Pergamon

Tetrahedron Letters, Vol. 37, No. 41, pp. 7377-7380, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01681-4

Solution Structures of a Monodentate Chiral Lithium Amide in the Presence of Lithium Halide

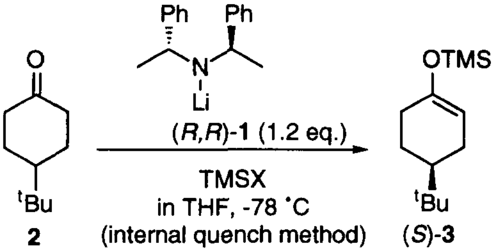
Keizo Sugasawa,[a] Mitsuru Shindo,[a] Hiroshi Noguchi,[b] and Kenji Koga[a]*
[a]Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan
[b]School of Pharmaceutical Sciences, University of Shizuoka, Shizuoka City, Shizuoka 422, Japan

Abstract: Enantioselectivity of deprotonation reaction of 4-*tert*-butylcyclohexanone (**2**) by a monodentate chiral lithium amide ((*R*,*R*)-**1**) in THF is strongly influenced by the presence of lithium halides. Aggregation states of this chiral lithium amide in THF-d_8 in the absence and in the presence of lithium halides were studied by ^{6}Li and ^{15}N NMR. It is concluded that the mixed dimer (**D**) is the species to give the high enantioselectivity of the reaction. Copyright © 1996 Elsevier Science Ltd

Kinetic deprotonation of prochiral cyclic ketones by chiral lithium amides has become one of the useful methods for asymmetric synthesis.[1] It has been shown that a monodentate chiral lithium amide ((*R*,*R*)-**1**)[1b] can convert prochiral 4-substituted cyclohexanones into the corresponding enantiomerically enriched silyl enol ethers by one of two procedures: the lithium amide and TMSCl are premixed prior to the addition of the ketone (internal quench method),[2] or the lithium amide is allowed to react with the ketone before TMSCl is introduced (external quench method). The internal quench method, in general, gives higher enantioselectivity than the external quench method. Recently, it has been reported that the improvement in enantiomeric excess (ee) under external quench conditions can be achieved in this asymmetric deprotonation reaction by the inclusion of LiCl in the reaction mixture.[3] Therefore, the higher enantioselection in the internal quench method, compared to the external quench method, could be due to LiCl, formed as the silyl enol ether formation proceeds.[4] This LiCl effect has been *assumed* to involve conversion of a poorly selective aggregate into a much more selective mixed aggregate. Herein we describe the elucidation of the solution structures of the chiral lithium amide by ^{6}Li, ^{15}N NMR using the ^{6}Li-^{15}N double labeling method, along with new results obtained for asymmetric deprotonation reactions in relation to lithium halide effects.[5]

Our initial study was to investigate TMSX (X: halide) effects on the enantioselectivity in internal quench method. Interestingly, it is shown that the ee of the product[6] is highly dependent on TMSX employed as shown in Scheme 1.

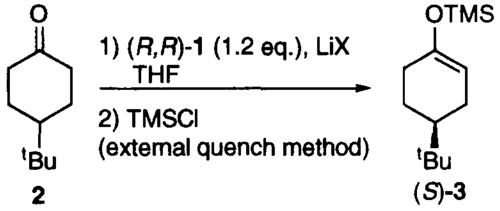
Scheme 1



X = Cl: 90% ee (71% yield)
X = Br: 65% ee (86% yield)
X = I: 31% ee (97% yield)

It is conceivable that lithium halides (LiX), generated as the silylation proceeds, affect enantioselectivity of the reaction. We therefore examined the deprotonation reaction of **2** by (*R*,*R*)-**1** in THF in the absence and in the presence of LiX under external quench conditions as shown in Scheme 2. In the absence of a lithium salt, enantioselectivity was relatively low. In the presence of LiCl at -78 °C, the ee of (*S*)-**3** increased sharply on adding 0.6 equiv. of LiCl, and no subsequent change in selectivity was seen when 1.2 equiv. or more of LiCl were used. At -114 °C, however, the enantioselectivity of the reaction in the presence of 0.6 equiv. of LiCl did not reach the maximum, which was obtained in the presence of 1.2 equiv. of LiCl or more. In reactions employing LiBr at -78 °C, the ee of (*S*)-**3** produced with 1.2 equiv. of LiBr was lower than that with 3.6 equiv. of LiBr. This value (86% ee) was higher than that obtained under the internal quench conditions using TMSBr and was close to the maximum ee (88% ee) obtained in the reactions with LiCl. Unexpectedly, the ee at -78 °C was higher than that at -114 °C. In the presence of LiI, enhancement of ee was not observed.

Scheme 2



LiX (eq.)	at -78 °C	at -114 °C
none	44% ee (y. 84%)	41% ee (y. 93%)
LiCl (0.6)	87% ee (y. 86%)	79% ee (y. 92%)
LiCl (1.2)	88% ee (y. 87%)	91% ee (y. 90%)
LiCl (3.6)	88 %ee (y. 73%)	91% ee (y. 97%)
LiBr (1.2)	63% ee (y. 89%)	52% ee (y. 87%)
LiBr (3.6)	86% ee (y. 82%)	71% ee (y. 83%)
LiI (1.2)	44% ee (y. 85%)	38% ee (y. 85%)
LiI (3.6)	43% ee (y. 79%)	37% ee (y. 79%)

Since stereoselectivity was assumed to depend on the solution structures of **1** affected by LiX, ^{6}Li and ^{15}N NMR spectral studies were carried out on the solution structures of [^{6}Li,^{15}N]-(*S*,*S*)-**1** in THF-d_8 in the absence and in the presence of ^{6}LiX in order to clarify these phenomena. The spectra are shown in Figures 1 and 2.

Based on the coupling patterns and the detailed NMR spectral analysis on the solution structures of lithium dialkylamides such as LDA reported by Collum,[7] four species (**A**, **B**, **C**, and **D**) are recognized.[8] In the absence of lithium salt, (*S*,*S*)-**1** exists almost entirely as a homo dimer (**B**)[9] (Figure 1a). In the presence of LiCl, two new mixed aggregates (**C** and **D** (X=Cl))[10] appear. The mixed dimer (**D** (X=Cl)) is not major with 0.5 equiv. of LiCl (Figure 1b), but is major with 3 equiv. of LiCl (Figure 1d). Since the reaction in the presence of only 0.6 equiv. (0.5 equiv. based on the amount of the lithium amide) of added LiCl gives high enantioselectivity, it seems reasonable to consider **D** (X=Cl) as the reacting species to give the product in high ee. In the presence of LiBr, species **D** (X=Br) is also observed. It should be noted, however, that **D** (X=Br) is very minor in the presence of 1 equiv. of LiBr (Figure 2a), and that the homo dimer (**B**) still exists in a reasonable amount even in the presence of 3 equiv. of LiBr (Figure 2b). On the other hand, it is shown that LiI does not change the aggregation states of this lithium amide (Figure 2c).

It is concluded that the difference in enantioselectivity of the deprotonation reaction of **2** by (*R*,*R*)-**1** to give (*S*)-**3** in the presence of TMSX (internal quench method) comes from the LiX formed during the course of the silylation reaction. Thus, (*R*,*R*)-**1** forms the mixed dimers (**D** (X=Cl or Br)) with LiCl or LiBr, respectively, but does not form this species with LiI. The mixed dimers (**D**) show higher enantioselection and higher reaction rate than those of the homo dimer (**B**). Since the equilibrium rate between these species (**A**, **B**, **C**, and **D**) might be fast enough compared with the reaction rate of **D** (X=Cl), the ee is high even if **D** (X=Cl) is not major in the reaction mixture as shown in Figure 1b. In the case of LiBr, however, the equilibrium rate might not be fast enough, and the mixed dimer (**D** (X=Br)) might be thermodynamically less stable than **D** (X=Cl);

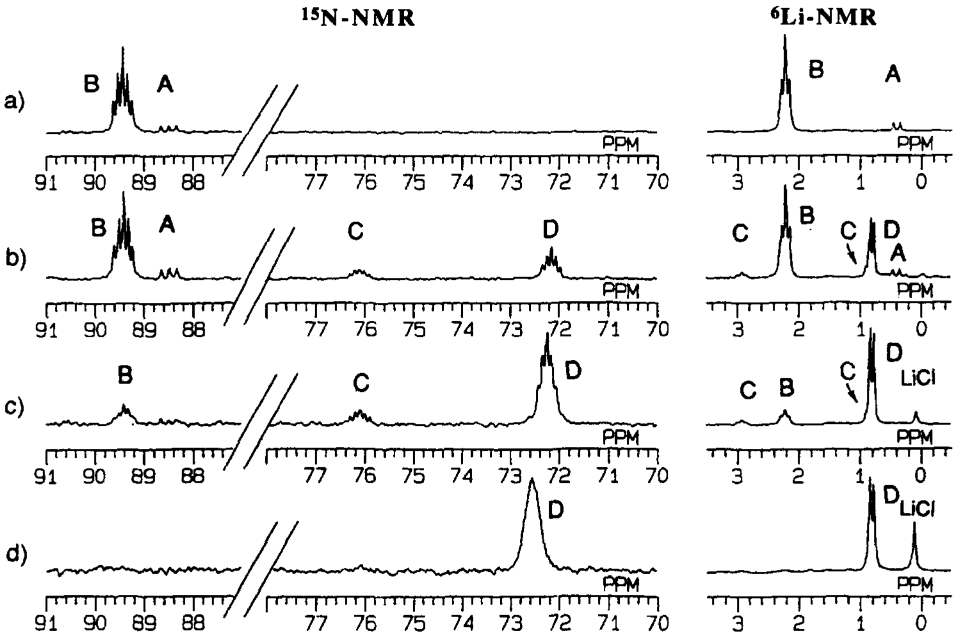


Figure 1. NMR spectra of [^{6}Li,^{15}N]-(*S,S*)-**1** (0.05M in THF-d_8 at -115 °C). a) Without lithium salt; b) With LiCl (0.5 eq.); c) With LiCl (1.0 eq.); d) With LiCl (3.0 eq.).

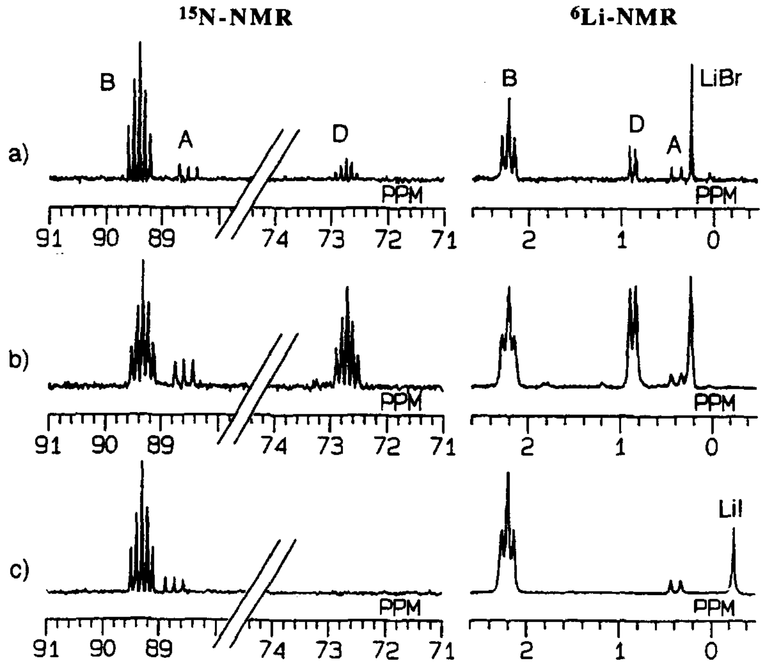
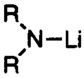
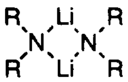


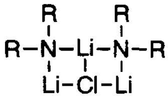
Figure 2. NMR spectra of [^{6}Li,^{15}N]-(*S,S*)-**1** (0.05M in THF-d_8 at -115 °C). a) With LiBr (1.0 eq.); b) With LiBr (3.0 eq.); c) With LiI (3.0 eq.).



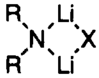
A



B



C



D (X=Cl or Br)

consequently, the contribution of dimer (**B**) to the reaction might not be small, especially at -114 °C. Thus, evaluating the equilibrium rate among aggregated species, the difference in enantioselectivity of the reactions discussed above seems to be rationalized.

We have disclosed solution structures of the monodentate chiral lithium amide in relation to lithium halide effects on enantioselectivity. By elucidation of the reaction species, it should be possible to gain further insight into the reaction mechanism.[11]

References and Notes

1. For reviews, see: (a) Koga, K. *J. Synth. Org. Chem. Jpn.* **1990**, *48*, 463-475. (b) Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 1-26. (c) Koga, K. *Pure Appl. Chem.* **1994**, *66*, 1487-1492. (d) Koga, K.; Shindo, M *J. Synth. Org. Chem. Jpn.* **1995**, *53*, 1021-1032.
2. Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495-498.
3. (a) Majewski, M.; Gleave, D. M. *J Org. Chem.* **1992**, *57*, 3599-3605. (b) Bunn, B. J.; Simpkins, N. S. *J. Org. Chem.* **1993**, *58*, 533-534. (c) Bunn, B. J.; Simpkins, N. S.;Spavold, Z.; Crimmin, M. J. *J. Chem. Soc. Perkin Trans. 1* **1993**, 3113-3116. (d) Majewski, M.; Lazny, R. *Tetrahedron Lett.* **1994**, *35*, 3653-3656. (e) Majewski, M.; Lanzy, R.; Nowak, P. *Tetrahedron Lett.* **1995**, *36*, 5465-5468. For reviews, including discussion of salt effects, see (f) Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1624-1654. (g) Juaristi, E.; Beck, A. K.; Hansen, J.; Matt, T.; Mukhopadhyay, T.; Simson, M.; Seebach, D. *Synthesis* **1993**, 1271-1290. (h) Seebach, D.; Beck, A. K.; Studer, A. *Modern Synthetic Methods* Vol. 7; VCH: Weinheim, 1995; pp. 1-178.
4. A small amount of LiCl could be released on mixing the lithium amide and TMSCl. See: Lipshutz, B. H.; Wood, M. R.; Lindsley, C. W. *Tetrahedron Lett.* **1995**, *36*, 4385-4388.
5. Solution structures of bidentate chiral lithium amides were elucidated using the double labeling method. See (a) Sato, D.; Kawasaki, H.; Shimada, I.; Arata, Y.; Okamura, K.; Date, T.; Koga, K. *J. Am. Chem. Soc.* **1992**, *114*, 761-763. (b) Aoki, K.; Noguchi, H.; Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1993**, *34*, 5105-5105.
6. Aoki, K.; Nakajima, M.; Tomioka, K.; Koga, K. *Chem. Pharm. Bull.* **1993**, *41*, 994-996.
   Reinvestigation has shown that maximum rotation of (*R*)-**3** should be $[\alpha]_{365}^{25}$+237°(benzene).
7. (a) Galiano-Roth, A. S.; Kim, Y-J.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 5053-5055. (b) Hall, P. L.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9575-9585. For review, (c) Collum, D. B. *Acc. Chem. Res.* **1993**, *26*, 227-234.
8. ^{6}Li NMR (73.6 MHz) spectroscopic data (ppm) of (*S,S*)-**1** in THF-d_8 at -115 °C (reference: ^{6}LiCl (0 ppm)): **A**: 0.41 (d, $J_{\text{Li-N}}$ = 7.9 Hz). **B**: 2.22 (t, $J_{\text{Li-N}}$ = 4.9 Hz). **C**: 2.92 (t, $J_{\text{Li-N}}$ = 5.5 Hz), 0.87 (d, $J_{\text{Li-N}}$ = 4.3 Hz). **D** (X=Cl): 0.81 (d, $J_{\text{Li-N}}$ = 4.9 Hz). **D** (X=Br): 1.20 (d, $J_{\text{Li-N}}$ = 4.9 Hz).
   ^{15}N NMR (50.7 MHz) spectroscopic data (ppm) of (*S,S*)-**1** in THF-d_8 at -115 °C (reference: ^{15}N-aniline (52.0 ppm)): **A**: 88.5 (t, $J_{\text{N-Li}}$ = 7.9 Hz). **B**: 89.4 (quintet, $J_{\text{N-Li}}$ = 4.9 Hz). **C**: 76.1 (triplet of triplets, $J_{\text{N-Li}}$ = 5.5, 4.3 Hz). **D** (X=Cl): 72.2 (quintet, $J_{\text{N-Li}}$ = 4.9 Hz). **D** (X=Br): 72.7 (quintet, $J_{\text{N-Li}}$ = 4.9 Hz).
9. Homo dimer (**B**) was isolated as crystals from THF: Edwards, A. J.; Hockey, S.; Mair, F. S.; Raithby, P. R.; Snaith, R.; Simpkins, N. S. *J. Org. Chem.* **1993**, *58*, 6942-6943.
10. Crystal structures of mixed aggregates of lithium amides and lithium chloride have been published. (a) Engelhardt, L. M.; Jacobsen, G. E.; White, A. H.; Raston, C. L. *Inorg. Chem.* **1991**, *30*, 3978-3980. (b) Mair, F. S.; Clegg, W.; O'Neil, P. A. *J. Am. Chem. Soc.* **1993**, *115*, 3388-3389.
11. The eight-membered cyclic transition state model including LiX in the ring, as discussed recently on MO calculations, may be reasonable rather than Ireland's six-membered cyclic transition state model.[12] See (a) Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1995**, *117*, 2166-2178. (b) Henderson, K. W.; Dorigo, A. E.; Liu, Q-Y.; Williard, P. G.; Schleyer, P. v. R.; Bernstein, P. R. *J. Am. Chem. Soc.* **1996**, *118*, 1339-1347.
12. Ireland, R. E.; Mueller, R. H., Williard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868-2877.

(*Received in Japan* 2 *July* 1996; *accepted* 26 *August* 1996)