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Steric Tuning in Chiral Ligand Mediated Enantioselective Alkylation of Imines

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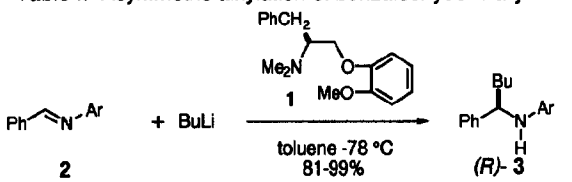
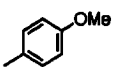
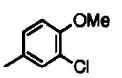
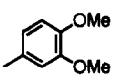
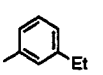
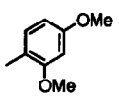
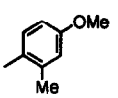
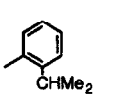
Abstract: Enantioselective alkylation of achiral aldimines **4** prepared from 2-methylanisidine with organolithiums was mediated by a chiral aminoether **1** to give the corresponding amines **5** in high ee.

External chiral ligand mediated enantioselective addition of organometallic reagents to imines has a high potential in the production of optically active amines.[1] As a research program aimed at the development of asymmetric reactions mediated by external chiral ligands,[2] we have already reported the first asymmetric addition of organolithiums to imines derived from 4-anisidine and aldehydes, giving the product amines in 75~48% ee.[3,4] We describe herein a steric tuning of the reaction resulting in higher ee of up to 90%.

Since the anisidine moiety is sterically and electronically tunable, we examined reactions of butyllithium (2 eq) in toluene at -78 °C in the presence of **1** (2.6 eq) with several imines derived from

Table I. Asymmetric alkylation of benzaldehyde *N*-arylimines



Ar					
	a	**b**	**c**	**d**	**e**
ee %	58	58	12	41	54
Ar					
	f	**g**	**h**	**i**	**j**
ee %	34	65	68	70	52

benzaldehyde and various substituted anilines (Table I). A 4-methoxy substituent does not affect the selectivity, **2a** and **2b** both giving the same level of enantioselectivity 58%.[5] Substituents at C-3 exerted a profound effect on enantioselectivity, electron withdrawing group chlorine (**2c**), electron donating groups

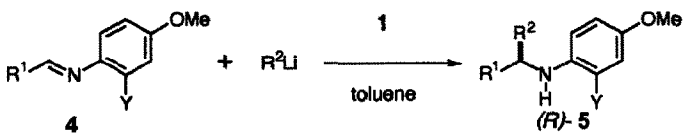
methoxy (**2d**) and ethyl (**2e**), providing decreased 12, 41, and 54% ees, respectively. A 2-methoxy (**2f**) substituent gave a lower 34% ee, probably due to disfavorable coordination with an organolithium-ligand complex. To our delight, 2-substitution, methyl (**2g**), ethyl (**2h**), and isopropyl (**2i**) groups provided higher enantioselectivities, 65, 68, and 70% ees, respectively, along with increased bulkiness. However, 2,6-dimethyl substitution (**2j**) provided a lower 52% ee.

2-Alkyl substituents really exert profound effects on the enantioselectivity in the reaction with methyllithium at -78 °C (Table II, entries 1~3). Benzaldehyde imines derived from 2-isopropyl- (**4** Y=iPr), 2-methyl- (**4** Y=Me), and anisidine (**4** Y=H) were converted to the corresponding amines **5** (R^1=Ph, R^2=Me) in 90, 86, and 70% ee, respectively.

However, oxidative removal of the 2-isopropyl-4-methoxyphenyl moiety from **5** (R^1=Ph, R^2=Me, Y=iPr) via **6** was unsuccessful, and then we selected commercially available 2-methylanisidine as a removable amine component.

The reaction of organolithiums with **4** (Y=Me), derived from aldehydes and 2-methylanisidine, in toluene at -100 °C gave **5** in high ee (Table II, entries 4~8).

Table II. Asymmetric alkylation of imines derived from 2-substituted anisidine

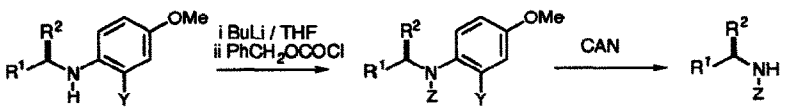


4 (R)-**5**

Entry	R^1	Y	R^2	temp °C	ee %	yield %
1	Ph	iPr	Me	-78	90	94
2	Ph	Me	Me	-78	86	98
3	Ph	H	Me	-78	70	98
4	Ph	Me	Me	-100	90	97
5	Ph	Me	Bu	-100	70	96*
6	Ph	Me	CH_2=CH	-100	90	90
7	Ph-CH=CH	Me	Me	-100	90	90
8	1-Naph	Me	Me	-100	78	94

* In ether

Enantiomerically pure **5** (R^1=Ph, R^2=Y=Me) was available in 78% yield by recrystallization of **5** (90% ee) from hexane, and was converted to the optically pure benzyloxycarbonyl derivative of phenethylamine **7** in two steps.



(R)-**5** (R)-**6** (R)-**7**

It is noteworthy that the reaction of methyllithium with 4 (R^1=Ph, Y=Me) was catalyzed by 0.3 equivalent of 1 in toluene at -40 °C to afford 5 (R^1=Ph, R^2=Y=Me) in 66% ee and 88% yield.[6]

Further studies toward development of much more effective ligand are in progress in our laboratories.[7]

Experimental[8]

Preparation of the imine 4 (R^1=Ph, Y=Me)

A mixture of 4-methoxy-2-methylaniline (1.90 g, 14 mmol) and benzaldehyde (1.38 g, 13 mmol) was stirred at 100 °C for 1 h and diluted with 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 170 °C/3 mmHg) gave 4 (R^1=Ph, Y=Me, 2.71 g, 87%) as a pale yellow oil. IR ($CHCl_3$): 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$, TMS) δ: 2.39 (3H, s), 3.81 (3H, s), 6.74 (1H, dd, J=2.9, 8.3Hz), 6.80 (1H, d, J=2.9 Hz), 6.95 (1H, d, J=8.3 Hz), 7.36-7.96 (5H, m), 8.38 (1H, s). MS *m/z*: 225 (M^+). Anal. Calcd for $C_{15}H_{15}NO$: C 79.97, H 6.71, N 6.22. Found: C 79.69, H 6.56, N 6.17.

Asymmetric alkylation of 4 (Y=Me) with organolithium (Table II, entry 4)

To a solution of 4 (R^1=Ph, Y=Me) (88 mg, 3.92 mmol) and 1 (2.91 g, 10.2 mmol) in toluene (80 ml) was added an ether solution of methyllithium (low halide, 5.03 ml, 7.84 mmol) at -100 °C over a period of 2 min. The mixture was stirred at -100 °C for 2 h and quenched with water (50 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)) gave 5 (R^1=Ph, Y=R^2=Me) as pale yellow solid. Distillation (bp 160 °C/0.3 mmHg) gave 5 (Y=R=Me) (912 mg, 97%) as pale yellow solid of mp 84.0-86.5 °C. $[\alpha]_D^{20}$ -41.7 °(c 1.40, $CHCl_3$). IR ($CHCl_3$): 3420 cm^{-1}. ^{1}H-NMR ($CDCl_3$, TMS) δ: 1.52 (3H, d, J=6.7 Hz), 2.20 (3H, s), 3.54 (1H, bs), 3.67 (3H, s), 4.45 (1H, q, J=6.7 Hz), 6.29 (1H, d, J=8.6 Hz), 6.53 (1H, dd, J=3.3, 8.6 Hz), 6.70 (1H, d, J=3.3 Hz), 7.10-7.40 (5H, m). MS *m/z*: 241 (M^+). Anal. Calcd for $C_{16}H_{19}NO$: C 79.63, H 7.94, N 5.80. Found: C 79.55, H 7.64, N 5.51.

Ee was determined by HPLC analysis to be 90% (Waters OptiPak TC, hexane-EtOH (100:1), 0.3 ml/min, 19.7 min (major enantiomer) : 24 min (minor enantiomer)=94.8:5.2).

Recrystallization of the solid obtained above from hexane gave optically pure enantiomer 5 (R^1=Ph, Y=R^2=Me) of mp 87.5-88.0 °C in 78% recovery. $[\alpha]_D^{20}$ -45.5 (c 1.23, $CHCl_3$).

Preparation of (R)-N-benzyloxycarbonyl-α-methylbenzylamine 7 (R^1=Ph, R^2=Me) by successive benzyloxycarbonylation and CAN oxidation

To a solution of 5 (R^1=Ph, Y=R^2=Me, >99% ee)(470 mg, 1.95 mmol) in THF (23 ml) was added a hexane solution of butyllithium (2.6 ml, 3.9 mmol) at -78 °C. The mixture was stirred at –78 °C for 10 min and at rt for 10 min. Benzyloxycarbonyl chloride (0.56 ml, 3.9 mmol) was added to the mixture at -78 °C, and whole was stirred at -78 °C for 1 h and allowed to warm-up to rt. After the addition of water (10 ml), CH_2Cl_2 (200 ml), and 10% aq. NaOH (40 ml), the organic layer was separated and washed successively with 10% aq. HCl, satd. aq. $NaHCO_3$, and brine, and then dried over K_2CO_3. Concentration and silica gel column chromatography (hexane-ether (5:1)) gave 6 (R^1=Ph, Y=R^2=Me, 611 mg, 84%) as a colorless oil.

To a solution of **6** (R^1=Ph, Y=R^2=Me) obtained above in CH_3CN (27 ml) was added ceric ammonium nitrate (CAN) (2.68 g, 4.89 mmol) in water (13 ml) at 0 °C over a period of 5 min. After stirring at rt for 1 h, a solution of CAN (1.79 g, 3.26 mmol) in water (4 ml) was added to the mixture and the whole was stirred another 1 h. After addition of water (200 ml), the mixture was extracted with AcOEt. The organic layer was washed successively with 5% aq. $NaHCO_3$, 10% aq. Na_2SO_4, 5% aq. $NaHCO_3$, and brine, and then dried over $MgSO_4$. Concentration and purification by silica gel column chromatography (hexane-AcOEt (3:1)) gave optically pure (*R*)-*N*-benzyloxycarbonyl-α-methylbenzylamine **7** (R^1=Ph, R^2=Me) (205 mg, 50%) as pale yellow solid of mp 60-62 °C. $[\alpha]_D^{20}$ -45.0 (c 1.23, EtOH). IR ($CHCl_3$): 1715 cm^{-1}. ^{1}H-NMR ($CDCl_3$, TMS) δ: 1.45 (2H, d, J=7.0 Hz), 4.6-5.0 (1H, m), 7.20 (10H, s). MS *m/z*: 255 (M^+). Anal. Calcd for $C_{16}H_{17}NO_2$: C 75.27, H 6.71, N 5.49. Found: C 75.04, H 6.61, N 5.48.

Absolute configuration and optical purity were determined by comparison of optical rotation ($[\alpha]_D^{20}$ -45.3 (c 1.28, EtOH)) of the authentic sample prepared from optically pure (*R*)-α-methylbenzylamine.

References and Notes

1. K. Tomioka, *Synthesis*, **1990**, 541.
2. K. Tomioka, M. Shindo and K. Koga, *J. Am. Chem. Soc.* **1992**, *114*, 8732; and references cited therein.
3. K. Tomioka, I. Inoue, M. Shindo and K. Koga, *Tetrahedron Lett.* **1990**, *31*, 6681.
4. Similar approaches have been reported. S. Itsuno, H. Yanaka, C. Hachisuka and K. Ito, *J. Chem. Soc., Perkin Trans. I*, **1991**, 1341; A. R. Katritzky and P. A. Harris, *Tetrahedron: Asymmetry*, **1992**, *3*, 437; K. Soai, T. Hatanaka and T. Miyazawa, *J. Chem. Soc., Chem. Commun.* **1992**, 1097.
5. Ee was determined by HPLC using chiral column. Absolute configuration was determined by converting **3** or **5** to the benzyloxycarbonyl amides **7** or the corresponding amines.
6. The reaction was not catalyzed by **1** at -100 °C and gave **5** in the yield corresponding to the amount of **1** used. Catalyst turnover was observed at -40 °C to bring the reaction complete. Stoichiometric reaction gave **5** in 77% ee at -40 °C.
7. We are grateful to The Research Foundation for Optically Active Compounds, Grant-in-Aid for Scientific Research, Ministry of Education, Science and Culture, Japan, and Ono Pharmaceutical Company Ltd., for partial support of this work. We are also grateful to the Material Analysis Center of ISIR, Osaka University, for NMR measurements.
8. 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. ^{1}H-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-24 spectrometer at 60 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.