

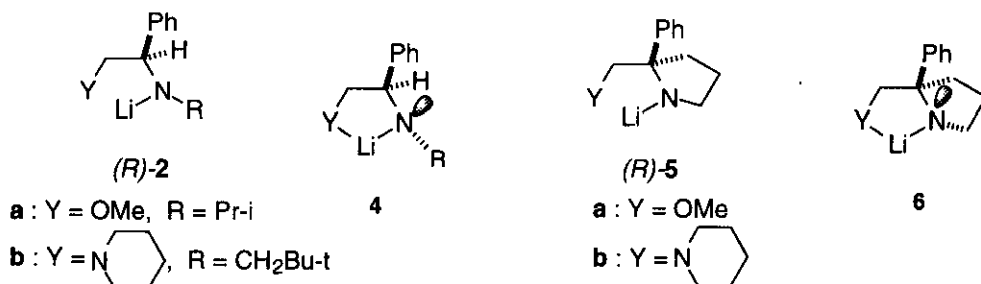
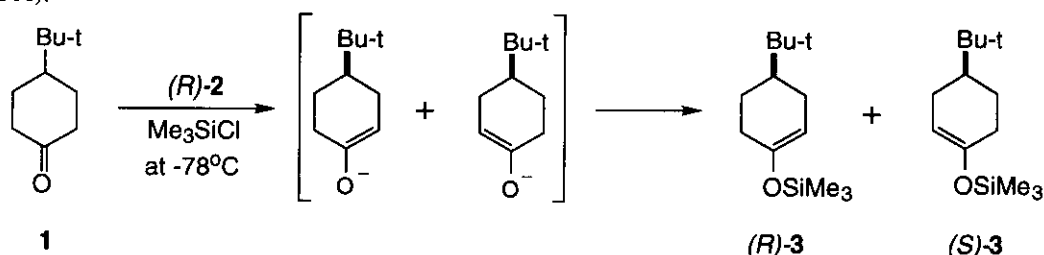
CHIRAL BIDENTATE LITHIUM AMIDES HAVING A CHIRAL AMIDE NITROGEN FOR ENANTIOSELECTIVE DEPROTONATION OF 4-*tert*-BUTYLCYCLOHEXANONE¹

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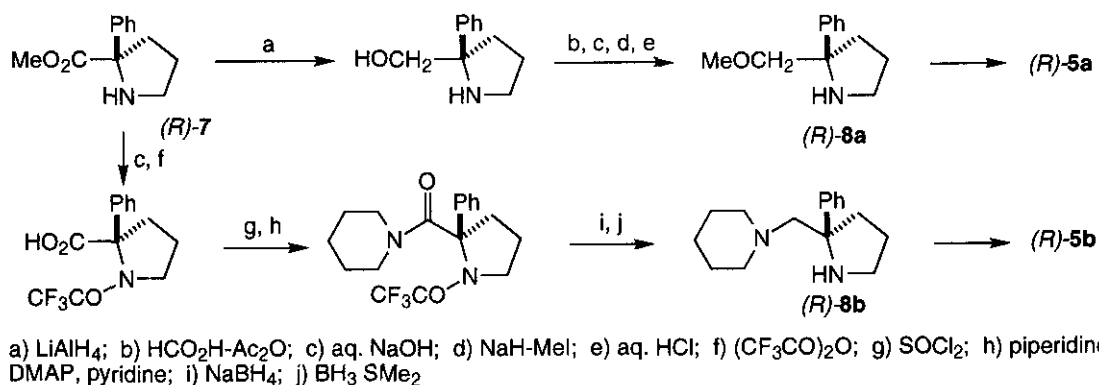
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Abstract - Enantioselective deprotonation of 4-*tert*-butylcyclohexanone (**1**) by chiral bidentate lithium amides ((*R*)-**5a**~**b**) was examined in the presence of excess TMSCl in several solvents containing 2 equivalents of HMPA. The sense of asymmetric induction was found to be the same with that by using (*R*)-**2a**~**b**. This result suggests the formation of a similar chiral amide nitrogen in these chiral lithium amides.

Enantioselective asymmetric synthesis using chiral lithium amides has received much attention in recent years.² We have previously reported enantioselective deprotonation of 4-*tert*-butylcyclohexanone (**1**) by chiral bidentate lithium amides ((*R*)-**2a**,**b**) in several solvents in the presence of excess trimethylsilyl chloride (TMSCl) (internal quench method³) to give the corresponding chiral trimethylsilyl enol ether ((*R*)-**3**).^{4,5} It is shown that the enantioselectivity of the reaction is highly dependent on the solvent used, but is almost independent on the solvent in the presence of 2 equivalents of hexamethylphosphoric triamide (HMPA).^{4b,5}



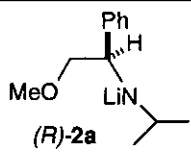
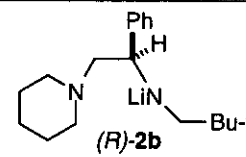
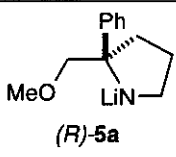
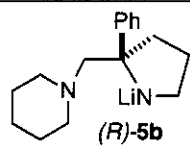
Detailed ^6Li - and ^{15}N -NMR spectral analyses of $[\text{}^6\text{Li},^{15}\text{N}_2]\text{-(R)-2b}$ have shown that $(R)\text{-2b}$ exists as a chelated monomer in THF and in DME, as a chelated dimer in ether and in toluene, and as a chelated monomer in all of these solvents in the presence of 2 equivalents of HMPA.^{4b,6} This result is rationalized by assuming that a five-membered chelated structure is formed by internal coordination of the substituent Y in **2** to the lithium, the chelated monomer aggregates in solution depending on the solvent used to satisfy the valency of the lithium, and HMPA deaggregates the chelated dimer to the chelated monomer due to its strong coordinating ability to the lithium. By X-ray analysis of the crystalline chelated dimer, we speculated that the chelated monomer should be as shown in **4**,^{4b,6} where a chiral amide nitrogen is formed efficiently simply by virtue of chelation. Since it is reported that the lone pair on the amide nitrogen is involved at the transition state of deprotonation of carbonyl compounds by LDA,⁷ it is conceivable that the sense of asymmetric induction in deprotonation of **1** by $(R)\text{-2}$ is determined by the chiral amide nitrogen. We therefore intended to design and synthesize such chiral lithium amides ($(R)\text{-5a,b}$) that have a chiral amide nitrogen. Based on the structural analyses on $(R)\text{-2b}$, it seems quite reasonable to assume that the lithium amides ($(R)\text{-5a,b}$) exist as a five-membered chelated form, because they have the same internal ligation site (methoxy or piperidino group) for the lithium. We also expected that these lithium amides ($(R)\text{-5a,b}$) should exist as chelated monomeric forms as shown in **6** in the presence of 2 equivalents of HMPA. Since it is known that *cis*-bicyclo[3.3.0]nonane is highly more stable than the corresponding *trans*-isomer,⁷ the bicyclo[3.3.0]nonane ring system in **6** should be exclusively *cis*. This means that **6** has a chiral amide nitrogen, whose configuration is similar to that in **4**. We therefore intended to examine the sense of asymmetric induction in enantioselective deprotonation of **1** by $(R)\text{-5a}$ and $(R)\text{-5b}$ in the presence of 2 equivalents of HMPA.



Chiral amines ($(R)\text{-8a}^{9a}$ and $(R)\text{-8b}^{9b}$) were synthesized from $(R)\text{-7}^{10,11}$ as shown above in optically pure forms.¹²

Deprotonation reactions of **1** by $(R)\text{-5a}$ and $(R)\text{-5b}$ were carried out at -78°C for 10 min in the presence of excess TMSCl in several solvents containing 2 equivalents of HMPA.¹³⁻¹⁵ The results are summarized and compared with those by using $(R)\text{-2a}$ and $(R)\text{-2b}$ as shown in Table 1.

Table 1. Enantioselective Deprotonation of **1** in the Presence of HMPA (2 equivalents) to give **3**^a

	 (<i>R</i>)- 2a			 (<i>R</i>)- 2b			 (<i>R</i>)- 5a			 (<i>R</i>)- 5b		
Solvent	Isolated y. (%)	E. e. (%) (Confign.)	Isolated y. (%)	E. e. (%) (Confign.)	Isolated y. (%)	E. e. (%) (Confign.)	Isolated y. (%)	E. e. (%) (Confign.)	Isolated y. (%)	E. e. (%) (Confign.)		
THF	90	42(<i>R</i>)	82	82(<i>R</i>)	47	43(<i>R</i>)	14	55(<i>R</i>)				
DME	90	40(<i>R</i>)	87	87(<i>R</i>)	41	38(<i>R</i>)	17	57(<i>R</i>)				
ether	88	41(<i>R</i>)	89	89(<i>R</i>)	44	45(<i>R</i>)	38	61(<i>R</i>)				
toluene	27	41(<i>R</i>)	87	87(<i>R</i>)	44	51(<i>R</i>)	58	43(<i>R</i>)				

^a Data by using (*R*)-**2a** and (*R*)-**2b** are taken from Ref. 3a and 3b.

It is shown that, in four representative solvents containing 2 equivalents of HMPA, the sense of asymmetric induction in the present deprotonation reactions of **1** by (*R*)-**5a** and (*R*)-**5b** is the same with that by (*R*)-**2a** and (*R*)-**2b** to give (*R*)-**3** in excess. Since it is reasonable to assume that the solution structure of (*R*)-**5a** and (*R*)-**5b** is monomeric as shown in **6** in the presence of 2 equivalents of HMPA, it is reasonable to conclude that the chiral amide nitrogen of (*R*)-**2a** and (*R*)-**2b** is similar to that of (*R*)-**5a** and (*R*)-**5b** in these solvent systems as shown in **4**, and determines the stereochemical course of the present deprotonation reaction.¹⁶

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9. a) $[\alpha]_D^{25} +31.6^\circ$ ($c = 1.02$, CHCl_3), as a colorless oil of bp 180°C (bath temperature) (1 mmHg). b) $[\alpha]_{435}^{25} +4.7^\circ$ ($c = 5.02$, benzene), as a colorless oil of bp 180°C (bath temperature) (1.5 mmHg).
10. a) *dl*-**7**¹¹ was resolved by salt formation with dibenzoyl-L-tartaric acid. Recrystallizations from EtOH gave the less soluble salt as colorless prisms, whose structure was determined to be (*R*)-**7**·dibenzoyl-L-tartaric acid by X-ray analysis. (*R*)-**7** was obtained from this salt in the usual manner as a colorless oil of bp 180°C (bath temperature) (5 mmHg), $[\alpha]_{365}^{25} -134^\circ$ ($c = 1.01$, CHCl_3). By using dibenzoyl-D-tartaric acid, (*S*)-**7** was obtained by the same procedure.
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12. All new compounds gave satisfactory spectral and microanalytical data.
13. A typical experimental procedure is as follows. Under argon atmosphere, a solution of BuLi in hexane (1.45*N*, 0.87 mL, 1.26 mmol) was added to a solution of (*R*)-**8b** (319.6 mg, 1.31 mmol) in toluene (10 mL) at -78°C , and the whole was stirred for 10 min. HMPA (0.44 mL, 2.51 mmol) was added, and the whole was stirred at 0°C for 5 min, and was then cooled down to -78°C . A solution of TMSCl (0.66 mL, 5.23 mmol) in toluene (2 mL) was added, and then a solution of **1** (161.9 mg, 1.05 mmol) in toluene (5 mL) was added. The reaction mixture was stirred at -78°C for 10 min. Triethylamine (2.0 mL) and saturated aqueous NaHCO_3 (5.0 mL) were added to the reaction mixture, and the whole was extracted with hexane (30 mL) three times. The organic extracts were combined, washed successively with water (30 mL), 0.1*N* aqueous citric acid (60 mL) three times, water (30 mL), saturated aqueous NaHCO_3 (30 mL), and brine (30 mL), and dried over anhydrous Na_2SO_4 . Evaporation of the solvent gave a residue, which was purified by column chromatography (silica gel, hexane) followed by bulb-to-bulb distillation to give (*R*)-**3** (137 mg, 58%) as a colorless oil of bp 150°C (bath temperature) (10 mmHg), $[\alpha]_{365}^{25} +103^\circ$ ($c = 1.57$, benzene), corresponding to be 43% (*R*).¹⁴
14. Since enantiomers of **3** could not be separated by chiral columns using HPLC and GC, ee's of **3** were determined polarimetrically. It is reported that the maximum rotation of (*R*)-**3** is $[\alpha]_{365}^{25} +237^\circ$ (benzene).¹⁵
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16. (*R*)-**5a** and (*R*)-**5b** are inferior as chiral bases, because chemical yields and ee's of (*R*)-**3** are lower than those obtained by using (*R*)-**2a** and (*R*)-**2b**. One of the possible reasons would be due to the less bulky alkyl substituent on amide nitrogen. Details are under investigation.