A temporary stereocentre approach for the asymmetric synthesis of chiral cyclopropane-carboxaldehydes†

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A novel way of combining chiral auxiliaries and substrate directable reactions is described that employs a three-step sequence of aldol/cyclopropanation/retro-aldol reactions for the asymmetric synthesis of enantiopure cyclopropane-carboxaldehydes. In the first step, reaction of the boron enolate of (*S*)-*N*-propionyl-5,5-dimethyl-oxazolidin-2-one with a series of α,β-unsaturated aldehydes affords their corresponding *syn*-aldol products in high de. In the second step, directed cyclopropanation of the alkene functionalities of these *syn*-aldols occurs under the stereodirecting effect of their 'temporary' β-hydroxyl stereocentres to give a series of cyclopropyl-aldols in high de. Finally, retro-aldol cleavage of the lithium alkoxide of these cyclopropyl-aldols results in destruction of their temporary β-hydroxy stereocentres to afford the parent chiral auxiliary and chiral cyclopropane-carboxaldehydes in >95% ee. The potential of this methodology has been demonstrated for the asymmetric synthesis of the cyclopropane containing natural product cascarillic acid in good yield.

Introduction

Chiral aldehydes containing α-stereocentres are widely employed as versatile chiral building blocks[1] for the asymmetric synthesis of complex natural products[2] and drug like molecules,[3] which has resulted in a wide range of methodology being developed for their asymmetric synthesis. They may be prepared directly *via* reduction of chiral amides,[4] Weinreb amides,[5] *N*-acyl-5,5-dimethyl-oxazolidin-2-ones,[6] *N*-acyl-thiazolidine-2-thiones,[7] *N*-acyl-sultams,[8] thioesters,[9] and oxazolines,[10] although the yield of chiral aldehyde produced may be low due to competing over-reduction to its corresponding alcohol. Enantiopure α-substituted aldehydes may also be prepared *via* oxidation of their corresponding chiral primary alcohols,[11] although care must be taken to ensure that racemisation of their α-stereocentres does not occur.[12] Alternative oxidative protocols based on the cleavage of chiral diols,[13] or ozonolysis of chiral alkenes/hydrazones have also been widely reported.[14] A wide range of asymmetric methodologies have also been developed that do not employ oxidative or reductive steps to generate the aldehyde functionality, including strategies based on the hydroformylation of alkenes,[15] rearrangement reactions,[16] conjugate addition reactions,[17] cycloaddition reactions,[18,19] as well as approaches that rely on the kinetic resolution of racemic substrates.[20] There has also recently been great progress in the development of efficient organocatalytic approaches that employ transient iminium/enamine intermediates for the asymmetric synthesis of chiral α-substituted aldehydes. These include protocols that employ asymmetric α-halogenation, α-sulfenylation, epoxidation, cyclopropanation, transfer hydrogenation, aldol, Mannich and conjugate addition reactions for stereocontrol.[21]

A number of chiral auxiliary based approaches have also been reported that rely on derivatisation of an achiral aldehyde with a chiral auxiliary to reversibly afford chiral oxathiane,[22] oxazolidine,[23] imidazolidine,[24] acetal,[25] or α-acetoxy-sulfone equivalents.[26] These chiral aldehyde equivalents are then stereoselectively transformed into new chiral intermediates that contain new α-stereogenic centres in high de, with diastereoselectivity being controlled by the presence of the chiral auxiliary fragment. Subsequent cleavage of the chiral auxiliary fragment then affords a chiral aldehyde containing an α-stereogenic centre in high ee. We are interested in developing new ways of combining chiral auxiliaries and substrate directable reactions for asymmetric synthesis, and now report on the development of novel 'temporary stereocentre' methodology that enables chiral cyclopropane-carboxaldehydes to be prepared in high ee. Part of this research has been communicated previously.[27]

Results and discussion

We were interested in developing new methodology for the asymmetric synthesis of chiral cyclopropane-carboxaldehydes using a novel 'temporary stereocentre' approach for stereocontrol that would employ the stereodirecting ability of a chiral auxiliary fragment to create remote stereocentres in high de (Scheme 1).[28] In this 'temporary stereocentre' approach it was envisaged that an *N*-acyl-oxazolidin-2-one **1** would react as a chiral auxiliary with an α,β-unsaturated aldehyde **2** to afford *syn*-aldol **3** in high de (Step 1). Secondly, stereoselective cyclopropanation of the alkene functionality of *syn*-aldol **3** would then occur under the stereodirecting effect[29] of its β-hydroxyl functionality to afford cyclopropyl-aldol **4** with good levels of diastereocontrol (Step 2). Finally, retro-aldol fragmentation of cyclopropyl-aldol **4** would occur to afford the desired chiral cyclopropane-carboxaldehyde **5**

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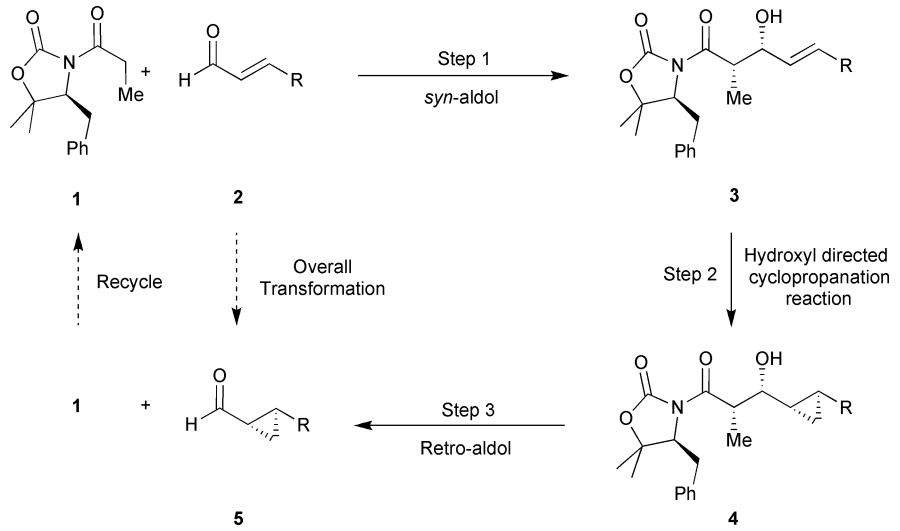


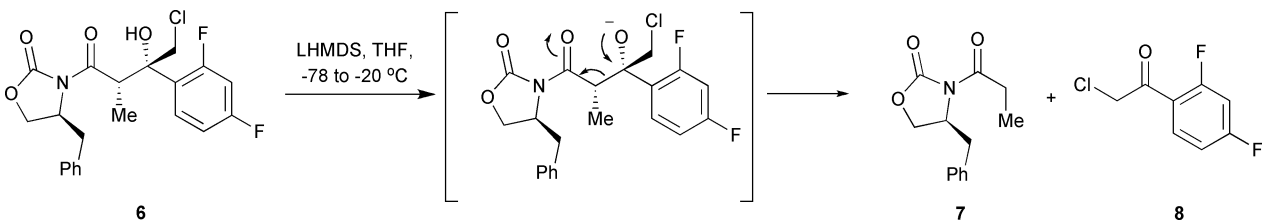
Scheme 1 Three-step protocol for the asymmetric synthesis of chiral cyclopropane-carboxaldehydes **5**.

and chiral auxiliary **1** that could be recycled as required (Step 3).[30] The overall outcome of this three-step protocol would therefore be the stereoselective transformation of achiral α,β-unsaturated aldehyde **2** into enantiopure cyclopropane-carboxaldehyde **5**, using reversible formation of the temporary β-hydroxyl stereocentre of *syn*-aldol **3** to control the diastereofacial selectivity of its cyclopropanation reaction (Scheme 1).

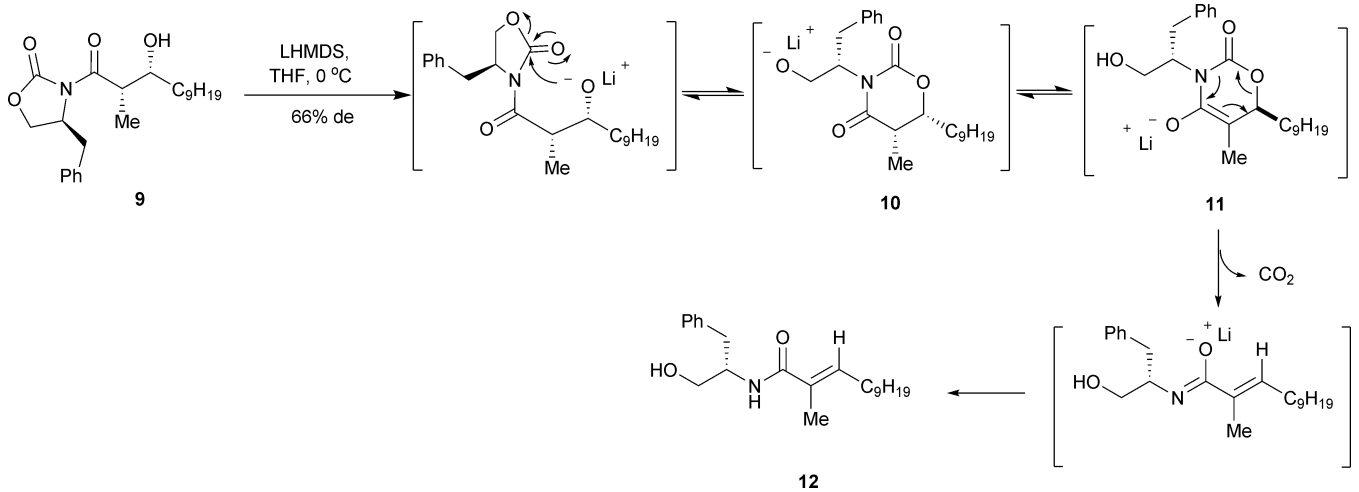
There was well established precedent that reaction of (*Z*)-boron enolates of *N*-propionyl-oxazolidin-2-ones **1** with α,β-unsaturated aldehydes **2** should afford β-vinyl-*syn*-aldols **3** in high de.[31] Furthermore, it was known that stereoselective cyclopropanation of the alkene functionalities of *syn*-aldols **3** using coordinated zinc carbenoid species should occur under the stereodirecting effect of their β-hydroxyl functionalities to afford cyclopropyl-aldols **4** in high de.[32] Whilst we could find no previous reports of β-hydroxy-*N*-acyl-oxazolidin-2-ones undergoing retro-aldol reactions, Bartroli and co-workers had previously described that the lithium alkoxide of ketol **6**[33] underwent clean retro-ketol cleavage to afford *N*-propionyl-oxazolidin-2-one **7** and α-chloroketone **8** in good yield (Scheme 2).

However, although this precedent appeared promising, we were aware that alkoxides of Evans' derived *N*-acyl-oxazolidin-2-one-*syn*-aldols did not undergo retro-aldol cleavage, instead undergoing alternative rearrangement/elimination reactions to afford trisubstituted (*E*)-α,β-unsaturated amides in >95% de.[34,35] For example, treatment of *syn*-aldol **9** with LHMDS in toluene at 0 °C affords a β-alkoxide that undergoes intramolecular attack at its oxazolidin-2-one carbonyl to afford an unstable oxazinane-2,4-dione alkoxide **10**,[36] that equilibrates to a 1,3-oxazinane-2,4-dione enolate **11** which eliminates carbon dioxide *in situ* to afford (*E*)-α,β-unsaturated amide **12** in 66% de and 92% yield (Scheme 3).[37]

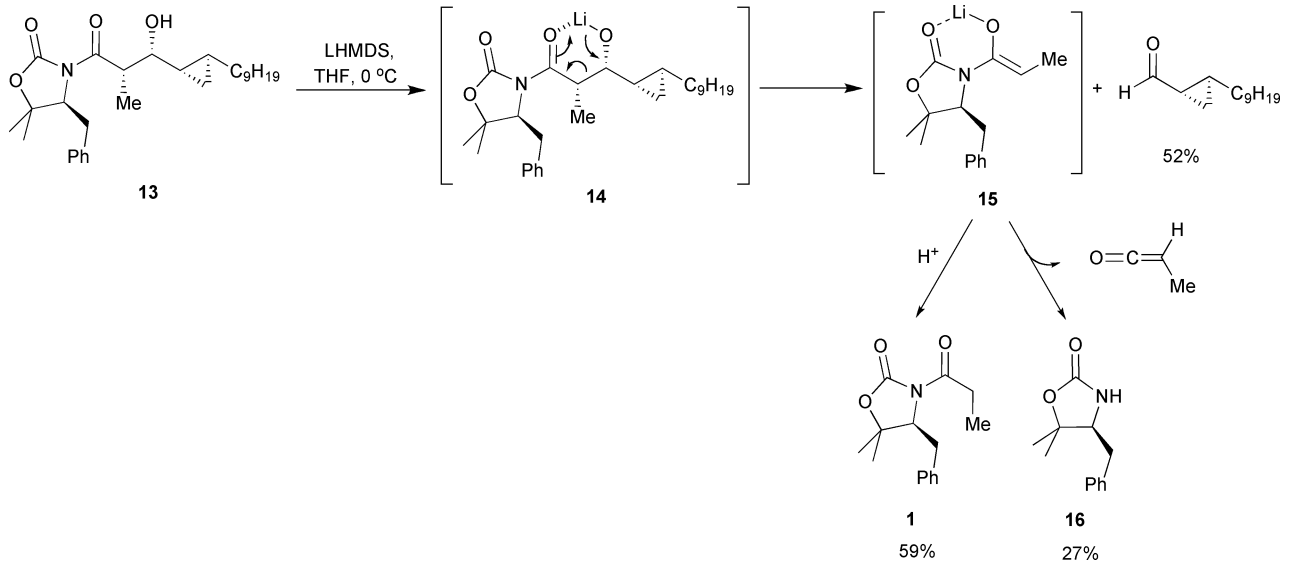
In order to prevent this unwanted rearrangement/cyclisation pathway from occurring it was decided to employ *N*-propionyl-5,5-dimethyl-oxazolidinone **1** as a chiral auxiliary for asymmetric synthesis. These 'SuperQuat' 5,5-dimethyl-oxazolidin-2-ones[38] were originally developed by Davies and coworkers to address endocyclic cleavage problems that occur when sterically hindered *N*-acyl-oxazolidin-2-ones are treated with hard nucleophiles,[39] with their *gem*-5,5-dimethyl substituents blocking intermolecular attack of nucleophiles at their oxazolidin-2-one carbonyls.[40] We reasoned that the presence of the *gem*-5,5-dimethyl substituents of SuperQuat derived alkoxide **14** would also block intramolecular attack of its β-alkoxide at its oxazolidin-2-one carbonyl, which would result in the rearrangement/elimination pathway being disfavoured, thus allowing the desired retro-aldol cleavage reaction to proceed. In order to test this hypothesis, *syn*-aldol **13** was treated with 1.1 equivalents of LHMDS in toluene at 0 °C, which resulted in formation of a lithium alkoxide **14** that underwent clean retro-aldol cleavage to afford the parent auxiliary **1** (59%), decanal (52%) and oxazolidine-2-one **16** (27%).[41] In this reaction, it is likely that lithium alkoxide **14** first undergoes a retro-aldol reaction to afford decanal and lithium enolate **15** which may be protonated on work-up to afford *N*-propionyl-oxazolidin-2-one **1**, or decompose *via* elimination of a ketene equivalent to afford the lithium anion of oxazolidin-2-one **16** (Scheme 4).[38a]



Scheme 2 Retro-ketol reaction of the lithium alkoxide of ketol **6**.



Scheme 3 Rearrangement/elimination mechanism of potassium alkoxides of (*rac*)-aldol **9** to afford (*E*)-α,β-unsaturated amide **12** in high de.

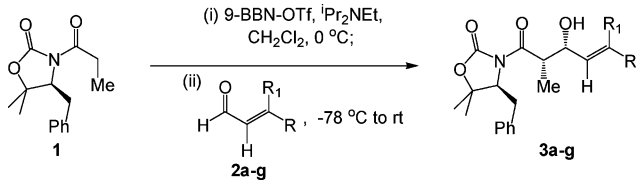


Scheme 4 Retro-aldol reaction of β-hydroxy-*N*-acyl-5,5-dimethyl-oxazolidin-2-one **13**.

Having established conditions that resulted in lithium alkoxides of aldol **13** undergoing clean retro-aldol cleavage our attention then turned towards using *N*-propionyl-5,5-dimethyl-oxazolidin-2-one (*S*)-**1** as a chiral auxiliary for the asymmetric synthesis of a series of chiral cyclopropane-carboxaldehydes **5a-i** (see Scheme 1). Therefore, treatment of (*S*)-**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 (*E*)-α,β-unsaturated aldehyde **2a-g**, gave a range of *syn*-aldol products **3a-g** in >95% de and 76–87% isolated yields (Table 1).[42] (*Z*)-*syn*-Aldol **3h** was prepared in an alternative manner because (*Z*)-α,β-unsaturated aldehydes are more difficult to prepare, and likely to isomerise to their corresponding (*E*)-isomers under the Lewis acidic conditions used in these aldol reactions.[43] Therefore, reaction of the (*Z*)-boron enolate of *N*-propionyl-5,5-dimethyl-oxazolidin-2-one (*S*)-**1** with oct-2-yn-al gave an alkyne-aldol **17**,[44] which was hydrogenated with Lindlar's catalyst to give (*Z*)-*syn*-aldol **3h** in >95% de and an overall 60% yield (Scheme 5).[45] The *syn*-configuration of aldols **3a-h** were assigned from literature precedent,[46] and confirmed from their small $J_{(2,3)}$ coupling constants of <5.0 Hz, in comparison with the larger $J_{(2,3)}$ coupling constant of >7.0 Hz expected for their corresponding *anti*-aldol diastereoisomers.[47]

It was then necessary to identify conditions that would enable the alkene functionalities of *syn*-aldols **3a-h** to be cyclopropanated in high de. It was found that treatment of *syn*-aldols **3a-h** with Et_2Zn and CH_2I_2 in CH_2Cl_2 at a temperature between −10 and 0 °C resulted in highly diastereoselective cyclopropanation reactions occurring to afford cyclopropyl-aldols **4a-h** in >95% de and 89–99% yield (Table 2).[41] Cyclopropanation of allylic alcohols under modified Furukawa conditions are known to be *syn*-selective due to minimisation of $A_{1,3}$ strain in the transition state,[48] and as a consequence the configuration of the cyclopropane rings of cyclopropyl-aldols **4a-h** were assigned accordingly.[49] The configuration of nitrophenyl-*syn*-aldol **4d** was subsequently confirmed by X-ray crystallographic analysis, that revealed the all *syn*-configuration of the stereocentres contained within its *N*-acyl side-chain (Fig. 1). The stereochemical outcome of these cyclopropanation reactions is therefore consistent with the hydroxyl

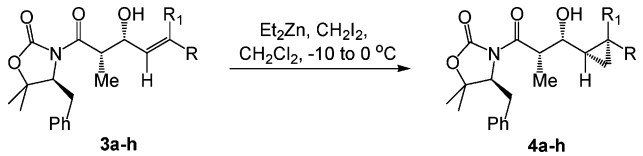
Table 1 Asymmetric synthesis of (*E*)-*syn*-aldols **3a-g**



Entry	Aldehydes **2a-g**	R	R_1	de (%)[a]	*syn*-Aldols **3a-g**	Yield (%)
1	**2a**	Ph	H	95	**3a**	80
2	**2b**	$Me(CH_2)_6$-	H	95	**3b**	81
3	**2c**	*p*-$MeOC_6H_4$-	H	95	**3c**	77
4	**2d**	*o*-$NO_2C_6H_4$-	H	95	**3d**	87
5	**2e**	2-Furyl-	H	95	**3e**	85
6	**2f**	Me	H	95	**3f**	76
7	**2g**	Me	Me	95	**3g**	76

[a] Diastereoisomeric excess of each *syn*-aldol reaction determined from examination of the ^{1}H-NMR spectra of their crude reaction products.

Table 2 Asymmetric synthesis of cyclopropyl-aldols **4a-h**



Entry	*syn*-Aldols **3a-h**	R	R_1	Cyclopropyl-aldols **4a-h**	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	H	**4f**	95	99
7	**3g**	Me	Me	**4g**	95	95
8	**3h**	H	*n*-C_5H_{11}	**4h**	95	96

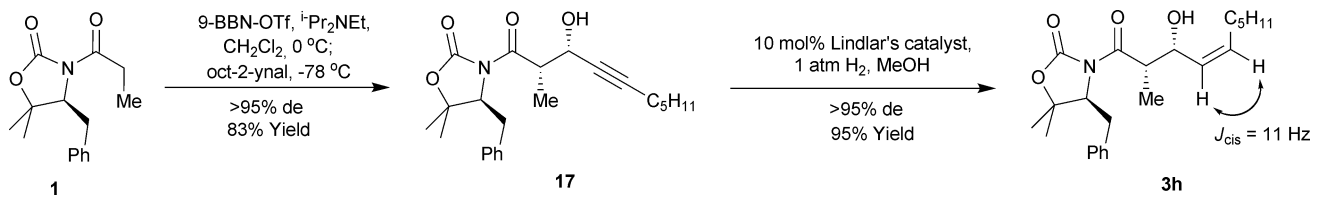
[a] Diastereoisomeric excess determined from examination of the crude 300 MHz ^{1}H NMR spectra.

groups of *syn*-aldols **4a-h** coordinating to a zinc-carbenoid species which is then delivered to one face of their alkene functionalities in a *syn*-selective manner that minimizes $A_{1,3}$ allylic strain in the transition state.[4]

We wished to confirm that the high diastereoselectivities observed in these cyclopropanation reactions of *syn*-aldols **3a-h** was due to the stereodirecting effect of their β-hydroxyl 'temporary stereocentres' and that the oxazolidin-2-one and α-methyl stereocentres were not contributing towards diastereocontrol. Therefore, it was decided to determine what level of diastereocontrol would be observed for cyclopropanation of the alkene functionality of aldol-ester **21** that contains a single β-hydroxyl stereocentre. Ester **21** was prepared in three steps *via* reaction of the (*Z*)-boron enolate of α-chloro-propionyl-oxazolidin-2-one **18** with crotonaldehyde to afford *syn*-aldol **19** in 83% yield that was α-dechlorinated *via* treatment with zinc and ammonium chloride in methanol to afford *syn*-aldol **20** in 74% yield,[50] which was then cleaved *via* treatment with sodium methoxide in 71% yield. Subsequent cyclopropanation of aldol-ester **21** afforded cyclopropyl-aldol **22** in >95% de and 95% yield, thus confirming the dominant stereodirecting effect of the β-hydroxyl functionality of aldols **3a-h** in controlling the diastereoselectivity of these type of cyclopropanation reactions (Scheme 6).

To complete our new three-step synthesis of chiral cyclopropane-carboxaldehydes it was then necessary to develop conditions that would facilitate retro-aldol cleavage of β-cyclopropyl-*syn*-aldols **4a-h** to afford (*S*)-**1** and their corresponding cyclopropane-carboxaldehydes **5a-h**.[51] Screening a range of conditions revealed that the success or failure of these retro-aldol reactions was highly dependent on the temperature at which the cleavage reaction was performed. For example, deprotonation of *syn*-aldol **4a** with LHMDS in toluene at −20 °C for 4 hours resulted in recovery of large quantities of unreacted *syn*-aldol **4a** with <10% of any retro-aldol cleavage products. Alternatively, carrying out the retro-aldol cleavage reaction at 20 °C resulted in complete consumption of *syn*-aldol **4a** to afford its parent 5,5-dimethyl-oxazolidin-2-one **16**, with <10% of the desired cyclopropane-carboxaldehyde **5a** being formed. Nevertheless, it was subsequently found that treatment of cyclopropane aldol **4a** with LHMDS in the non-coordinating solvent toluene at an optimal temperature range of between 0–10 °C resulted in retro-aldol reaction to afford the desired cyclopropane-carboxaldehyde **5a** in >95% de and an acceptable 75% isolated yield. These conditions were then employed to cleave all of the cyclopropyl-*syn*-aldols **4b-e** and **4h**, to give a range of cyclopropane-carboxaldehydes (*S*,*S*)-**5b-e** and (1*S*,2*R*)-**5h** in >95% de and 55–73% isolated yields after purification by chromatography.[52]

Close examination of the ^{1}H NMR spectra of the crude reaction products of these retro-aldol reactions revealed that equimolar amounts (55–75% yield) of the cyclopropane-carboxaldehydes **5a-e** and **5h** and *N*-propionyl-oxazolidin-2-one (*S*)-**1** had been formed in each case, as well as varying amounts of the parent 5,5-dimethyl-oxazolidin-2-one **16** (15–30%) (Table 3). Indeed, it was apparent that the yields of cyclopropane-carboxaldehyde **5a-e** and **5h** obtained were inversely proportional to the amount of 5,5-dimethyl-oxazolidin-2-one **16** formed, with any decomposition of enolate **15** being accompanied by a proportional loss in yield of the corresponding cyclopropane-carboxaldehyde **5a-e**/**5h**. Unfortunately, despite repeated efforts, we were unable to isolate/identify any other products formed in these retro-aldol reactions that might explain the loss in yield of



Scheme 5 Asymmetric synthesis of (*Z*)-*syn*-β-vinyl-aldol **3h**.

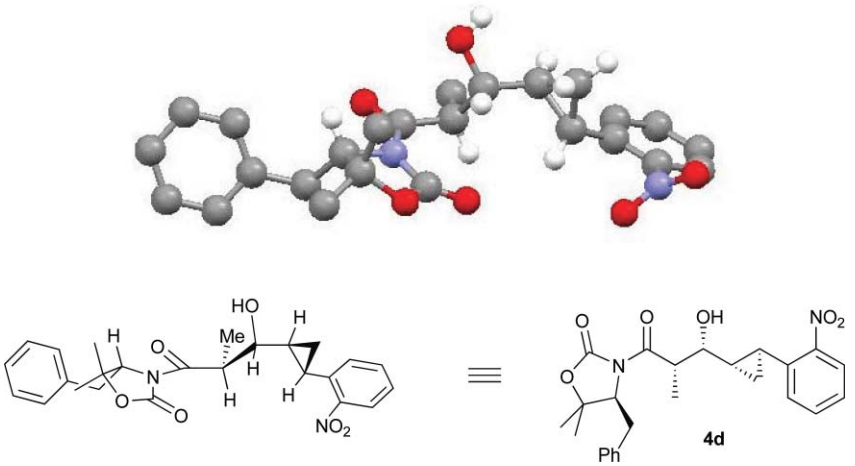
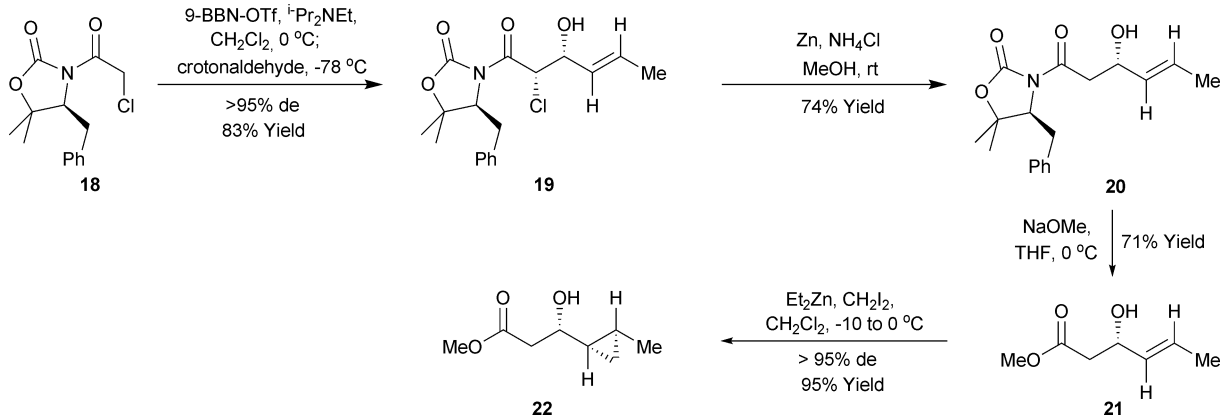


Fig. 1 X-Ray crystal structure of *o*-nitrophenyl-α-methyl-β-cyclopropyl *syn*-aldol **4d** with selected hydrogen atoms omitted for clarity.



Scheme 6 Highly diastereoselective cyclopropanation reaction of *syn*-aldol **21**.

cyclopropane-carboxaldehydes **5a-e/5h**. However, examination of the ^{1}H NMR spectra of the crude reaction products also revealed that no epimerisation of the α-stereocentres of the cyclopropane-carboxaldehydes **5a-e/5h** had occurred in these retro-aldol reactions. This included *cis*-cyclopropane-carboxaldehyde (1*S*,2*R*)-**5h** that was potentially susceptible to epimerisation to its more thermodynamically stable *trans*-(*R*,*R*)-diastereoisomer under basic conditions.[53] Therefore, since simultaneous scrambling of their β-stereocentres was unlikely to have occurred, it was concluded that all of the cyclopropane-carboxaldehydes **5a-e** and **5h** had been formed in >95% ee. The absolute configurations and high enantiomeric excesses of cyclopropane-carboxaldehydes (*S*,*S*)-**5a** and (*S*,*S*)-**5b** were subsequently confirmed by comparison of their specific rotations with those previously reported for their corresponding (*R*,*R*)-**5a** and (*S*,*S*)-**5b** enantiomers (see Table 3).[54,55]

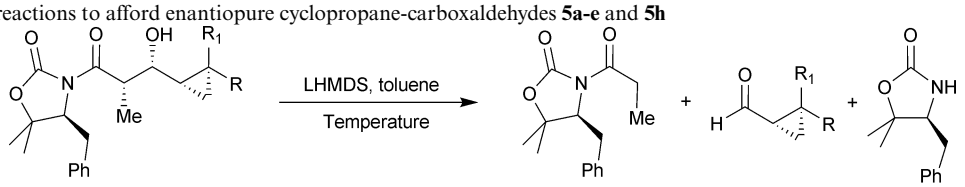
Attempts to prepare cyclopropane-carboxaldehydes **5f** and **5g** using these standard retro-aldol cleavage conditions proved unsuccessful because their inherent volatility meant that they were lost during removal of solvent *in vacuo* as part of the reaction work-up. To solve this isolation problem, an alternative protocol was devised in which a solution of one equivalent of LHMDS in toluene-d_8 was added to a solution of cyclopropyl-aldols **4f** and **4g** in toluene-d_8 at 10 °C. Each reaction was then quenched with 5 drops of ammonium chloride solution, dried over 3 Å molecular sieves, filtered, and the crude reaction mixtures distilled under atmospheric pressure to afford pure cyclopropane-carboxaldehydes (*S*,*S*)-**5f** and (*S*)-**5g** as solutions in toluene-d_8 (Scheme 7). The 51% and 61% yields of the respective cyclopropane-carboxaldehydes (*S*,*S*)-**5f** (>95% de) and (*S*)-**5g** were then calculated by addition of a known amount of 2,5-dimethylfuran[57] as an internal standard to each toluene-d_8 distillate, which enabled their concentration to be accurately determined by comparison of the relative intensities of their respective integrals in their ^{1}H NMR spectra.

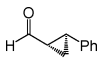
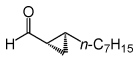
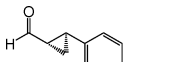
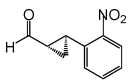
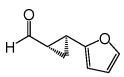
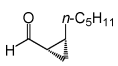
The enantiomeric excess of dimethyl cyclopropane-carboxaldehyde (*S*)-**5g** was determined using (*S*,*S*)-*N*,*N*′-dimethyl-1,2-diphenylethane-1,2-diamine **23** as a chiral derivatisation agent for imidazolidine formation (Scheme 8).[58] Examination of the crude ^{1}H-NMR spectrum of this derivatisation reaction revealed a single set of resonances corresponding to the formation of a single imidazolidine diastereoisomer **24**, and as a consequence the enantiomeric excess of cyclopropane-carboxaldehyde (*S*)-**5g** was assigned as >95% ee.[59]

Asymmetric synthesis of cascarillic acid

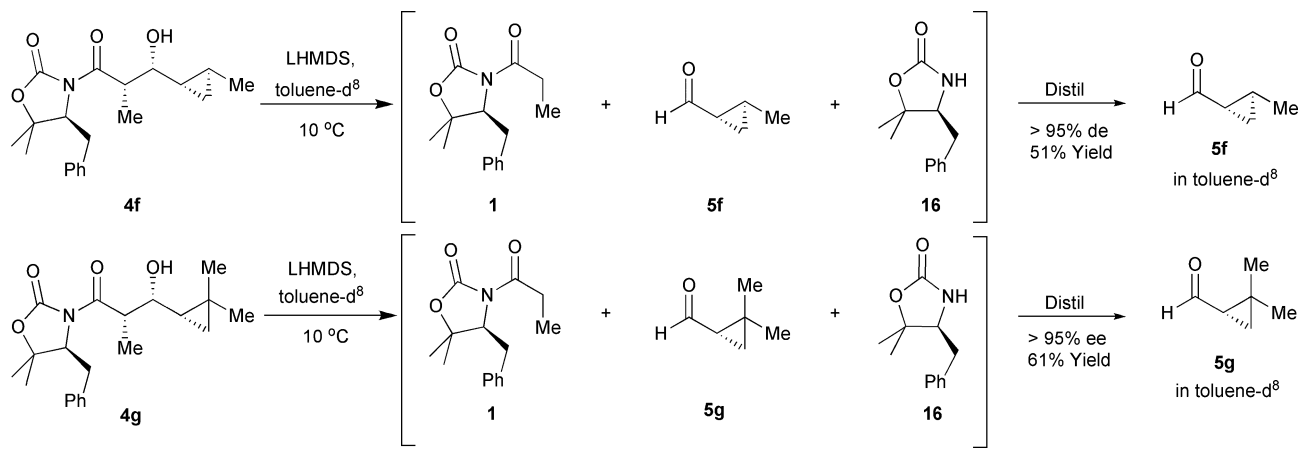
Cascarillic acid (1*S*,2*R*)-**25** is a cyclopropane containing natural product that is a major component of cascarilla essential oil that

Table 3 Retro-aldol reactions to afford enantiopure cyclopropane-carboxaldehydes **5a-e** and **5h**



Entry	Cyclopropyl-aldols **4a-e** and **4h**	Cyclopropane–carboxaldehydes **5a-e** and **5h**	Temp. (°C)	de (%)[a]	Yield (%)	$[\alpha]_D^{25}$
1	**4a**	 **5a**	0	95	75	+392 ($Lit_{(R,R)}$ = −324)[54]
2	**4b**	 **5b**	0	95	73	+45 ($Lit_{(S,S)}$ = +41)[55]
3	**4c**	 **5c**	5	95	63	+228
4	**4d**	 **5d**	10	95	55	+110
5	**4e**	 **5e**	0	95	71	+320
6	**4h**	 **5h**	0	95	61	−10[56]

[a] Determined by examination of the crude 300 MHz ^{1}H-NMR spectra.



Scheme 7 Retro-aldol protocol for the formation of volatile cyclopropane-carboxaldehydes **5f** and **5g**.

has been used for many years in the treatment of colds and bronchitis.[60] It contains a *trans*-cyclopropane ring in its fatty acid side-chain, whose configuration has been shown to be (3*S*,4*R*) *via* total synthesis from *meso-cis*-1,2-dihydroxymethylcyclopropane in eleven steps.[61] It was proposed that our 'temporary stereocentre' methodology might prove useful for the efficient preparation of cascarillic acid (1*S*,2*R*)-**25** in fewer steps, using a synthetic strategy whereby cyclopropane-carboxaldehyde (*R*,*R*)-**5i** would be transformed into the natural product using an oxidative one-carbon homologation reaction (Fig. 2).[62]

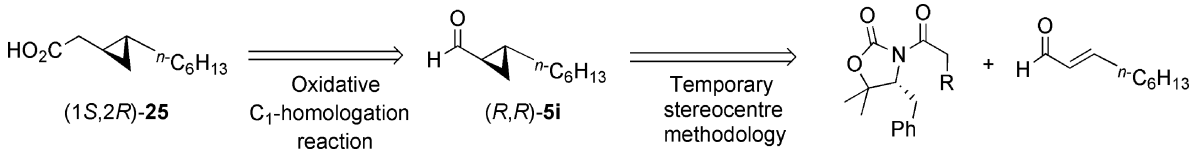
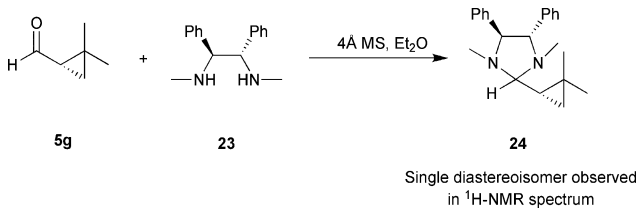
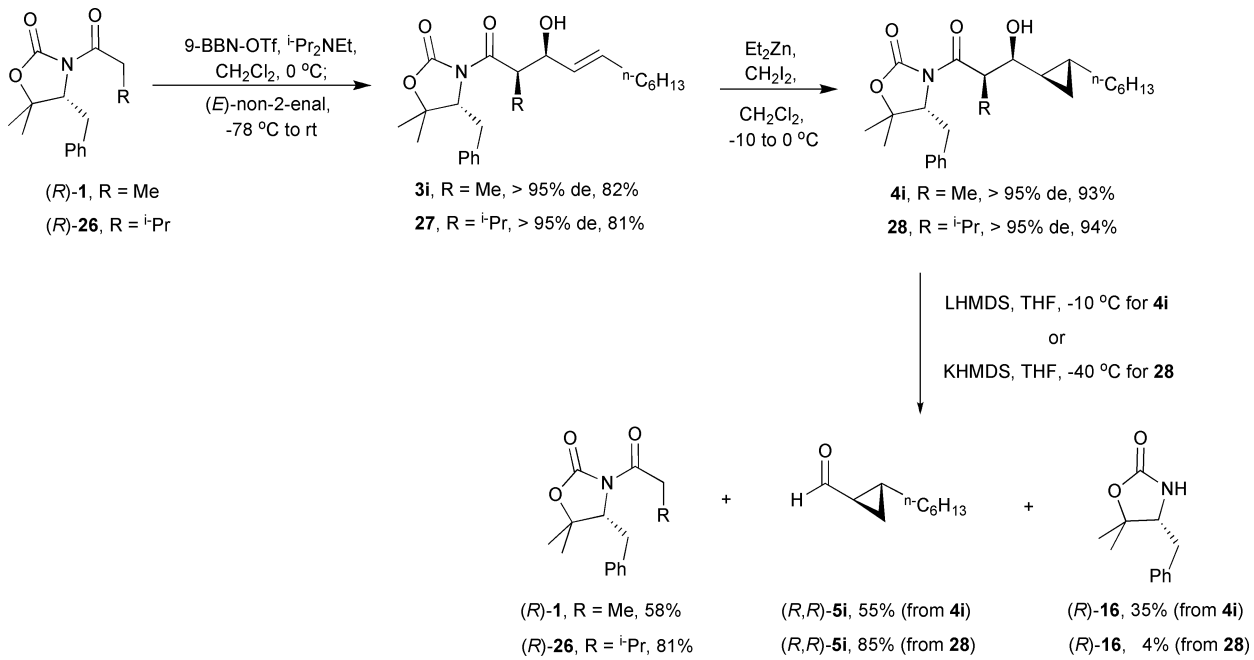


Fig. 2 Retrosynthetic analysis of cascarillic acid (1*S*,2*R*)-**25**.

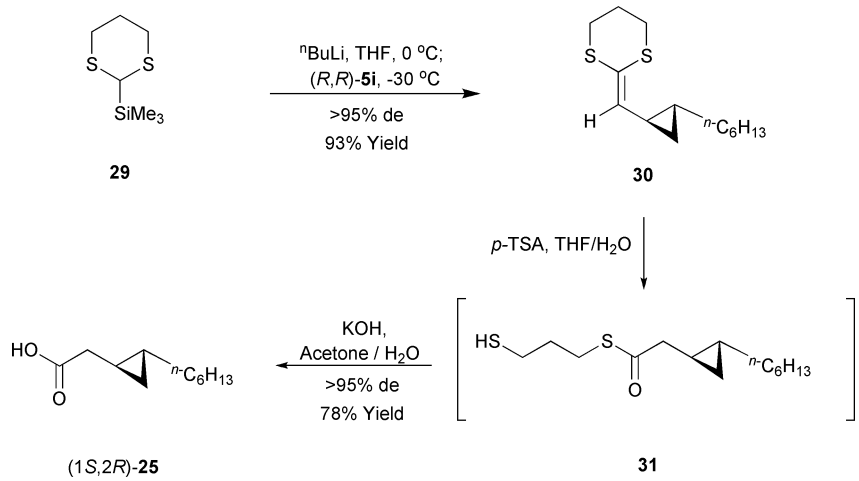


Scheme 8 Determination of the enantiomeric excess of cyclopropane–carboxaldehyde **5g**.

Therefore, *N*-propionyloxazolidin-2-one auxiliary (*R*)-**1** was reacted with (*E*)-non-2-enal using our standard boron enolate *syn*-aldol conditions to afford β-vinyl-*syn*-aldol **3i** in >95% de and 82% isolated yield, followed by treatment with diethylzinc and diiodomethane in CH_2Cl_2 at −10 °C to give cyclopropyl-aldol **4i** in >95% de and 93% isolated yield. Cyclopropyl-aldol **4i** was then treated with LHMDS in toluene at 0 °C to afford the key cyclopropane-carboxaldehyde (*R*,*R*)-**5i** in a disappointing 55% yield after chromatographic purification (Scheme 9). Analysis of the ^{1}H NMR spectra of the crude reaction product of this retro-aldol reaction revealed that oxazolidin-2-one (*R*)-**16** had also been formed in 35% yield that we had shown was always accompanied by a proportional loss in yield of its respective cyclopropane-carboxaldehyde (*vide supra*). Consequently, it was decided to redesign the structure of the chiral auxiliary used for synthesis, with the aim of obtaining a better yield of cyclopropane-carboxaldehyde (*R*,*R*)-**5i** in the retro-aldol cleavage step. The stability of lithium enolates of *N*-acyl-oxazolidin-2-ones were known to be highly dependent on the temperature at which they are generated, with elevated temperatures (>0 °C) resulting in rapid rates of decomposition to afford their parent oxazolidin-2-one **16**.[38a,63] Therefore, we proposed that retro-aldol cleavage of the lithium alkoxide of α-isopropyl-cyclopropyl-aldol **28** might proceed at a faster rate than for the lithium alkoxide of α-methyl-cyclopropyl-aldol **4i**, because its more sterically demanding α-isopropyl substituent would result in increased relief of steric strain that should result in its retro-aldol reaction proceeding at lower temperature. This would result in the enolate of *N*-isovaleroyl-5,5-dimethyl-oxazolidin-2-one **26** being generated at a lower temperature, resulting in less decomposition and a better yield of cyclopropane-carboxaldehyde (*R*,*R*)-**5i** being obtained. Therefore, the boron enolate of *N*-isovaleroyl-oxazolidin-2-one (*R*)-**26** was reacted with (*E*)-non-2-enal under our standard *syn*-aldol conditions to afford α-isopropyl-cyclopropyl-aldol **27** in >95% de and 81% yield, followed by cyclopropanation under our standard conditions to afford α-isopropyl-aldol **28** in >95% de and 94% yield. Deprotonation of α-isopropyl-cyclopropyl-aldol **28** with a range of different bases (NaHMDS or KHMDS), at different temperatures (−78 to 0 °C), revealed that optimum retro-aldol conditions were achieved when α-isopropyl-cyclopropyl-aldol **28** was treated with 1.1 equivalents of KHMDS in THF at −40 °C. These conditions resulted in formation of cyclopropane-carboxaldehyde (*R*,*R*)-**5i** in a much improved 85% yield, with <5% of the parent oxazolidin-2-one (*R*)-**16** being formed from



Scheme 9 Three-step asymmetric synthesis of cyclopropane-carboxaldehyde **5i**.



Scheme 10 Asymmetric synthesis of cascarillic acid (1*S*,2*R*)-**25**.

the competing enolate decomposition pathway (Scheme 9).[64] This compares with treatment of the corresponding α-methyl-cyclopropyl-aldol **4i** with KHMDS in THF at −40 °C which resulted in <5% retro-aldol cleavage occurring, thus demonstrating that the rate of retro-aldol cleavage of this class of *syn*-aldol is highly dependent on the steric demand of its α-substituent.

With the desired cyclopropane-carboxaldehyde (*R*,*R*)-**5i** in hand, we then carried out a two-step oxidative one-carbon homologation protocol to afford cascarillic acid (1*S*,2*R*)-**25**.[60] Therefore, nucleophilic addition of the lithium anion of (1,3-dithian-2-yl)trimethylsilane **29** to cyclopropane-carboxaldehyde (*R*,*R*)-**5i** resulted in formation of ketene-1,3-dithioacetal (*R*,*R*)-**30** in >95% de and 93% yield. Attempts to directly hydrolyse the ketene-1,3-dithioacetal functionality of (*R*,*R*)-**30** under acidic hydrolysis conditions resulted in formation of a stable thioester **31**. However, sequential exposure of ketene-1,3-dithioacetal (*R*,*R*)-**30** to acidic (*p*-TsOH in THF/H_2O) and basic (KOH in acetone/H_2O) hydrolytic conditions resulted in formation of cascarillic acid **25** in >95% de and 78% yield (Scheme 10). The magnitude and negative sign obtained for the specific rotation of our synthetic sample of cascarillic acid **25** ($[\alpha]_D^{25} = -11$, *c* 0.41, $CHCl_3$) compared well with the previously reported value for the (1*S*,2*R*)-enantiomer of the natural product ($[\alpha]_D^{25} = -10.5$, *c* 0.55, $CHCl_3$).[60a]

Conclusion

In conclusion, a novel three-step aldol/cyclopropanation/retro-aldol reaction sequence has been developed for the direct asymmetric synthesis of enantiopure cyclopropane-carboxaldehydes under non-oxidative/non-reductive conditions that we have used for the efficient asymmetric synthesis of the cyclopropane containing natural product cascarillic acid. This methodology demonstrates the potential of employing a chiral auxiliary to reversibly generate temporary stereocentres that can act as stereodirecting groups to control the facial selectivity of substrate-directable reactions.[65] We anticipate that this new strategy will prove applicable to combinations of other types of chiral auxiliary and substrate-directable reactions,[66] thus enabling its potential for asymmetric synthesis to be realized in other reaction scenarios.

Experimental

All reactions were carried out under nitrogen or argon using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen. THF and toluene were distilled from sodium/benzophenone ketyl, whilst CH_2Cl_2 was distilled from CaH_2 under nitrogen. All other reagents were used as supplied without further purification. Flash chromatography was performed on silica gel (Kieselgel 60). Thin layer chromatography was performed on Merck aluminium sheets coated with 0.2 mm silica gel 60 F254. Plates were visualised either by UV light (254 nm), iodine, ammonium molybdate (7% solution in ethanol) or potassium permanganate (1% in 2% aqueous acetic acid, containing 7% potassium carbonate). Infrared spectra were recorded as thin films or KBr discs using a Perkin-Elmer PARAGON 1000 FT-IR spectrometer, with selected peaks reported in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer. Chemical shifts are reported in parts per million (ppm) and referenced to the residual solvent peak, with coupling constants (*J*) measured in Hertz (Hz). Low resolution mass spectra (*m*/*z*) were recorded on either a Finnigan MAT 8340 instrument or a Finnigan MAT 900 XLT instrument. Major peaks are listed with intensities quoted as percentages of the base peak. Accurate mass measurements were recorded on a Finnigan MAT 900 XLT instrument. Optical rotations were recorded on an Optical Activity Ltd AA-10 automatic polarimeter in spectroscopic grade solvents (Aldrich) with concentrations (*c*) given in g per 100 mL, solvent and temperature as recorded. Melting points were recorded on a Büchi 535 melting point apparatus and are uncorrected. Single crystal X-ray diffraction data were collected on a NoniusKappa CCD machine. Structural determination and refinement were achieved using the SHELZ suite of programmes; drawings were produced using ORTEX. Crystal data for cyclopropyl-aldol **4d**: $C_{25}H_{28}N_2O_6$, M = 452.49, orthorhombic, a = 7.6700(1), b = 14.8370(3), c = 20.5190(3) Å, V = 2335.06(7) Å^3, T = 150(2) K, space group $P2_12_12_1$, Z = 4, μ(Mo-Kα) = 0.092 mm^{-1}, 43530 measured reflections, 5310 unique (Rint = 0.1280) which were used in these calculations. GOF on F^2 = 1.028, R_1 = 0.0382, wR_2 = 0.0792, [$I > 2\sigma(I)$], R_1 = 0.0568, wR_2 = 0.0862 (for all data). CCDC = 257652.

General procedure A for the synthesis of *N*-acyl-oxazolidin-2-ones

n-BuLi (1.01 equivalents, 2.5 M solution in hexane) was added to a solution of the parent oxazolidin-2-one (1 equivalent) in dry THF at −78 °C under nitrogen, and stirred for 30 minutes. The appropriate acid chloride (1.1 equivalents) was then added dropwise to the stirred solution over a period of 5 minutes and the reaction mixture stirred for a further 2 hours, during which time the reaction was allowed to warm to 0 °C. The reaction was quenched *via* addition of aqueous saturated ammonium chloride solution (5 mL), extracted with ethyl acetate (10 mL) and CH_2Cl_2 (3 × 20 mL), dried ($MgSO_4$), and solvent removed under reduced pressure to give a crude product that was purified by chromatography or crystallisation.

General procedure B for the synthesis of *syn*-aldols

9-BBN-OTf (1.1 equivalents, 0.5 M solution in hexane) was added dropwise to a stirred solution of an *N*-acyl-oxazolidin-2-one (1 equivalent) in dry CH_2Cl_2 at 0 °C under nitrogen. After 30 minutes, diisopropylethylamine (1.2 equivalents) was added dropwise and the resulting solution stirred for a further 30 minutes at 0 °C. The solution was then cooled to −78 °C and the appropriate aldehyde (1.1 equivalents) added dropwise, before allowing the reaction mixture to warm to room temperature overnight. The reaction was quenched by addition of Na_2PO_4/NaH_2PO_4 buffer solution (pH 7, 10 mL), then stirred for 10 minutes before addition of a 2:1 methanol-hydrogen peroxide solution (30%, 10 mL), followed by stirring for a further 2 hours. The reaction mixture was then extracted with CH_2Cl_2 (3 × 20 mL), washed with saturated sodium hydrogen carbonate solution (10 mL), brine (10 mL), dried ($MgSO_4$), and the solvent removed under reduced pressure to afford a crude product that was purified by chromatography or recrystallisation.

General procedure C for the asymmetric synthesis of chiral cyclopropyl-aldols

Diethyl zinc (5 equivalents, 1.0 M solution in hexane) was added to a stirred solution of *syn*-aldol (1 equivalent) in dry CH_2Cl_2 at −10 °C, followed by addition of diiodomethane (5 equivalents) in one portion under nitrogen in the absence of light. The solution was then warmed to 0 °C over a period of 2 hours before being quenched with saturated sodium sulfite solution (5 mL) and stirred for 10 minutes. Hydrochloric acid (1.0 M solution in water) was then added to dissolve the resultant white precipitate and the crude product extracted with CH_2Cl_2 (3 × 10 mL), washed with brine (10 mL), dried ($MgSO_4$), and solvent removed under reduced pressure to afford a crude product that was purified by chromatography or recrystallisation.

General procedure D for the synthesis of non-volatile cyclopropane-carboxaldehydes

LHMDS (1.1 equivalents, 1.0 M solution in THF) was added to a stirred solution of a cyclopropyl-aldol (1 equivalent) in dry toluene (10 mL) under nitrogen, at a temperature between 0 °C and 10 °C, and the reaction mixture stirred at this temperature for 2 hours. The reaction mixture was then quenched *via* dropwise addition of saturated aqueous ammonium chloride solution (5 mL), followed by addition of saturated aqueous sodium hydrogencarbonate solution (10 mL) to dissolve the resulting white precipitate. The reaction mixture was then extracted with CH_2Cl_2 (3 × 10 mL), washed with brine (10 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure to give a crude product that was purified by chromatography.

(*S*)-4-Benzyl-3-((*E*)-(2*S*,3*R*)-3-hydroxy-2-methyl-5-phenyl-pent-4-enoyl)-5,5-dimethyl-oxazolidin-2-one 3a

9-BBN-OTf (1.7 mmol) was added to a solution of oxazolidin-2-one **1** (400 mg, 1.53 mmol) in CH_2Cl_2 (20 mL) followed by addition of diisopropylethylamine (237 mg, 1.83 mmol) and (*E*)-cinnamaldehyde **2a** (221 mg, 1.68 mmol) according to general protocol **B** to afford a crude product that was purified by chromatography to afford the title compound **3a** (481 mg, 1.23 mmol) as a white solid in 80% yield; M.p. 148–150 °C (Et_2O); $[\alpha]_D^{25}$ = +4.0 (*c* 1.07, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.13 (10H, m, Ar*H*), 6.59 (1H, dd, *J* = 16.0, 1.5 Hz, CH=C*H*Ph), 6.12 (1H, dd, *J* = 16.0, 6.0 Hz, C*H*=CHPh), 4.54 (1H, m, C*H*OH), 4.47 (1H, dd, *J* = 9.0, 5.0 Hz, C*H*N), 3.94 (1H, qd, *J* = 7.0, 4.0 Hz, COC*H*), 3.00 (1H, dd, *J* = 14.0, 5.0 Hz, CH_AH_BPh), 2.84 (1H, dd, *J* = 14.0, 9.0 Hz, CH_ACH_BPh), 2.74 (1H, broad s, O*H*), 1.32 (3H, s, C(CH_3)), 1.30 (3H, s, C(CH_3)), 1.13 (3H, d, *J* = 7.0 Hz, CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.7, 152.9, 138.1, 135.1, 129.3, 129.2, 129.1, 128.7, 127.7, 127.3, 126.7, 126.3, 82.7, 73.0, 63.8, 43.7, 35.3, 28.3, 22.5, 12.3; IR (KBr, cm^{-1}): 3517 (broad OH), 1778 (C=O_{ox}), 1698 (C=O); HRMS (ES+): *m*/*z* calculated for $C_{24}H_{27}NO_4$: $[M + NH_4]^+$ requires 411.2278; found 411.2273.

(*S*)-4-Benzyl-3-[(2*S*,3*R*)-3-hydroxy-2-methyl-3-((1*S*,2*S*)-2-phenyl-cyclopropyl)-propionyl]-5,5-dimethyl-oxazolidin-2-one 4a

Diethylzinc (1.9 mmol) and diiodomethane (510 mg, 1.9 mmol) were added to *syn*-aldol **3a** (150 mg, 0.38 mmol) in CH_2Cl_2 (5 mL) according to general protocol **C** to afford a crude product that was purified by chromatography to afford the title compound **4a** (146 mg, 0.36 mmol) as a yellow oil in 95% yield; $[\alpha]_D^{25}$ = +58 (*c* 2.30, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28–6.93 (10H, m, Ar*H*), 4.35 (1H, dd, *J* = 9.0, 5.0 Hz, C*H*N), 3.97 (1H, qd, *J* = 7.0, 4.5 Hz, COC*H*), 3.37 (1H, m, C*H*OH), 3.00 (1H, dd, *J* = 14.5, 5.0 Hz, CH_AH_BPh), 2.78 (1H, dd, *J* = 14.5, 9.0 Hz, CH_ACH_BPh), 2.54 (1H, broad s, O*H*), 1.84 (1H, app. dt, *J* = 9.0, 5.0 Hz, cyclopropyl-C*H*Ar), 1.25 (3H, s, C(CH_3)), 1.23 (1H, obs. m, cyclopropyl-C*H*), 1.18 (3H, d, *J* = 7.0 Hz, CHCH_3), 1.04 (3H, s, C(CH_3)), 1.00 (1H, app. dt, *J* = 8.5, 5.5 Hz, cyclopropyl-CH_AH_B), 0.89 (1H, app. dt, *J* = 8.5, 5.5 Hz, cyclopropyl-CH_AH_B); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.8, 152.8, 142.7, 137.2, 129.5, 129.1, 128.8, 127.3, 126.2, 126.1, 82.6, 75.9, 63.8, 43.8, 35.7, 28.5, 27.0, 22.6, 21.7, 14.4, 12.9; IR (film, cm^{-1}): 3447 (broad OH), 1772 (C=O_{ox}), 1685 (C=O); HRMS (ES+): *m*/*z* calculated for $C_{25}H_{29}NO_4$: $[M + NH_4]^+$ requires 425.2435; found 425.2439.

(*S*,*S*)-2-Phenylcyclopropane-carboxaldehyde 5a[54]

LHMDS (0.33 mmol) was added to a solution of cyclopropyl-aldol **4a** (125 mg, 0.31 mmol) in toluene (5 mL) at 0 °C according to general protocol **D** to afford a crude reaction product that was purified by chromatography (to remove oxazolidin-2-ones **1** and **16**) to afford the title compound **5a** (34 mg, 0.23 mmol) as a yellow

oil in 75% yield; $[\alpha]_D^{25} = +392$ (*c* 1.44, $CHCl_3$) ([Lit][54] $[\alpha]_D^{25} = -324$ for (*R*,*R*)-**5a**, *c* 0.33, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.33 (1H, d, *J* = 5.0 Hz, C*H*O), 7.34–7.09 (5H, m, Ar*H*), 2.63 (1H, ddd, *J* = 11.0, 7.0, 5.0 Hz, C*H*Ar), 2.18 (1H, m, OHCC*H*), 1.74 (1H, app. dt, *J* = 10.0, 5.0 Hz, cyclopropyl-CH_AH_B), 1.54 (1H, ddd, *J* = 10.0, 7.0, 5.0 Hz, cyclopropyl-CH_AH_B); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.2, 139.4, 129.0, 127.3, 126.7, 34.2, 27.0, 16.9; IR (film, cm^{-1}): 1699 (C=O); HRMS (ES+): *m*/*z* calculated for $C_{10}H_{10}O$: $[M + NH_4]^+$ requires 164.1070; found 164.1069.

(*S*,*S*)-2-Methylcyclopropane-carboxaldehyde 5f[67]

LHMDS (0.33 mmol) was added to a stirred solution of cyclopropyl-aldol **4f** (100 mg, 0.29 mmol) in dry toluene-d_8 (5 mL) at 10 °C under nitrogen over a period of 2 hours. The reaction mixture was then worked up *via* dropwise addition of saturated aqueous ammonium chloride solution (5 drops), and the mixture allowed to warm to room temperature over a period of thirty minutes. The reaction mixture was dried (3 Å molecular sieves), filtered, and the filtrate washed with toluene-d_8 (1 mL), before the resultant mixture was distilled at atmospheric pressure (120 °C) to give the title compound **5f** as a solution in toluene-d_8 in 51% yield. $[\alpha]_D^{25} = +54$ (*c* 0.71, toluene-d_8); ^{1}H NMR (300 MHz, toluene-d_8): δ = 8.67 (1H, d, *J* = 5.0 Hz, C*H*O), 1.11 (1H, app. sextet, *J* = 4.5 Hz, OHCC*H*), 0.98–0.87 (2H, m, cyclopropyl-C*H*) and cyclopropyl-CH_AH_B), 0.80 (1H, m, cyclopropyl-CH_AH_B), 0.67 (3H, d, *J* = 6.0 Hz, CH_3); ^{13}C NMR (75 MHz, toluene-d_8): δ = 197.3, 29.9, 15.8, 14.8, 14.0. The yield of **5f** was calculated by adding a known amount of 2,5-dimethylfuran (0.2 mmol) to the solution of **5f** in toluene-d_8, which allowed ^{1}H NMR spectroscopic analysis to be used to determine the concentration of **5f** *via* comparison of the relative intensity of its integrals with the integrals of 2,5-dimethylfuran.[57]

(*R*)-4-Benzyl-3-((*E*)-(2*R*,3*S*)-3-hydroxy-2-isopropyl-undec-4-enoyl)-5,5-dimethyl-oxazolidin-2-one 27

9-BBN-OTf (3.30 mmol) was added to a solution of oxazolidin-2-one **26** (891 mg, 3.08 mmol) in CH_2Cl_2 (50 mL) followed by addition of diisopropylethylamine (477 mg, 3.70 mmol) and (*E*)-non-2-enal **2d** (474 mg, 3.39 mmol) according to general protocol **B** to afford a crude product that was purified by chromatography to afford the title compound **27** (1.07 g, 2.47 mmol) as a yellow oil in 81% yield; $[\alpha]_D^{25} = +22$ (*c* 0.85, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27–7.11 (5H, m, Ar*H*), 5.71–5.54 (2H, m, C*H*=C*H*), 4.53 (1H, dd, *J* = 10.0, 4.0 Hz, C*H*N), 4.36 (1H, app. t, *J* = 7.0 Hz, C*H*OH), 4.09 (1H, dd, *J* = 9.0, 7.0 Hz, OHCC*H*), 3.09 (1H, dd, *J* = 14.5, 4.0 Hz, CH_AH_BPh), 2.81 (1H, dd, *J* = 14.5, 10.0 Hz, CH$_A$*H*$_B$Ph), 2.04–1.88 (4H, obs. m, O*H*, CH=CHCH_2 and $(CH_3)_2$C*H*), 1.35–1.12 (8H, m, $(CH_2)_4$), 1.24 (6H, app. s, C(CH_3)$_2$), 0.90 (3H, d, *J* = 7.0 Hz, CHCH_3), 0.82 (3H, obs. d, *J* = 7.0 Hz, CHCH_3), 0.80 (3H, obs. t, *J* = 7.0 Hz, alkyl-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.7, 153.9, 137.4, 135.8, 129.5, 129.1, 128.9, 127.2, 82.4, 73.8, 64.3, 54.1, 35.9, 32.7, 32.1, 29.5, 29.3, 28.7, 28.6, 23.0, 22.6, 21.0, 20.4, 14.5; IR (film, cm^{-1}): 3501 (broad OH), 1778 (C=O_{ox}), 1693 (C=O); HRMS (ES+): *m*/*z* calculated for $C_{26}H_{39}NO_4$: $[M + NH_4]^+$ requires 447.3217; found 447.3213.

(*R*)-4-Benzyl-3-{(*R*)-2-[(*S*)-((1*R*,2*R*)-2-hexyl-cyclopropyl)-hydroxy-methyl]-3-methyl-butyryl}-5,5-dimethyl-oxazolidin-2-one 28

Diethylzinc (7.2 mmol) and diiodomethane (1.92 g, 7.2 mmol) were added to *syn*-aldol **27** (620 mg, 1.44 mmol) in CH_2Cl_2 (10 mL) according to general protocol **C** to afford a crude reaction product that was purified by chromatography to afford the title compound **28** (602 mg, 1.36 mmol) as a yellow oil in 94% yield; $[\alpha]_D^{25} = -21$ (*c* 0.62, MeO*H*); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.18 (5H, m, Ph), 4.56 (1H, dd, *J* = 10.0, 3.5 Hz, C*H*N), 4.22 (1H, dd, *J* = 8.5, 6.0 Hz, COC*H*), 3.39 (1H, dd, *J* = 8.5, 6.0 Hz, C*H*OH), 3.23 (1H, dd, *J* = 14.5, 3.5 Hz, CH_AH_BPh), 2.86 (1H, dd, *J* = 14.5, 10.0 Hz, CH$_A$CH_BPh), 2.31 (1H, m, C*H*(CH$_3$)$_2$), 1.85 (1H, broad s, O*H*), 1.44–1.20 (10H m, $(CH_2)_5$), 1.34 (3H, s, C(CH_3)), 1.33 (3H, s, C(CH_3)), 1.02 (3H, d, *J* = 7.0 Hz, CHCH_3), 1.00 (1H, obs. m, cyclopropyl-C*H*), 0.93 (3H, d, *J* = 7.0 Hz, CHCH_3), 0.88 (3H, t, *J* = 7.0 Hz, alkyl-CH_3), 0.76 (1H, m, cyclopropyl-C*H*), 0.43 (1H, app. dt, *J* = 8.5, 5.0 Hz, cyclopropyl-CH_AH_B), 0.28 (1H, app. dt, *J* = 8.5 Hz, 5.0 Hz, cyclopropyl-CH$_A$*H*$_B$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.1, 153.7, 137.5, 129.4, 129.1, 127.2, 82.2, 75.5, 64.4, 54.5, 35.8, 34.2, 32.3, 29.6, 29.5, 28.8, 28.6, 23.1, 22.8, 22.2, 21.4, 21.1, 18.8, 14.5, 9.6; IR (film, cm^{-1}): 3516 (broad O-H), 1778 (C=O_{ox}), 1693 (C=O); HRMS (ES+): *m*/*z* calculated for $C_{27}H_{41}NO_4$: $[M + NH_4]^+$ requires 461.3374; found 461.3370.

(((*R*,*R*)-2-Hexylcyclopropyl)methylene)-1,3-dithiane 30

n-BuLi (1.1 mmol) was added to a stirred solution of (1,3-dithian-2-yl)trimethylsilane **29** (224 mg, 1.17 mmol) in dry THF (5 mL) at 0 °C under nitrogen and the reaction mixture stirred for 1 hour. The reaction mixture was then cooled to −30 °C and a solution of cyclopropane-carboxaldehyde (*R*,*R*)-**5i** (140 mg, 0.9 mmol) in dry THF (2 mL) added, before allowing the reaction mixture to warm to room temperature over 2 hours. The reaction was then quenched with aqueous saturated ammonium chloride solution (2 mL), extracted with ether (3 × 10 mL), sodium hydrogen carbonate solution (10 mL), dried ($MgSO_4$), and the solvent removed under reduced pressure to give a crude product that was purified by chromatography to afford the title compound **30** as a colorless oil (215 mg, 0.84 mmol) in 93% yield; $[\alpha]_D^{25} = -20$ (*c* 0.30, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.42 (1H, d, *J* = 10.0 Hz, C*H*=C), 2.91 (4H, m, S(CH_2)$_2$, 2.22–2.13 (2H, m, SCH$_2$CH_2), 1.58 (1H, m, cyclopropyl-C*H*), 1.41–1.20 (10H, m, $(CH_2)_5$), 0.88 (3H, t, *J* = 7.0 Hz, CH_3), 0.79 (1H, m, cyclopropyl-C*H*), 0.65–0.56 (2H, m, cyclopropyl-CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.4, 121.6, 34.1, 32.3, 31.3, 30.5, 29.7, 29.5, 26.0, 23.1, 22.2, 20.3, 15.2, 14.5; IR (film, cm^{-1}): 1678 (C=C), (C-S); HRMS (ES+): *m*/*z* calculated for $C_{14}H_{24}S_2$: $[M + H]^+$ requires 257.1392; found 257.1393.

2-((1*S*,2*R*)-2-Hexylcyclopropyl)acetic acid (cascarillic acid) 25[60]

para-TsOH (5 mg) was added to a solution of dithiane **30** (150 mg, 0.60 mmol) in THF/water (8 : 1) (5 mL) and the reaction mixture heated at 75 °C for six hours, before cooling and removal of the solvent under reduced pressure. The resulting residue was then dissolved in acetone/water (8 : 1) (5 mL), potassium hydroxide (150 mg) added, and the reaction mixture heated at 85 °C for two hours, before cooling to room temperature. The reaction mixture was cautiously acidified *via* dropwise addition

of concentrated hydrochloric acid and the resulting solution was extracted ethyl acetate (3 × 5 mL), dried ($MgSO_4$) and solvent removed under reduced pressure to give a crude product that was purified by chromatography to afford the title compound **25** as a colorless oil (86 mg, 47 mmol) in 78% yield; $[\alpha]_D^{25} = -11$ (*c* 0.41, $CHCl_3$), ([Lit][60a] $[\alpha]_D^{25} = -10.5$, *c* 0.55, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.26 (2H, app. d, *J* = 7.0 Hz, CH_2CO_2H), 1.41–1.18 (10H, m, $(CH_2)_5$), 0.88 (3H, t, *J* = 7.0 Hz, CH_3), 0.77 (1H, m, cyclopropyl-C*H*), 0.56 (1H, m, cyclopropyl-C*H*), 0.33 (2H, m, cyclopropyl-CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.6, 37.5, 32.8, 30.9, 28.3, 28.1, 21.6, 17.7, 13.1, 13.0, 10.6; IR (film, cm^{-1}): 1711 (C=O); HRMS (EI): *m*/*z* calculated for $C_{11}H_{20}O_2$: $[M]^+$ requires 184.1458; found 184.1458.

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