N,N'-Dibenzoylcystine as an Efficient Chiral Auxiliary for Asymmetric Reduction of Ketones with Lithium Borohydride

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Aromatic and α,β-unsaturated ketones were reduced enantioselectively with lithium borohydride in the presence of *N,N'*-dibenzoylcystine and t-butyl alcohol to afford optically active secondary alcohols with high enantiomeric excesses (76—90% e.e.).

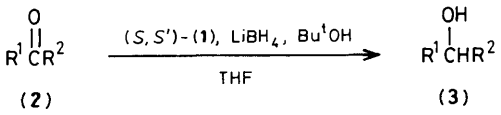
Although cystine plays an important role in the regulation of the stereochemistry of peptides and proteins, it has not been utilized in asymmetric reduction. Enantioselective reduction of ketones by chirally modified complex metal hydrides has recently attracted considerable attention.[1] However, only limited success has been reported in asymmetric reduction with chiral metal borohydrides.[2] During our continuing study on the reactivity[3] and stereoselectivity[4] of metal borohydrides, we found that *N,N'*-dibenzoylcystine (**1**) is an excellent chiral auxiliary for enantioselective reduction of ketones with lithium borohydride.

When phenyl propyl ketone (**2b**) was reduced by a previously refluxed mixture of (*S,S'*)-(**1**),[5] $LiBH_4$, and a small amount of t-butyl alcohol in tetrahydrofuran (THF), (*R*)-(+)-1-phenylbutanol was obtained in 98% synthetic yield, 92% optical yield, and 90% enantiomeric excess. The results for

Table 1. Asymmetric reduction of ketones (**2a**—**c**) to (*R*)-alcohols (**3a**—**c**) using (*S,S'*)-(**1**), $LiBH_4$, and Bu^tOH.[a]

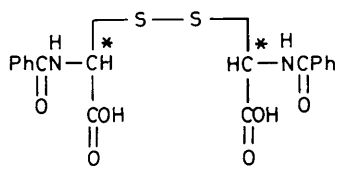
		(3)			
(2)	Temperature (°C)	Yield (%)	Observed $[\alpha]_D^{22}$(*c*, solvent)	Optical yield (%)	Enantiomeric excess[e] (% e.e.)
a	−78→−30	94	+41.80° (5.15, $CHCl_3$)	92[b]	86[f]
b	−78→−40	98	+40.03° (4.05, C_6H_6)	92[c]	90[g]
	−100→−88	30	+40.26° (2.67, C_6H_6)	92[c]	87[g]
c	−100	44[j]	+25.0° (3.36, $CHCl_3$)	101[d,i]	76[h,i]

[a] Molar ratio of (**2**):(**1**):$LiBH_4$:Bu^tOH = 1:1.2:3.6:1.6. Molar ratio has not been optimized. [b] Based on the reported value of $[\alpha]_D$ +45.45° (*c* 5.15, $CHCl_3$). R. H. Richard and J. Kenyon, *J. Chem. Soc.*, 1914, 1115. [c] Based on the reported value of $[\alpha]_D^{20}$ + 43.6° (*c* 4.18, C_6H_6). J. Kenyon and S. M. Partridge, *J. Chem. Soc.*, 1936, 128. [d] Based on the reported value of $[\alpha]_D$ +24.7° (*c* 5.00, $CHCl_3$). J. Kenyon, S. M. Partridge, and H. Phillips, *J. Chem. Soc.*, 1936, 85. [e] Determined as the corresponding (+)-α-methoxy-α-tri(fluoromethyl)phenylacetic acid esters. J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543. [f] By g.l.c. analysis [poly(ethylene glycol) (PEG)-20M, 25 m capillary column, column temp. 153 °C, flame ionisation detector]. Retention time 27 and 29 min for the two diastereoisomeric esters. [g] The same conditions as in footnote f. Retention time 29 and 31 min for the two diastereoisomeric esters. [h] By ^1H n.m.r. spectroscopic analysis. [i] The disagreement between the values for the optical yield and enantiomeric excess of the alcohol has also been reported; T. Sato, Y. Gotoh, Y. Wakabayashi, and T. Fujisawa, *Tetrahedron Lett.*, 1983, 4123. [j] (*R*)-4-Phenylbut-3-en-2-ol.



(2) (3)

a; R^1 = Ph, R^2 = Et
b; R^1 = Ph, R^2 = Pr^n
c; R^1 = Ph, R^2 = Me



(S,S')-(1)

compounds (**2a—c**) are summarised in Table 1. Both aromatic and α,β-unsaturated ketones were reduced to (*R*)-alcohols when (*S,S'*)-(**1**) was used. When the reduction mixture was extracted with aqueous alkali and the extract left overnight under air, (*S,S'*)-(**1**) was recovered in moderate yield.

We would like to point out that either enantiomer of (**1**) can be readily prepared from the corresponding enantiomer of commercially available cystine (L or D).[5] Though no experimentation has been attempted, it is very likely that (*S*)-alcohols can be synthesised by using (*R,R'*)-(**1**).

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