Enantioface-differentiating Addition of Butyllithium to Acetophenone by the Use of (1*S*,2*S*,5*S*)-3-[(*S*)-2-Methoxy-1-alkylethylimino]-2-pinanols as Chiral Ligands

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Synopsis. Butyllithium and acetophenone gave optically active 2-phenyl-2-hexanol (33% e.e.) in good yield in the presence of (1*S*,2*S*,5*S*)-3-[(*S*)-2-methoxy-1-alkylethylimino]-2-pinanol (**1**).

Although successful asymmetric reductions of prochiral ketones to optically active secondary alcohols by chiral hydride reagents have been extensively reported,[1,2] studies on enantioface-differentiating additions by metal alkyls to yield optically active tertiary alcohols are limited.[3-6] We wish to report here an example of asymmetric addition of butyllithium (BuLi) to acetophenone in the presence of chiral ligands.

Experimental

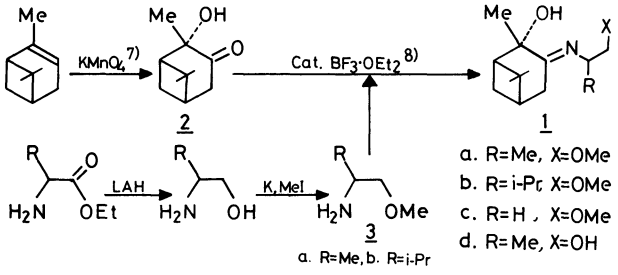
General. The ^{1}H NMR spectra were recorded at 60 MHz with tetramethylsilane as an internal standard, and the chemical shifts are given in δ values.

Syntheses of the Schiff Bases. The Schiff bases (**1a—1d**) used in this study as chiral ligands were synthesized according to Scheme 1.

(1S,2S,5S)-3-[(S)- or (R)-2-Methoxy-1-methylethylimino]-2-pinanol ((S)- or (R)-1a): (1*S*,2*S*,5*S*)-2-Hydroxy-3-pinanone (**2**) (4.1 g, 25 mmol) was caused to react with (*S*)-1-methoxy-2-propanamine ((*S*)-**3a**) (3.3 g, 37 mmol) in dichloromethane under reflux for 4 h. After quenching with sodium carbonate, (*S*)- or (*R*)-**1a** was isolated by distillation (3.7 g, 67%). Other Schiff bases (1*S*,2*S*,5*S*)-3-[(*S*)-2-methoxy-1-isopropyl-ethylimino]-2-pinanol ((*S*)-**1b**), (1*S*,2*S*,5*S*)-3-[2-methoxyethylimino]-2-pinanol **1c**), and (1*S*,2*S*,5*S*)-3-[(*S*)-2-hydroxy-1-methylethylimino]-2-pinanol ((*S*)-**1d**) were synthesized similarly to (*S*)-**1a**. Physical constants of the schiff bases are shown in Table 1.

Typical Asymmetric Addition Reactions to Aectophenone. In situ *System*: BuLi (4.6 mmol) was subjected to react with (*S*)-**1a** (0.3 g, 1.3 mmol) for 1 h in hexane (23 ml) at room temperature. After the reaction system was cooled down to −78 °C, acetophenone (0.16 g, 1.3 mmol) was added, and the reaction was quenched with 1 M hydrochloric acid (6 ml (1 M = 1 mol dm^{-3})) after 2 h. After usual work-up, 2-phenyl-2-hexanol was isolated by column chromatography (silica gel, ethyl acetate).

Prereacted System: After the reaction of BuLi with (*S*)-**1a** in specified molar ratio for 1 h, the reaction system was evacuated under vacuum, and the solid product was washed with hexane for several times. The product was suspended in hexane and treated with newly added one equivalent BuLi for 1 h. Acetophenone was added to the reaction system and allowed to react for 2 h.



Scheme 1. Synthetic routes to the chiral ligands. Me, MeO, and *i*-Pr are methyl, methoxyl, and isopropyl groups, respectively.

TABLE 1. ANALYTICAL DATA OF SCHIFF BASE LIGANDS **1a—1d**

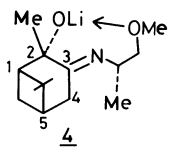
Compd	Bp (θ_m/°C)/mmHg†	$[\alpha]_D$ °	Analysis (%)[a] C	H	N	IR[b] ν/cm^{-1}	^{1}H NMR[c] (δ)ppm
(*S*)-**1a**	74.5/0.22	+16.8[d]	70.29 (70.25)	10.58 (10.53)	5.67 (5.85)	3440 1640 1385 1370 1105	1.06 (3H, d, *J*=6.0Hz, C*H*$_3$CH), 0.87 and 1.33 (6H, two s, (C*H*$_3$)$_2$C), 1.43 (3H, s, C*H*$_3$C-O), 1.88—2.20 (2H, m, C*H*$_2$), 1.90—2.48 (2H, m, C*H*), 2.48—2.70 (2H, m, C*H*$_2$ C=N), 3.30 (3H, s, OC*H*$_3$), 3.30—3.42 (2H, AMX type q, J_1=6.0Hz, J_2=2.0Hz, C*H*$_2$O), 3.41—4.00 (1H, AMX type m, J_1=6.0Hz, J_2=2.0Hz, NC*H*)
(*R*)-**1a**	—	0.0[e]	—	—	—		
(*S*)-**1b**	90.0/0.36	−16.4[f]	71.66 (71.86)	10.51 (10.93)	4.83 (5.24)	3440 1640 1385 1370 1100	0.87 and 0.96 (6H, dd, *J*=5.8Hz, (C*H*$_3$)$_2$CH), 0.89 and 1.33 (6H, two s, (C*H*$_3$)$_2$CH), 1.43 (3H, s, C*H*$_3$ C-O), 1.90—2.21 (2H, m, C*H*$_2$), 1.87—2.47 (2H, m, C*H*), 2.47—2.69 (2H, m, C*H*$_2$ C=N), 3.28 (3H, s, C*H*$_3$O), 3.30—3.70 (3H, m, OC*H*$_2$C*H*N)
1c	76.0/0.40	+6.2[g]	69.10 (69.30)	10.29 (10.29)	5.86 (6.22)	3440 1640 1385 1370	0.87 and 1.33 (6H, two s, (C*H*$_3$)$_2$C), 1.45 (3H, s, C*H*$_3$C-O), 1.87—2.40 (4H, m, C*H*$_2$, C*H*), 2.40—2.67 (2H, broad s, C*H*$_2$ C=N), 3.30 (3H, s, C*H*$_3$O), 3.30—3.88 (4H, m, NC*H*$_2$C*H*$_2$O)
(*S*)-**1d**	101—103[h]	+40.6[i]	68.86 (69.30)	9.91 (10.29)	6.23 (6.22)	1110 —	0.88 and 1.31 (6H, two s, (C*H*$_3$)$_2$C), 1.08 (3H, d, *J*=6.0Hz, C*H*$_3$CH), 1.46 (3H, s, C*H*$_3$C-O), 1.80—2.12 (2H, broad, C*H*$_2$), 2.12—2.60 (2H, m, C*H*), 2.60—2.88 (2H, broad, C*H*$_2$C=N), 3.35—4.05 (3H, m, NC*H*C*H*$_2$O)

a) Values in parentheses are calculated ones. b) Measured as NaCl sandwich. c) Measured in $CDCl_3$ except (*S*)-**1d**, which was measured in CD_3OD. d) c 1.79, $CHCl_3$, 23 °C. e) c 2.56, $CHCl_3$, 21 °C. f) c 0.73, $CHCl_3$, 21 °C. g) c 1.78, $CHCl_3$, 22 °C. h) mp (θ_m/°C). i) c 3.29, $CHCl_3$, 23 °C. †1 mmHg=133.322 Pa.

The enantiomeric excess (% e.e.) was determined by the α-methyl signal splitting in ^{1}H NMR using chiral shift reagent, tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorate]europium (III) (Eu(tfc)$_3$).[9]

Results and Discussion

Species Responsible for Asymmetric Induction. ^{1}H NMR and IR spectra of the reaction system of BuLi and (*S*)-**1a** indicated the structure **4** for the reaction product in 1:1 molar ratio. Peak broadening of the methylene protons of BuLi in the ^{1}H NMR of the reaction system in 2:1 molar ratio suggested that the principal product in this molar ratio was the associated species of BuLi with **4**. In the ^{1}H NMR of the product in 3.5:1 molar ratio, not only peak broadening but also further changes were observed: C-4 Methylene signal decreased and a new peak appeared around at 4.5 ppm. This signal is assignable to olefinic proton of lithioenamine.[10] Quantitative analysis of Li (5.68%) and incorporation of deuterium atom at 4-position by quenching with dilute D_2O–DCl strongly suggested the formation of lithioenamine **5** in the reaction of 3.5:1 molar ratio.



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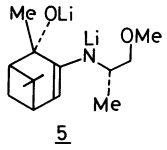

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The results of asymmetric addition are shown in Table 2. The reaction did not proceed when less than two equimolar amounts of BuLi to (*S*)-**1a** were used. No reaction was observed either, when one equivalent BuLi was added to prereacted system **4** (run No. 9). Only small optical yield was obtained in 3:1 *in situ* system (No. 2), or when one equivalent BuLi was added to the prereacted system (2:1) (No. 10), although high chemical yield could be attained. The species of 3.5:1 systems gave reasonably high chemical and optical yields (No. 3, 11), and the highest optical yield was obtained when one equivalent BuLi was used with 3.5:1 prereacted system (No. 12). Only small asymmetric induction was observed when acetophenone was added immediately after (*S*)-**1a** was mixed with 3.5 mole equivalent BuLi at −78°C. Since formation of **5** from BuLi and **4** takes a little time, the above mentioned facts strongly indicate the importance of the formation of lithioenamine **5** in the asymmetric induction. It seems that species responsible for the asymmetric addition is formed through the interaction of BuLi with **5**, and that the contribution of the species is the highest at 3.5:1 molar ratio in *in situ* system. The optical yield decreased when the molar ratio became higher than 4:1, although chemical yield remained high. Under this condition, proportion of free BuLi which added to acetophenone without the influence of chiral ligand system **5** is high, resulting in a decrease of the optical yield.

Effects of α-Substituent on Optical Yield. The effects of the configuration, and alkyl substituent at α-carbon of imino ether component of **1** are also shown in Table 2. Bulky substituent at α-carbon seems to have higher regulating power (No. 6). (*R*)-**1a** gave opposite sign in the product (No. 4). These facts indicate that α-substituent directly influences the enantioface-selection, and that in BuLi-(*S*)-**1** systems, the regulation by α-alkyl group and pinane skeleton work to same direction, but in (*R*)-**1** to opposite direction. This speculation is supported by that in BuLi-**1c** system, where no substituent was attached to α-carbon, small positive value was observed by the influence of pinane skeleton (No. 7). Racemic **1a** gave small (−) value for the product (No. 5). Imino alcohol ligand (*S*)-**1d** showed only a weak regulating power (No. 8), which indicates the importance of methoxyl group in the ligand **1** to form species responsible for the asymmetric induction.

Table 2. Enantioface-differentiating addition of BuLi to acetophenone[a]

No.	Ligand System	[BuLi]/[Ligand]	Conv.[b] %	$[\alpha]_D^{25}$ ° (Conc. g dl^{-1})[c]	% e.e.
	In situ system[d]				
1	(*S*)-**1a**	1.0	0	—	—
2	(*S*)-**1a**	3.0	61	+2.9 (1.53)	11
3	(*S*)-**1a**	3.5	80	+6.3 (0.79)	23
4	(*R*)-**1a**	3.5	29	−2.4 (3.3)[e]	4
5	rac-**1a**	3.5	—	−0.5 (1.0)	2
6	(*S*)-**1b**	3.5	48	+9.0 (0.23)	33
7	**1c**	3.5	71	+2.2 (1.75)	8
8	(*S*)-**1d**	3.5	80	+0.4 (1.2)	2
	Prereacted system[d]				
9	(*S*)-**1a** (1 :1)[f]	1.0	0	—	—
10	(*S*)-**1a** (2 :1)[f,g]	1.0	70	+0.7 (4.47)	3
11	(*S*)-**1a** (3.5:1)[f,g]	0	80	+4.7 (0.60)	20
12	(*S*)-**1a** (3.5:1)[f]	1.0	8	+7.1 (0.42)	26

a) Reactions were carried out in hexane at −78°C at the concentration of acetophenone and ligand ranging 0.08—0.50 mol/l. b) Determined by disappearance of acetophenone in GLC. c) Solvent $CHCl_3$. d) See experimental. e) 28°C. f) Molar ratio of BuLi to ligand in the preparation of prereacted system. g) Prereacted system as evacuated without washing with hexane was used.

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