Enantioselective Alkylation at the α-Position of Cyclic Ketones using a Chiral Lithium Amide as a Base in the Presence of Lithium Bromide

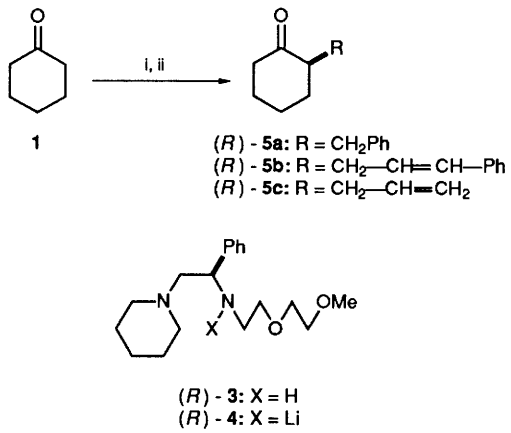
Masatoshi Murakata, Makoto Nakajima and Kenji Koga*

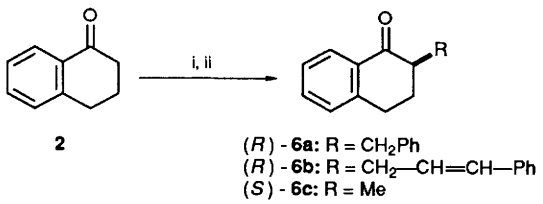
Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan

An efficient enantioselective alkylation reaction at the α-position of cyclic ketones (**1**, **2**) can be realized in up to 92% enantiometric excess (e.e.) by first forming their lithium enolates using a chiral lithium amide **4** in the presence of lithium bromide, followed by treatment with alkyl halides.

Asymmetric carbon–carbon bond forming reactions by alkylation at the α-position of ketones have been a focus in synthetic organic chemistry.[1] Among the various methods developed so far, diastereoselective alkylation of chiral chelated lithioenamines has met with great success.[1,2] By employing chiral lithium amides as a base to generate achiral lithium enolates, enantioselective protonation,[3] carboxylation,[4] alkylation[5] and aldol condensation[6] have been reported to give optically active products. These results are understandable because lithium enolates prepared from ketones and lithium amides are shown to form complexes in solution with amines coming from the lithium amides used,[7] and therefore, symmetrical π-systems of achiral lithium enolates possibly exist in a chiral environment, which could influence the direction and the rate of the reactions with electrophiles. We describe here an efficient enantioselective alkylation of cyclohexanone **1** and 1-tetralone **2** that can be realized by first forming their lithium enolates using a chiral lithium amide **4** in the presence of lithium bromide (LiBr), followed by treatment with alkyl halides as shown in Scheme 1 and Table 1.

The degree of asymmetric induction was found to be dependent on the solvent used. Without addition of lithium bromide, the degree of asymmetric induction in toluene increased (as did the chemical yield) with alkylation time (runs 4–6). This interesting phenomenon is ascribable to the presence of LiBr, which is liberated as the alkylation proceeds. It is thus found that the degree of asymmetric induction is increased greatly by adding LiBr from the beginning. Among several lithium salts (LiF, LiCl, LiBr, LiI, LiOBu^t and $LiOSO_2CF_3$) examined, LiBr gave the best result.





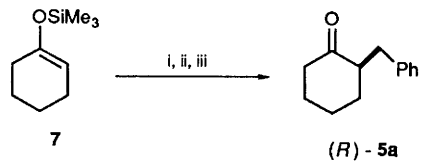
Scheme 1 *Reagents*: (i) (*R*)-**4**, LiBr; (ii) RX

A typical experimental procedure (entry 14) is as follows. Under argon atmosphere, LiBr (1.1 mmol) was dissolved in a solution of the chiral amine [(*R*)−**3**]† (1.0 mmol) in toluene (7 ml) by the aid of ultrasonic vibration. A solution of n-butyllithium (1.0 mmol) in hexane (1.71 mol dm^{-3} solution) was added at −20 °C, and the whole was stirred for 30 min. A solution of **2** (1.0 mmol) in toluene (3 ml) was added, the whole was stirred at −20 °C for 30 min, and then cooled to −78 °C. A solution of benzyl bromide (10 mmol) in toluene (2 ml) was added at −78 °C. The reaction mixture was warmed to −45 °C, and was stirred at this temperature for 18 h. After addition of aqueous hydrochloric acid (0.5 mol dm^{-3}; 10 ml), the product was isolated by the usual work-up and purification [column chromatography (silica gel, benzene) followed by bulb-to-bulb distillation (160 °C at 0.3 mmHg)] to give (*R*)-2-benzyl-1-tetralone [(*R*)-**6a**]{$[\alpha]_D^{25}$ +17.8° (*c*, 1.89, MeOH)} in 92% e.e. (89% chemical yield).

Absolute configurations of **5a**,[8] **5c**[8,9] and **6c**[8,10,11] are known and were determined for **5b**, **6a** and **6b** by circular dichroism.‡ It is shown that the sense of asymmetric induction in alkylations using **4** as a chiral base is the same as that shown in Scheme 1.

The present enantioselective alkylation reaction can also be carried out efficiently in a different way as shown in Scheme 2. Thus, lithium enolate was prepared from trimethylsilyl enol ether **7** (1.0 mmol) of **1** with a solution of MeLi–LiBr complex (1.0 mmol) in ether. After addition of (*R*)-**3**, the resulting mixture was treated with benzyl bromide (10 mmol) in toluene as described above (−45 °C, 18 h) to afford (*R*)-**5a** in 92% e.e. (68% chemical yield).

It is thus reasonable to assume that the formation of lithium enolate–chiral secondary amine–LiBr complex is responsible for this highly enantioselective alkylation.



Scheme 2 *Reagents*: (i) MeLi–LiBr in ether; (ii) (*R*)-**3**; (iii) $PhCH_2Br$, toluene

† Optically pure (*R*)-**3** was prepared from (*R*)-phenylglycine by the conventional method.

‡ **5b** {$[\alpha]_D^{25}$ +30.4° (*c*, 1.27, MeOH), 87% e.e. by HPLC (Opti-Pak TA)} was hydrogenated (10% Pd–C, H_2, EtOH) to 2-(3-phenylpropyl)cyclohexanone (91%) of $[\alpha]_D^{25}$ +15.9° (*c*, 0.43, MeOH), $[\theta]_{291}$ + 2580 (*c*, 0.13, MeOH), having *R*-configuration.[11]

6a {$[\alpha]_D^{25}$ +17.8° (*c*, 1.89, MeOH), 92% e.e. by HPLC (Opti-Pak TA)} showed $[\theta]_{336}$ −1760 (*c*, 0.12, EtOH), having *R*-configuration.[11]

6b {$[\alpha]_D^{25}$ +16.0° (*c*, 1.02, EtOH), 88% e.e. by HPLC (Opti-Pak TA)} showed $[\theta]_{334}$ −1560 (*c*, 0.12, EtOH), having *R*-configuration.[11]

Table 1 Enantioselective alkylation of **1** and **2**[a]

Run	Ketone	Solvent	LiBr (equiv.)	RX	Alkylation time/h	Product	Isolated yield (%)	E.e.(%)[b]	Confign.
1	**1**	THF[c]	0	$PhCH_2Br$	18	**5a**	42	0	—
2	**1**	Ether	0	$PhCH_2Br$	18	**5a**	14	25	*R*
3	**1**	DME[d]	0	$PhCH_2Br$	18	**5a**	69	30	*R*
4	**1**	Toluene	0	$PhCH_2Br$	3	**5a**	29	36	*R*
5	**1**	Toluene	0	$PhCH_2Br$	18	**5a**	62	58	*R*
6	**1**	Toluene	0	$PhCH_2Br$	180	**5a**	74	62	*R*
7	**1**	THF	1.1	$PhCH_2Br$	18	**5a**	87	0	—
8	**1**	Ether	1.1	$PhCH_2Br$	18	**5a**	56	91	*R*
9	**1**	DME	1.1	$PhCH_2Br$	18	**5a**	86	41	*R*
10	**1**	Toluene	1.1	$PhCH_2Br$	18	**5a**	63	92	*R*
11	**1**	Toluene	1.1	$PhCH{=}CHCH_2Br$	18	**5b**	60	87	*R*
12	**1**	Toluene	1.1	$CH_2{=}CHCH_2Br$	18	**5c**	41	80	*R*
13	**2**	Toluene	0	$PhCH_2Br$	18	**6a**	88	62	*R*
14	**2**	Toluene	1.1	$PhCH_2Br$	18	**6a**	89	92	*R*
15	**2**	Toluene	1.1	$PhCH{=}CHCH_2Br$	18	**6b**	93	88	*R*
16	**2**	Toluene	1.1	MeI	18	**6c**	71	88	*S*

[a] For general procedure, see text. Alkylation was carried out using benzyl bromide (2 equiv.) at −20 °C in runs 1–6, and at −50 to 40 °C using RX (10 equiv.) in runs 7–16. [b] Determined by HPLC using a chiral column (Waters Opti-Pak TA for **5a**, **5b**, **6a** and **6b**, Opti-Pak XC for **6c**) and by optical rotation for **5c**. [c] THF = tetrahydrofuran. [d] DME = 1,2-dimethoxyethane.

The method outlined above provides a new, simple and efficient approach to enantioselective asymmetric synthesis of α-alkylcycloalkanones, which should be useful as synthons for the synthesis of various optically active compounds.

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References

1 For reviews, see: *Asymmetric Synthesis*, ed. J. D. Morrison, Academic Press, New York, 1983, vol. 2 and 1984, vol. 3.
2 For example, see: A. I. Meyers, D. R. Williams and M. Druelinger, *J. Am. Chem. Soc.*, 1976, **98**, 3032; D. Enders and H. Eickenauer, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 549; J. K. Whitesell and M. A. Whitesell, *J. Org. Chem.*, 1977, **42**, 377; S. Hashimoto and K. Koga, *Tetrahedron Lett.*, 1978, 753.
3 L. Duhamel and J.-C. Plaquevent, *Tetrahedron Lett.*, 1980, **21**, 2521; L. Duhamel, P. Duhamel, J.-C. Launay and J.-C. Plaquevent, *Bull. Soc. Chim. Fr.*, 1984, II-421; H. Hogeveen and L. Zwart, *Tetrahedron Lett.*, 1982, **23**, 105; M. B. Eleveld and H. Hogeveen, *Tetrahedron Lett.*, 1986, **27**, 631.
4 H. Hogeveen and W. M. P. B. Menge, *Tetrahedron Lett.*, 1986, **27**, 2767.
5 T. Yamashita, M. Mitsui, H. Watanabe and N. Nakamura, *Bull. Chem. Soc. Jpn.*, 1982, **55**, 961; A. Ando and T. Shioiri, *J. Chem. Soc., Chem. Commun.*, 1987, 656; K. Tomioka, M. Shindo and K. Koga, *Chem. Pharm. Bull.*, 1989, **37**, 1120.
6 C. H. Heathcock, in *Asymmetric Synthesis*, ed. J. D. Morrison, Academic Press, New York, 1984, vol. 3, pp. 200–206; A. C. Regan and J. Staunton, *J. Chem. Soc., Chem. Commun.*, 1987, 520; J. Mulzer, P. de Lasalle, A. Chucholowski, V. Blaschek, G. Bruntrup, I. Jibril and G. Huttner, *Tetrahedron*, 1984, **40**, 2211; A. Ando and T. Shioiri, *J. Chem. Soc., Chem. Commun.*, 1987, 1620; M. Muraoka, H. Kawasaki and K. Koga, *Tetrahedron Lett.*, 1988, **29**, 337.
7 D. Seebach, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 1624 and references cited therein.
8 A. I. Meyers, D. R. Williams, G. W. Erickson, S. White and M. Druelinger, *J. Am. Chem. Soc.*, 1981, **103**, 3081.
9 M. Kitamoto, K. Hiroi, S. Terashima and S. Yamada, *Chem. Pharm. Bull.*, 1974, **22**, 459.
10 G. Jaouen and A. Meyer, *J. Am. Chem. Soc.*, 1975, **97**, 4677.
11 G. Snatzke and F. Snatzke, in *Fundamental Aspects and Recent Developments in Optical Rotatory Dispersion and Circular Dichroism*, eds. F. Ciardelli and P. Salvadori, Heyden, London, 1973, ch. 3.2.