



Enantioselective Deprotonation of 4-*tert*-Butylcyclohexanone by Fluorine-Containing Chiral Lithium Amides Derived from α -Phenethylamine

Kazumasa Aoki and Kenji Koga*

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

Abstract: An α -phenethylamine-derived chiral lithium amide ((*R*)-**5c**) possessing a 2,2,2-trifluoroethyl group on the amide nitrogen was found to induce high enantioselectivity in the kinetic deprotonation of 4-*tert*-butylcyclohexanone (**1**) in the presence of excess trimethylsilyl chloride to give the corresponding silyl enol ether ((*S*)-**2**) in up to 92% ee (86% chemical yield). © 1997 Elsevier Science Ltd.

Enantioselective deprotonation of σ -symmetric cyclohexanone derivatives such as 4-*tert*-butylcyclohexanone (**1**) can be carried out by using various chiral lithium amides.¹ We have previously reported enantioselective deprotonation of **1** in the presence of excess trimethylsilyl chloride² (TMSCl) by a chiral chelated lithium amide ((*R*)-**3**) possessing a piperidino group as an internal ligation site for the lithium and a 2,2,2-trifluoroethyl group on the amide nitrogen to give the corresponding silyl enol ether ((*R*)-**2**) in reasonably good chemical and optical yields.³ It is shown that the 2,2,2-trifluoroethyl group plays a crucial role in inducing high enantioselectivity. In search of easily accessible chiral lithium amides that induce good enantioselectivity in the present kinetic deprotonation reaction, we designed α -phenethylamine-derived chiral lithium amides having a fluorine-containing alkyl group ((*R*)-**5a-c**)⁴, and compared their ability as chiral bases with those having an alkyl group ((*R*)-**5d-e**) or a 2-(dimethylamino)ethyl group ((*R*)-**5f**) on the amide nitrogen. All reactions were carried out in THF in the presence of excess TMSCl. Results are summarized in Table 1.

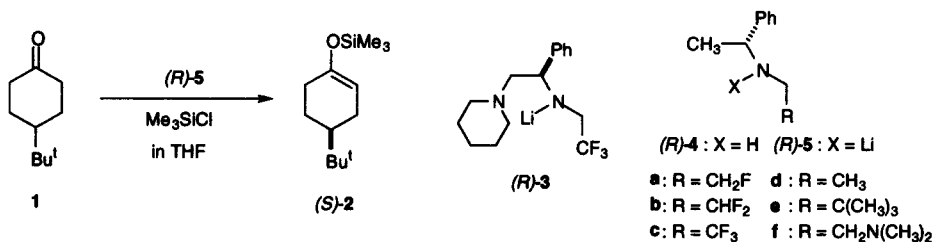


Table 1. Enantioselective Deprotonation of **1** Using **5**

Run	Chiral lithium amide		Temp. (°C)	Product		
	5	R		2	Chem. y. (%)	Optical y. (%)
1	(<i>R</i>)- 5a	CH_2F	-78	(<i>S</i>)- 2	61	43
2	(<i>R</i>)- 5b	CHF_2	-78	(<i>S</i>)- 2	66	59
3	(<i>R</i>)- 5c	CF_3	-78	(<i>S</i>)- 2	98	89
4	(<i>R</i>)- 5c	CF_3	-100	(<i>S</i>)- 2	86	92
5	(<i>S</i>)- 5c	CF_3	-100	(<i>R</i>)- 2	83	92
6	(<i>R</i>)- 5d	CH_3	-78	(<i>S</i>)- 2	55	41
7	(<i>R</i>)- 5e	$\text{C}(\text{CH}_3)_3$	-78	(<i>S</i>)- 2	94	32
8	(<i>R</i>)- 5f	$\text{CH}_2\text{N}(\text{CH}_3)_2$	-78	(<i>S</i>)- 2	92	18

It is shown that chemical and optical yields of the product (**2**^{5,6}) depend heavily on the substituent on the amide nitrogen. Thus, among the amides ((*R*)-**5a-c**) having a fluorine-containing alkyl group, enantioselectivity of the reaction increases as the number of the fluorine atoms increases (runs 1,2,3). It is shown that the amides ((*R*)-**5d-e**) having an alkyl group on the amide nitrogen gave (*S*)-**2** in low optical yields (runs 6,7). It is again shown that the 2,2,2-trifluoroethyl group is necessary to get the product in high efficiency.

Based on the assumption that one of the fluorine atoms and the lithium in (*R*)-**5c** may be forced to come into close proximity due to the electrostatic interaction, as was observed in (*R*)-**3**,³ (*R*)-**5f** was designed with the expectation that the dimethylamino group will orient itself in close proximity to the lithium by coordination. It is shown, however, that (*R*)-**5f** gave (*S*)-**2** in quite low enantioselectivity (run 8).

A typical experimental procedure (Table 1, run 4) is as follows. Under argon atmosphere, a solution of butyllithium in hexane (1.55 *N*, 1.55 mL, 2.4 mmol) was added to a solution of (*R*)-**4c** (508 mg, 2.5 mmol) in THF (50 mL) at -78 °C. The resulting solution was stirred at -78 °C for 30 min and was then cooled to -100 °C. After addition of TMSCl (1.27 mL, 10 mmol), a solution of **1** (308 mg, 2.0 mmol) in THF (4 mL) was added dropwise over a period of 6 min, and the whole was stirred at -100 °C for 50 min. The reaction mixture was quenched with triethylamine (4 mL) and satd. aq. NaHCO₃ (10 mL), and the whole was allowed to warm to room temperature. After addition of water (15 mL), the mixture was extracted with hexane (3 x 50 mL). The organic extracts were combined, washed successively with water (2 x 20 mL), 0.1 *N* aq. citric acid (2 x 100 mL, 3 x 50 mL), water (20 mL), satd. aq. NaHCO₃ (20 mL), brine, and then dried (Na₂SO₄). Evaporation of the solvent *in vacuo* gave a yellow oil, which was purified by column chromatography (silica gel, hexane) followed by bulb-to-bulb distillation to give (*S*)-**2** as a colorless oil (388 mg, 86% yield) of bp 150 °C (0.5 mmHg) (bath temperature), [α]₃₆₅²⁵ -217.1 (*c*, 1.49, benzene), corresponding to be 92% ee.⁵ (*R*)-**4c** was recovered (67% isolated yield) without any loss of optical purity.

Since (*R*)- and (*S*)- **5c** are easily accessible in optically pure forms from commercially available (*R*)- and (*S*)- α -phenethylamine, these chiral lithium amides are practically useful bases for the present enantioselective deprotonation reaction.

Acknowledgement A predoctoral fellowship to K. A. from the Japan Society for the Promotion of Science is gratefully acknowledged.

REFERENCES AND NOTES

- For reviews, see: (a) Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymmetry* **1991**, 2, 1-26; (b) Koga, K. *Pure Appl. Chem.* **1994**, 66, 1487-1492; (c) Koga, K.; Shindo, M. *J. Synth. Org. Chem., Jpn.* **1995**, 52, 1021-1032; (d) Simpkins, N. S. *Pure Appl. Chem.* **1996**, 68, 691-694.
- Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, 25, 495-498.
- Aoki, K.; Noguchi, H.; Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1993**, 34, 5105-5108.
- The chiral amines ((*R*)-**4a**, **4b**, and **4c**) were prepared in optically pure forms from commercially available (*R*)- α -phenethylamine by converting it to the corresponding amides using RCOOC₂H₅ (R = CH₂F, CHF₂, and CF₃, respectively), followed by reduction with BH₃-THF.
- It is shown that the maximum rotation of (*S*)-**2** is [α]₃₆₅²⁵ -237 (benzene).⁶ Optical yields of the product were calculated by using this value.
- Aoki, K.; Nakajima, M.; Tomioka, K.; Koga, K. *Chem. Pharm. Bull.* **1993**, 41, 994-996.

(Received in Japan 27 January 1997; revised 17 February 1997; accepted 21 February 1997)