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An Approach to Catalytic Asymmetric Deprotonation of 4-Substituted Cyclohexanones

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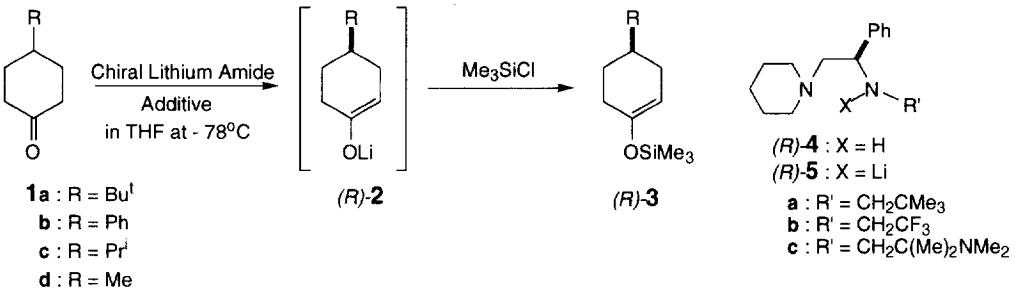
Abstract: Lithium-hydrogen interchange between a chiral bidentate amine (*(R)*-**4b**) and an achiral tridentate lithium amide (**8**) occurs rapidly *in situ*, favoring the exclusive formation of a chiral bidentate lithium amide (*(R)*-**5b**). Based on this finding, catalytic asymmetric deprotonation of 4-substituted cyclohexanones (**1a~d**) was realized by using less than a stoichiometric amount of *(R)*-**4b** as a chiral auxiliary.

Kinetic deprotonation of prochiral cyclic ketones by chiral lithium amides has become one of the useful methods for asymmetric synthesis.[1] We have previously reported enantioselective deprotonation of prochiral 4-substituted cyclohexanones (**1a~d**)[2] using a little more than a stoichiometric amount of bidentate chiral lithium amides (such as *(R)*-**5a**[2b] and *(R)*-**5b**[2d]) in THF in the presence of HMPA (2 equivalents to the chiral lithium amide). Treatment of the resulting solution with excess trimethylsilyl chloride (TMSCl) gave the corresponding silyl enol ethers (*(R)*-**3a~d**) in optically active forms (Table1, runs 1~5). However, by using a tridentate chiral lithium amide (*(R)*-**5c**), which has a dimethylamino group instead of one of the methyl groups in *(R)*-**5a**, **1a** gave *(R)*-**3a** in relatively lower chemical and optical yields under the same conditions (run 6).

Scheme 1



1a : R = Bu^t
b : R = Ph
c : R = Pr^i
d : R = Me

(R)-**2**

(R)-**3**

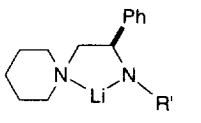
(R)-**4** : X = H
(R)-**5** : X = Li
a : R' = CH_2CMe_3
b : R' = CH_2CF_3
c : R' = $CH_2C(Me)_2NMe_2$

It is already shown by ^{6}Li- and ^{15}N-NMR spectral studies that [^{6}Li,$^{15}N_2$]-*(R)*-**5a**[2b] and [^{6}Li,$^{15}N_2$]-*(R)*-**5b**[2d] exist as chelated monomeric forms (**6a** and **6b**, respectively) in THF-d_8 in the presence of HMPA-d_{18} (2 equivalents). By the same technique, it is now shown that [^{6}Li,$^{15}N_3$]-*(R)*-**5c** exists as a chelated monomeric form (**6c**) in the same solvent system.[3] Since deprotonation of a carbonyl compound by a lithium amide is considered to occur *via* the coordination of the carbonyl oxygen to the lithium,[4] this result suggests that *(R)*-**5c** is inferior to *(R)*-**5a** and *(R)*-**5b** as a base for the deprotonation reaction due to the decrease in Lewis acidity of the lithium, because the lithium in *(R)*-**5c** is coordinated additionally by a dimethylamino group.

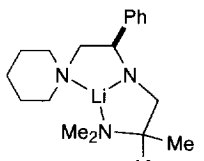
Table 1 Asymmetric deprotonation of **1a~d**

		Chiral Lithium Amide			Additive		Product		
Run	**1**	*(R)*-**4** (eq.)	**7** (eq.)	n-BuLi (eq.)	HMPA (eq.)	DABCO (eq.)	*(R)*-**3**	Chem. y (%)	Opt. y. (%)
1	**1a**	**4a** (1.24)	0	1.2	2.4	0	**3a**	86	77
2	**1a**	**4b** (1.24)	0	1.2	2.4	0	**3a**	85	81
3	**1b**	**4b** (1.24)	0	1.2	2.4	0	**3b**	77	80
4	**1c**	**4b** (1.24)	0	1.2	2.4	0	**3c**	75	79
5	**1d**	**4b** (1.24)	0	1.2	2.4	0	**3d**	82	78
6	**1a**	**4c** (1.24)	0	1.2	2.4	0	**3a**	54	53
7	**1a**	**4b** (0.30)	3.6	3.6	0	0	**3a**	57	31
8	**1a**	**4b** (0.30)	2.4	2.4	2.4	0	**3a**	75	70
9	**1a**	**4b** (0.30)	2.4	2.4	2.4	1.5	**3a**	83	79
10	**1b**	**4b** (0.30)	2.4	2.4	2.4	1.5	**3b**	77	76
11	**1c**	**4b** (0.30)	2.4	2.4	2.4	1.5	**3c**	80	76
12	**1d**	**4b** (0.30)	2.4	2.4	2.4	1.5	**3d**	70	75

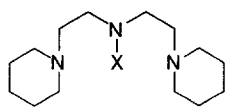
It should be possible, therefore, for the present enantioselective deprotonation reaction to be carried out in a similar efficiency by employing less than a stoichiometric amount of a bidentate chiral amine (*(R)*-**4a** or *(R)*-**4b**) in the presence of a sufficient amount of a tridentate achiral lithium amide (such as **8**), if hydrogen-lithium interchange[5] between the former and the latter occurs rapidly *in situ*, favoring the formation of the chiral lithium amide (*(R)*-**5a** or *(R)*-**5b**).



6a : R' = CH_2CMe_3
b : R' = CH_2CF_3



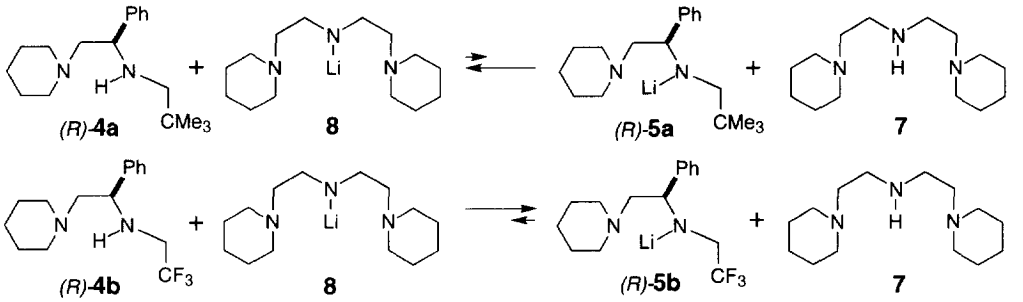
6c



7 : X = H
8 : X = Li

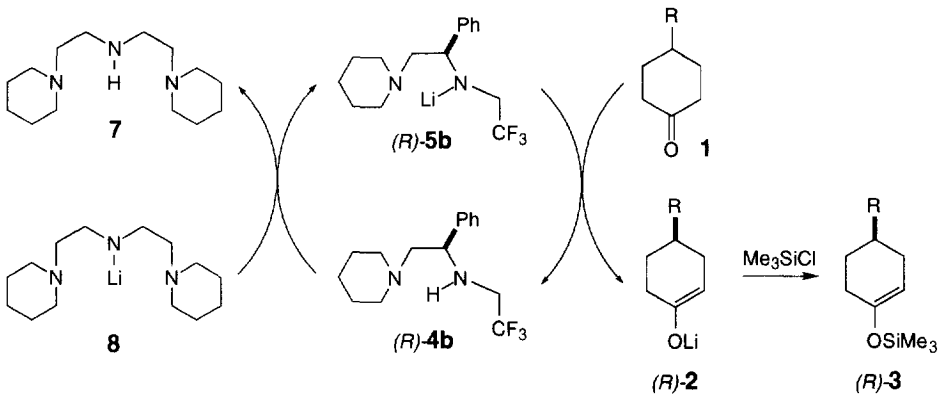
^{1}H-NMR spectral studies were made on hydrogen-lithium interchange between bidentate chiral amines (*(R)*-**4a** and *(R)*-**4b**) and a tridentate achiral lithium amide (**8**) in THF-d_8 in the presence of HMPA-d_{18} (2 equivalents to the lithium amide).[6,7] Thus, the spectrum of a solution prepared by mixing **8** (2 equivalents) with *(R)*-**4a** (1 equivalent) at room temperature showed the presence of *(R)*-**4a** and the absence of *(R)*-**5a**. The spectrum of a solution prepared by mixing *(R)*-**5a** (2 equivalents) with **7** (1 equivalent) showed the presence of *(R)*-**4a** and *(R)*-**5a** in about 1:1 ratio. These facts mean that hydrogen-lithium interchange actually occurs between *(R)*-**4a** and **8**, favoring the exclusive formation of *(R)*-**4a**, conceivably because the lithium in *(R)*-**5a** is di-coordinated, while that in **8** is tri-coordinated. On the other hand, the spectrum of a solution prepared by mixing **8** (2 equivalents) with *(R)*-**4b** (1 equivalent) showed the presence of *(R)*-**5b** and the absence of *(R)*-**4b**, and the spectrum of a solution prepared by mixing *(R)*-**5b** (2 equivalents) with **7** (1 equivalent) showed the presence of *(R)*-**5b** and the absence of *(R)*-**4b**. These results indicate that the formation of *(R)*-**5b** is favored exclusively by mixing *(R)*-**4b** and **8**, as summarized in Scheme 2. It is conceivable that, in the former case, the number of intramolecular coordination to the lithium (2 for *(R)*-**5a**, 3 for **8**) determines the exclusive formation of *(R)*-**4a** at equilibrium, while the increased acidity of the amine proton of *(R)*-**4b** induced by the electron-withdrawing trifluoroethyl group on the amine nitrogen overcomes the effect of the number of coordination to give *(R)*-**5b** exclusively at equilibrium in the latter case.

Scheme 2



Using the above equilibrium data, an approach to catalytic asymmetric deprotonation of **1a~d** was examined based on Scheme 3, employing 0.3 equivalent of *(R)*-**4b** and excess **8** (Table 1, runs 7~12). Since N-silylation of *(R)*-**4b** occurs by internal quench method,[8,9] TMSCl was added after deprotonation completed to isolate the products as *(R)*-**3a~d**.[10]

Scheme 3



It is shown that chemical and optical yields of the present catalytic deprotonation reaction are increased in the presence of HMPA (run 7 vs. run 8) and DABCO (run 8 vs. run 9).[11] By comparing runs 9, 10, 11, and 12 with runs 2, 3, 4, and 5, respectively, it is clear that a tridentate achiral lithium amide (**8**) works as a lithium supplier to generate and recycle a chiral bidentate lithium amide (*(R)*-**5b**) according to Scheme 3. This is the first example of catalytic asymmetric deprotonation of prochiral cyclic ketones.[12]

References and Notes

1. (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 & Applied Chem.* **1994**, *66*, 1487-1492. (d) Koga, K.; Shindo, M. *J. Synth. Org. Chem., Jpn.* **1995**, *53*, 1021-1032.

2. (a) Shirai, R.; Tanaka, M.; Koga, K. *J. Am. Chem. Soc.* **1986**, *108*, 543-545. (b) Sato, D.; Kawasaki, H.; Shimada, I.; Arata, Y.; Okamura, K.; Date, T.; Koga, K. *J. Am. Chem. Soc.* **1992**, *114*, 761-763. (c) Aoki, K.; Nakajima, M.; Tomioka, K.; Koga, K. *Chem. Pharm. Bull.* **1993**, *41*, 994-996. (d) Aoki, K.; Noguchi, H.; Tomioka, K.; Koga, K. *Tetrahedron Lett.*, **1993**, *34*, 5105-5108.
3. (a) The ^{6}Li-NMR signal appears at 2.2 ppm (using ^{6}LiCl (0 ppm) in methanol as a reference) as a doublet of triplets (J=7, 1.2, and 1.2 Hz). (b) The ^{15}N-NMR signals appear at 28.3, 44.0, and 48.2 ppm (using ^{15}N-aniline (52.0 ppm) in THF as a reference) as a triplet (J=1.2 Hz), a triplet (J=7 Hz), and a triplet (J=1.2 Hz), respectively.
4. Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868-2877.
5. Hydrogen-lithium interchange between lithium amides and secondary amines is reported: Fraser, R. R.; Baignée, A.; Bresse, M.; Hata, K. *Tetrahedron Lett.* **1982**, *23*, 4195-4198.
6. Benzylic proton signals of *(R)*-**4a**, *(R)*-**4b**, *(R)*-**5a**, and *(R)*-**5b** appear at ca. 4.2, ca. 4.3, ca. 3.7, and ca. 3.95 ppm, respectively, as a doublet-like quartet. Tridentate achiral lithium amide (**8**) and its corresponding amine (**7**) have no signals in this region.
7. Similar results were obtained in the absence of HMPA-d_{18}.
8. Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495-498.
9 For details, see footnote 7 in ref. 2d.
10. A typical experimental procedure (run 9) is as follows. Under argon atmosphere, a solution of n-butyllithium in hexane (1.50 N, 2.30 ml, 3.40 mmol) was added to a solution of **7** (855 mg, 3.57 mmol) in THF (18 ml) at -78°C. After stirring for 40 min, a solution of *(R)*-**4b** (123 mg, 0.43 mmol) in THF (9 ml) was added, and the whole was stirred for 20 min. After addition of a solution of HMPA (0.60 ml, 3.40 mmol) and DABCO (240 mg, 2.10 mmol) in THF (9 ml) followed by stirring for 40 min, a solution of **1a** (220 mg, 1.43 mmol) in THF (5 ml) was added dropwise during 4 min, and the whole was stirred for 1.5 hr. After addition of TMSCl (0.91 ml, 7.20 mmol) followed by stirring for 15 min, triethylamine (3.0 ml) and satd. aq. $NaHCO_3$ (5 ml) were added, and the whole was allowed to warm to room temperature. After addition of water (15 ml), the whole was extracted with hexane (50 ml x 3). The organic extracts were combined, washed successively with water, 0.1 N aq. citric acid, water, satd. aq. $NaHCO_3$, brine, dried over Na_2SO_4, and evaporated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, hexane) followed by bulb-to-bulb distillation (155°C/0.8 mmHg) to give *(R)*-**3a** (267.3 mg, 83%) as a colorless liquid of $[\alpha]_{365}^{25}$ +186.1 (c=2.20, benzene), corresponding to be 79% ee.[2c]
11. The reasons are not yet clear and are under investigation.
12. An example of catalytic asymmetric deprotonation of *meso*-epoxides is reported: Asami, M.; Ishizaki, T.; Inoue, S. *Tetrahedron: Asymmetry* **1994**, *5*, 793-796.

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