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APPLICATION OF *erythro*-2-METHOXY-1,2-DIPHENYLETHYLAMINE TO ENANTIOSELECTIVE ALKYLATION OF CYCLOHEXANONE

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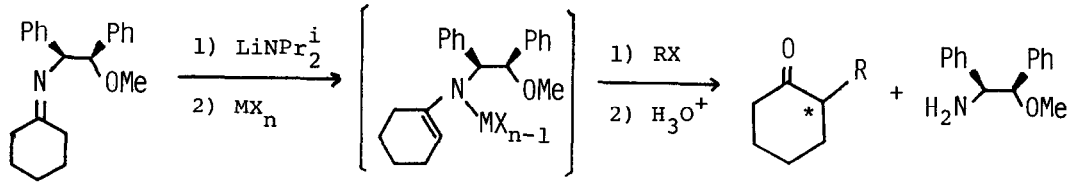
Abstract: The chiral imine, prepared from (-)- or (+)-*erythro*-2-methoxy-1,2-diphenylethylamine and cyclohexanone, is metalated and alkylated at 0°C to give the corresponding 2-alkylcyclohexanone in 79-92% optical purity.

The utilization of a chiral amino ether in forming the imine is known to afford the opportunity for asymmetric induction.[1] On the other hand, successful optical resolution of *erythro*-2-amino-1,2-diphenylethanol was reported as a part of our study on the resolution of artificial chiral components,[2] which would make it possible to use properly the both enantiomers for asymmetric induction in required situation. In the present paper, we wish to describe the enantioselective synthesis of 2-alkylcyclohexanone having desired absolute configuration by the alternative use of (-)- or (+)-*erythro*-2-methoxy-1,2-diphenylethylamine derived from the optically active amino alcohol.



After several investigations on the reaction conditions, it was established that both optical purity and chemical yield of 2-alkylcyclohexanone were strongly influenced by the metal in the metalloenamine and by reaction temperature. The optimum purity and yield were given when the enaminozinc bromide was allowed to react with alkyl halide at 0°C as shown in the Table.

A typical procedure is described for benzylation: To a solution of lithium diisopropylamide (5.0 mmol) in THF/hexane (10 ml/3 ml) was added a solution of (+)-*erythro*-N-cyclohexylidene-2-methoxy-1,2-diphenylethylamine[3] (1228 mg, 4.0 mmol) in THF (5 ml) at around -23°C in a period of 15 min. After stirring for 1 h at the temperature, zinc bromide (1125 mg, 5.0 mmol) was added, and the reaction mixture was stirred for 30 min at room temperature followed by refluxing

for 30 min. To the solution was added benzyl bromide (770 mg, 4.5 mmol) in THF (10 ml) at 0°C in a period of 45 min, and stirring was continued for 3 h at 0°C. After quenching with methanol (0.5 ml), the mixture was concentrated under reduced pressure. Pentane (25 ml) and sat. oxalic acid solution (15 ml) were added to the remaining residue and stirred for 1 h. The precipitates appeared were filtered off and washed with pentane (10 ml x 3). The organic layer of the filtrate and the washings were combined, washed with 1M HCl solution and sat. NaCl solution, successively, and dried with Na_2SO_4. After evaporation of the solvent, bulb-to-bulb distillation gave 634 mg of 2-benzylcyclohexanone.

Table. Enantioselective Alkylation of Cyclohexanone

The Imine Used	RX	Temp. (°C)	MX_{n-1}	Yield (%)	$[\alpha]_D$ (*c*, MeOH)	O.P. (%)	(Config.)
(+)	$PhCH_2Br$	-78	Li	72	+13.5° (3.6)	29	(R)
(+)	$PhCH_2Br$	-78	MgBr	46	-30.5° (4.6)	65	(S)
(+)	$PhCH_2Br$	-78	ZnBr	23	+33.9° (2.5)	72	(R)
(+)	$PhCH_2Br$	0	ZnBr	84	+37.3° (4.9)	79	(R)
(-)	$PhCH_2Br$	0	ZnBr	79	-38.8° (5.2)	82	(S)
(+)	$CH_2=CHCH_2Br$	0	ZnBr	76	+14.7° (3.1)	92	(R)
(-)	$CH_2=CHCH_2Br$	0	ZnBr	71	-14.2° (3.0)	89	(S)
(+)	CH_3CH_2I	0	ZnBr	78	+22.2° (3.9)	86	(S)
(-)	CH_3CH_2I	0	ZnBr	70	-22.8° (3.8)	88	(R)

Optical purities were calculated based on the values in the literature.[1)]

References

1) A. I. Meyers, D. R. Williams, G. W. Erickson, S. White, and M. Druelinger, *J. Am. Chem. Soc.*, 103, 3081 (1981); and references cited therein.

2) K. Saigo, S. Ogawa, S. Kikuchi, A. Kasahara, and H. Nohira, *Bull. Chem. Soc. Jpn.*, 55, 1568 (1982).

3) A benzene solution of (-)-*erythro*-2-methoxy-1,2-diphenylethylamine (mp 73-74°C, $[\alpha]_D^{30}$ -84.2° (*c* 1.1, 99% MeOH)) and 1.05 equimolar amount of cyclohexanone was refluxed, and the water formed was removed azeotropically. After evaporation of the solvent, the solid mass was thoroughly dried *in vacuo* to give (+)-*erythro*-N-cyclohexylidene-2-methoxy-1,2-diphenylethylamine in quantitative yield, which was used for the present experiment without further purification; mp 50-51°C, $[\alpha]_D^{30}$ +51.3° (*c* 1.0, MeOH). In a similar fashion, (+)-*erythro*-2-methoxy-1,2-diphenylethylamine (mp 71-72°C, $[\alpha]_D^{28}$ +84.6° (*c* 1.0, 99% MeOH)) was converted into (-)-imine; mp 50.5-52°C $[\alpha]_D^{26}$ -51.1° (*c* 1.0, MeOH).

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