Asymmetric Synthesis of 2-Aryl Substituted Oxetanes by Enantioselective Reduction of β-Halogenoketones using Lithium Borohydride modified with *N,N'*-Dibenzoylcystine

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Optically active 2-aryl substituted oxetanes are synthesised in high enantiomeric excesses (up to 89% e.e.) *via* enantioselective reduction of β-halogenoketones with lithium borohydride using (*R,R'*)-*N,N'*-dibenzoylcystine and t-butyl alcohol as ligands.

The synthetic utility of oxetanes is increasing because of recently developed ring opening[1a—g] and ring expansion reactions.[1h—k] Optically active oxetanes are needed to study the stereochemistry of reactions in which oxetanes participate,[2] but only a few optically active oxetanes are known. Multistep sequences are required to synthesise optically active aliphatic 2-methyloxetanes by transformation from ethyl lactate or threonine or by the microbial reduction of ethyl acetoacetate.[3]

We report here an asymmetric synthesis of 2-aryl substituted oxetanes (**1**) in high enantiomeric excesses (e.e.) from β-halogenoketones (**2**) *via* enantioselective reduction with lithium borohydride–(*R,R'*)-*N,N'*-dibenzoylcystine (**3**)–Bu^tOH. When β-chloropropiophenone (**2a**) was reduced at −78 to −30 °C by a mixture of $LiBH_4$, (*R,R'*)-(**3**), and Bu^tOH in tetrahydrofuran (THF),[4] (*R*)-3-chloro-1-phenylpropan-1-ol {(**4a**), 83% e.e., $[\alpha]_D^{22}$ +22.7° (*c* 2.82, $CHCl_3$)} was obtained in 74% yield.† Acetylation of (**4a**) followed by cyclisation using KOH[5] afforded (*R*)-(+)-2-phenyloxetane {(**1a**), $[\alpha]_D^{20}$ +153.2° (c 2.39, $CHCl_3$)}. When (*R*)-(+)-(**1a**) was treated

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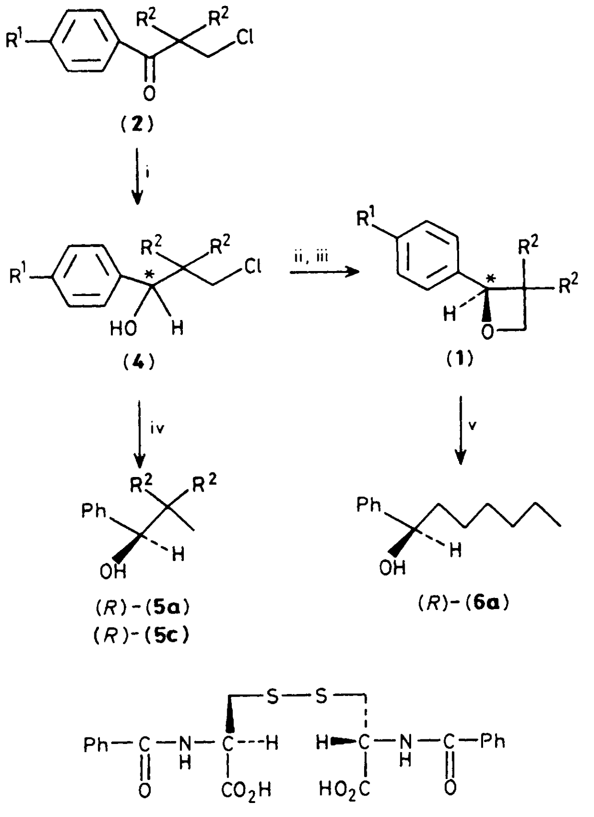
† To a mixture of (*R,R'*)-(**3**) (1.80 mmol) and Bu^tOH (2.40 mmol, 2.35 ml of 1.02 M THF solution) in THF (12 ml), $LiBH_4$ (5.43 mmol, 5.60 ml of 0.97 M THF solution) was added under an argon atmosphere. After refluxing for 30 min, the mixture was cooled to −78 °C and (**2a**) (1.50 mmol) in THF (3 ml) was added during 15 min. The mixture was stirred for 9 h, while the temperature was allowed to increase from −78 to −30 °C. The reaction was quenched with 1 M HCl (4.5 ml), and the mixture made alkaline with 5% aq. $NaHCO_3$, and extracted with chloroform. The organic extract was washed with 5% aq. $NaHCO_3$ and dried (Na_2SO_4). Evaporation under reduced pressure and purification of the residue by t.l.c. on silica gel with $CHCl_3$ as eluant gave (**4a**), which was further purified by bulb-to-bulb distillation (74% yield).



a; $R^1 = R^2 = H$
b; $R^1 = F, R^2 = H$
c; $R^1 = H, R^2 = Me$

Scheme 1.[a] *Reagents:* i, (*R*,*R*′)-(**3**), $LiBH_4$, Bu^tOH, ii, AcCl, C_5H_5N, iii, KOH, iv, $LiAlH_4$, v, Bu^nLi, $BF_3 \cdot OEt_2$. The absolute configuration of (**4a**) was determined as (*R*) because reductive dehalogenation with $LiAlH_4$ afforded (*R*)-(+)-(**5a**), {$[\alpha]_D^{24}$ +39.3° (*c* 1.76, $CHCl_3$), 86% optical purity[7]}. The e.e. of (**4a**) was determined as 83% by g.l.c. analysis of the corresponding (−)-methoxy(trifluoromethyl)-phenylacetyl (MTPA) ester[6] of (*R*)-(+)-(**5a**). (*R*)-(+)-(**5c**) {$[\alpha]_D^{22}$ +26.2° (*c* 0.47, $CHCl_3$), 89% e.e. by ^1H n.m.r. analysis using the chiral shift reagent tris-[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III), $Eu(hfc)_3$} was obtained from (**4c**) using $LiAlH_4$–$CeCl_3$.[8] From correlation with (*R*)-(+)-(**5a**), the absolute configuration of (**1a**) was determined as (*R*)-(+). From correlation with (*R*)-(**5a**) and (*R*)-(**1a**), the absolute configuration of (**6a**) was considered to be (*R*).

with n-butyl-lithium in the presence of boron trifluoride–diethyl ether,[1c] (*R*)-(+)-1-phenylheptan-1-ol {(**6a**), $[\alpha]_D^{17}$ +25.5 ° (c 2.10, $CHCl_3$)} was obtained in 81% yield. The (**6a**) obtained had 84% e.e. (by g.l.c. analysis of MTPA ester[6]) and the e.e. value was in good agreement with that of (**4a**) within experimental error. Therefore, the e.e. of (**1a**) was considered to be 83—84%. Moreover the present result suggests that this ring opening[1c] proceeds without racemisation. Other 2-aryl substituted oxetanes {(**1b**), 79% e.e., $[\alpha]_D^{22}$ +117.6° (*c* 3.17, $CHCl_3$); (*S*)-(**1c**), 89% e.e., $[\alpha]_D^{21}$ + 100.1° (*c* 2.04, $CHCl_3$)} were obtained similarly. Thus the present method may be useful not only for the preparation of optically active 2-aryl substituted oxetanes but also for the study of the asymmetric versions of recently reported reactions of oxetane.[1,2]

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