# A novel strategy for the asymmetric synthesis of chiral cyclopropane carboxaldehydes†

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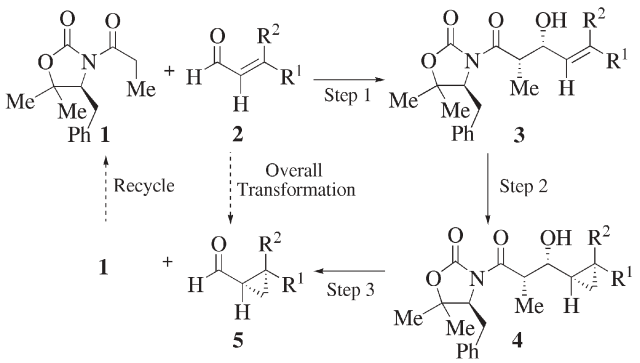
**A new way of combining chiral auxiliaries and substrate-directable reactions for asymmetric synthesis is described that employs a three-step sequence of aldol–cyclopropanation–*retro*-aldol reactions for the stereoselective synthesis of enantiopure cyclopropane carboxaldehydes.**

Chiral auxiliaries[1] and substrate-directable reactions[2] have often been combined to afford powerful synthetic protocols for the asymmetric synthesis of chiral building blocks for natural product synthesis.[3] In these approaches a chiral auxiliary is first employed to prepare a chiral intermediate containing a new stereogenic centre in high de. This new stereocentre is then employed to control the facial selectivity of a substrate-directable reaction to afford a second chiral intermediate containing further stereogenic centres. Finally, the second chiral intermediate is then cleaved to afford the chiral auxiliary and a chiral product.[4] We were interested in developing new ways of combining chiral auxiliaries and substrate-directable reactions for asymmetric synthesis, and now report herein on a novel three-step protocol that employs a sequence of aldol–cyclopropanation–*retro*-aldol reactions for the stereoselective synthesis of chiral cyclopropane carboxaldehydes in enantiopure form.[5]

The novel three-step protocol that was envisaged for the asymmetric synthesis of chiral cyclopropane carboxaldehydes is described in Scheme 1. Firstly, (*S*)-*N*-propionyl-5,5-dimethyl-oxazolidin-2-one **1**[6] would undergo a stereoselective aldol reaction with an α,β-unsaturated aldehyde substrate **2** to afford a *syn*-aldol product **3** in high de (Step 1). Secondly, stereoselective cyclopropanation of the allylic alcohol functionality of **3** would occur under the stereodirecting effect of its β-hydroxyl functionality to afford cyclopropane **4** in high de (Step 2). Finally, *retro*-aldol fragmentation of cyclopropane **4** would afford the desired chiral cyclopropane carboxaldehyde **5** and the chiral auxiliary fragment **1** that could then be recycled as required (Step 3).[7] The overall outcome of this three-step protocol would therefore be the stereoselective transformation of an achiral α,β-unsaturated aldehyde **2** into a chiral cyclopropane carboxaldehyde **5** in enantiopure form (Scheme 1).

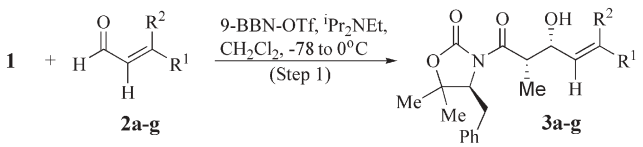



**Scheme 1** Novel three-step strategy for the asymmetric synthesis of chiral cyclopropane carboxaldehydes.

The first step of this new strategy was well precedented since it had been reported previously that reaction of (*Z*)-boron enolates of *N*-acyl-oxazolidin-2-ones, with α,β-unsaturated aldehydes, gave *syn*-aldol products in high de.[8] Consequently, we found that treatment of (*S*)-*N*-propionyl-5,5-dimethyl-oxazolidin-2-one **1** with 9-BBN-OTf and $^{i}Pr_2NEt$ in $CH_2Cl_2$ at 0 °C, followed by cooling to −78 °C and addition of the appropriate α,β-unsaturated aldehyde **2a–g**,[9] gave a range of *syn*-aldol products **3a–g** in >95% de, and in acceptable 76–87% isolated yields (Table 1).[10] (*Z*)-*syn*-Aldol **3h** was prepared in >95% de and in an overall 60% yield, *via* an alternative two-step reaction sequence, involving reaction of the (*Z*)-boron enolate of **1** with oct-2-yn-al **6**,[11] followed by hydrogenation of the resultant *syn*-aldol product using Lindlar's catalyst (Scheme 2).[12]

We next determined conditions that would enable the alkene functionality of *syn*-aldol products **3a–h** to be cyclopropanated in high de.[13] It was found that treatment of *syn*-aldols **3a–h** with

**Table 1** Asymmetric synthesis of *syn*-aldols **3a–g** in high de (Step 1)




| Entry | Aldehyde | $R^1$ | $R^2$ | Aldol | de (%)[a,b] | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | **2a** | Ph- | H | **3a** | >95 | 80 |
| 2 | **2b** | $Me(CH_2)_6$– | H | **3b** | >95 | 81 |
| 3 | **2c** | *p*-$MeOC_6H_4$– | H | **3c** | >95 | 77 |
| 4 | **2d** | *o*-$NO_2C_6H_4$– | H | **3d** | >95 | 87 |
| 5 | **2e** | 2-Furyl | H | **3e** | >95 | 85 |
| 6 | **2f** | Me | Me | **3f** | >95 | 76 |
| 7 | **2g** | Me | H | **3g** | >95 | 76 |

[a] The des of aldols **3a–g** were determined from $^1$H NMR spectra of their crude reaction products. [b] Aldols **3a–g** exhibited $J_{(2',3')}$ coupling constants of between 2.0 and 6.0 Hz in their $^1$H NMR spectra, consistent with the assigned *syn*-configuration.

† Electronic supplementary information (ESI) available: representative experimental details and data for the asymmetric synthesis of cyclopropane carboxaldehyde (*S*,*S*)-**5d**. See http://www.rsc.org/suppdata/cc/b5/b501847a/

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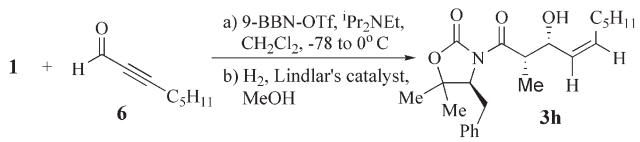
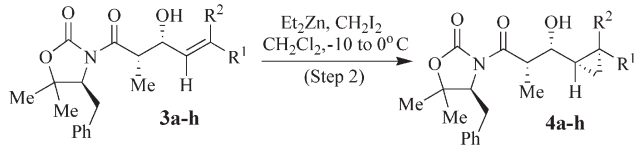



**Scheme 2** Alternative two-step *syn*-aldol–hydrogenation protocol for the synthesis of *syn*-aldol **3h**.

**Table 2** Cyclopropanation occurs under the stereocontrol of the β-hydroxy group to afford *syn*-cyclopropyl-aldols **4a–h** in high de (Step 2)




| Entry | Aldol | $R^1$ | $R^2$ | Cyclopropane | de (%)[a] | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | **3a** | Ph | H | **4a** | >95 | 95 |
| 2 | **3b** | $Me(CH_2)_6$– | H | **4b** | >95 | 89 |
| 3 | **3c** | *p*-$MeOC_6H_4$– | H | **4c** | >95 | 90 |
| 4 | **3d** | *o*-$NO_2C_6H_4$– | H | **4d** | >95 | 90 |
| 5 | **3e** | 2-Furyl | H | **4e** | >95 | 92 |
| 6 | **3f** | Me | Me | **4f** | >95 | 99 |
| 7 | **3g** | Me | H | **4g** | >95 | 95 |
| 8 | **3h** | H | $C_5H_{11}$– | **4h** | >95 | 96 |

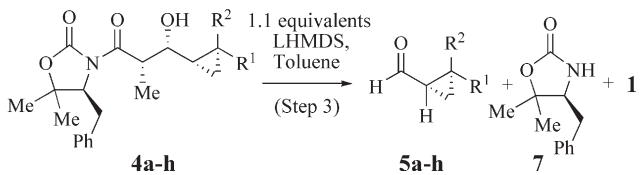
[a] The des of *syn*-cyclopropyl-aldols **4a–h** were determined from the $^1$H NMR spectra of their crude reaction products.

$Et_2Zn$ and $CH_2I_2$ in $CH_2Cl_2$ at a temperature between −10 and 0 °C resulted in a highly diastereoselective cyclopropanation reaction,[14] affording *syn*-cyclopropyl-aldols **4a–h** in >95% de and 89–99% yield (Table 2). Cyclopropanations of this type of allylic alcohol substrate under modified Furukawa conditions are normally *syn*-selective due to minimisation of $A^{1,3}$ strain in the transition state,[14] and as a consequence the configurations of *syn*-cyclopropyl-aldols **4a–h** were assigned accordingly.[15,16]

Conditions were next identified that would enable *syn*-cyclopropyl-aldols **4a–h** to undergo *retro*-aldol cleavage to afford their desired cyclopropane carboxaldehydes **5a–h**.[17] Extensive screening of a range of bases and conditions revealed that treatment of *syn*-cyclopropyl-aldols **4a–e** with LHMDS in toluene, at temperatures between 0 °C and 10 °C, resulted in clean *retro*-aldol cleavage to afford a mixture of the desired chiral cyclopropane carboxaldehydes **5a–e**, (*S*)-*N*-propionyl-5,5-dimethyl-oxazolidin-2-one **1**, and 5,5-dimethyl-oxazolidin-2-one **7** (<20%) with excellent mass recovery. Presumably, competing formation of **7** arises from partial decomposition of the lithium enolate of *N*-propionyl-oxazolidin-2-one **1** *via* a *retro*-ketene addition mechanism.[18] Purification of each *retro*-aldol reaction product by chromatography gave cyclopropane carboxaldehydes (*S*,*S*)-**5a–e** in >95% de and in 55–75% isolated yields (Table 3). The absolute configuration of cyclopropane carboxaldehydes (*S*,*S*)-**5a** and (*S*,*S*)-**5b** were confirmed from their positive specific rotations,[19,20] whilst the enantiomeric purity of (*S*,*S*)-**5b** was confirmed as >95% ee by conversion to its corresponding imidazolidinone using (*R*,*R*)-(+)-dimethyl-1,2-diphenyl-1,2-ethane-diamine as a chiral derivatising agent.[21]

Treatment of *syn*-cyclopropyl-aldols **4f** and **4g** with LHMDS at 0 °C also resulted in clean *retro*-aldol reactions, however attempted purification of aldehydes **5f** and **5g** by chromatography was less successful due to their inherent volatility which led to poor yields of aldehyde being isolated. Consequently, the *retro*-aldol reactions of cyclopropyl-aldols **4f** and **4g** were repeated using LHMDS in toluene-$d_8$ at 0 °C, and each reaction worked-up *via* addition of five drops of $NH_4Cl_{aq}$, before drying over $MgSO_4$. Resulting distillation of the respective crude reaction products afforded a solution of the desired aldehydes **5f** (>95% ee) and **5g** (>95% de) in toluene-$d_8$,[22] the yields of which were determined as 51% and 65% respectively *via* $^1$H NMR spectroscopic analysis in the presence of a known concentration of 2,5-dimethylfuran as an

**Table 3** Anionic *retro*-aldol reactions afford chiral cyclopropane carboxaldehydes **5a–h** in enantiopure form (Step 3)




| Entry | Aldol | $R^1$ | $R^2$ | Aldehyde | Conditions | de (%)[a] | Yield (%)[c] |
|---|---|---|---|---|---|---|---|
| 1 | **4a** | Ph | H | **5a** | 1 h / 0 °C | >95[24] | 75 |
| 2 | **4b** | $Me(CH_2)_6$– | H | **5b** | 1 h / 0 °C | >95 | 73 |
| 3 | **4c** | *p*-$MeOC_6H_4$– | H | **5c** | 3 h / 5 °C | >95 | 63 |
| 4 | **4d** | *o*-$NO_2C_6H_4$– | H | **5d** | 5 h / 10 °C | >95 | 55 |
| 5 | **4e** | 2-Furyl | H | **5e** | 1 h / 0 °C | >95 | 71 |
| 6 | **4f** | Me | Me | **5f** | 1 h / 0 °C | >95% ee[b] | 51[d] |
| 7 | **4g** | Me | H | **5g** | 1 h / 0 °C | >95 | 65[d] |
| 8 | **4h** | H | $C_5H_{11}$– | **5h** | 1 h / 0 °C | >95[25] | 61 |

[a] The des of cyclopropane carboxaldehydes **5a–h** were determined from the $^1$H NMR spectra of their crude *retro*-aldol reaction products. [b] The ee of cyclopropane carboxaldehyde **5f** was determined *via* derivatisation with (*R*,*R*)-(+)-dimethyl-1,2-diphenyl-1,2-ethane-diamine.[21] [c] $^1$H NMR spectroscopic analysis of the crude reaction products revealed that all cyclopropane carboxaldehydes had been formed in >70% yield. [d] Yields were determined from $^1$H NMR spectroscopic analysis of the cyclopropane carboxaldehyde in toluene-$d_8$ in the presence of a known concentration of 2,5-dimethylfuran.[22]

internal standard (Table 3).[23] Finally, treatment of *cis*-cyclopropyl-aldol (*Z*)-**4h** with LHMDS at 0 °C also resulted in a clean *retro*-aldol reaction affording *cis*-cyclopropane carboxaldehyde (1*S*,2*R*)-**5h** in 61% yield,[24] with no epimerisation to its more stable (1*R*,2*R*)-epimer having occurred under the basic conditions used to facilitate the *retro*-aldol reaction.[25]

In summary, a novel three-step aldol–cyclopropanation–*retro*-aldol sequence for the direct asymmetric synthesis of enantiopure cyclopropane carboxaldehydes under non-oxidative/non-reductive conditions has been developed. This protocol demonstrates the potential of a novel synthetic strategy that employs a chiral auxiliary to *reversibly* generate a *temporary* stereocentre that is then employed as a stereodirecting group to control facial selectivity for a substrate-directable reaction. We anticipate that this new strategy will prove applicable to the combination of other types of chiral auxiliary and substrate-directable reaction, thus enabling its potential for asymmetric synthesis to be realised in a wide range of different reaction scenarios.

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