ENANTIOSELECTIVE DEPROTONATION OF THE MESO-FORMS OF 2,6- AND 3,5-DIMETHYLCYCLOHEXANONES[1)]

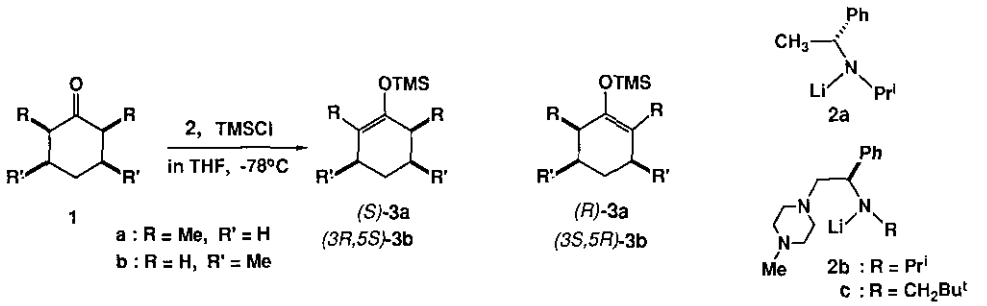
Hee-doo Kim, Ryuichi Shirai, Hisashi Kawasaki, Makoto Nakajima, and Kenji Koga*
Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan

Abstract ——— Kinetic deprotonation of meso-dimethylcyclohexanones (**1a-c**) by chiral lithium amides (**2a-c**) in the presence of excess trimethylsilyl chloride afforded the corresponding silyl enol ethers (**3a-b**) in good yields and in reasonably high enantiomeric excesses.

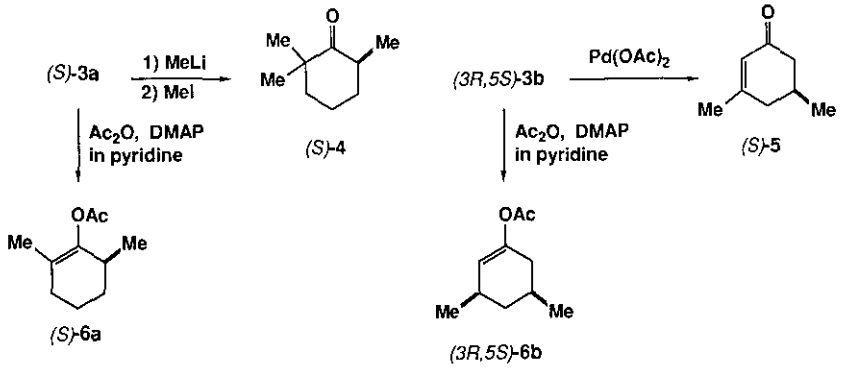
The design of highly efficient methods for enantioselective asymmetric synthesis, in which chirality is induced intermolecularly, has been a focus in synthetic organic chemistry.

We have previously reported that kinetic deprotonation of prochiral 4-substituted cyclohexanones by chiral lithium amides occurs enantioselectively in the presence of excess trimethylsilyl chloride (TMSCl) to give the corresponding trimethylsilyl enol ethers in reasonably high enantiomeric excesses.[2)] Simpkins has also reported that kinetic deprotonation of meso-2,6-dimethylcyclohexanone (**1a**) by chiral lithium amides occurs enantioselectively to give the corresponding chiral enolate, which was quenched with acetic anhydride to isolate the product as the enol acetate (**6a**) in up to 74% enantiomeric excess.[3)]

The present paper describes our approach to enantioselective deprotonation of **1a** and meso-3,5-dimethylcyclohexanone (**1b**) by chiral lithium amides (**2a-c**) in the presence of excess TMSCl to give the corresponding trimethylsilyl enol ethers (**3a-b**). Chiral lithium amides examined here have one chiral center, and **2a** has no internal ligation site for lithium, while **2b** and **2c** have N-methylpiperazino group to form a five-membered chelated ring. Therefore, **2b** and **2c** are expected to carry chiral amide nitrogen by virtue of chelation.[2)]



Absolute configurations of **3a** and **3b** were determined by converting them to the *known* **4**[4] *and* **5**,[5] respectively. Optical purities of **3a** and **3b** were determined after conversion to their corresponding enol acetates (**6a-b**).[6,7]



The results are summarized in Table 1. A typical experimental procedure (run 6) is as follows. A solution of chiral lithium amide (**2c**) was prepared under argon atmosphere by adding a solution of n-butyllithium (2.0 mmol) in hexane (1.58 M solution) to a solution of the corresponding amine (2.1 mmol) in tetrahydrofuran (THF) (15 ml) under stirring at -78°C for 30 min. Hexamethylphosphoric triamide (HMPA) (2.1 mmol) was added[2] and the resulting solution was warmed to room temperature for 5 min, and then recooled to -78°C. To this solution were added TMSCl (5 mmol) quickly, and then a solution of **1a** (126 mg, 1.0 mmol) in THF (5 ml) *dropwise during 5 min, and the whole was* stirred at -78°C for 20 min. After addition of triethylamine (2.0 ml) and saturated aqueous sodium bicarbonate (4.0 ml), the reaction mixture was allowed to warm to room temperature. Usual work-up by using pentane as an extracting solvent gave a crude product. Purification by column chromatography (silica gel, pentane) followed by bulb-to-bulb distillation (170°C/10 mmHg) gave **3a** (145 mg, 73%) as a colorless liquid of $[\alpha]_{365}^{25}$ -153.5° (c=1.20, benzene).

Table 1. Enantioselective Deprotonation of 1[a)]

Run	Ketone	Base	equiv.[b)]	TMSCl equiv.[b)]	HMPA equiv.[c)]	Silyl enol ether[d)]	Chem. y.(%)	ee(%)	Confign.
1	**1a**	**2a**	1.2	5	0	**3a**	53	60	S
2	**1a**	**2a**	1.2	10	0	**3a**	63	65	S
3	**1a**	**2b**	1.2	10	0	**3a**	33	85	S
4	**1a**	**2b**	1.2	5	1.0	**3a**	34	78	S
5	**1a**	**2b**	4.4	10	0	**3a**	89	89	S
6	**1a**	**2c**	2.0	5	1.0	**3a**	73	96	S
7	**1b**	**2a**	1.2	10	0	**3b**	54	76	3R,5S
8	**1b**	**2b**	1.2	10	0	**3b**	69	64	3S,5R
9	**1b**	**2c**	2.0	5	1.0	**3b**	88	90	3S,5R

a) For procedure, see text. b) Relative to **1**. c) Relative to **2**. d) Maximum rotations were calculated to be $[\alpha]_{365}^{25}$ -160°(benzene) for (S)-**3a**, and $[\alpha]_{365}^{25}$ +105° (benzene) for (3S,5R)-**3b**.[7)]

Efficient enantioselective deprotonation of meso-cyclohexanones (**1a-b**) to give their corresponding silyl enol ethers (**3a-b**) is thus realized. The best results were obtained by using **2c**, which has an N-methylpiperazino group for internal ligation site to lithium and has a neopentyl group on amide nitrogen.

It is shown that subtle change in the structure of chiral base causes significant change in the stereoselectivity of the reaction. It should also be noted that the sense of asymmetric induction for **1b** using **2a-2c** and for **1a** using **2b-c** is the same as that for 4-substituted cyclohexanones reported previously,[2)] while it is opposite for **1a** using **2a**. Mechanistic details are under investigation.

Since both enantiomeric forms of chiral lithium amides (**2a-c**) are available easily from optically active phenethylamine or phenylglycine in optically pure states, the present method provides a new approach to both enantiomeric forms of silyl enol ethers (**3a-b**), which are expected to be useful as synthons for the synthesis of various optically active compounds.

ACKNOWLEDGEMENT

Partial financial supports from the Ministry of Education, Science, and Culture, Japan (Grant-in-aid for Scientific Research on Priority Areas, No. 01607002) and from the Japan Research Foundation for Optically Active Compounds are gratefully acknowledged.

REFERENCES AND NOTES

1) This paper is dedicated to the late Professor Tetsuji Kametani.

2) a) R. Shirai, M. Tanaka, and K. Koga, J. Am. Chem. Soc., 1986, **108**, 543. b) K. Koga, 'Organic Synthesis: Modern Trends,' ed. by O. Chizhov, Blackwell Scientific Publ., 1987, pp. 285-291.

3) a) N. S. Simpkins, J. Chem. Soc., Chem. Commun., 1986, 88. b) Dr. Simpkins has kindly informed us personally that in-situ TMSCl quench technique to isolate the enolate as its silyl enol ether is superior and improved levels of asymmetric induction reported by him.

4) (-)-**3a**($[\alpha]_{365}^{26}$ -100.4°(benzene)) afforded (S)-**4**($[\alpha]_{D}^{20}$ +79.8°($CHCl_3$)). For the absolute configuration of **4**, see: M. B. Eleveld and H. Hogeveen, Tetrahedron Lett., 1986, **27**, 631.

5) (-)-**3b**($[\alpha]_{365}^{25}$ -78.6°(benzene)) afforded (S)-**5**($[\alpha]_{D}^{26}$ +82.4°($CHCl_3$)). For the absolute configuration of **5**, see: N. L. Allinger and C. K. Riew, J. Org. Chem., 1975, **40**, 1316.

6) Cf. a) J. K. Rasmussen, Synthesis, 1977, 91. b) H.-d. Kim, H. Kawasaki, M. Nakajima, and K. Koga, Tetrahedron Lett., submitted.

7) Enantiomeric excesses of **6a-b** were determined by proton nmr spectroscopy using $Eu(hfc)_3$. (S)-**3a**($[\alpha]_{365}^{25}$ -153.5°(benzene)) afforded (S)-**6a**($[\alpha]_{365}^{25}$ -274.6° (benzene)) of 96% ee. (3S,5R)-**3b**($[\alpha]_{365}^{25}$ +65.8°(benzene)) afforded (3S,5R)-**6b** ($[\alpha]_{365}^{25}$ +18.5°(benzene)) of 63% ee. Enantiomeric excesses of **3a-b** were calculated by these data and should be minimum.

Received, 23rd August, 1989