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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 chloride[2] (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.

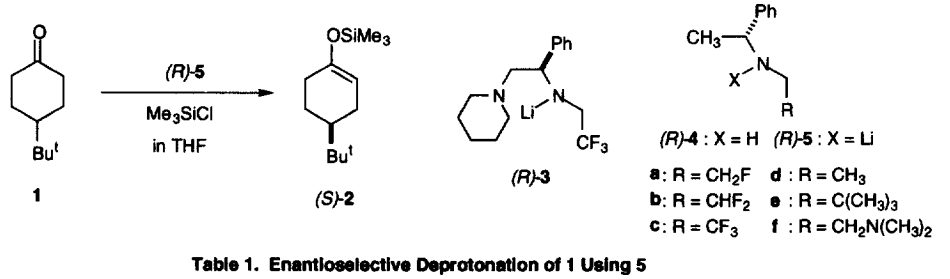

Table 1. Enantioselective Deprotonation of 1 Using 5

Run	Chiral lithium amide 5	R	Temp. (°C)	Product 2	Chem. y. (%)	Optical y. (%)
1	*(R)*-**5a**	CH_2F	-78	*(S)*-**2**	61	43
2	*(R)*-**5b**	CHF_2	-78	*(S)*-**2**	66	59
3	*(R)*-**5c**	CF_3	-78	*(S)*-**2**	98	89
4	*(R)*-**5c**	CF_3	-100	*(S)*-**2**	86	92
5	*(S)*-**5c**	CF_3	-100	*(R)*-**2**	83	92
6	*(R)*-**5d**	CH_3	-78	*(S)*-**2**	55	41
7	*(R)*-**5e**	$C(CH_3)_3$	-78	*(S)*-**2**	94	32
8	*(R)*-**5f**	$CH_2N(CH_3)_2$	-78	*(S)*-**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. $NaHCO_3$ (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. $NaHCO_3$ (20 mL), brine, and then dried (Na_2SO_4). 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), $[\alpha]_{365}^{25}$ -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.

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4. 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 $RCOOC_2H_5$ (R = CH_2F, CHF_2, and CF_3, respectively), followed by reduction with BH_3-THF.
5. It is shown that the maximum rotation of *(S)*-**2** is $[\alpha]_{365}^{25}$ -237 (benzene).[6] Optical yields of the product were calculated by using this value.
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