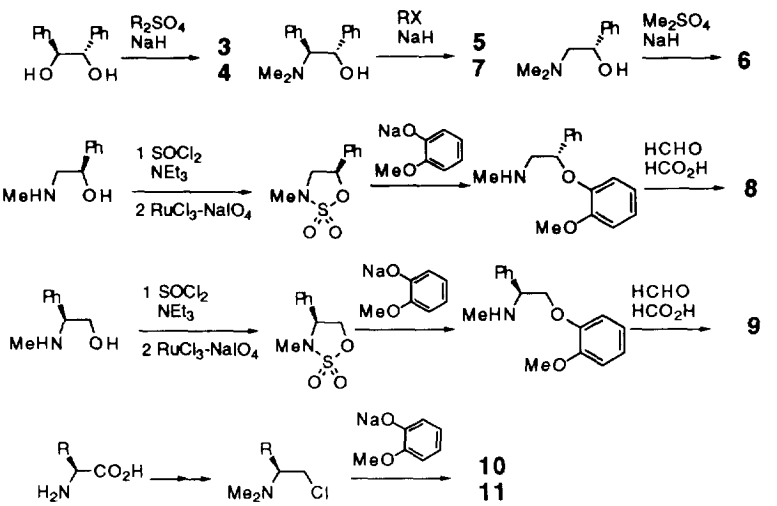


Synthesis of The Chiral Aminoethers

The chiral ethers **3** and **4** were prepared from the corresponding chiral diol as shown in Scheme 2.[3] Aminoethers **5** and **7** were prepared from the corresponding easily available chiral aminoalcohol. Aminoethers **6** and **8**[6] were prepared from mandelic acid *via* reduction, methylation, and ether formation. Aminoethers **9**[6] was prepared from from phenylglycine. Aminoethers **10**[7] and **11** were prepared from the corresponding commercially available amino acids via the acid chlorides.

Dedicated to the memory of Professor Hidemasa Takaya, deceased on 5 October 1995

Scheme 2

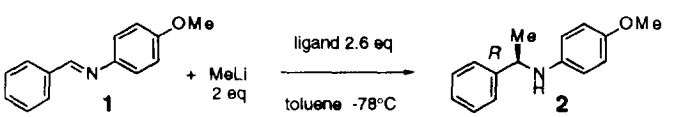


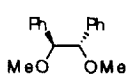
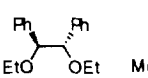
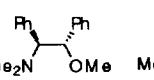
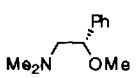
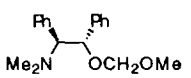
Structure-Enantioselectivity Relationships of The Chiral Aminoethers

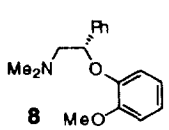
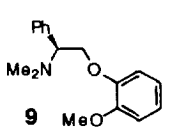
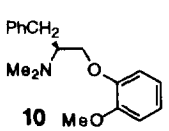
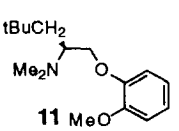
We started our research with the reaction of *p*-anisidineimine of benzaldehyde with methyllithium (2 eq) in toluene at -78 °C in the presence of stoichiometric amount (2.6 eq) of the chiral ligands.

The chiral bidentate ethers **3** and **4** exhibited moderate enantioselectivity, both producing *R*-**2** in 46% ee (Table 1).[8] Enantioselectivity was determined by HPLC analysis (Waters Optipak TC,

Table 1. Chiral ligand mediated enantioselective methylation of the imine



ligand	 **3**	 **4**	 **5**	 **6**	 **7**
ee%	46	46	38	36	56
Confgn	*R*	*R*	*R*	*R*	*R*
yield%	90	90	90	94	95

ligand	 **8**	 **9**	 **10**	 **11**
ee%	43	70	70	53
Confgn	*R*	*R*	*R*	*R*
yield%	97	96	94	93

hexane-iPrOH (9:1), 0.25 mL/min, 23.6 min (minor enantiomer):25.6 min (major enantiomer)). The absolute configuration was determined by convertion to the known secondary amine as shown in Scheme 1.

Replacement of one of the methoxy groups of **3** with a dimethylamino function **5** caused lower enantioselectivity, 38% ee. Replacement of a phenyl group on one of the stereogenic carbons with hydrogen **6** maintained the ee, at 36%. However, **7**, bearing an additional coordinating site, improved the ee to 56%.

The tridentate ligand **8** produced *R*-**2** in 43% ee. The same type ligand **9**,[6] bearing a phenyl group on the carbon attached by dimethylamino function, exhibited an improved enantioselectivity, 70%. Replacement of the phenyl with a benzyl group **10** gave the same level of enantioselectivity, 70% ee. Unfortunately, **11**, bearing the more bulky neopentyl group, did not improve the ee, 53%.

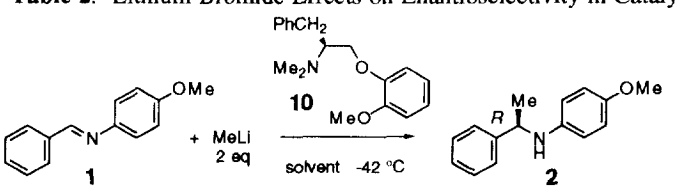
It is noteworthy that the ligands of *S*-configuration gave constantly *R*-**2**, indicating that similar chelated structures of methyllithium-ligands are involved in the reaction.

Lithium Bromide Influence on Enantioselectivity

It has been shown that lithium halide influences the enantioselectivity through changing aggregation structures of organolithiums.[9] In the presence of a stoichiometric amount of **10**, the reactions with halide free and lithium bromide-complexed methyllithiums at -42 °C gave the same level of enantioselectivities 66-60%, regardless to the solvent used (entries 1, 3, 5, Table 2). On the other hand, although the reaction with halide free methyllithium and 0.2 eq **10** gave the same level of enantioselectivity, 58% ee (entry 2), the reactions with lithium bromide-methyllithium complex in toluene and ether solvents gave *R*-**2** in significantly decreased ee, 34 and 16%, respectively (entries 4, 6).

These data imply the following: (1) methyllithium-lithium bromide-**10**, three component complex gave the same level of enantioselectivity regardless to the solvents, (2) there is small possibility that the chiral ligand is trapped by lithium bromide and does not operative in the addition reaction, (3) in ether solvent, the reactivity of methyllithium-lithium bromide complex is enhanced rather than

Table 2. Lithium Bromide Effects on Enantioselectivity in Catalytic Reactions



entry	MeLi	**10** eq	solvent	ee%	yield%
1	MeLi	2.6	toluene	66	95
2	MeLi	0.2	toluene	58	85
3	MeLi-LiBr	2.6	toluene	64	97
4	MeLi-LiBr	0.2	toluene	34	81
5	MeLi-LiBr	2.6	Et_2O	60	97
6	MeLi-LiBr	0.2	Et_2O	16	90

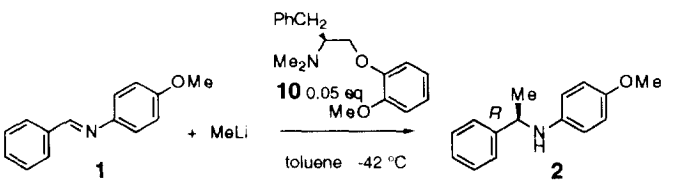
methyllithium-lithium-bromide-**10** complex, or (4) regeneration of methyllithium-lithium bromide-**10**, three component complex through ligand exchange is retarded in ether solvent rather than in toluene solvent.

Influence of Methyllithium/Chiral Ligand Ratio on Enantioselectivity

It is important to clarify the influence of methyllithium/ligand ratio on enantioselectivity, because regeneration of methyllithium-ligand complex takes place through ligand transfer from the produced lithium amide-ligand complex to methyllithium.

In the presence of 0.05 eq **10** the reaction of **1** with methyllithium in a range of 1.2 to 8.0 eq gave *R*-**2** in 40 to 33% ees (Table 3). It is apparent from these data that the reactive species, methyllithium-**10** complex, is efficiently regenerated through ligand transfer.

Table 3. Influence of Methyllithium Equivalents on Enantioselectivity



entry	MeLi/eq	MeLi/**10** ratio	ee%	yield%
1	1.2	24	36	91
2	2.0	40	40	96
3	4.0	80	36	98
4	8.0	160	33	98

Further studies towards the development of much more effective chiral ligands are in progress in our laboratories.

Acknowledgement:

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Experimental[10]

Preparation of the chiral ligands

(-)-(1*S*,2*S*)-*N*,*N*-Dimethyl-2-methoxy-1,2-diphenylethylamine 5: A mixture of (-)-(1*S*,2*S*)-*N*,*N*-dimethylamino-1,2-diphenylethanol[11] (579 mg, 2.4 mmol) and 60% sodium hydride (120 mg, 3 mmol) in DMF (2.5 mL) was stirred under argon at rt for 1.5 h. A solution of methyl iodide (365 mg,

2.5 mmol) in DMF (2.5 mL) was added at 0°C. The whole was stirred at rt for 1.5 h and poured onto ice water (10 mL). The mixture was extracted with ethyl acetate (40 ml x 2). The combined extracts were washed with brine (20 mL) and dried over Na_2SO_4. Concentration and following silica gel column chromatography ($CHCl_3$-MeOH, 10:1) afforded a pale yellow oil. Distillation (bp 130 °C/0.3 mmHg) afforded a colorless oil (526 mg, 86%). $[\alpha]_D^{20}$ -45.2 (c 1.05, $CHCl_3$). IR ($CHCl_3$): 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$, TMS) δ: 2.30 (6H, s), 3.24 (3H, s), 3.78 and 4.58 (each 1H, d, J=9.3 Hz), 6.9-7.3 (10H, m). MS *m/z*: 256 (M^+). Anal. Calcd for $C_{17}H_{21}NO$: C 79.96, H 8.29, N 5.49. Found: C 79.82, H 8.40, N 5.48.

(+)-(*S*)-*N*,*N*-Dimethyl-2-methoxy-2-phenylethylamine 6: A mixture of (+)-(*S*)-2-dimethylamino-1-phenylethanol[12] (1.63 g, 9.9 mmol) and 60% sodium hydride (0.48 g, 12.4 mmol) in DMF (10.5 mL) was stirred under argon at rt for 1.5 h. A solution of methyl iodide (1.51 mg, 10.4 mmol) in DMF (2.0 mL) was added at 0°C. The whole was stirred at rt for 1.5 h and poured onto ice water (100 mL). The mixture was extracted with ethyl acetate (50 ml x 2). The combined extracts were washed with brine (20 mL) and dried over Na_2SO_4. Concentration and following silica gel column chromatography ($CHCl_3$-MeOH, 10:1) afforded a pale yellow oil. Distillation (bp 140 °C/50 mmHg) afforded a colorless oil (1.05 g, 59%). $[\alpha]_D^{20}$ +118 (c 1.18, MeOH). IR (film): 1460 cm^{-1}. ^{1}H-NMR ($CDCl_3$, TMS) δ: 2.28 (1H, dd, J=3.5, 13.2 Hz), 2.31 (6H, s), 2.73 (1H, dd, J=8.9, 13.2 Hz), 3.24 (3H, s), 4.29 (1H, dd, J=3.5, 8.9 Hz), 7.31 (5H, s). MS *m/z*: 179 (M^+). Anal. Calcd for $C_{11}H_{17}NO$: C 73.70, H 9.56, N 7.81. Found: C 73.40, H 9.41, N 7.57.

(+)-(1*S*,2*S*)-*N*,*N*-Dimethyl-2-methoxymethoxy-1,2-diphenylethylamine 7: A mixture of (-)-(1*S*,2*S*)-*N*,*N*-dimethylamino-1,2-diphenylethanol[11] (534 mg, 2.2 mmol) and 60% sodium hydride (133 mg, 3.3 mmol) in DMF (10 mL) was stirred under argon at rt for 1.5 h. A solution of methoxymethyl chloride (223 mg, 2.8 mmol) in DMF (2.5 mL) was added at 0°C. The whole was stirred at rt for 1.5 h and poured onto ice water (10 mL). The mixture was extracted with ethyl acetate (40 ml x 2). The combined extracts were washed with brine (20 mL) and dried over Na_2SO_4. Concentration and following silica gel column chromatography ($CHCl_3$-MeOH, 10:1) afforded a pale yellow oil. Distillation (bp 140 °C/0.3 mmHg) afforded a colorless oil (496 mg, 79%). $[\alpha]_D^{20}$ +41.7 (c 0.88, $CHCl_3$). IR ($CHCl_3$): 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$, TMS) δ: 2.31 (6H, s), 3.89 (1H, d, J=9.8 Hz), 4.54 and 4.65 (each 1H, d, J=6.9 Hz), 5.15 (1H, d, J=9.8 Hz), 6.9-7.3 (10H, m). MS *m/z*: 284 (M^+-1). Anal. Calcd for $C_{18}H_{23}NO_2$: C 75.76, H 8.12, N 4.91. Found: C 76.05, H 8.26, N 4.94.

(+)-1-[(*S*)-2-Dimethylamino-1-phenylethoxy]-2-methoxybenzene 8: Prepared according to the reported procedure.[6] $[\alpha]_D^{20}$ +35.9 (c 2.33, $CHCl_3$).

(+)-1-[(*S*)-2-Dimethylamino-2-phenylethoxy]-2-methoxybenzene 9: Prepared according to the reported procedure.[6] $[\alpha]_D^{25}$ +25.9 (c 1.14, EtOH).

(+)-(*S*)-2-Amino-4,4-dimethylpentanol: To a suspension of $LiAlH_4$ (5.31 g, 0.14 mol) in THF (350 mL) was added (*S*)-2-amino-4,4-dimethylpentanoic acid (10.2 g, 0.07 mol) portionwise at 0 C. The mixture was stirred under reflux for 4 h, and was then added successively with water (6 mL), 15% NaOH (6 mL), and water (18 mL) at 0 C. Filtration, concentration, and followed by distillation (bp 112-114 °C/20 mmHg) afforded a colorless oil (6.8 g, 74%). $[\alpha]_D^{20}$ +5.7 (c 1.90, MeOH). IR (nujol): 3360, 3300, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$, TMS) δ: 0.95 (9H, s), 0.9-1.4 (2H, m), 2.04 (3H, bs), 2.8-3.0 (1H, m), 3.19

(1H, dd, J=8.3, 10.0 Hz), 3.51 (1H, dd, J=4.0, 10.0 Hz). MS *m/z*: 132 (M^+). Anal. Calcd for $C_7H_{17}NO$: C 64.07, H 13.06, N 10.67. Found: C 64.30, H 13.20, N 10.73.

(+)-(*S*)-2-Dimethylamino-4,4-dimethylpentanol: To a solution of the above alcohol (6.62 g, 0.05 mol), 98% HCO_2H (14.1 g, 0.3 mol) in water (15 mL) was added dropwise 35% HCHO (12.9 g, 0.15 mol) under reflux. The mixture was stirred under reflux for 7 h and then added with 10% NaOH (pH 11). The mixture was extracted with $CHCl_3$ (80 mL x 3). The combined extracts were washed with brine and dried over K_2CO_3. Concentration followed by distillation (bp 135 C/87 mmHg) afforded a colorless oil (6.58 g, 82%). $[\alpha]_D^{20}$ +9.9 (c 1.11, MeOH). IR (film): 3380 cm^{-1}. ^{1}H-NMR ($CDCl_3$, TMS) δ: 0.73 (1H, dd, J=8.3, 14.4 Hz), 0.90 (9H, s), 1.43 (1H, dd, J=1.5, 14.4 Hz), 2.1 (1H, bs), 2.18 (6H, s), 2.7 (1H, m), 3.24 (1H, dd, J=10.2, 10.2 Hz), 3.50 (1H, dd, J=5.5, 10.2 Hz). MS *m/z*: 160 (M^++1). Anal. Calcd for $C_9H_{21}NO$: C 67.87, H 13.29, N 8.79. Found: C 67.73, H 13.37, N 8.75.

(+)-(*S*)-1-Chloro-2-dimethylamino-4,4-dimethylpentane hydrochloride: To a solution of the above alcohol (6.47 g, 0.04 mol) in dioxane (90 mL) was added dropwise $SOCl_2$ (6.3 mL, 0.086 mol) at 0 °C. The mixture was stirred under reflux for 3 h. After standing over night at rt, the precipitated was colorless solid of mp 184.5-185.0 °C was filtered (5.84 g, 67%). $[\alpha]_D^{20}$ +11.1 (c 1.11, MeOH). IR (film): 2600 cm^{-1}. ^{1}H-NMR ($CDCl_3$, TMS) δ: 0.98 (9H, s), 1.65 (1H, dd, J=7.7, 15.3 Hz), 1.92 (1H, dd, J=3.4, 15.3 Hz), 2.81 (6H, s), 3.2-3.6 (2H, m), 4.5 (1H, m), 10.6 (1H. bs). MS *m/z*: 177 (M^+). Anal. Calcd for $C_9H_{20}NCl$ HCl: C 50.47, H 9.88, N 6.54, Cl 33.11. Found: C 50.56, H 10.11, N 6.42, Cl 33.33.

(+)-1-[(*S*)--4,4-Dimethyl-2-dimethylaminopentoxy]-2-methoxybenzene 11: A mixture of guaiacol (3.46 g, 27.9 mmol) and sodium hydride (60% dispersion, 1.26 g, 31.5 mmol) in DMF (15 mL) was stirred at room temperature for 1 h. A solution of the above chloride (1.93 g, 9 mmol) in DMF (110 mL) was added at 0 °C over a period of 50 min. The mixture was stirred at room temperature for 43 h and diluted with water (200 ml). The mixture was extracted with AcOEt (200 mL x 2). The extracts were diluted with hexane (400 mL) and then washed with brine. Concentration gave an oil which was diluted with Et_2O (100 mL) and extracted with 10% aq. HCl (15 mL x 3). The combined aqueous extracts were washed with Et_2O. After addition of 10% NaOH (to pH 11), the aqueous layer was extracted with Et_2O. The extract was washed with brine and concentrated to give a pale yellow oil. Purification by silica gel column chromatography ($CHCl_3$-MeOH 20:1) followed by distillation (bp 120 °C/0.3 mmHg) gave a colorless oil (0.96 g, 42%). $[\alpha]_D^{20}$ +8.6 (c 1.96, $CHCl_3$). IR (film): 1600 cm^{-1}. ^{1}H-NMR($CDCl_3$, TMS) δ: 0.96 (9H, s), 1.18 (1H, dd, J=5.6, 14.1 Hz), 1.48 (1H, dd, J=4.9, 14.1 Hz), 2.38 (6H, s), 2.7 (1H, m), 3.83 (1H, dd, J=4.6, 10 Hz), 3.84 (3H, s), 4.08 (1H, dd, J=7.6, 10 Hz), 7.25 (4H, s). MS *m/z*: 265 (M^+). Anal. Calcd for $C_{16}H_{27}NO_2$: C 72.41, H 10.25, N 5.28. Found: C 72.67, H 10.45, N 5.26.

Asymmetric methylation of the imine in the presence of the chiral aminoether* 10 *(Table 2, entry 2)

(+)-(*R*)-*N*-(4-Methoxyphenyl)-α-methylbenzenemethanamine 2: To a solution of **1** (317 mg, 1.5 mmol) and **10** (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*-**2** (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 **10** quantitatively.

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10. Melting points were measured using a Yamato MODEL MP-21 melting point apparatus and are not corrected. Optical rotations were taken with a Jasco DIP-370 polarimeter. IR spectra were taken with a HITACHI infrared spectrometer model 260-10. ^{1}H-NMR spectra were taken with a JEOL GX-400 spectrometer at 400 MHz, a HITACHI R-90H spectrometer at 90 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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