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TETRAHEDRON: *ASYMMETRY*

SuperQuat, (*S*)-4-benzyl-5,5-dimethyl-oxazolidin-2-one for the asymmetric synthesis of α-substituted aldehydes

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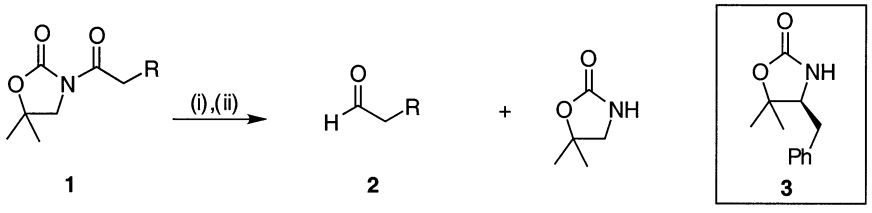
Abstract

Reduction of α-substituted-(*S*)-*N*-acyl-4-benzyl-5,5-dimethyl-oxazolidin-2-ones with DIBAL-H in CH_2Cl_2 affords α-substituted aldehydes with no loss of stereochemical integrity at their α-centre.

The generation of α-substituted aldehydes from α-substituted-*N*-acyl-oxazolidin-2-ones is normally achieved via overreduction to the α-substituted alcohol followed by oxidation,[1] or conversion to either a Weinreib amide[2] or ester/thioester[3] and reduction. We have recently reported that achiral *N*-acyl-5,5-dimethyl-oxazolidin-2-ones **1** can be reductively cleaved directly to aldehydes **2** with DIBAL-H (Scheme 1).[4] This, combined with the ability of the SuperQuat 4-benzyl-5,5-dimethyl-oxazolidin-2-one auxiliary **3** to control alkylations of attached enolate fragments,[5] suggested a direct stereoselective synthesis of α-substituted aldehydes which is described herein.[6]



Scheme 1. *Reagents and conditions:* (i) DIBAL-H (2.0 equiv.), CH_2Cl_2, −78°C; (ii) NaOH, $NaHSO_3$

Meyers et al. have reported an isolated example of the direct reduction of an *N*-acyl-oxazolidin-2-one aldol product with Red-Al in THF at −78°C to afford the corresponding aldehyde which was trapped in situ with the anion of triethylphosphonoacetate to give an α,β-unsaturated ester in 32% yield.[7] In order to investigate the suitability of Red-Al for the reduction of simple

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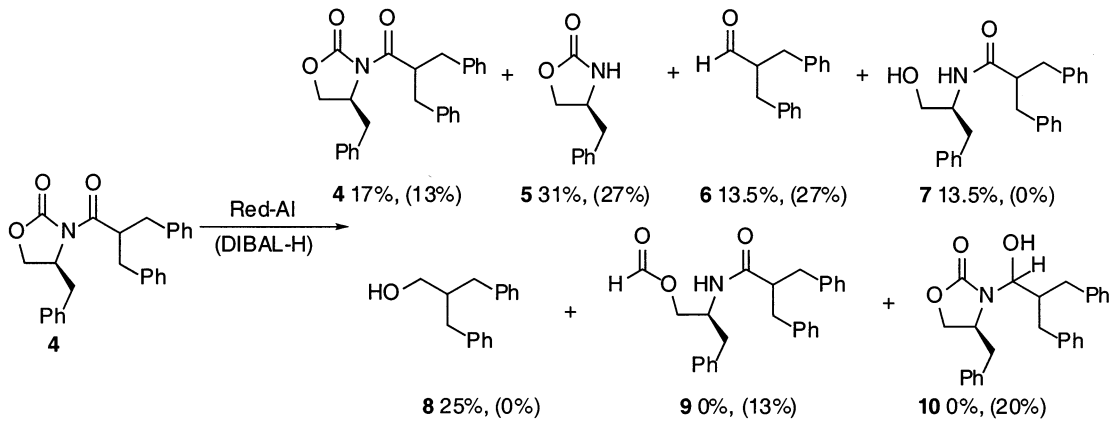
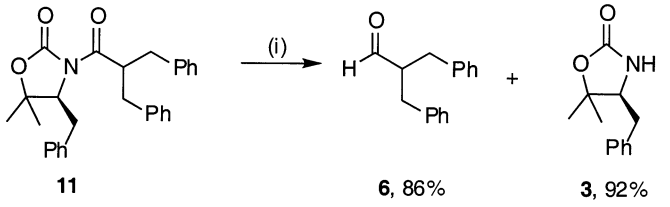
N-acyl-oxazolidin-2-ones without a coordinating β-hydroxyl group in its *N*-acyl side-chain, the sterically demanding *N*-acyl-oxazolidin-2-one **4** was reduced with Red-Al to afford a complex mixture of products which was purified to afford starting material **4**, (*S*)-4-benzyl-oxazolidin-2-one **5**, and 2-benzyl-3-phenyl-propanal **6**, the product of endocyclic cleavage *N*-acyl-2-amino-ethanol **7**, and 2-benzyl-3-phenyl-propanol **8**. Similarly, reduction of *N*-acyl-oxazolidin-2-one **4** with DIBAL-H in CH_2Cl_2 at −78°C gave a complex reaction product which was purified to afford starting material **4**, (*S*)-4-benzyl-oxazolidin-2-one **5**, aldehyde **6**, (*S*)-*N*-acyl-*O*-formyl-2-benzyl-2-amino-1,1-dimethyl-ethanol **9** and (4*S*)-*N*-(1′-hydroxy-alkyl)-4-oxazolidin-2-one **10** as a single diastereoisomer (C-1′ stereocentre of **10** undefined) (Scheme 2).



Scheme 2. Ratio of products determined by integration of resonances in the 400 MHz ^{1}H NMR spectra of the crude product mixtures. *Reagents and conditions:* Red-Al, THF, −78 to −50°C or DIBAL-H, CH_2Cl_2, −78°C; $NH_4Cl_{(aq)}$

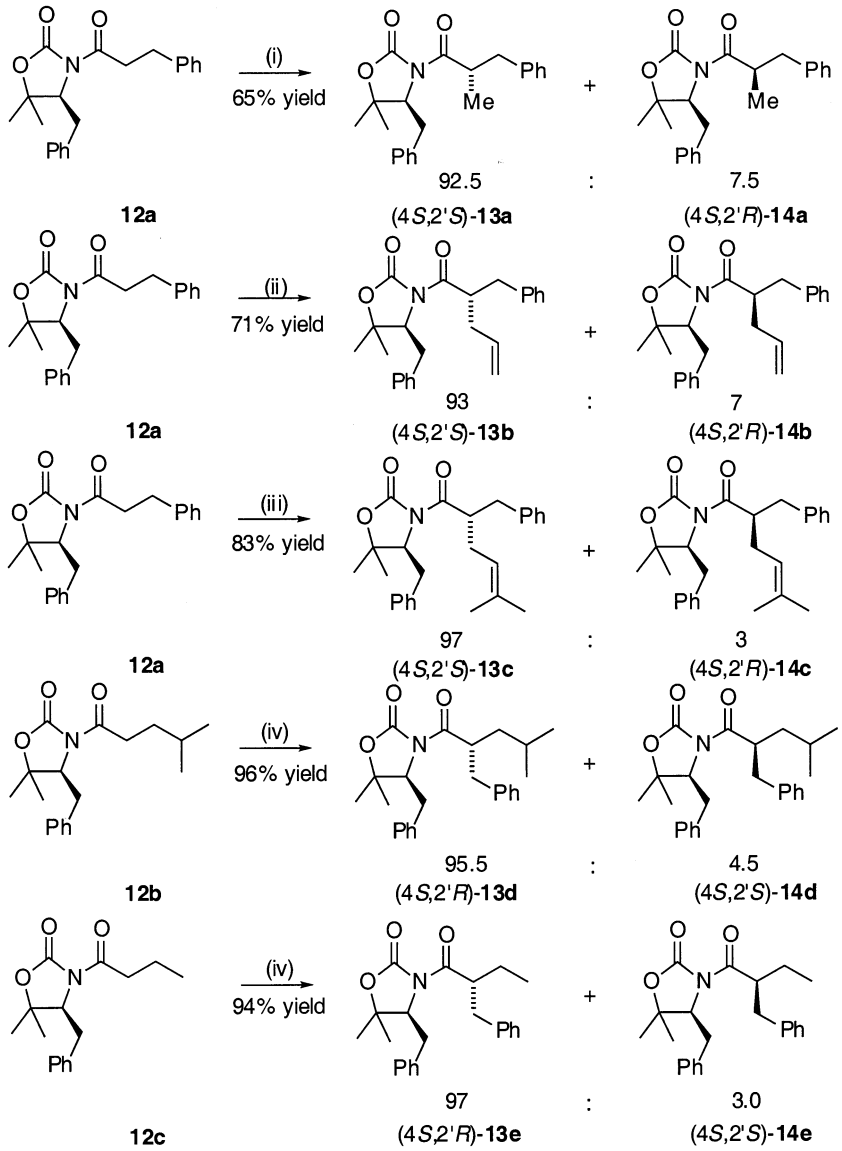
In contrast, while reduction of *N*-acyl-5,5-dimethyl-oxazolidin-2-one **11** with Red-Al gave a complex mixture of products, reduction with DIBAL-H in CH_2Cl_2 at −78°C went to completion affording cleanly a mixture of the desired reaction products which were purified to afford the aldehyde **6** in 86% isolated yield and (*S*)-4-benzyl-5,5-dimethyl-oxazolidin-2-one **3** in 92% isolated yield, with no evidence of any products arising from the endocyclic cleavage pathway (Scheme 3).



Scheme 3. *Reagents and conditions:* (i) DIBAL-H, CH_2Cl_2, −78°C; $NH_4Cl_{(aq)}$

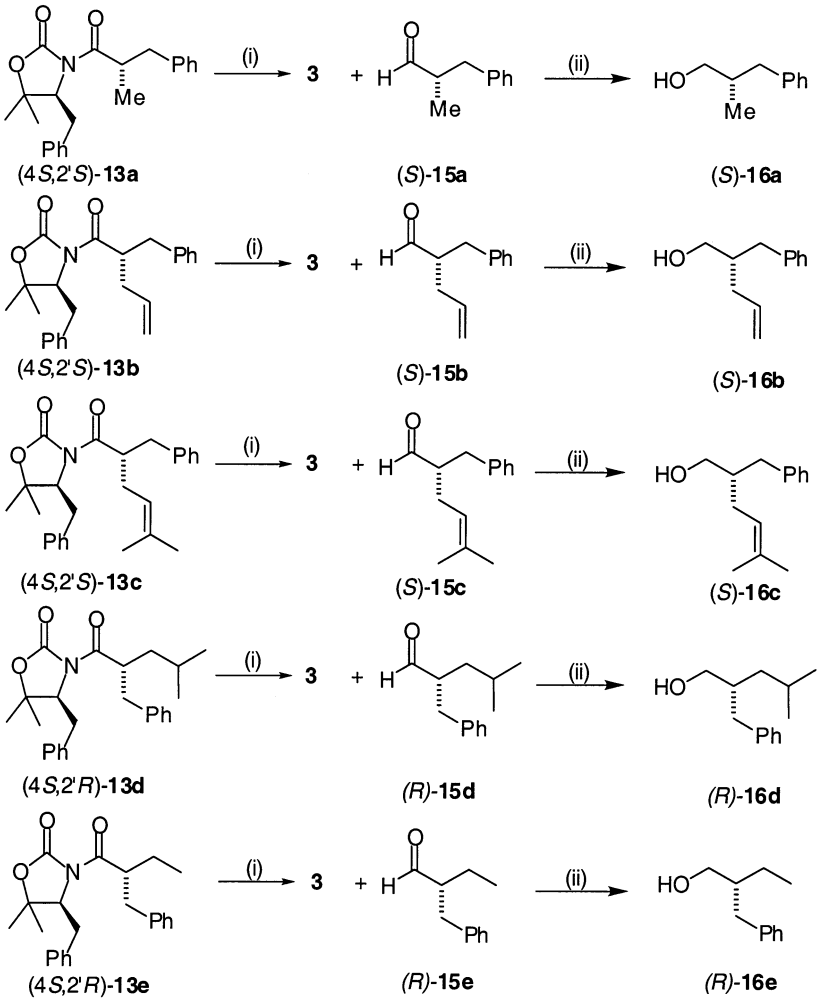
Attention was next directed towards investigating the reduction of α-substituted-*N*-acyl-4-benzyl-5,5-dimethyl-oxazolidin-2-ones **13a–e** to afford α-substituted aldehydes **15a–e**. Thus, the enolate of (*S*)-(*N*-hydrocinnamoyl)-4-benzyl-5,5-dimethyl-oxazolidin-2-one **12a** in THF was alkylated with methyl iodide, allyl bromide and 4-bromo-2-methyl-2-butene to afford (4*S*,2′*S*)-*N*-[(2′-methyl)-dihydrocinnamoyl]-4-benzyl-5,5-dimethyl-oxazolidin-2-one **13a** in 85% d.e.,

(4*S*,2′*S*)-*N*-[(2′-allyl)-dihydrocinnamoyl]-4-benzyl-5,5-dimethyl-oxazolidin-2-one **13b** in 86% d.e. and (4*S*,2′*S*)-*N*-[(2′-3,3-dimethyl-2-butene)-dihydrocinnamoyl]-4-benzyl-5,5-dimethyl-oxazolidin-2-one **13c** in 94% d.e. (Scheme 4). Similarly, alkylation of the enolates of (*S*)-(*N*-*iso*-valeroyl)-4-benzyl-5,5-dimethyl-oxazolidin-2-one **12b** or (*S*)-(*N*-butanoyl)-4-benzyl-5,5-dimethyl-oxazolidin-2-one **12c** with benzyl bromide gave (4*S*,2′*R*)-*N*-[(2′-benzyl)-*iso*-valeroyl]-4-benzyl-5,5-dimethyl-oxazolidin-2-one **13d** in 91% d.e., and (4*S*,2′*R*)-*N*-[(2′-benzyl)-butanoyl]-4-benzyl-5,5-dimethyl-oxazolidin-2-one **13e** in 94% d.e. All d.e.'s were calculated from integration of the resonances corresponding to the major **13a–e** and minor diastereoisomers **14a–e** in the 400 MHz ^{1}H NMR spectra of the crude reaction products.



Scheme 4. *Reagents and conditions:* (i) LHMDS, THF, −78°C, MeI; (ii) LHMDS, THF, −78°C, allyl bromide; (iii) LHMDS, THF, −78°C, 4-bromo-2-methyl-2-butene; (iv) LHMDS, THF, −78°C, BnBr

The mixtures of diastereoisomers **13a–e**/**14a–e** (85–94% d.e.) were reduced with DIBAL-H in CH_2Cl_2 at −78°C to afford a mixture of (*S*)-4-benzyl-oxazolidin-2-one **3** and the enantiomerically enriched aldehydes **15a–e** which were separated via chromatography {silica, hexane:ether (12:1)} (Scheme 5, Table 1). The enantiomeric excesses of the resulting aldehydes **15a–e** were determined by immediate reduction of the purified aldehydes **15a–e** with $LiAlH_4$ to afford alcohols **16a–e**, which were derivatised via treatment with (*R*)-Mosher's acid chloride to afford diastereoisomeric Mosher's esters whose ^{19}F NMR spectra were compared with authentic racemic esters. Authentic racemic alcohols **16a–e** required for determining the enantiomeric excess of the products of these reductions were prepared via repetition of the enolate alkylation protocol described in Scheme 4 using analogous substrates derived from achiral *N*-acyl-5,5-dimethyl oxazolidin-2-ones **1**, followed by reduction of the resulting racemic α-alkylated-*N*-acyl-oxazolidin-2-ones with $LiAlH_4$. Comparison of the d.e.'s obtained for ^{19}F NMR analysis of the Mosher esters of 2-alkyl alcohols **16a–e** with the d.e.'s of the parent α-substituted-*N*-acyl-5,5-dimethyl-oxazolidin-2-ones **13a–e** employed for DIBAL-H reduction clearly revealed that no racemisation had occurred at the stereogenic centres of aldehydes **15a–e** under these conditions.



Scheme 5. *Reagents and conditions:* (i) DIBAL-H, CH_2Cl_2, −78°C; $NH_4Cl_{(aq)}$; (ii) $LiAlH_4$, THF, 0°C

Table 1
Yields and $[\alpha]_D^{23}$ for aldehydes **15a–e** from reduction of *N*-acyl-oxazolidin-2-ones **13a–e** and d.e.'s of Mosher's esters of 2-alkyl-alcohols **16a–e**

N-acyl-SuperQuats **13a–13e**	% Yield of aldehydes **15a–e**	$[\alpha]_D^{23}$ of aldehydes **15a–e** in $CHCl_3$	D.e. of (*R*)-Mosher's ester of 2-alkyl alcohols **16a–e**
13a (85% d.e.)	**15a** 87	**15a** −1.10 (*c* 1.0)[a]	**16a** 87% d.e.
13b (86% d.e.)	**15b** 76	**15b** −28.4 (*c* 1.0)	**16b** 87% d.e.
13c (92% d.e.)	**15c** 81	**15c** −58.4 (*c* 1.0)	**16c** 94% d.e.
13d (91% d.e.)	**15d** 95	**15d** +24.9 (*c* 1.0)	**16d** 91% d.e
13e (94% d.e.)	**15e** 95	**15e** +2.25 (*c* 2.0)	**16e** 94% d.e.

[a] Literature value for $[\alpha]_D^{23}$ of (*R*)-**15a** (82% e.e.) = +4.0, *c* 1.25 in acetone.[8]

In conclusion, we have demonstrated that α-substituted-*N*-acyl-4-benzyl-5,5-dimethyl-oxazolidin-2-ones **13a–e** may be reduced with DIBAL-H in CH_2Cl_2 to afford α-substituted aldehydes **15a–e** with no loss of stereochemical integrity at their α-centre.[9] All novel compounds were fully characterised including elemental analysis or HRMS.

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