ASYMMETRIC α-ALKYLATION OF CYCLOHEXANONE BY MEDIATION OF A CHIRAL LIGAND AND THE LEAVING-GROUP EFFECT OF ELECTROPHILES ON ENANTIOSELECTIVITY

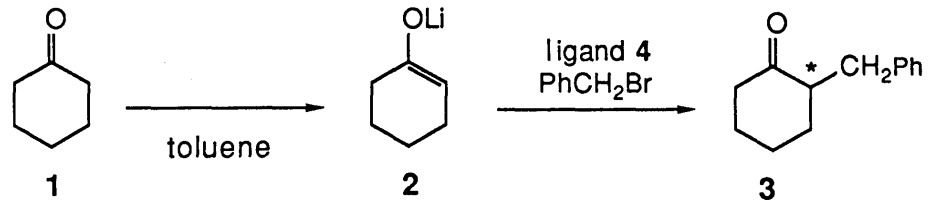
Kiyoshi TOMIOKA,* Mitsuru SHINDO, and Kenji KOGA*

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

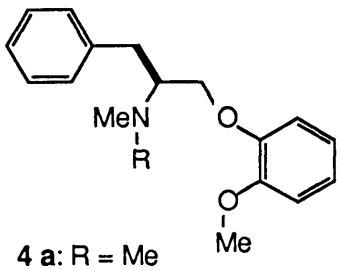
*By the mediation of a chiral amino ether (**4**), the asymmetric α-benzylation of cyclohexanone (**1**) was effected via an achiral lithioenamine (**6**) to give α-benzylcyclohexanone (**3**) in up to 52% ee. A dramatic leaving-group effect of electrophiles on enantioselectivity was also observed.*

KEYWORDS asymmetric alkylation; chiral ligand; leaving group effect; enantioselectivity; lithioenamine

Asymmetric α-alkylation of cycloalkanones has been a focus in recent decades and various methods have been developed.[1] Among them, the method using of chiral lithioenamine has proved to be the basis for the efficient intramolecular asymmetric induction resting on the rigidity of the lithioenamine by an internal ligand.[2] Unlike this progress in the intramolecular asymmetric induction, the asymmetric alkylation of an achiral enolate and/or azaenolate by the mediation of an external chiral ligand still remains to be developed.[3~5] As part of continuing effort toward development of an asymmetric reaction mediated by a chiral ligand,[6] we now report the first asymmetric α-alkylation of cyclohexanone (**1**) by the mediation of a chiral amino ether (**4**). A dramatic leaving-group effect of benzylation reagents on enantioselectivity was also observed.



Cyclohexanone (**1**) was lithiated with lithium amide (1.2 eq), generated from **4b**[7] and *n*-BuLi, in toluene at -20°C for 1.5 h then treated with benzyl bromide (2 eq) at -78°C. The reaction was allowed to warm up to 0°C and stirred for 10 h at 0°C. The usual work-up and purification by silica gel column chromatography afforded 27% ee of *(S)*-**3** in 40% yield.[8] Similarly the alkylation of **2**, generated from the corresponding trimethylsilyl enol ether and MeLi in toluene in the presence of **4a** (1.3 eq), afforded 17% ee of *(R)*-**3** in 21% yield. Although efficiency in the sense of asymmetric induction and of chemical reactivity is moderate, these are the first examples of a direct asymmetric alkylation of cyclohexanone by the mediation of an external chiral ligand.



4 a: R = Me
b: R = $(CH_2)_2NHMe$

The major drawback of these reactions of the enolate **2** is the requirement of the relatively high reaction temperature which is attributed to the poor efficiency of asymmetric induction. To realize the reaction at a lower

temperature, alkylation of more reactive lithioenamine[9] was studied.

Cyclohexylimine (**5**) was then lithiated with *s*-BuLi (1.2 eq) in the presence of **4a** (0.4 eq)[10] in toluene at -20°C for 1.5 h and was then treated with benzyl chloride (2 eq) in the presence of 1.3 eq of **4a** at -100°C for 1 h. Acidic hydrolysis and a standard work-up afforded, after silica gel column chromatography, 51% ee of *(S)*-**3** in 36% yield. Use of 3.3 eq of **4a** provided 52% ee of *(S)*-**3** in 34% yield. As shown in these reactions the slight effect of the amount of chiral ligand (**4a**) on efficiency in the asymmetric induction indicates the formation of relatively tight complexes between lithioenamine (**6**) and ligand (**4**). The ligand **4b** effected asymmetric alkylation of **6** with benzyl bromide to afford *(R)*-**3** of 23% ee in 30% yield. It is noteworthy that 52% ee of alkylation product was obtained by the mediation of chiral ligand.

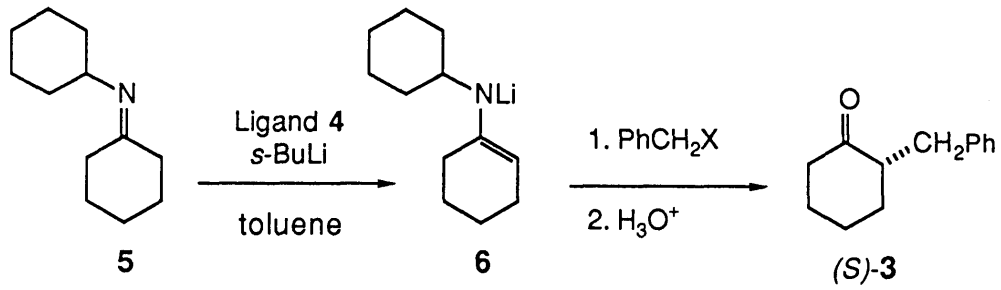


Table I. Leaving Group Effects on the Asymmetric Alkylation of **5** by the Mediation of **4a**[a]

		(S)-**3**		
Entry	$PhCH_2X$	Yield/%[b]	$[\alpha]_D^{25}$ °(MeOH)[c]	ee/%[d]
1	$PhCH_2Cl$	36	-24.2	51
2	$PhCH_2Br$	50	-18.1	39
3	$PhCH_2I$	47	-7.6	16
4	$PhCH_2OSO_2Ph$	43	-0.1	0

a) Reactions of **5** were performed in the presence of 1.3 eq of **4a** at -100°C for 1 h. b) Yield isolated by column chromatography. c) For the maximum optical rotation, see ref. 2a. d) Determined by the optical rotation.

Then we turned our focus to the systematic study on the leaving group effect of electrophiles. The results are summarized in Table I. The reaction of **6** with benzyl chloride in the presence of 1.3 eq of **4a** provided 51% ee of *(S)*-**3**, whereas reactions with benzyl bromide, benzyl iodide, and benzyl benzenesulfonate afforded 39, 16, and 0% ee of *(S)*-**3**, respectively. The dramatic leaving group effect of the electrophiles on the asymmetric induction was apparent, but the reason for these phenomena remains to be solved.[11]

In summary, we showed that achiral enolate and azaenolate are alkylated with alkyl halides to afford promising %ee of the α-alkylated products by the mediation of an external chiral ligand. Encouraged by these results, further investigations along this line are in progress in our laboratory.

ACKNOWLEDGEMENT A part of the work was financially supported by a grant from Hoan-sha.

REFERENCES AND NOTES

1) Review: "Asymmetric Synthesis," ed. by J. D. Morrison, Vol. 1~5, 1982~1984, Academic Press, New York.

2) a) A. I. Meyers, D. R. Williams, G. W. Erickson, S. White, and M. Druelinger, *J. Am. Chem. Soc.*, **103**, 3081 (1981); b) S. Hashimoto and K. Koga, *Chem. Pharm. Bull.*, **27**, 2760 (1979); c) D. Enders and H. Eichenauer, *Chem. Ber.*, **112**, 2933 (1979); d) J. K. Whitesell and M. A. Whitesell, *J. Org. Chem.*, **42**, 377 (1977); e) K. Tomioka, W. Seo, K. Ando, and K. Koga, *Tetrahedron Lett.*, **28**, 6637 (1987) and references cited therein.

3) Asymmetric carboxylation of 2,2,6-trimethylcyclohexanone has been reported. H. Hogeveen and W. M. P. B. Menge, *Tetrahedron Lett.*, **27**, 2767 (1986).

4) Asymmetric alkylation of achiral ester enolates with alkyl halides has been reported. T. Yamashita, H. Mitsui, H. Watanabe, and N. Nakamura, *Bull. Chem. Soc. Jpn.*, **55**, 961 (1982); A. Ando and T. Shioiri, *J. Chem. Soc., Chem. Commun.*, **1987**, 656.

5) Asymmetric addition reactions of achiral enolates to carbonyl compounds have been reported. N. Iwasawa and T. Mukaiyama, *Chemistry Lett.*, **1983**, 297; A. Ando, and T. Shioiri, *J. Chem. Soc., Chem. Commun.*, **1987**, 1620; M. Muraoka, H. Kawasaki, and K. Koga, *Tetrahedron Lett.*, **29**, 337 (1988).

6) a) K. Tomioka, M. Sudani, Y. Shinmi, and K. Koga, *Chemistry Lett.*, **1985**, 329; b) K. Tomioka, M. Nakajima, and K. Koga, *Ibid.*, **1987**, 65; c) *Idem, Tetrahedron Lett.*, **28**, 1291 (1987); d) *Idem, J. Am. Chem. Soc.*, **109**, 6213 (1987); e) *Idem, Tetrahedron Lett.*, **29**, 573 (1988).

7) Chiral ligands **4a** and **4b** were prepared from L-phenylalanine as described earlier. See reference 6a.

8) Absolute configuration and enantiomeric excess were determined by comparing the optical rotation. See reference 2a.

9) G. Stork and S. Dowd, *J. Am. Chem. Soc.*, **85**, 2178 (1963); G. Wittig, H. D. Frommeld, and P. Suchanek, *Angew. Chem.*, **75**, 978 (1963).

10) Direct lithiation in the presence of 1.3 eq of **4a** resulted in a significant destruction of the ligand **4a**. However 0.4 eq of **4a** effected smooth lithiation of the Schiff base (**5**) without detectable destruction of the ligand. The active species for the lithiation appeared to be the complexes of 1 eq of **4a** and more than 2 eq of BuLi.

11) The leaving group effects on the efficiency of the asymmetric induction were also observed in the diastereoface differentiating alkylation reaction. See S. E. Denmark and J. J. Ares, *J. Am. Chem. Soc.*, **110**, 4432 (1988).

(Received January 19, 1989)