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ASYMMETRIC REDUCTION OF ALKYL PHENYL KETONES WITH A CHIRAL HYDRIDE REAGENT PREPARED FROM LITHIUM ALUMINUM HYDRIDE AND (S)-4-ANILINO-3-METHYLAMINO-1-BUTANOL

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Summary· *The asymmetric reduction of alkyl phenyl ketones with a chiral hydride reagent derived from lithium aluminum hydride and (S)-4-anilino-3-methylamino-1-butanol, which is prepared from (S)-aspartic acid, gives (S)-alkylphenylcarbinols in high chemical and optical yields*

Recently asymmetric reductions of prochiral ketones to optically active secondary alcohols with chiral hydride reagents have been studied extensively [1,2] Most of such studies have been carried out by the use of lithium aluminum hydride derivatives modified by the chiral unidentate or bidentate ligands such as alcohol,[2a] phenol,[2b] aminoalcohol[2c,d] or amine derivatives.[2e] On the other hand, there has not yet been to our knowledge an example of an asymmetric reduction with a chiral hydride reagent possessing a tridentate ligand. A tridentate ligand is considered to be more profitable for asymmetric reduction by a rigid complex formation than an unidentate or bidentate ligand. We wish to report here an effective asymmetric reduction of alkyl phenyl ketones with lithium aluminum hydride partially decomposed by a tridentate ligand, (S)-4-anilino-3-methylamino-1-butanol (1) derived easily from (S)-aspartic acid.

The chiral ligand 1 was easily prepared in 80% overall yield through two steps from β-benzyl N-benzyloxycarbonyl-(S)-aspartate.[3] Treatment of β-benzyl N-benzyloxycarbonylaspartate with ethyl chloroformate, N-methylmorpholine and aniline gave the corresponding anilide, which was reduced with lithium aluminum hydride to furnish 1, bp 139 ∿ 140 °C/0.7 mmHg; $[\alpha]_D^{23}$ -13.7° (C 1.00, $CHCl_3$).

Chiral aluminum hydride reagent 2 (empirical formula) was prepared *in situ* from lithium aluminum hydride and the chiral diaminoalcohol 1. For example, 1 (3

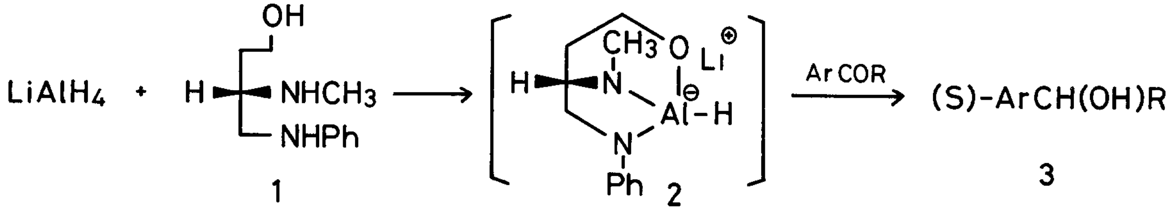
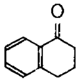
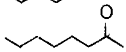


Table. The Asymmetric Reduction of Alkyl Phenyl Ketones with Chiral Reagent (2)

Ketone	Chemical Yield(%)[a]	Obsd $[\alpha]_D^{23}$ (C, solvent)	Reported $[\alpha]_D$	Optical Yield(%ee)	Config.
$PhCOCH_3$	87	-22.0°(7.00, C_5H_{10})	-43.1°[b]	51	S
$PhCOCH_2CH_3$	93	-30.9°(5.475, $CHCl_3$)	-45.45°[c]	68	S
$PhCOCH(CH_3)_2$	93	-36.7°(7.46, Et_2O)	-47.7°[d]	77	S
$PhCOC(CH_3)_3$	84	-19.8°(2.32, $CHCl_3$)	-22.9°[e]	86	S
	89	+28.9°(4.255, $CHCl_3$)	+32.7°[f]	88	S
	92	+3.3°(5.77, EtOH)	+10.1°[g]	33	S

[a] All products were identified by ^{1}H NMR and IR spectroscopy and/or comparison with authentic materials Isolated yields by distillation. [b] See ref 2d [c] R H Pickard and J Kenyon, *J Chem. Soc.*, 105, 1115 (1914). [d] R MacLeod, F J Welch, and H S Mosher, *J. Am Chem Soc.*, 82, 876 (1960). [e] D R Clark and H S Mosher, *J Org. Chem* , 35, 1114 (1970) [f] A G Davies and A. M White, *J Chem Soc.*, 1952, 3300 [g] R. K Hill, *J. Am. Chem Soc.*, 80, 1611 (1958)

mmol) in THF (9 ml) was added to ca. 1M THF solution of lithium aluminum hydride (3 mmol) at 0 °C. After stirring the mixture at room temperature for 1 h, the solution of chiral complex was cooled to -100 °C and ketone (1 mmol) in THF (2 ml) was added slowly. The mixture was stirred at this temperature for 3 ∿ 4 h and quenched by adding wet ether and water. The organic layer was washed with 3M hydrochloric acid. The product was purified by TLC on silica gel and further by bulb to bulb distillation. The diaminoalcohol 1 was recovered from the acidic aqueous layer in a yield of over 85% without any racemization.

The results of asymmetric reduction of several alkyl phenyl ketones are listed in Table. In every case, the absolute configuration of the alkylphenylcarbinol (3) obtained is the S-configuration. It should be noted that t-butyl phenyl ketone possessing a bulky alkyl group and α-tetralone gave the corresponding (S)-carbinols in high optical yields of 86 and 88%, respectively. These values are the highest ones so far reported.[1,2] The reduction of a simple dialkyl ketone, 2-octanone gave similarly the (S)-carbinol but did not give satisfactory optical yield (33%).

Further applications of this complex lithium aluminum hydride reagent to asymmetric reduction are under progress.

References

1. D. Valentine, Jr. and J. W. Scott, *Synthesis*, 1978, 329, J. W. ApSimon and R. P. Seguin, *Tetrahedron*, 35, 2797 (1979).
2. For example, a) S. R. Landor, B. J. Miller, and A. R. Tatchell, *J. Chem. Soc C*, 1967, 197. b) R. Noyori, I. Tomino, and Y. Tanimoto, *J. Am. Chem. Soc* , 101, 3129 (1979). c) S. Terashima, N. Tanno, and K. Koga, *Chem. Lett.*, 1980, 981. d) S. Yamaguchi and H. S. Mosher, *J Org Chem* , 38, 1870 (1973). e) M. Asami and T. Mukaiyama, *Heterocycles*, 12, 499 (1979) and references cited therein.
3. L. Benoiton, *Can. J Chem.*, 40, 570 (1962).

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