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Stereochemistry of Enantioselective Deprotonation of 4-Substituted Cyclohexanones by Chiral Bidentate Lithium Amides

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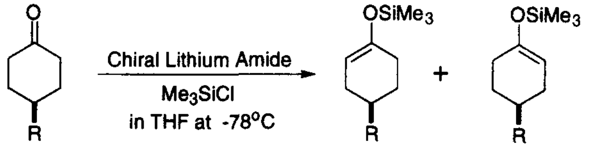
Abstract: Enantioselective deprotonation of 4-substituted cyclohexanones (**1**) in the presence of excess trimethylsilyl chloride was examined using chiral bidentate lithium amides ((*R*)-**3**~(*R*)-**7**) in THF. The solution structures of (*R*)-**3a** in THF in the presence and in the absence of lithium chloride were studied by NMR. It is concluded that the eight-membered cyclic transition state (**10**) offers reasonable explanation of the stereochemical course of the present reaction using (*R*)-**3a**.

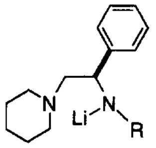
Deprotonation of a carbonyl compound is the most fundamental and widely used reaction in synthetic organic chemistry to give the corresponding enolate anion, because it can further react with various electrophiles to undergo important synthetic reactions such as alkylation, aldolization, acylation, halogenation, and protonation. We have previously reported the enantioselective deprotonation reaction of prochiral 4-substituted cyclohexanones (**1a** and **1b**) by chiral bidentate lithium amides ((*R*)-**3a** and (*R*)-**3b**) in the presence of excess trimethylsilyl chloride (TMSCl) (Corey's internal quench method[1]) to isolate the corresponding enolate anions as their trimethylsilyl enol ethers ((*R*)-**2a** and (*R*)-**2b**) in reasonably good chemical and optical yields.[2-4]



1
a: R = Me
b: R = Bu^t

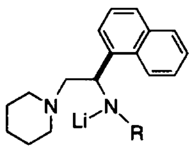
(*R*)-**2**
a: R = Me
b: R = Bu^t

(*S*)-**2**
a: R = Me
b: R = Bu^t

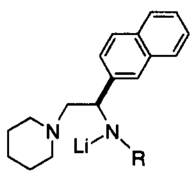


(*R*)-**3**
a: R = CH_2Bu^t
b: R = CH_2CF_3

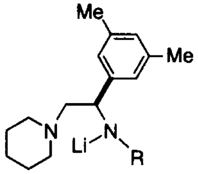
Assuming that chiral lithium amides having a substituent on the chiral carbon bulkier than phenyl in (*R*)-**3** would exhibit better enantioselectivity in this deprotonation reaction, we prepared similar chiral bidentate lithium amides whose substituent on the chiral carbon is α-naphthyl ((*R*)-**4**), β-naphthyl ((*R*)-**5**), 3,5-dimethylphenyl ((*R*)-**6**), or 3,5-di-*tert*-butylphenyl ((*R*)-**7**). The deprotonation reaction of **1a** and **1b** by these chiral lithium amides was examined under the same conditions,[5] and the results were compared with those obtained by using (*R*)-**3**, as summarized in the Table.



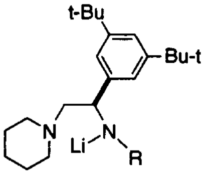
(*R*)-4
a: R = CH_2Bu^t
b: R = CH_2CF_3



(*R*)-5
a: R = CH_2Bu^t
b: R = CH_2CF_3



(*R*)-6
a: R = CH_2Bu^t
b: R = CH_2CF_3



(*R*)-7
a: R = CH_2Bu^t
b: R = CH_2CF_3

Table Enantioselective Deprotonation of **1**

	Ketone		Lithium amide		Product			
Run	Compound	R	Compound	Ar	Compound	Chem. Y. (%)	Opt. Y. (%)	Confign.
1	**1a**	Me	(*R*)-**3a**	C_6H_5	**2a**	86	84	*R*
2	**1a**	Me	(*R*)-**3b**	C_6H_5	**2a**	88	84	*R*
3	**1b**	^{t}Bu	(*R*)-**3a**	C_6H_5	**2b**	95	84	*R*
4	**1b**	^{t}Bu	(*R*)-**3b**	C_6H_5	**2b**	89	83	*R*
5	**1a**	Me	(*R*)-**4a**	α-$C_{10}H_7$	**2a**	72	90	*R*
6	**1a**	Me	(*R*)-**4b**	α-$C_{10}H_7$	**2a**	78	86	*R*
7	**1b**	^{t}Bu	(*R*)-**4a**	α-$C_{10}H_7$	**2b**	84	86	*R*
8	**1b**	^{t}Bu	(*R*)-**4b**	α-$C_{10}H_7$	**2b**	89	85	*R*
9	**1a**	Me	(*R*)-**5a**	β-$C_{10}H_7$	**2a**	74	86	*R*
10	**1a**	Me	(*R*)-**5b**	β-$C_{10}H_7$	**2a**	87	84	*R*
11	**1b**	^{t}Bu	(*R*)-**5a**	β-$C_{10}H_7$	**2b**	93	72	*R*
12	**1b**	^{t}Bu	(*R*)-**5b**	β-$C_{10}H_7$	**2b**	92	72	*R*
13	**1a**	Me	(*R*)-**6a**	3,5-Me_2-C_6H_3	**2a**	76	86	*R*
14	**1a**	Me	(*R*)-**6b**	3,5-Me_2-C_6H_3	**2a**	85	82	*R*
15	**1b**	^{t}Bu	(*R*)-**6a**	3,5-Me_2-C_6H_3	**2b**	99	41	*R*
16	**1b**	^{t}Bu	(*R*)-**6b**	3,5-Me_2-C_6H_3	**2b**	99	43	*R*
17	**1a**	Me	(*R*)-**7a**	3,5-$^tBu_2$-C_6H_3	**2a**	57	49	*R*
18	**1a**	Me	(*R*)-**7b**	3,5-$^tBu_2$-C_6H_3	**2a**	80	42	*R*
19	**1b**	^{t}Bu	(*R*)-**7a**	3,5-$^tBu_2$-C_6H_3	**2b**	76	24	*S*
20	**1b**	^{t}Bu	(*R*)-**7b**	3,5-$^tBu_2$-C_6H_3	**2b**	86	12	*S*

It is shown that the lithium amides ((*R*)-**4a** and (*R*)-**4b**) having an α-naphthyl group exhibited almost the same (a little higher) enantioselectivity in the deprotonation of both **1a** and **1b** (runs 5~8) than the lithium amides ((*R*)-**3a** and (*R*)-**3b**) did (runs 1~4). On the other hand, by using the chiral lithium amides ((*R*)-**5a** and (*R*)-**5b**) having a β-naphthyl group, **1a** gave (*R*)-**2a** in similar enantioselectivity (runs 9~10 vs. runs 1~2), while **1b** gave (*R*)-**2b** in lower enantioselectivity (runs 11~12 vs. runs 3~4). This tendency was also observed in the reactions using (*R*)-**6a** and (*R*)-**6b** having a 3,5-dimethylphenyl group (runs 13~14 vs. runs 1~2, and runs 15~16 vs. runs 3~4). By using the chiral lithium amides ((*R*)-**7a** and (*R*)-**7b**) having a very bulky 3,5-di-*tert*-butylphenyl group, **1a** gave (*R*)-**2a** in considerably lower enantioselectivity (runs 17~18 vs. runs 1~2), and

1b gave (*S*)-**2b** in very low enantioselectivity (runs 19~20 vs. runs 3~4). It seems quite reasonable to assume, therefore, that the transition state of the reaction of **1a** and **1b** with these chiral lithium amides should have the structure in which steric interaction arises between the substituent at the 4-position of the cyclohexanones and the substituent on a chiral carbon of the lithium amides, as the bulkiness of these two substituents increases. In the model studies, such interactions can not be seen by the so-called Ireland's six-membered cyclic transition state model,[6] in which these two substituents are considered to be far apart.

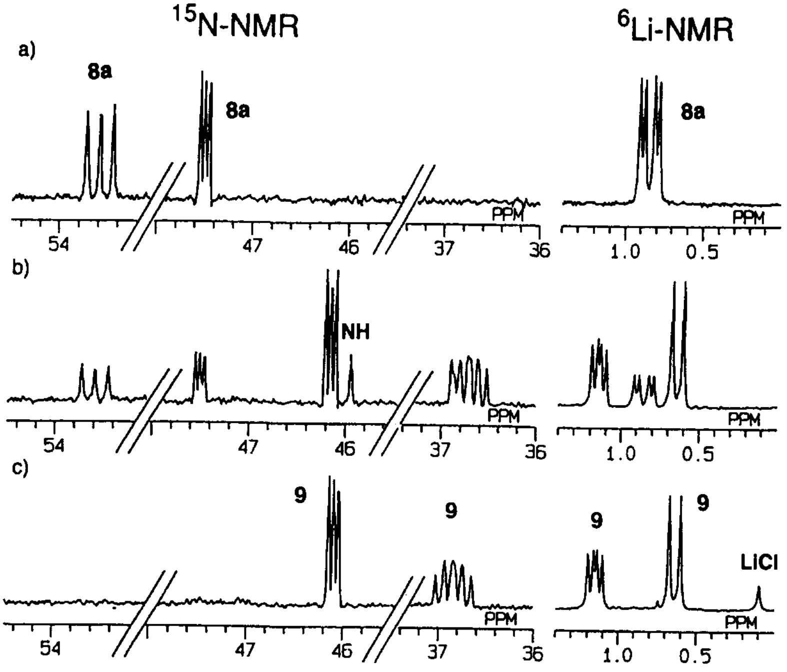
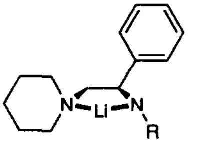
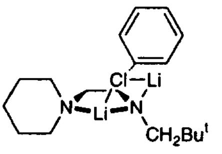


Figure NMR Spectra of [^{6}Li,^{15}N$_2$]-(*R*)-**3a** in THF-d_8 (0.05M, at -115°C)
a) Without ^{6}LiCl. b) With ^{6}LiCl (0.9 eq.). c) With ^{6}LiCl (1.3 eq.).



8 **a**: R = CH_2Bu^t
b: R = CH_2CF_3



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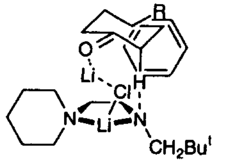

10

We have already reported that (*R*)-**3a** and (*R*)-**3b** exist in THF as chelated monomeric forms (**8a** and **8b**, respectively), where the alkyl substituent on the amide nitrogen orients itself exclusively *trans* to the phenyl group on the chiral carbon.[2c-d, 3, 4] It is also shown that the LiCl, generated as the silyl enol ether formation proceeds during the deprotonation in the presence of TMSCl, changes the structure of the lithium amide in solution and affects the stereochemistry of the reaction.[7,8] Therefore, as shown in the Figure, the solution structures of $[^6\mathrm{Li},^{15}\mathrm{N}_2]$-(*R*)-**3a** were examined by ^{6}Li- and ^{15}N-NMR in THF-d_8 in the absence and in the presence of ^{6}LiCl. From the ^{6}Li-^{15}N coupling patterns,[9] the mixed dimer (**9**) is proved to be formed in the presence of ^{6}LiCl, and is considered to be a responsible species for the deprotonation reaction.[7f]

From these data, it is therefore concluded that the eight-membered cyclic transition state model (**10**) including LiCl[7f, 10,11] offers reasonable explanation of the stereochemical course of the deprotonation reaction of **1** by (*R*)-**3a** in the presence of TMSCl.

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9. ^{6}Li NMR (73.6 MHz) spectroscopic data (ppm) of (*R*)-**3a** in THF-d_8 at -115°C (reference: ^{6}LiCl (0 ppm)): **8a** (Figure a): 0.85 (dd, $J_{\mathrm{Li\text{-}N}} = 7.0$ and 2.4 Hz). **9** (Figure c): 0.64 (d, $J_{\mathrm{Li\text{-}N}} = 4.9$ Hz), 1.14 (dd, $J_{\mathrm{Li\text{-}N}} = 4.3$ and 2.7 Hz). ^{15}N NMR (50.7 MHz) spectroscopic data (ppm) of (*R*)-**3a** in THF-d_8 at -115°C (reference: ^{15}N-aniline (52.0 ppm)): **8a** (Figure a): 47.5 (t, $J_{\mathrm{N\text{-}Li}} = 2.4$ Hz), 53.6 (t, $J_{\mathrm{N\text{-}Li}} = 7.0$ Hz). **9** (Figure c): 36.7 (tt, $J_{\mathrm{N\text{-}Li}} = 4.3$ and 4.9 Hz), 46.2 (t, $J_{\mathrm{N\text{-}Li}} = 2.7$ Hz).
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