Asymmetric synthesis of β²-amino acids: 2-substituted-3-aminopropanoic acids from *N*-acryloyl SuperQuat derivatives†

James E. Beddow, Stephen G. Davies,* Kenneth B. Ling, Paul M. Roberts, Angela J. Russell, Andrew D. Smith and James E. Thomson

Received 22nd May 2007, Accepted 20th June 2007
First published as an Advance Article on the web 25th July 2007
DOI: 10.1039/b707689d

Conjugate addition of lithium dibenzylamide to (*S*)-*N*(3)-acryloyl-4-isopropyl-5,5-dimethyloxazolidin-2-one (derived from L-valine) and alkylation of the resultant lithium β-amino enolate provides, after deprotection, a range of (*S*)-2-alkyl-3-aminopropanoic acids in good yield and high ee. Alternatively, *via* a complementary pathway, conjugate addition of a range of secondary lithium amides to (*S*)-*N*(3)-(2′-alkylacryloyl)-4-isopropyl-5,5-dimethyloxazolidin-2-ones, diastereoselective protonation with 2-pyridone, and subsequent deprotection furnishes a range of (*R*)-2-alkyl- and (*R*)-2-aryl-3-aminopropanoic acids in good yield and high ee. Additionally, the boron-mediated aldol reaction of β-amino *N*-acyl oxazolidinones is a highly diastereoselective method for the synthesis of a range of β-amino-β′-hydroxy *N*-acyl oxazolidinones.

Introduction

α-Substituted-β-amino acids (β²-amino acids), like their β-substituted-β-amino acid counterparts (β³-amino acids), are of immense chemical and biological interest.[1] They occur naturally within pseudopeptides[2] and highly potent biological effects are observed with both naturally occurring and synthetic derivatives.[3] They have also been shown to display interesting structural properties as constituents of β-peptides.[4] Despite their importance in biology and peptide chemistry, the synthesis of β²-amino acids has received little attention in the literature when compared to their β³-amino acid counterparts.[5] To date the stereoselective Mannich reaction[6] and the asymmetric alkylation of chiral β-alanine derivatives[7,8] have received most attention as synthetic routes to β²-amino acids; other routes based upon conjugate addition,[9,10] Curtius rearrangement,[11] catalytic C–H insertion,[12] dynamic kinetic resolution,[13] enantioselective hydrogenation[14] and catalytic asymmetric addition of cyanide to α,β-unsaturated imides[15] amongst others[16] have also proved successful. Previous investigations from this laboratory have shown that the conjugate addition of a homochiral secondary lithium amide derived from α-methylbenzylamine to an α,β-unsaturated ester or amide represents an efficient entry to β³-amino acids and derivatives.[17] We wished to extend our methodology to incorporate the synthesis of β²-amino acids and their derivatives, and report herein our full investigations within this area concerning the conjugate addition of lithium amides to *N*-acryloyl SuperQuat derivatives, followed by stereoselective enolate functionalisation. Part of this work has been communicated previously.[18]

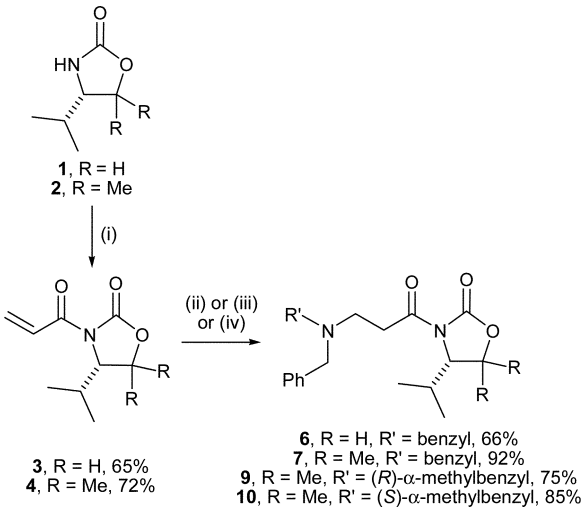
Department of Organic Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford, UK OX1 3TA. E-mail: steve.davies@chem.ox.ac.uk

† Electronic supplementary information (ESI) available: Experimental details. See DOI: 10.1039/b707689d

Results and discussion

Conjugate addition of lithium amides to *N*-acryloyl oxazolidin-2-ones

Although a range of amines have been shown to add in a conjugate fashion to acrylates,[10] conjugate addition of metal amides to this type of α,β-unsaturated carbonyl system is rare, presumably due to facile polymerisation of the activated olefin.[19] In order to test the susceptibility of *N*-acryloyl oxazolidinones toward conjugate addition of lithium amides, *N*-acryloyl oxazolidin-2-ones **3** and **4** were prepared.[20] The standard protocol for *N*-acylation of an oxazolidin-2-one (*via* the lithium anion) could not by employed in the synthesis of the 3-acryloyl acceptors, as the oxazolidin-2-one anion is itself able to undergo a conjugate addition reaction with an acrylate.[21] A milder procedure using acrylic anhydride was therefore employed,[21] giving *N*-acryloyl Evans derivative **3** and *N*-acryloyl SuperQuat **4** in 65 and 72% yield, respectively (Scheme 1). The conjugate addition reaction of lithium dibenzylamide **5** to *N*-acryloyl Evans **3** was attempted at high dilution (40 μM w. r. t. **3**) in an attempt to suppress polymerisation; however, a mixture of products was obtained from which **6** was isolated in 66% yield. Similar reaction of *N*-acryloyl SuperQuat **4** under identical conditions gave, after 5 min, complete conversion to a single product **7**, which was isolated in 92% yield (Scheme 1). The incorporation of the 5,5-dimethyl group into the oxazolidin-2-one skeleton not only serves to suppress the endocyclic cleavage pathway upon cleavage but also restricts the conformation of the C(4)-stereodirecting isopropyl group such that it mimics the steric demands of a *tert*-butyl group.[22] It is apparent from this study that the conformational restriction also decreases the extent of unwanted side reactions of *N*-acryloyl SuperQuat **4** upon conjugate addition of lithium dibenzylamide **5**, relative to the corresponding *N*-acryloyl Evans derivative **3**. The conjugate addition of both antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **8** to *N*-acryloyl SuperQuat

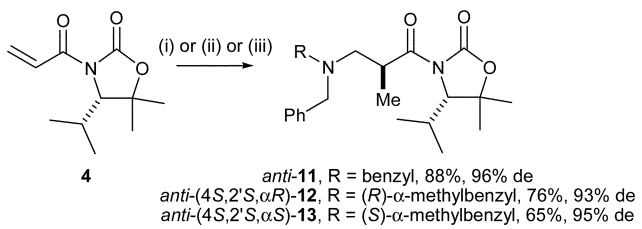


Scheme 1 *Reagents and conditions:* (i) acrylic anhydride, Et_3N, LiCl, THF, rt, 2 h; (ii) lithium dibenzylamide **5**, THF, −78 °C, 5 min, then NH_4Cl (sat., aq.); (iii) lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **8**, THF, −78 °C, 5 min, then NH_4Cl (sat., aq.); (iv) lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **8**, THF, −78 °C, 5 min, then NH_4Cl (sat., aq.).

4 was next investigated and, in each case, the corresponding β-alanine derivatives (4*S*,α*R*)-**9** and (4*S*,α*S*)-**10** were isolated in 75 and 85% yields respectively (Scheme 1).

Tandem conjugate addition and enolate alkylation

Having demonstrated that the conjugate addition of lithium dibenzylamide **5** to *N*-acryloyl SuperQuat **4** proceeds efficiently, the utility of this methodology for the synthesis of α-alkyl-β[2]-amino acid derivatives was probed *via* the *in situ* alkylation of the lithium β-amino enolate arising from the conjugate addition reaction; methyl iodide was chosen as a representative electrophile for pilot studies. In this manner, conjugate addition of lithium dibenzylamide **5** to *N*-acryloyl SuperQuat **4** followed by addition of 1.5 eq. of methyl iodide after 5 min gave *anti*-**11** as the major diastereoisomer in 96% de.[23] Purification gave *anti*-**11** in 88% yield and 96% de (Scheme 2). The relative stereochemistry of the major diastereoisomer *anti*-**11** was determined unambiguously by single crystal X-ray analysis, with the absolute (4*S*,2′*S*) configuration assigned from the L-valine derived stereocentre of the oxazolidin-2-one (Fig. 1). The effect of incorporation of a homochiral α-methylbenzyl substituent within the lithium amide upon the



Scheme 2 *Reagents and conditions:* (i) lithium dibenzylamide **5**, THF, −78 °C, 5 min, then MeI, −78 °C to rt; (ii) lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **8**, THF, −78 °C, 5 min, then MeI, −78 °C to rt; (iii) lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **8**, THF, −78 °C, 5 min, then MeI, −78 °C to rt.

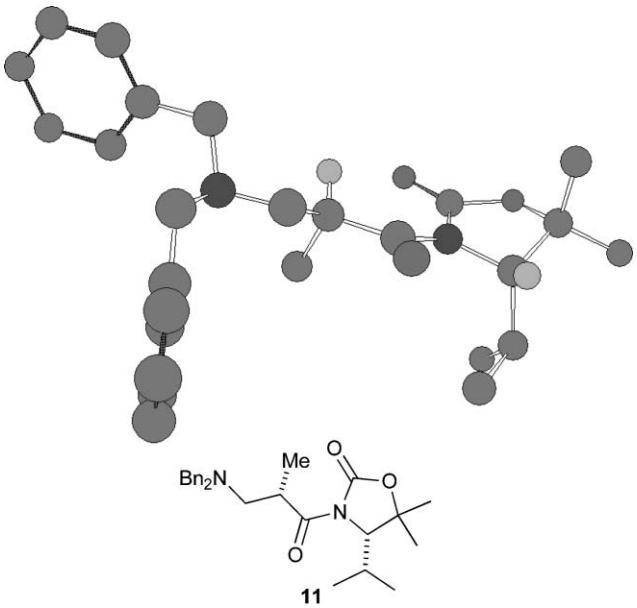
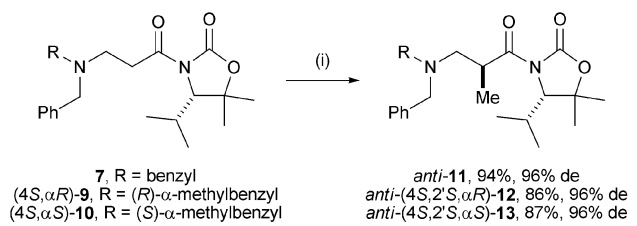


Fig. 1 Chem 3D representation of the X-ray crystal structure of *anti*-**11** (some H atoms removed for clarity).

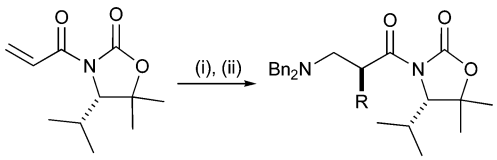
reaction diastereoselectivity was next assessed. Conjugate addition of lithium amide (*R*)-**8** to *N*-acryloyl SuperQuat **4** and quenching with methyl iodide gave *anti*-**12** in 93% de, whilst an analogous reaction using lithium amide (*S*)-**8** gave *anti*-**13** in 95% de, indicating that the oxazolidinone auxiliary has the dominant effect on determining the alkylation selectivity, with the configuration of the α-methylbenzyl stereocentre having little effect (Scheme 2).

A stepwise procedure was next investigated, with deprotonation of **7** with LiHMDS followed by alkylation with methyl iodide giving *anti*-**11** in an identical 96% de to that observed in the tandem reaction, indicating that both tandem and stepwise alkylation procedures may be employed with equal efficiency within this system (Scheme 3). Deprotonation of (4*S*,α*R*)-**9** and (4*S*,α*S*)-**10** gave preferentially the corresponding *anti* diastereoisomers, **12** and **13** respectively, in 96% de in each case, indicating that the presence of a homochiral α-methylbenzyl stereocentre has no effect on the reaction diastereoselectivity of the stepwise alkylation reaction (Scheme 3).



Scheme 3 *Reagents and conditions:* (i) LiHMDS, THF, −78 °C, 30 min; (ii) MeI, −78 °C to rt.

With these results in hand, the generality of this conjugate addition and enolate alkylation protocol was explored further by employing the conjugate addition of lithium dibenzylamide followed by quenching with a range of alkylating agents (Scheme 4). In all cases, the diastereoselectivity for the alkylation was excellent (≥96% de); alkylation with the activated electrophiles benzyl

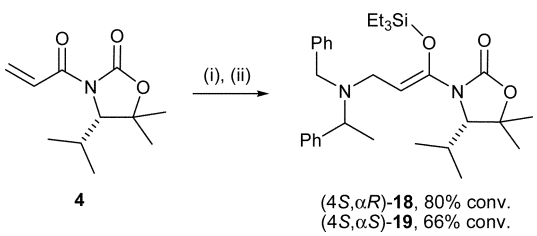


RX	Product	Yield %	de %
MeI	**11**	88	96
BnBr	**14**	85	97
allyl bromide	**15**	82	96
EtI	**16**	62	96
^{i}PrI	**17**	8	96

Scheme 4 *Reagents and conditions:* (i) lithium dibenzylamide **5**, THF, −78 °C, 5 min; (ii) RX, −78 °C to rt.

bromide and allyl bromide gave good conversion to the corresponding products **14** and **15** which were isolated in good yields, whilst the less reactive electrophiles ethyl iodide and isopropyl iodide gave lower conversions to the corresponding 2′-substituted products **16** and **17**, particularly in the latter case (8% isolated yield of **17**). In these two cases, the mass balance was made up by *N*-(β-aminoacyl) SuperQuat **7**. The stereochemistry of the major diastereoisomeric alkylation products **14–17** from this protocol was assigned as *anti*-(4*S*,2′*S*) by analogy to that unambiguously proven for 2′-methyl **11**.

Having demonstrated unambiguously that both the tandem and stepwise protocols generate stereoselectively the (2′*S*)-configuration upon enolate alkylation, the mechanism of these transformations was explored *via* the trapping of the lithium enolates arising from both the stepwise and tandem procedures. Conjugate addition of lithium amide (*R*)-**8** to *N*-acryloyl SuperQuat **4** and treatment of the resultant enolate with triethylsilyl chloride (TESCl) gave 80% conversion to the corresponding silyl enol ether **18** (Scheme 5). NOE enhancements within **18** were consistent with the enol ether having the (*Z*)-geometry, with free rotation around the *N*(3)-vinylic bond (Fig. 2). Irradiation of the vinylic proton H_2 showed an enhancement into protons H_4, H_3, $H_{3'}$ and H_α, with no enhancement to the triethylsilyl group. Irradiation of the triethylsilyl $SiCH_2$ protons gave only an enhancement into H_4, H_3, $H_{3'}$, H_5, and $H_{5'}$ (Fig. 2). Following an identical experimental procedure, conjugate addition of lithium amide (*S*)-**8** to **4** and subsequent addition of TESCl gave 66% conversion to the corresponding silyl enol ether **19**, for which NOE data was also consistent with a (*Z*)-geometry.



Scheme 5 *Reagents and conditions:* (i) lithium (*R*)- or (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **8**; (ii) TESCl.

Enolate trapping was subsequently carried out on the enolates formed from the deprotonation of (4*S*,α*R*)-**9** and (4*S*,α*S*)-**10**, in each case furnishing the corresponding enol ethers **18** and **19**, respectively, in 80% conversion (Scheme 6). ^{1}H NMR spectroscopic analysis indicated that the enol ethers formed had the same respective geometry as those formed in the corresponding tandem reactions.

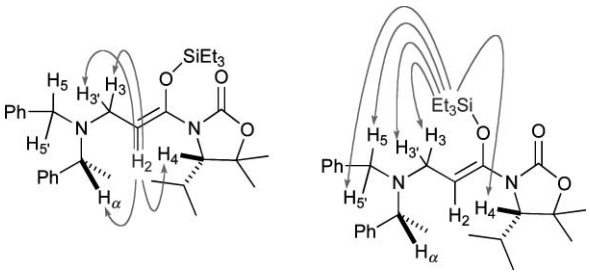
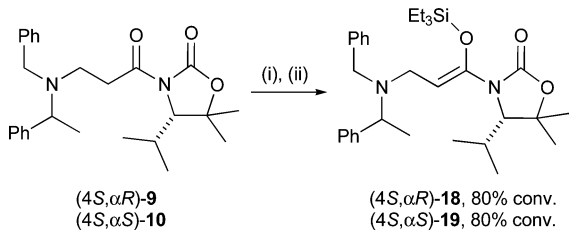


Fig. 2 NOE enhancements for **18**.



Scheme 6 *Reagents and conditions:* (i) LiHMDS, THF, −78 °C; (ii) TESCl.

With these data in hand, the selectivity in these alkylation reactions was postulated to arise as follows. Initial lithium amide conjugate addition occurs to the *N*-acryloyl oxazolidinone **4** in the *anti*-s-*cis* conformation **20** to generate the (*Z*)-β-amino enolate **21**.[24] In the stepwise protocol, deprotonation of **7** in accordance with the Ireland model **22** also furnishes (*Z*)-enolate **21**. Enolate **21** may switch from conformation **21a** to conformation **21b** with the lithium chelated between the two oxygen atoms. The high levels of stereoselectivity upon alkylation in favour of the (4*S*,2′*S*) diastereoisomer **23** are consistent with alkylation of the chelated intermediate **21b** from the least hindered face (Fig. 3).[25]

In order to validate the utility of this strategy for the synthesis of homochiral β^2-amino acids, deprotection to furnish the amino acids was pursued. 2′-Methyl **11** was subjected to catalytic hydrogenolysis conditions, giving a mixture of products presumably arising from the intramolecular nucleophilic ring opening of the oxazolidinone ring by the free 3′-amino group.[26] It was therefore envisaged that removal of the auxiliary prior to the hydrogenolysis of the *N*-benzyl protecting groups would circumvent this problem. 2′-Methyl **11** was stirred with lithium hydroxide in THF–H_2O to furnish the tertiary β-amino acid (*S*)-**24** in quantitative yield. The auxiliary **2** was not separated from the product at this stage; instead the mixture of (*S*)-**24** and **2** was subjected to catalytic hydrogenolysis, the crude product (*S*)-**25** was transformed to the HCl salt and purified by ion-exchange chromatography to furnish the free amino acid (*S*)-**25** in 84% yield over two steps, with spectroscopic properties in good agreement with those in the literature {$[a]_D^{25}$ +17.0 (*c* 1.0 in H_2O); lit.[27] for enantiomer $[a]_D^{17}$ −14.2 (*c* 1.0 in H_2O)} (Scheme 7). Application of this protocol to (4*S*,2′*S*,α*R*)-**12** and (4*S*,2′*S*,α*S*)-**13** similarly gave tertiary β-amino acids **26** and **27** as single diastereoisomers, indicating there was no epimerisation in the hydrolysis step. Subsequent hydrogenolysis of **26** and **27** followed by ion-exchange chromatography gave

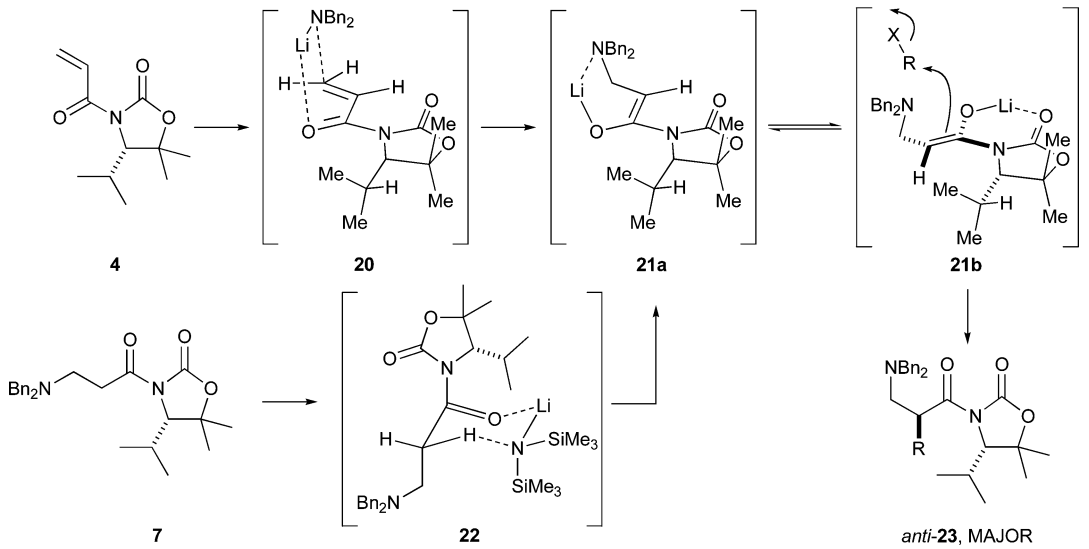
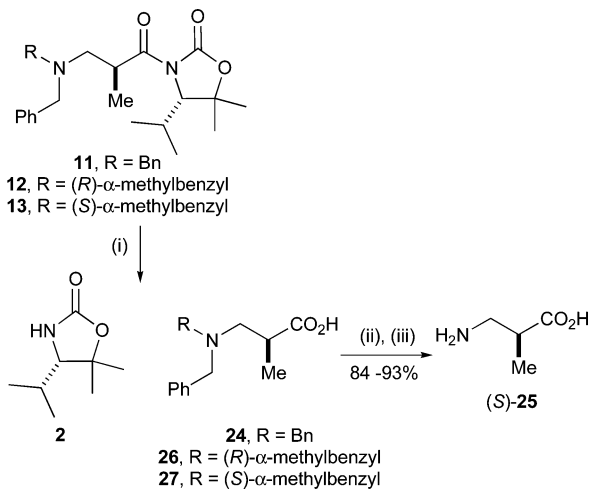
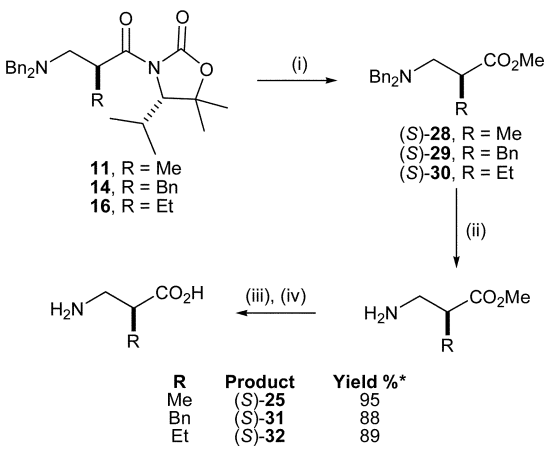


Fig. 3 Postulated origin of the diastereoselectivity in the alkylation of enolate **21**.



Scheme 7 *Reagents and conditions:* (i) LiOH, THF, H_2O, rt, 15 h; (ii) H_2 (1 atm), Pd/C, MeOH, AcOH, H_2O, rt, 24 h, then HCl (aq.); (iii) Dowex 50WX8-200.



R	Product	Yield %*
Me	(*S*)-**25**	95
Bn	(*S*)-**31**	88
Et	(*S*)-**32**	89

Scheme 8 *Reagents and conditions:* (i) BuLi, MeOH, 0 °C; (ii) H_2 (1atm), Pd/C, MeOH, AcOH, H_2O, rt, 24 h; (iii) LiOH, THF, H_2O, Δ, 15 h, then HCl (aq.); (iv) Dowex 50WX8-200. [* Yields quoted are overall from the corresponding *N*-(β-aminoacyl) oxazolidinone.]

β²-amino acid (*S*)-**25** in 90 and 93% yield respectively over two steps with spectroscopic properties again consistent with those in the literature.

Under the same conditions, attempted hydrolysis of 2′-benzyl **14** and 2′-ethyl **16** with lithium hydroxide returned only starting material. Likewise, attempted cleavage of the auxiliary with lithium hydroperoxide showed only low (<10%) conversion. However, treatment of 2′-methyl **11** (96% de), 2′-benzyl **14** (97% de) and 2′-ethyl **16** (96% de) with lithium methoxide resulted in clean conversion to the corresponding methyl esters (*S*)-**28**, (*S*)-**29** and (*S*)-**30**. Hydrogenolysis of the β-amino esters (*S*)-**28**, (*S*)-**29** and (*S*)-**30** followed by saponification with lithium hydroxide furnished β²-amino acids (*S*)-**25**, (*S*)-**31** and (*S*)-**32** in excellent overall yields from the corresponding oxazolidinones **11**, **14** and **16**, and with spectroscopic properties consistent with those of the literature {2-Bn (*S*)-**31** $[\alpha]_D^{25}$ −13.1 (*c* 0.3 in H_2O); lit.[8] for enantiomer $[\alpha]_D^{25}$ +11.3 (*c* 1.0 in H_2O); lit.[27] for enantiomer $[\alpha]_D^{25}$ +17.8 (*c* 1.0 in H_2O); 2-Et (*S*)-**32** $[\alpha]_D^{25}$ −6.8 (*c* 0.4 in H_2O); lit.[28] for enantiomer $[\alpha]_D^{28}$ +4.6 (*c* 1.0 in H_2O)} (Scheme 8).

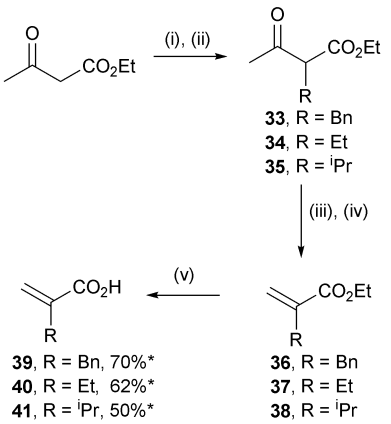
In order to confirm that no epimerisation had occurred under the reaction conditions, β²-amino acids 2-methyl (*S*)-**25** and 2-benzyl (*S*)-**31** were derivatised with both homochiral and racemic Mosher's acid chloride to give the corresponding amides,[29] and shown to be of 96 and 97% ee, respectively, in accordance with the observed diastereoselectivities of the corresponding acyl oxazolidinones 2′-methyl **11** (96% de) and 2′-benzyl **14** (97% de), indicating no loss of stereochemical integrity.

With a procedure for the diastereoselective synthesis of (*S*)-2′-alkyl-3′-amino acids delineated, attention was turned to conjugate addition of lithium dibenzylamide **5** to 2-substituted acrylates and subsequent diastereoselective protonation of the resulting enolates. It was anticipated that, in addition to furnishing the enantiomeric β²-amino acids, this complementary approach would also provide a means to synthesise α-substituted-β-amino acids not

readily accessible *via* the tandem conjugate addition and alkylation procedure, *e.g.* α-isopropyl and α-aryl-β-amino acids.

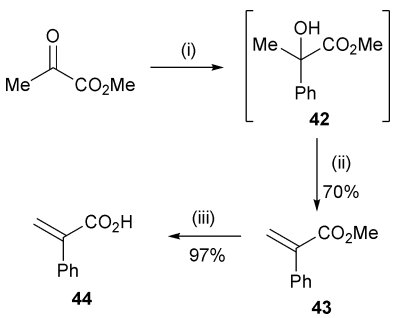
Conjugate addition and diastereoselective protonation

A series of acrylic acids substituted with an alkyl group at the 2-position was synthesised from ethyl acetoacetate.[10] Monoalkylation with an alkyl halide, followed by deprotonation and treatment with paraformaldehyde gave the 2-substituted ethyl acrylates **36–38**. Finally, saponification produced the 2-substituted acrylic acids **39–41** in good overall yields (Scheme 9).



Scheme 9 *Reagents and conditions:* (i) KO^{t}Bu, ^{t}BuOH, THF, reflux, 0 °C, 30 min; (ii) RX, 70 °C, 12 h; (iii) LiHMDS, THF, −78 °C, 30 min; (iv) $(CH_2O)_n$, −78 °C to rt; (v) LiOH, THF, H_2O, reflux, 15 h. [* Yields quoted are overall from ethyl acetoacetate.]

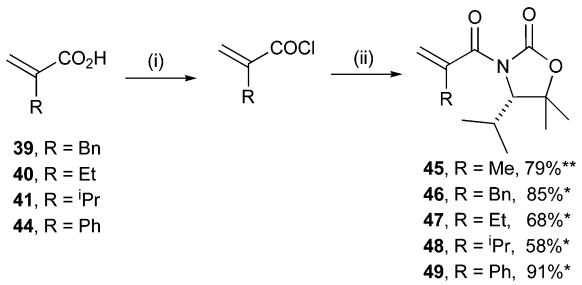
2-Phenylacrylic acid **44** was prepared *via* a two-step procedure from methyl pyruvate (Scheme 10).[30] The addition of one equivalent of phenyl magnesium bromide to methyl pyruvate followed by dehydration of the intermediate α-hydroxy ester **42** with TsOH generated methyl 2-phenyl acrylate **43** in 70% yield over two steps. Saponification furnished 2-phenyl acrylic acid **44** in 97% isolated yield.



Scheme 10 *Reagents and conditions:* (i) PhMgBr, THF, 60 °C, 30 min; (ii) TsOH, PhMe, reflux, 4 h; (iii) LiOH, THF, H_2O, reflux, 15 h.

N-Acryloyl-2′-substituted-oxazolidinones **45–49** were synthesised *via* the coupling of the lithium anion of oxazolidinone **2** with commercially available methacryloyl chloride and the acid chlorides produced from treatment of acrylic acids **39–41** and **44** with oxalyl chloride (Scheme 11).

With **45–49** in hand, attention was turned to the conjugate addition of lithium dibenzylamide **5** and stereoselective protonation of the resulting enolate with a variety of proton sources. In a preliminary study, 3-methacryloyl oxazolidinone **45** was treated with lithium dibenzylamide **5** and quenched with saturated aqueous NH_4Cl to give an inseparable mixture of *syn*-**50** and *anti*-**11** in a ratio of 66 : 34. However, when the procedure was repeated using the bulky 2,6-di-*tert*-butylphenol (2,6-DTBP),[31] or 2-pyridone[32] as the proton sources, the ratio of **50**–**11** increased to 92 : 8 and 98 : 2, respectively. Recrystallisation gave *syn*-**50** as a single diastereoisomer, indicating that the reaction proceeds to give the opposite diastereoisomer as the tandem conjugate addition and enolate alkylation (Scheme 12).

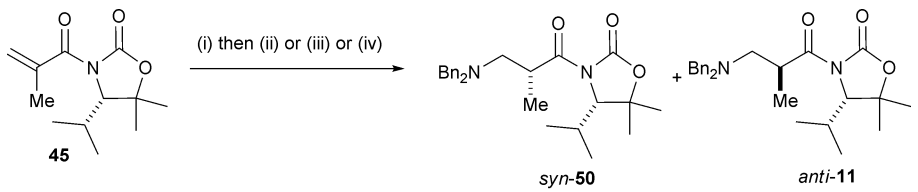


Scheme 11 *Reagents and conditions:* (i) $(COCl)_2$, Et_2O, NEt_3, rt, 1 h; (ii) **2**, BuLi, THF, −78 °C to rt, 2 h. [*Yield over 2 steps; **yield over 1 step from commercially available methacryloyl chloride.]

With this result in hand, the remaining 2′-substituted acceptors **46–49** were treated with lithium dibenzylamide **5** followed by saturated aqueous NH_4Cl, 2,6-DTBP or 2-pyridone (Scheme 13).

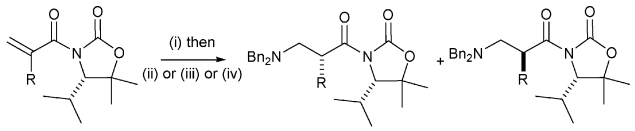
A trend was observed in the case of 2′-alkyl acryloyl derivatives, 2′-methyl **45**, 2′-ethyl **47** and 2′-isopropyl **48**. The ratio of *syn–anti* diastereoisomers increases when saturated aqueous NH_4Cl is used as the proton source; when 2,6-DTBP or 2-pyridone is used as the proton source, the resultant *syn–anti* ratios observed are generally higher than those for NH_4Cl, with 2-pyridone delivering the highest selectivity upon protonation. The ratios decrease, however, with the increasing steric bulk of the α-substituent; this effect is more pronounced with 2,6-DTBP. Meanwhile, protonation of the enolate derived from 2′-benzyl **46** with saturated aqueous NH_4Cl gave the corresponding *anti* diastereoisomer **14** as the major product; a reversal of selectivity was observed with both 2,6-DTBP and 2-pyridone, giving a *syn–anti* ratio of 79 : 21 and 90 : 10, respectively. Protonation of the enolate derived from 2′-phenyl **49** with saturated aqueous NH_4Cl gave the *syn* diastereoisomer **54** as the major product in a 62 : 38 *syn–anti* ratio, whilst 2,6-DTBP and 2-pyridone both formed the *anti* diastereoisomer **55** as the major product, giving *syn–anti* ratios of 40 : 60 and 12 : 88, respectively. In all cases, 2-pyridone gave the highest levels of diastereoselectivity upon protonation. Subsequent tandem addition–protonation studies therefore focused on the use of 2-pyridone as the proton source.

In an effort to improve the diastereoselectivity upon conjugate addition and protonation, and to probe the possibility of double diastereodifferentiation, the conjugate additions of both antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **8**, and subsequent diastereoselective protonation with 2-pyridone, were investigated.[33] Thus, the 2′-substituted acceptors **45–49** were treated with either lithium (*R*)- or (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **8** followed by 2-pyridone (Scheme 14). For 2′-methyl **45** and 2′-ethyl **47**, (*R*)-**8** gave rise to the "matched" combination,



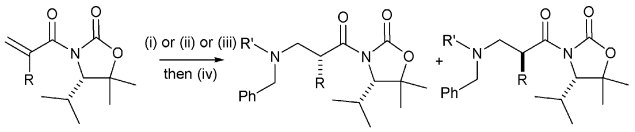
Proton source	Yield %*	*syn*:*anti* ratio
NH_4Cl (sat, aq)	96	66:34
2,6-DTBP	91	92:8
2-pyridone	87	98:2

Scheme 12 *Reagents and conditions:* (i) lithium dibenzylamide **5**, THF, −78 °C, 2 h; (ii) NH_4Cl (sat., aq.); (iii) 2,6-DTBP; (iv) 2-pyridone. [*Yields quoted are for the inseparable mixture of diastereoisomers.]



	R	Proton source	Products	*syn*:*anti* ratio
45	Me	NH_4Cl (sat, aq) 2,6-DTBP 2-pyridone	*syn*-**50**:*anti*-**11**	66:34 92:8 98:2
46	Bn	NH_4Cl (sat, aq) 2,6-DTBP 2-pyridone	*syn*-**51**:*anti*-**14**	20:80 79:21 90:10
47	Et	NH_4Cl (sat, aq) 2,6-DTBP 2-pyridone	*syn*-**52**:*anti*-**16**	87:13 92:8 97:3
48	^{i}Pr	NH_4Cl (sat, aq) 2,6-DTBP 2-pyridone	*syn*-**53**:*anti*-**17**	93:7 82:18 95:5
49	Ph	NH_4Cl (sat, aq) 2,6-DTBP 2-pyridone	*syn*-**54**:*anti*-**55**	62:38 40:60 12:88

Scheme 13 *Reagents and conditions:* (i) lithium dibenzylamide **5**, THF, −78 °C, 2 h; (ii) NH_4Cl (sat., aq.), −78 °C to rt, 12 h; (iii) 2,6-DTBP, −78 °C to rt, 12 h; (iv) 2-pyridone, −78 °C to rt, 12 h.



	R	R'	Products	*syn*:*anti* ratio
45	Me	Bn (*R*)-α-methylbenzyl (*S*)-α-methylbenzyl	*syn*-**50**:*anti*-**11** *syn*-**56**:*anti*-**12** *syn*-**57**:*anti*-**13**	98:2 98:2 84:16
46	Bn	Bn (*R*)-α-methylbenzyl (*S*)-α-methylbenzyl	*syn*-**51**:*anti*-**14** *syn*-**58**:*anti*-**59** *syn*-**60**:*anti*-**61**	90:10 86:14 92:8
47	Et	Bn (*R*)-α-methylbenzyl (*S*)-α-methylbenzyl	*syn*-**52**:*anti*-**16** *syn*-**62**:*anti*-**63** *syn*-**64**:*anti*-**65**	97:3 98:2 89:11
48	^{i}Pr	Bn (*R*)-α-methylbenzyl (*S*)-α-methylbenzyl	*syn*-**53**:*anti*-**17** *syn*-**66**:*anti*-**67** *syn*-**68**:*anti*-**69**	95:5 92:8 97:3
49	Ph	Bn (*R*)-α-methylbenzyl (*S*)-α-methylbenzyl	*syn*-**54**:*anti*-**55** *syn*-**70**:*anti*-**71** *syn*-**72**:*anti*-**73**	12:88 7:93 34:66

Scheme 14 *Reagents and conditions*: (i) lithium dibenzylamide **5**, THF, −78 °C, 2 h; (ii) lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **8**, THF, −78 °C, 2 h; (iii) lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **8**, THF, −78 °C, 2 h; (iv) 2-pyridone, −78 °C to rt, 12 h.

giving improved diastereoselectivities with *syn–anti* products in a ratio of 98 : 2 and 97 : 3 respectively, whereas (*S*)-**8** gave rise to the "mismatched" combination, furnishing *syn–anti* products in a ratio of 84 : 16 and 89 : 11, respectively. Similarly, for 2′-phenyl **49**, (*R*)-**8** offered the "matched" combination, offering an increase in diastereoselectivity (*anti–syn* ratio 93 : 7), whereas (*S*)-**8** offered the "mismatched" combination (*anti–syn* ratio 66 : 34). *Syn*-**70** and *anti*-**71** proved partially seperable by chromatography, affording *anti*-**71** in an improved 96% de. Conversely, for 2′-benzyl **46** and 2′-isopropyl **48**, (*S*)-**8** appeared to be the "matched" combination, affording improved diastereoselectivities (*syn–anti* ratio 92 : 8 and 97 : 3, respectively), and (*R*)-**8** appeared to be the "mismatched" combination (*syn–anti* ratio 86 : 14 and 92 : 8, respectively).

Assuming that the conjugate addition of lithium amides **5**, (*R*)-**8** and (*S*)-**8** to a 2′-substituted acryloyl oxazolidinone **74** occurs *via* a similar transition state to that for conjugate addition to **4** (**75**, Fig. 4), protonation of the enolate in conformation **76a** would lead to the *anti*-product **23** whilst protonation in conformation **76b** would lead to *syn*-product **77** (Fig. 4). When saturated aqueous NH_4Cl is used as the proton source, protonation may occur on oxygen as well as on carbon and the resultant enol tautomerises upon warming, thus affecting the reaction diastereoselectivity, which is highly dependent on the nature of the 2′-substituent of **74**. When 2,6-DTBP is used as the proton source, protonation is anticipated to occur mostly on carbon, with the major product arising from protonation *anti* to the C(4)-isopropyl directing group of the oxazolidinone. The use of 2-pyridone as the proton source is postulated to occur *via* a relay mechanism: binding of the carbonyl of the 2-pyridone to the β-amino lithium enolate **76** (resulting from conjugate addition) *anti* to the stereodirecting C(4)-isopropyl group of the oxazolidinone directs the regio- and facial selectivity of C-protonation. The change in the sense of selectivity at C(2′) from the alkyl to the aryl cases arises from the preference of the β-amino enolate for the conformations **76a** and **76b**. In the cases of 2′-benzyl and the 2′-alkyl series, conformer **76b** is preferred, leading to the (4*S*,2′*R*) configuration upon protonation. In the 2′-phenyl series, conformer **76b** is precluded due to steric interactions between the C(4)-isopropyl group of the oxazolidinone and the C(2′)-phenyl group. Conformer **76a** is therefore preferred, with protonation giving rise to the observed (4*S*,2′*S*) configuration of the major product (Fig. 4).

With β-amino oxazolidin-2-ones in hand, attention turned towards their deprotection to the corresponding β^2-amino acids. Treatment of 2′-Me **50** (96% de) with lithium hydroxide followed by hydrogenation and ion-exchange chromatography afforded 2-Me (*R*)-**25** in 89% yield and >95% ee[29] with spectroscopic properties consistent with those of the literature {$[\alpha]_D^{25}$ −12.4 (*c* 1.0 in H_2O); lit.[27] $[\alpha]_D^{17}$ −14.2 (*c* 1.0 in H_2O)}. Treatment of 2′-Et **52** (94% de) and 2′-^{i}Pr **53** (90% de) under the same conditions

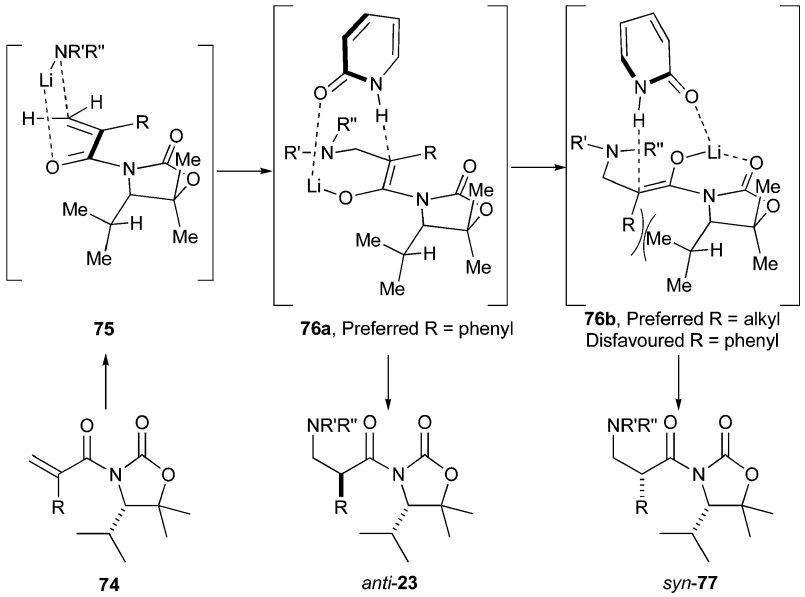
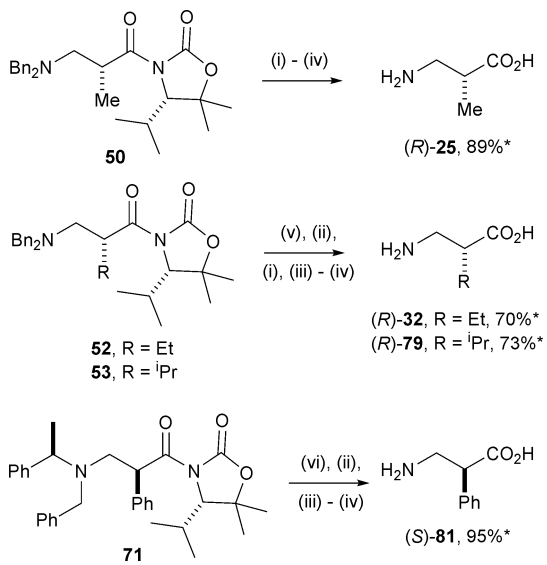


Fig. 4 Proposed origin of the diastereoselectivity in the protonation of enolate conformations **76a** and **76b**.

gave only returned starting material. However, treatment with lithium methoxide gave clean conversion to the methyl esters (*R*)-**30** and (*R*)-**78** respectively; subsequent sequential hydrogenation and saponification gave (*R*)-α-alkyl-β-amino acids 2-Et (*R*)-**32** in 70% yield and 94% ee,[29] and 2-^{i}Pr (*R*)-**79** in 73% yield and 88% ee,[29] with spectroscopic properties consistent with those of the literature {2-Et (*R*)-**32** $[\alpha]_D^{22}$ +4.5 (*c* 1.0 in H_2O); lit.[28] $[\alpha]_D^{28}$ +4.6 (*c* 1.0 in H_2O); 2-^{i}Pr (*R*)-**79** $[\alpha]_D^{25}$ −10.0 (*c* 0.1 in H_2O), lit.[27] $[\alpha]_D^{25}$ −11.4 (*c* 1.0 in H_2O)} (Scheme 15). In the case of deprotection of 2′-Ph **71** (96% de), however, treatment with lithium methoxide gave extensive epimerisation of the C(2′)-stereocentre. Stirring with lithium hydroperoxide gave clean conversion to a mixture of the corresponding tertiary β-amino acid (*S*)-**80** and SuperQuat **2**, which was subjected to catalytic hydrogenolysis and subsequent purification by ion-exchange chromatography to give 2-Ph (*S*)-**81** in 95% yield and >95% ee,[29] with spectroscopic properties consistent with those of the literature {$[\alpha]_D^{25}$ +93.0 (*c* 1.0 in H_2O), lit.[34] $[\alpha]_D^{21}$ +95.0 (*c* 1.0 in H_2O)} (Scheme 15).

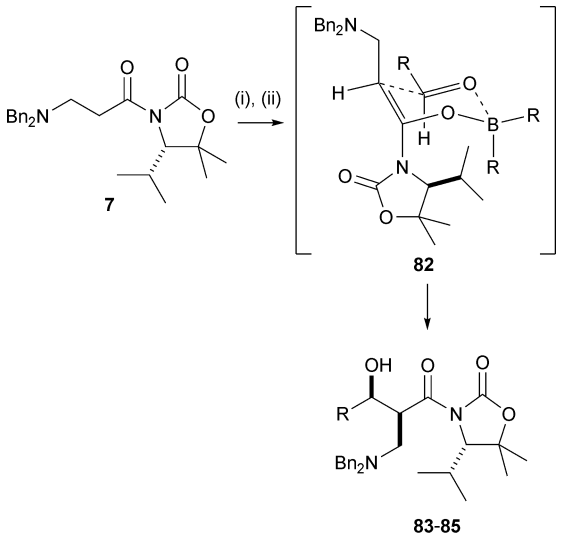


Scheme 15 *Reagents and conditions:* (i) LiOH, THF, H_2O, Δ, 15 h; (ii) H_2 (1 atm), Pd/C, MeOH, AcOH, H_2O, rt, 24 h; (iii) HCl (aq.); (iv) Dowex 50WX8-200; (v) BuLi, MeOH, 0 °C; (vi) LiOH, H_2O_2, THF, H_2O, 0 °C to rt, 24 h. [* Yields quoted are overall from the corresponding *N*-acryloyl oxazolidinone.]

Aldol reactions

In order to expand the scope and utility of the lithium amide conjugate addition–alkylation/protonation protocol for the synthesis of β^2-amino acids, attention was next turned toward aldol reactions of the enolate of **7** for the synthesis of β-amino-β′-hydroxy-acids. Members of this sub-class include β^2-homothreonine (β^{2}hThr), residues of which are found in a range of carbapenem antibiotics.[35] The pharmaceutical importance of β^{2}hThr and its derivatives as precursors to the β-lactam sub-unit of antibiotics has led to several highly stereoselective and high yielding syntheses of this motif, including catalytic asymmetric hydrogenation of a β-amino-β′-ketoester,[36] conjugate addition of secondary amines to homochiral alkenoate species,[37] addition of homochiral silyl ketene acetals to nitrones[38] and asymmetric aldol reactions of *N*-acyl oxazolidinones.[39] Our approach centred upon an aldol reaction of the enolates derived from β-amino-*N*-acryloyl oxazolidinones **7**, **9** and **10**. Initial investigations focused on the development of a tandem addition–aldol protocol. However, the attempted treatment of **4** with lithium dibenzylamide **5** and an aldehyde gave mixtures of inseparable diastereoisomeric products. Attempted *in situ* transmetallation of the lithium enolate to the titanium enolate and subsequent aldol reaction gave none of the desired aldol products, whilst transmetallation to boron gave no significant improvement in diastereoselectivity in the aldol reaction. The tandem approach was therefore abandoned in favour of a stepwise protocol, involving enolisation of a β-amino-*N*-acryloyl oxazolidinone followed by addition of the aldehyde. Thus formation of the boron enolate of **7**, followed by aldol reaction with acetaldehyde was investigated as a model system. Thus, treatment

of **7** at 0 °C with 1.2 eq. of 9-BBNOTf and 1.4 eq. of Hünig's base, followed by addition of acetaldehyde at −78 °C, revealed that the aldol reaction had proceeded to <10% conversion, consistent with the diminished reactivity of the boron enolate when compared to the corresponding lithium enolate. Optimisation showed that formation of the boron enolate at 0 °C followed by addition of acetaldehyde at −78 °C and subsequent warming to 0 °C over 1 h gave good conversion (~70%), giving aldol product **83** as a single diastereoisomer in 65% isolated yield. The relative *syn*-configuration of the product was assigned by analogy to standard boron aldol reactions of *N*-acyl oxazolidinones,[40] assuming that the reaction proceeds preferentially *via* a Zimmermann–Traxler chelated transition state **82** in which the aldehyde substituent adopts a pseudo-equatorial position (Scheme 16).[41]



Aldehyde	Product	Yield %	de %	$J_{2'-3'}$ Hz
MeCHO	**83**	65	>98	N. D.
PhCHO	**84**	36	>98	9.2
^{i}PrCHO	**85**	64	>98	8.9

Scheme 16 *Reagents and conditions:* (i) 9-BBNOTf (1.2 eq.), 10 min, 0 °C, then $^{i}Pr_2NEt$ (1.4 eq.), 20 min, 0 °C; (ii) RCHO, −78 °C, 30 min, then 0 °C, 1 h, then MeOH, H_2O_2 (aq.). [N. D. = not determined.]

With the conditions for the aldol reaction with acetaldehyde optimised, the aldol reaction of *N*-acyl oxazolidinone **7** with alternative aldehydes was investigated. Using the optimised conditions, reaction of **7** with benzaldehyde and isobutyraldehyde proceeded in moderate to good conversion (40–70%) to give aldol products **84** and **85** respectively, as single diastereoisomers,[23] which were isolated in moderate yield (36–64%) after chromatography (Scheme 16).

The stereochemistry of the major diastereoisomer aldol products **84** and **85** arising from this protocol was unambiguously established by single crystal X-ray analysis, confirming the expected relative *syn*-configuration between C(2′) and C(3′), with the absolute (4*S*,2′*S*,3′*S*)-**84** and (4*S*,2′*S*,3′*R*)-**85** configurations determined relative to the known (*S*)-configuration of the auxiliary (Fig. 5). The relative stereochemistry within aldol product **83** was therefore assigned by analogy.

^{1}H NMR analysis indicated a larger coupling constant ($J_{2'-3'}$ ~9 Hz) for the *syn* configuration than would be expected upon the basis of intramolecular hydrogen bonding between the C(3′)-hydroxyl and the C(1′) carbonyl.[42] Analysis of the X-ray crystal structures of **84** and **85** revealed that an intramolecular hydrogen bond was present within the solid state structures of these compounds, but between the C(3′) hydroxyl and the C(3) amino group, giving a dihedral angle of ϕ ~180° for C(2′)*H*-C(3′)*H*. Assuming a similar hydrogen-bonded structure also exists in solution, this would account for the larger than expected ^{3}J values (Fig. 5).

Although the aldol reactions of β-amino-*N*-acyl oxazolidinone **7** have proven to be highly diastereoselective, the reactions suffer from low conversions in many cases. It was postulated that incomplete conversion could be attributable to incomplete formation of the boron enolate; however, use of 2 eq. of 9-BBNOTf decreased the conversion of the reaction, and varying the temperature of enolisation had very little effect. An alternative explanation to account for the relatively modest reactivity of the boron enolate derived from **7** is that the amino group binds to the 9-BBNOTf, thereby hampering reactivity. This effect could potentially be overcome by increasing the steric bulk of the amino group to disfavour binding of the bulky boron reagent, thereby increasing the reactivity of the boron reagent towards an aldehyde. Investigations turned towards the effect of incorporation of a

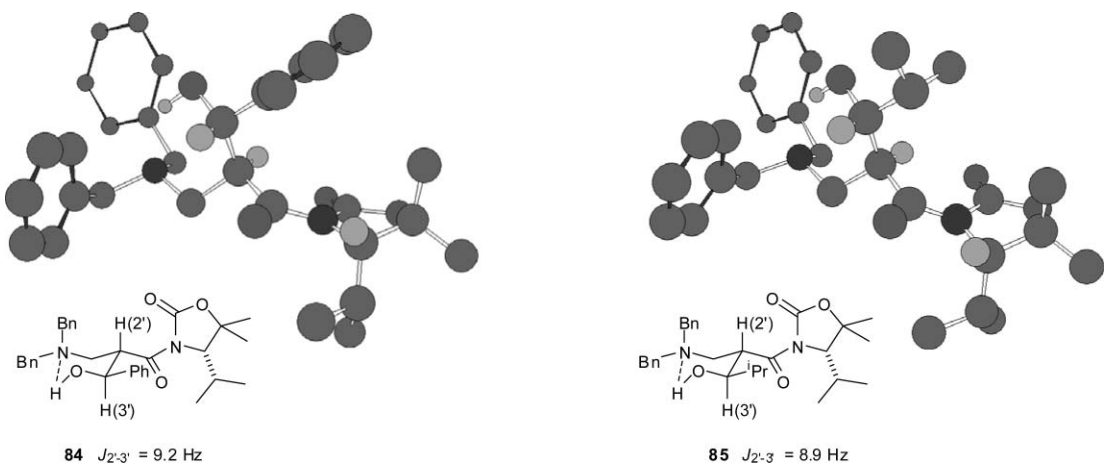
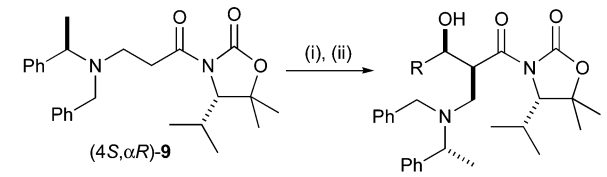


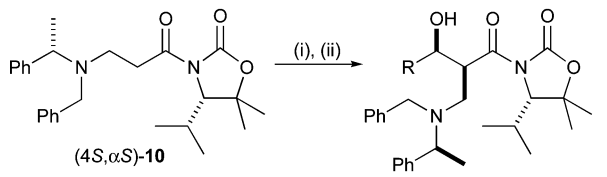
Fig. 5 Chem 3D representations of the X-ray crystal structures of **84** and **85** (some H atoms removed for clarity).

N-benzyl-*N*-(α-methylbenzyl)amino moiety in an attempt to increase the reactivity and to allow the possibility of double asymmetric induction. The aldol reactions of the boron enolates derived from *N*-benzyl-*N*-(α-methylbenzyl) derivatives (4*S*,α*R*)-**9** and (4*S*,α*S*)-**10** were therefore investigated.

Treatment of (4*S*,α*R*)-**9** with 9-BBNOTf and Hünig's base, followed by addition of acetaldehyde gave >90% conversion to a 92 : 8 mixture of *syn*-**86** and *anti*-**87**, whilst the analogous reaction of (4*S*,α*S*)-**10** gave >90% conversion to a 94 : 6 mixture of two products *syn*-**88** and *anti*-**89**. The *syn*-configurations of the major reaction products were assigned by analogy to **84** and **85**, and on the assumption that the *N*-α-methylbenzyl group has a relatively small effect on the stereoselectivity of the reaction. The relative configurations of the minor diastereoisomers **87** and **89** were arbitrarily assigned as *anti* (Scheme 17).

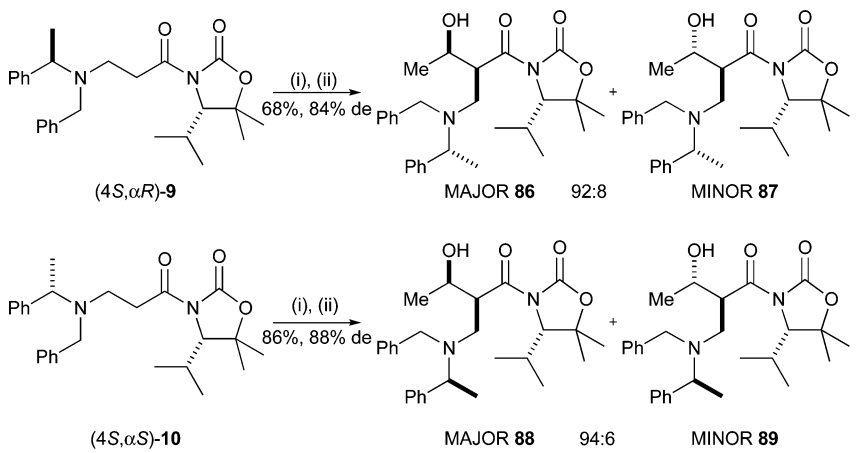
These results demonstrate that, in both cases, the conversion of the reaction improved dramatically in comparison to the simple dibenzylamino case although a concomitant decrease in the reaction diastereoselectivity is observed (84% de for **9** and 88% de for **10**). Both observations may be attributed to the greater reactivity of the enolates in the systems when compared to the dibenzylamino case; a possible result of decreased binding of the amino nitrogen to boron. It was therefore postulated that the reaction of *N*-(β-aminoacyl) SuperQuats (4*S*,α*R*)-**9** and (4*S*,α*S*)-**10** with less reactive aldehydes may proceed with similarly high conversions but with improved diastereoselectivities. The aldol reactions of **9** and **10** with benzaldehyde and isobutyraldehyde were therefore investigated. Treatment of (4*S*,α*R*)-**9** and (4*S*,α*S*)-**10** with 9-BBNOTf and Hünig's base followed by isobutyraldehyde gave the corresponding aldol products **90** and **92**, as single diastereoisomers, in 42 and 28% yield respectively, the mass balance being returned starting materials in both cases. These data suggest that the *N*-α-methylbenzyl group has little effect on the diastereoselectivity of the reaction, with the dominant stereocontrol originating from the SuperQuat auxiliary. However, while treatment of (4*S*,α*R*)-**9** with 9-BBNOTf and Hünig's base followed by benzaldehyde gave **91** in 52% yield and >98% de, (4*S*,α*S*)-**10** gave a 77 : 23 mixture of diastereoisomers, with **93** as the major product, in 68% yield under the same conditions (54% de), indicating that the (*R*)-*N*-α-methylbenzyl group has a significant effect on the stereochemical outcome of the aldol reaction in this case. Although the absolute configurations of the aldol products **90–93** were not proven unambiguously, comparison with the analogous dibenzylamino aldol products **84** and **85** suggests that, based on analysis of coupling constants for the C(2′) and C(3′) protons, the *syn*-configuration is produced, with 8.6 Hz ≤ $J_{2'\text{-}3'}$ ≤ 9.1 Hz in all cases (Scheme 18).



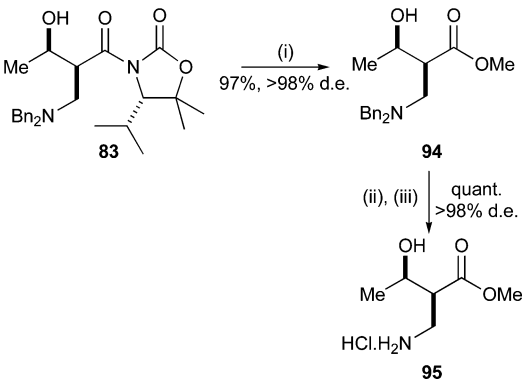


Scheme 18 *Reagents and conditions:* (i) 9-BBNOTf (1.2 eq.), 10 min, 0 °C, then $^{i}Pr_2NEt$ (1.4 eq.), 20 min, 0 °C; (ii) RCHO (1.5 eq.), −78 °C, 30 min, then 0 °C, 1 h, then MeOH, H_2O_2 (aq.).

In order to confirm the stereochemistry of the aldol product **83**, the auxiliary was cleaved by treatment with LiOMe, with ^{1}H NMR spectroscopic analysis revealing no epimerisation had occurred. Methyl ester **94** was successfully deprotected to give the known β-amino-β′-hydroxy methyl ester hydrochloride (β^2-homothreonine methyl ester) **95** in quantitative yield, and with spectroscopic data in excellent agreement with that in the literature {$[a]_D^{23}$ −6.7 (*c* 0.9 in MeOH), lit.[38] $[a]_D^{30}$ −7.0 (*c* 0.9 in MeOH)} (Scheme 19).



Scheme 17 *Reagents and conditions:* (i) 9-BBNOTf (1.2 eq.), 10 min, 0 °C, then $^{i}Pr_2NEt$ (1.4 eq.), 20 min, 0 °C; (ii) MeCHO (1.5 eq.), −78 °C, 30 min, then 0 °C, 1 h, then MeOH, H_2O_2 (aq.).



Scheme 19 *Reagents and conditions:* (i) LiOMe, MeOH, THF, 0 °C to rt, 5 h; (ii) H_2 (1 atm), Pd/C (10% w/w), MeOH, H_2O, AcOH; (iii) HCl (2.0 M in Et_2O).

Conclusion

In conclusion, conjugate addition of lithium dibenzylamide to homochiral (*S*)-*N*-acryloyl SuperQuat **4** and alkylation of the resultant β-amino enolate with an alkyl halide allows access to homochiral (*S*)-2-alkyl β²-amino acids. Conjugate addition of lithium amides to 2′-substituted (*S*)-*N*-acryloyl SuperQuats **45**–**49** and stereoselective protonation with 2-pyridone gives access to the enantiomeric (*R*)-2-alkyl β²-amino acids, as well as (*S*)-2-aryl β²-amino acids. As both enantiomers of the SuperQuat chiral auxiliary are readily available, the combination of these complementary strategies allows a general synthetic pathway to either enantiomer of 2-substituted-3-aminopropanoic acids with a range of substituents.

The boron mediated aldol reaction between β-amino-*N*-acyl oxazolidinones **7**, **9** and **10** and a range of aldehydes has been investigated and shown to proceed with excellent levels of diastereoselectivity to give *syn*-aldol products. Cleavage of the auxiliary and debenzylation to give a highly functionalised β-amino-β′-hydroxy methyl ester has been shown to proceed efficiently for a model system. The further application of this methodology for the synthesis of highly functionalised β-amino-β′-hydroxy-*N*-acyl SuperQuats as building blocks for natural product synthesis is currently under investigation in our laboratory.

Experimental

General experimental

All reactions involving organometallic or other moisture sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. The solvents were dried according to the procedure outlined by Grubbs and co-workers.[43] Water was purified by an Elix® UV-10 system. All other solvents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. The plates were visualised using UV light (254 nm), iodine, 1% aq. $KMnO_4$ or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica.

Elemental analyses were recorded by the microanalysis service of the Inorganic Chemistry Laboratory, University of Oxford, UK. Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded on a Bruker Tensor 27 FTIR spectrometer as either a thin film on NaCl plates (film), a chloroform cell ($CHCl_3$) or a KBr disc (KBr), as stated. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated. The field was locked by external referencing to the relevant deuteron resonance. Low-resolution mass spectra were recorded on either a VG MassLab 20–250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF and were internally calibrated with polyanaline in positive and negative modes, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m × 0.25 mm) using amyl acetate as a lock mass.

(*S*)-5,5-Dimethyl-4-isopropyl-3-[3′-(*N*,*N*-dibenzylamino)propanoyl]oxazolidin-2-one 7

n-BuLi (0.91 mL, 2.3 mmol, 1.6 eq.) was added dropwise to a stirred solution of dibenzylamine (0.44 mL, 2.30 mmol, 1.6 eq.) in THF (0.3 mL) at −78 °C. After stirring for 30 min at −78 °C, a solution of *N*-acryloyl-oxazolidinone **4** (296 mg, 1.40 mmol, 1.0 eq.) in THF (0.1 mL), also at −78 °C, was added dropwise *via* cannula. The resulting solution was stirred for between 2 h before the addition of sat. aq. NH_4Cl solution (0.1 mL). The product was extracted with ether (3 ×), the combined organic extracts were washed with aq. citric acid solution (10% w/v), sat. aq. $NaHCO_3$ solution and brine. The resultant organic solution was dried and concentrated *in vacuo*. Purification of the residue *via* column chromatography (silica, 9 : 1 pentane–ether, v/v) afforded **7** (525 mg, 92%) as a viscous, colourless oil; $[\alpha]_D^{25}$ +17.5 (*c* 1.6, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 1772, 1700; δ_H (400 MHz, $CDCl_3$) 0.96 (3H, d, *J* 6.8, CH*Me*$_2$), 1.04 (3H, d, *J* 7.0, CH*Me*$_2$), 1.37 (3H, s, C*Me*$_2$), 1.52 (3H, s, C*Me*$_2$), 2.11–2.19 (1H, m, C*H*Me$_2$), 2.93–3.00 (2H, m, C*H*$_2$NBn$_2$), 3.16–3.23 (1H, m, COC*H*$_2$), 3.28–3.35 (1H, m, COC*H*$_2$), 3.68 (4H, app s, N(C*H*$_2$Ph)$_2$), 4.16 (1H, d, *J* 3.2, NC*H*), 7.25–7.44 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.1, 21.4, 28.8, 29.5, 33.0, 49.0, 57.9, 66.2, 82.8, 126.9, 128.2, 128.9, 140.4, 153.6, 172.6; *m*/*z* (ESI⁺) 409 ([M+H]⁺, 100%); HRMS (ESI⁺) 409.2488 ($C_{25}H_{33}N_2O_3$ requires 409.2491).

(2′*S*,4*S*)-5,5-Dimethyl-4-isopropyl-3-[3′-(*N*,*N*-dibenzylamino)-2′-methylpropanoyl]oxazolidin-2-one 11

Method A. *n*-BuLi (4.34 mL, 11.5 mmol, 1.6 eq.) was added dropwise to a stirred solution of dibenzylamine (2.18 mL, 11.5 mmol, 1.6 eq.) in THF (6.0 mL) at −78 °C. After stirring for 30 min at −78 °C, a solution of *N*-acryloyl-oxazolidinone **4** (1.48 g, 7.0 mmol, 1.0 eq.) in THF (0.6 mL), also at −78 °C, was added *via* cannula. The resulting solution was stirred for between 2 h at −78 °C before methyl iodide (0.65 mL, 10.5 mmol, 1.5 eq.) was added. The mixture was stirred at −78 °C for a further 2 h before allowing it to warm to rt over 16 h. The solvent was removed *in vacuo* and the resulting residue was taken up in ether. The

organic layer was washed with aq. citric acid solution (10% w/v) and sat. aq. $NaHCO_3$ solution, then dried and concentrated *in vacuo* to give **11** in 96% de. Purification of the residue *via* column chromatography (silica, 19 : 1 pentane–ether, v/v) afforded **11** (2.60 g, 88%) as a white crystalline solid (Found: C, 73.8; H, 7.8; N, 6.6%. $C_{26}H_{34}N_2O_3$ requires C, 73.9; H, 8.1; N, 6.6%); mp 82–83 °C; $[a]_D^{25}$ +12.0 (*c* 1.6, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 1772, 1700; δ_H (400 MHz, $CDCl_3$) 0.96 (3H, d, *J* 6.8, CH*Me*$_2$), 1.01 (3H, d, *J* 7.0, CH*Me*$_2$), 1.22 (3H, d, *J* 6.8, COCH*Me*), 1.43 (3H, s, C*Me*$_2$), 1.53 (3H, s, C*Me*$_2$), 2.10–2.20 (1H, m, C*H*Me$_2$), 2.50 (1H, dd, J_{AB} 12.7, J_{AX} 6.7, CH_2NBn$_2$), 2.90 (1H, dd, J_{BA} 12.7, J_{BX} 7.5, CH_2NBn$_2$), 3.52 (2H, d, *J* 13.7, NCH_2Ph), 3.68 (2H, d, *J* 13.8, NCH_2Ph), 4.19 (1H, d, *J* 3.4, NC*H*^{i}Pr), 4.21–4.24 (1H, m, COC*H*Me), 7.21–7.39 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.5, 17.0, 21.4, 21.5, 28.7, 29.6, 36.3, 56.9, 58.3, 66.1, 82.5, 126.8, 128.1, 129.0, 139.1, 153.2, 176.8; *m*/*z* (ESI^+) 423 ($[M+H]^+$, 100%); HRMS (ESI^+) 423.2652 ($C_{26}H_{35}N_2O_3$ requires 423.2648).

Method B. LiHMDS (0.30 mL, 0.2 mmol, 1.1 eq.) was added dropwise to a solution of β-amino-oxazolidinone **7** (100 mg, 0.24 mmol, 1.0 eq.) in THF (0.1 mL) at −78 °C. After 30 min, methyl iodide (23 μL, 0.37 mmol, 1.5 eq.) was added and the resultant mixture was stirred at −78 °C for a further 2 h before allowing it to warm to rt over 16 h. The solvent was then removed *in vacuo* and the residue was taken up in ether. The organic layer was washed with sat. aq. NH_4Cl solution and brine then dried and concentrated *in vacuo* to give **11** in 96% de. Purification of the residue *via* column chromatography (silica, 9 : 1 pentane–ether, v/v) afforded **11** (95 mg, 94%) with identical physical and spectroscopic properties to those described above.

X-Ray crystal structure determination for 11

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, all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[44]

X-Ray crystal structure data for **11** [$C_{26}H_{34}N_2O_3$]: $M = 422.57$, monoclinic, space group $P\,2_1$, $a = 14.1180(3)$ Å, $b = 6.1198(2)$ Å, $c = 14.4072(4)$ Å, $\beta = 108.4415(11)°$, $V = 1180.85(6)$ Å^3, $Z = 4$, $\mu = 0.077$ mm^{-1}, colourless block, crystal dimensions = 0.2 × 0.2 × 0.2 mm^3. A total of 2840 unique reflections were measured for $5 < \theta < 27$ and 2657 reflections were used in the refinement. The final parameters were $wR_2 = 0.0354$ and $R_1 = 0.0335$ [$I > 3\sigma(I)$].‡ Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 616167. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

Methyl (*S*)-3-(*N*,*N*-dibenzylamino)-2-methyl propanoate 28

n-BuLi (890 μL, 1.6 M, 1.42 mmol, 3.0 eq.) was added dropwise to MeOH (2.8 mL) at 0 °C. After 5 min, a solution of 3′-amino-2′-methyl-oxazolidinone **11** (200 mg, 0.47 mmol, 1.0 eq.) in MeOH (1.0 mL) was added dropwise. The resulting mixture was stirred at 0 °C for 30 min before being allowed to warm to rt, then stirred for a further 15 h. The solvent was removed *in vacuo* and the residue was partitioned between sat. aq. NH_4Cl solution and EtOAc. The aqueous layer was extracted with EtOAc (2 ×) and the combined organic extracts were washed with brine, dried and then concentrated *in vacuo*. Purification of the residue *via* column chromatography (silica, 49 : 1 to 19 : 1 pentane–ether, v/v) afforded (*S*)-**28** as a colourless oil (137 mg, 98%); $[a]_D^{25}$ +9.9 (*c* 0.5, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 1728; δ_H (400 MHz, $CDCl_3$) 1.13 (3H, d, *J* 6.2, CH*Me*), 2.44 (1H, dd, J_{AB} 16.1, J_{AX} 10.1, CCHCH_2), 2.75–2.82 (2H, m, CC*H*CH$_2$, CCHCH_2), 3.50 (2H, d, *J* 13.4, NCH_2Ph), 3.64 (2H, d, *J* 13.4, NCH_2Ph), 3.66 (3H, s, O*Me*), 7.22–7.42 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.3, 38.6, 51.4, 57.4, 58.4, 126.9, 128.1, 128.9, 139.2, 176.2; *m*/*z* (ESI^+) 298 ($[M+H]^+$, 100%); HRMS (ESI^+) 298.1803 ($C_{19}H_{24}NO_2$ requires 298.1807).

(*S*)-3-Amino-2-methyl propanoic acid 25

Pd (50 mg, 10% wt on C) was added to a degassed solution of β-amino ester **28** (100 mg, 0.34 mmol, 1.0 eq.) in MeOH (2.0 mL)–H_2O (0.2 mL)–AcOH (0.05 mL). The suspension was stirred under H_2 (1 atm) for 24 h before being filtered though Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo*. The residue was re-dissloved in THF (5.0 mL) and a solution of lithium hydroxide (71 mg, 1.70 mmol, 5.0 eq.) in water (0.5 mL) was subsequently added. After 15 h stirring at rt, the solvents were removed *in vacuo* and the residue co-evaporated with aq. HCl (2 M). Purification of the residue *via* ion exchange chromatography yielded the free amino acid (*S*)-**25** (33 mg, 95%) as a white crystalline solid; mp 175–177 °C {lit.[27] 179–181 °C}; $[a]_D^{25}$ +17.0 (*c* 1.0, H_2O) {lit.[27] $[a]_D^{25}$ +14.2 (*c* 1.0, H_2O)}; δ_H (200 MHz, $CDCl_3$) 1.05 (3H, d, *J* 7.3, CH*Me*), 2.44–2.51 (1H, m, CC*H*CH$_2$), 2.84 (1H, dd, J_{AB} 12.8, J_{AX} 7.3, CCHCH_2), 2.97 (1H, dd, J_{BA} 12.8, J_{BX} 8.3, CCHCH_2).

(2′*R*,4*S*)-5,5-Dimethyl-4-isopropyl-3-[3′-(*N*,*N*-dibenzylamino)-2′-methyl-propanoyl]oxazolidin-2-one 50 and (2′*S*,4*S*)-5,5-dimethyl-4-isopropyl-3-[3′-(*N*,*N*-dibenzylamino)-2′-methyl-propanoyl] oxazolidin-2-one 11

Method A. *n*-BuLi (0.712 mL, 1.78 mmol, 2.0 eq.) was added dropwise to a stirred solution of dibenzylamine (0.34 mL, 1.78 mmol, 2.0 eq.) in THF (0.25 mL) at −78 °C. After stirring for 30 min at −78 °C, a solution of *N*-acryloyl-oxazolidinone **45** (200 mg, 0.89 mmol, 1.0 eq.) in THF (0.1 mL), also at −78 °C, was added dropwise *via* cannula. The resulting solution was stirred for 2 h before the addition of sat. aq. NH_4Cl solution. The product was extracted with ether (3 ×) and the combined organic extracts were washed with aq. citric acid solution (10% w/v), sat. aq. $NaHCO_3$ solution and brine. The resultant organic solution was dried and concentrated *in vacuo* to give a non-separable mixture of diastereoisomers **50** and **11** in a ratio of 66 : 34. Purification of the residue *via* column chromatography (silica, 9 : 1 pentane–ether, v/v) afforded the 66 : 34 mixture of diastereoisomers **50** and **11** as a colourless, viscous oil (360 mg, 96%).

Method B. *n*-BuLi (0.71 mL, 1.78 mmol, 2.0 eq.) was added dropwise to a stirred solution of dibenzylamine (0.34 mL,

‡ CCDC reference numbers 616167–616169. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b707689d

1.78 mmol, 2.0 eq.) in THF (1.0 mL) at −78 °C. After stirring for 30 min at −78 °C, a solution of *N*-acryloyl-oxazolidinone **45** (200 mg, 0.89 mmol, 1.0 eq.) in THF (0.1 mL), also at −78 °C, was added *via* cannula. The resulting solution was stirred for 30 min at −78 °C and then a solution of 2,6-di-*tert*-butylphenol (551 mg, 2.67 mmol, 3.0 eq.) in THF (0.5 mL) was added dropwise *via* syringe. The mixture was stirred at −78 °C for a further 30 min before being allowed to warm to rt over 16 h. The solvent was removed *in vacuo* and the residue was taken up in ether. The organic layer was washed with aq. citric acid solution (10% w/v) and sat. aq. $NaHCO_3$ solution, then dried and concentrated *in vacuo* to give a mixture of diastereoisomers **50** and **11** in a ratio of 92 : 8. Purification of the residue *via* column chromatography (silica, 49 : 1 to 9 : 1 pentane–ether, v/v) followed by recrystallisation (pentane–ether) afforded **50** as a white crystalline solid (342 mg, 91%); mp 74–75 °C; $[\alpha]_D^{25}$ +53.7 (*c* 1.3, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 1769, 1697; δ_H (400 MHz, $CDCl_3$) 1.00 (3H, d, *J* 6.9, CH*Me*$_2$), 1.07 (3H, d, *J* 7.0, CH*Me*$_2$), 1.17 (3H, d, *J* 6.8, COCH*Me*), 1.36 (3H, s, C*Me*$_2$), 1.54 (3H, s, C*Me*$_2$), 2.12–2.21 (1H, m, C*H*Me$_2$), 2.48 (1H, dd, J_{AB} 12.4, J_{AX} 7.8, CH_2NBn$_2$), 2.95 (1H, dd, J_{BA} 12.4, J_{BX} 6.7, CH_2NBn$_2$), 3.54 (2H, d, *J* 13.8, NCH_2Ph), 3.77 (2H, d, *J* 13.8, NCH_2Ph), 4.19 (1H, d, *J* 3.4, NC*H*^{i}Pr), 4.22–4.30 (1H, m, COC*H*), 7.16–7.41 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.6, 17.1, 21.3, 21.5, 28.8, 29.5, 36.1, 57.1, 58.3, 66.3, 82.6, 126.9, 128.1, 129.0, 139.2, 153.4, 176.5; *m*/*z* (ESI$^+$) 423 ([M+H]$^+$, 100%); HRMS (ESI$^+$) 423.2658 ($C_{26}H_{35}N_2O_3$ requires 423.2658).

Method C. To a stirred solution of dibenzylamine (0.26 mL, 1.34 mmol, 2.0 eq.) in THF (0.8 mL) at −78 °C was added *n*-BuLi (0.84 mL, 1.34 mmol, 2.0 eq.) dropwise. After stirring for 30 min at −78 °C, a solution of *N*-acryloyl-oxazolidinone **45** (150 mg, 0.67 mmol, 1.0 eq.) in THF (0.05 mL), also at −78 °C, was added *via* cannula. The resulting solution was stirred for 30 min at −78 °C before a solution of 2-pyridone (127 mg, 1.34 mmol, 2.0 eq.) in THF (0.08 mL) was added dropwise *via* syringe. The mixture was stirred at −78 °C for a further 30 min before being allowed to warm to rt over 16 h. The solvent was removed *in vacuo* and the residue taken up in ether. The organic layer was washed with aq. citric acid solution (10% w/v) and sat. aq. $NaHCO_3$ solution, then dried and concentrated *in vacuo* to give a mixture of diastereoisomers **50** and **11** in a ratio of 98 : 2. Purification of the residue *via* column chromatography (silica, 9 : 1 pentane–ether, v/v) furnished **50** (245 mg, 87%) with identical physical and spectroscopic properties as those described above.

(4*S*,2′*R*,α*R*)-5,5-Dimethyl-4-isopropyl-3-{3′-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-2′-methyl-propanoyl}oxazolidin-2-one 56 and (4*S*,2′*S*,α*R*)-5,5-dimethyl-4-isopropyl-3-{3′-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-2′-methyl-propanoyl}oxazolidin-2-one 12

To a stirred solution of (*R*)-*N*-benzyl-(*N*-α-methylbenzyl)amine (283 mg, 1.34 mmol, 2.0 eq.) in THF (0.8 mL) at −78 °C was added *n*-BuLi (0.84 mL, 1.34 mmol, 1.6 eq.) dropwise. After stirring for 30 min at −78 °C, a solution of the acceptor *N*-acryloyl-oxazolidinone **45** (150 mg, 0.67 mmol, 1.0 eq.) in THF (0.05 mL), also at −78 °C, was added *via* cannula. The resulting solution was stirred for 30 min at −78 °C before a solution of 2-pyridone (127 mg, 1.34 mmol, 2.0 eq.) in THF (0.08 mL) was added dropwise *via* syringe. The mixture was stirred at −78 °C for a further 30 min before being allowed to warm to rt over 16 h. The solvent was removed *in vacuo* and the residue was taken up in ether. The organic layer was washed with aq. citric acid solution (10% w/v) and sat. aq. $NaHCO_3$ solution, then dried and concentrated *in vacuo*, giving a mixture of diastereoisomers **56** and **12** in a ratio of 98 : 2. Purification of the residue *via* column chromatography (silica, 9 : 1 pentane–ether, v/v) furnished **56** (240 mg, 82%) as a colourless oil; $[\alpha]_D^{25}$ +51.4 (*c* 1.5, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 1769, 1698; δ_H (400 MHz, $CDCl_3$) 0.95 (3H, d, *J* 6.8, CH*Me*$_2$), 1.02 (3H, d, *J* 6.8, CH*Me*$_2$), 1.17 (3H, d, *J* 6.8, COCH*Me*), 1.35 (3H, s, C*Me*$_2$), 1.43 (3H, d, *J* 6.8, NCH*Me*), 1.50 (3H, s, C*Me*$_2$), 2.08–2.17 (1H, m, C*H*Me$_2$), 2.60 (1H, dd, J_{AB} 12.6, J_{AX} 8.3, COCHCH_2), 2.77 (1H, dd, J_{BA} 12.6, J_{BX} 6.1, COCHCH_2), 3.43 (1H, d, *J* 14.4, NCH_2Ph), 3.82 (1H, d, *J* 14.4, NCH_2Ph), 3.98 (1H, q, *J* 7.1, NC*H*Ph), 4.06–4.16 (1H, m, COC*H*Me), 4.14 (1H, d, *J* 3.3, NC*H*^{i}Pr), 7.19–7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.5, 16.7, 17.0, 21.3, 21.3, 28.8, 29.5, 36.6, 53.1, 54.6, 57.8, 66.3, 82.5, 126.6, 127.8, 128.1, 128.2, 128.7, 128.9, 140.3, 141.6, 153.5, 176.7; *m*/*z* (ESI$^+$) 437 ([M+H]$^+$, 100%); HRMS (ESI$^+$) 437.2814 ($C_{27}H_{36}N_2O_3$ requires 437.2804).

(4*S*,2′*R*,α*S*)-5,5-Dimethyl-4-isopropyl-3-{3′-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-2′-methyl-propanoyl}oxazolidin-2-one 57 and (4*S*,2′*S*,α*S*)-5,5-dimethyl-4-isopropyl-3-{3′-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-2′-methyl-propanoyl}oxazolidin-2-one 13

To a stirred solution of (*S*)-*N*-benzyl-(*N*-α-methylbenzyl)amine (283 mg, 1.34 mmol, 2.0 eq.) in THF (0.8 mL) at −78 °C was added *n*-BuLi (0.84 mL, 1.34 mmol, 2.0 eq.) dropwise. After stirring for 30 min at −78 °C, a solution of *N*-acryloyl-oxazolidinone **45** (150 mg, 0.67 mmol, 1.0 eq.) in THF (0.06 mL), also at −78 °C, was added *via* cannula. The resulting solution was stirred for 30 min at −78 °C before a solution of 2-pyridone (127 mg, 1.34 mmol, 2.0 eq.) in THF (0.08 mL) was added dropwise *via* syringe. The mixture was stirred at −78 °C for a further 30 min before being allowed to warm to rt over 16 h. The solvent was removed *in vacuo* and the residue taken up in ether. The organic layer was washed with aq. citric acid solution (10% w/v) and sat. aq. $NaHCO_3$ solution, then dried and concentrated *in vacuo*, giving a mixture of diastereoisomers **57** and **13** in a ratio of 84 : 16. Purification of the residue *via* column chomatography (silica, 9 : 1 pentane–ether, v/v) furnished an inseparable mixture of **57** and **13** (349 mg, 90%) as a yellow oil; $[\alpha]_D^{25}$ +12.9 (*c* 0.7, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 1770, 1694. Data for the major diastereoisomer **57**; δ_H (400 MHz, $CDCl_3$) 1.02 (3H, d, *J* 6.1, CH*Me*$_2$), 1.04 (3H, d, *J* 7.2, CH*Me*$_2$), 1.07 (3H, d, *J* 5.8, COCH*Me*), 1.36 (3H, s, C*Me*$_2$), 1.41 (3H, d, *J* 6.8, NCH*Me*), 1.52 (3H, s, C*Me*$_2$), 2.12–2.22 (1H, m, C*H*Me$_2$), 2.24 (1H, dd, J_{AB} 12.6, J_{AX} 7.5, COCHCH_2), 3.11 (1H, dd, J_{BA} 12.6, J_{BX} 6.5, COCHCH_2), 3.63 (2H, d, *J* 2.4, NCH_2Ph), 4.02 (1H, q, *J* 7.1, NC*H*Ph), 4.06–4.15 (1H, m, COC*H*Me), 4.17 (1H, d, *J* 2.8, NC*H*^{i}Pr), 7.18–7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.3, 15.4, 17.1, 21.4, 21.5, 28.7, 29.5, 36.6, 52.6, 54.5, 56.6, 66.3, 82.5, 126.7 127.8, 128.1, 128.3, 128.6, 128.9, 140.3, 142.4, 153.4, 176.8; *m*/*z* (ESI$^+$) 437 ([M+H]$^+$, 100%); HRMS (ESI$^+$) 437.2802 ($C_{27}H_{36}N_2O_3$ requires 437.2804).

(*R*)-3-Amino-2-methyl propanoic acid 25

LiOH (596 mg, 14.2 mmol, 5.0 eq.) in H_2O (40 mL) was added to a stirred solution of 3′-amino-2′-methyl-oxazolidinone **50** (1.20 g,

2.84 mmol, 1.0 eq.) in THF (80 mL) and the resultant solution was stirred at rt for 24 h, after which time the solution was acidified to pH 3 with sat. aq. $KHSO_4$ solution. The product was then extracted with EtOAc (3 ×), the combined organic extracts were dried and concentrated *in vacuo*. The crude reaction mixture was re-dissolved in MeOH (20 mL)–H_2O (2 mL)–AcOH (0.5 mL). The resultant solution was degassed and treated with Pd (400 mg, 10% wt on C). The resultant suspension was stirred under H_2 (1 atm) for 24 h before being filtered though Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo*. The residue was co-evaporated with aq. HCl (2 M) and purified by ion exchange chromatography (Dowex 50W-X8, 1 M aq. NH_4OH eluent) to afford the free amino acid (*R*)-**25** as a white crystalline solid (260 mg, 89%); mp 175–177 °C {lit.[27] 179–181 °C}; $[\alpha]_D^{25}$ −12.4 (*c* 1.0, H_2O) {lit. for enantiomer[27] $[\alpha]_D^{25}$ +14.2 (*c* 1.0, H_2O)}.

(4*S*,2′*S*,3′*R*)-5,5-Dimethyl-4-isopropyl-3-{[2′-(*N*,*N*-dibenzylamino)methyl]-3′-hydroxybutanoyl} oxazolidin-2-one 83

To a stirred solution of 3′-amino-oxazolidinone **7** (100 mg, 0.24 mmol, 1.0 eq.) in DCM (2.0 mL) at 0 °C was added 9-BBNOTf (0.58 mL, 0.29 mmol, 1.2 eq.) followed by Hünig's base (0.06 mL, 0.34 mmol, 1.4 eq.) after 10 min. The resultant solution was stirred for a further 20 min at 0 °C before being cooled to −78 °C followed by addition of acetaldehyde (0.02 mL, 0.36 mmol, 1.5 eq., distilled from $CaCl_2$). The resultant solution was stirred for a further 30 min at −78 °C before being allowed to warm to 0 °C and stirring was continued for a further 1 h before addition of a 1 : 1 (v/v) mixture of MeOH–H_2O_2 (30% aq. solution). The reaction mixture was then allowed to warm to rt and extracted with DCM (3 ×). The combined organic extracts were washed with sat. aq. $NaHCO_3$, dried and concentrated *in vacuo*. Purification of the residue *via* column chromatography (silica, 9 : 1 petrol–ether v/v) gave **83** as a viscous, pale yellow oil (72 mg, 65%); $[\alpha]_D^{22}$ +119.4 (*c* 0.5, $CHCl_3$); ν_{max}/cm^{-1} (film) 3425, 1771, 1693; δ_H (400 MHz, $CDCl_3$) 0.96 (3H, d, *J* 6.8, CH*Me*$_2$), 1.00 (3H, d, *J* 7.2, CH*Me*$_2$), 1.12 (3H, d, *J* 5.8, C(OH)*Me*), 1.39 (3H, s, C*Me*$_2$), 1.52 (3H, s, C*Me*$_2$), 2.04–2.22 (1H, m, C*H*Me$_2$), 2.72–2.78 (1H, m, C*H*$_2$NBn$_2$), 3.02–3.07 (1H, m, C*H*$_2$NBn$_2$), 3.26 (2H, d, *J* 13.3, N(C*H*$_2$Ph)$_2$), 3.89–4.03 (1H, m, C*H*OH), 4.06–4.22 (3H, m, N(C*H*$_2$Ph)$_2$, NC*H*^{i}Pr), 4.28–4.49 (1H, m, COC*H*), 6.35 (1H, br s, O*H*), 7.17–7.45 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.1, 20.9, 21.3, 21.6, 28.6, 29.4, 46.7, 56.2, 58.4, 67.6, 70.9, 82.9, 127.5, 128.2, 129.3, 137.2, 153.5, 172.9; *m*/*z* (ESI$^+$) 453 ([M+H]$^+$, 100%); HRMS (ESI$^+$) 453.2746 ($C_{27}H_{37}N_2O_4$ requires 453.2753).

Methyl (2*S*,3*R*)-2-(*N*,*N*-dibenzylamino)methyl-3-hydroxybutanoate 94

n-BuLi (2.5 M, 0.13 mL, 0.32 mmol, 1.0 eq.) was added dropwise to MeOH (0.6 mL) at 0 °C. After 5 min, a solution of aldol adduct **83** (147 mg, 0.32 mmol, 1.0 eq.) in MeOH (0.6 mL) was added dropwise. The resultant mixture was stirred at 0 °C for 30 min before being allowed to warm to rt, then stirred for a further 15 h. The solvent was removed *in vacuo* and the residue was partitioned between sat. aq. NH_4Cl solution and EtOAc. The aqueous layer was extracted with EtOAc (2 ×) and the combined organic extracts were washed with brine, dried and then concentrated *in vacuo*. Purification of the residue *via* column chromatography (silica, 4 : 1 petrol–ether, v/v) gave **94** as a colourless oil (103 mg, 97%); $[\alpha]_D^{22}$ +80.0 (*c* 0.4, $CHCl_3$); ν_{max}/cm^{-1} (film) 3443, 1643; δ_H (400 MHz, $CDCl_3$) 1.14 (3H, d, *J* 6.1, CH*Me*), 2.71 (1H, dd, J_{AB} 12.5, J_{AX} 4.2, CHC*H*$_2$N), 2.76–2.82 (1H, m, COC*H*), 3.05 (1H, dd, J_{BA} 11.9, J_{BX} 10.9, CHC*H*$_2$N), 3.31 (2H, d, *J* 13.1, N(C*H*$_2$Ph)$_2$), 3.66 (3H, s, O*Me*), 3.79–3.86 (1H, m, C*H*OH), 3.91 (2H, d, *J* 13.1, N(C*H*$_2$Ph)$_2$), 7.27–7.38 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.7, 50.4, 52.1, 55.8, 59.0, 70.8, 127.9, 129.0, 129.7, 137.7, 173.3; *m*/*z* (ESI$^+$) 328 ([M+H]$^+$, 100%); HRMS (ESI$^+$) 328.1912 ($C_{20}H_{26}NO_3$ requires 328.1913).

Acknowledgements

The authors would like to thank the BBSRC and Yamanouchi, UK for an industrial CASE studentship (A. J. R.), and New College, Oxford for a Junior Research Fellowship (A. D. S.).

References and Notes

1 M. Liu and M. P. Sibi, *Tetrahedron*, 2002, **58**, 7991–8035.
2 G. Trimurtula, I. Ohtani, G. M. L. Patterson, R. E. Moore, T. H. Corbett, F. A. Valeroite and L. Demchik, *J. Am. Chem. Soc.*, 1994, **116**, 4729–4737; C. Shih, L. S. Gossett, J. M. Gruber, C. S. Grossman, S. L. Andis, R. M. Schulz, J. F. Worzalla, T. H. Corbett and J. T. Metz, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 69–74; J. Schmidt and J. Langner, *J. Chem. Soc., Chem. Commun.*, 1994, 2381–2382.
3 L. M. Pratt, R. P. Beckett, S. J. Davies, S. B. Launchbury, A. Miller, Z. M. Spavold, R. S. Todd and M. Whittaker, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 2585–2588.
4 T. Hintermann and D. Seebach, *Synlett*, 1997, **5**, 437–438; D. Seebach, S. Abele, K. Gademann and B. Juan, *Angew. Chem., Int. Ed.*, 1999, **38**, 1595–1597.
5 D. C. Cole, *Tetrahedron*, 1994, **50**, 9517–9582; M. Liu and M. P. Sibi, *Tetrahedron*, 2002, **58**, 7991–8035; O. Munoz-Muniz and E. Juaristi, *Tetrahedron*, 2003, **59**, 4223–4229.
6 E. Arvanitis, H. Ernst, A. A. Ludwig, A. J. Robinson and P. B. Wyatt, *J. Chem. Soc., Perkin Trans. 1*, 1998, 521–528; Y. Chi, E. P. English, W. C. Pomerantz, W. S. Horne, L. A. Joyce, L. R. Alexander, W. S. Fleming, E. A. Hopkins and S. H. Gellman, *J. Am. Chem. Soc.*, 2007, **129**, 6050–6055.
7 E. Juaristi, D. Quintana, B. Lamatsch and D. Seebach, *J. Org. Chem.*, 1991, **56**, 2553–2557; G. Nagula, V. J. Huber, C. Lum and B. A. Goodman, *Org. Lett.*, 2000, **2**, 3527–3529; R. Ponsinet, G. Chassaing, J. Vaissermann and S. Lavielle, *Eur. J. Org. Chem.*, 2000, **1**, 83–90; V. M. Gutiérrez-García, H. López-Ruiz, G. Reyes-Rangel and E. Juaristi, *Tetrahedron*, 2001, **57**, 6487–6496.
8 E. Juaristi, D. Quintana, M. Balderas and E. Garciá-Pérez, *Tetrahedron: Asymmetry*, 1996, **7**, 2233–2246.
9 J. d'Angelo, D. Desmaele, F. Dumas and A. Guingant, *Tetrahedron: Asymmetry*, 1992, **3**, 459–505; I. T. Barnish, M. Corless, P. J. Dunn, D. Ellis, P. W. Finn, J. D. Hardstone and K. James, *Tetrahedron Lett.*, 1993, **34**, 1323–1326; F. Fernández, J. M. Otero, J. C. Estévez and R. J. Estévez, *Tetrahedron: Asymmetry*, 2006, **17**, 3063–3066; A. Duursma, A. J. Minnaard and B. L. Feringa, *J. Am. Chem. Soc.*, 2003, **125**, 3700–3711; U. Eilitz, F. Lessmann, O. Seidelmann and V. Wendisch, *Tetrahedron: Asymmetry*, 2003, **14**, 189–191; U. Eilitz, F. Lessmann, O. Seidelmann and V. Wendisch, *Tetrahedron: Asymmetry*, 2003, **14**, 3095–3097; A. Rimkus and N. Sewald, *Org. Lett.*, 2003, **5**, 79–80.
10 H. S. Lee, J. S. Park, B. M. Kim and S. H. Gellman, *J. Org. Chem.*, 2003, **68**, 1575–1578.
11 M. P. Sibi and P. K. Deshpande, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1461–1466.
12 H. M. L. Davies and C. Venkataramani, *Angew. Chem., Int. Ed.*, 2002, **41**, 2197–2199.
13 A. Kubo, H. Kubota, M. Takahashi and K. I. Nunami, *J. Org. Chem.*, 1997, **62**, 5830–5837.
14 J. Elaridi, A. Thaqi, A. Prosser, W. R. Jackson and A. J. Robinson, *Tetrahedron: Asymmetry*, 2005, **16**, 1309–1319; H. Huang, X. Liu, J. Deng, M. Qiu and Z. Zheng, *Org. Lett.*, 2006, **8**, 3359–3362; R. Hoen,

T. Tiemersma-Wegman, B. Procuranti, L. Lefort, J. G. De Vries, A. J. Minnaard and B. L. Feringa, *Org. Biomol. Chem.*, 2007, **5**, 267–275.
15 G. M. Sammis and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2003, **125**, 4442–4443.
16 M. P. Sibi and K. Patil, *Tetrahedron: Asymmetry*, 2006, **17**, 516–519; M. P. Sibi and K. Patil, *Angew. Chem., Int. Ed.*, 2004, **43**, 1235–1238.
17 S. G. Davies, N. M. Garrido, D. Kruchinin, O. Ichihara, L. J. Kotchie, P. D. Price, A. J. Price Mortimer, A. J. Russell and A. D. Smith, *Tetrahedron: Asymmetry*, 2006, **17**, 1793–1811. For a review see: S. G. Davies, A. D. Smith and P. D. Price, *Tetrahedron: Asymmetry*, 2005, **16**, 2833–2891.
18 J. E. Beddow, S. G. Davies, A. D. Smith and A. J. Russell, *Chem. Commun.*, 2004, 2778–2779.
19 For addition of other nucleophiles to *N*-acryloyl-oxazolidinones see: G. Li, X. Xu, D. Chen, C. Timmons, M. D. Carducci and A. D. Headley, *Org. Lett.*, 2003, **5**, 329–331.
20 S. D. Bull, S. G. Davies, S. Jones and H. J. Sanganee, *J. Chem. Soc., Perkin Trans. 1*, 1999, 387–398.
21 D. A. Evans, S. J. Miller, T. Lectka and P. von Matt, *J. Am. Chem. Soc.*, 1999, **121**, 7559–7573.
22 S. D. Bull, S. G. Davies, A. C. Garner, D. Kruchinin, M. S. Key, P. M. Roberts, E. D. Savory, A. D. Smith and J. E. Thomson, *Org. Biomol. Chem.*, 2006, **4**, 2945–2964.
23 In all cases, the reaction diastereoselectivity was assessed by peak integration of the 400 MHz ^{1}H NMR spectrum of the crude reaction product.
24 N. Asao, T. Uyehara and Y. Yamamoto, *Tetrahedron*, 1988, **44**, 4173–4180; N. Asao, T. Uyehara and Y. Yamamoto, *Tetrahedron*, 1990, **46**, 4563–4572; S. G. Davies, G. J. Hermann, A. D. Smith and M. J. Sweet, *Chem. Commun.*, 2004, 1128–1129.
25 S. Hosokawa, K. Sekiguchi, M. Enemoto and S. Kobayashi, *Tetrahedron Lett.*, 2000, **41**, 6429–6433.
26 A similar observation has been reported following the ring opening of an aziridine attached to an oxazolidinone; see: G. Cardillo, L. Gentilucci and V. De Matteis, *J. Org. Chem.*, 2002, **67**, 5957–5962.
27 Y. Jin and D. H. Kim, *Synlett*, 1998, **11**, 1189–1190.
28 E. Juaristi, M. Balderas, H. López-Ruiz, V. M. Jiménez-Pérez, M. L. Kaiser-Carril and Y. Ramírez-Quirós, *Tetrahedron: Asymmetry*, 1999, **10**, 3493–3505.
29 J. A. Dale, D. L. Dull and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543–2549.
30 M. Y. Chang, S. T. Chen and N. C. Chang, *Tetrahedron*, 2002, **58**, 3623–3628.
31 S. G. Davies, O. Ichihara and I. A. S. Walters, *Synlett*, 1993, 461–461; S. G. Davies, O. Ichihara, I. Lenoir and I. A. S. Walters, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1411–1415.
32 2-Pyridone has been shown to effect a rate enhancement upon the mutarotation of glucose, potentially through its ability to act as both a base and an acid at the same time; see: M. Kuzuya, A. Noguchi and T. Okuda, *Bull. Chem. Soc. Jpn.*, 1984, **57**, 3461–3465.
33 S. Masamune, W. Choy, J. S. Petersen and L. R. Sita, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 1–30; W. Harb, M. F. Ruiz-Lopex, F. Coutrot, C. Grison and P. Coutrot, *J. Am. Chem. Soc.*, 2004, **126**, 6996–7008.
34 J. A. Garbarino and O. Nunez, *J. Chem. Soc., Perkin Trans. 1*, 1981, 906–908.
35 M. Sunagawa, H. Matsumura, T. Inoue, M. Fukasawa and M. Kato, *J. Antibiot.*, 1990, **43**, 519–532.
36 R. Noyori, T. Ikeda, T. Ohkuma, M. Widhalm, M. Kitamura, H. Takaya, S. Akutagawa, N. Sayo, T. Saito, T. Taketomi and H. Kumobayashi, *J. Am. Chem. Soc.*, 1989, **111**, 9134–9135; K. Mashima, K. H. Kusano, N. Sato, Y. Matsumura, K. Nozaki, H. Kumobayashi, N. Sayo, Y. Hori, T. Ishizaki, S. Akutagawa and H. Takaya, *J. Org. Chem.*, 1994, **59**, 3064–3076; H. U. Blaser, C. Malan, B. Pugin, F. Spindler, H. Steiner and M. Studer, *Adv. Synth. Catal.*, 2003, **345**, 103–151; T. Saito, T. Yokozawa, T. Ishizaki, T. Moroi, N. Sayo, T. Miura and H. Kumobayashi, *Adv. Synth. Catal.*, 2001, **343**, 264–267.
37 P. Perlmutter and M. Tabone, *J. Org. Chem.*, 1995, **60**, 6515–6522 and references cited therein.
38 H. Ohtake, Y. Imada and S. I. Murahashi, *J. Org. Chem.*, 1999, **64**, 3790–3791.
39 D. Seebach, L. Schaeffer, F. Gessier, P. Bindschädler, C. Jäger, D. Josien, S. Kopp, G. Lelais, Y. R. Mahajan, P. Micuch, R. Sebesta and B. W. Schweizer, *Helv. Chim. Acta*, 2003, **86**, 1852–1861.
40 D. A. Evans, J. Bartroli and T. L. Shih, *J. Am. Chem. Soc.*, 1981, **103**, 2127–2129.
41 D. A. Evans, J. M. Takacs, L. R. McGee, M. D. Ennis, D. J. Mathre and J. Bartroli, *Pure Appl. Chem.*, 1981, **53**, 1109–1127.
42 According to the Heathcock model, *syn*-aldol products of *N*-acyl oxazolidinones are expected to have $J_{2'-3'}$ 2–6 Hz, while *anti*-aldol products are expected to have $J_{2'-3'}$ 7–10 Hz. See: C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn and J. Lampe, *J. Org. Chem.*, 1979, **44**, 4294–4299.
43 A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen and F. J. Timmers, *Organometallics*, 1996, **15**, 1518–1520.
44 P. W. Betteridge, J. R. Carruthers, R. I. Cooper, C. K. Prout and D. J. Watkin, *CRYSTALS*, 2004, Issue 12, Chemical Crystallography Laboratory, University of Oxford, UK.