SuperQuat 5,5-dimethyl-4-*iso*-propyloxazolidin-2-one as a mimic of Evans 4-*tert*-butyloxazolidin-2-one†

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Received 11th April 2006, Accepted 8th June 2006
First published as an Advance Article on the web 3rd July 2006
DOI: 10.1039/b605244d

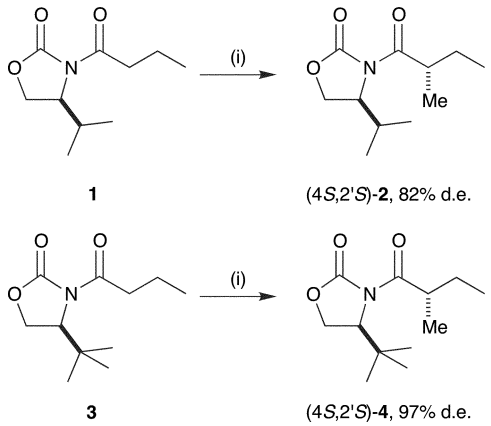
The incorporation of a *gem*-dimethyl group at the 5-position of a chiral oxazolidinone biases the conformation of the adjacent C(4)-stereodirecting group such that the *gem*-dimethyl-4-*iso*-propyl combination mimics a C(4)-*tert*-butyl group, providing higher levels of stereocontrol than a simple 4-*iso*-propyloxazolidinone. The generality of this principle is demonstrated with applications in stereoselective enolate alkylations, kinetic resolutions, Diels–Alder cycloadditions and Pd-catalysed asymmetric acetalisation reactions.

Introduction

The oxazolidin-2-one family of chiral auxiliaries is one of the most versatile and widely used in synthetic organic chemistry.[1] First developed by Evans *et al.* for use in diastereoselective enolate reactions,[2] they are easily synthesised from readily available α-amino acids and can be introduced into the substrate in a variety of ways.[3] The high diastereoselectivity offered by oxazolidinones, together with their low molecular weight and their recyclable nature has made these compounds an attractive choice of auxiliary in synthesis. Oxazolidin-2-ones exhibit good stereocontrol for a number of diastereoselective reactions, such as aldol additions,[4] halogenations,[5] and alkylations,[6] and have been used extensively for the synthesis of natural product fragments. Within this area, it is well recognised that derivatives of *tert*-leucine derived 4-*tert*-butyloxazolidin-2-one usually afford superior diastereoselectivities to other amino acid derived 4-substituted oxazolidinones (4-methyl, 4-*iso*-propyl or 4-benzyl) due to conformational control of the C(4)-stereodirecting group. For the quaternary *tert*-butyl stereodirecting group, this ensures that one of the methyl groups of the *tert*-butyl group must be oriented toward the reaction centre, leading to high stereocontrol, while with a straight chain or *mono*-branched directing fragment conformational control directs a hydrogen atom, rather than the alkyl fragment, toward the reaction centre resulting in lower levels of stereocontrol. For example, methylation of the lithium enolate of (*S*)-*N*-butyryl-4-*iso*-propyloxazolidin-2-one **1** affords (4*S*,2′*S*)-**2** in 82% d.e., while methylation of (*S*)-*N*-butyryl-4-*tert*-butyloxazolidin-2-one **3** affords (4*S*,2′*S*)-**4** in 97% d.e. (Scheme 1).[2] However, whilst 4-*tert*-butyloxazolidin-2-one clearly affords improved performance in stereoselective synthesis, its widespread use is limited by its cost, since its parent non-proteinogenic α-amino acid (*S*)-*tert*-leucine is prohibitively expensive.[7]

Although oxazolidinones have been widely used for asymmetric synthesis, nucleophilic cleavage of *N*-acyloxazolidin-2-ones has proven to be problematic in some cases. For simple *N*-acyloxazolidinones, the desired exocyclic cleavage pathway usually predominates, however if the *N*-acyl fragment is sterically demanding, then an alternative undesired endocyclic cleavage pathway becomes more favourable. In order to address this problem, the SuperQuat 5,5-dimethyloxazolidin-2-one family of chiral auxiliaries was developed within our laboratory,[8,9] and this idea was adopted and modified by the groups of Seebach[10] and Gibson.[11] The incorporation of *gem*-dimethyl groups at C(5) within the oxazolidin-2-one structure prevents the undesired endocyclic cleavage, since the *gem*-dimethyl substituents protect the endocyclic carbonyl group from nucleophilic attack by sterically blocking nucleophilic approach along the required Bürgi–Dunitz angle. For example, hydrolysis of *N*-pivaloyl SuperQuat derivatives **5** and **6** gave exclusive exocyclic cleavage, furnishing only the corresponding oxazolidinones **7** and **8**, while under identical conditions *N*-pivaloyloxazolidinones **9** and **10** gave a mixture of products derived from exo- and endocyclic cleavage pathways (Fig. 1).[12]

Although the primary function in introducing a *gem*-dimethyl group within *N*-acyl-5,5-dimethyloxazolidin-2-ones was to suppress the undesired endocyclic cleavage pathway, it was proposed[13] that the presence of this functionality may also serve a secondary



Scheme 1 *Reagents and conditions*: (i) LDA, THF, −78 °C then MeI, THF, −30 °C.

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† Electronic supplementary information (ESI) available: synthetic procedures. See DOI: 10.1039/b605244d

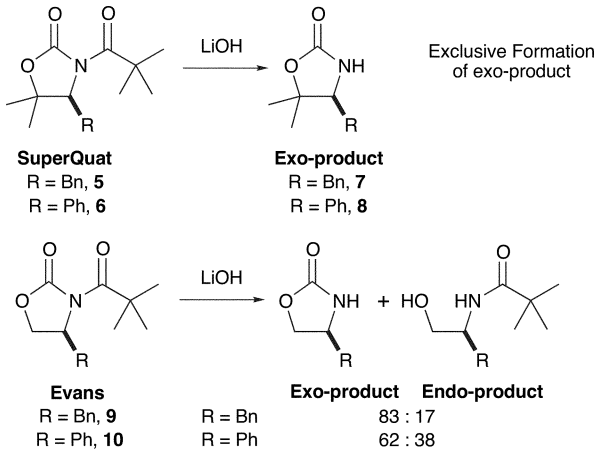


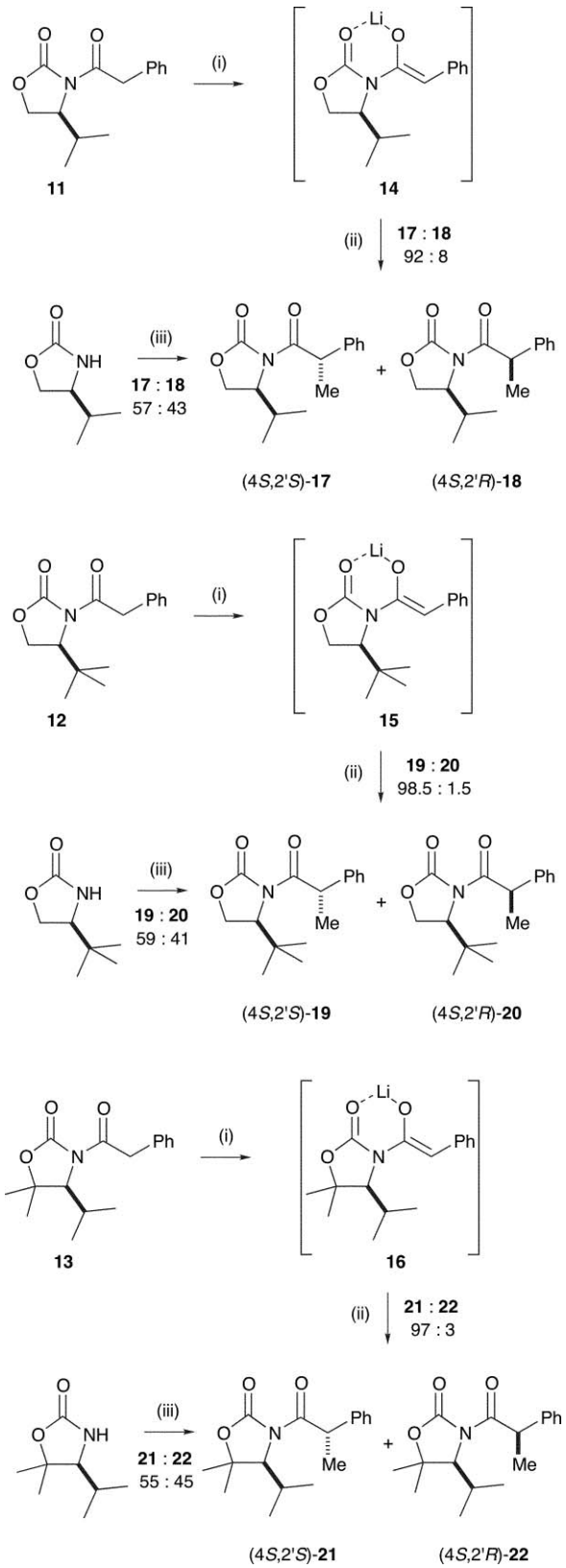
Fig. 1 Product distributions from hydrolysis of *N*-pivaloyl SuperQuat derivatives **5** and **6** and *N*-pivaloyloxazolidinones **9** and **10**.

function to improve the diastereocontrol of asymmetric transformations. It was hypothesised that the C(5)-*gem*-dimethyl group might bias the conformation of the adjacent C(4)-stereodirecting group such that the combination of the *gem*-dimethyl and 4-*iso*-propyl groups within the oxazolidinone would mimic the steric demands of a C(4)-*tert*-butyl group within an oxazolidinone. In this manner, readily available *N*-acyl-5,5-dimethyl-4-*iso*-propyloxazolidin-2-ones would react with enhanced diastereoselectivity in comparison to the corresponding *N*-acyl-4-*iso*-propyloxazolidinone derivatives, and with comparable stereoselectivity to *N*-acyl-4-*tert*-butyloxazolidinone derivatives.[14] We now detail herein our full investigations within this area, part of which has been communicated previously.[13]

Results and discussion

Diastereoselective enolate alkylations: conformational analysis of enolates derived from *N*-acyl-5,5-dimethyl-4-*iso*-propyloxazolidin-2-ones and 4-*iso*-propyloxazolidin-2-ones

In order to confirm the above hypothesis, initial investigations were directed toward probing the diastereoselectivity observed for alkylation of the enolates derived from *N*-acyl-5,5-dimethyl-4-*iso*-propyl-, *N*-acyl-4-*iso*-propyl- and *N*-acyl-4-*tert*-butyloxazolidin-2-ones. It was predicted that the diastereoselectivity arising from alkylation of the enolate derived from a 5,5-dimethyl-4-*iso*-propyloxazolidin-2-one derivative would be comparable to that derived from the corresponding 4-*tert*-butyloxazolidin-2-one, and significantly higher than that observed for alkylation of the 4-*iso*-propyloxazolidin-2-one derivative. Under identical conditions, enolate methylations of the lithium enolates **14**–**16** derived from the corresponding *N*-acyloxazolidin-2-ones **11**–**13** were carried out, *via* deprotonation with LiHMDS in THF at −78 °C and subsequent addition of methyl iodide. As predicted, analysis of the product distributions arising from these studies revealed that the diastereoselectivity for methylation of 4-*iso*-propyl enolate **14** {(4*S*,2′*S*)-**17** : (4*S*,2′*R*)-**18**; 92 : 8; 84% d.e.} was significantly lower than that observed for both the (*S*)-4-*tert*-butyl enolate **15** {(4*S*,2′*S*)-**19** : (4*S*,2′*R*)-**20**; 98.5 : 1.5; 97% d.e.} and the (*S*)-5,5-dimethyl-4-*iso*-propyl enolate **16** {(4*S*,2′*S*)-**21** : (4*S*,2′*R*)-**22**; 97 : 3; 94% d.e.} (Scheme 2).[15] Furthermore,



Scheme 2 *Reagents and conditions*: (i) LiHMDS, THF, −78 to 0 °C; (ii) MeI (1.1 eq.); (iii) *n*-BuLi (1.1 eq.) then (*RS*)-2-phenylpropanoyl chloride (1.3 eq.), THF, −78 °C to rt.

direct comparison studies were also facilitated through carrying out enolate methylation reactions on a 50 : 50 mixture of (*S*)-4-*iso*-propyl enolate **14** and (*S*)-5,5-dimethyl-4-*iso*-propyl enolate **16**, and a 50 : 50 mixture of (*S*)-4-*tert*-butyl enolate **15** and (*S*)-5,5-dimethyl-4-*iso*-propyl enolate **16**, in the same reaction vessel. These reactions gave comparable stereoselectivities to the separate enolate studies, affording (4*S*,2′*S*)-4-*tert*-butyl **19** (97% d.e.), (4*S*,2′*S*)-5,5-dimethyl-4-*iso*-propyl enolate **21** (94% d.e.) and (4*S*,2′*S*)-4-*iso*-propyl **17** (84% d.e). The configuration at C(2′) within each of the major diastereoisomers **17**, **19** and **21** was assigned by analogy to the established sense of stereochemical induction of oxazolidin-2-one enolates in alkylation reactions. Unambiguous determination of the reaction diastereoselectivity was also available in each case through the preparation of authentic samples of the major and minor diastereoisomers *via* *N*-acylation of the lithium anions of each of the homochiral parent (*S*)-oxazolidin-2-ones (1 eq.) with (*RS*)-2-phenylpropanoyl chloride (1.3 eq.). These reactions proceeded to full conversion, although the ratio of diastereoisomers arising from this protocol was not 50 : 50 in each case, giving a 57 : 43 mixture of **17** : **18** (14% d.e.), a 55 : 45 mixture of **19** : **20** (10% d.e.) and a 59 : 41 mixture of **21** : **22** (18% d.e.), consistent with partial kinetic resolution occurring in this protocol.

The relative configuration within major diastereoisomer **21** was confirmed unambiguously *via* single crystal X-ray analysis, with the absolute (4*S*,2′*S*) configuration derived from the known (*S*)-configuration of the L-valine derived oxazolidin-2-one (Fig. 2).

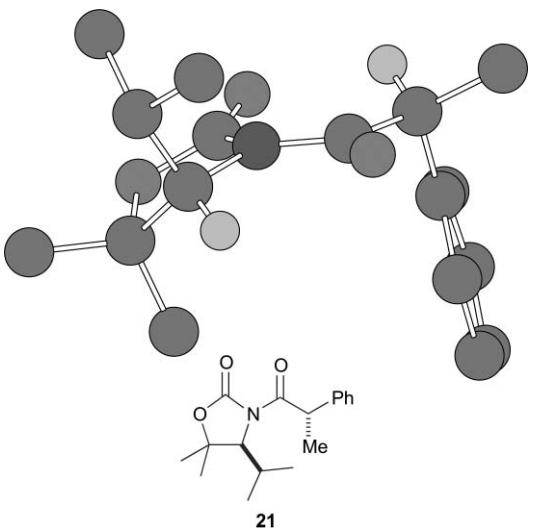


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Fig. 2 Chem3D representation of the X-ray crystal structure of **21** (some H atoms omitted for clarity).

Having demonstrated that methylation of 5,5-dimethyl-4-*iso*-propyl enolate **16** with methyl iodide occurred with higher stereoselectivity than methylation of the corresponding 4-*iso*-propyl enolate **14**, their conformation in solution was probed directly by ^{1}H 500 MHz nOe NMR spectroscopic analysis. Treatment of *N*-acyloxazolidin-2-ones **11** and **13** with LiHMDS (1 eq.) at −78 °C in d_8-THF, followed by warming the resulting solution to 0 °C generated the (*Z*)-enolates **14** and **16**.[16] In the ^{1}H NMR spectrum of enolates **14** and **16**, the resonances corresponding to the *iso*-propyl C*H*(Me)$_2$ protons each showed small vicinal coupling constants (*J* 3.2 Hz and *J* 2.3 Hz, respectively) between the *iso*-propyl C*H*(Me)$_2$ proton and C(4)H of the oxazolidin-2-one. This is consistent with both enolates **14** and **16** adopting conformations in which the C*H*(Me)$_2$ protons of their *iso*-propyl groups lie approximately *syn*- or *anti*-periplanar to the C_4–C_5 bond of the oxazolidin-2-one. Furthermore, it follows from this conformational analysis that both methyl groups of the oxazolidinone *iso*-propyl units must be either directed towards or away from the attached enolate fragment. Qualitative ^{1}H nOe NMR spectroscopic analysis for 4-*iso*-propyl enolate **14** in d_8-THF revealed a strong enhancement between the C(2′) vinylic proton of the enolate and the oxazolidin-2-one *iso*-propyl C*H*(Me)$_2$ proton. No nOe enhancement was observed to either of the *iso*-propyl CH(C*H*$_3$)$_2$ groups, while strong nOe enhancements were observed between the *pro*-(*S*) H_5 proton and both of *iso*-propyl CH(C*H*$_3$)$_2$ methyl groups. These nOe enhancements are entirely consistent with a preferred conformation of enolate **14** in which both the *iso*-propyl methyl groups are directed away from the attached enolate fragment (Fig. 3). In direct contrast, similar analysis of 5,5-dimethyloxazolidinone enolate **16** revealed a medium and small enhancement between the C(2′) vinylic proton of the enolate and each of the methyl groups of the *iso*-propyl CH(C*H*$_3$)$_2$ group; a strong nOe enhancement was observed between the C*H*(Me)$_2$ proton and one of the C(5)-*gem*-dimethyl groups. These spectroscopic data are consistent with the 5,5-dimethyl-4-*iso*-propyl enolate **16** adopting a major conformation in solution that has both methyl groups of the stereocontrolling *iso*-propyl group directed towards the enolate fragment (Fig. 3).

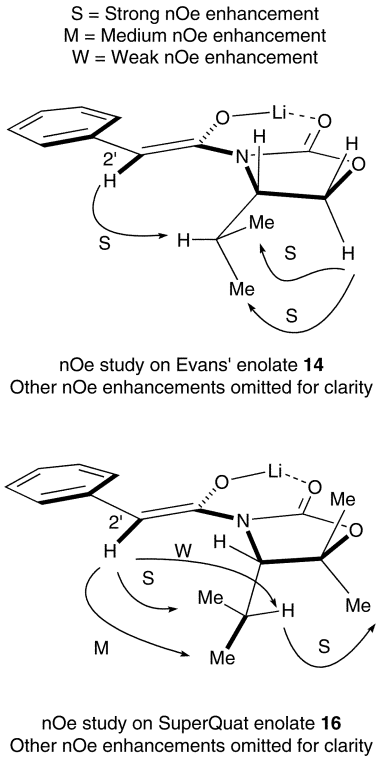


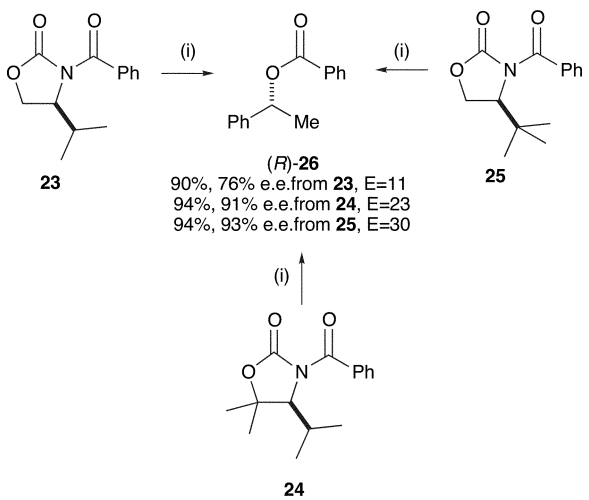
Fig. 3 Qualitative ^{1}H nOe NMR studies upon *N*-acyloxazolidin-2-one enolates **14** and **16**.

These NMR studies reveal that conformational control in the enolates of *N*-acyl-5,5-dimethyl-4-*iso*-propyloxazolidin-2-ones re-

sults in the stereodirecting effect of its C(4)-4-*iso*-propyl group exhibiting comparable levels of stereocontrol normally associated with enolates derived from *N*-acyl-4-*tert*-butyloxazolidin-2-ones. Further studies were therefore directed toward establishing the scope and limitation of the 4-*iso*-propyl-5,5-dimethyl combination as a *tert*-butyl mimic for a range of alternative asymmetric transformations.

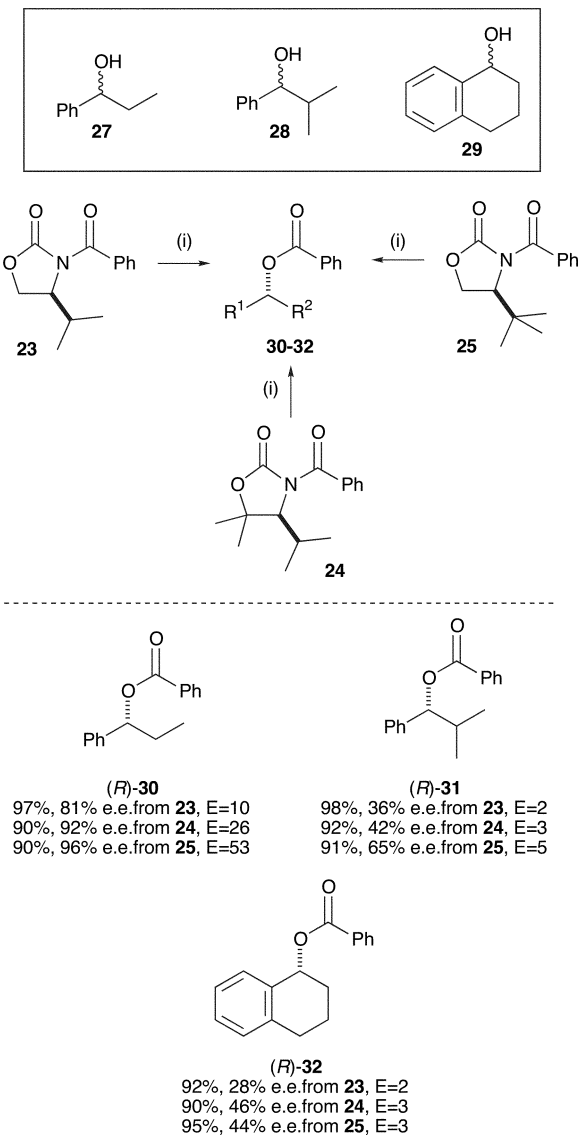
Kinetic resolution of alcohols with *N*-acyloxazolidinones

A variety of reagents have been introduced as asymmetric acyl transfer reagents, with the use of 2-acyl-3-phenyl-*l*-menthopyrazoles,[17] DMAP derivatives[18] and 1,3-thiazolidine-2-thiones[19] all having been reported for this purpose. Evans *et al.* first introduced (*S*)-*N*-benzoyl-4-*tert*-butyloxazolidin-2-one as a stoicheiometric asymmetric acyl transfer reagent, with a high correlation noted between the reaction stereoselectivity and the stereodirecting group of the chiral fragment.[20] In order to probe the level of stereoselectivity induced by *N*-benzoyl-5,5-dimethyl-4-*iso*-propyloxazolidin-2-one in this reaction, direct comparison of its reactivity with the corresponding 4-*iso*-propyl and 4-*tert*-butyl Evans derivatives were examined. In our hands, treatment of an excess of (*RS*)-1-phenyl ethanol (10 eq.) with MeMgBr (1 eq.) and subsequent addition of 1 eq. of the *N*-benzoyl derivative of 4-*iso*-propyloxazolidin-2-one **23**, 5,5-dimethyl-4-*iso*-propyloxazolidin-2-one **24**, or 4-*tert*-butyloxazolidin-2-one **25**, gave benzoate **26** in over 90% isolated yield (with respect to the oxazolidinone) in each case. Determination of the specific rotation of the ester product **26** and comparison with literature data confirmed that (*R*)-**26** had been formed as the major stereoisomer in each case. Accurate determination of the e.e. of **26** was achieved by chiral HPLC analysis in comparison with an authentic racemic standard, with *iso*-propyl Evans **23** affording ester **26** in 76% e.e., SuperQuat **24** affording ester **26** in 91% e.e. and *tert*-butyl Evans **25** giving ester **26** in 93% e.e., consistent with $E = 11$, 23 and 30, respectively (Scheme 3). In each case, the E values were calculated based on the assumption that the reaction proceeded to completion with respect to the oxazolidinone, *i.e.* to 10% conversion with respect to the alcohol; the measured e.e. of the isolated ester allowed the e.e. of the remaining alcohol to be back calculated and an E value extrapolated.[21]



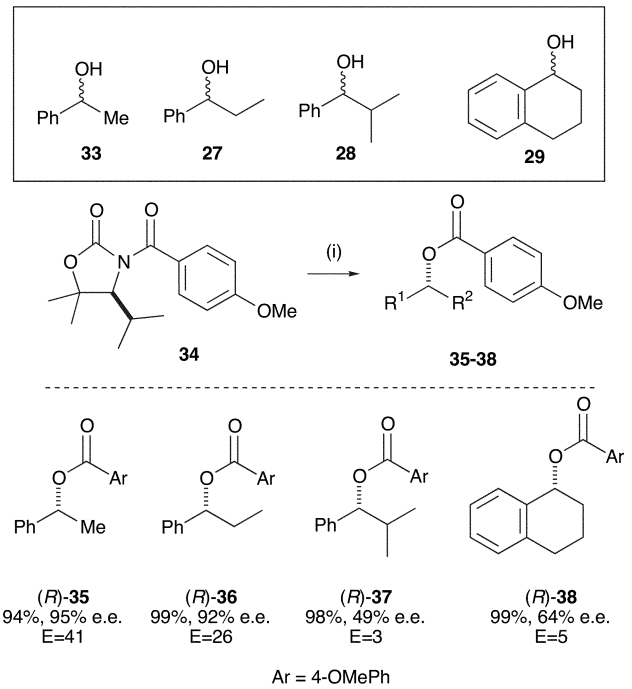
Scheme 3 *Reagents and conditions*: (i) (*RS*)-1-phenylethanol (10 eq.), MeMgBr (1 eq.), 0 °C, DCM.

These initial results strongly suggest that *N*-benzoyl SuperQuat **24** exhibits comparable levels of enantioselectivity to *N*-benzoyl *tert*-butyl Evans **25** for the kinetic resolution of racemic secondary alcohols, with subsequent studies directed towards probing the generality of this esterification reaction. Following the standard reaction protocol, (*RS*)-alcohols **27**–**29** were treated with MeMgBr prior to addition of *N*-benzoyloxazolidin-2-ones **23**–**25**, giving the corresponding benzoates **30**–**32** in good isolated yields in each case (>90%). Comparison of the e.e. values obtained for each benzoate product indicate that *N*-benzoyl SuperQuat oxazolidin-2-one **24** generally exerts comparable levels of enantiocontrol to the corresponding *tert*-butyloxazolidin-2-one derivative **25**, and significantly higher levels of selectivity compared to the *iso*-propyloxazolidin-2-one **23**. For example, treatment of (*RS*)-1-phenylpropanol **27** with *N*-benzoyl SuperQuat **24** gave **30** in 92% e.e. ($E = 26$), while under identical conditions *N*-benzoyl *tert*-butyloxazolidinone **25** gave **30** in 96% e.e. ($E = 53$) and *N*-benzoyl *iso*-propyloxazolidinone **23** gave **30** in 81% e.e. ($E = 10$) (Scheme 4).



Scheme 4 *Reagents and conditions*: (i) (*RS*)-alcohol **27**, **28** or **29** (10 eq.), MeMgBr (1 eq.), 0 °C, DCM.

The effect of incorporating electron donor substituents on the aryl ring of the benzoylating agent was next investigated, in the expectation that the rate of reaction would be retarded, delivering enhanced chiral recognition. Treatment of (*RS*)-alcohols **27**–**29** and **33** with MeMgBr and subsequently with *N*-4-methoxylbenzoyloxazolidinone **34** gave the corresponding 4-methoxybenzoates **35**–**38** in excellent yield (>94%) and with consistently higher enantioselectivity than the corresponding *N*-benzoyloxazolidinone **24** (Scheme 5).

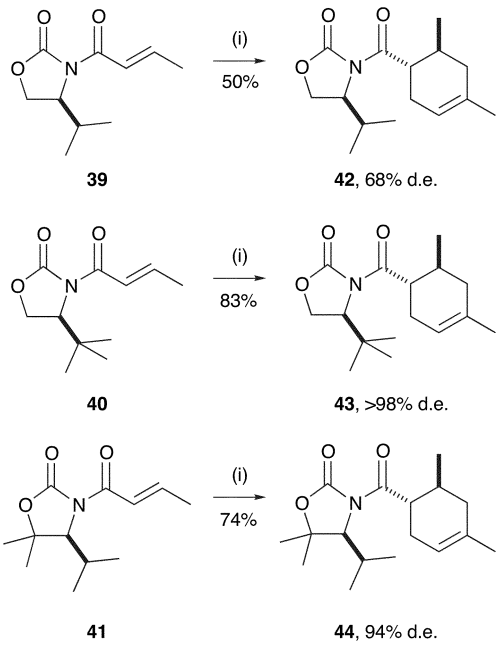


Scheme 5 *Reagents and conditions*: (i) (*RS*)-alcohol **27**, **28**, **29** or **33** (10 eq.), MeMgBr (1 eq.), 0 °C, DCM.

These results show that *N*-benzoyl derivatives of *iso*-propyl SuperQuat show comparable levels of enantioselectivity to the corresponding *tert*-butyl Evans derivatives in benzoyl transfer reactions. The ability of *N*-acyl derivatives of *iso*-propyl SuperQuat to act as *tert*-butyl Evans surrogates in Diels–Alder cycloaddition reactions was next investigated.

Diels–Alder reactions with *N*-acyloxazolidinones

The Diels–Alder reaction is one of the most powerful tools in organic synthesis for C–C bond forming reactions.[22] For this reaction, chiral oxazolidin-2-ones show high levels of stereocontrol, with a dramatic increase in the diastereoisomeric excess of the product observed with change in the stereodirecting group from an *iso*-propyl group (68% d.e.) to a *tert*-butyl group (>99% d.e.) for the reaction of *N*-crotonoyloxazolidin-2-ones with isoprene.[23] Attention was therefore focused on carrying out Diels–Alder cycloaddition reactions using *N*-acyl derivatives of a range of oxazolidin-2-ones to investigate the influence on diastereoselectivity caused by the incorporation of a *gem*-dimethyl group within the oxazolidin-2-one. Following the literature procedure,[23] *N*-crotonoyl-5,5-dimethyl-4-*iso*-propyloxazolidin-2-one **41**, *N*-crotonoyl-4-*iso*-propyloxazolidin-2-one **39** and *N*-crotonoyl-4-*tert*-butyloxazolidin-2-one **40** were treated with isoprene and Et_2AlCl (1.4 eq.) to give the cycloaddition products **42**–**44** as single diastereoisomers in moderate to good yield. In each case, the stereoselectivity of the reaction was unambiguously determined from the crude reaction products by comparison with authentic samples of both (4*S*,1′*S*,6′*S*)- and (4*S*,1′*R*,1′*R*)-diastereoisomers.[24] Examination of the stereoselectivities of these reactions revealed that the level of stereocontrol using *N*-crotonoyl-5,5-dimethyl-4-*iso*-propyloxazolidin-2-one **41** (94% d.e.) was considerably greater than that observed of the 4-*iso*-propyloxazolidin-2-one derivative **39** (68% d.e.), and comparable with that of the 4-*tert*-butyloxazolidin-2-one derivative **40** (>99% d.e.) (Scheme 6).



Scheme 6 *Reagents and conditions*: (i) isoprene, Et_2AlCl, DCM, −30 °C.

The relative configuration between C(1′) and C(6′) within the minor diastereoisomer-**45** arising from the Diels–Alder reaction of SuperQuat derivative **41** and isoprene was unambiguously determined by X-ray crystal structure analysis, with the absolute configuration of (4*S*,1′*R*,6′*R*)-**45** being derived from the known (*S*)-valine derived stereocentre of the oxazolidinone (Fig. 4).

To probe further the generality of this observation, *N*-propenoyl-5,5-dimethyl-4-*iso*-propyloxazolidin-2-one **48**, *N*-propenoyl-4-*iso*-propyloxazolidin-2-one **46** and *N*-propenoyl-4-*tert*-butyloxazolidin-2-one **47** were also treated with isoprene and Et_2AlCl, giving the desired products **49**–**51** in good yield. Again, the stereoselectivity of the reaction in each case was unambiguously assessed from the crude reaction products by comparison with authentic samples of the (4*S*,1′*S*) and (4*S*,1′*R*) diastereoisomers.[25] Comparison of the stereoselectivity of these reactions revealed that the stereocontrol using the 5,5-dimethyl-4-*iso*-propyloxazolidin-2-one derivative **48** (94% d.e.) was considerably greater than that observed for the 4-*iso*-propyloxazolidin-2-one derivative **46** (54% d.e.), and comparable to that of the 4-*tert*-butyloxazolidin-2-one derivative **47** (98% d.e.) (Scheme 7).

Further attention was directed towards the Diels–Alder reaction of *N*-crotonoyloxazolidin-2-ones **39**–**41** and

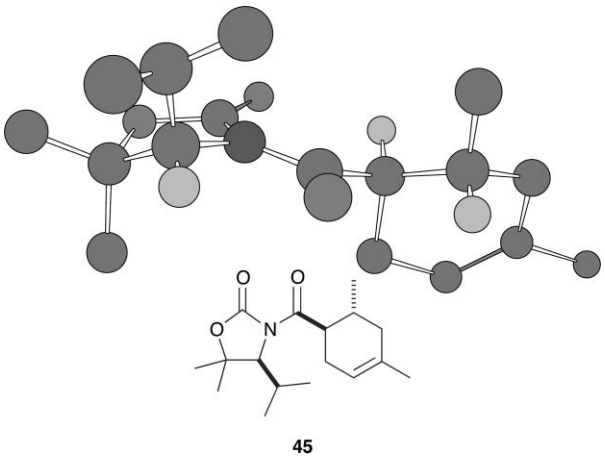
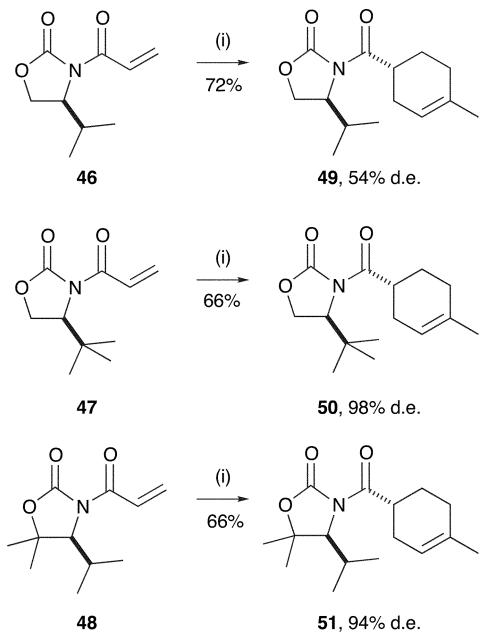
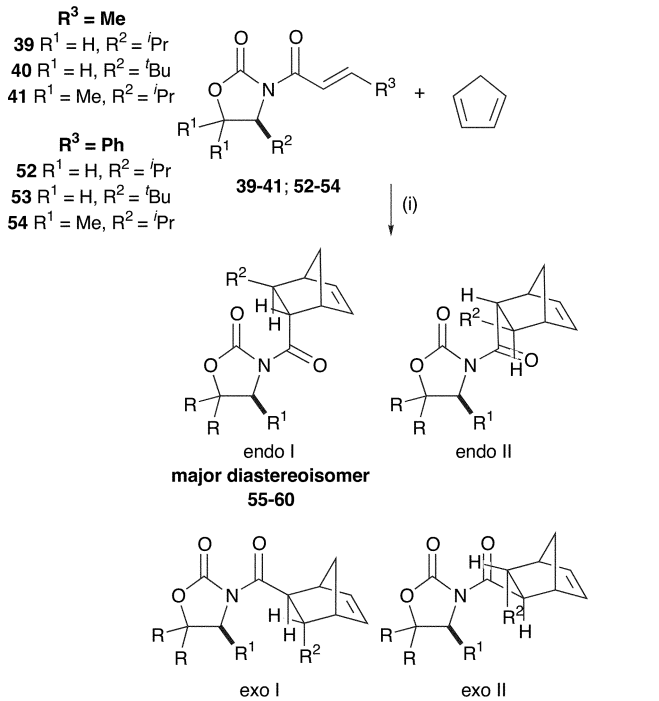


Fig. 4 Chem3D representation of the X-ray crystal structure of **45** (some H atoms omitted for clarity).



Scheme 7 *Reagents and conditions*: (i) isoprene, Et_2AlCl, DCM, −30 °C.

N-cinnamoyloxazolidin-2-ones **52**–**54** with cyclopentadiene. In these reactions, four diastereoisomeric products may be formed, arising from *endo*- and *exo*-addition of cyclopentadiene to the *Re* and *Si* faces of the dienophile. In each case, the stereoselectivity of the reaction was assessed by 500 MHz ^{1}H NMR spectroscopic analysis of the crude reaction products, with reference to authentic samples of the four possible diastereoisomers arising from these reactions, which were prepared following established literature protocols.[23,26,27] In both the crotonoyl and cinnamoyl series the *endo* : *exo* ratio and stereoselectivity using all oxazolidin-2-ones were excellent, although the stereocontrol using the 5,5-dimethyl-4-*iso*-propyloxazolidin-2-one derivatives **41** and **54** (99% and >99% d.e., respectively) is consistently greater than that observed for the 4-*iso*-propyloxazolidin-2-one derivatives **39** and **40** (93 and 97% d.e. respectively), and comparable to that of the 4-*tert*-butyloxazolidin-2-one derivative **50** and **53** (99% d.e. and >99% d.e., respectively) (Scheme 8).



R^2 = Me	∑ endo : ∑ exo	d.e. endo (%)		yield (%)
R = H, R^1 = ^{i}Pr	>100:1	93	**55**	72
R = H, R^1 = ^{t}Bu	>100:1	99	**56**	74
R = Me, R^1 = ^{i}Pr	>100:1	99	**57**	67

R^2 = Ph	∑ endo : ∑ exo	d.e. endo (%)		yield (%)
R = H, R^1 = ^{i}Pr	>100:1	97	**58**	67
R = H, R^1 = ^{t}Bu	>100:1	>99	**59**	69
R = Me, R^1 = ^{i}Pr	>100:1	>99	**60**	80

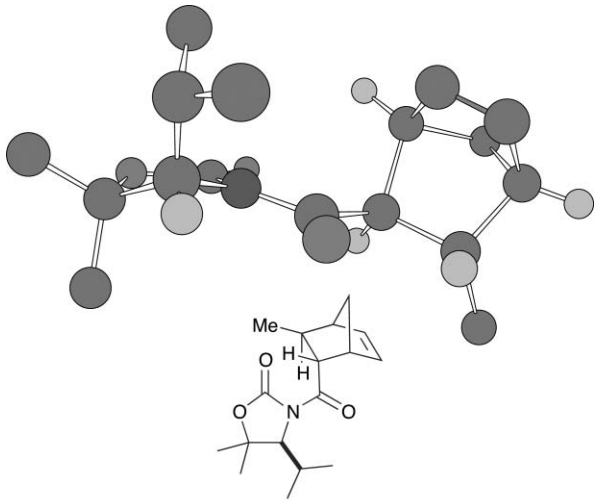
Scheme 8 *Reagents and conditions*: (i) *N*-crotonoyl or *N*-cinnamoyl-oxazolidinones **39**–**41** and **52**–**54**, cyclopentadiene, Et_2AlCl, DCM, −100 °C.

Unambiguous assignment of the *endo* selectivity of the Diels–Alder reaction of 5,5-dimethyl-4-*iso*-propyloxazolidin-2-one derivative **57** with cyclopentadiene was achieved through single crystal X-ray analysis of the purified major diastereoisomeric cycloaddition product *endo*-**57**, with the absolute configuration being derived from the known L-valine derived stereocentre of the oxazolidin-2-one (Fig. 5).

With *N*-acyl derivatives of 5,5-dimethyl-4-*iso*-propyloxazolidin-2-one shown to act as *tert*-butyloxazolidin-2-one surrogates in enolate alkylations, kinetic resolutions and Diels–Alder cycloadditions, its stereodirecting capability in a Pd-catalysed asymmetric acetalisation protocol was investigated.

Pd-catalysed asymmetric acetalisation

The conversion of a carbonyl group to an acetal is a commonly-used strategy for the protection of carbonyl groups against nucleophilic attack and enolisation.[28] While acetals are usually formed by treatment of carbonyl groups with alcohols in the presence of an acid catalyst, the acetalisation of alkenes utilizing palladium catalysis can be carried out efficiently,[29] and this protocol has been expanded into an industrial process.[30] Within this area, Hosokawa *et al.* have reported that diastereoselective acetalisation can be achieved *via* the incorporation of a chiral oxazolidin-2-one as a

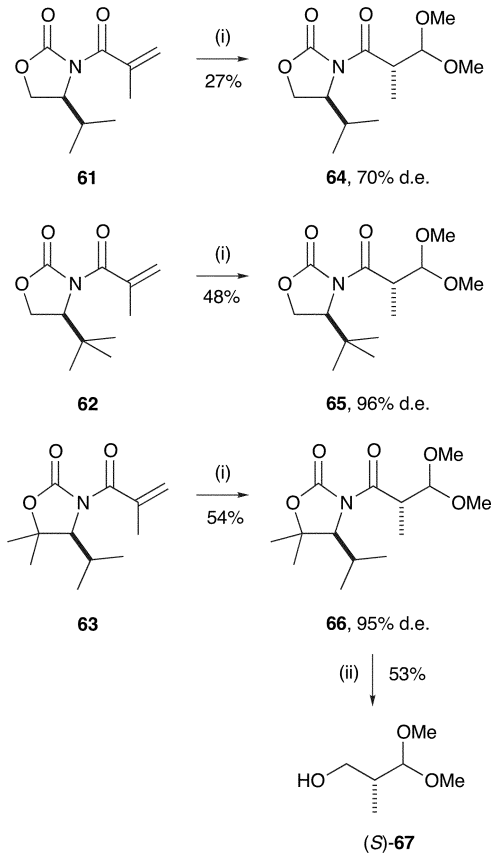


endo-**57**

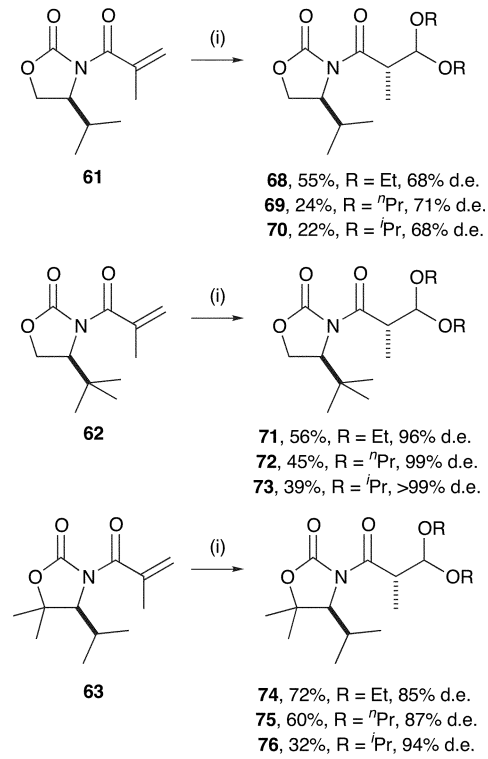
Fig. 5 Chem3D representation of the X-ray crystal structures of *endo*-**57** (some H atoms omitted for clarity).

stereodirecting component adjacent to the alkene.[31] The diastereoselectivity of this acetalisation process is highly dependent on the nature of the stereodirecting fragment, with a dramatic increase in stereoselectivity noticed upon changing the stereodirecting fragment within an *N*-methyacryloyloxazolidin-2-one from an *iso*-propyl group to a *tert*-butyl group for acetalisation using MeOH. In our hands, treatment of *N*-methacryloyloxazolidin-2-ones **61**–**63** under the literature conditions using $PdCl_2$, CuCl and MeOH in DME proceeded to completion, furnishing the desired products in moderate to high yields after chromatographic purification. In each case, the stereoselectivity was unambiguously established by the preparation of authentic samples of the possible diastereoisomers of these reactions. Notably, the stereocontrol using the 5,5-dimethyl-4-*iso*-propyloxazolidin-2-one derivative **63** (95% d.e.) is greater than that observed for the 4-*iso*-propyloxazolidin-2-one derivative **61** (70% d.e.), and comparable to that of the 4-*tert*-butyloxazolidin-2-one derivative **62** (96% d.e.).[32] The absolute configuration of the C(2′) stereocentre within SuperQuat derivative **66** was determined by reductive cleavage of **66** with $LiAlH_4$, affording alcohol **67** in 53% yield. Comparison of the specific rotation of **67** $\{[\alpha]_D^{23}$ +25.7 (*c* 1.00 in $CHCl_3)\}$ with the literature value $\{[\alpha]_D^{25}$ +23.0 (*c* 0.92 in $CHCl_3)\}$[31] allowed assignment of the absolute configuration of the C(2′) stereocentre as (*S*), consistent with the reported absolute configuration of the acetal product by Hosokawa *et al.* (Scheme 9).

With high asymmetric induction in the acetalisation of **63** with MeOH established, the effect of changing the alcohol upon the stereoselectivity of these reactions was investigated, with the effectiveness of EtOH, *n*-PrOH and *i*-PrOH in this protocol attempted. In each case, a similar trend in stereoselectivity was noted, with the stereocontrol using the 5,5-dimethyl-4-*iso*-propyloxazolidin-2-one derivative **63** (85 to 94% d.e.) greater than that observed for the corresponding 4-*iso*-propyloxazolidin-2-one derivative **61** (68 to 71% d.e.), and comparable to that of the corresponding 4-*tert*-butyloxazolidin-2-one derivative **62** (96 to >99% d.e.) (Scheme 10). Although the stereoselectivity within each series was not markedly affected by a change of alcohol, a slow reaction rate and a resulting compromise in the yield of the acetal products was observed



Scheme 9 *Reagents and conditions*: (i) $PdCl_2$, CuCl, DME, MeOH, under O_2, rt; (ii) $LiAlH_4$, THF, 0 °C.



Scheme 10 *Reagents and conditions*: (i) $PdCl_2$, CuCl, DME, alcohol, under O_2, rt.

for the branched alcohol *i*-PrOH, The absolute configuration at C(2′) within all of the major diastereoisomeric products **68**–**76** was assigned as (*S*) by analogy to that unambiguously proven previously in the reaction with MeOH.

Conclusion

In conclusion, the incorporation of a *gem*-dimethyl group at the 5-position within chiral oxazolidin-2-ones biases the conformation of the vicinal C(4)-stereodirecting group such that the 5,5-dimethyl-4-*iso*-propyl group combination mimics a C(4)-*tert*-butyl group. This allows a 5,5-dimethyl-4-*iso*-propyloxazolidin-2-one to provide higher levels of stereocontrol than a simple 4-*iso*-propyloxazolidin-2-one, while simultaneously facilitating exclusive regioselective exocyclic auxiliary cleavage. The generality of this principle has been demonstrated with applications in stereoselective enolate alkylations, kinetic resolutions, Diels–Alder cycloadditions and Pd-catalysed asymmetric acetalisation reactions. While 4-*tert*-butyloxazolidin-2-one derivatives undoubtedly afford excellent performance in stereoselective synthesis, the prohibitive cost of the parent auxiliary limits its widespread synthetic use, while 5,5-dimethyl-4-*iso*-propyloxazolidinone derivatives are readily available from valine.[8] Further applications of this strategy for the preparation of a range of chiral building blocks for natural product synthesis are currently ongoing within this laboratory.

Experimental

General experimental

All reactions involving organometallic or other moisture-sensitive reagents were performed under an atmosphere of dry nitrogen using standard vacuum line techniques. All glassware was flame-dried and allowed to cool under vacuum. In all cases, the reaction diastereoselectivity was assessed by peak integration in the ^{1}H NMR spectrum of the crude reaction mixture. THF and Et_2O were distilled from sodium benzophenone ketyl under an atmosphere of dry nitrogen. DCM was distilled from CaH_2 under dry nitrogen, all other solvents were used as supplied (analytical or HPLC grade) without prior purification. *n*-Butyllithium (BuLi) was used as a solution in hexanes and was titrated against diphenylacetic acid prior to use. DIBAL-H was used as supplied (Aldrich), as a 1.0 M solution in hexanes. All other reagents were used as supplied, without further purification. Unless otherwise stated, all aqueous solutions were saturated, and all organic layers were dried with $MgSO_4$. Column chromatography was performed on silica gel (Kieselgel 60) or basic alumina. T.l.c. was performed on Merck plates, aluminium sheets coated with silica gel 60 F_{254}. Plates were visualized either by UV light (254 nm), iodine, Dragendorff's reagent,[33] phosphomolybdic acid (10% in ethanol) or potassium permanganate (1% in 2% NaOH solution, containing 7% potassium carbonate). Nuclear magnetic resonance (NMR) spectra were recorded on Varian Gemini 200 (200 MHz), Bruker AM-200 (200 MHz), Bruker DPX-400 (400 MHz), or Bruker AMX-500 (500 MHz) spectrometers in the deuterated solvents stated. ^{1}H chemical shifts (δ_H) are reported in parts per million (ppm) and are referenced to the residual solvent peak. Coupling constants (*J*) are measured in Hertz and are calculated using a first order approximation. ^{13}C chemical shifts (δ_C) are quoted in ppm and are referenced using residual solvent signals. nOe spectra were obtained on the Bruker DRX-500 (500 MHz) spectrometer. Infrared spectra were recorded on a Perkin-Elmer 1750 IR Fourier transform spectrophotometer using either KBr disc (KBr) or as thin film (film). Selected peaks are reported in cm^{-1}. Low resolution mass spectra (*m*/*z*) were recorded on VG Masslab 20–250 or Micromass Platform 1 spectrometers and high-resolution mass spectra (HRMS) on a Micromass Autospec 500 OAT spectrometer. Techniques used were chemical ionisation (CI, NH_3), atmospheric pressure chemical ionisation (APCI) using partial purification by HPLC with methanol–acetonitrile–water (40 : 40 : 20) as eluent or electrospray ionisation (ESI). Major peaks are listed with intensities quoted as percentages of the base peak. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter, using a path length of 10 cm, with concentrations (*c*) given in g per 100 mL solvent and temperature as recorded. Specific rotations are quoted in units of 10^{-1} deg cm^2 g^{-1}. Melting points were recorded on a Leica VMTG Galen III apparatus and are uncorrected. Elemental analysis was performed by the Microanalysis Service of the Inorganic Chemistry Laboratory, University of Oxford, UK.

General procedure 1: *N*-acylation of oxazolidin-2-ones

BuLi (1.01 eq.) was added to a stirred solution of oxazolidin-2-one (1.0 eq.) in THF at −78 °C over 10 min. The corresponding acid chloride (1.1 eq.) was then added and the resultant mixture was stirred for a further 30 min at −78 °C, after which the reaction mixture was allowed to warm to room temperature over 30 min and sat. aq. NH_4Cl solution was added. The organic material was extracted twice with EtOAc and the combined organic extracts were washed sequentially with sat. aq. $NaHCO_3$ solution and brine then dried over $MgSO_4$ and filtered and concentrated *in vacuo*. Purification of the residue *via* either recrystallisation or column chromatography on silica furnished the required product.

General procedure 2: methylation of *N*-acyloxazolidin-2-ones

LiHMDS (1.2 eq.) was added dropwise *via* syringe to a stirred solution of oxazolidin-2-one (1.0 eq.) in THF at −78 °C under nitrogen and the resulting mixture was stirred for 30 min, after which it was allowed to warm to 0 °C and stirred for 2 h. MeI (1.1 eq.) was then added and the reaction mixture was stirred at 0 °C for 30 min before being allowed to warm to rt. The reaction mixture was quenched with sat. aq. NH_4Cl solution and the organic material was extracted into EtOAc, the resultant organic solution washed with sat. aq. $NaHCO_3$ solution and brine, and then dried over $MgSO_4$ before being concentrated *in vacuo*.

General procedure 3: enantioselective acylation of racemic secondary alcohols[34]

To a stirred solution of racemic secondary alcohol (10 eq.) in DCM (5.0 mL) at 0 °C an ethereal MeMgBr solution (1.1 eq.) was added. Oxazolidin-2-one (1.0 eq.) in DCM (2.66 mL) at 0 °C was added *via* cannula and stirred until the reaction came to completion (2–24 h). The reaction mixture was then quenched with sat. aq. NH_4Cl solution, the organic material extracted into DCM and the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude reaction product. Purification *via*

column chromatography on silica afforded the required product. Enantiomeric excesses of the required products were determined either by chiral HPLC using Diacel Chiralcel OJ Column or chiral CG with a CYDEX-β Column.

General procedure 4: Diels–Alder cycloadditions of α,β-unsaturated *N*-acyloxazolidin-2-ones

Et_2AlCl (1.4 eq.) was added to a stirred solution of oxazolidin-2-one (1.0 eq.) and isoprene (1.00 mL/0.30 mmol of oxazolidin-2-one) in DCM at −78 °C *via* syringe. The resultant reaction mixture was allowed to warm to −30 °C, stirred for 3 and quenched with HCl (1 M, aq.). The organic material was then extracted with DCM and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude reaction product. Diastereoisomeric excesses were determined by chiral CG, GC or 400 MHz ^{1}H NMR spectroscopy. Purification of the residue *via* column chromatography on silica afforded the required product.

General procedure 5: palladium catalysed acetalisation of oxazolidin-2-ones[31]

The alcohol was added to a stirred slurry of oxazolidin-2-ones (1.0 eq.), $PdCl_2$ (0.1 eq.) and CuCl (1.0 eq.) in DME under an oxygen atmosphere *via* a syringe. The resultant reaction mixture was stirred at a given temperature for a certain time and was filtered through Florisil®, eluting with Et_2O. Concentration of the filtrate *in vacuo* afforded the crude product and purification of this residue *via* column chromatography on silica afforded the required product.

(*S*)-4-*iso*-Propyl-3-(2′-phenylacetyl)oxazolidin-2-one 11

Following general procedure 1, (*S*)-4-*iso*-propyloxazolidin-2-one (300 mg, 2.33 mmol), BuLi (1.02 mL, 2.5 M in hexanes, 2.56 mmol) and phenylacetyl chloride (466 mg, 3.02 mmol) gave **11** as a pale yellow oil (502 mg, 87%) after purification *via* column chromatography (ethyl acetate–hexanes 1 : 15) with spectroscopic properties consistent with the literature.[34]

(*S*)-4-*tert*-Butyl-3-(2′-phenylacetyl)oxazolidin-2-one 12

Following general procedure 1, (*S*)-4-*tert*-butyloxazolidin-2-one (150 mg, 1.05 mmol), BuLi (0.72 mL, 1.6 M in hexanes, 1.15 mmol) and phenylacetyl chloride (210 mg, 1.36 mmol) gave **12** as a white solid (190 mg, 69%) after purification *via* column chromatography (ethyl acetate–hexanes 1 : 15); $[\alpha]_D^{22}$ + 88.5 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 1761 (C=O_{exo}), 1714 (C=O_{endo}); δ_H (400 MHz, $CDCl_3$) 0.87 (9H, s, C(CH_3)$_3$), 4.17–4.27 (2H, m, CH_2Ph), 4.28–4.31 (1H, m, CHN), 4.42–4.46 (2H, m, OCH_2), 7.12–7.36 (5H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 25.5, 35.8, 41.5, 61.0, 65.3, 127.2, 128.5, 129.7, 133.8, 154.7, 171.3; *m*/*z* (APCI$^+$) 262 ([M + H]$^+$, 30%), 144 (100); HRMS (ESI$^+$) $C_{15}H_{19}NO_3$ ([M + H]$^+$) requires 262.1446; found 262.1443.

(*S*)-4-*iso*-Propyl-3-(2′-phenylacetyl)-5,5-dimethyloxazolidin-2-one 13

Following general procedure 1, 4-(*S*)-*iso*-propyl-5,5-dimethyl-oxazolidin-2-one (300 mg, 1.91 mmol), BuLi (0.84 mL, 2.5 M in hexanes, 2.10 mmol) and phenylacetyl chloride (383 mg, 2.48 mmol) gave **13** (351 mg, 67%) as a colourless oil after purification *via* column chromatography (ethyl acetate–hexanes 1 : 15); $[\alpha]_D^{22}$ + 52.2 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1777 (C=O_{exo}), 1701 (C=O_{endo}); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, d, *J* 6.9, CH(CH_3)$_2$), 0.96 (3H, d, *J* 6.9, CH(CH_3)$_2$), 1.32 (3H, s, C(CH_3)$_2$), 1.50 (3H, s, C(CH_3)$_2$), 2.11 (1H, septd, *J* 6.9 and 3.2, C*H*(CH$_3$)$_2$), 4.14 (1H, d, *J* 3.2, NC*H*), 4.26 (1H, d, *J* 15.0, CH_2Ph), 4.38 (1H, d, *J* 15.0, CH_2Ph), 7.25–7.36 (5H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 17.3, 21.8, 21.9, 29.2, 30.1, 40.2, 66.9, 83.4, 127.6, 129.0, 130.1, 134.0, 154.0, 172.2; *m*/*z* (APCI$^+$) 276 ([M + H]$^+$,12%), 158 (100); HRMS (CI$^+$) $C_{16}H_{15}NO_2$ ([M + H]$^+$) requires 276.1597; found 276.1600.

(4*S*,2′*S*)-4-*iso*-Propyl-3-(2′-phenylpropionyl)oxazolidin-2-one 17

Following general procedure 2, oxazolidinone **11** (200 mg, 0.81 mmol), LiHMDS (0.97 mL, 1.0 M in hexanes, 0.97 mmol) and MeI (126 mg, 0.89 mmol) afforded (4*S*,2*S*)-**17** (160 mg, 76%) after purification *via* column chromatography (EtOAc–hexanes 1 : 14) with spectroscopic properties consistent with the literature;[35] Both diastereoisomers (4*S*,2′*S*)-**17** and (4*S*,2*R*)-**18** were synthesized as a 57 : 43 mixture *via* *N*-acylation of oxazolidinone with racemic acid chloride as described in the ESI.

(4*S*,2′*S*)-4-*tert*-Butyl-3-(2′-phenylpropionyl)oxazolidin-2-one 19

Following general procedure 2, oxazolidinone **12** (50 mg, 0.19 mmol), LiHMDS (0.23 mL, 1.0 M in hexanes, 0.23 mmol) and MeI (30 mg, 0.21 mmol) afforded (4*S*,2*S*)-**19** (27 mg, 51%) as a colourless oil after purification *via* column chromatography (EtOAc–hexanes 1 : 13) with spectroscopic properties consistent with the literature;[36] Both diastereoisomers (4*S*,2′*S*)-**19** and (4*S*,2*R*)-**20** were synthesized as a 59 : 41 mixture *via* *N*-acylation of oxazolidinone with racemic acid chloride as described in the ESI.

(4*S*,2*S*)-4-*iso*-Propyl-3-(2′-phenylpropionyl)-5,5-dimethyloxazolidin-2-one 21

Following general procedure 2, oxazolidinone **13** (200 mg, 0.73 mmol), LiHMDS (0.87 mL, 1.0 M in hexanes, 0.87 mmol) and MeI (114 mg, 0.80 mmol) afforded (4*S*,2*S*)-**21** (187 mg, 89%) as white crystals after purification *via* column chromatography (EtOAc–hexanes 1 : 15); (Found: C, 70.5; H, 8.0; N, 4.9. $C_{17}H_{23}NO_3$ requires C, 70.6; H, 8.0; N, 4.8%); mp 107–108 °C; $[\alpha]_D^{22}$ +103.0 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 1763 (C=O_{exo}), 1691 (C=O_{endo}); δ_H (400 MHz, $CDCl_3$) 0.99 (3H, d, *J* 6.8, CH(CH_3)$_2$), 0.99 (3H, s, C(CH_3)$_2$), 1.08 (3H, d, *J* 6.8, CH(CH_3)$_2$), 1.44 (3H, s, C(CH_3)$_2$), 1.53 (3H, d, *J* 7.0, CHCH_3), 2.15 (1H, septd, *J* 6.8 and 3.4, C*H*(CH$_3$)$_2$), 4.02 (1H, d, *J* 3.4, C*H*N), 5.15 (1H, q, *J* 7.0, C*H*CH$_3$), 7.21–7.35 (5H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 17.1, 19.4, 21.3, 21.5, 28.2, 29.5, 43.1, 67.2, 82.8, 127.2, 128.0, 128.5, 140.4, 153.3, 175.0; *m*/*z* (APCI$^+$) 290 (8%, [M + H]$^+$), 158 (100%, [Aux + H]$^+$); Both diastereoisomers (4*S*,2′*S*)-**21** and (4*S*,2*R*)-**22** were synthesized as a 55 : 45 mixture *via* *N*-acylation of oxazolidinone with racemic acid chloride as described in the ESI.

X-Ray crystal structure determination for 21. Data were collected using an Enraf–Nonius κ-CCD diffractometer with graphite monochromated Mo Kα radiation using standard procedures at

190 K. The structure was solved by direct methods (SIR92), all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[37]

X-Ray crystal structure data for **21** [$C_{17}H_{23}NO_3$]: $M = 289.37$, monoclinic, space group $P12_11$, $a = 6.5167(1)$ Å, $b = 7.9303(2)$ Å, $c = 15.8324(4)$ Å, $\beta = 92.8893(9)°$, $V = 817.17(3)$ Å^3, $Z = 2$, $\mu = 0.080$ mm^{-1}, yellow block, crystal dimensions = 0.2 × 0.2 × 0.2 mm. A total of 1991 unique reflections were measured for $5 < \theta < 27$ and 1805 reflections were used in the refinement. The final parameters were $wR_2 = 0.033$ and $R_1 = 0.031$ [$I > 3\sigma(I)$].

CCDC reference number 280124. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b605244d.

nOe analysis of enolate 14 derived from oxazolidinone 11

A solution of LiHMDS (33 mg, 0.20 mmol) in d_8-THF was added dropwise *via* syringe to a stirred solution of **11** (10 mg, 0.04 mmol) under a nitrogen atmosphere at −78 °C and stirred for 30 min. The reaction mixture was then allowed to warm to 0 °C and stirred for 2 h, after which nOe analysis was performed on a crude sample using a 500 MHz NOESY experiment with a mixing time of 16.28 s; δ_H (500 MHz, $CDCl_3$) 0.92 (3H, d, *J* 7.0, CH(CH_3)$_2$), 0.94 (3H, d, *J* 7.0, CH(CH_3)$_2$), 2.59 (1H, septd, *J* 7.0 and 3.2, C*H*(CH$_3$)$_2$), 4.18–4.20 (1H, m, C*H*N), 4.29–4.35 (2H, m, OCH_2), 4.58 (1H, s, C=C*H*), 6.77 (1H, t, *J* 7.5 *p-Ph*), 7.06 (2H, t, *J* 7.5 *m-Ph*), 7.60 (2H, d, *J* 7.5 *o-Ph*); δ_C (125 MHz, $CDCl_3$) 14.1, 17.5, 27.6, 60.9, 62.2, 84.2, 121.1, 125.3, 127.6, 141.7, 152.6, 158.0.

nOe analysis of enolate 16 derived from oxazolidinone 13

A solution of LiHMDS (33 mg, 0.20 mmol) in d_8-THF was added dropwise *via* syringe to a stirred solution of **13** (20 mg, 0.04 mmol) under nitrogen atmosphere at −78 °C and stirred for 30 min. The reaction mixture was then allowed to warm to 0 °C and stirred for 2 h, after which nOe analysis was performed on the crude sample using a 500 MHz NOESY experiment with a mixing time of 19.53 s; δ_H (500 MHz, $CDCl_3$) 1.06 (3H, d, *J* 6.7, CH(CH_3)$_2$), 1.13 (3H, d, *J* 7.1, CH(CH_3)$_2$), 1.45 (3H, s, C(CH_3)$_2$), 1.47 (3H, s, C(CH_3)$_2$), 2.19–2.25 (1H, m, C*H*(CH$_3$)$_2$), 3.94 (1H, d, *J* 2.3, C*H*N), 4.68 (1H, s, C=C*H*), 6.77 (1H, t, *J* 7.2, *p-Ph*), 7.06 (2H, t, *J* 7.6, *m-Ph*), 7.58 (2H, d, *J* 8.1, *o-Ph*); δ_C (125 MHz, $CDCl_3$) 17.3, 21.1, 21.4, 28.8, 30.1, 69.6, 80.9, 85.4, 121.2, 125.2, 127.6, 141.6, 154.4, 157.1.

(*S*)-3-Benzoyl-4-*iso*-propyloxazolidin-2-one 23

Following general procedure 1, (*S*)-4-*iso*-propyloxazolidin-2-one (1.07 g, 8.28 mmol), BuLi (3.35 mL, 2.5 M in hexane, 8.36 mmol), and benzoyl chloride (1.06 mL, 9.11 mmol) in THF (25.0 mL) afforded the title compound **23** (1.83 g, 95%) as an amorphous solid after purification *via* recrystallisation (hexanes–DCM) with spectroscopic properties consistent with the literature.[38]

(*S*)-3-Benzoyl-4-*iso*-propyl-5,5-dimethyloxazolidin-2-one 24

Following general procedure 1, 4-(*S*)-*iso*-propyl-5,5-dimethyl-oxazolidin-2-one (1.30 g, 8.28 mmol), BuLi (3.35 mL, 2.5 M in hexane, 8.36 mmol), and benzoyl chloride (1.06 mL, 9.11 mmol) in THF (25.0 mL) afforded the title compound **24** (1.61 g, 75%) as white needles after purification *via* recrystallisation (hexanes–DCM); mp 62–64 °C; $[\alpha]_D^{22}$ +168.7 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 1772 (C=O$_{exo}$), 1678 (C=O$_{endo}$); δ_H (400 MHz, $CDCl_3$) 1.08 (3H, d, *J* 6.9, CH(CH_3)$_2$), 1.11 (3H, d, *J* 6.9, CH(CH_3)$_2$), 1.50 (3H, s, C(CH_3)$_2$), 1.58 (3H, s, C(CH_3)$_2$), 2.26 (1H, septd, *J* 6.9, 3.5, C*H*(CH$_3$)$_2$), 4.42 (1H, d, *J* 3.5, NC*H*), 7.43–7.74 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.8, 21.9, 22.1, 29.7, 30.2, 66.9, 83.2, 128.3, 129.8, 132.8, 133.8, 153.4, 171.0; *m/z* (APCI$^+$) 262 ([M + H]$^+$,100%); HRMS (ESI$^+$) $C_{15}H_{20}NO_3$ ([M + H]$^+$) requires 262.1443; found 262.1431.

(*S*)-3-Benzoyl-4-*tert*-butyloxazolidin-2-one 25

Following general procedure 1, (*S*)-4-*tert*-butyloxazolidin-2-one (1.18 g, 8.28 mmol), BuLi (3.35 mL, 2.5 M in hexane, 8.36 mmol), and benzoyl chloride (1.06 mL, 9.11 mmol) in THF (25.0 mL) afforded the title compound **25** (1.674 g, 82%) as an amorphous solid after purification *via* recrystallisation (hexanes–DCM) with spectroscopic properties consistent with the literature.[20]

(*R*)-1-Phenylethan-1-yl benzoate 26

(*RS*)-1-Phenyl ethanol (0.46 mL, 3.83 mmol) was added to a stirred solution of **23**, **24** or **25** (0.38 mmol) in DCM (7.66 mL) at room temperature followed by the addition of $MgBr_2{\cdot}OEt_2$ (99 mg, 0.38 mmol) and *N*-methylpiperidine (0.05 mL, 0.38 mmol). The reaction mixture was then stirred for 30 min before the addition of sat. aq. NH_4Cl solution. The organic material was extracted with DCM and the combined organic layers were dried over $MgSO_4$and concentrated *in vacuo* to afford a colourless oil. Purification of this residue *via* column chromatography on silica afforded the title compound **26** as a colourless oil (81 mg, 94%, 91% e.e. from **24**), with spectroscopic properties consistent with the literature;[39] Racemic **26** was synthesized as described in the ESI. The enantiomeric excess was determined by chiral HPLC giving resolution of both enantiomers: Daicel Chiralcel OJ Column, 10% EtOH, 90% heptane, 0.75 mL min^{-1}, (*R*) t_R = 10.3 min and (*S*) t_R = 13.0 min.

(*R*)-1-Phenylpropan-1-yl benzoate 30

Following general procedure 3, **23**, **24** or **25** (0.38 mmol), MeMgBr (0.14 mL, 3.0 M in Et_2O, 0.42 mmol) and (*RS*)-1-phenylpropan-1-ol **27** (0.52 mL, 3.83 mmol) afforded the title compound **30** (83 mg, 90%, 92% e.e. from **24**) as a colourless oil after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40] 1 : 18) with spectroscopic properties consistent with the literature;[40] $[\alpha]_D^{22}$ −25.6 (*c* 0.5 in $CHCl_3$); racemic **30** was synthesized as described in the ESI. The enantiomeric excess was determined by chiral HPLC giving resolution of both enantiomers: Daicel Chiralcel OJ Column, 10% EtOH, 90% heptane, 0.75 mL min^{-1}, (*R*) t_R = 11.4 min and (*S*) t_R = 15.2 min.

(*R*)-2-Methyl-1-phenylpropan-1-yl benzoate 31

Following general procedure 3, **23**, **24** or **25** (0.38 mmol), MeMgBr (0.14 mL, 3.0 M in Et_2O, 0.42 mmol) and (*RS*)-2-methyl-1-phenylpropan-1-ol **28** (0.60 mL, 3.83 mmol) afforded the title compound **31** (90 mg, 92%, 42% e.e. from **24**) as a colourless oil, after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40] 1 : 18) with spectroscopic properties

consistent with the literature;[41] $[\alpha]_D^{22}$ −17.1 (*c* 1.0 in $CHCl_3$). Racemic **31** was synthesized as described in the ESI. The enantiomeric excess was determined by chiral HPLC giving resolution of both enantiomers: Daicel Chiralcel OJ Column, 10% EtOH, 90% heptane, 0.75 mL min^{-1}, (*R*) t_R = 10.1 min and (*S*) t_R = 12.9 min.

(*R*)-1,2,3,4-Tetrahydronaphth-1-yl benzoate 32

Following general procedure 3, **23**, **24** or **25** (0.38 mmol), MeMgBr (0.14 mL, 3.0 M in Et_2O, 0.42 mmol), and (*RS*)-1,2,3,4-tetrahydronaphth-1-ol **29** (567 mg, 3.83 mmol) afforded the title compound **32** (87 mg, 90%, 46% e.e. from **24**) as a colourless oil, after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40] 1 : 18) with spectroscopic properties consistent with the literature;[42] $[\alpha]_D^{22}$ +22.3 (*c* 1.0 in $CHCl_3$). Racemic **32** was synthesized as described in the ESI. The enantiomeric excess was determined by chiral GC giving resolution of both enantiomers: CYDEX-β column, 160 °C 90 min, (*R*) t_R = 61.4 min and (*S*) t_R = 63.8 min.

(*S*)-3-(4′-Methoxybenzoyl)-4-*iso*-propyl-5,5-dimethyloxazolidin-2-one 34

Following general procedure 1, 4-(*S*)-*iso*-propyl-5,5-dimethyl-oxazolidin-2-one (700 mg, 4.46 mmol), BuLi (1.80 mL, 2.5 M in hexane, 4.50 mmol), and *p*-anisoyl chloride (839 mg, 4.90 mmol) in THF (13.4 mL) afforded the title compound **34** (724 mg, 56%) as a white solid, after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40] 1 : 7); mp 49–51 °C; $[\alpha]_D^{24}$ +116.7 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 1777 (C=O_{exo}), 1680 (C=O_{endo}); δ_H (400 MHz, $CDCl_3$) 1.05 (3H, d, *J* 6.9, $CH(CH_3)_2$), 1.09 (3H, d, *J* 6.9, $CH(CH_3)_2$), 1.49 (3H, s, $C(CH_3)_2$), 1.57 (3H, s, $C(CH_3)_2$), 2.23 (1H, septd, *J* 6.9, 3.7, $CH(CH_3)_2$), 3.87 (3H, s, OCH_3), 4.42 (1H, d, *J* 3.7, NC*H*), 6.94 (2H, d, *J* 8.9, C(3′)*H* and C(5′)*H*), 7.78 (2H, d, *J* 8.9, C(2′)*H* and C(6′)*H*); δ_C (100 MHz, $CDCl_3$) 17.4, 21.4, 21.7, 29.3, 29.7, 55.4, 66.5, 82.5, 113.2, 125.1, 132.2, 153.6, 165.3, 169.8; *m*/*z* (ESI$^+$) 350 (86%, [M + MeCN + NH_4]$^+$), 314 (100, [M + Na]$^+$); HRMS (ESI$^+$) $C_{16}H_{22}NO_4$ ([M + H]$^+$) requires 292.1549; found 292.1540.

(*R*)-1-Phenylethan-1-yl 4′-methoxybenzoate 35

Following general procedure 3, oxazolidinone **34** (111 mg, 0.38 mmol), MeMgBr (0.14 mL, 3.0 M in Et_2O, 0.42 mmol), and (*RS*)-1-phenyl ethanol **33** (0.46 mL, 3.83 mmol) afforded the title compound **35** (94 mg, 94%) as a colourless oil, after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40] 1 : 18) with spectroscopic properties consistent with the literature;[43] $[\alpha]_D^{22}$ −65.0 (*c* 0.5 in $CHCl_3$). Preparation of racemic (*RS*)-**35** is detailed in the ESI, and the enantiomeric excess was determined by chiral GC giving resolution of both enantiomers: CYDEX-β column.

(*R*)-1-Phenylpropan-1-yl 4′-methoxybenzoate 36

Following general procedure 3, oxazolidinone **34** (111 mg, 0.38 mmol), MeMgBr (0.14 mL, 3.0 M in Et_2O, 0.42 mmol), and (*RS*)-1-phenylpropan-1-ol **27** (0.52 mL, 3.83 mmol) afforded the title compound **36** 102 mg, 99%) as a colourless oil, after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40] 1 : 18); $[\alpha]_D^{22}$ −46.2 (*c* 0.5 in $CHCl_3$); ν_{max} (film) 1716 (C=O); δ_H (500 MHz, $CDCl_3$) 0.96–0.99 (3H, m, CH_2CH_3), 1.90–2.11 (2H, m, CH_2CH_3), 3.87 (3H, s, OCH_3), 5.91 (1H, t, *J* 6.8, $CHCH_2$), 6.93–6.95 (2H, m, C(3′)*H* and C(5′)*H*), 7.27–7.43 (5H, m, *Ph*), 8.05–8.08 (2H, m, C(2′)*H* and C(6′)*H*); δ_C (125 MHz, $CDCl_3$) 10.4, 30.0, 55.9, 77.4, 114.0, 123.5, 126.9, 128.2, 128.8, 132.1, 141.3, 163.8, 166.1; *m*/*z* (CI$^+$) 271 ([M + H]$^+$, 16), 288 ([M + NH_4]$^+$, 100); HRMS (ESI$^+$) $C_{17}H_{22}NO_3$ ([M + H]$^+$) requires 288.1594; found 288.160. Preparation of racemic (*RS*)-**36** is detailed in the ESI, and the enantiomeric excess was determined by chiral GC giving resolution of both enantiomers: CYDEX-β column.

(*R*)-2-Methyl-1-phenylpropan-1-yl 4′-methoxybenzoate 37

Following general procedure 3, oxazolidinone **34** (111 mg, 0.38 mmol), MeMgBr (0.14 mL, 3.0 M in Et_2O, 0.42 mmol), and (*RS*)-2-methyl-1-phenylpropan-1-ol **28** (0.60 mL, 3.83 mmol) afforded the title compound **37** (106 mg, 98%) as a colourless oil, after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40] 1 : 18); $[\alpha]_D^{22}$ −35.4 (*c* 0.5 in $CHCl_3$); ν_{max} (film) 1713 (C=O); δ_H (500 MHz, $CDCl_3$) 0.91 (3H, d, *J* 6.8, $CH(CH_3)_2$), 1.05 (3H, d, *J* 6.7, $CH(CH_3)_2$), 2.23–2.27 (1H, m, $CH(CH_3)_2$), 3.87 (3H, s, OCH_3), 5.72 (1H, d, *J* 7.1, $CHCH(CH_3)_2$), 6.93–6.95 (2H, m, C(3′)*H* and C(5′)*H*), 7.27–7.39 (5H, m, *Ph*), 8.05–8.07 (2H, m, C(2′)*H* and C(6′)*H*); δ_C (125 MHz, $CDCl_3$) 18.3, 18.7, 33.8, 55.3, 80.9, 113.5, 122.9, 126.8, 127.5, 128.0, 131.5, 139.8, 163.2, 165.4; *m*/*z* (CI$^+$) 302 (62%, [M + NH_4]$^+$), 285 (14, [M + H]$^+$); HRMS (ESI$^+$) $C_{18}H_{24}NO_3$ ([M + NH_4]$^+$) requires 302.1751; found 302.1756. Preparation of racemic (*RS*)-**37** is detailed in the ESI, and the enantiomeric excess was determined by chiral GC giving resolution of both enantiomers: CYDEX-β column.

(*R*)-1,2,3,4-Tetrahydronaphth-1-yl 4′-methoxybenzoate 38

Following general procedure 3, oxazolidinone **34** (111 mg, 0.38 mmol), MeMgBr (0.14 mL, 3.0 M in Et_2O, 0.42 mmol), and (*RS*)-1,2,3,4-tetrahydronaphth-1-ol **29** (567 mg, 3.83 mmol) afforded the title compound **38** (107 mg, 99%) as a clear colourless oil after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40] 1 : 18); $[\alpha]_D^{22}$ +10.6 (*c* 0.5 in $CHCl_3$); ν_{max} (film) 1707 (C=O); δ_H (500 MHz, $CDCl_3$) 1.87–1.92 (1H, m, C(3)H_2), 2.04–2.14 (3H, m, C(2)H_2 and C(3)H_2), 2.79–2.85 (1H, m, C(4)H_2), 2.91–2.96 (1H, m, C(4)H_2), 3.86 (OCH_3), 6.23–6.25 (1H, m, C(1)*H*), 6.90–6.92 (2H, m, C(3′)*H* and C(5′)*H*), 7.16–7.38 (4H, m, C(5)*H*, C(6)*H*, C(7)*H* and C(8)*H*), 8.01–8.03 (2H, m, C(2′)*H* and C(6′)*H*); δ_C (125 MHz, $CDCl_3$) 19.0, 29.0, 29.2, 55.3, 70.2, 113.4, 123.0, 125.9, 127.8, 128.9, 129.4, 131.6, 134.8, 137.9, 163.2, 165.9; *m*/*z* (CI$^+$) 300 ([M + NH_4]$^+$, 47%), 283 ([M + H]$^+$, 3); HRMS (ESI$^+$) $C_{18}H_{22}NO_3$ ([M+ NH_4]$^+$) requires 300.1588; found 300.1600. Preparation of racemic (*RS*)-**38** is detailed in the ESI. The enantiomeric excess of (*R*)-**38** was determined by chiral GC, giving resolution of both enantiomers.

(4*S*,2′*E*)-3-(But-2′-enoyl)-4-*iso*-propyloxazolidin-2-one 39

Following general procedure 1, (*S*)-4-*iso*-propyloxazolidin-2-one (4.00 g, 31.0 mmol), BuLi (19.5 mL, 1.6 M in hexane, 31.2 mmol), and *trans*-crotonyl chloride (3.28 mL, 34.1 mmol) in THF

(117 mL) afforded the title compound **39** (5.62 g, 92%) as a white crystalline solid after purification *via* recrystallisation (DCM–pentane) with spectroscopic properties consistent with the literature.[23]

(4*S*,2′*E*)-3-(But-2′-enoyl)-4-*tert*-butyloxazolidin-2-one 40

Following general procedure 1, (*S*)-4-*tert*-butyloxazolidin-2-one (700 mg, 4.90 mmol), BuLi (1.97 mL, 2.5 M in hexane, 4.92 mmol), and *trans*-crotonyl chloride (0.52 mL, 5.38 mmol) in THF (17.0 mL) afforded the title compound **40** (839 mg, 81%) as a white solid after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40], 1 : 10); mp 43–45 °C; $[\alpha]_D^{22}$ +101.2 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 1772 (C=O_{exo}), 1703 (C=O_{endo}); δ_H (400 MHz, $CDCl_3$) 0.94 (9H, s, C(CH_3)$_3$), 1.96 (3H, d, *J* 5.3, HC=CHCH_3), 4.23–4.31 (2H, m, OCH_2), 4.52 (1H, dd, *J* 7.4, 1.8, NC*H*), 7.12–7.20 (1H, m, *H*C=CHCH$_3$), 7.27–7.34 (1H, m, HC=C*H*CH$_3$); δ_C (100 MHz, $CDCl_3$) 18.5, 25.6, 35.9, 60.8, 65.2, 121.9, 146.9, 154.7, 165.3; *m*/*z* (ESI$^+$) 234 ([M + Na]$^+$, 100); HRMS (ESI$^+$) $C_{12}H_{20}NO_3$ ([M + H]$^+$) requires 226.1443; found 226.1445.

(4*S*,2′*E*)-3-(But-2′-enoyl)-4-*iso*-propyl-5,5-dimethyloxazolidin-2-one 41

Following general procedure 1, 4-(*S*)-*iso*-propyl-5,5-dimethyloxazolidin-2-one (700 mg, 4.46 mmol), BuLi (2.80 mL, 1.6 M in hexane, 4.48 mmol), and *trans*-crotonyl chloride (0.47 mL, 4.90 mmol) in THF (16.8 mL) afforded the title compound **41** (862 mg, 86%) as a white solid after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40], 1 : 10); mp 71–72 °C; $[\alpha]_D^{22}$ +14.5 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 1754 (C=O_{exo}), 1687 (C=O_{endo}); δ_H (400 MHz, $CDCl_3$) 0.96 (3H, d, *J* 6.9, CH(CH_3)$_2$), 1.03 (3H, d, *J* 6.9, CH(CH_3)$_2$), 1.38 (3H, s, C(CH_3)$_2$), 1.51 (3H, s, C(CH_3)$_2$), 1.95–1.97 (3H, m, HC=CHCH_3), 2.15 (1H, septd, *J* 6.9, 3.4, C*H*(CH$_3$)$_2$), 4.21 (1H, d, *J* 3.4, NC*H*), 7.10–7.19 (1H, m, *H*C=CHCH$_3$), 7.27–7.34 (1H, m, HC=C*H*CH$_3$); δ_C (100 MHz, $CDCl_3$) 17.1, 18.4, 21.3, 21.4, 28.8, 29.6, 66.3, 82.7, 121.9, 146.5, 153.5, 165.6; *m*/*z* (ESI$^+$) 284 ([M + MeCN + NH_4]$^+$, 100); HRMS (ESI$^+$) $C_{12}H_{20}NO_3$ ([M + H]$^+$) requires 226.1443; found 226.1446.

(4*S*,1′*S*,6′*S*)-3-[(4′,6′-Dimethylcyclohex-3′-ene-1′-yl)carbonyl]-4-*iso*-propyloxazolidin-2-one 42

Following general procedure 4, oxazolidinone **39** (118 mg, 0.60 mmol), Et_2AlCl (0.47 mL, 1.8 M in toluene, 0.84 mmol) and isoprene (2.00 mL, 20.0 mmol) in DCM (2.00 mL) afforded the title compound (4*S*,1′*S*,6′*S*)-**42** (80 mg, 50%) as a white solid after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40], 1 : 22);[20] mp 64–65 °C; $[\alpha]_D^{23}$ +171.7 (*c* 0.5 in $CHCl_3$); ν_{max} (KBr) 1762 (C=O_{exo}), 1699 (C=O_{endo}); δ_H (400 MHz, $CDCl_3$) 0.85–0.96 (9H, m, CH(CH_3)$_2$ and C(2′)HCH_3), 1.64 (3H, s, H(5′)C=C(4′)CH_3), 1.70–1.78 (1H, m, C(3′)H_2), 1.99–2.15 (3H, m, C(2′)*H*, C(3′)H_2 and C(6′)H_2), 2.31–2.39 (1H, m, C(6′)H_2), 3.59–3.66 (1H, m, C(1′)*H*), 4.18–4.30 (2H, m, OCH_2), 4.46–4.51 (1H, m, NC*H*), 5.36 (1H, br s, *H*(5′)C=C(4′)CH$_3$); δ_C (100 MHz, $CDCl_3$) 14.6, 17.9, 19.6, 23.2, 28.4, 29.9, 30.4, 38.1, 44.3, 58.4, 63.1, 118.6, 133.6, 153.7, 176.5; *m*/*z* (ESI$^+$) 288 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{15}H_{24}NO_3Na$ ([M + Na]$^+$) requires 266.1756; found 266.1759. Spectral data of the minor (4*S*,1′*R*,6′*R*)-diastereoisomer is available in the ESI. The diastereoisomeric excess was determined by GC giving resolution of both diastereoisomers: BPX5 column, 160 °C 10 min, 4 °C min^{-1}, 220 °C 20 min, (4*S*,1′*S*,6′*S*)-**42** t_R = 28.8 min and (4*S*,1′*R*,6′*R*)-diastereoisomer t_R = 30.0 min.

(4*S*,1′*S*,6′*S*)-3-[(4′,6′-Dimethylcyclohex-3′-ene-1′-yl)carbonyl]-4-*tert*-butyloxazolidin-2-one 43

Following general procedure 4, oxazolidinone **40** (127 mg, 0.60 mmol), Et_2AlCl (0.47 mL, 1.8 M in toluene, 0.84 mmol) and isoprene (2.00 mL, 20.0 mmol) in DCM (2.00 mL) afforded the title compound (4*S*,1′*S*,6′*S*)-**43** (139 mg, 83%) as a white solid after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40], 1 : 22); mp 47–49 °C; $[\alpha]_D^{23}$ +147.5 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 1780 (C=O_{exo}), 1702 (C=O_{endo}); δ_H (400 MHz, $CDCl_3$) 0.92 (9H, s, C(CH_3)$_3$), 0.93 (3H, d, *J* 6.4, C(2′)HCH_3), 1.65 (3H, s, H(5′)C=C(4′)CH_3), 1.71–1.78 (1H, m, C(3′)H_2), 2.00–2.19 (3H, m, C(2′)*H*, C(3′)H_2 and C(6′)H_2), 2.34–2.39 (1H, m, C(6′)H_2), 3.62–3.69 (1H, m, C(1′)*H*), 4.23 (1H, dd, *J* 9.2, 7.5, OCH_2), 4.28 (1H, dd, *J* 9.2, 1.5, OCH_2), 4.51 (1H, dd, *J* 7.4, 1.6, NC*H*), 5.38 (1H, br s, *H*(5′)C=C(4′)CH$_3$); δ_C (100 MHz, $CDCl_3$) 19.5, 23.2, 25.6, 30.3, 30.4, 35.8, 38.1, 44.3, 60.7, 65.1, 118.6, 133.7, 154.3, 176.4; *m*/*z* (ESI$^+$) 302 ([M + Na]$^+$, 23%); HRMS (ESI$^+$) $C_{16}H_{26}NO_3$ ([M + H]$^+$) requires 280.1913; found 280.1909. Spectral data of the minor (4*S*,1′*R*,6′*R*)-diastereoisomer is available in the ESI. The diastereoisomeric excess was determined by GC, giving resolution of both diastereoisomers: BPX5 column, 160 °C 10 min, 4 °C min^{-1}, 220 °C 20 min, (4*S*,1′*S*,6′*S*)-**43** t_R = 30.2 min. The (4*S*,1′*R*,6′*R*)-diastereoisomer was not detected in the crude mixture.

(4*S*,1′*S*,6′*S*)-3-[(4′,6′-Dimethylcyclohex-3′-ene-1′-yl)carbonyl]-4-*iso*-propyl-5,5-dimethyloxazolidin-2-one 44

Following general procedure 4, oxazolidinone **41** (135 mg, 0.60 mmol), Et_2AlCl (0.47 mL, 1.8 M in toluene, 0.84 mmol) and isoprene (2.00 mL, 20.0 mmol) in DCM (2.00 mL) afforded the title compound (4*S*,1′*S*,6′*S*)-**44** (130 mg, 74%) as a white solid after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40], 1 : 22); mp 65–67 °C; $[\alpha]_D^{23}$ + 117.8 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 1772 (C=O_{exo}), 1698 (C=O_{endo}); δ_H (400 MHz, $CDCl_3$) 0.93–0.95 (6H, m, CH(CH_3)$_2$ and C(2′)HCH_3), 1.01 (3H, d, *J* 7.0, CH(CH_3)$_2$), 1.38 (3H, s, C(CH_3)$_2$), 1.51 (3H, s, C(CH_3)$_2$), 1.65 (3H, s, H(5′)C=C(4′)CH_3), 1.71–1.78 (1H, m, C(3′)H_2), 1.99–2.21 (4H, m, C*H*(CH$_3$)$_2$, C(2′)*H*, C(3′)H_2 and C(6′)H_2), 2.39–2.43 (1H, m, C(6′)H_2), 3.63–3.70 (1H, m, C(1′)*H*), 4.22 (1H, d, *J* 3.3, NC*H*), 5.39 (1H, br s, *H*(5′)C=C(4′)CH$_3$); δ_C (100 MHz, $CDCl_3$) 17.0, 19.6, 21.3, 21.6, 23.2, 28.6, 30.0, 30.2, 30.5, 38.0, 44.4, 66.1, 82.4, 118.8, 133.6, 153.3, 177.2; *m*/*z* (ESI$^+$) 352 ([M + MeCN + NH_4]$^+$, 100%), 316 ([M + Na]$^+$, 55%); HRMS (ESI$^+$) $C_{17}H_{28}NO_3$ ([M + H]$^+$) requires 294.2069; found 294.2070. Spectral data of the minor diastereoisomer (4*S*,1′*R*,6′*R*)-**45** is available in the ESI. The diastereoisomeric excess was determined by GC giving resolution of both diastereoisomers: BPX5 column, 140 °C 10 min, 4 °C min^{-1}, 220 °C 20 min, (4*S*,1′*S*,6′*S*)-**44** t_R = 35.8 min and (4*S*,1′*R*,6′*R*)-**45** t_R = 36.2 min.

X-Ray crystal structure determination for 45. Data were collected using an Enraf–Nonius κ-CCD diffractometer with graphite monochromated Mo Kα radiation using standard procedures at 190 K. The structure was solved by direct methods (SIR92), all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[37]

X-Ray crystal structure data for **45** [$C_{17}H_{27}NO_3$]: $M = 293.41$, monoclinic, space group $P12_11$, $a = 6.9391(2)$ Å, $b = 8.0963(3)$ Å, $c = 15.5077(5)$ Å, $\beta = 101.182(3)°$, $V = 854.70(5)$ Å^3, $Z = 2$, $\mu = 0.077$ mm^{-1}, colourless block, crystal dimensions = 0.2 × 0.2 × 0.2 mm. A total of 2627 unique reflections were measured for $5 < \theta < 30$ and 2155 reflections were used in the refinement. The final parameters were $wR_2 = 0.061$ and $R_1 = 0.051$ [$I > 3\sigma(I)$].

CCDC reference number 280122. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b605244d.

(*S*)-3-(Prop-2′-enoyl)-4-*iso*-propyloxazolidin-2-one 46

Acrolyl chloride (0.21 mL, 2.62 mmol) was added to a stirred solution of acrylic acid (0.18 mL, 2.62 mmol) and NEt_3 (0.37 mL, 2.62 mmol) in EtOAc (13.2 mL) at 0 °C, over 2 min and the resultant mixture was stirred for a further 40 min. The reaction mixture was then allowed to warm to room temperature over 30 min and was then filtered. Evaporation of the solvent *in vacuo* afforded a cloudy oil which was re-dissolved in hexanes and the resulting suspension was filtered and re-concentrated *in vacuo* to afford a colourless oil which was dissolved in THF (0.52 mL) and used immediately. NEt_3 (0.37 mL, 2.62 mmol) was added to a stirred suspension of (*S*)-4-*iso*-propyloxazolidin-2-one (271 mg, 2.10 mmol) and LiCl (111 mg, 2.62 mmol) in THF (1.89 mL) at room temperature, followed by addition of the anhydride. The reaction mixture was then stirred for 4 h. Evaporation of the solvent *in vacuo* afforded a white paste which was dissolved in HCl (1.0 M, aq.). The organic material was extracted with DCM and the combined organic layers were washed sequentially with sat. aq. $NaHCO_3$ solution and brine, then dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the crude product as a pale yellow oil. Purification of this residue *via* column chromatography on silica (EtOAc–hexanes 1 : 9) afforded the title compound **46** as a white solid (300 mg, 78%) with spectroscopic properties consistent with the literature.[23]

(*S*)-3-(Prop-2′-enoyl)-4-*tert*-butyloxazolidin-2-one 47

Acrolyl chloride (0.21 mL, 2.62 mmol) was added to a stirred solution of acrylic acid (0.18 mL, 2.62 mmol) and NEt_3 (0.37 mL, 2.62 mmol) in EtOAc (13.2 mL) at 0 °C, over 2 min and stirred for a further 40 min. The resultant reaction mixture was allowed to warm to room temperature over 30 min and was then filtered and concentrated *in vacuo* to afford a cloudy oil. The crude reaction mixture was then dissolved in hexanes and the resulting suspension was filtered and re-concentrated *in vacuo* to afford a colourless oil which was dissolved in THF (0.52 mL) and used immediately. NEt_3 (0.37 mL, 2.62 mmol) was added to a stirred suspension of (*S*)-4-*tert*-butyloxazolidin-2-one (300 mg, 2.10 mmol) and LiCl (111 mg, 2.62 mmol) in THF (1.89 mL) at room temperature, followed by addition of the anhydride. The reaction mixture was then stirred for 4 h. Evaporation of the solvent *in vacuo* afforded a white paste which was dissolved in HCl (1.0 M, aq.). The organic material was then extracted with DCM and the combined organic layers were washed sequentially with sat. aq. $NaHCO_3$ and brine, then dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the crude product as a pale yellow oil. Purification of this residue *via* column chromatography on silica (EtOAc–hexanes 1 : 9) afforded the title compound **47** as a white solid (271 mg, 66%) with spectroscopic properties consistent with the literature.[44]

(*S*)-3-(Prop-2′-enoyl)-4-*iso*-propyl-5,5-dimethyloxazolidin-2-one 48

Acrolyl chloride (0.65 mL, 7.96 mmol) was added to a stirred solution of acrylic acid (0.55 mL, 7.96 mmol) and NEt_3 (1.11 mL, 7.96 mmol) in EtOAc (40.0 mL) at 0 °C, over 2 min. The resultant reaction mixture was stirred for a further 40 min before being allowed to warm to room temperature, stirred for 30 min and then filtered and concentrated *in vacuo* to afford a colourless oil. The crude reaction mixture was re-dissolved in hexanes and the resulting suspension was filtered and reconcentrated *in vacuo* to furnish a colourless oil which was re-dissolved in THF (1.59 mL) and used immediately. NEt_3 (1.11 mL, 7.96 mmol) was added to a stirred suspension of 4-(*S*)-*iso*-propyl-5,5-dimethyloxazolidin-2-one (1.00 g, 6.37 mmol) and LiCl (338 mg, 7.96 mmol) in THF (5.73 mL) at room temperature, followed by addition of the anhydride. The reaction mixture was stirred for 4 h. Evaporation of the solvent *in vacuo* afforded a white paste which was dissolved in HCl (1.0 M, aq.). The organic material was extracted with DCM and the combined organic layers were washed sequentially with sat. aq. $NaHCO_3$ solution and brine, then dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the crude product as brown oil. Purification of this residue *via* column chromatography on silica (EtOAc–petroleum ether [30–40], 1 : 9) afforded the title compound **48** as a white solid (1.06 g, 78%); mp 56–57 °C; $[\alpha]_D^{20}$ +58.0 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 1775 (C=O_{exo}), 1689 (C=O_{endo}); δ_H (400 MHz, $CDCl_3$) 0.97 (3H, d, *J* 6.8, CH(CH_3)$_2$), 1.05 (3H, d, *J* 6.8, CH(CH_3)$_2$), 1.40 (3H, s, C(CH_3)$_2$), 1.53 (3H, s, C(CH_3)$_2$), 2.18 (1H, septd, *J* 6.8, 3.3, C*H*(CH$_3$)$_2$), 4.23 (1H, d, *J* 3.3, NC*H*), 5.19 (1H, d, *J* 10.5, CH=CH_2), 6.55 (1H, d, *J* 17.0, CH=CH_2), 7.57 (1H, dd, *J* 17.0, 10.5, C*H*=CH$_2$); δ_C (100 MHz, $CDCl_3$) 17.1, 21.4, 21.5, 28.8, 29.7, 66.4, 83.0, 127.5, 131.6, 153.4, 165.5; *m*/*z* (ESI$^+$) 270 ([M + MeCN + NH_4]$^+$, 100); HRMS (ESI$^+$) $C_{11}H_{18}NO_3$ ([M + H]$^+$) requires 212.1287; found 212.1281.

(4*S*,1′*S*)-3-[(4′-Methylcyclohex-3′-ene-1′-yl)carbonyl]-4-*iso*-propyloxazolidin-2-one 49

Following general procedure 4, oxazolidinone **46** (110 mg, 0.60 mmol), Et_2AlCl (0.47 mL, 1.8 M in toluene, 0.84 mmol) and isoprene (2.00 mL, 20.0 mmol) in DCM (2.00 mL) afforded an inseparable mixture of diastereoisomers (54% d.e.) as a white solid (109 mg, 72%) after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40], 1 : 22), with spectroscopic properties consistent with the literature;[23] Both diastereoisomers were synthesized as a 1 : 1 mixture in the ESI. The diastereoisomeric excess was determined by chiral GC giving resolution of both diastereoisomers: CYDEX-β column, 40 °C 10 min, 4 °C min^{-1}, 140 °C 240 min, (4*S*,1′*S*)-**49** t_R = 205.3 min and (4*S*,1′*R*)-diastereoisomer t_R = 209.6 min.

(4*S*,1′*S*)-3-[(4′-Methylcyclohex-3′-ene-1′-yl)carbonyl]-4-*tert*-butyloxazolidin-2-one 50

Following general procedure 4, oxazolidinone **47** (118 mg, 0.60 mmol), Et_2AlCl (0.47 mL, 1.8 M in toluene, 0.84 mmol) and isoprene (2.00 mL, 20.0 mmol) in DCM (2.00 mL) afforded the title compound (4*S*,1′*S*)-**50** (106 mg, 66%) as a colourless oil after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40], 1 : 22); $[\alpha]_D^{22}$ +117.8 (*c* 1.3 in $CHCl_3$); ν_{max} (KBr) 1778 (C=O_{exo}), 1703 (C=O_{endo}); δ_H (400 MHz, $CDCl_3$) 0.92 (9H, s, C(CH_3)$_3$), 1.66 (3H, s, H(5′)C=C(4′)CH_3), 1.69–1.79 (1H, m, C(2′)H_2), 1.85–1.98 (2H, m, C(2′)H_2 and C(3′)*H*), 2.01–2.21 (2H, m, C(3′)H_2 and C(6′)H_2), 2.40–2.44 (1H, m, C(6′)H_2), 3.65–3.73 (1H, m, C(1′)*H*), 4.22–4.30 (2H, m, OCH_2), 4.48 (1H, dd, *J* 7.4, 1.9, NC*H*), 5.40 (1H, br s, *H*(5′)C=C(4′)CH_3); δ_C (100 MHz, $CDCl_3$) 23.4, 24.9, 25.6, 29.0, 29.3, 35.8, 38.6, 60.6, 65.1, 119.0, 134.0, 154.2, 176.6; *m*/*z* (ESI$^+$) 288 ([M + Na]$^+$, 100%), 266 ([M + H]$^+$, 47); HRMS (ESI$^+$) $C_{15}H_{24}NO_3$ ([M + H]$^+$) requires 266.1756; found 266.1754. Both diastereoisomers were synthesized as a 1 : 1 mixture, see the ESI. The diastereoisomeric excess was determined by chiral GC giving resolution of both diastereoisomers: CYDEX-β column, 40 °C 10 min, 4 °C min^{-1}, 140 °C 280 min, (4*S*,1′*S*)-**50** t_R = 249.3 min and (4*S*,1′*R*)-diastereoisomer t_R = 257.2 min, which was not observed.

(4*S*,1′*S*)-3-[(4′-Methylcyclohex-3′-ene-1′-yl)carbonyl]-4-*iso*-propyl-5,5-dimethyloxazolidin-2-one 51

Following general procedure 4, oxazolidinone **48** (127 mg, 0.60 mmol), Et_2AlCl (0.47 mL, 1.8 M in toluene, 0.84 mmol) and isoprene (2.00 mL, 20.0 mmol) in DCM (2.00 mL) afforded the title compound (4*S*,1′*S*)-**51** as a white solid (110 mg, 66%), after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40], 1 : 22); mp 60–61.5 °C; $[\alpha]_D^{22}$ +114.1 (*c* 0.8 in $CHCl_3$); ν_{max} (KBr) 1760 (C=O_{exo}), 1699 (C=O_{endo}); δ_H (500 MHz, $CDCl_3$) 0.95 (3H, d, *J* 6.9, CH(CH_3)$_2$), 1.01 (3H, d, *J* 6.9, CH(CH_3)$_2$), 1.39 (3H, s, C(CH_3)$_2$), 1.51 (3H, s, C(CH_3)$_2$), 1.67 (3H, s, H(5′)C=C(4′)CH_3), 1.70–1.78 (1H, m, C(2′)H_2), 1.87–1.91 (1H, m, C(2′)H_2), 1.96–2.00 (1H, br s, C(3′)*H*), 2.07–2.23 (3H, m, C*H*(CH_3)$_2$, C(3′)H_2 and C(6′)H_2), 2.36–2.40 (1H, m, C(6′)H_2), 3.71–3.74 (1H, m, C(1′)*H*), 4.19 (1H, d, *J* 3.3, NC*H*), 5.41 (1H, br s, *H*(5′)C=C(4′)CH_3); δ_C (125 MHz, $CDCl_3$) 16.8, 21.2, 21.4, 23.3, 25.2, 28.5, 28.7, 29.3, 29.5, 38.4, 66.0, 82.5, 119.0, 133.7, 153.1, 176.9; *m*/*z* (ESI$^+$) 302 ([M + Na]$^+$,100%), 280 ([M + H]$^+$, 99); HRMS (ESI$^+$) $C_{16}H_{26}NO_3$ ([M + H]$^+$) requires 280.1913; found 280.1916. Both diastereoisomers were synthesized as a 1 : 1 mixture, see the ESI. The diastereoisomeric excess was determined by integration of the resonance at δ_H 2.36–2.40 (4*S*,1′*S*)-**51** (C(6′)H_2) and δ_H 2.28–2.31 (4*S*,1′*R*)-diastereoisomer (C(6′)H_2).

(4*S*,2′*E*)-3-(3′-Phenylprop-2′-enoyl)-4-*iso*-propyloxazolidin-2-one 52

Following general procedure 1, (*S*)-4-*iso*-propyloxazolidin-2-one (361 mg, 2.80 mmol), BuLi (1.12 mL, 2.5 M in hexane, 2.81 mmol) and *trans*-cinnamoyl chloride (0.44 mg, 3.08 mmol) in THF (11.0 mL) afforded the title compound **52** (690 mg, 95%) as a white solid after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40], 1 : 7), with spectroscopic properties consistent with the literature.[23]

(4*S*,2′*E*)-3-(3′-Phenylprop-2′-enoyl)-4-*tert*-butyloxazolidin-2-one 53

Following general procedure 1, (*S*)-4-*tert*-butyloxazolidin-2-one (400 mg, 2.80 mmol), BuLi (1.12 mL, 2.5 M in hexane, 2.81 mmol) and *trans*-cinnamoyl chloride (0.44 mg, 3.08 mmol) in THF (11.0 mL) afforded the title compound **53** as a white solid (670 mg, 88%) after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40], 1 : 7), with spectroscopic properties consistent with the literature.[45]

(4*S*,2′*E*)-3-(3′-Phenylprop-2′-enoyl)-4-*iso*-propyl-5,5-dimethyloxazolidin-2-one 54

Following general procedure 1, (*S*)-4-*iso*-propyl-5,5-dimethyl-oxazolidin-2-one (1.00 g, 6.37 mmol), BuLi (2.56 mL, 2.5 M in hexane, 6.40 mmol) and *trans*-cinnamoyl chloride (1.00 g, 7.01 mmol) in THF (25 mL) afforded the title compound **54** (1.80 g, 98%) as a white solid after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40], 1 : 7), with spectroscopic properties consistent with the literature.[46]

(4*S*,1′*R*,2′*R*,3′*S*,4′*S*)-3-[(3′-Methylbicyclo[2.2.1]hept-5′-ene-2′-yl)carbonyl]-4-*iso*-propyloxazolidin-2-one (*endo* I)-55

Following general procedure 4, oxazolidinone **39** (118 mg, 0.60 mmol), cyclopentadiene (1.20 mL) and Et_2AlCl (0.47 mL, 1.8 M in toluene, 0.84 mmol) in DCM (1.20 mL) afforded the title compound (4*S*,1′*R*,2′*R*,3′*S*,4′*S*)-**55** (113 mg, 72%) as a pale yellow solid after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40], 1 : 20), with spectroscopic properties consistent with the literature;[23] Authentic samples of all other possible diastereoisomers were prepared as detailed in the ESI. The diastereoisomeric excess was determined by integration of the resonances at δ_H 5.72 (*endo* I)-**55** (C(2′)*H*), and δ_H 5.80 (*endo* II)-diastereoisomer (C(2′)*H*) and δ_H 2.90–2.91 (*exo* I)-diastereoisomer (C(5′)*H*) and (*exo* II)-diastereoisomer (C(6′)*H*).

(4*S*,1′*R*,2′*R*,3′*S*,4′*S*)-3-[3′-Methylbicyclo[2.2.1]hept-5-ene-2′-yl)-carbonyl]-4-*tert*-butyloxazolidin-2-one (*endo* I)-56

Following general procedure 4, oxazolidinone **40** (127 mg, 0.60 mmol), cyclopentadiene (1.20 mL) and Et_2AlCl (0.47 mL, 1.8 M in toluene, 0.84 mmol) in DCM (1.20 mL) afforded the title compound (4*S*,1′*R*,2′*R*,3′*S*,4′*S*)-**56** (124 mg, 74%) as a pale yellow solid after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40], 1 : 20); mp 120–122 °C; $[\alpha]_D^{24}$ +176.7 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 1778 (C=O_{exo}), 1690 (C=O_{endo}); δ_H (400 MHz, $CDCl_3$) 0.91 (9H, s, C(CH_3)$_3$), 1.11 (1H, d, *J* 7.0, CHCH_3), 1.49 (1H, dd, *J* 8.6, 1.5, C(7′)H_2), 1.73 (1H, d, *J* 8.6, C(7′)H_2), 2.07–2.10 (1H, m, C(3′)*H*), 2.52 (1H, br s, C(4′)*H*), 3.42 (1H, br s, C(1′)*H*), 3.51–3.53 (1H, m, C(2′)*H*), 4.21–4.29 (2H, m, OCH_2), 4.42 (1H, dd, *J* 7.5, 1.8, NC*H*), 5.81 (1H, dd, *J* 5.7, 2.8, C(6)*H*), 6.39 (1H, dd, *J* 5.6, 3.1, C(5′)*H*); δ_C (100 MHz, $CDCl_3$) 20.4, 25.7, 35.7, 35.8, 47.5, 48.3, 49.3, 51.7, 60.9, 65.2, 131.0, 139.8, 154.6, 174.1; *m*/*z* (ESI$^+$) 336 ([M + MeCN + NH_4]$^+$, 82%), 300 ([M + Na]$^+$, 100); HRMS (ESI$^+$) $C_{16}H_{24}NO_3$ ([M + H]$^+$)

requires 278.1756; found 278.1765. Authentic samples of all other possible diastereoisomers were prepared as detailed in the ESI. The diastereoisomeric excess was determined by integration of the resonances at δ_H 3.53 (*endo* I)-**56** (C(4′)*H*), δ_H 3.65 (*endo* II)-diastereoisomer (C(4′)*H*) and δ_H 2.75 (*exo* I)-diastereoisomer (C(3′)*H*) and (*exo* II)-diastereoisomer (C(3′)*H*).

(4*S*,1′*R*,2′*R*,3′*S*,4′*S*)-3-[3′-Methylbicyclo[2.2.1]hept-5′-ene-2′-yl)carbonyl]-4-*iso*-propyl-5,5-dimethyloxazolidin-2-one (*endo* I)-57

Following general procedure 4, oxazolidinone **41** (135 mg, 0.60 mmol), cyclopentadiene (1.20 mL) and Et_2AlCl (0.47 mL, 1.8 M in toluene, 0.84 mmol) in DCM (1.20 mL) afforded the title compound 4*S*,1′*R*,2′*R*,3′*S*,4′*S*)-**57** (120 mg, 67%) as a pale yellow solid after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40], 1 : 20); mp 125–127 °C; $[\alpha]_D^{22}$ +148.0 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 1785 (C=O_{exo}), 1692 (C=O_{endo}); δ_H (400 MHz, $CDCl_3$) 0.96 (3H, d, *J* 6.6, CH(CH_3)$_2$), 0.97 (3H, d, *J* 7.0, CH(CH_3)$_2$), 1.12 (3H, d, *J* 7.0, CHCH_3), 1.38 (3H, s, C(CH_3)$_2$), 1.47–1.50 (1H, m, C(7′)H_2), 1.50 (3H, s, C(CH_3)$_2$), 1.74 (1H, d, *J* 8.6, C(7′)H_2), 2.08–2.15 (2H, m, CH(CH_3)$_2$ and C(3′)*H*), 2.53 (1H, br s, C(4′)*H*), 3.44 (1H, br s, C(1′)*H*), 3.52–3.55 (1H, m, C(2′)*H*), 4.18 (1H, d, *J* 4.6, NC*H*), 5.81 (1H, dd, *J* 5.4, 2.6, C(6′)*H*), 6.40 (2H, dd, *J* 5.2, 3.2, C(5′)*H*); δ_C (100 MHz, $CDCl_3$) 16.9, 20.5, 21.4, 21.5, 28.9, 29.6, 35.7, 47.3, 48.2, 49.4, 51.9, 66.1, 82.5, 131.0, 139.8, 153.4, 174.6; *m*/*z* (ESI$^+$) 350 ([M + MeCN + NH_4]$^+$, 100%); HRMS (ESI$^+$) $C_{17}H_{26}NO_3$ ([M + H]$^+$) requires 292.1913; found 292.1906. Authentic samples of all other possible diastereoisomers were prepared as detailed in the ESI. The diastereoisomeric excess was determined by integration of the resonances at δ_H 4.16 (*endo* I)-**57** (NC*H*), δ_H 4.04 (*endo* II)-diastereoisomer (NC*H*) and δ_H 6.14–6.17 (*exo* I)-diastereoisomer (C(2′)*H*) and (*exo* II)-diastereoisomer (C(2′)*H*).

X-Ray crystal structure determination for 57. Data were collected using an Enraf–Nonius κ-CCD diffractometer with graphite monochromated Mo Kα radiation using standard procedures at 190 K. The structure was solved by direct methods (SIR92), all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[37]

X-Ray crystal structure data for **57** [$C_{17}H_{25}NO_3$]: $M = 291.39$, orthorhombic, space group $P2_12_12_1$, $a = 7.2402(1)$ Å, $b = 11.8197(2)$ Å, $c = 18.4670(5)$ Å, $V = 1580.35(5)$ Å^3, $Z = 4$, $\mu = 0.083$ mm^{-1}, colourless block, crystal dimensions = 0.2 × 0.2 × 0.2 mm. A total of 2050 unique reflections were measured for $5 < \theta < 27$ and 1759 reflections were used in the refinement. The final parameters were $wR_2 = 0.040$ and $R_1 = 0.032$ [$I > 3\sigma(I)$].

CCDC reference number 280123. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b605244d.

(4*S*,1′*R*,2′*R*,3′*S*,4′*S*)-3-[(3′-Phenylbicyclo[2.2.1]hept-5′-ene-2′-yl)carbonyl]-4-*iso*-propyloxazolidin-2-one (*endo* I)-58

Following general procedure 4, oxazolidinone **52** (155 mg, 0.60 mmol), cyclopentadiene (1.20 mL) and Et_2AlCl (0.47 mL, 1.8 M in toluene, 0.84 mmol) in DCM (1.20 mL) afforded the title compound (4*S*,1′*R*,2′*R*,3′*S*,4′*S*)-**58** (131 mg, 67%) as a pale yellow solid after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40], 1 : 20) with spectroscopic properties consistent with the literature.[23] Authentic samples of all other possible diastereoisomers were prepared as detailed in the ESI. The diastereoisomeric excess was determined by integration of the resonance at δ_H 5.90 (*endo* I)-**58** (C(1′)*H*), δ_H 5.95 (*endo* II)-diastereoisomer (C(1′)*H*), δ_H 6.06 (*exo* I)-diastereoisomer (C(2′)*H*) and δ_H 6.04 (*exo* II)-diastereoisomer (C(2′)*H*).

(4*S*,1′*R*,2′*R*,3′*S*,4′*S*)-3-[(3′-Phenylbicyclo[2.2.1]hept-5′-ene-2′-yl)carbonyl]-4-*tert*-butyloxazolidin-2-one (*endo* I)-59

Following general procedure 4, oxazolidinone **53** (164 mg, 0.60 mmol), cyclopentadiene (1.20 mL) and Et_2AlCl (0.47 mL, 1.8 M in toluene, 0.84 mmol) in DCM (1.20 mL) afforded the title compound (4*S*,1′*R*,2′*R*,3′*S*,4′*S*)-**59** (141 mg, 69%) as a pale yellow oil after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40], 1 : 20); $[\alpha]_D^{23}$ +172.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1779 (C=O_{exo}), 1702 (C=O_{endo}); δ_H (400 MHz, $CDCl_3$) 0.95 (9H, s, C(CH_3)$_3$), 1.63 (1H, dd, *J* 8.7, 1.3, C(7′)H_2), 2.02 (1H, d, *J* 8.6, C(7′)H_2), 2.98 (1H, br s, C(1′)*H*), 3.35–3.36 (1H, m, C(2′)*H*), 3.64 (1H, br s, C(4′)*H*), 4.19–4.23 (2H, m, OCH_2 and C(3′)*H*), 4.28 (1H, dd, *J* 9.2, 1.3, OCH_2), 4.45 (1H, dd, *J* 7.6, 1.3, NC*H*), 5.97 (1H, dd, *J* 5.6, 2.7, C(5′)*H*), 6.56 (1H, dd, *J* 5.4, 3.2, C(6′)*H*), 7.18–7.32 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.7, 35.7, 46.4, 48.2, 48.4, 49.7, 50.7, 61.0, 65.2, 126.1, 127.6, 128.5, 132.3, 140.3, 143.9, 154.5, 173.6; *m*/*z* (ESI$^+$) 398 ([M + MeCN + NH_4]$^+$, 100%,); HRMS (ESI$^+$) $C_{21}H_{26}NO_3$ ([M + H]$^+$) requires 340.1913; found 340.1906. Authentic samples of all other possible diastereoisomers were prepared as detailed in the ESI. The diastereoisomeric excess was determined by integration of the resonances at δ_H 5.97 (*endo* I)-**59** (C(1′)*H*), δ_H 5.90 (*endo* II)-diastereoisomer (C(1′)*H*), δ_H 6.07 (*exo* I)-diastereoisomer (C(2′)*H*) and δ_H 6.43 (*exo* II)-diastereoisomer (C(1′)*H*).

(4*S*,1′*R*,2′*R*,3′*S*,4′*S*)-3-[(3′-Phenylbicyclo[2.2.1]hept-5′-ene-2′-yl)carbonyl]-4-*iso*-propyl-5,5-dimethyloxazolidin-2-one (*endo* I)-60

Following general procedure 4, oxazolidinone **54** (172 mg, 0.60 mmol), cyclopentadiene (1.20 mL) and Et_2AlCl (0.47 mL, 1.8 M in toluene, 0.84 mmol) in DCM (1.20 mL) afforded the title compound (4*S*,1′*R*,2′*R*,3′*S*,4′*S*)-**60** (170 mg, 80%) as a pale yellow solid after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40], 1 : 18); $[\alpha]_D^{25}$ +150.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1772 (C=O_{exo}), 1698 (C=O_{endo}); δ_H (400 MHz, $CDCl_3$) 1.00 (3H, d, *J* 7.0, CH(CH_3)$_2$), 1.02 (3H, d, *J* 7.0, CH(CH_3)$_2$), 1.35 (3H, s, C(CH_3)$_2$), 1.51 (3H, s, C(CH_3)$_2$), 1.61–1.63 (1H, m, C(7′)H_2), 1.99 (1H, d, *J* 8.6, C(7′)H_2), 2.14 (1H, septd, *J* 7.0, 4.0, C*H*(CH$_3$)$_2$), 3.01 (1H, br s, C(1′)*H*), 3.39 (1H, dd, *J* 5.2 and 1.4, C(2′)*H*), 3.64 (1H, br s, C(4′)*H*), 4.19–4.21 (2H, m, NC*H* and C(3′)*H*), 5.97 (1H, dd, *J* 5.7, 2.8, C(5′)*H*), 6.56 (1H, dd, *J* 5.6, 3.2, C(6′)*H*), 7.17–7.32 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.9, 21.4, 21.6, 28.9, 29.7, 46.3, 48.2, 48.3, 49.6, 50.9, 66.2, 82.6, 126.1, 127.6, 128.5, 132.3, 140.3, 144.0, 153.3, 174.2; *m*/*z* (ESI$^+$) 412 ([M + MeCN + NH_4)]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{28}NO_3$ ([M + H]$^+$) requires 354.2069; found 354.2057. Authentic samples of all other possible diastereoisomers were prepared as detailed in the ESI. The diastereoisomeric excess was determined by integration of the resonances at δ_H 5.97

(*endo* I)-**60** (C(1′)*H*), and δ_H 5.90 (*endo* II)-diastereoisomer (C(1′)*H*), δ_H 6.05 (*exo* I)-diastereoisomer (C(2′)*H*) and δ_H 6.43 (*exo* II)-diastereoisomer (C(1′)*H*).

(*S*)-3-(2′-Methylacryloyl)-4-*iso*-propyloxazolidin-2-one 61

Following general procedure 1, (*S*)-4-*iso*-propyloxazolidin-2-one (600 mg, 4.65 mmol), BuLi (2.05 mL, 2.5 M in hexane, 5.12 mmol), and methacryloyl chloride (0.52 mL, 5.35 mmol) in THF (6.8 mL) afforded the title compound **61** (815 mg, 89%) as a white solid after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40], 1 : 5) with spectroscopic properties consistent with the literature.[23]

(*S*)-3-(2′-Methylacryloyl)-4-*tert*-butyloxazolidin-2-one 62

Following general procedure 1, (*S*)-4-*tert*-butyloxazolidin-2-one (665 mg, 4.65 mmol), BuLi (2.05 mL, 2.5 M in hexane, 5.12 mmol), and methacryloyl chloride (0.52 mL, 5.35 mmol) in THF (6.80 mL) afforded the title compound **62** (823 mg, 91%) as a white solid after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40], 1 : 5) with spectroscopic properties consistent with the literature.[31]

(*S*)-3-(2′-Methylacryloyl)-4-*iso*-propyl-5,5-dimethyloxazolidin-2-one 63

Following general procedure 1, 4-(*S*)-*iso*-propyl-5,5-dimethyl-oxazolidin-2-one (700 mg, 4.46 mmol), BuLi (3.07 mL, 1.6 M in hexane, 4.90 mmol), and methacryloyl chloride (0.50 mL, 5.13 mmol) in THF (6.52 mL) afforded the title compound **63** (872 mg, 87%) as a white solid after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40], 1 : 7); mp 44–45 °C; $[\alpha]_D^{24}$ +45.0 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 1769 (C=O_{exo}), 1685 (C=O_{endo}); δ_H (400 MHz, $CDCl_3$) 0.99 (3H, d, *J* 6.8, CH(CH_3)$_2$), 1.03 (3H, d, *J* 6.8, CH(CH_3)$_2$), 1.41 (3H, s, C(CH_3)$_2$), 1.52 (3H, s, C(CH_3)$_2$), 2.07 (3H, s, C(CH_3)=CH_2), 2.17 (1H, septd, *J* 6.8, 3.4, C*H*(CH$_3$)$_2$), 4.19 (1H, d, *J* 3.4, NC*H*), 5.40–5.42 (2H, m, CH_2 = CCH_3); δ_C (100 MHz, $CDCl_3$) 17.0, 19.5, 21.4, 21.5, 29.0, 29.5, 66.1, 82.9, 120.0, 140.0, 152.7, 171.7; *m*/*z* (ESI$^+$) 248 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{20}NO_3$ ([M + H]$^+$) requires 226.1443; found 226.1442.

(4*S*,2′*S*)-3-(3′,3′-Dimethoxy-2′-methylpropionyl)-4-*iso*-propyloxazolidin-2-one 64

Following general procedure 5, oxazolidinone **61** (99 mg, 0.50 mmol), $PdCl_2$ (9 mg, 0.05 mmol), CuCl (50 mg, 0.50 mol) and MeOH (0.51 mL, 12.5 mmol) in DME (1.00 mL) at room temperature for 4 d afforded the title compound **64** (35 mg, 27%, >95% d.e.) as yellow oil after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40], 1 : 7), with spectroscopic properties consistent with the literature;[31] Spectral data of the minor (4*S*,2′*R*)-diastereoisomer is available in the ESI. The diastereoisomeric excess was determined by integration of the resonance at δ_H 4.58 (4*S*,2′*S*)-**64** (C*H*(OCH$_3$)$_2$) and δ_H 4.61 (4*S*,2′*R*)-diastereoisomer (C*H*(OCH$_3$)$_2$).

(4*S*,2′*S*)-3-(3′,3′-Dimethoxy-2′-methylpropionyl)-4-*tert*-butyloxazolidin-2-one 65

Following general procedure 5, oxazolidinone **62** (106 mg, 0.50 mmol), $PdCl_2$ (9 mg, 0.05 mmol), CuCl (50 mg, 0.50 mol) and MeOH (0.51 mL, 12.5 mmol) in DME (1.00 mL) at room temperature for 4 d afforded the title compound **65** (65 mg, 48%) as a yellow oil, after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40], 1 : 7) with spectroscopic properties consistent with the literature;[31] Spectral data of the minor (4*S*,2′*R*)-diastereoisomer is available in the ESI. The diastereoisomeric excess was determined by integration of the resonance at δ_H 4.57 (4*S*,2′*S*)-**65** (C*H*(OCH$_3$)$_2$) and δ_H 4.62 (4*S*,2′*R*)-diastereoisomer (C*H*(OCH$_3$)$_2$).

(4*S*,2′*S*)-3-(3′,3′-Dimethoxy-2′-methylpropionyl)-4-*iso*-propyl-5,5-dimethyloxazolidin-2-one 66

Following general procedure 5, oxazolidinone **63** (113 mg, 0.50 mmol), $PdCl_2$ (9 mg, 0.05 mmol), CuCl (50 mg, 0.50 mol) and MeOH (0.51 mL, 12.5 mmol) in DME (1.00 mL) at room temperature for 4 d afforded the title compound **66** (70 mg, 54%) as a yellow oil, after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40], 1 : 7); mp 66–68 °C; $[\alpha]_D^{23}$ +85.7 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 1763 (C=O_{exo}), 1692 (C=O_{endo}); δ_H (400 MHz, $CDCl_3$) 0.95 (3H, d, *J* 6.9, CH(CH_3)$_2$), 1.02 (3H, d, *J* 6.9, CH(CH_3)$_2$), 1.24 (3H, d, *J* 6.8, CHCH_3), 1.40 (3H, s, C(CH_3)$_2$), 1.51 (3H, s, C(CH_3)$_2$), 2.13 (1H, septd, *J* 6.9, 3.5, C*H*(CH$_3$)$_2$), 3.32 (6H, s, OCH_3), 4.15 (1H, d, *J* 3.5, NC*H*), 4.38–4.43 (1H, m, C*H*CH$_3$), 4.54 (1H, d, *J* 8.3, C*H*(OCH$_3$)$_2$); δ_C (100 MHz, $CDCl_3$) 13.5, 16.9, 21.2, 21.4, 28.2, 29.4, 39.2, 50.7, 55.2, 66.4, 82.7, 105.5, 153.5, 174.6; *m*/*z* (ESI$^+$) 310 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{26}NO_5$ ([M + H]$^+$) requires 288.1811; found 288.1798. Spectral data of the minor (4*S*,2′*R*)-diastereoisomer is available in the ESI. The diastereoisomeric excess was determined by integration of the resonance at δ_H 4.53 (4*S*,2′*S*)-**66** (C*H*(OCH$_3$)$_2$) and δ_H 4.64 (4*S*,2′*R*)-diastereoisomer (C*H*(OCH$_3$)$_2$).

(*R*)-3,3-Dimethoxy-2-methylpropan-1-ol 67

$LiAlH_4$ (0.70 mL, 1.0 M in THF, 0.70 mmol) was added dropwise to a stirred solution of **66** (100 mg, 0.35 mmol) in THF (4.00 mL) at 0 °C. The resultant reaction mixture was stirred for 10 min before ice and EtOAc were added. The resultant mixture was stirred for a further 3 h at room temperature before being filtered through Celite® and dried over $MgSO_4$. Evaporation of the solvent *in vacuo* afforded the crude product as a yellow solid. Purification of this residue *via* Kugelrohr distillation afforded the title compound **67** as a colourless oil (25 mg, 53%) with spectroscopic properties consistent with the literature.[47]

(4*S*,2′*S*)-3-(3′,3′-Diethoxy-2′-methylpropionyl)-4-*iso*-propyloxazolidin-2-one 68

Following general procedure 5, oxazolidinone **61** (99 mg, 0.50 mmol), $PdCl_2$ (9 mg, 0.05 mmol), CuCl (50 mg, 0.50 mol) and EtOH (0.74 mL, 12.5 mmol) in DME (1.00 mL) at room

temperature for 4 d afforded the title compound **68** (83 mg, 55%) as a yellow oil, after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40], 1 : 7) with spectroscopic properties consistent with the literature.[31] Spectral data of the minor (4*S*,2′*R*)-diastereoisomer is available in the ESI. The diastereoisomeric excess was determined by integration of the resonance at δ_H 4.72 (4*S*,2′*S*)-**68** (C*H*(OCH_2CH_3)$_2$) and δ_H 4.78 (4*S*,2′*R*)-diastereoisomer (C*H*(OCH_2CH_3)$_2$).

(4*S*,2′*S*)-3-(3′,3′-Dipropoxy-2′-methylpropionyl)-4-*iso*-propyloxazolidin-2-one 69

Following general procedure 5, oxazolidinone **61** (99 mg, 0.50 mmol), $PdCl_2$ (9 mg, 0.05 mmol), CuCl (50 mg, 0.50 mol) and *n*-PrOH (0.94 mL, 12.5 mmol) in DME (1.00 mL) at room temperature for 4 d afforded the title compound **69** (38 mg, 24%) as a yellow oil after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40], 1 : 7) with spectroscopic properties consistent with the literature.[31] Spectral data of the minor (4*S*,2′*R*)-diastereoisomer is detailed in the ESI. The diastereoisomeric excess was determined by integration of the resonance at δ_H 4.67 (4*S*,2′*S*)-**69** (C*H*($OCH_2CH_2CH_3$)$_2$) and δ_H 4.75 (4*S*,2′*R*)-diastereoisomer (C*H*($OCH_2CH_2CH_3$)$_2$).

(4*S*,2′*S*)-3-(3′,3′-Di-*iso*-propoxy-2′-methylpropionyl)-4-*iso*-propyloxazolidin-2-one 70

Following general procedure 5, oxazolidinone **61** (113 mg, 0.50 mmol), $PdCl_2$ (9 mg, 0.05 mmol), CuCl (50 mg, 0.50 mol) and *i*-PrOH (0.96 mL, 12.5 mmol) in DME (1.00 mL) at room temperature for 4 d afforded the title compound **70** (35 mg, 22%) as a yellow oil after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40], 1 : 7); $[\alpha]_D^{24}$ +83.2 (*c* 0.8 in $CHCl_3$); ν_{max} (film) 1782 (C=O_{exo}), 1700 (C=O_{endo}); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, d, *J* 7.0, CH(CH_3)$_2$), 0.93 (3H, d, *J* 7.0, CH(CH_3)$_2$), 1.05 (3H, d, *J* 7.0, OCH(CH_3)$_2$), 1.10 (3H, d, *J* 6.5, OCH(CH_3)$_2$), 1.20 (3H, d, *J* 6.9, OCH(CH_3)$_2$), 1.24 (3H, d, *J* 7.0, OCH(CH_3)$_2$), 1.27 (3H, d, *J* 7.1, CHCH_3), 2.36 (1H, septd, *J* 7.0, 4.1, CH(CH_3)$_2$), 3.85–3.91 (1H, m, OC*H*(CH_3)$_2$), 3.96–4.03 (1H, m, OC*H*(CH_3)$_2$), 4.19–4.26 (3H, m, NC*H* and OCH_2), 4.38–4.41 (1H, m, C*H*CH_3), 4.78 (1H, d, *J* 7.6, C*H*(O(CH(CH_3)$_2$)$_2$); δ_C (100 MHz, $CDCl_3$) 13.4, 14.9, 18.0, 21.8, 23.1, 23.3, 23.6, 28.8, 42.1, 58.8, 63.3, 67.6, 68.7, 100.9, 153.8, 174.2; *m*/*z* (ESI$^+$) 374 ([M + MeCN + NH_4]$^+$, 28%), 338 ([M + Na]$^+$, 28); HRMS (ESI$^+$) $C_{16}H_{29}NO_5Na$ ([M + Na]$^+$) requires 338.1943; found 338.1938. Spectral data of the minor (4*S*,2′*R*)-diastereoisomer is detailed in the ESI. The diastereoisomeric excess was determined by integration of the resonance at δ_H 4.76 (4*S*,2′*S*)-**70** (C*H*(OCH(CH_3)$_2$)$_2$) and δ_H 4.88 (4*S*,2′*R*)-diastereoisomer (C*H*(OCH(CH_3)$_2$)$_2$).

(4*S*,2′*S*)-3-(3′,3′-Diethoxy-2′-methylpropionyl)-4-*tert*-butyloxazolidin-2-one 71

Following general procedure 5, oxazolidinone **62** (106 mg, 0.50 mmol), $PdCl_2$ (9 mg, 0.05 mmol), CuCl (50 mg, 0.50 mol) and EtOH (0.74 mL, 12.5 mmol) in DME (1.00 mL) at room temperature for 4 d afforded the title compound **71** (83 mg, 55%, 96% d.e.) as a yellow oil after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40], 1 : 7); $[\alpha]_D^{23}$ +120.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1780 (C=O_{exo}), 1705 (C=O_{endo}); δ_H (400 MHz, $CDCl_3$) 0.93 (9H, s, C(CH_3)$_3$), 1.13 (3H, t, *J* 7.1, CH_2CH_3), 1.21 (3H, t, *J* 7.1, CH_2CH_3), 1.25 (3H, d, *J* 7.0, CHCH_3), 3.42–3.51 (1H, m, CH_2CH_3), 3.56–3.62 (2H, m, OCH_2CH_3), 3.66–3.72 (1H, m, OCH_2CH_3), 4.18–4.20 (1H, m, OCH_2), 4.26–4.34 (2H, m, OCH_2 and C*H*CH_3), 4.42 (1H, dd, *J* 7.4 and 1.4, NC*H*), 4.64 (1H, d, *J* 8.3, C*H*(OCH_2CH_3)$_2$); δ_C (100 MHz, $CDCl_3$) 13.9 (CH*C*H_3), 15.1, 15.3, 25.6, 35.7, 40.3, 59.6, 61.2, 63.6, 65.1, 103.9, 154.5, 174.3; *m*/*z* (ESI$^+$) 324 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{15}H_{27}NO_5Na$ ([M + H]$^+$) requires 324.1787; found 324.1794. Spectral data of the minor (4*S*,2′*R*)-diastereoisomer is reported in the ESI. The diastereoisomeric excess was determined by integration of the resonance at δ_H 4.63 (4*S*,2′*S*)-**71** (C*H*(OCH_2CH_3)$_2$) and δ_H 4.78 (4*S*,2′*R*)-diastereoisomer (C*H*(OCH_2CH_3)$_2$).

(4*S*,2′*S*)-3-(3′,3′-Dipropoxy-2′-methylpropionyl)-4-*tert*-butyloxazolidin-2-one 72

Following general procedure 5, oxazolidinone **62** (106 mg, 0.50 mmol), $PdCl_2$ (9 mg, 0.05 mmol), CuCl (50 mg, 0.50 mol) and *n*-PrOH (0.94 mL, 12.5 mmol) in DME (1.00 mL) at room temperature for 4 d afforded the title compound **72** (74 mg, 45%) as a colourless oil after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40], 1 : 7); $[\alpha]_D^{22}$ +95.2 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1784 (C=O_{exo}), 1704 (C=O_{endo}); δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, *J* 7.4, $OCH_2CH_2CH_3$), 0.93 (9H, s, C(CH_3)$_3$), 0.93–0.96 (3H, m, $OCH_2CH_2CH_3$), 1.25 (3H, d, *J* 6.9, CHCH_3), 1.47–1.66 (4H, m, $OCH_2CH_2CH_3$), 3.31–3.37 (1H, m, O$CH_2CH_2CH_3$), 3.44–3.50 (2H, m, O$CH_2CH_2CH_3$), 3.57–3.62 (1H, m, O$CH_2CH_2CH_3$), 4.18 (1H, dd, *J* 8.9, 7.6, OCH_2), 4.26 (1H, d, *J* 9.2, OCH_2), 4.32–4.39 (1H, m, C*H*CH_3), 4.41 (1H, d, *J* 7.5, NC*H*), 4.64 (1H, d, *J* 8.3, C*H*($OCH_2CH_2CH_3$)$_2$); δ_C (100 MHz, $CDCl_3$) 10.5, 10.7, 13.9, 22.9, 23.1, 25.6, 35.7, 40.1, 61.1, 65.1, 65.5, 69.7, 104.0, 154.5, 173.7; *m*/*z* (ESI$^+$) 388 ([M + MeCN + NH_4]$^+$, 100%); HRMS (ESI$^+$) $C_{17}H_{31}NO_5Na$ ([M + Na]$^+$) requires 352.2100; found 352.2100. Spectral data of the minor (4*S*,2′*R*)-diastereoisomer is reported in the ESI. The diastereoisomeric excess was determined by integration of the resonance at δ_H 4.63 (4*S*,2′*S*)-**72** (C*H*($OCH_2CH_2CH_3$)$_2$) and δ_H 4.78 (4*S*,2′*R*)-diastereoisomer (C*H*($OCH_2CH_2CH_3$)$_2$).

(4*S*,2′*S*)-3-(3′,3′-Di-*iso*-propoxy-2′-methylacryloyl)-4-*tert*-butyloxazolidin-2-one 73

Following general procedure 5, oxazolidinone **62** (106 mg, 0.50 mmol), $PdCl_2$ (9 mg, 0.05 mmol), CuCl (50 mg, 0.50 mol) and *i*-PrOH (0.96 mL, 12.5 mmol) in DME (1.00 mL) at room temperature for 4 d afforded the title compound **73** (64 mg, 39%, >99% d.e.) as a yellow oil after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40], 1 : 7); $[\alpha]_D^{24}$ +86.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1783 (C=O_{exo}), 1704 (C=O_{endo}); δ_H (400 MHz, $CDCl_3$) 0.93 (9H, s, C(CH_3)$_3$), 1.04 (3H, d, *J* 6.0, OCH(CH_3)$_2$), 1.13 (3H, d, *J* 6.2, OCH(CH_3)$_2$), 1.16 (3H, d, *J* 6.1, OCH(CH_3)$_2$), 1.20 (3H, d, *J* 6.2, OCH(CH_3)$_2$), 1.26 (3H, d, *J* 6.9, CHCH_3), 3.84–3.88 (1H, m, OC*H*(CH_3)$_2$),

3.99–4.03 (1H, m, OC*H*$(CH_3)_2$), 4.18 (1H, dd, *J* 9.1, 7.5, OCH_2), 4.26–4.32 (2H, m, OCH_2 and C*H*CH_3), 4.40 (1H, dd, *J* 7.4, 1.2, NC*H*), 4.71 (1H, d, *J* 8.0, C*H*$((OCH(CH_3)_2)_2)$; δ_C (50 MHz, $CDCl_3$) 14.5, 22.1, 23.7, 23.8, 24.1, 26.1, 36.1, 41.8, 61.6, 65.5, 67.7, 68.9, 101.2, 155.0, 174.7; *m*/*z* (ESI^+) 388 ($[M + MeCN + NH_4]^+$, 100%); HRMS (ESI^+) $C_{17}H_{31}NO_5Na$ ($[M + Na]^+$) requires 352.2100; found 352.2101. Spectral data of the minor fraction (4*S*,2′*R*)-oxazolidinone is reported in the ESI. The diastereoisomeric excess was determined by integration of the resonance at δ 4.71 (4*S*,2′*S*)-**73** (C*H*$(OCH(CH_3)_2)_2$) and δ 5.02 (4*S*,2′*R*)-oxazolidinone (C*H*$(OCH(CH_3)_2)_2$).

(4*S*,2′*S*)-3-(3′,3′-Diethoxymethylacryloyl)-4-*iso*-propyl-5,5-dimethyloxazolidin-2-one 74

Following general procedure 5, oxazolidinone **63** (113 mg, 0.50 mmol), $PdCl_2$ (9 mg, 0.05 mmol), CuCl (50 mg, 0.50 mol) and EtOH (0.74 mL, 12.5 mmol) in DME (1.00 mL) at room temperature for 4 d afforded the title compound **74** (113 mg, 72%) as a yellow oil after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40], 1 : 7); $[a]_D^{23}$ +73.6 (*c* 0.5 in $CHCl_3$); ν_{max} (film) 1778 (C=O_{exo}), 1699 (C=O_{endo}); δ_H (400 MHz, $CDCl_3$) 0.94 (3H, d, *J* 6.9, CH(C$H_3)_2$), 1.02 (3H, d, *J* 6.9, CH(C$H_3)_2$), 1.11 (3H, t, *J* 7.1, OCH_2CH_3), 1.20 (3H, t, *J* 7.1, OCH_2CH_3), 1.24 (3H, d, *J* 6.9, CHCH_3), 1.39 (3H, s, C(C$H_3)_2$), 1.50 (3H, s, C(C$H_3)_2$), 2.13 (1H, septd, *J* 6.9, 3.5, C*H*$(CH_3)_2$), 3.43–3.50 (1H, m, OCH_2CH_3), 3.55–3.72 (3H, m, OCH_2CH_3), 4.13 (1H, d, *J* 3.5, NC*H*), 4.30–4.37 (1H, m, C*H*CH_3), 4.68 (1H, d, *J* 8.4, C*H*$(OCH_2CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 14.0, 15.1, 15.3, 17.0, 21.3, 21.5, 28.4, 29.5, 40.3, 59.6, 63.4, 66.4, 82.7, 104.0, 153.5, 174.9; *m*/*z* (ESI^+) 374 ($[M + MeCN + NH_4]^+$, 100%); HRMS (ESI^+) $C_{16}H_{33}N_2O_5$ ($[M + NH_4]^+$) requires 333.2389; found 333.2400. Spectral data of the minor fraction (4*S*,2′*R*)-oxazolidinone is reported in the ESI. The diastereoisomeric excess was determined by integration of the resonance at δ 4.64 (4*S*,2′*S*)-**74** (C*H*$(OCH_2CH_3)_2$) and δ 4.77 (4*S*,2′*R*)-oxazolidinone (C*H*$(OCH_2CH_3)_2$).

(4*S*,2′*S*)-3-(3′,3′-Dipropoxy-2′-methylacryloyl)-4-*iso*-propyl-5,5-dimethyloxazolidin-2-one 75

Following general procedure 5, oxazolidinone **63** (113 mg, 0.50 mmol), $PdCl_2$ (9 mg, 0.05 mmol), CuCl (50 mg, 0.50 mol) and *n*-PrOH (0.94 mL, 12.5 mmol) in DME (1.00 mL) at room temperature for 4 d afforded the title compound **75** (103 mg, 60%) as a yellow oil after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40], 1 : 7); $[a]_D^{23}$ +77.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1779 (C=O_{exo}), 1699 (C=O_{endo}); δ_H (400 MHz, $CDCl_3$) 0.85 (3H, t, *J* 7.4, $OCH_2CH_2CH_3$), 0.92-.096 (6H, m, CH(C$H_3)_2$ and $OCH_2CH_2CH_3$), 1.02 (3H, d, *J* 7.0, CH(C$H_3)_2$), 1.25 (3H, d, *J* 6.8, CHCH_3), 1.39 (3H, s, C(C$H_3)_2$), 1.43–1.65 (4H, m, $OCH_2CH_2CH_3$), 1.50 (3H, s, C(C$H_3)_2$), 2.13 (1H, septd, *J* 7.0, 3.5, C*H*$(CH_3)_2$), 3.34–3.40 (1H, m, OC$H_2CH_2CH_3$), 3.44–3.52 (2H, m, OC$H_2CH_2CH_3$), 3.54–3.60 (1H, m, OC$H_2CH_2CH_3$), 4.13 (1H, d, *J* 3.5, NC*H*), 4.29–4.36 (1H, m, C*H*CH_3), 4.70 (1H, d, *J* 8.4, C*H*$(OCH_2CH_2CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 10.6, 10.8, 14.1, 17.0, 21.3, 21.5, 22.8, 23.1, 28.4, 29.5, 40.4, 65.6, 66.3, 69.6, 82.7, 104.0, 153.4, 174.9; *m*/*z* (ESI^+) 402 ($[M + MeCN + NH_4]^+$, 100%); HRMS (ESI^+) $C_{18}H_{34}NO_5$ ($[M + H]^+$) requires 344.2437; found 344.2445. Spectral data of the minor fraction (4*S*,2′*R*)-oxazolidinone is reported in the ESI. The diastereoisomeric excess was determined by integration of the resonance at δ 4.68 (4*S*,2′*S*)-**75** (C*H*$(OCH_2CH_2CH_3)_2$) and δ 4.79 (4*S*,2′*R*)-oxazolidinone (C*H*$(OCH_2CH_2CH_3)_2$).

(4*S*,2′*S*)-3-(3′,3′-Di-*iso*-propoxy-2′-methylacryloyl)-4-*iso*-propyl-5,5-dimethyloxazolidin-2-one 76

Following general procedure 5, oxazolidinone **63** (113 mg, 0.50 mmol), $PdCl_2$ (9 mg, 0.05 mmol), CuCl (50 mg, 0.50 mol) and *i*-PrOH (0.96 mL, 12.5 mmol) in DME (1.00 mL) at room temperature for 4 d to afforded the title compound **76** (55 mg, 32%) as a yellow oil after purification *via* column chromatography on silica (EtOAc–petroleum ether [30–40], 1 : 7); $[a]_D^{22}$ +74.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1779 (C=O_{exo}), 1700 (C=O_{endo}); δ_H (400 MHz, $CDCl_3$) 0.95 (3H, d, *J* 6.9, CH(C$H_3)_2$), 1.02 (3H, d, *J* 6.9, CH(C$H_3)_2$), 1.05 (3H, d, *J* 6.1, OCH(C$H_3)_2$), 1.12 (3H, d, *J* 6.2, OCH(C$H_3)_2$), 1.17 (3H, d, *J* 6.1, OCH(C$H_3)_2$), 1.21 (3H, d, *J* 6.2, OCH(C$H_3)_2$), 1.27 (3H, d, *J* 6.9, CHCH_3), 1.42 (3H, s, C(C$H_3)_2$), 1.51 (3H, s, C(C$H_3)_2$), 2.14 (1H, septd, *J* 6.9, 3.5, C*H*$(CH_3)_2$), 3.87–3.93 (1H, m, OC*H*$(CH_3)_2$), 3.98–4.05 (1H, m, OC*H*$(CH_3)_2$), 4.13 (1H, d, *J* 3.5, NC*H*), 4.25–4.32 (1H, m, C*H*CH_3), 4.80 (1H, d, *J* 8.1, C*H*$(OCH(CH_3)_2)_2$); δ_C (100 MHz, $CDCl_3$) 14.3, 17.0, 21.3, 21.5, 23.4, 23.4, 23.7, 25.3, 28.5, 29.5, 41.7, 66.3, 67.5, 68.2, 82.6, 101.2, 153.4, 174.9; *m*/*z* (ESI^+) 402 ($[M + MeCN + NH_4]^+$, 100%); HRMS (ESI^+) $C_{18}H_{33}NO_5Na$ ($[M + Na]^+$) requires 366.2256; found 366.2247. Spectral data of the minor fraction (4*S*,2′*R*)-oxazolidinone is reported in the ESI. The diastereoisomeric excess was determined by integration of the resonance at δ 4.78 (4*S*,2′*S*)-**75** (C*H*$(OCH(CH_3)_2)_2$) and δ 4.98 (4*S*,2′*R*)-oxazolidinone (C*H*$(OCH(CH_3)_2)_2$).

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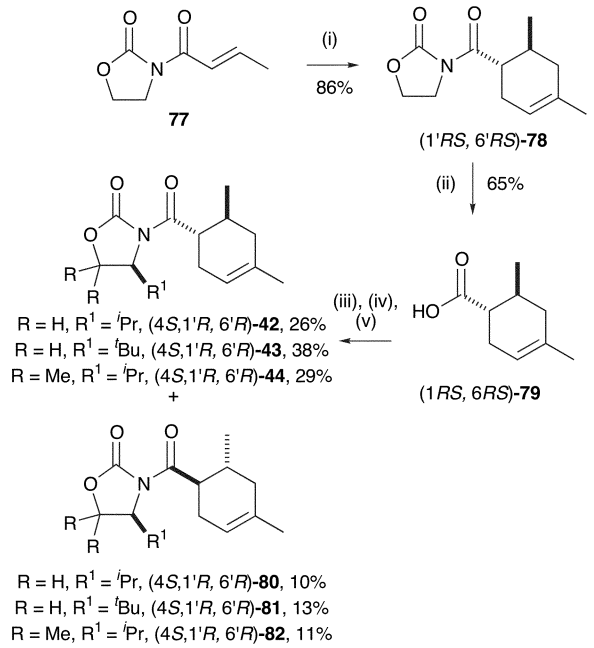
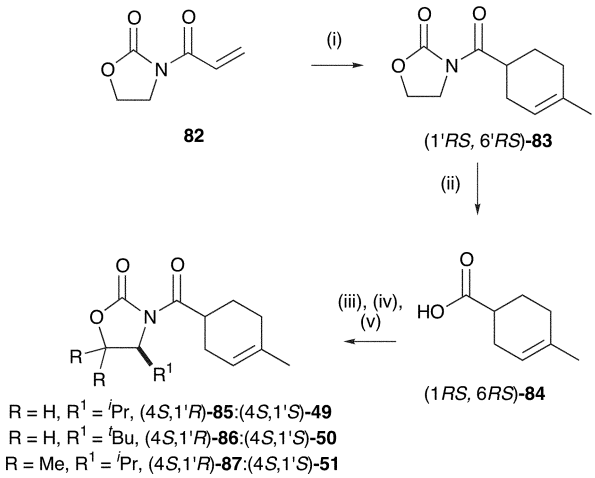
24 To unambiguously assess the diastereoselectivity of these Diels–Alder reactions, authentic samples of the *endo*-diastereoisomers arising from the cycloadditions were prepared following the protocol below. Reaction of achiral *N*-acyloxazolidin-2-one **77** with excess isoprene and Et_2AlCl afforded **78** in 86% yield, with hydrolysis with LiOH and H_2O_2 affording acid **79** in 65% yield. Acid **79** was treated successively with oxalyl chloride and the lithium anion of the corresponding oxazolidinone, yielding a 50 : 50 mixture of the two diastereoisomeric *N*-acyl products (4*S*,1′*S*,6′*S*)-**80**–**82** and (4*S*,1′*R*,6′*R*)-**42**–**44** that were separated by exhaustive chromatography (Scheme 11). See the ESI for experimental details.

25 Authentic samples of the *endo*-diastereoisomers arising from the cycloadditions were prepared following the protocol below. Reaction of *N*-propenoyloxazolidin-2-one **82** with isoprene and Et_2AlCl afforded **83**, with hydrolysis with LiOH and H_2O_2 affording acid **84**. Acid **84** was treated successively with oxalyl chloride and the lithium anion of the corresponding oxazolidinone, yielding a 50 : 50 mixture of the two diastereoisomeric *N*-acyl products (4*S*,1′*S*)-**49**–**51** and (4*S*,1′*R*)-**85**–**87** (Scheme 12). See the ESI for experimental details.

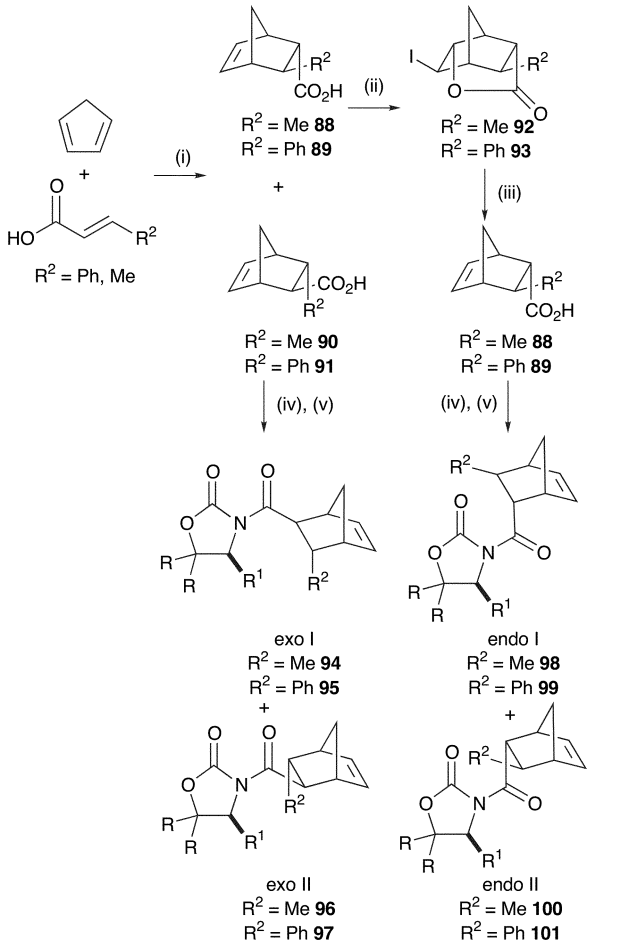
26 *trans*-Cinnamic acid and *trans*-crotonic acid with were heated to reflux with cyclopentadiene giving the desired racemic products in 56 and 50% isolated yields, respectively as inseparable *endo* : *exo* mixtures in a ratio of 57 : 43 (from crotonic acid) and 42 : 58 (from cinnamic acid) after chromatography. The *endo*- and *exo*-cycloadducts **88**–**89** and **90**–**91**, respectively were separated by iodolactonisation; *endo*-**88** and **89** gave the corresponding iodolactone, while *exo*-acids **90** and **91** were unreactive under these conditions. Separation of the resultant products afforded diastereoisomerically pure *exo*-acids **90** and **91** in 22 and 40% yield, respectively, and the lactones **92** and **93** in 47 and 42% yield, respectively. Subsequent retroiodolactonisation of **92** and **93** furnished diastereomerically pure *endo*-acids **88** and **89** in 87 and 65% yield. Conversion of **88**–**91** to the corresponding acid chlorides



Scheme 11 *Reagents and conditions*: (i) isoprene, Et_2AlCl, DCM, −30 °C; (ii) LiOH, H_2O_2, H_2O, THF, 0 °C to rt; (iii) oxalyl chloride, DMF, DCM, 0 °C to rt; (iv) lithium anion of 4-*iso*-propyl, 4-*tert*-butyl and 5,5-dimethyl-4-*iso*-propyloxazolidinones, THF, −78 °C; (v) 0 °C.



Scheme 12 *Reagents and conditions*: (i) isoprene, Et_2AlCl, DCM, −30 °C; (ii) LiOH, H_2O_2, H_2O, THF, 0 °C to rt; (iii) oxalyl chloride, DMF, DCM, 0 °C to rt; (iv) lithium anion of 4-*iso*-propyl, 4-*tert*-butyl and 5,5-dimethyl-4-*iso*-propyloxazolidin-2-ones, THF, −78 °C; (v) 0 °C.



Scheme 13 *Reagents and conditions*: (i) cyclopentadiene, Δ; (ii) $NaHCO_3$, KI, I_2, H_2O, THF; (iii) Zn, TMSCl, AcOH, Et_2O; (iv) thionyl chloride, Δ; or oxalyl chloride, DMF, DCM, 0 °C to rt; (v) lithium anion of 4-*iso*-propyl, 4-*tert*-butyl and 5,5-dimethyl-4-*iso*-propyloxazolidin-2-ones, THF, −78 °C then 0 °C.

and treatment with the lithium anion of the corresponding oxazolidin-2-ones gave authentic samples of **94**–**101** (Scheme 13). See the ESI for experimental details.

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