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A Temporary Stereocentre Approach for the Stereodivergent Synthesis of Either Enantiomer of α-Methyloctanal

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The aldol reaction of a chiral *N*-(acyl)oxazolidin-2-one with 2-methyleneoctanal or (*E*)-2-methyloct-2-enal affords chiral aldol products whose alkene functionalities were hydrogenated using Brown's or Wilkinson's catalyst to afford *syn*- or *anti*-selective products with excellent levels of diastereocontrol. Subsequent *retro*-aldol cleavage of these *syn*- or *anti*-adducts resulted in the formation of either (*R*)- or (*S*)-enantiomer of α-methyloctanal with no racemisation occurring, which could be derivatised in-situ to afford chiral dithiane, alcohol or α,β-unsaturated ester products in enantiopure form.

We have recently reported the development of novel synthetic strategies to reversibly generate temporary stereogenic centres that can be used to create remote stereocentres using substrate-directable reactions.[1–3] In one of these reports, a novel three-step aldol/directed cyclopropanation/*retro*-aldol protocol was used for the asymmetric synthesis of chiral cyclopropane carboxaldehydes in high *ee*.[1] We now report that replacing the directed cyclopropanation reaction of this three-step protocol with a stereoselective hydrogenation reaction enables either enantiomer of a chiral α-methyl aldehyde to be prepared in high *ee*.

In this new approach (Figure 1), it was proposed that the chiral *N*-(acyl)oxazolidin-2-one (*S*)-**1**[4] would react with the α,β-unsaturated aldehyde **2** to give an aldol product **3** (step 1), whose β-hydroxy stereocentre would then be used to control the facial selectivity of a directed hydrogenation reaction to afford the aldol **4** containing a new C^4-stereogenic centre in high *de* (step 2). *retro*-Aldol cleavage of the aldol **4** would then destroy the "temporary" β-hydroxy stereocentre of the aldol **4**, affording the chiral auxiliary fragment **1** and the enantiopure α-methyl aldehyde **5** in high *ee* (step 3).

Therefore, our first goal was to identify conditions that would enable the alkene functionalities of the *syn*-aldols **6** or **8** to be hydrogenated in high *de*.[5] Evans et al. had previously reported that Brown's catalyst ([Rh(NBD)(DIPHOS-4)]PF_6) could be used for the diastereoselective hydrogenation of structurally related γ-δ-unsaturated *syn*-aldols in high *de*.[6,7] Therefore, under optimal conditions, we found that the hydrogenation of *syn*-methylene aldol **6** with 17.5 mol-% of a commercially available Brown's catalyst ([Rh(NBD)(DIPHOS-5)]PF_6) in CH_2Cl_2 under 5 bar of hydrogen gave aldol (4*R*)-**7** in 80% *de*.[8] Alternatively, hydrogenation of the *syn*-aldol **8**, which contains a trisubstituted alkene functionality, gave the *opposite* diastereoisomeric aldol (4*S*)-**9** in 64% *de* under otherwise identical conditions.[9] A review of the literature revealed that Wilkinson's catalyst [$Rh(PPh_3)_3Cl$] had previously been used as a catalyst for the directed hydrogenation of chiral allylic alcohols with moderate levels of diastereocontrol.[10] Therefore, the *syn*-methylene aldol **6** was hydrogenated with 17.5 mol-% Wilkinson's catalyst in CH_2Cl_2 under 5 bar of hydrogen to give aldol (4*R*)-**7** in 60% *de*.[9] However, in contrast to Brown's catalyst, hydrogenation of *syn*-trisubstituted-aldol **8** with Wilkinson's catalyst under the same conditions gave the *same* aldol (4*R*)-**7** in 78% *de* (Scheme 1).

The observation that hydrogenation of the *syn*-aldol **8** with Wilkinson's catalyst gave aldol (4*R*)-**7**, rather than the opposing aldol diastereomer (4*S*)-**9** predicted from allylic strain models,[6] lead us to postulate that the conformation of the aldol substrate was important in controlling the diastereoselectivity of its hydrogenation using Wilkinson's catalyst.[9] Consequently, it was decided to determine whether the diastereocontrol observed for hydrogenation of diastereoisomeric *anti*-aldols **10** and **12** might be improved using Wilkinson's catalyst.[11] Therefore, hydrogenation of the *anti*-methylene aldol **10** with 17.5 mol-% Wilkinson's catalyst in CH_2Cl_2 under 5 bar of hydrogen, resulted in aldol (4*S*)-**11** in a much improved 96% *de*.[9] Furthermore, hydrogenation of the trisubstituted alkene of *anti*-aldol **12** gave the opposite diastereoisomeric aldol (4*R*)-**13**, albeit in a re-

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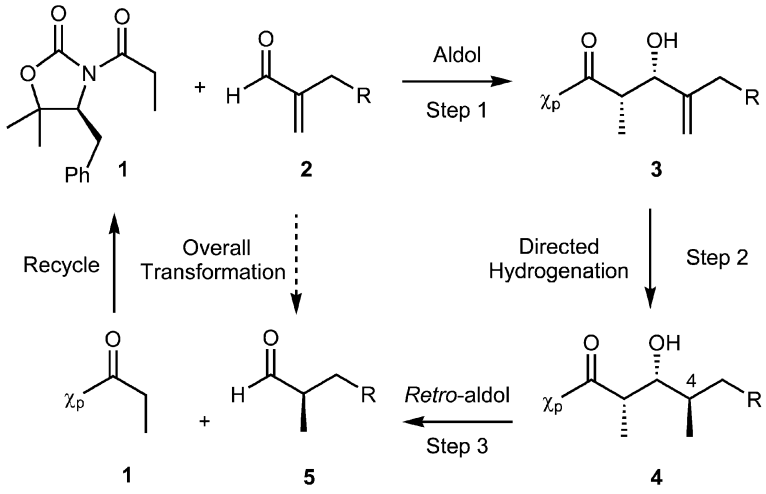
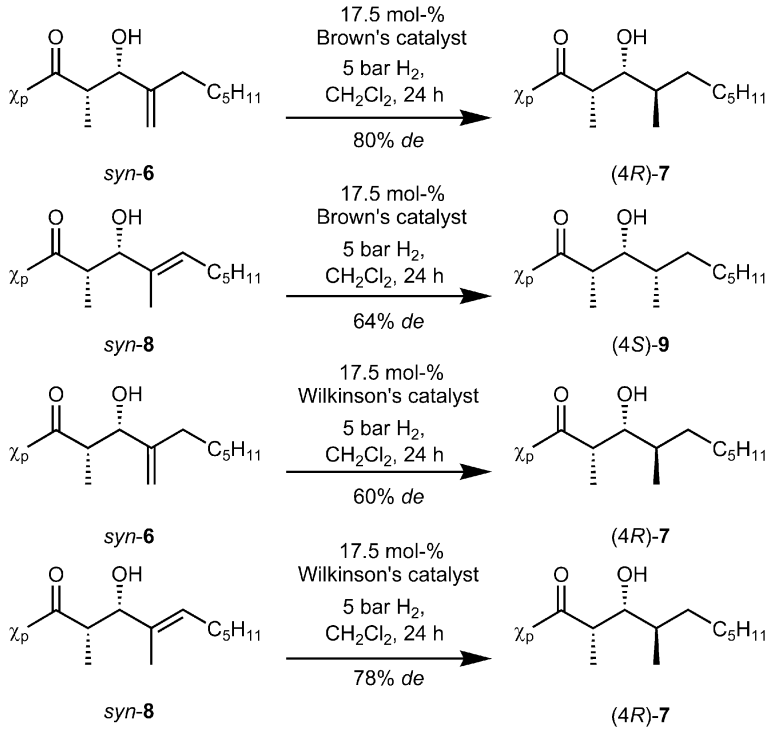


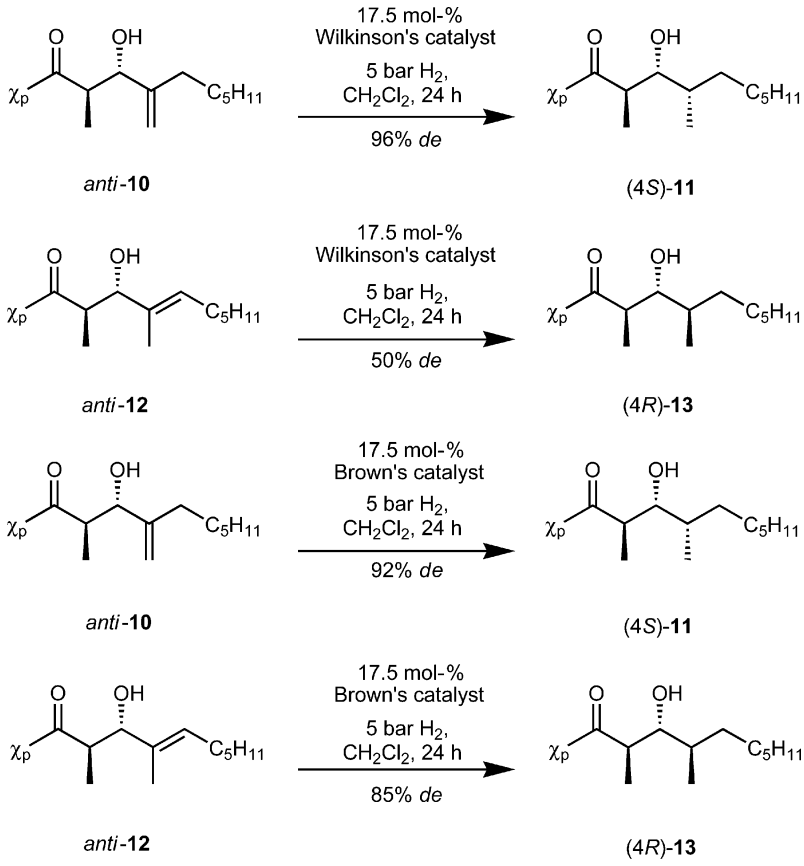
Figure 1. Temporary stereocentre approach for the asymmetric synthesis of chiral α-methyl aldehydes.



Scheme 1. Diastereoselective hydrogenation of the *syn*-aldols **6** and **8** using Brown's and Wilkinson's catalyst.

duced 50% *de*.[9] For completeness, we also carried out hydrogenation of *anti*-aldols **10** and **12** using Brown's catalyst which gave the corresponding aldol (4*S*)-**11** and aldol (4*R*)-**13** in 92% *de* and 85% *de* respectively (Scheme 2).[9]

These results demonstrated that facial selectivity could be achieved under catalyst control, since hydrogenation of *syn*-aldol **8** with Brown's catalyst gave aldol (4*S*)-**9** in 64% *de*, whilst hydrogenation of *syn*-aldol **8** with Wilkinson's catalyst gave aldol (4*R*)-**7** in 78% *de* (Scheme 1). Alternatively, the substitution pattern of the alkene functionality could be used for diastereocontrol, since hydrogenation of *anti*-methylene aldol **10** with Brown's catalyst gave aldol (4*S*)-**11** in 92% *de*, whilst hydrogenation of trisubstituted *anti*-aldol **12** with Brown' catalyst gave aldol (4*R*)-**13** in 85% *de* (Scheme 2). Finally, configurational control at the α-stereocentre of the aldol substrate could also be used, because hydrogenation of the *syn*-methylene aldol **6** with Brown's catalyst gave aldol (4*R*)-**7** in 80% *de*, whilst hydrogenation of the *anti*-methylene aldol **10** with Brown's catalyst gave aldol (4*S*)-**11** in 92% *de* (see Schemes 1 and 2). Therefore,



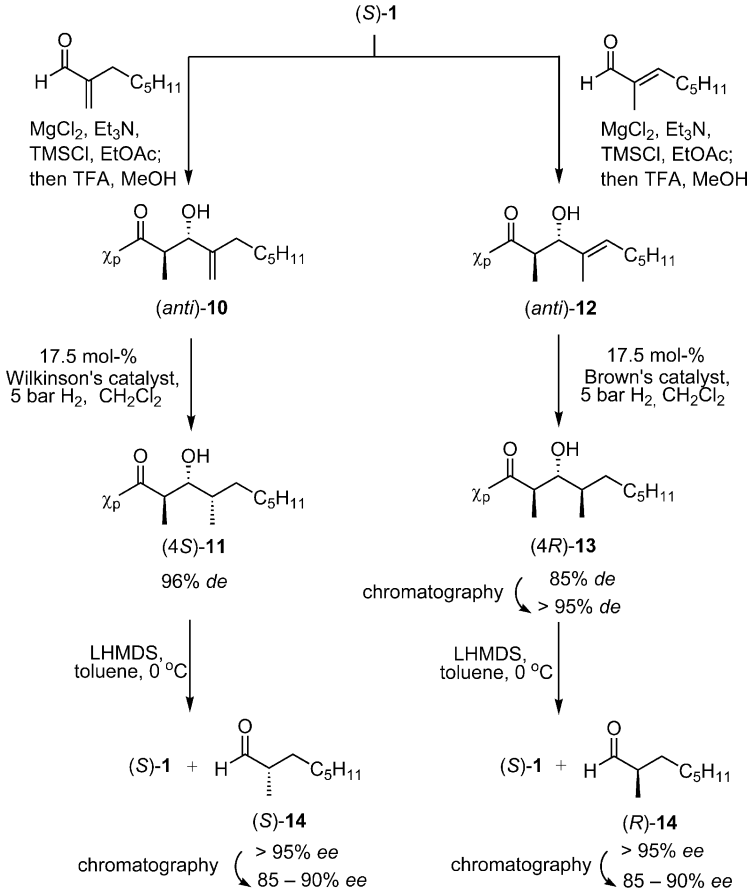
Scheme 2. Hydrogenation of *anti*-aldols **10** and **12** using Wilkinson's and Brown's catalyst.

judicious choice of the aldol substrate and catalyst used in these hydrogenation reactions enables the contiguous stereogenic triad of all four possible diastereoisomers *syn*,*anti*-**7**, *syn*,*syn*-**9**, *anti*,*syn*-**11** and *anti*,*anti*-**13** to be selectively accessed in good to excellent 64–96% *de*.

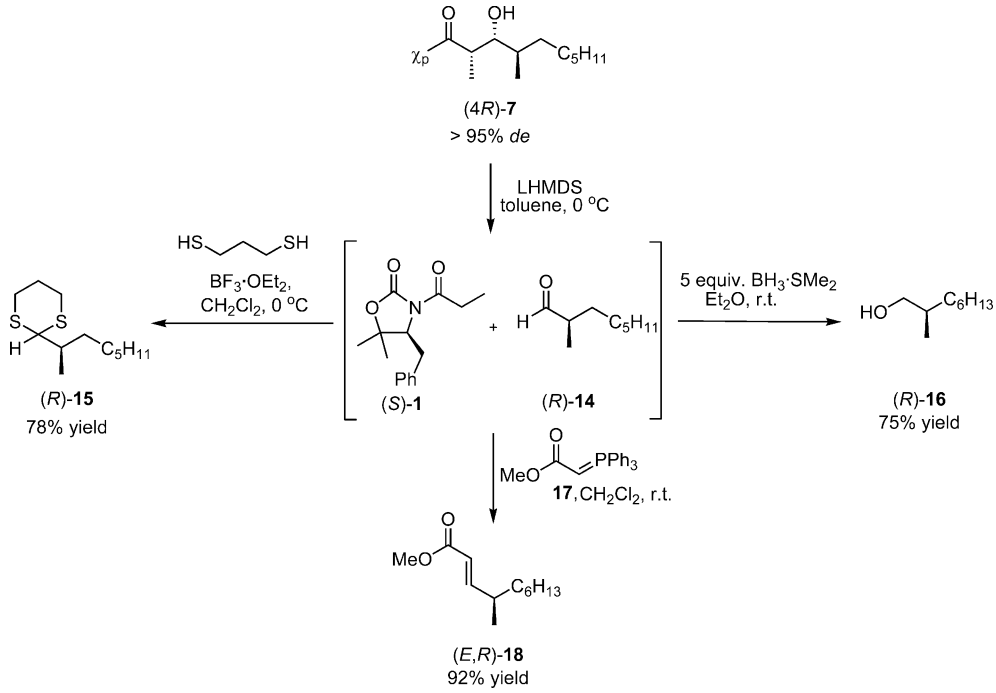
Overall, the best level of (4*S*)-diastereocontrol of 96% *de* was obtained by hydrogenation of the *anti*-aldol **10** with Wilkinson's catalyst, whilst the best level of (4*R*)-diastereocontrol of 85% *de* was obtained from hydrogenation of *anti*-aldol **12** with Brown's catalyst. Therefore, aldol (4*S*)-**11** (96% *de*) was treated with 1.1 equiv. of LHMDS in toluene at 0 °C,[1] which resulted in a clean *retro*-aldol reaction to afford *N*-propionyloxazolidin-2-one [(*S*)-**1**] and (*S*)-α-methyloctanal (**14**) in >95% *ee*. Similarly, aldol (4*R*)-**13** (85% *de*) was purified to >95% *de* by chromatography, followed by *retro*-aldol cleavage to afford *N*-propionyloxazolidin-2-one [(*S*)-**1**] and (*R*)-α-methyloctanal (**14**) in >95% *ee* (Scheme 3).

The enantiomeric purities of the (*S*)- and (*R*)-α-methyloctanal produced in these *retro*-aldol reactions were determined by derivatisation of their respective crude reaction products with (*S*,*S*)-*N*,*N*′-dimethyl-1,2-diphenylethylenediamine (DMPEDA).[12] This enabled their enantiopurities to be confirmed as >95% *ee* from comparison of the ^{1}H NMR spectra of their resultant imidazolidines with the ^{1}H NMR spectrum of an authentic 50:50 mixture of diastereoisomeric imidazolidines formed from derivatisation of *rac*-α-methyloctanal (**14**) with (*S*,*S*)-DMPEDA. Attempts to purify the crude products of these *retro*-aldol reactions to remove *N*-propionyloxazolidin-2-one [(*S*)-**1**] by distillation or chromatography over silica, lead to partial racemisation of the α-stereogenic centre affording pure α-methyloctanal (**14**) in good yield and in 70–90% *ee*.[13] However, careful purification by chromatography using neutral alumina and neutral glassware enabled pure (*S*)- or (*R*)-α-methyloctanal (**14**) to be reproducibly isolated from these *retro*-aldol reactions in good 75–85% yield and in 85–90% *ee* (Scheme 3).[14]

In order to address this partial racemisation problem, a series of protocols were developed that enabled the chiral aldehyde **14** to be derivatised in situ to afford chiral building blocks less susceptible to racemisation. Therefore, treatment of the crude *retro*-aldol cleavage product of aldol (4*R*)-**7** (95% *de*) with propane-1,3-dithiol and $BF_3{\cdot}Et_2O$, gave chiral dithiane (*R*)-**15** ($[\alpha]_D^{21}$ = +8.0, *c* = 3.0, Et_2O; ref.[15] $[\alpha]_D^{21}$ = +8.3, *c* = 13.0, Et_2O) in 78% yield. Alternatively, reduction of the crude *retro*-aldol cleavage product of aldol (4*R*)-**7** (95% *de*) with $BH_3{\cdot}SMe_2$ in Et_2O gave 2-methyloctan-1-ol [(*R*)-**16**] (+ 10.0, *c* = 1.00, CH_2Cl_2; ref.[13f] +10.3, *c* = 1.00, CH_2Cl_2) in 75% yield. Finally, treatment of the crude *retro*-aldol cleavage product of aldol (4*R*)-**7** (95% *de*) with stabilised ylide **17** in CH_2Cl_2[16] gave chiral α,β-unsaturated ester (*E*,*R*)-**18** in an excellent 92% yield (Scheme 4).[17,18]



Scheme 3. Temporary stereocentre approach for the enantiodivergent synthesis of both (*S*)- and (*R*)-enantiomers of α-methyloctanal (**14**).



Scheme 4. *retro*-Aldol cleavage of aldol (4*R*)-**7** followed by in situ derivatization of (*R*)-α-methyloctanal (**14**) to afford the (*R*)-dithiane **15**, the (*R*)-alcohol **16** and the (*E*,*R*)-α,β-unsaturated ester **18**.

In conclusion, we have developed a novel three-step aldol/hydrogenation/*retro*-aldol protocol for the enantiodivergent synthesis of either enantiomer of α-methyloctanal, which may be derivatised in situ to afford a range of synthetically useful chiral dithiane, alcohol, or ester products. We anticipate that this type of temporary stereocentre approach should prove readily applicable to the asymmetric synthesis of other chiral α-methyl aldehydes of use as chiral building blocks for natural product applications.

Supporting Information (see also the footnote on the first page of this article): This supporting information contains representative protocols for aldol, hydrogenation, *retro*-aldol and aldehyde derivatisation reactions, and spectroscopic data for compounds **6**, **7**, **10**, **11**, **12**, **13**, (*R*)-**14**, **15**, **16** and **18**. It also contains protocols for determining the *ee* value of aldehyde **14** through in situ derivatisation with (*S*,*S*)-TMPEDA to afford diastereoisomeric imidazolidines whose *de* may be analysed by ^{1}H NMR spectroscopy.

Acknowledgments

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[8] The absolute configuration of the newly formed stereocentres of aldols (4*R*)-**7** and (4*S*)-**9** were assigned from literature precedent (see ref.[6]).
[9] The configuration of the C^4 stereocentres of all (4*S*)- and (4*R*)-aldols were assigned from the sign of the specific rotation of the (*R*)- or (*S*)-α-methyloctanal (**14**) generated from their *retro*-aldol cleavage, as well as from the identity of the major imidazolidine diastereoisomer formed from its derivatization with (*S*,*S*)-DMPEDA.
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