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Bifunctional Chiral Auxiliaries 3: Synthesis of Homochiral 1,3-Diols *via* Asymmetric Aldol Reactions of Dialkylboron Enolates of 1,3-Dipropionyl-*trans*-4,5-diphenyl-imidazolidin-2-one and Aldehydes

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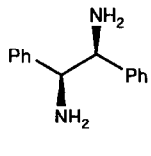
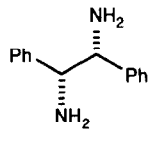
Abstract: Dibutylboron enolates derived from both racemic and homochiral 1,3-dipropionyl-*trans*-4,5-diphenylimidazolidin-2-one **3** react with aldehydes in highly diastereoselective dialdol reactions to give, after reductive cleavage of the acyl sidechain, substituted 1,3-diols.

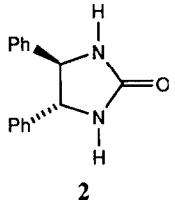
The recent use of derivatives of homochiral 1,2-diphenyl-1,2-diaminoethane **1**[1] as highly effective stereodirecting groups in both catalytic and stoicheiometric asymmetric processes has demonstrated the previously unrealised potential of 1,2-diamines in asymmetric synthesis. We have already reported that dibutylboron enolates of racemic 1,3-dipropionyl-*trans*-4,5-tetramethyleneimidazolidin-2-one, itself synthesised from *trans*-1,2-diaminocyclohexane[2], undergo highly diastereoselective dialdol reactions to provide the first reported use of a bifunctional chiral auxiliary[3]. Recently Yamada[4] has reported that the N-methyl-N'-propionyl derivative of *trans*-4,5-diphenylimidazolidin-2-one **2** functions as a highly stereoselective simple chiral auxiliary and this prompts us to report our findings that the N,N'-dipropionyl derivative of **2** functions as a bifunctional chiral auxiliary, allowing two acyl sidechains to elaborated simultaneously with good stereocontrol.



S,S-1



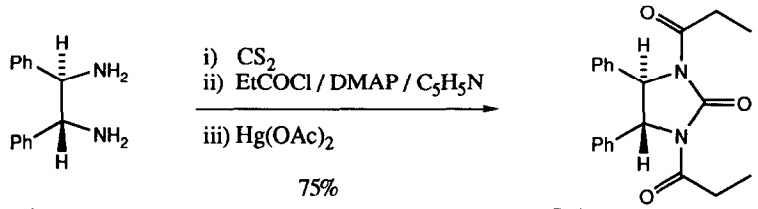
R,R-1



2

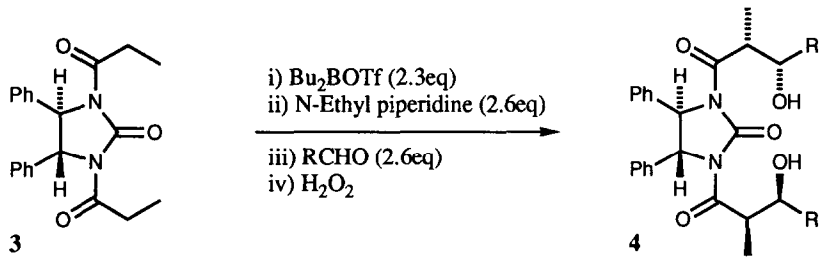
The (1R,2R) enantiomer of 1,3-dipropionyl-*trans*-4,5-diphenylimidazolidin-2-one (**R,R**)-**3** was synthesised in three steps from a commercial sample of (1R,2R)-1,2-diphenyl-1,2-diaminoethane (**R,R**)-**2**[5] according to the general procedure described previously for the synthesis of racemic 1,3-diacylimidazolidin-2-ones[2]. The enantiomeric purity of the final product was determined by a 300MHz ^{1}H n.m.r. chiral shift experiment using (S)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol. Using ten equivalents of this reagent on a sample of racemic **3**, the methyl triplets at δ 1.17 ppm were clearly discriminated. As the resonances due to the second

enantiomer could not be detected in the spectrum containing the sample of **3** prepared from homochiral **2**, the enantiomeric excess was estimated to be >99%.



R,R-1 **R,R-3**

Aldol reactions of dibutylboron enolates derived from racemic 1,3-dipropionyl-*trans*-4,5-diphenyl-imidazolidin-2-one **3** with simple aldehydes were investigated. Under analogous conditions to those employed by Evans for the aldol reactions of N-acyl oxazolidones[6], **3** underwent clean dialdol reactions with representative aldehydes in good chemical yield. In all three examples investigated only a single diastereoisomer of dialdolate product could be observed by 300MHz ^1H n.m.r. spectroscopy , leading to an estimation of the diastereosomeric excesses of the products certainly being >96%. The proposed *syn*-stereochemistry of the sidechains was supported by characteristic H_2/H_3 coupling constants in the ^1H n.m.r. spectrum and chemical shifts due to the α-methyl group in the ^{13}C n.m.r. spectrum[7]. The relative configuration between the residual chiral centres of the auxiliary and those newly created on the acyl sidechains was assigned by correlation to the known X-ray crystal structure of the product of the dibutylboron enolate of 1,3-dipropionyl-*trans*-4,5-tetramethyleneimidazolidin-2-one with benzaldehyde[8], although this was later confirmed by the acyl cleavage reaction of the dialdol product derived from homochiral **3** (*vide infra*).



3 **4**

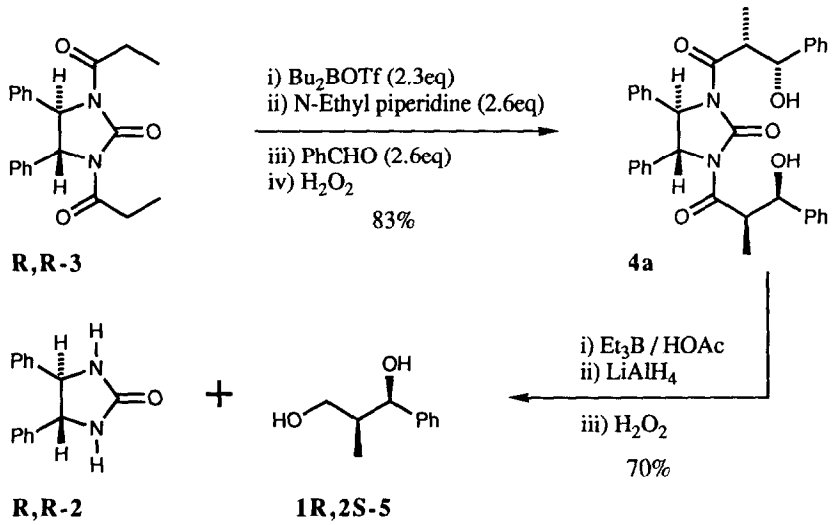
Compound	R	Yield	d.e.
4a	Ph	72%	>96%
4b	*i*-Pr	67%	>96%
4c	Me	74%	>96%

Repetition of this reaction using the homochiral 1,3-dipropionyl-*trans*-4,5-diphenylimidazolidin-2-one (**R,R-3**) and benzaldehyde gave a single diastereoisomer of dialdolate product, identical spectroscopically to the sample prepared previously using racemic **3**.

We have found that reductive cleavage of the two acyl sidechains of non-functionalised 1,3-diacylimidazolidin-2-ones occurs simply by treatment of a THF solution of the substrate with excess lithium

aluminium hydride at -20°C for 2h[9]. After quenching the reaction and working it up under standard conditions, the desired primary alcohols are obtained in good yield, and the bifunctional chiral auxiliary recovered. Evans has found that reductive deacylation of aldol products obtained from N-acyl oxazolidones requires initial protection of the β-hydroxyl group so as to supress the retro-aldol reaction[10]. Typically the protecting group so employed is a dialkyl borate, introduced by use of a trialkylborane and acetic acid in THF solution at ambient temperature.

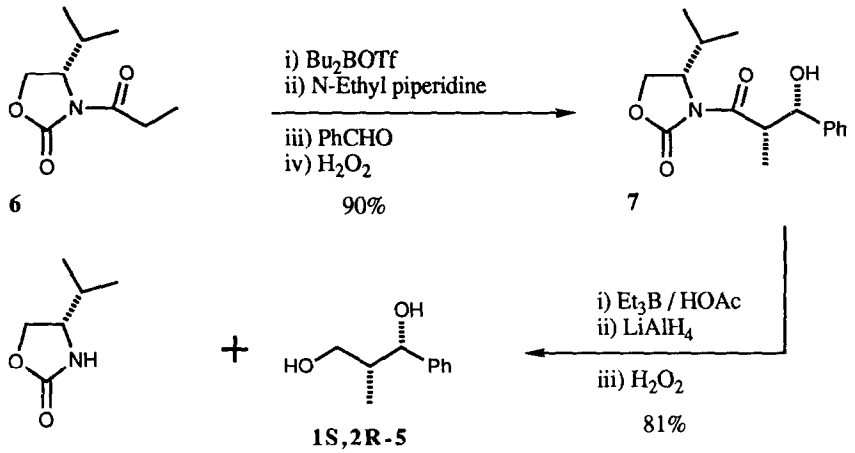
A solution of triethylborane (1.0M in hexanes) (2.5eq) was added to a THF solution of homochiral **4a** containing acetic acid (3.0eq). After stirring at ambient temperature for 2h the solution was transferred by cannula to a suspension of lithium aluminium hydride in THF at -20°C and stirred for a further 2h before being quenched and worked up. 1-Phenyl-2-methylpropane-1,3-diol **5** was obtained in 70% yield after hydrogen peroxide mediated removal of the protecting group and chromatography. The ^{1}H n.m.r. spectrum of the crude reaction mixture confirmed the expected *syn*-stereochemistry and showed that **5** was free from contamination with the diol derived from the *anti*-aldol reaction, indicating that this method of reductive cleavage occurs without detectable epimerisation.



Although the diol **5** was found to have optical activity, the correlation of optical rotation with absolute configuration is not known nor is the specific rotation of the material in a homochiral form available. To circumvent this problem, a sample of **5** was prepared from N-propionyl-4-isopropyloxazolidone **6** according to the general protocol previously described by Evans[11]. Thus the dibutylboron enolate of **6** was quenched with benzaldehyde and the resulting diastereoisomerically pure aldolate cleaved to the β-hydroxy carboxylic acid before reduction with lithium aluminium hydride furnished the desired diol **5**. Once again the diol was obtained in diastereoisomerically pure form, indicating that no epimerisation had occurred during either reduction or hydroperoxide mediated deacylation. The specific rotation of the diol was found to be $[\alpha]_D^{20}$ +53 (c=0.75, $CHCl_3$). By comparison, the specific rotation of the diol obtained by reductive cleavage of homochiral **4a** was found to be $[\alpha]_D^{20}$ -53 (c=0.57, $CHCl_3$). As the N-acyl oxazolidone aldol reaction is known to give products with diastereoisomeric excesses of >99%, and as no epimerisation was detectable in the subsequent conversion

to the diol, the specific rotation, $[\alpha]_D^{20}$ +53, must refer to effectively homochiral material. The homochirality of both diols was confirmed by ^1H n.m.r. analysis, in the presence of ten equivalents of the the chiral shift reagent (S)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol since the resonances due to the benzylic methine protons were clearly distinguishable.

It is therefore clear that the use of 1,3-dipropionyl-*trans*-4,5-diphenylimidazolidin-2-one **3** allows ready access to substituted 1,3-diols in homochiral form and in good chemical yield.



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