Tetrahedron Letters, Vol. 34, No. 32, pp. 5105-5108, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

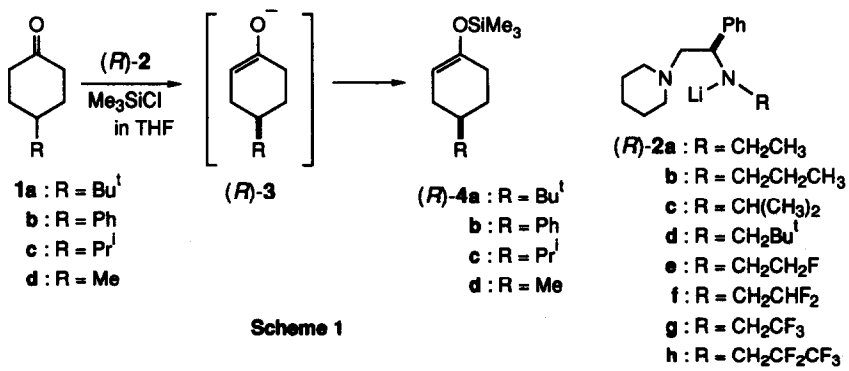
Enantioselective Deprotonation of 4-Substituted Cyclohexanones by Chiral Chelated Lithium Amides Having a Fluorine-containing Alkyl Group on Amide Nitrogen

Kazumasa Aoki, Hiroshi Noguchi, Kiyoshi Tomioka,[1] and Kenji Koga*

Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan

Abstract: Chiral chelated lithium amides (**2e~h**) having a fluorine-containing alkyl group on amide nitrogen were found to induce high enantioselectivity in kinetic deprotonation of 4-substituted cyclohexanones (**1a~d**).

Conversion of a carbonyl compound into the corresponding enolate anion is the most fundamental and widely used process in synthetic organic chemistry. We have previously reported enantioselective deprotonation of prochiral 4-substituted cyclohexanones (**1a~d**) by chiral lithium amides (**2**, R = alkyl) in the presence of excess trimethylsilyl chloride (TMSCl) (Corey's internal quench method[2]) to isolate the corresponding chiral enolate anions (**3a~d**) as their trimethylsilyl enol ethers (**4a~d**).[3,4] The stereochemical course of the reaction was found to be as shown below. It is previously shown that **2d** exists as a chelated monomeric form by coordination of the piperidino nitrogen to the lithium in THF in the presence and in the absence of hexamethylphosphoric triamide (HMPA).[3b]



Scheme 1

In search of superior chiral lithium amides inducing higher enantioselectivity in the present kinetic deprotonation reaction, we examined chiral lithium amides (**2e~h**) having a fluorine-containing alkyl group on amide nitrogen. The reaction was carried out in THF in the presence of excess TMSCl and in the absence or in the presence of HMPA.[3] Some results are summarized in Table 1.[5,6]

Table 1. Deprotonation of **1** by (*R*)-**2** in THF in the Presence of Me_3SiCl to give (*R*)-**4**[a]

Run	Ketone 1	Ketone R	Lithium amide (*R*)-2	Lithium amide R	HMPA (eq.)	Temp. (°C)	Product (*R*)-4	Product Chem. y. (%)	Product Optical y. (%)
1	**1a**	Bu^t	**2a**	CH_2CH_3	0	-78	**4a**	86	52
2	**1a**	Bu^t	**2a**	CH_2CH_3	1.2	-78	**4a**	93	78
3	**1a**	Bu^t	**2b**	$CH_2CH_2CH_3$	0	-78	**4a**	96	62
4	**1a**	Bu^t	**2b**	$CH_2CH_2CH_3$	1.2	-78	**4a**	97	81
5	**1a**	Bu^t	**2c**	$CH(CH_3)_2$	0	-78	**4a**	87	65
6	**1a**	Bu^t	**2c**	$CH(CH_3)_2$	1.2	-78	**4a**	73	75
7	**1a**	Bu^t	**2d**	CH_2Bu^t	0	-78	**4a**	93	86
8	**1a**	Bu^t	**2d**	CH_2Bu^t	1.2	-78	**4a**	94	84
9	**1a**	Bu^t	**2e**	CH_2CH_2F	0	-78	**4a**	85	69
10	**1a**	Bu^t	**2e**	CH_2CH_2F	1.2	-78	**4a**	67	85
11	**1a**	Bu^t	**2f**	CH_2CHF_2	0	-78	**4a**	93	77
12	**1a**	Bu^t	**2f**	CH_2CHF_2	1.2	-78	**4a**	92	89
13	**1a**	Bu^t	**2g**	CH_2CF_3	0	-78	**4a**	88	84
14	**1a**	Bu^t	**2g**	CH_2CF_3	1.2	-78	**4a**	74	87
15	**1a**	Bu^t	**2h**	$CH_2CF_2CF_3$	0	-78	**4a**	79	85
16	**1a**	Bu^t	**2h**	$CH_2CF_2CF_3$	1.2	-78	**4a**	77	87
17	**1a**	Bu^t	**2d**	CH_2Bu^t	1.2	-100	**4a**	78	89
18	**1a**	Bu^t	**2g**	CH_2CF_3	1.2	-100	**4a**	88	93
19	**1a**	Bu^t	**2h**	$CH_2CF_2CF_3$	0	-100	**4a**	77	90
20	**1a**	Bu^t	**2h**	$CH_2CF_2CF_3$	1.2	-100	**4a**	84	92
21	**1b**	Ph	**2g**	CH_2CF_3	1.2	-100	**4b**	95	93
22	**1c**	Pr^i	**2g**	CH_2CF_3	1.2	-100	**4c**	92	95
23	**1d**	Me	**2g**	CH_2CF_3	1.2	-100	**4d**	76	94

[a]See ref. 5 and 6.

By using chiral lithium amides (**2a~d**) having no fluorine on the alkyl group, enantioselectivity of the reaction generally increases as the size of the alkyl group increases in the absence (runs 1,3,5,7) and in the presence (runs 2,4,6,8) of HMPA, and is higher in the presence of HMPA. It is interesting to note, by using those chiral lithium amides (**2e~h**) that have fluorine(s) on the alkyl group, that enantioselectivity of the reaction increases as the number of the fluorine on the alkyl group increases in the absence of HMPA (runs 9,11,13,15), while it is reasonably higher and almost independent on the number of the fluorine in the presence of HMPA (runs 10,12,14,16).[7] By using (*R*)-**2g** at -100°C in THF in the presence of HMPA, 4-substituted

cyclohexanones (**1a~d**) were converted to the corresponding silyl enol ethers ((R)-**4a~d**) in good enantioselectivity irrespective of the bulkiness of the substituent at 4-position in **1** (runs 18,21,22,23). It is thus shown that chiral lithium amides (**2e~h**) having a fluorine-containing ethyl or propyl group on amide nitrogen are distinctly superior to **2a** or **2b** having an ethyl or propyl group there.

It is reported[8] that effective van der Waals radius of fluorine (1.47 Å) is larger than that of hydrogen (1.20 Å) but smaller than that of methyl (1.80 Å), while that of trifluoromethyl (2.2 Å) is larger than that of methyl but reasonably smaller than that of *tert*-butyl (3.6 Å). In Table 1, it is shown that **2e** having a monofluoroethyl group on amide nitrogen induces higher enantioselectivity than **2b** having a propyl group there (runs 3,4,9,10). It is also shown that **2g** having a trifluoroethyl group induces almost the same enantioselectivity as **2d** having a neopentyl group (runs 7,8,13,14). It is thus clear that the superiority of fluorine-containing lithium amides (**2e~h**) over the corresponding fluorine-lacking lithium amides (**2a~d**) is not ascribable to the difference in bulkiness of the alkyl group on amide nitrogen.

Another possible reason for this interesting stereoselectivity would be that the fluorine might be working as an internal ligation site for the lithium to form an additional chelated ring. We therefore prepared [^{6}Li, $^{15}N_2$]-(*S*)-**2g** in optically pure form to examine ^{15}N-, ^{6}Li-, and ^{19}F-NMR in THF-d_8. As shown in Figure 1, ^{15}N signals appear as a triplet ($J_{N(1)\text{-}Li}$ = 7.0 Hz) and a triplet ($J_{N(2)\text{-}Li}$ = 2.4 Hz), ^{6}Li signal appears as a double doublet ($J_{N(1)\text{-}Li}$ = 7.0, $J_{N(2)\text{-}Li}$ = 2.4 Hz), and ^{19}F signal appears as a triplet ($J_{F\text{-}H}$ = 11 Hz), indicating that (*S*)-**2g** exists as a chelated monomeric form in THF and suggesting that the fluorine is not working as an internal ligand.[9]

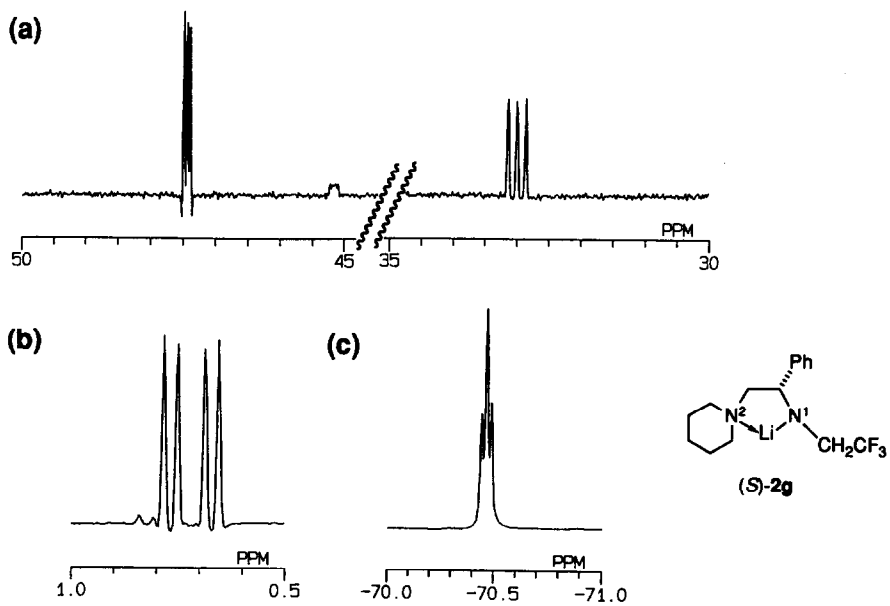


Figure 1. NMR spectra of (*S*)-**2g** in THF-d_8 at 20°C. (a) ^{15}N-spectrum (reference: ^{15}N-aniline (52.0 ppm)); (b) ^{6}Li-spectrum (reference: ^{6}LiCl (0 ppm)); (c) ^{19}F-spectrum (reference: $CFCl_3$(0 ppm)).

It is conceivable that electrostatic interaction between the partial negative charge of the fluorine and the partial positive charge of the lithium fixes the conformation of the chelated monomeric form of **2e~h**. Studies along this line are in progress.

Acknowledgement The authors are grateful to Tokyo Biochemical Research Foundation for partial financial support of this work.

References and Notes

1) Present address: Institute of Scientific and Industrial Research, Osaka University, Ibaraki, Osaka 567, Japan

2) Corey, E. J; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495.

3) (a) Shirai, R. ; Tanaka, M.; Koga, K. *J. Am. Chem. Soc.* **1986**, *108*, 543; (b) Sato, D. ; Kawasaki, H. ; Shimada, I. ; Arata, Y. ; Okamura, K. ; Date. T. ; Koga, K. *ibid.* **1992**, *114*, 761; (c) Aoki, K. ; Nakajima, M. ; Tomioka, K. ; Koga, K. *Chem. Pharm. Bull* ., in press.

4) For reviews, see: (a) Koga, K. *J. Synth. Org. Chem. Jpn.* **1990**, *48*, 463. (b) Cox, P. J. ; Simpkins, N. S. *Tetrahedron: Asymmetry*, **1991**, *2*, 1.

5) Reinvestigation[3c] has shown that maximum rotations of (*R*)-**4a**, (*R*)-**4b**, (*R*)-**4c**, and (*R*)-**4d** should be $[\alpha]_{365}^{25}$+237° (benzene), $[\alpha]_{365}^{25}$+146° (benzene),$[\alpha]_{365}^{25}$+228° (benzene),$[\alpha]_{365}^{25}$+238° (benzene), respectively. Optical yields of the products (**4a~d**) were calculated using these values.

6) A typical experimental procedure is as follows (Table 1, run 18). Under argon atmosphere, a solution of n-butyllithium in hexane (1.457 N, 1.65 ml, 2.4 mmol) was added to a solution of **2g** (716 mg, 2.5 mmol) in THF (50 ml) at -78°C, and the resulting solution was stirred for 30 min. After addition of HMPA (0.50 ml, 2.9 mmol), the whole was stirred at -78°C for 20 min and was then cooled to -100°C. A solution of **1a** (308 mg, 2.0 mmol) and TMSCl (1.27 ml, 10 mmol) in THF (4 ml) was added dropwise during 6 min, and the reaction mixture was stirred at -100°C for 35 min. Triethylamine (4 ml) and satd. aq. $NaHCO_3$ (10 ml) were added, and the whole was allowed to warm to room temperature. After addition of H_2O (15 ml), the whole was extracted with hexane (50 ml x 3). The organic extacts were combined, washed successively with H_2O, 0.1 N aq. citric acid, H_2O, 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 (150°C/0.5 mmHg) to give (*R*)-**4a** (400 mg, 88 %) as a colorless liquid of $[\alpha]_{365}^{25}$+220° (c =1.33, benzene), corresponding to be 93 % ee.

7) In cases where lithium amides (**2e~h**) are used in THF in the presence of HMPA, a solution of **1** and TMSCl in THF should be added to a solution of lithium amide to get good yields. By adding TMSCl prior to the addition of **1**, chemical yield of the reaction drops sharply due to the formation of the corresponding N-silylated chiral amine.

8) (a) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441; (b) Bott, G. ; Field, L. D. ; Sternhell, S. *J. Am. Chem. Soc.* **1980**, *102*, 5618, and references cited therein.

9) Cf: Pieper, U.; Walter, S.; Klingebiel, U.; Stalke, D. *Angew. Chem, Int. Ed. Engl.* **1990**, *29*, 209.

(Received in Japan 8 March 1993; accepted 11 June 1993)