Asymmetric three- and [2 + 1]-component conjugate addition reactions for the stereoselective synthesis of polysubstituted piperidinones†

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The efficiency and stereoselectivity of the conjugate addition of lithium (*Z*)- or (*E*)-β-amino ester enolates, generated by lithium amide conjugate addition to an α,β-unsaturated ester or deprotonation of a β-amino ester, respectively, to a range of α,β-unsaturated acceptors has been investigated. Deprotonation of a β-amino ester with LDA, followed by conjugate addition to a chiral α,β-unsaturated oxazolidinone gives high 2,3-*anti* selectivity (~90% d.e.), with hydrogenolysis and purification to homogeneity generating stereodefined trisubstituted piperidinones as single stereoisomers. Asymmetric three-component couplings of α,β-unsaturated esters and alkylidene malonates initiated by lithium amide conjugate addition proceeds with high levels of 2,3-*anti* stereoselectivity, with hydrogenolysis giving tetrasubstituted piperidinones.

Introduction

The piperidine ring is a common feature of numerous alkaloid natural products with immense structural diversity, ranging from simple 2-substituted derivatives such as (*S*)-coniine **1** and (*S*)-anabasine **2** to complex polycyclic products such as morphine **3** (Fig. 1). Although less prominent in nature, the related piperidinone structural family, as represented by adalinine **4** and adaline **5**, have received increasing interest, as these versatile scaffolds readily serve as advanced intermediates for piperidine synthesis. Numerous methodologies have been developed for the synthesis of these related structural classes in enantiomerically pure form, and this area of research has been extensively reviewed.[1]

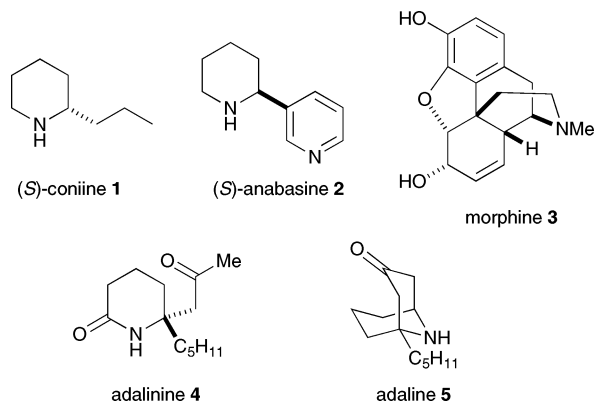
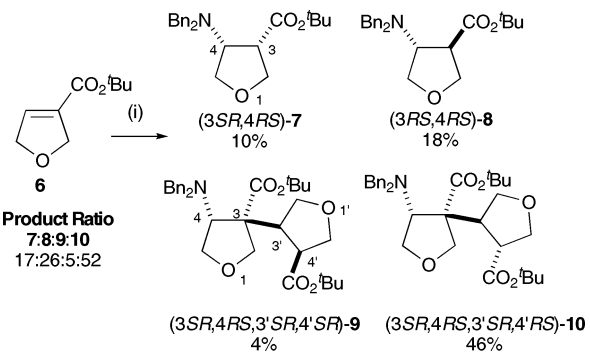


Fig. 1 Natural products containing the piperidine and piperidinone skeletons.

Previous investigations from this laboratory have shown that a variety of *N*-alkyl lithium amides derived from α-methylbenzylamine may be considered as efficient homochiral ammonia equivalents,[2,3] with conjugate addition, followed by enolate functionalisation[4,5] giving rise to a range of enantiomerically pure β-amino acid derivatives.[6] In these conjugate addition reactions, only the discrete monomeric β-amino ester products are normally observed, with no observable oligomerisation of the α,β-unsaturated ester, consistent with the rate of lithium amide conjugate addition to the α,β-unsaturated ester being considerably greater than the rate of β-amino enolate conjugate addition. Although conjugate addition and intramolecular cyclisation reactions occur upon addition of lithium amides to dienedioates,[7–9] we have recently reported that addition of *tert*-butyl 2,5-dihydrofuran-3-carboxylate **6** to lithium dibenzylamide (1.6 eq.) gave a complex mixture of four products **7**–**10**, comprising the C(3)-epimeric β-amino esters **7** and **8**, and the oligomeric β-amino esters **9** and **10**, which presumably derive from conjugate addition of the *in situ* generated (*Z*)-β-amino lithium enolate to **6** (Scheme 1).[10]



Scheme 1 *Reagents and conditions*: (i) lithium dibenzylamide, THF, −78 °C.

In order to probe the possible synthetic applications of this oligomerisation protocol, an investigation concerned with the ability of lithium amides to promote the bespoke stereoselective oligomerisation of α,β-unsaturated acceptors was instigated. While it was expected that regiocontrol in such anionic processes

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may be complicated by competing 1,2-addition,[11] the ability to promote stereoselective and discrete oligomerisation rather than initiate uncontrolled polymerisation was envisaged to be the main synthetic hurdle within this reaction manifold. In the literature, several groups have reported controlled anionic dimerisation procedures of α,β-unsaturated acceptors.[12] For example, Mioskowski *et al.* have noted the formation of discrete oligomeric products upon conjugate addition to nitroalkenes,[13] while Takahashi *et al.* have utilised multiple conjugate addition reactions as an approach to steroidal building blocks.[14] Similarly, Ley *et al.* have demonstrated that the lithium anion of a glycolic acid derivative allows the asymmetric coupling of α,β-unsaturated lactones and nitroalkenes,[15] and Hanessian *et al.* have shown that chiral phosphonamides can be used for consecutive asymmetric conjugate additions.[16] It was envisaged that addition of an α,β-unsaturated acceptor to lithium (*Z*)- or (*E*)-β-amino enolates, generated either from lithium amide conjugate addition to an α,β-unsaturated acceptor or deprotonation of a β-amino ester, respectively, would selectively promote the oligomerisation process *via* three- and [2 + 1]-component couplings. *N*-Benzyl deprotection and intramolecular cyclisation of the resulting β-amino acid derivatives would give rise to polysubstituted, stereodefined piperidinones (Fig. 2). We report herein our full investigations within this area, part of which has been communicated previously.[17]

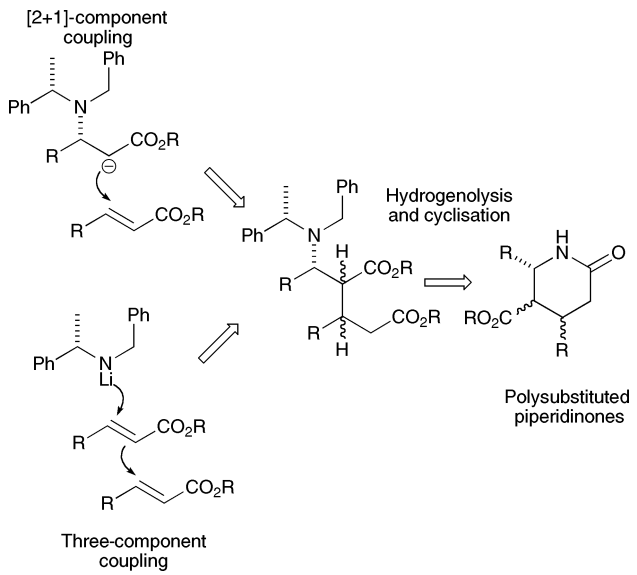
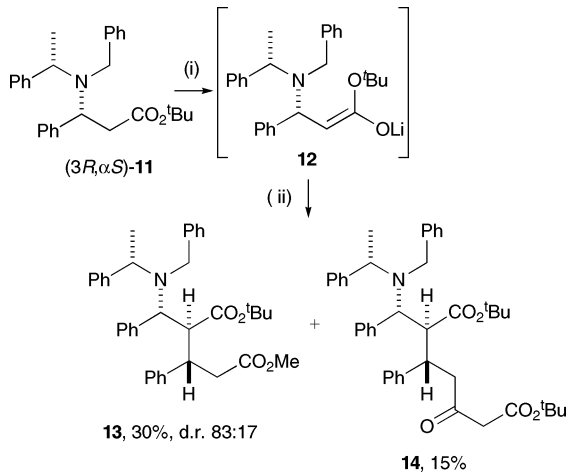


Fig. 2 Proposed three- and [2 + 1]-component conjugate addition reactions for the synthesis of piperidinones.

Results and discussion

Stepwise [2 + 1]-component coupling reactions of lithium β-amino enolates with α,β-unsaturated esters and oxazolidinones

Initial investigations concentrated upon a stepwise [2 + 1]-component coupling procedure involving generation of the lithium (*E*)-enolate **12**[18] of the known β-amino ester (3*R*,α*S*)-**11** and subsequent reaction with an α,β-unsaturated acceptor. It was envisaged that screening of the susceptibility of a range of α,β-unsaturated esters acceptors in this reaction manifold would enable their reactivity to be quantified and facilitate high reaction diversity. Deprotonation of (3*R*,α*S*)-**11** with LDA (1.1 eq.) gave lithium (*E*)-β-amino enolate **12**, with subsequent addition of *tert*-butyl acrylate resulting in polymerisation of the activated olefin. Similarly, addition of *tert*-butyl methylene malonate to lithium (*E*)-β-amino enolate **12** gave a complex mixture of oligomeric products. Although addition of *tert*-butyl cinnamate to β-amino enolate **12** returned only starting material, addition of methyl cinnamate to β-amino enolate **12** and warming to 0 °C gave, at approximately 60% conversion, a complex crude product mixture that upon purification gave the desired product (2*S*,3*S*,1′*R*,α*S*)-**13** in 66% d.e.[19] and 30% yield, and the β-keto ester (2*S*,3*S*,1′*R*,α*S*)-**14**[20] in 15% yield (Scheme 2).[21]



Scheme 2 *Reagents and conditions*: (i) **11** (1.0 eq.), LDA (1.1 eq.), THF, −78 °C to 0 °C; (ii) methyl cinnamate, THF, −78 °C to 0 °C.

Recrystallisation of **13** to homogeneity and subsequent single-crystal X-ray analysis established the relative configuration within **13**, with the absolute (2*S*,3*S*,1′*R*,α*S*) configuration established relative to the known (*S*)-α-methylbenzyl fragment, allowing unambiguous assignment of the preferential C(2)–C(3) *anti*-selectivity for the conjugate addition process (Fig. 3).

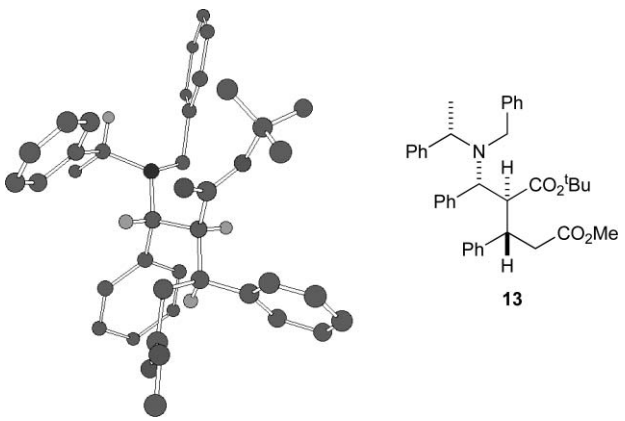


Fig. 3 Chem 3D representation of the X-ray crystal structure of (2*S*,3*S*,1′*R*,α*S*)-**13** (some H atoms removed for clarity).

In order to promote further the desired conjugate addition manifold, it was reasoned that the formation of a stable enolate could drive the reaction, preventing any possible polymerisation or retro-conjugate addition. *N*-Cinnamoyl oxazolidinones were

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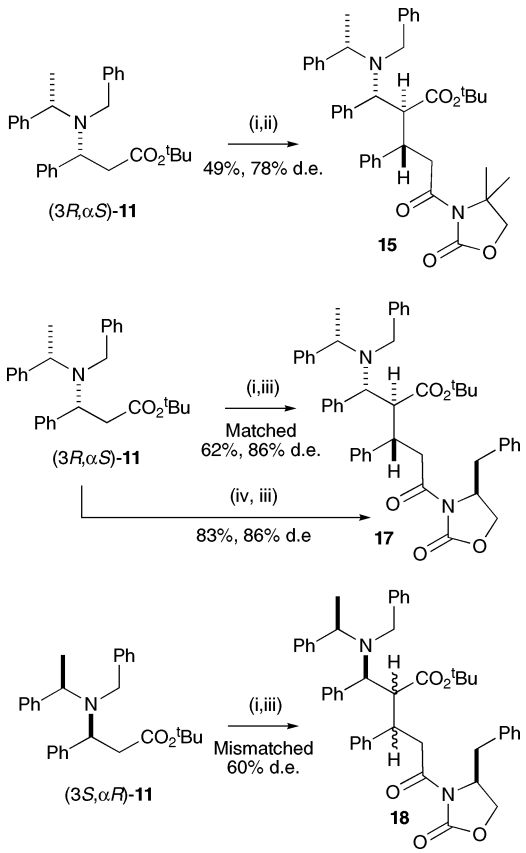
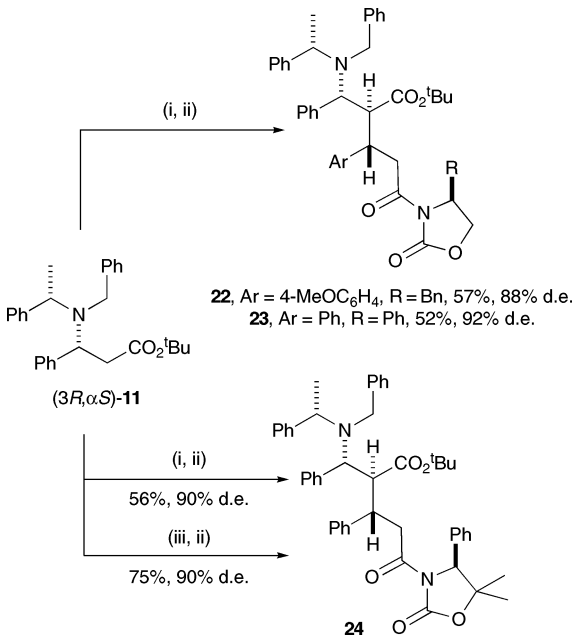
considered to fulfil these properties, as conjugate addition of the β-amino enolate **12** to such an oxazolidinone derivative would generate a stable chelated enolate, while the steric encumberance of the oxazolidinone would disfavour any competitive 1,2-addition. Indeed, addition of *N*-cinnamoyl-4,4-dimethyl-oxazolidin-2-one to lithium (*E*)-β-amino enolate **12** gave an inseparable 89 : 11 mixture of diastereoisomers **15**, isolated in 49% yield and 78% d.e. after purification.[22] Encouraged by this result, it was proposed that higher levels of stereoselectivity in this protocol could be achieved by employing double asymmetric induction.[23] In the matched case, addition of homochiral (*S*)-*N*-cinnamoyl-4-benzyl-oxazolidin-2-one **16** to lithium (*E*)-β-amino enolate **12** gave (2*S*,3*S*,1′*R*,4″*S*,α*S*)-**17** in 86% d.e. and 62% yield, while addition of oxazolidinone (*S*)-**16** to the enantiomeric lithium (*E*)-β-amino enolate **12** derived from (3*S*,α*R*)-**11** proceeded to give **18** in only low conversion (~30%) and 60% d.e.[24] Further optimisation of the matched combination [lithium (*E*)-β-amino enolate **12** and (*S*)-**16**] by changing the reaction stoichiometry gave improved yields of the desired product **17**: addition of 1.6 eq. of lithium (*E*)-β-amino enolate **12** to *N*-cinnamoyl oxazolidinone **16** gave **17** with identical stereoselectivity (86% d.e.), but in an improved 83% yield (Scheme 3).



Scheme 3 *Reagents and conditions*: (i) **11** (1.0 eq.), LDA (1.1 eq.), THF, −78 °C to 0 °C; (ii) *N*-cinnamoyl-4,4-dimethyl-oxazolidin-2-one (1.0 eq.), THF, −78 °C to rt; (iii) (*S*)-*N*-cinnamoyl-4-benzyl-oxazolidin-2-one **16** (1.0 eq.), THF, −78 °C to 0 °C; (iv) **11** (1.6 eq.), LDA (1.7 eq.), THF, −78 °C to 0 °C.

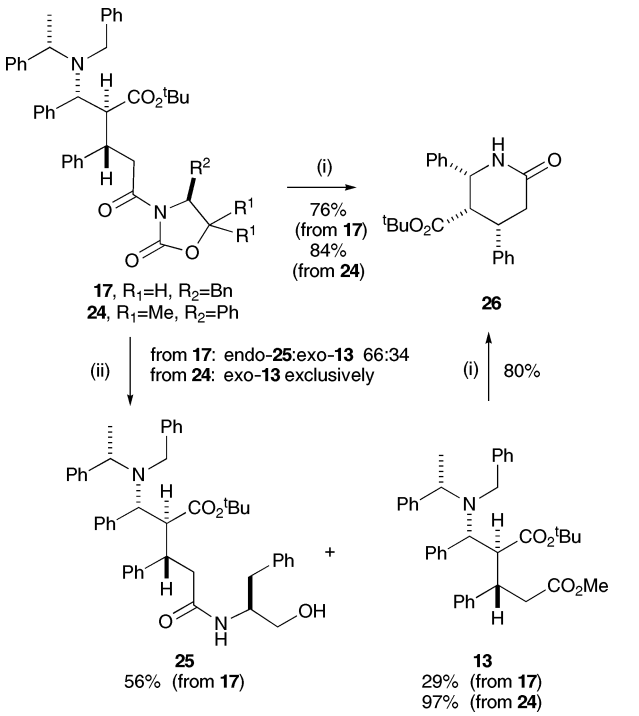
Further application of the 'matched' combination of this double asymmetric induction protocol was next investigated. (*S*)-4-Benzyl-*N*-(*p*-methoxycinnamoyl)oxazolidinone **19**, (*S*)-4-phenyl-*N*-cinnamoyloxazolidinone **20** and (*S*)-4-phenyl-5,5-dimethyl-*N*-cinnamoyloxazolidinone **21** were used as the chiral α,β-unsaturated acceptor components, furnishing the desired products (2*S*,3*S*,1′*R*,4″*S*,α*S*)-**22**–**24** in 88, 92 and 90% d.e. and in 57, 52 and 56% isolated yields respectively. It is noteworthy that the 4-benzyl- and 4-phenyloxazolidinones offer similar levels of stereocontrol in this reaction manifold, in marked contrast to the vastly different levels of diastereoselectivity observed upon addition of organocuprates to similar systems.[25] An improved yield of oxazolidinone derivative **24** could be achieved using 1.6 eq. of lithium (*E*)-β-amino enolate **12** in the addition to oxazolidinone **19**, giving **24** in 75% isolated yield (Scheme 4).



Scheme 4 *Reagents and conditions*: (i) **11** (1.0 eq.), LDA (1.1 eq.), THF, −78 °C to 0 °C; (ii) (*S*)-*N*-*p*-methoxycinnamoyl-4-benzyloxazolidinone **19** (1.0 eq.) or (*S*)-*N*-cinnamoyl-4-phenyloxazolidinone **20** (1.0 eq.) or (*S*)-4-phenyl-5,5-dimethyl-*N*-cinnamoyloxazolidinone **21** (1.0 eq.), THF, −78 °C to 0 °C; (iii) **11** (1.6 eq.), LDA (1.7 eq.), THF, −78 °C to 0 °C.

The absolute configurations within **17** and **24** were proven by chemical correlation. Treatment of SuperQuat oxazolidinone derivative **24** with LiOMe in MeOH gave diester **13** in 97% yield by regioselective exocyclic cleavage[26] of the oxazolidinone auxiliary, while under the same reaction conditions oxazolidinone **17** gave a 66 : 34 ratio of (2*S*,3*S*,1′*R*,4″*S*,α*S*)-**25** and **13**, the products of endocyclic and exocyclic oxazolidinone cleavage, in 56 and 29% yields respectively. Furthermore, hydrogenolysis of β-amino esters **13**, **17** and **24** and concomitant cyclisation furnished (4*S*,5*S*,6*R*)-piperidinone **26**, in 80, 76 and 84% yields as a single diastereoisomer in each case after purification (Scheme 5).

The relative configuration within piperidinone **26** was assigned using NMR spectroscopic analysis. ^{1}H coupling constants were used to indicate the axial and equatorial relationships between the ring protons, and the 1,3-diaxial relationship between C(4)-H and C(6)-H was confirmed through NOE difference analysis. The absolute (4*S*,5*S*,6*R*) configuration of **26** was established on the assumption that the configuration at C(6) derived from



Scheme 5 *Reagents and conditions*: (i) $Pd(OH)_2/C$, MeOH, H_2 (5 atm); (ii) LiOMe, MeOH.

lithium amide conjugate addition was (*R*), by analogy with previous models developed to explain the consistently high stereoselectivity observed during addition of lithium *N*-benzyl-*N*-α-methylbenzylamide to α,β-unsaturated esters. The absolute configurations within **17** and **22**–**24** were assigned by analogy (Fig. 4).

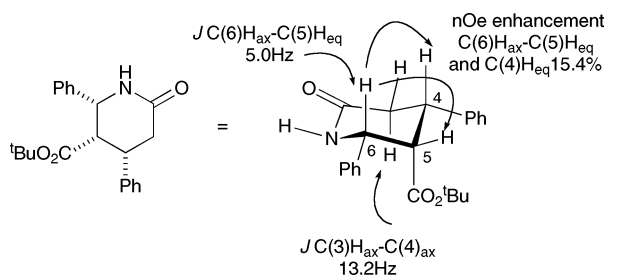


Fig. 4 ^3J coupling constants and NOE data for piperidinone **26**.

Having probed the susceptibility of a range of α,β-unsaturated esters and oxazolidinones toward the conjugate addition of a β-amino ester enolate, extension to a 'one-pot' three-component coupling protocol was investigated.

Three-component coupling reactions

As the [2 + 1] conjugate addition protocol proceeded efficiently with chiral *N*-cinnamoyl oxazolidinones as the α,β-unsaturated acceptor component, the development of a tandem oligomerisation protocol concentrated upon their use in a tandem, 'one-pot' strategy. As previous investigations from this laboratory have shown that double diastereoselectivity is observed upon conjugate addition of chiral lithium amides to chiral *N*-cinnamoyl oxazolidinones,[27] and with matched and mismatched combinations already observed upon (*E*)-β-amino enolate additions to these acceptors, it was predicted that double diastereoselectivity and crossed conjugate addition products may complicate this reaction manifold. Addition of *tert*-butyl cinnamate to lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide and subsequent addition of oxazolidinone (*S*)-**16** gave a 25 : 15 : 60 mixture of components that were identified as β-amino ester **11**, β-amino oxazolidinone **27** (66% d.e.) and the desired product **28** (85% d.e.). Chromatographic purification yielded the desired oxazolidinone derivative **28** in 38% yield and 85% d.e. Subsequent hydrogenolysis of **28** (85% d.e.) gave (4*R*,5*S*,6*R*)-piperidinone **29** in 68% yield and >95% d.e. after chromatographic purification. Addition of *tert*-butyl cinnamate to lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide and subsequent addition of oxazolidinone (*S*)-**16** gave a 45 : 20 : 35 mixture of components that were identified as β-amino ester **11**, β-amino oxazolidinone **30** (>98% d.e.) and oxazolidinone derivative **31** (50% d.e.). Chromatographic purification gave β-amino ester **11** as the major reaction product in 35% yield and the desired oxazolidinone derivative **31** (28% isolated yield, 50% d.e.). Further exhaustive purification yielded a diastereomerically enriched sample of the major diastereoisomer of oxazolidinone derivative **31** (90% d.e.), which upon hydrogenolysis gave piperidinone (4*S*,5*R*,6*S*)-**29** as the major reaction product. Hydrogenolytic deprotection in both reaction manifolds to give the enantiomeric piperidinones (4*R*,5*S*,6*R*)-**29** and (4*S*,5*R*,6*S*)-**29** (indicates preferential *syn*-selectivity for the tandem conjugate addition protocol, while the complex product distributions from these reactions demonstrate that for an efficient 'one-pot' procedure, any possible crossed conjugate addition products must be minimised (Scheme 6).

The use of alkylidene malonates as suitable acceptors in this tandem reaction manifold was next investigated. Although lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide adds in a conjugate fashion to α,β-unsaturated esters with high diastereoselectivity, its reaction with alkylidenemalonates has not previously been explored. Initial studies therefore focused upon treatment of model alkylidenemalonates with lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide. Addition of diethyl benzylidenemalonate to lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide returned only starting material, although addition of diethyl phenylallylidenemalonate gave a low yield of the reduced product **32**.[28,29] In both cases no trace of any conjugate addition products were noted (Scheme 7).

It was proposed that the inability of lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide to act as a nucleophile in conjugate additions to alkylidenemalonates could be used to advantage, minimising competing cross-conjugate addition in a one-pot reaction manifold. Furthermore these acceptors would also promote the efficient capping of the oligomerisation reaction, as conjugate addition of a β-amino enolate to an alkylidenemalonate would generate a stabilised malonate enolate. Addition of *tert*-butyl cinnamate (1 eq.) to lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide (2 eq.) generated the lithium (*Z*)-β-amino enolate **33**, with subsequent addition of a THF solution of diethyl benzylidenemalonate (2 eq.) giving (2*S*,3*R*,1′*R*,α*S*)-**34** in 90% d.e. (the ratio of **34** to the one minor diastereoisomer in the crude product was 95 : 5). Chromatographic purification gave **34** in 81% yield and in >95% d.e., with hydrogenolysis giving tetrasubstituted piperidinone (3*S*,4*R*,5*S*,6*R*)-**35** in 81% yield and as a single diastereoisomer (>98% d.e.) after purification. The relative configuration within

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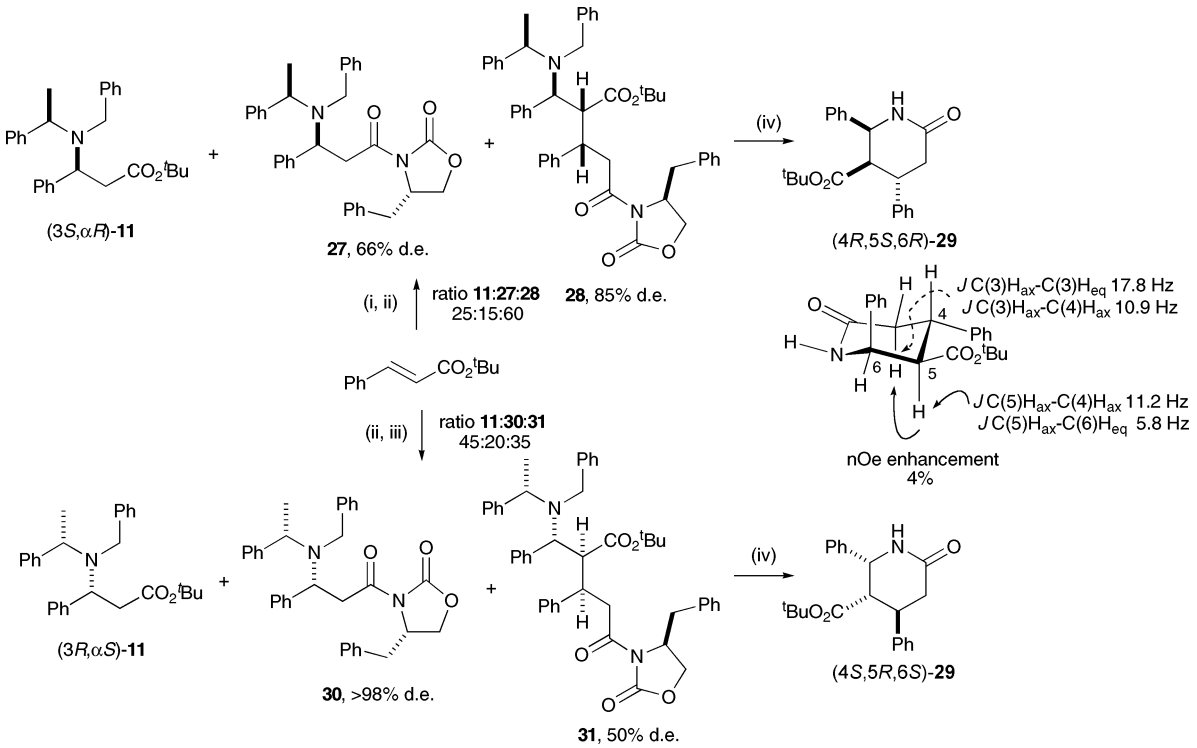
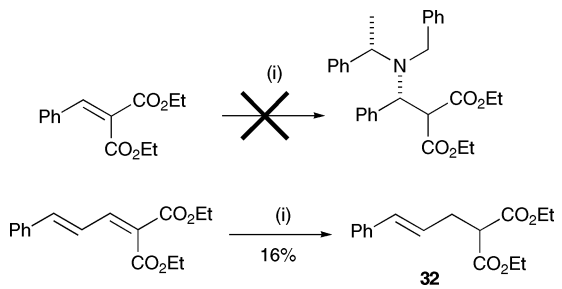


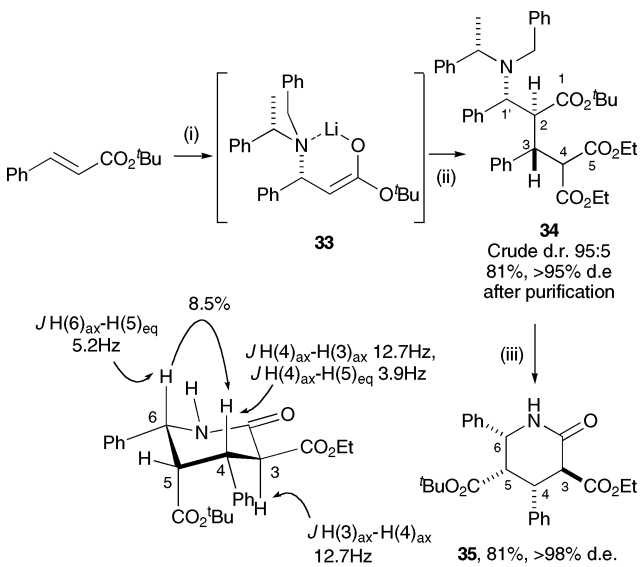
Scheme 6 *Reagents and conditions*: (i) lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide (1.1 eq.), THF, −78 °C; (ii) lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide (1.1 eq.), THF, −78 °C; (iii) (*S*)-*N*-cinnamoyl-4-benzyl-oxazolidin-2-one **16** (1.0 eq.), THF, −78 °C to 0 °C; (iv) $Pd(OH)_2/C$, MeOH, H_2 (5 atm).



Scheme 7 *Reagents and conditions*: (i) lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide (1.6 eq.), THF, −78 °C.

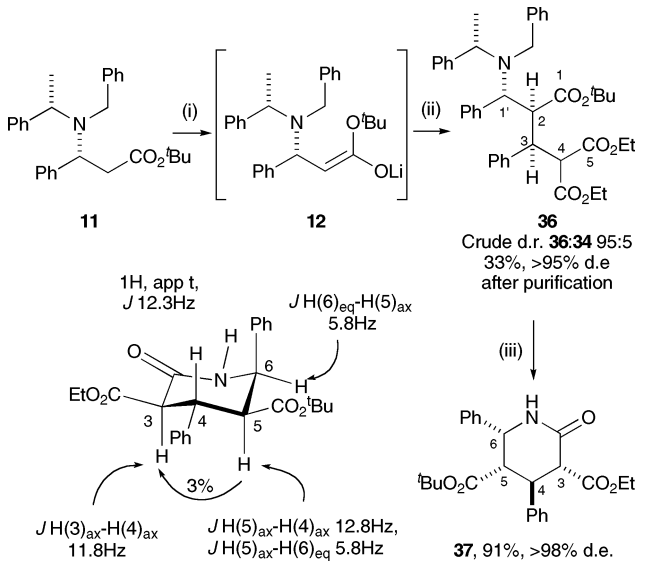
piperidinone **35** was assigned using NMR spectroscopic analysis, relative to the known configuration at C(6) arising from lithium amide conjugate addition (Scheme 8).

In an attempt to identify the configuration within the minor product diastereoisomer in this protocol, a stepwise [2 + 1]-component coupling procedure was investigated. Treatment of β-amino ester (3*R*,α*S*)-**11** with LDA gave the corresponding lithium (*E*)-β-amino enolate-**12**, and subsequent addition of diethyl benzylidenemalonate gave (2*S*,3*S*,1′*R*,α*S*)-**36** in 90% d.e. (crude product ratio **36**:**34** 95 : 5). Although this unoptimised procedure proceeded to only 40% conversion, **36** was isolated by chromatography in 33% yield and >95% d.e. after purification. Comparison of the ^{1}H NMR spectrum of **36** and that of the crude product mixture from the three-component coupling protocol indicated no trace of **36** in the tandem reaction, indicating that the minor diastereoisomer in the tandem coupling reaction manifold arises from incomplete stereocontrol at C(2) upon alkylation of



Scheme 8 *Reagents and conditions*: (i) lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide (2.0 eq.), THF, −78 °C; (ii) diethyl benzylidenemalonate (1.0 eq.), THF, −78 °C to 0 °C; (iii) $Pd(OH)_2/C$, MeOH, H_2 (5 atm).

β-amino enolate **33**. Treatment of **36** with Pearlman's catalyst and H_2 (5 atm) promoted hydrogenolysis and concomitant cyclisation, giving piperidinone (3*R*,4*S*,5*S*,6*R*)-**37** in 91% yield and as a single diastereoisomer (>98% d.e.) after chromatography. The relative configuration within **37** was elucidated by ^{1}H NMR spectroscopy and NOE difference experiments (Scheme 9).

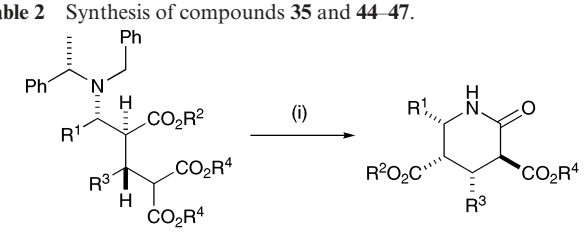


Scheme 9 *Reagents and conditions*: (i) **11** (1.0 eq.), LDA (1.1 eq.), THF, −78 °C to 0 °C; (ii) diethyl benzylidenemalonate (1.0 eq.), THF, −78 °C to 0 °C; (iii) $Pd(OH)_2/C$, MeOH, H_2 (5 atm).

The generality of this one-pot three-component coupling reaction protocol was then examined further. Variation of the α,β-unsaturated ester component (cinnamic and crotonic esters) and incorporation of a range of aryl-, alkenyl- and alkyl-substituted malonates was investigated (Table 1). Analysis of the product distributions from these reactions show that higher yields and diastereoselectivities are observed with β-aryl substituents in both ester and malonate components (d.r. typically >95 : <5), although the reaction successfully tolerates both β-alkyl and β-alkenyl functionality (d.r. 94 : 6 to 89 : 11). The desired β-amino esters **38**–**40** generated in this fashion could be purified to homogeneity in good yield by chromatographic purification, although **42** and **43** required further purification by recrystallisation. The C(2)–C(3) *anti*-stereochemical induction observed in this tandem reaction protocol was confirmed by single crystal X-ray analysis of **42**,[30] with the absolute configurations of the major diastereoisomers **38**–**41** and **43** assigned by direct analogy.

With a range of β-amino esters prepared utilising this three-component coupling procedure, their conversion to piperidinones was investigated. Hydrogenolysis of β-amino esters **38** and **40**–**42** gave the tetrasubstituted piperidinones **44**–**47** in high yields (>75%) and as single diastereoisomers in each case after chromatography. The relative configuration within piperidinones **44**–**47** was confirmed by ^{1}H NMR spectroscopy and NOE difference experiments, with the absolute configuration derived from the predictable C(6) configuration arising from lithium amide conjugate addition (Table 2).

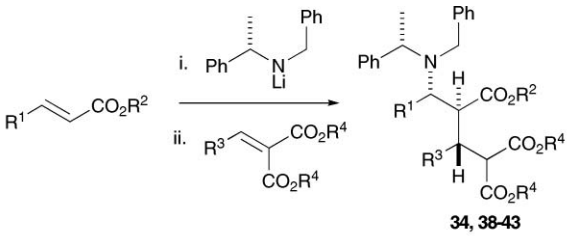
Table 2 Synthesis of compounds **35** and **44**–**47**.



Reagents and conditions: (i) $Pd(OH)_2/C$, MeOH, H_2 (5 atm).

Substrate	R^1	R^2	R^3	R^4	Product	Yield (%)
34	Ph	^{t}Bu	Ph	Et	**35**	81
38	Ph	^{t}Bu	Ph	Me	**44**	91
40	Ph	^{t}Bu	Me	Me	**45**	78
41	Ph	^{t}Bu	$PhCH_2CH_2$	Et	**46**	80
42	Me	^{i}Pr	$PhCH_2CH_2$	Et	**47**	75

Table 1 Synthesis of compounds **34** and **38**–**43**.



Reagents and conditions: (i) lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide (2.0 eq.), THF, 2 h, (ii) alkylidene malonate (2.0 eq.), THF, -78 °C to 0 °C.

R^1	R^2	R^3	R^4	Crude d.r.[a]	Product	Yield (%)
Ph	^{t}Bu	Ph	Et	>95 : <5	**34**	81[b]
Ph	^{t}Bu	4-BrC_6H_4	Me	>95 : <5	**38**	63[b]
3,4-$(MeO)_2C_6H_3$	^{t}Bu	4-BrC_6H_4	Me	>95 : <5	**39**	70[b]
Ph	^{t}Bu	Me	Me	94 : 6	**40**	67[b]
Ph	^{t}Bu	Et	Et	91 : 9	**41**	64[c]
Me	^{i}Pr	Et	Et	92 : 8	**42**	63[c] (46)[d]
Me	^{i}Pr	Et	Et	89 : 11	**43**	52[c] (37)[d]

[a] As determined by 400 MHz ^{1}H spectroscopic analysis of the crude reaction mixture. [b] Isolated yield of single diastereoisomer. [c] Isolated yield of inseparable diastereoisomeric mixture. [d] Isolated yield of a single diastereomer after recrystallisation.

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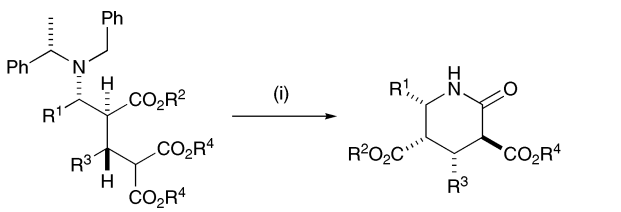
Stereochemical outcome of ester enolate conjugate additions

Many explanations for the observed stereoselectivity of intermolecular enolate conjugate addition reactions have been proposed.[31] In the above reaction manifolds, the 2,3-*anti* or 2,3-*syn* stereoselectivity observed within these conjugate addition reactions alternates with a change in enolate geometry and variation in the α,β-unsaturated ester component from an ester/oxazolidinone to a malonate derivative. On the assumption that the reacting β-amino enolate is monomeric in solution[32] and that the favourable transition state for conjugate addition of the (*E*)- or (*Z*)-β-amino enolate to the α,β-unsaturated acceptor has substituents on the two prostereogenic centres staggered to minimise unfavourable non-bonding interactions,[31b] speculative models consistent with the stereochemical outcome of these reactions may be presented. The selectivity observed at C(2) upon conjugate addition in each case can be accounted for using the concept of allylic strain,[33] with either the lithium (*E*)-enolate **12** formed from deprotonation of β-amino ester **11** with LDA or the lithium (*Z*)-enolate **33** formed by conjugate addition predicted to adopt a reactive conformation in which the C(3)-H bond is eclipsed with the C=C bond of the enolate, with preferential alkylation *anti* to the *N*-benzyl-*N*-α-methylbenzyl group. The variation in configuration at C(3) in these conjugate addition reactions is striking and must be due in part to the nature of the α,β-unsaturated acceptor in each case. The α,β-unsaturated acceptors may undergo conjugate addition through either the s-*cis* or s-*trans* conformation, although attempts to delineate their preferred conformation in these reaction manifolds by enolate trapping proved inconclusive. However, assuming that chelation control between the lithium β-amino enolate and the α,β-unsaturated acceptor is operating in each case, the C=C of the α,β-unsaturated acceptor is restricted to occupy a synclinal/gauche orientation to the C=C of the enolate. Quantitatively, the correct configuration at C(3) can be predicted by allowing preferential orientation of the C=C of the α,β-unsaturated acceptor *syn* to the quadrant occupied by the C–OLi bond and *anti* to that of the C–OR bond. For example, using these constraints, the stepwise [2 + 1] reactions of the lithium (*E*)-enolate with methyl (*E*)-cinnamate permits reaction *via* either transition state **48** or **49**, which allow the cinnamate to react *via* either the s-*cis* or s-*trans* conformation. Similarly, the high matched diastereoselectivity observed upon enolate addition to the chiral *N*-cinnamoyl-oxazolidinones is consistent with transition state **50** or **51**, in which the *syn*-s-*trans* or *anti*-s-*cis* conformation is adopted (Fig. 5). A similar transition state has been used to account for the diastereoselectivity observed upon addition of *tert*-butyl ester enolates to α,β-unsaturated esters by Yamaguchi *et al.*[34]

These constraints can also be used to account for the preferential 2,3-*syn* selectivity of the lithium (*E*)-enolate and 2,3-*anti*-selectivity of the lithium (*Z*)-enolates upon addition to the malonate-derived acceptors. In these cases, allowing the smallest C(3)-H substituent of the electrophile rather then the C(3)-alkyl group to occupy the sector occupied by the C(3)-alkyl substituent of the β-amino enolate predicts the correct 2,3-*syn* or 2,3-*anti* configuration respectively (Fig. 6).



β-amino ester	Piperidinone	Yield (%)	R^1	R^2	R^3	R^4
34	**35**	81	Ph	^{t}Bu	Ph	Et
38	**44**	91	Ph	^{t}Bu	Ph	Me
40	**45**	78	Ph	^{t}Bu	Me	Me
41	**46**	80	Ph	^{t}Bu	$PhCH_2CH_2$	Et
42	**47**	75	Me	^{i}Pr	$PhCH_2CH_2$	Et

Fig. 5 Rationale for the stereochemical outcome of the [2 + 1] stepwise and tandem conjugate addition reactions.

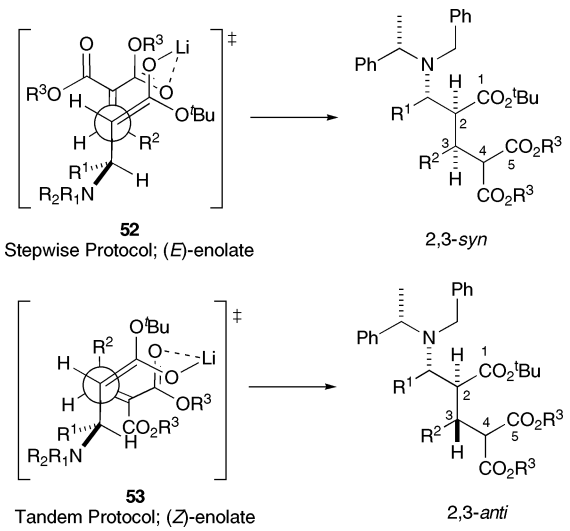


Fig. 6 Rationale for the stereochemical outcome of the stepwise and tandem conjugate addition reactions to alkylidene malonates.

Conclusion

In conclusion, the deprotonation of a β-amino ester, followed by conjugate addition to a chiral α,β-unsaturated oxazolidinone gives high 2,3-*syn* selectivity (~90% d.e.), with hydrogenolysis and purification to homogeneity generating stereodefined, trisubstituted piperidinones as single diastereoisomers. Asymmetric three-component couplings of α,β-unsaturated esters and alkylidene malonates initiated by lithium amide conjugate addition proceed with high levels of 2,3-*anti* stereoselectivity, with hydrogenolysis giving tetrasubstituted piperidinones. The utility of this methodology for a variety of applications including total synthesis is currently under investigation in our laboratory.

Experimental

General

All reactions involving organometallic or other moisture-sensitive reagents were performed under an atmosphere of nitrogen using standard vacuum line techniques. All glassware was flame-dried and allowed to cool under vacuum. THF was distilled under an

atmosphere of dry nitrogen from sodium benzophenone ketyl. Water was distilled. *n*-Butyllithium was used as a solution in hexanes at the molarity stated. All other solvents and reagents were used as supplied (Analytical or HPLC grade), without prior purification. Reactions were dried with $MgSO_4$. Thin layer chromatography (t.l.c.) was performed on aluminium sheets coated with 60 F_{254} silica. Sheets were visualised using iodine, UV light or 1% aqueous $KMnO_4$ solution. Flash chromatography was performed on Kieselgel 60 silica. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker DPX 400 (^{1}H: 400 MHz and ^{13}C: 100.6 MHz) spectrometer, or where stated on a Bruker AMX 500 (^{1}H: 500 MHz and ^{13}C: 125.3 MHz) spectrometer in the deuterated solvent stated. All chemical shifts (δ) are quoted in ppm and coupling constants (J) in Hz. Coupling constants are quoted twice, each being recorded as observed in the spectrum without averaging. Residual signals from the solvents were used as an internal reference. ^{13}C multiplicities were assigned using a DEPT sequence. In all cases, the reaction diastereoselectivity was assessed by peak integration of the ^{1}H NMR spectrum of the crude reaction mixture. Infrared spectra were recorded on a Perkin–Elmer 1750 IR Fourier Transform spectrophotometer using either thin films on NaCl plates (film) or KBr discs (KBr) as stated. Only the characteristic peaks are quoted. 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 or on a Waters 2790 Micromass LCT Exact Mass Electrospray Ionisation mass spectrometer. Techniques used were chemical ionisation (CI, NH_3), atmospheric pressure chemical ionisation (APCI) or electrospray ionisation (ESI) using partial purification by HPLC with methanol–acetonitrile–water (40 : 40 : 20) as eluent. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter with a water-jacketed 10 cm cell and are given in units of 10^{-1} deg cm^2 g^{-1}. Concentrations are quoted in g per 100 ml. Melting points were recorded on a Leica VMTG Galen III apparatus and are uncorrected. Elemental analyses were performed by the microanalysis service of the Inorganic Chemistry Laboratory, Oxford.

Representative procedure 1

LDA (1 M, 1.1 eq.) was added dropwise to a stirred solution of the requisite β-amino ester (1 eq.) in anhydrous THF at −78 °C under nitrogen and after 10 min was allowed to warm to 0 °C. After 30 min, the enolate solution was recooled to −78 °C, prior to the addition of a conjugate acceptor (1 eq.) in anhydrous THF *via* cannula. After 15 min the solution was warmed to 0 °C for 2 h before cooling to −78 °C and the addition of saturated aqueous ammonium chloride. After warming to rt, the resultant solution was partitioned between brine and 1 : 1 DCM–Et_2O, and the organic extracts were dried, filtered and concentrated *in vacuo* before purification by column chromatography.

Representative procedure 2

n-Butyllithium (1.55 eq.) was added dropwise to a stirred solution of (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (1.6 eq.) in anhydrous THF at −78 °C and stirred for 30 min under nitrogen. A solution of the α,β-unsaturated ester in anhydrous THF was added dropwise *via* cannula and stirred at −78 °C for 2 h before the addition of another α,β-unsaturated carbonyl component. After 10 min, the reaction was warmed to 0 °C for 2 h before cooling to −78 °C and the addition of saturated aqueous ammonium chloride. After warming to rt, the resultant solution was partitioned between brine and 1 : 1 DCM–Et_2O, and the organic extracts dried, filtered and concentrated *in vacuo* before purification by column chromatography.

Representative procedure 3

$Pd(OH)_2/C$ (50% by mass) was added to a solution of the substrate in degassed MeOH and the resultant black suspension stirred under a hydrogen atmosphere (5 atm) for 16 h. After depressurisation, the reaction mixture was filtered through a plug of Celite (eluent MeOH), concentrated *in vacuo* and the residue purified by column chromatography on silica gel.

Preparation of 1-*tert*-butyl-5-methyl (2*S*,3*S*,1′*R*,α*S*)-2-[1′-phenyl-1′-(*N*-benzyl-*N*-α-methylbenzylamino)methyl]-3-phenylpentanedioate 13 and 1,7-di-*tert*-butyl (2*S*,3*S*,1′*R*,α*S*)-2-[1′-phenyl-1′-(*N*-benzyl-*N*-α-methylbenzylamino)methyl]-3-phenyl-5-oxoheptanedioate 14

Following Representative procedure 1, LDA (2.0 M, 2.64 mmol, 1.32 ml), **11** (2.4 mmol, 1.0 g) in THF (5 ml) and methyl cinnamate (2.4 mmol, 390 mg) gave, after column chromatography on silica gel (hexane–Et_2O 15 : 1 to 10 : 1), **13** (408 mg, 30%) as a mixture of diastereoisomers (66% d.e.). Recrystallisation (hexane–Et_2O) gave **13** as white blocks and as a single diastereoisomer, $[\alpha]_D^{24}$ +30.4 (*c* 1.0, $CHCl_3$); $C_{38}H_{43}NO_4$ requires C 79.0; H 7.5; N, 2.4%; found C 78.7; H 7.5; N, 2.3%; ν_{max} (KBr) 3027, 2933 (C–H), 1741, 1722 (C=O), 1146 (C–O); δ_H (500 MHz, $CDCl_3$) 1.01 (3H, d, *J*7.0, C(α)*Me*), 1.26 (9H, s, OC(*Me*)$_3$), 2.42 (1H, dd, $J_{4A,4B}$16.0, $J_{4A,3}$3.4, C(4)H_A), 2.94 (1H, dd, $J_{4B,4A}$16.0, $J_{4B,3}$12.0, C(4)H_B), 3.09 (1H, app dt, $J_{3,4B}$12.0, $J_{3,4A;3,2}$3.5, C(3)*H*), 3.32 (3H, s, CO_2Me), 3.47 (1H, dd, $J_{2,1'}$11.9, $J_{2,3}$3.9, C(2)*H*), 3.58 (1H, AB, *J*14.2, NCH_A), 4.05 (1H, AB, *J*14.2, NCH_B), 4.21 (1H, q, *J*7.0, C(α)*H*), 4.30 (1H, d, $J_{5,4}$11.9, C(1′)*H*), 7.05–7.44 (20H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 16.5 (C(α)*Me*), 28.0 (OC(*Me*)$_3$), 32.4 (*C*(*4*)H_2), 40.3 (*C*(*3*)H), 51.1 (N*C*H_2), 51.3 (O*Me*), 54.2, 57.2, 62.8 (*C*(*2*)H, *C*(*1′*)H and *C*(α)H), 80.7 (O*C*(Me)$_3$), 126.4, 126.5, 126.7, 127.6, 127.8, 128.2, 128.4, 129.0, 129.6 ($Ph_{o/m/p}$), 136.8, 140.2, 141.7, 144.2 (Ph_{ipso}), 171.8, 172.6 (*C*=O); *m/z* APCI$^+$ 578.4, (MH$^+$, 75%), 522.1 (MH$^+$ − C_4H_8, 10%). The mother liquors were further purified by column chromatography to give the minor diastereoisomer of unknown absolute configuration as a white foam (13 mg, 1%); ν_{max} 3030, 2978 (C–H), 1738, 1721 (C=O), 1151 (C–O); δ_H (300 MHz, $CDCl_3$) 0.84 (9H, s, OC(*Me*)$_3$), 0.91 (3H, d, *J*7.0, C(α)*Me*), 2.01 (1H, dd, $J_{4A,4B}$16.6, $J_{4A,3}$2.9, C(4)H_A), 2.69 (1H, dd, $J_{4B,4A}$16.6, $J_{4B,3}$12.8, C(4)H_B), 3.24 (1H, dd, $J_{2,1'}$11.7, $J_{2,3}$3.0, C(2)*H*), 3.58 (3H, s, CO_2Me), 3.78 (1H, AB, *J*13.5, NCH_A), 4.00 (1H, d, *J*11.7, C(1′)*H*), 4.16–4.25 (2H, m, C(α)*H* and C(3)*H*), 4.30 (1H, AB, *J*13.5, NCH_B), 6.99–7.71 (20H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 14.0 (C(α)*Me*), 27.2 (OC(*Me*)$_3$), 32.7 (*C*(*4*)H_2), 38.7 (*C*(*2*)H), 50.9 (N*C*H_2), 51.3, 55.0, 55.2, 59.7 (O*Me*, *C*(*3*)H, *C*(1′)H and *C*(α)H), 80.2 (O*C*(Me)$_3$), 126.5, 126.9, 127.3, 127.7, 127.9, 128.2, 128.4, 128.7, 129.3, 129.8 ($Ph_{o/m/p}$), 139.1, 139.7, 142.7 (Ph_{ipso}), 171.3, 173.1 (*C*=O); *m/z* APCI$^+$ 578.4, (MH$^+$, 100%), 600.7 (MNa$^+$,

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10%). Further elution gave **14** (121 mg, 15%) as a white foam, $C_{43}H_{51}NO_5$ requires C, 78.0; H, 7.8; N, 2.1%; found C, 77.7; H, 7.7; N, 2.1%; $[\alpha]_D^{23}$ +27.0 (*c* 1.0, $CHCl_3$); ν_{max} (KBr) 2978 (C–H), 1722 (C=O), 1147 (C–O); δ_H (500 MHz, $CDCl_3$) 1.02 (3H, d, *J*6.8, C(α)*Me*), 1.28 and 1.38 (2 × 9H, s, OC(*Me*)$_3$), 2.57 (1H, dd, $J_{4A,4B}$17.2, $J_{4A,3}$2.8, C(4)H_A), 2.94 (2H, s, C(6)H_2), 3.12–3.16 (1H, m, C(3)*H*), 3.23 (1H, dd, $J_{4B,4A}$17.2, $J_{4B,3}$11.5, C(4)H_B), 3.46 (1H, dd, $J_{2,1'}$11.8, $J_{2,3}$3.7, C(2)*H*), 3.60 (1H, AB, *J*14.2, NCH_A), 4.08 (1H, AB, *J*14.2, NCH_B), 4.23 (1H, q, *J*6.8, C(α)*H*), 4.28 (1H, d, $J_{1',2}$11.8, C(1′)*H*), 7.02–7.44 (20H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 16.4 (C(α)*Me*), 27.9, 28.0 (OC(*Me*)$_3$ × 2), 39.2 (*C(3)*H), 41.0, 50.4, 51.1 (*C(4)*H_2, *C(6)*H_2 and N*C*H_2), 54.2, 57.1, 62.9 (*C(2)*H, *C*(1′)H, *C*(α)H), 80.7, 81.5 (2 × O*C*(Me)$_3$), 126.5, 126.6, 126.7, 127.7, 127.8, 128.2, 128.3, 128.6, 129.0, 129.7 ($Ph_{o/m/p}$), 136.8, 140.1, 141.7, 144.3 (Ph_{ipso}), 166.1, 172.0 (2 × *C*O_2C(Me)$_3$), 201.2 (*C(5)*=O); *m/z* APCI$^+$ 662.4 (MH$^+$, 100%), 684.0 (MNa$^+$, 15%).

X-Ray crystal structure determination for 13. Data were collected using an Enraf–Nonius DIP2000 diffractometer with graphite-monochromated Mo-Kα radiation using standard procedures at 100 K. The structure was solved by direct methods, full matrix and least-squares refinement with non-hydrogen atoms in anisotropic approximation. Hydrogen atoms were placed in calculated positions and included in the final refinement with fixed positional and thermal parameters. A total of 388 parameters were refined. A three-term Chebychev polynomial was used as the weighting scheme. All crystallographic and refinement calculations were carried out using CRYSTALS.[35]

13 ($C_{38}H_{43}NO_4$): M = 577.76, orthorhombic, space group $P2_12_12_1$, a = 11.2640(2) Å, b = 16.6340(3) Å, c = 17.0480(2) Å, V = 3194.2 Å^3, Z = 4, μ = 0.07 mm^{-1}, colourless block, crystal dimensions = 0.4 × 0.4 × 0.5 mm^3. A total of 3793 unique reflections were measured for 1.81 < 2θ < 26.78°, and 3618 reflections were used in the refinement. The final parameters were wR_2 = 0.031 and R_1 = 0.025 [$I > 3\sigma(I)$]. CCDC reference number 634494. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b701226h.†

Preparation of *tert*-butyl (2*S*,3*S*,1′*R*,4″*S*,α*S*)-2-(1′-phenyl-1′-*N*-benzyl-*N*-α-methylbenzylamino)-3-phenyl-5-oxo-5-(4″-benzyloxazolidin-2″-one)pentanoate 17

Following Representative procedure 1, LDA (2.0 M, 1.06 mmol, 0.53 ml), **11** (0.96 mmol, 400 mg) in THF (5 ml) and (*S*)-*N*-cinnamoyl-4-benzyloxazolidin-2-one **16** (0.96 mmol, 295 mg) in THF (5 ml) gave, after purification by column chromatography on silica gel (hexane–Et_2O 5 : 1), **17** (432 mg, 62%) as a white foam (86% d.e.); $[\alpha]_D^{22}$ +51.8 (*c* 1.0, $CHCl_3$); ν_{max} (KBr) 2977 (C–H), 1782, 1718, 1702 (C=O), 1147 (C–O); δ_H (500 MHz, $CDCl_3$) 1.06 (3H, d, *J*6.8, C(α)*Me*), 1.46 (9H, s, OC(*Me*)$_3$), 2.37 (1H, dd, $J_{A,B}$13.5, $J_{A,4''}$9.6, C(4″)CH_APh), 2.78 (1H, dd, $J_{B,A}$13.5, $J_{B,4''}$3.1, C(4″)CH_BPh), 2.91 (1H, dd, $J_{4A,4B}$17.4, $J_{4A,3}$4.8, C(4)H_A), 3.26–3.30 (1H, m, C(3)*H*), 3.52 (1H, dd, $J_{2,1'}$11.8, $J_{2,3}$3.5, C(2)*H*), 3.57 (1H, AB, *J*14.2, NCH_A), 3.86 (1H, dd, $J_{4B,4A}$17.4, $J_{4B,3}$10.6, C(4)H_B), 4.02–4.10 (2H, m, C(5″)H_2), 4.05 (1H, AB, *J*14.2, NCH_B), 4.20 (1H, q, *J*6.8, C(α)*H*), 4.36–4.40 (1H, m, C(4″)*H*), 4.45 (1H, d, *J*11.8, C(1′)*H*), 6.96–7.42 (25H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 16.9 (C(α)*Me*), 28.2 (OC(*Me*)$_3$), 34.7 (*C(4)*H_2), 37.4 (C(4″)*C*H_2Ph), 40.5 (*C(2)*H), 51.2 (N*C*H_2), 54.7, 54.9, 57.7, 63.6 (*C(3)*H, *C(1′)*H, *C(4″)*H and *C(α)*H), 65.8 (*C(5″)*H_2), 81.1 (O*C*(Me)$_3$), 126.5, 127.1, 127.7, 127.8, 128.3, 128.4, 128.8, 129.1, 129.4, 129.8 ($Ph_{o/m/p}$), 135.2, 137.4 140.5, 142.9, 144.2 (Ph_{ipso}), 153.4, 171.7, 171.9 (*C*=O); *m/z* APCI$^+$ 723.7 (MH$^+$, 100%), 745.6 (MNa$^+$, 35%); HRMS (CI$^+$) $C_{47}H_{51}N_2O_5$ requires 723.3798; found 723.3794.

Using 1.6 eq. of enolate, following representative procedure 1, LDA (2.0 M, 1.28 mmol, 0.64 ml, 1.7 eq.), **11** (1.20 mmol, 500 mg, 1.6 eq.) in THF (5 ml) and **16** (0.75 mmol, 230 mg, 1.0 eq.) in THF (5 ml) gave, after purification by column chromatography on silica gel (hexane–Et_2O 5 : 1), **17** as a white foam (449 mg, 83%, 86% d.e.).

Preparation of (4*S*,5*S*,6*R*)-4,6-diphenyl-5-*tert*-butoxycarbonyl-piperidin-2-one 26 (from 13)

Following Representative procedure 3, Pd(OH)$_2$/C (60 mg) and **13** (120 mg, 0.20 mmol) in MeOH (5 ml) gave, after purification by column chromatography on silica gel (hexane–EtOAc 5 : 1), **26** as a white solid (56 mg, 80%); $[\alpha]_D^{21}$ −17.4 (*c* 0.65, $CHCl_3$); ν_{max} (KBr) 3387 (N–H), 2978 (C–H), 1711 (C=O_{ester}), 1654 (C=O_{lactam}), 1167 (C–O); δ_H (500 MHz, C_6D_6) 0.85 (9H, s, OC(*Me*)$_3$), 2.57 (1H, dd, $J_{3A,3B}$17.3, $J_{3A,4}$5.5, C(3)H_A), 2.88 (1H, m, C(4)*H*), 2.92 (1H, dd, $J_{5,4}$5.5, $J_{5,6}$5.0, C(5)*H*), 3.60 (1H, dd, $J_{3B,3A}$17.3, $J_{3B,4}$13.2, C(3)H_B), 4.30 (1H, d, $J_{6,5}$5.0, C(6)*H*), 6.92 (1H, br s, N*H*), 6.98–7.19 (10H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 27.4 (OC(*Me*)$_3$), 32.5 (*C*(*3*)H_2), 40.9 (*C*(*5*)H), 51.8 (*C*(*4*)H), 59.0 (*C*(*6*)H), 80.7 (O*C*(Me)$_3$), 126.5, 127.2, 127.3, 128.2, 128.5, 128.6 ($Ph_{o/m/p}$), 138.3, 140.0 (Ph_{ipso}), 168.7, 172.6 (*C*(2) and *C*O_2C(Me)$_3$); *m/z* APCI$^+$ 352.1 (MH$^+$, 10%), 374.1 (MNa$^+$, 20%), 296.1 (MH$^+$ − C_4H_8, 100%); HRMS (CI$^+$) $C_{22}H_{26}NO_3$ requires 352.1920; found 352.1913.

Preparation of (4*S*,5*S*,6*R*)-4,6-diphenyl-5-(*tert*-butoxycarbonyl)piperidin-2-one 26(from 17)

Following Representative procedure 3, Pd(OH)$_2$/C (75 mg) and **17** (150 mg, 0.21 mmol) in MeOH (5 ml) gave, after purification by column chromatography on silica gel (hexane–EtOAc 5 : 1), **25** as a white solid (50 mg, 76%) with identical spectroscopic properties to that above.

Preparation of 1-*tert*-butyl-5-ethyl (2*S*,3*R*,1′*R*,α*S*)-2-[1′-phenyl-1′-(*N*-benzyl-*N*-α-methylbenzylamino)methyl]-3-phenyl-4-ethoxycarbonyl-pentanedioate 34

Following Representative procedure 2, *n*-BuLi (2.5 M, 2.24 mmol, 0.89 ml), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (500 mg, 2.30 mmol) in THF (5 ml), *tert*-butyl cinnamate (234 mg, 1.15 mmol) in THF (3 ml) and diethyl benzylidenemalonate (571 mg, 2.30 mmol) in THF (2 ml) gave, after purification by column chromatography on silica gel (hexane–Et_2O 6 : 1), **34** as a hygroscopic white foam (617 mg, 81%); ν_{max} (film) 2978 (C–H), 1757, 1732 (C=O), 1141 (C–O); $[\alpha]_D^{24}$ −29.3 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.72 (3H, t, *J*7.1, OCH_2CH_3), 1.06 (3H, d, *J*6.8, C(α)*Me*), 1.25 (3H, t, *J*7.1, OCH_2CH_3), 1.66 (9H, s, CO_2C(*Me*)$_3$), 3.32 (1H, dd, $J_{3,4}$12.0, $J_{3,2}$1.0, C(3)*H*), 3.44 (1H, AB, *J*14.4, NCH_A), 3.55 (1H, dd, $J_{2,1'}$12.2, $J_{2,3}$1.0, C(2)*H*), 3.62–3.66 (3H, m, OC$H_2$$CH_3$ and C(4)*H*), 3.83 (1H, AB, *J*14.4, NCH_B), 4.02 (1H, dq, $J_{A,B}$10.7, $J_{A,CH3}$7.1, OC$H_A$$CH_3$), 4.11 (1H, q, *J*6.8, C(α)*H*), 4.17 (1H, dq, $J_{B,A}$10.7, $J_{B,CH3}$7.1, OC$H_B$$CH_3$), 4.72 (1H, d, *J*12.2, C(1′)*H*), 6.94–6.98 (2H, m, *Ph*), 7.14–7.37 (18H, m,

Ph); δ_C (50 MHz, $CDCl_3$) 13.4, 14.1 (OCH_2CH_3), 17.5 (C(α)*Me*), 28.3 ($CO_2C(Me)_3$), 43.6 (*C*(*3*)H), 51.3 (NCH_2), 54.1, 57.0, 58.1 (*C*(*4*)H, *C*(*2*)H, and *C*(*a*)H), 60.9, 61.3 (OCH_2CH_3), 64.1 (*C*(*1′*)H), 81.2 ($CO_2C(Me)_3$), 126.2, 126.3, 126.7, 127.3, 127.7, 127.9, 128.3, 128.8, 129.1, 130.5 ($Ph_{o/m/p}$), 137.2, 140.6, 142.4, 144.7 (Ph_{ipso}), 167.7, 167.9, 171.9 ($CO_2C(Me)_3$ and CO_2Et × 2); *m*/*z* APCI$^+$ 664.7 (MH$^+$, 100%), 608.3 (MH$^+$ − C_4H_8, 10%); HRMS (CI$^+$) $C_{42}H_{50}NO_6$ requires 664.3638; found 664.3642.

Preparation of (3*S*,4*R*,5*S*,6*R*)-3-ethoxycarbonyl-4,6-diphenyl-5-(*tert*-butoxycarbonyl)piperidin-2-one 35

Following Representative procedure 3, $Pd(OH)_2/C$ (75 mg) and **34** (150 mg, 0.23 mmol) in MeOH (5 ml) gave, after purification by column chromatography on silica gel (Et_2O–hexane 2 : 1), **35** (78 mg, 81%) as a colourless oil, ν_{max} (film) 3311 (N–H), 2977 (C–H), 1723, 1666 (C=O), 1153 (C–O); $[\alpha]_D^{23}$ −72.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.92 (9H, s, $CO_2C(Me)_3$), 1.06 (3H, t, *J*7.1, OCH_2CH_3), 3.15 (1H, app t, $J_{5,4;5,6}$4.5, C(5)*H*), 3.93 (1H, dd, $J_{4,3}$12.7, $J_{4,5}$3.9, C(4)*H*), 4.03–4.13 (2H, m, OCH_2CH_3), 4.65 (1H, d, *J*12.7, C(3)*H*), 5.09 (1H, d, $J_{6,5}$5.2, C(6)*H*), 6.13 (1H, br s, N*H*), 7.23–7.37 (10H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 13.9 (OCH_2CH_3), 27.4 ($CO_2C(Me)_3$), 44.6, 49.8, 52.0 and 58.8 (*C*(*3*)H, *C*(*4*)H, *C*(*5*)H and *C*(*6*)H), 61.3 (OCH_2CH_3), 81.1 ($CO_2C(Me)_3$), 126.4, 127.6, 127.7, 128.3, 128.6, 128.7 ($Ph_{o/m/p}$), 137.8, 138.1 (Ph_{ipso}), 168.8, 170.0 (*C*(*2*)=O, $CO_2C(Me)_3$ and CO_2Et); *m*/*z* APCI$^+$ 424.2 (MH$^+$, 5%), 446.0 (MH$^+$, 100%), 368.1 (MH$^+$ − C_4H_8, 20%); HRMS (CI$^+$) $C_{25}H_{30}NO_5$ requires 424.2124; found 424.2126.

Preparation of 1-*tert*-butyl-5-ethyl (2*S*,3*S*,1′*R*,α*S*)-2-[1′-phenyl-1′-(*N*-benzyl-*N*-α-methylbenzylamino)methyl]-3-phenyl-4-ethoxycarbonyl-pentanedioate 36

Following Representative procedure 1, LDA (2.0 M, 0.53 mmol, 0.27 ml), **11** (200 mg, 0.48 mmol) in THF (5 ml) and diethyl benzylidenemalonate (120 mg, 0.48 mmol) in THF (2 ml) gave, after purification by column chromatography on silica gel (hexane–Et_2O 10 : 1), **36** (105 mg, 33%) as a colourless oil and as an inseparable 8 : 1 mixture with diethyl benzylidenemalonate; ν_{max} (film) 2977 (C–H), 1754, 1731 (C=O), 1140 (C–O); δ_H (400 MHz, $CDCl_3$) 0.68 (3H, t, *J*7.3, OCH_2CH_3), 1.13 (3H, d, *J*6.8, C(α)*Me*), 1.28 (3H, t, *J*7.3, OCH_2CH_3), 1.66 (9H, s, $CO_2C(Me)_3$), 3.42 (1H, AB, *J*14.9, NCH_A), 3.51 (1H, AB, *J*14.9, NCH_B), 3.54–3.61 (2H, m, C(3)*H* and C(2)*H*), 3.64–3.69 (2H, m, OCH_2CH_3), 3.89 (1H, d, *J*12.2, C(4)*H*), 4.06 (1H, d, *J*11.5, C(1′)*H*), 3.98 (1H, q, *J*6.8, C(α)*H*), 4.14–4.23 (2H, m, OCH_2CH_3), 7.08–7.33 (20H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 13.4, 14.0, 19.9 (OCH_2CH_3 × 2 and C(α)*Me*), 28.2 ($CO_2C(Me)_3$), 44.1, 49.4 (*C*(*3*)H and *C*(*2*)H), 51.2 (NCH_2), 56.1 (*C*(*4*)H), 61.1, 61.6 (OCH_2CH_3 × 2), 63.8 (*C*(*1′*)H), 81.0 ($CO_2C(Me)_3$), 126.0, 126.3, 127.0, 127.1, 127.2, 127.4, 127.9, 128.0, 128.8, 129.4, 130.2, 130.5 ($Ph_{o/m/p}$), 135.2, 135.7, 141.4, 145.1 (Ph_{ipso}), 167.5, 167.8, 171.5 ($CO_2C(Me)_3$ and CO_2Et × 2); *m*/*z* APCI$^+$ 664.3 (MH$^+$, 100%), 686.6 (MNa$^+$, 10%), 608.6 (MH$^+$ − C_4H_8, 5%); HRMS (CI$^+$) $C_{42}H_{50}NO_6$ requires 664.3638; found 664.3644.

Preparation of (3*S*,4*S*,5*S*,6*R*)-3-ethoxycarbonyl-4,6-diphenyl-5-*tert*-butoxycarbonyl-piperidin-2-one 37

Following Representative procedure 3, $Pd(OH)_2/C$ (50mg), **36** (100 mg, 0.13 mmol) in MeOH (10 ml) gave, after purification by column chromatography on silica gel (Et_2O–hexane 2 : 1), **37** (52 mg, 91%) as a colourless oil; ν_{max} (film) 3309 (N–H), 2979 (C–H), 1725, 1670 (C=O), 1159 (C–O); $[\alpha]_D^{23}$ −61.8 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.78 (9H, s, $CO_2C(Me)_3$), 1.09 (3H, t, *J*7.1, OCH_2CH_3), 3.47 (1H, d, $J_{3,4}$11.8, C(3)*H*), 3.54 (1H, dd, $J_{5,4}$12.8, $J_{5,6}$5.8, C(5)*H*), 3.78 (1H, app t, $J_{4,3;4,5}$12.3, C(4)*H*), 4.06–4.16 (2H, m, OCH_2CH_3), 5.06 (1H, dd, $J_{6,5}$5.8, $J_{6,NH}$3.6, C(6)*H*), 6.50 (1H, br s, N*H*), 7.11–7.41 (10H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 13.9 (OCH_2CH_3), 27.0 ($CO_2C(Me)_3$), 39.3, 50.5, 56.8 and 57.5 (*C*(*3*)H, *C*(*4*)H, *C*(*5*)H and *C*(*6*)H), 61.4 (OCH_2CH_3), 81.7 ($CO_2C(Me)_3$), 127.3, 127.5, 128.1, 128.5, 128.6 ($Ph_{o/m/p}$), 138.0, 139.9 (Ph_{ipso}), 167.3, 168.3, 169.2 (*C*(*2*)=O, $CO_2C(Me)_3$ and CO_2Et); *m*/*z* APCI$^+$ 424.2 (MH$^+$, 35%), 446.1 (MNa$^+$, 30%), 368.2 (MH$^+$ − C_4H_8, 100%); HRMS (CI$^+$) $C_{25}H_{30}NO_5$ requires 424.2124; found 424.2127.

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References and notes

1 For example, see: M. G. P. Buffat, *Tetrahedron*, 2004, **60**, 1701; P. M. Weintraub, J. S. Sabol, J. M. Kane and D. R. Borcherding, *Tetrahedron*, 2003, **59**, 2953.
2 S. G. Davies and O. Ichihara, *Tetrahedron: Asymmetry*, 1991, **2**, 183.
3 For a review of this area, see: S. G. Davies, A. D. Smith and P. D. Price, *Tetrahedron: Asymmetry*, 2005, **16**, 2833.
4 S. G. Davies and I. A. S. Walters, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1129; S. G. Davies, O. Ichihara and I. A. S. Walters, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1141.
5 M. E. Bunnage, S. G. Davies and C. J. Goodwin, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1375; M. E. Bunnage, A. N. Chernega, S. G. Davies and C. J. Goodwin, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2373; M. E. Bunnage, A. J. Burke, S. G. Davies and C. J. Goodwin, *Tetrahedron: Asymmetry*, 1994, **5**, 203.
6 For the use of lithium *N*-benzyl-*N*-trimethylsilylamide as a nucleophile in conjugate addition reactions and elaboration of enolates using this methodology, see: N. Asao, T. Uyehara and Y. Yamamoto, *Tetrahedron*, 1988, **44**, 4173; T. Uyehara, N. Asao and Y. Yamamoto, *J. Chem. Soc., Chem. Commun.*, 1989, 753; N. Asao, T. Shimada, N. Tsukada and Y. Yamamoto, *Tetrahedron Lett.*, 1994, **45**, 8425; Y. Yamamoto, N. Asao and T. Uyehara, *J. Am. Chem. Soc.*, 1992, **114**, 5427.
7 T. Uyehara, N. Shida and Y. Yamamoto, *J. Chem. Soc., Chem. Commun.*, 1989, 113; N. Shida, T. Uyehara and Y. Yamamoto, *J. Org. Chem.*, 1992, **57**, 5049; T. Uyehara, S. Tadao and Y. Yamamoto, *J. Org. Chem.*, 1992, **57**, 3139.
8 J. G. Urones, N. M. Garridio, D. Díez, S. H. Dominguez and S. G. Davies, *Tetrahedron: Asymmetry*, 1997, **8**, 2683; J. G Urones, N. M. Garridio, D. Díez, S. H. Dominguez and S. G. Davies, *Tetrahedron: Asymmetry*, 1999, **10**, 1637; S. G. Davies, D. Díez, S. H. Dominguez, N. M. Garrido, D. Kruchinin, P. D. Price and A. D. Smith, *Org. Biomol. Chem.*, 2005, **3**, 1284.
9 For related Michael-initiated ring-closure reactions, see: R. D. Little and J. R. Dawson, *Tetrahedron Lett.*, 1980, **21**, 2609; E. Yoshii, K. Hori, K. Nomura and K. Yamaguchi, *Synlett*, 1995, 568; K. Takeda, N. Ohkawa, K. Hori, T. Koizumi and E. Yoshii, *Heterocycles*, 1998, **47**, 277; M. Ihara, M. Suzuki, K. Fukumoto and C. Kabuto, *J. Am. Chem. Soc.*, 1990, **112**, 1164, and references therein. For a review, see: C. Thebtaranonth and Y. Thebtaranonth, *Tetrahedron*, 1990, **46**, 1385.
10 M. E. Bunnage, S. G. Davies, P. M. Roberts, A. D. Smith and J. M. Withey, *Org. Biomol. Chem.*, 2004, **2**, 2763.
11 M. Yamaguchi, M. Tsukamoto and I. Hirao, *Chem. Lett.*, 1984, 375.
12 For the oligomerisation of methyl crotonate and intramolecular Claisen condensation for the formation of cyclohexanones upon conjugate addition of lithium diorganocuprates, see: T. Olsson, M. T. Rahman and C. Ullenius, *Tetrahedron Lett.*, 1977, **18**, 75. For related approaches, see: M. van Beylen, S. Bywater, G. Smets, M. Szwarc and D. J. Worsfold,

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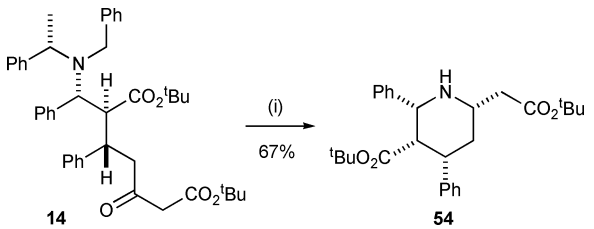
Adv. Polym. Sci., 1988, **86**, 87; G. H. Posner and E. M. Shulman-Roskes, *J. Org. Chem.*, 1989, **54**, 3514.
13 D. Lucet, S. Sabelle, O. Kostelitz, T. Le Gall and C. Mioskowski, *Eur. J. Org. Chem.*, 1999, 2583.
14 T. Takahashi, H. Okumoto and J. Tsuji, *Tetrahedron Lett.*, 1984, **25**, 1925; T. Takahashi, Y. Naito and J. Tsuji, *J. Am. Chem. Soc.*, 1981, **103**, 5261.
15 D. J. Dixon, S. V. Ley and F. Rodríguez, *Angew. Chem., Int. Ed.*, 2001, **40**, 4763; S. V. Ley, D. J. Dixon, R. T. Guy, F. Rodríguez and T. D. Sheppard, *Org. Biomol. Chem.*, 2005, **3**, 4095.
16 S. Hanessian, A. Gomtsyan, A. Payne, Y. Hervé and S. Beaudoin, *J. Org. Chem.*, 1993, **58**, 5032; S. Hanessian and A. Gomtsyan, *Tetrahedron Lett.*, 1994, **35**, 7509.
17 S. G. Davies, A. D. Smith and A. R. Cowley, *Synlett*, 2004, 1957.
18 R. E. Ireland, R. H. Mueller and A. K. Willard, *J. Am. Chem. Soc.*, 1976, **98**, 2868.
19 The absolute configuration of the minor diastereoisomer remains unknown.
20 Hydrogenolysis of β-keto-ester **14** furnished (2*R*,3*S*,4*S*,6*S*)-2,4-diphenyl-3-*tert*-butoxycarbonyl-6-(methyl *tert*-butoxycarbonyl)piperidine **54** in >90% crude d.e., and in 67% yield and >95% d.e. upon purification. The relative configuration within **54** was confirmed by ^{1}H NOE difference experiments, with the absolute configuration derived from the known (2*R*) configuration derived from (3*R*,α*S*)-**11**.



Reagents and conditions: (i) $Pd(OH)_2/C$, MeOH.

Preparation of (2*R*,3*S*,4*S*,6*S*)-2,4-diphenyl-3-*tert*-butoxycarbonyl-6-[(*tert*-butoxycarbonyl)methyl]piperidine **54**: Following Representative procedure 3, $Pd(OH)_2/C$ (50 mg) and **14** (100 mg, 0.15 mmol) in MeOH (5 ml) gave, after purification by column chromatography on silica gel (hexane–Et_2O 2 : 1), **54** as a white solid (45 mg, 67%); ν_{max} (KBr) 3432 (N–H), 2925, 2850 (C–H), 1725, 1695 (C=O), 1153 (C–O); $[\alpha]_D^{23}$ +12.3 (*c* 1.0, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 0.83, 1.48 (2 × 9 H, s, OC(*Me*)$_3$), 1.81 (1H, app dt, $J_{5ax,5eq}$12.8, $J_{5ax,4;5ax,6}$3.1, C(5)H_{ax}), 2.14 (1H, br s, N*H*), 2.28 (1H, app q, *J*12.7, C(5)H_{eq}), 2.55 (1H, dd, $J_{1'A,1'B}$15.0, $J_{1'A}$66.6, C(1′)H_A), 2.68 (1H, dd, $J_{1'B,1'A}$15.0, $J_{1'B,6}$6.8, C(1′)H_B), 3.05 (1H, app t, *J*4.2, C(3)*H*), 3.21–3.29 (2H, m, C(4)*H* and C(6)*H*), 4.19 (1H, d, *J*3.5, C(2)*H*), 7.18–7.36 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.4, 28.1 (2 × OC(*Me*)$_3$), 30.8 (*C*(5)H_2), 43.1 (*C*(*1′*)H_2), 44.6 (*C*(*3*)H), 51.7, 54.2 (*C*(*4*)H and *C*(*6*)H), 62.0 (*C*(*2*)H_2), 79.7, 80.5 (2 × O*C*(Me)$_3$), 126.3, 126.5, 126.8, 127.5, 127.9, 128.2 ($Ph_{o/m/p}$), 141.2, 142.5 (Ph_{ipso}), 171.0, 171.5 (2 × *C*O_2C(Me)$_3$); *m/z* APCI$^+$ 452.0 (MH^+, 100%), 474.3 (MNa^+, 30%), 396.3 ($MH^+ - C_4H_8$, 50%); HRMS (CI$^+$) $C_{28}H_{38}NO_4$ requires 452.2789; found 452.2800.

21 It is proposed that β-keto ester **14** may arise by two alternative routes. The first involves 1,2-addition of lithium (*E*)-enolate **12** to the cinnamate ester, followed by 1,4-conjugate addition of lithium (*E*)-enolate **12** and subsequent retro-Mannich reaction. Alternatively, 1,4-conjugate addition of lithium (*E*)-enolate **12** to the cinnamate ester, followed by enolate decomposition to the ketene, and subsequent reaction with lithium (*E*)-enolate **12** followed by retro-Mannich reaction also leads to β-keto ester **14**.
22 The absolute configuration of the major diastereoisomeric product **15** was assigned by analogy to **13**; the configuration of the minor product diastereoisomer was not unambiguously identified.
23 S. Masamune, W. Choy, J. S. Petersen and L. R. Sita, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 1.
24 The absolute configurations within the product diastereoisomers arising from the mismatched case were not unambiguously identified.
25 E. Nicolás, K. C. Russell and V. H. Hruby, *J. Org. Chem.*, 1993, **58**, 766.
26 S. G. Davies and H. J. Sanganee, *Tetrahedron: Asymmetry*, 1995, **6**, 671. For other uses of SuperQuat oxazolidinone auxiliaries in synthesis, see: S. G. Davies, R. L. Nicholson and A. D. Smith, *Synlett*, 2002, 1637; S. D. Bull, S. G. Davies, R. L. Nicholson, H. J. Sanganee and A. D. Smith, *Org. Biomol. Chem.*, 2003, **1**, 2886; S. G. Davies, I. A. Hunter, R. L. Nicholson, P. M. Roberts, E. D. Savory and A. D. Smith, *Tetrahedron*, 2004, **60**, 7553; S. G. Davies, R. L. Nicholson and A. D. Smith, *Org. Biomol. Chem.*, 2004, **2**, 3385; S. G. Davies, R. L. Nicholson and A. D. Smith, *Org. Biomol. Chem.*, 2005, **3**, 348.
27 S. G. Davies, G. J. Hermann, M. J. Sweet and A. D. Smith, *Chem. Commun.*, 2004, 1128.
28 For a review of the capability of lithium dialkylamides to act as reducing agents, see: M. Majewski and D. M. Gleave, *J. Organomet. Chem.*, 1994, **470**, 1. See also: G. Wittig, H.-J. Schmidt and H. Renner, *Chem. Ber.*, 1962, **95**, 2377; G. Wittig and H.-D. Frommeld, *Chem. Ber.*, 1964, **97**, 3541.
29 For a related reaction, see: B. A. Feit, U. Melamed, R. R. Schmidt and H. Speer, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1329.
30 Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 240141, see: S. G. Davies, A. D. Smith and A. R. Cowley, *Synlett*, 2004, 1957.
31 Probably the most successful of these are (a) the topological approach by D. Seebach and J. Golínski, *Helv. Chim. Acta*, 1981, **64**, 1413; and (b) that of D. A. Oare and C. H. Heathcock, *Top. Stereochem.*, 1989, **19**, 227.
32 Evidence has been presented for the existence of lithium enolate aggregates both in the solid state and in solution; for a review, see: D. Seebach, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 1624.
33 For a review, see: R. W. Hoffmann, *Chem. Rev.*, 1989, **89**, 1841.
34 M. Yamaguchi, M. Tsukamoto, S. Tanaka and I. Hirao, *Tetrahedron Lett.*, 1984, **25**, 5661.
35 P. W. Betteridge, J. R. Carruthers, R. I. Cooper, C. K. Prout and D. J. Watkin, *CRYSTALS*, issue 11, Chemical Crystallography Laboratory, University of Oxford, UK, 2001.