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ASYMMETRIC REDUCTION OF ALKYL ARYL KETONES WITH LITHIUM BOROHYDRIDE USING N-BENZOYLCYSTEINE AS CHIRAL LIGAND

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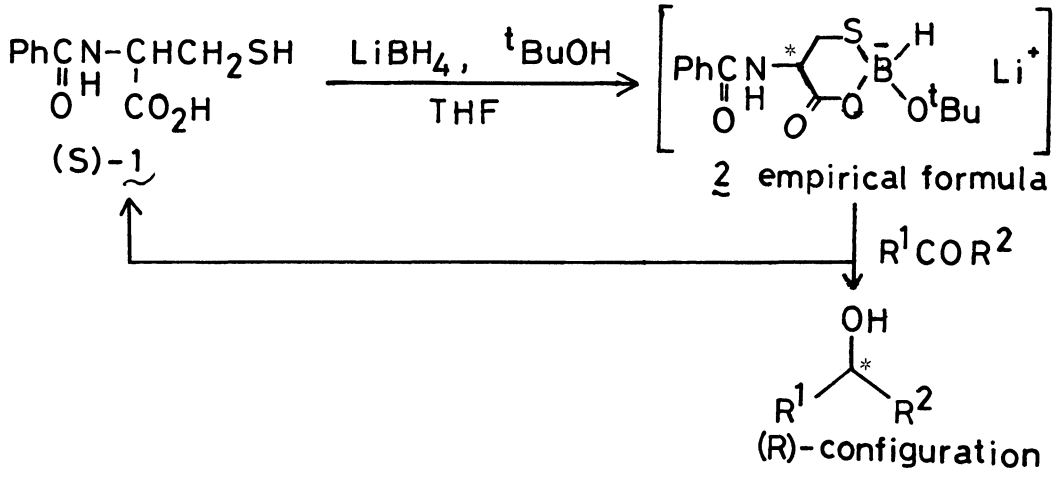
N-Benzoylcysteine, a chiral ligand possessing sulfur donor atom, was found to be highly effective in enantioselective reduction of alkyl aryl ketones with lithium borohydride (up to 92-93%e.e.).

Enantioselective asymmetric reduction of ketones with chiral complex metal hydrides has provided an efficient tool for the synthesis of optically active alcohols.[1] (1) However, donor atoms of the chiral ligands utilized in the reported methods have been limited to nitrogen, oxygen, and carbon.[2] (2) Moreover, despite many efforts,[2g-l] enantioselectivities of chiral complex borohydrides have been considerably lower (mostly below 40%e.e., max. 78-79%e.e.[2i,m]) than those of chiral lithium aluminium hydride.[2a-f]

We recently reported the use of complex borohydride with a small amount of methanol in diastereoselective reduction of chiral α-keto amides[3] and in functional group selective reductions of esters, epoxides and amides.[4-6]

We now describe the enantioselective reduction of alkyl aryl ketones with lithium borohydride ($LiBH_4$) using N-benzoylcysteine (1) as chiral ligand, which affords optically active alcohols of high enantiomeric excesses up to 92-93%e.e. To the best of our knowledge, this is the first example of the use of chiral ligand possessing sulfur donor atom in enantioselective reduction of ketones.[7] Also this is the highest enantioselectivity reported in the asymmetric reaction using chiral complex borohydride.



We chose 1 as chiral ligand for the following reasons: (1) Stabilization of anion by sulfur is well documented.[8] This sulfur mediated stability of borohydride anion may reduce the possibilities of the disproportionation of chiral ligand. (2) 1 can be easily prepared from cystine in high yields in two steps, Schotten-Baumann N,N'-dibenzoylation of cystine followed by the reduction with zinc-hydrochloric acid.[9] (3) Both enantiomers of cystine are commercially available. Therefore alcohols of the desired configuration can be synthesized by using the appropriate enantiomer of 1. (4) Because 1 is soluble in aqueous alkali, 1 may be removed from reaction mixture by washing with aqueous alkali. This character of 1 is unique compared with other amine containing chiral ligands which are acid soluble.[2a-d]

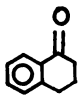
Our initial attempts to reduce ketones with the hydride prepared from $LiBH_4$ and (S)-1 without the use of additives resulted in unsatisfactory asymmetric inductions. We then examined the effect of additives. The addition of t-butyl alcohol (t-BuOH) was found to dramatically increase the enantioselectivities. Configuration of alcohol was determined by measurement of the optical rotation. Enantiomeric excess was determined by GLC (PEG20M, capillary column 25m) and ^1H-NMR (100 MHz) analyses of the corresponding esters of (+)-α- methoxy-α-trifluoromethylphenyl acetic acid [(+)-MTPA].[10] Chiral ligand (S)-1 was recovered in over 85% yield after acidification of the aq. alkali washings.

As can be seen from the results summarized in Table 1, enantiomeric excesses of the alcohols were high especially in the reductions of primary-alkyl phenyl ketones such as acetophenone, propiophenone, phenyl n-propyl ketone and n-butyl phenyl ketone (up to 92-93%e.e.). In all cases, alcohols of (R)- configuration were obtained when (S)-1 was used.

A typical experimental prodedure is as follows: 1.07 M THF solution of $LiBH_4$ (3.6 mmol) was added to the solution of 1 (2.4 mmol) and t-BuOH (1.6 mmol) in THF (8.5 ml) at room temperature under an argon atmosphere. After the mixture was refluxed for 30 min., the solution was cooled to -78 °C and propiophenone (0.134 g, 1 mmol) in THF (2 ml) was added.[11] The mixture was stirred for 4.5 h while the temperature was allowed to warm from -78 °C to -40 °C. The reaction was quenched by adding 1 M HCl (3 ml). Aqueous solution of $NaHCO_3$ (5%) was added until the pH of the mixture become about 10. The mixture was extracted with ether, and the organic layer was washed with 5% $NaHCO_3$ solution. The extract was dried over anhydrous sodium sulfate, and then evaporated on a rotary evaporator. The residue was purified on silica gel TLC (chloroform as developing solvent). (R)-(+)-1-Phenyl-butanol (0.096 g, 71%) was obtained as a colorless oil. After distillation with Kugel-rohr apparatus (bp 140 °C / 25 mmHg, bath temp, lit,[12] bp 107 °C / 15 mmHg), optical ratation was observed. $[\alpha]_D^{20}$ +41.45° (c 5.09, $CHCl_3$) (91.2%e.e.), lit,[13] $[\alpha]_D$ -45.45° (c 5.15, $CHCl_3$). Enantiomeric excess (85.5 ± 2.5 %e.e.) was determined as (+)-MTPA ester[10] as described in the text. Recovery of 1 was performed by extraction of aq. washings with ethyl acetate after acidification (85% yield).

As described above, the present reducing system of $LiBH_4$-N-benzoylcysteine-t-BuOH is highly effective in enantioselective reduction of alkyl aryl ketones.

Table 1. Enantioselective reduction of alkyl aryl ketones by in situ formed 2

Ketone	Temp / °C	Alcohol[a] Yield / %	Alcohol[a] Enantiomeric excess[b] by GLC	Alcohol[a] Enantiomeric excess[b] by ^{1}H-NMR
$C_6H_5COCH_3$	-100 ⟶ -78	66	87	—
$C_6H_5COC_2H_5$	-78 ⟶ -40	71	88	83
	-100 ⟶ -78	51	89	83
$C_6H_5CO(CH_2)_2CH_3$	-78	58	88	90
	-100 ⟶ -78	44	92	93
$C_6H_5CO(CH_2)_3CH_3$	-78 ⟶ -45	60	88	85
$C_6H_5COCH(CH_3)_2$	-78 ⟶ -50	60	57	49
	-78 ⟶ -30	100	48[c]	

a) Configurations were R in all cases, which were determined by optical ratation.
b) Determined by the analyses of the corresponding (+)-MTPA esters[10] unless otherwise noted. The diastereomeric (+)-MTPA esters of the racemic carbinols exhibited cleanly separated peaks with equal integrations both in GLC and NMR.
c) $[\alpha]_D$-15.7°(c 4.1, $CHCl_3$). Determined by optical rotation based on the reported value $[\alpha]_D$+32.7°(c 4.1, $CHCl_3$). J. Kenyon and S. M. Partridge, J. Chem. Soc., 1936, 128.

Further studies are in progress on the application to the reduction of other unsaturated compounds and on the modification of chiral ligands and reducing agents.

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