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Kinetic Resolution of Bicyclic Ketones by Enantioselective Deprotonation.

Hee-doo Kim

College of Pharmacy, Sookmyung Women's University, Chungpa-Dong, Yongsan-Ku, Seoul 142-742, Korea

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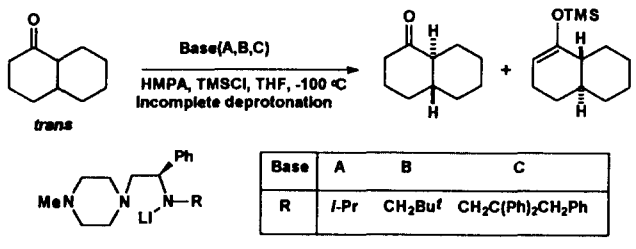
Optically active bicyclic ketones are key chiral synthons for the synthesis of biologically important compounds such as steroids. Everincreasing requirement for the synthesis of chiral compounds calls for their efficient and useful preparations in the optically active forms. Although a great deal of effort has been devoted to the synthesis of chiral monocyclic ketones such as cyclohexanones and cyclopentanones (Murakata *et al.*, 1990), only a few methods for bicyclic ketones are available at present time (Johnson *et al.*, 1984, Mori *et al.*, 1985, Krawczyk *et al.*, 1989). However, taking into account of the occurences and the various useful synthetic methods for racemic bicyclic ketones, resolution is still viable way to obtain chiral compounds. Recently, Koga *et al.* reported a novel kinetic resolution method (Kim *et al.*, 1989) for 2-substituted cyclohexanones based on the asymmetric deprotonation using chiral bases (Cox *et al.*, 1991, Koga, 1994). As a part of our research programs to investigate the scope and limitation of the reaction, we applied the methodology to resolve some important bicyclic ketones.

As shown in scheme 1, incomplete deprotonation of racemic bicyclic ketones with chiral bases in the presence of excess trimethylsilyl chloride (TMSCl) (Corey *et al.*, 1984) would produce a mixture of unreacted ketone and the corresponding trimethylsilyl enol ether. As the fast reacting enantiomer being swept away into the form of silyl enol ether, the slow reacting enantiomer become a major component in the remained ketone. A typical procedure is as follows: Chiral lithium amide (C) solution was prepared by adding *n*-BuLi in hexane to a stirred -78°C solution of the corresponding chiral amine (650 mg,1.33 mmol) in tetrahydrofuran(5 mL). To this solution was added 0.23 mL of hexamethylphosphoric triamide (HMPA) and then the mixture was warmed by removing cooling bath for 5 min. The resulting solution was added dropwise over 20 min to the precooled (-100°C) THF (10 mL) solution of TMSCl (0.95 mL) and racemic *trans*-1-decalone(238 mg, 1.56 mmol), and the whole was stirred for 30 min at -100°C under argon atmosphere. The reaction was quenched by addition of 2 mL of triethylamine and 4 mL of aqueous sodium bicarbonate at -100°C, and warmed to room temperature. After usual extractive work-up, the crude product was subjected to column chromatography (silanized silica gel, hexane) followed by kugelrohr distillation to give 103 mg (43%) of unreacted (9R, 10R)-1-decalone ($[\alpha]_D^{25}$+7.78° ethanol)) in 78% optical yield and 192.3 mg (55%) of the corresponding trimethylsilyl enol ether($[\alpha]_D^{25}$+129.9 (benzene)) in 59% optical yield.



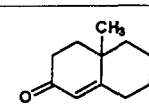
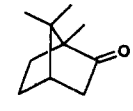
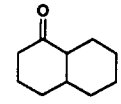
Base	A	B	C
R	*i*-Pr	CH_2Bu^t	$CH_2C(Ph)_2CH_2Ph$

Scheme 1.

By comparison with the reported data on 1-decalone (Fernandez *et al.*, 1982), camphor (Hodgson *et al.*, 1973) and 10-methyl-1(9)-octalone-2 (Johnson *et al.*, 1982), the absolute configurations and optical yields of unreacted bicyclic ketones were estimated.

Optical yields of trimethylsilyl enol ether were cal-

Table 1. Kinetic resolution of Racemic bicyclic ketones

Entry	Racemic Ketone	Base	ketone		Silyl enol ether
			cy*/ee(%)	R/S	cy*/ee(%)
1		A	73/1	S	26/2
2		B	74/11	S	25/35
3		B	37/72	R	62/44
4		B	79/8	9R, 10R	15/52
5		C	43/78	9R, 10R	55/59

*Chemical yields were calculated by GLC analysis.

Correspondence to: Hee-Doo Kim, College of Pharmacy, Sookmyung Women's University, Chungpa-Dong, Yongsan-Ku, Seoul 142-742, Korea

culated by conversion to the parent ketones. The results are summarized in Table 1.

As expected, conformationally stable and α-substituted ketone such as *trans*-1-decalone and camphor were resolved more efficiently than 10-methyl-1(9)-octalone-2 was. In addition, the enantioselectivities are greatly dependent on R groups on the chiral bases. Although base B is most frequently used chiral base at present time, chiral base C is the best in our case. We roughly estimated the enantioselectivity factor K_{rel} (K_{fast}/K_{slow}) (Eliel *et al.*, 1988), which is independent of the conversion yield. In cases of entry 3 and 5, K_{rel} are calculated to be 6 and 9 respectively. In summary, we resolved the some important bicyclic ketones with chiral bases in moderate enantioselectivities, and found better chiral base for this purpose. However, design of better chiral base is still to be remained for the future work to achieve the better enantioselectivity.

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REFERENCES CITED

Corey, E. J., Gross, A. W., Highly selective, kinetically controlled enolate formation using lithium dialkylamides in the presence of trimethylchlorosilane. *Tetrahedron Lett.*, 25, 495-498 (1984).

Cox, P. J., Simpkins, N. S., Asymmetric synthesis using homochiral lithium amide bases. *Tetrahedron Asymmetry*, 2, 1-26(1991) and references cited therein.

Eliel, E. L., Willen, S. H., Kinetic Resolution. In *Topics in stereochemistry*. 18, 249-330 (1988).

Fernandez, F., Alcaide, B., Tarazona, M. T., Polycyclic analogs of *trans*-decalones. *J. Chem. Soc. Perkins I*, 2117-2122 (1982).

Hodgson, G. L., MacSweeney, D. F., Mills, R. W., Money, T., Synthesis and absolute configuration of the terpenes (-)-Campherenone, (+)-Epicampherenone, (-)-Santalene, and (+)-Epi-β-Santalene. *J. Chem. Soc., Chem. Comm.* 235-236 (1973).

Johnson, C. R., Zeller, J. R., Sulfoximine-mediated resolution of ketones. *J. Am. Chem. Soc.*, 104, 4021-4023 (1982).

Johnson, C. R., Zeller, J. R., N,S-Dimethyl-S-phenylsulfoximine. A reagent for optical resolution of ketones. *Tetrahedron*, 40, 1225-1233 (1984).

Kim, H-d., Kawasaki, H., Nakajima, Koga, K., Kinetic resolution of racemic 2-substituted cyclohexanones. *Tetrahedron Lett.*, 30, 6537-6540 (1989).

Koga, K., Asymmetric synthesis mediated by chiral ligands. *Pure Appl. Chem.*, 66, 1487-1492 (1994) and references cited therein.

Krawczyk, A. R., Jones, J. B., Enzyme in organic synthesis. 46. Regioselective horse liver alcohol dehydrogenase catalyzed reduction of *cis*- and *trans*-bicyclo[4.3.0] nonanones. *J. Org. Chem.* 54, 1795-1801 (1989).

Mori, A., Yamamoto, H., Resolution of ketones via chiral acetals. Kinetic approach., *J. Org. Chem.*, 50, 5444-5446 (1985).

Murakata, M., Nakajima, M., Koga, K., Enantioselective alkylation at the α-posotion of cyclic ketones using a chiral lithium amide as a base in the presence of lithium bromide. *J. Chem. Soc., Chem. Comm.*, 1657-1658 (1990) and references cited therein.