(5*S*)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one as a Highly Effective Chiral Auxiliary for Asymmetric Reduction of α-Oxo Amides

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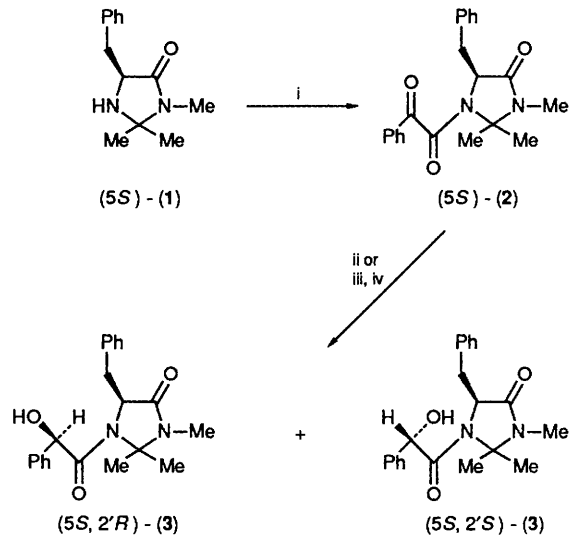
Reduction of the α-oxo amide derived from phenylglyoxylic acid, containing (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one as a chiral auxiliary, with $NaBH_4$ or *via* fluoride ion-induced hydrosilylation with $HSiMe_2Ph$ was found to proceed with 90—100% diastereoselectivity.

Reduction of α-oxo acid derivatives bearing the appropriate chiral auxiliary is the conventional route to optically active α-hydroxy-acids.[1,2] Recently the asymmetric reduction of chiral α-oxo amides bearing a heterocycle as the chiral auxiliary (proline,[3,4] *trans*-2,5-disubstituted pyrrolidines[5]) has been studied. This seems to be a promising approach owing to the well known planarity of the amide group and, consequently, the lower number of possible conformers in the transition state than with chiral α-oxo esters. We studied the reduction of the α-oxo amide (5*S*)-(**2**) (Scheme 1) derived from phenylglyoxylic acid and containing (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one[6] as a chiral auxiliary. Until now, this auxiliary has not been employed for asymmetric reduction. The chiral heterocycle (5*S*)-(**1**)† was prepared in 82% yield by the reaction of (*S*)-β-phenyl-α-alanine *N*-methylamide[7] and acetone (1.5 equiv.) by refluxing in dimethylformamide (DMF) (10 h). Subsequent *N*-acylation with PhCOCOCl[8] gave the α-oxo amide (5*S*)-(**2**)† in 72% yield. Reduction of (5*S*)-(**2**) with $NaBH_4$ (0.75 equiv.) in dimethoxyethane (DME) (25 °C) gives a mixture of α-hydroxy amides (5*S*, 2′*R*)-(**3**) and (5*S*, 2′*S*)-(**3**) in good yield with a considerable excess of one of the diastereoisomers (90.5 : 9.5).

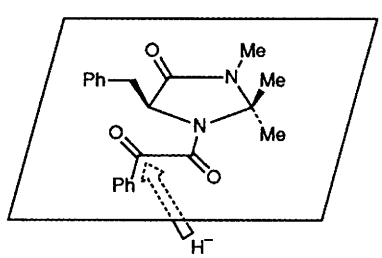
To determine the direction of asymmetric induction an alternative synthesis of authentic (5*S*, 2′*R*)-(**3**) was carried out [i, (*R*)-PhCH(OH)CO_2H (1 equiv.), $(COCl)_2$ (1 equiv.), CH_2Cl_2, 25 °C, 1 h; ii, (5*S*)-(**1**) (1 equiv.), Et_3N (2 equiv.), CH_2Cl_2, 0 °C]. The sample obtained in this way, (5*S*, 2′*R*)-(**3**) and the predominant diastereoisomer obtained from the reduction of the α-oxo amide (5*S*)-(**2**) with $NaBH_4$ were identical (^1H NMR, m.p., HPLC retention time). The α-hydroxy amide (5*S*, 2′*R*)-(**3**) can easily be isolated by crystallization (twice) from ether; the α-hydroxy amide (5*S*, 2′*S*)-(**3**) was isolated from the filtrates by preparative HPLC on silica (eluent dioxane–hexane, 25 : 75).†

Thus, reduction of the α-oxo amide (5*S*)-(**2**) with $NaBH_4$ proceeds with high diastereoselectivity which was comparable with the best results achieved when (2*R*, 5*R*)-*trans*-2,5-bis-(methoxymethoxymethyl)pyrrolidine was used as chiral auxiliary and $KB(OPr^i)_3H$, which is difficult to obtain, was used as a reducing agent.[5] As regards the direction of asymmetric induction in this reaction, it is obvious that, as in the case of reduction of other chiral α-oxo amides with different complex hydrides,[5] the hydride ion attacks the less hindered side of the α-carbonyl atom of the predominant *trans*-coplanar conformer (5*S*)-(**2**) (Scheme 2).

On the other hand, during the reduction of (−)-menthyl phenylglyoxylate *via* hydrosilylation with diarylsilanes catalysed by rhodium complexes, the direction of asymmetric induction is opposite to that occurring during the reduction by hydrides[9] and gives (*S*)-mandelic acid[10] after hydrolysis. This difference has been assumed to be due to the fact that the two carbonyl groups of phenylglyoxylate are in a *cis*-coplanar



Scheme 1. *Reagents and conditions*: i, PhCOCOCl (1 equiv.), Et_3N (1 equiv.), CH_2Cl_2, 0 °C; ii, $NaBH_4$ (0.75 equiv.), DME, 25 °C; iii, $HSiMe_2Ph$ (4 equiv.), CsF (5 mol%), 18-crown-6 (5 mol%), CH_2Cl_2, 25 °C; iv, HCl, $Me_2C{=}O$.



Scheme 2

† Compound (5*S*)-(**1**), viscous oil; $[\alpha]_D^{25}$ − 48.7° (*c* 2.92, EtOH); IR (neat) ν/cm^{-1} 3330, 2980, 1645, 1405, 1370; ^1H NMR ($CDCl_3$) δ 1.16 and 1.27 (each s, 3H, $NCMe_2N$), 1.87 (br.s, 1H, NH), 2.74 (s, 3H, NMe), 3.00—3.13 (m, 2H, $PhCH_2$), 3.71—3.87 (m, 1H, CHCO), 7.25 (s, 5H, Ph).

Compound (5*S*)-(**2**), m.p. 103—105 °C; $[\alpha]_D^{25}$ + 268.4° (*c* 2.06, EtOH); IR (Nujol) ν/cm^{-1} 1740, 1685, 1635, 1235; ^1H NMR ($CDCl_3$) δ 0.82 and 1.73 (each s, 3H, $NCMe_2N$), 2.62—3.38 (m, 2H, $PhCH_2$), 2.71 (s, 3H, NMe), 4.62—4.75 (m, 1H, CHCO), 6.98—8.18 (m, 10H, 2Ph).

Compound (5*S*, 2′*R*)-(**3**) m.p. 159—160 °C; $[\alpha]_d^{25}$ + 48.8° (*c* 5.28, EtOH); IR (CCl_4) ν/cm^{-1} 3440, 2950, 1720, 1665, 1370; ^1H NMR (CD_3SOCD_3–D_2O) δ 0.56 and 1.29 (each s, 3H, $NCMe_2N$), 2.53 (s, 3H, NMe), 3.02—3.47 (m, 2H, $PhCH_2$), 4.29—4.44 (m, 1H, CHCO), 5.47 (s, 1H, CHOH), 7.02—7.53 (m, 10H, 2Ph). Compound (5*S*, 2′*S*)-(**3**), m.p. 113—115 °C; $[\alpha]_D^{25}$ + 112.5° (*c* 1.06, EtOH); IR (CCl_4) ν/cm^{-1} 3410, 2945, 1715, 1660, 1370; ^1H NMR (CD_3SOCD_3–D_2O) δ 0.58 and 1.47 (each s, 3H, $NCMe_2N$), 2.56 (s, 3H, NMe), 3.04—3.18 (m, 2H, $PhCH_2$), 4.80—5.00 (m, 1H, CHCO), 5.38 (s, 1H, CHOH), 6.62—7.60 (m, 10H, 2Ph).

conformation during the reaction, and are chelated in the rhodium complex.[9,10] The hydrosilylation of the α-oxo amide (5*S*)-(**2**) by diphenylsilane with rhodium complexes {$RhCl(PPh_3)_3$, $[Rh(norbornadiene)(PPh_3)_2]^+PF_6^-$, $[Rh(cyclo\text{-}octadiene)Cl]_2$} fails to occur. Fluoride ion-induced hydrosilylation[11] of (5*S*)-(**2**) by dimethylphenylsilane in the presence of 18-crown-6 proceed stereospecifically to give (after desilylation) (5*S*, 2′*R*)-(**3**) in 40% yield (chemoselectivity 100%). Thus, the direction of asymmetric induction in this reaction is consistent with that in the reduction of (5*S*)-(**2**) by $NaBH_4$ [predominant formation of (2′*R*)-hydroxy amide]. In our opinion, this confirms the above stereochemical model, since it is known[12] that fluoride ion-catalysed hydrosilylation of the C=O bond of carbonyl compounds involves nucleophilic attack of this bond by the five-coordinated organosilicon intermediate $[HSiR_3F]^-$.

Thus, the reduction of the α-carbonyl group of the α-oxo amide in high asymmetric yield indicates the high stereodifferentiating ability of (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one in the reactions studied.

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