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Preparation of α-amino-carboxylic acid derivatives via diastereoselective reactions of glycine enolate equivalents

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Abstract—Protected glycine analogues tethered to an imidazolidinone auxiliary undergo diastereoselective alkylation and acylation reactions in moderate to good yields (9–91%) with high levels of stereocontrol (generally >95% de). Subsequent alkylation of these derivatives has been demonstrated for the production of non-racemic α,α-disubstituted amino acid precursors. Diastereoselective aldol reactions are also found to proceed with good yields and excellent stereocontrol (62–84%, 93–95% de). Chiral auxiliary cleavage and hydrogenolysis of these adducts affords the β-hydroxy-α-amino acid derivatives with no observed erosion of optical purity.

1. Introduction

α-Amino acids exist as an integral part of many branches of biology, chemistry and medicine. They are fundamental constituents of proteins and act as mediators of nitrogen metabolism, providing the raw materials for the production of many primary and secondary metabolites. Of the large numbers (~700) of naturally occurring α-amino acids many have exhibited important biological properties. Amino acids have played a pivotal role in the study of enzymatic reaction mechanisms and thus in the synthesis of enzyme inhibitors. Recently their potent biological activity in small drug molecules has prompted extensive pharmaceutical interest in amino acids as building blocks for combinatorial and parallel synthesis, chemistries that aid the identification of potential lead compounds. In addition proteinogenic amino acids are extensively utilised as chiral reagents in organic synthesis.

Despite the myriad of syntheses that already exist for the construction of α-amino acids, there is no single choice of method that is applicable to every amino acid scenario.[1] Current strategies include, for example, chemical and enzymatic resolution, or asymmetric synthesis using chiral reagents or substrates.[2] Whilst outstanding developments have resulted, particularly in the arena of catalytic asymmetric synthesis[3] there is still a compelling case for the development of additional methodologies which can offer a complement to existing protocols. In devising a stereoselective synthesis of amino acids we ideally require a concise and convergent approach that allows structure variability and facile incorporation of functional groups and ring systems. For α-amino acid synthesis the introduction of a diverse collection of groups, for both mono- and di-substituted compounds, at the α-position is paramount. Methods for the asymmetric synthesis of sterically demanding α,α-disubstituted amino acids are of great interest in the pharmaceutical industry because of the biological activities exhibited by such compounds.[4] Our interest was targeted toward the synthesis of α,α-disubstituted amino acids as potential neuropeptide cholecystokinin (CCK), bombesin and tachykinin receptor antagonists.[5] In this article we report the findings of our research outlining a chiral auxiliary approach to the stereoselective preparation of α-substituted, α,β-disubstituted and α,α-disubstituted carboxylic acid derivatives.

2. Results and discussion

The imidazolin-2-one (**1**) has been reported as a versatile auxiliary for stereoselective syntheses exhibiting excellent levels of stereocontrol.[6] From a practical perspective this auxiliary is appealing as it is readily available in either enantiomeric form, it is crystalline and it can be attached and removed under mild conditions. These factors have made this auxiliary a popular choice for a range of synthetic endeavours.[7] This chiral auxiliary has been employed for a Dynamic Kinetic Resolution approach to the synthesis of amino acids from within our group.[8] The work described in this paper will outline a complementary approach for the preparation of α-substituted carboxylic acid derivatives utilising diastereoselective reactions of glycine enolate equivalents.[9]

Keywords: aldol reaction; alkylation; diastereoselective; chiral auxiliary; imidazolidinone.

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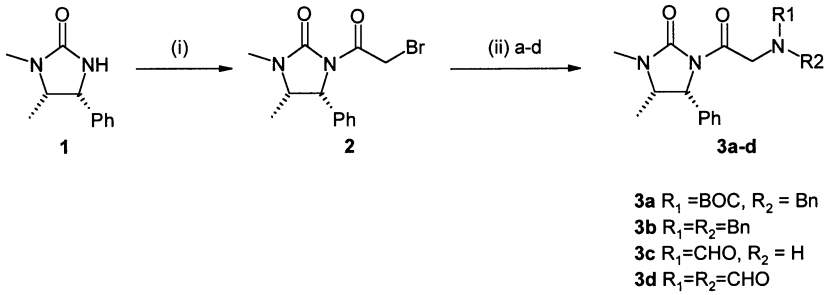


Scheme 1. *Reagents and conditions*: (i) $BrCOCH_2Br$. 2,6-lutidine, −78–0°C, CH_2Cl_2, 99%; (ii) (a) $PhCH_2NH_2$, THF, 99%; then Boc_2O, DMP, THF, 49%, (b) $(PhCH_2)_2NH$, THF, 74%, (c) $HCONH_2$, 2,6-lutidine, THF, 25%, (d) $NaN(CHO)_2$, THF, 43%.

A series of chiral glycine enolate precursors with differing electronic characteristics were prepared through the acylation of the imidazolidinone (**1**) with bromoacetylbromide. The resulting α-bromo-amides were displaced using a variety of primary and secondary amines, and protected where necessary, to produce the desired substrates (**3a**–**d**) (Scheme 1, Fig. 1).

Carbanions adjacent to heteroatoms such as oxygen and nitrogen are generally destabilised relative to their alkyl-substituted counterparts. The lone-pairs of electrons situated around the heteroatom impart an electrostatic repulsion on the neighbouring anion causing increased instability. This has led to some difficulties in devising entirely general protocols for high yielding and diastereoselective transformations of glycine enolate equivalents. However in recent times it has become apparent that the use of glycine imine derivatives can offer a reliable class of substrate from which functionalised amino-acids can be prepared.[10] In our preliminary studies the use of conventional methods for the generation of chiral enolates using LDA or LHMDS were found to cause significant amounts of ketene formation together with cleavage of the imidazolidinone from the enolate precursors (**3a**–**d**).[11] Employment of the more sterically demanding bases lithium *N*,*N*-dicyclohexylamide (LDCHA) and lithium *N*-isopropylcyclohexylamide[12] (LICA) with enolate equivalent (**3b**) proved more successful and we decided to study this species further. As can be seen from the results presented in Table 1, formation of the (*Z*)-enolate followed by directed alkylation with activated electrophiles proceeded with moderate yields to afford the products (**4**–**9**) (Scheme 2).

The observed diastereoselectivity of the alkylations was excellent with only a single diastereomer apparent in the NMR spectra. The addition of anhydrous lithium chloride to disassemble the lithium base aggregates present was found to assist some reactions, but in others it provided no discernible or even detrimental effects.[13] A variety of secondary bromides and alkyl iodides were used as the electrophilic species, but none of the desired α-alkylated products were isolated. This observation is in accordance with prior work which showed deprotonations using LDA on acylated quat auxiliaries proceeded with activated alkyl bromides at −78°C but with methyl iodide, where the reaction is slower, an elevated temperature (0°C) was required.[14] Reactions conducted at 0°C using (**5**) were found to produce alkylated imidazolidinone only. The reduced acidity of the remaining α-proton in the substituted analogues (**4**–**6**) was found to retard a second iterative alkylation step. Acylation of (**3b**) was designed to increase the acidity of the remaining α-proton sufficiently to facilitate disubstitution. Rapid quenching of the enolate was found to produce the highest yield of the products (**8**,**9**) however, with compound (**8**) a reduced level of selectivity was observed. Slow addition of the electrophile, or recrystallisation of the diastereomeric

Table 1. Results of the alkylation and acylation of (**3b**)

Compound	Electrophile	Yield % (de)
4	Benzyl bromide[a]	59 (>95)
5	Allyl bromide[b]	48 (>95)
6	2-Bromoacetophenone[b,c]	23 (>95)
7	4-Bromobenzyl bromide[b,c]	9 (>95)
8	Benzoyl chloride[b,c]	91 (43)
8	Benzoyl chloride[b,c,d]	83 (95)
9	4-Iodobenzoyl chloride[b,c]	37 (>95)

[a] LDCHA used as base.
[b] LICA used as base.
[c] Anhydrous LiCl (6 equiv.) was added.
[d] Slow addition of electrophile.

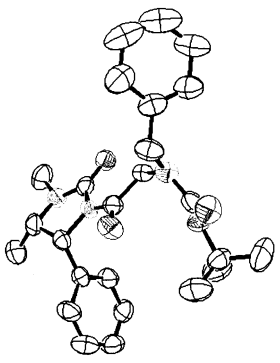
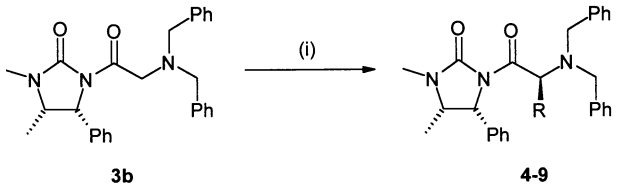


Figure 1. X-ray crystal structure of protected chiral glycine (**3a**).



Scheme 2. *Reagents and conditions*: (i) LICA, THF, −78°C then RX.

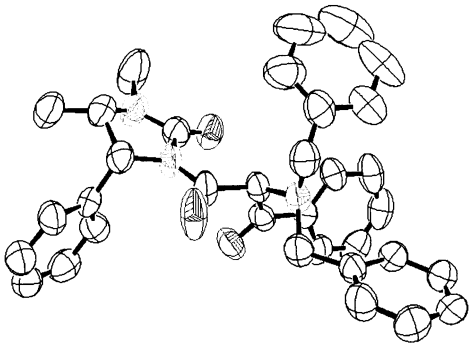


Figure 2. X-Ray crystal structure of 3′-oxo-(*S*)-phenylalanine derivative (**8a**).

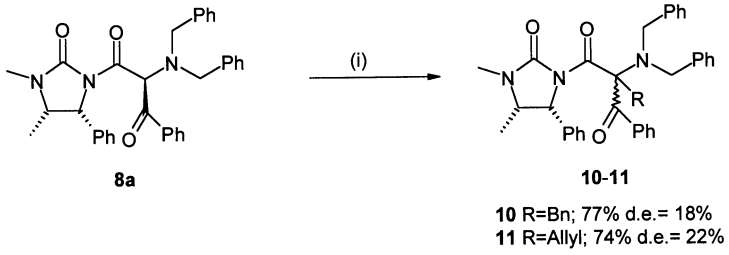
mixture, to afford the enantiomerically pure 2′-(*S*) diastereomer could overcome this problem (Fig. 2). Non-aromatic acyl chlorides and alkyl chloroformates failed to produce the desired α-substituted analogues.

The α-acyl derivative (**8a**) was found to undergo facile substitution at the α-position with activated electrophiles with good chemical yields, but poor stereoselectivity (Scheme 3).

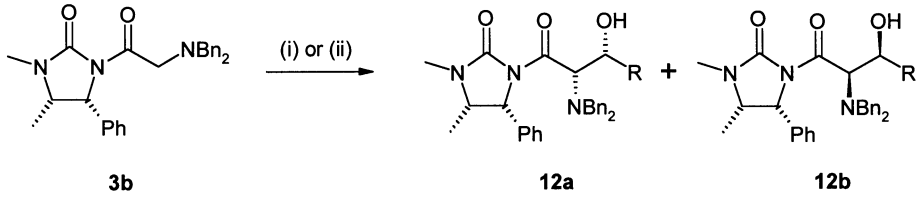
The poor levels of selectivity observed for this reaction were attributed to the generation of an enolate further removed from the steric control element, thus diminishing its influence in directing the approach of the electrophile. Attempts to increase selectivity by controlling the enolate geometry using bulky silyl enol ethers groups or coordinatively unsaturated Lewis acids proved unsuccessful.

Having investigated the use of lithium enolates attention was then turned to the use of boron enolates. Diastereoselective boron mediated aldol condensation chemistries have been widely explored and used in conjunction with auxiliaries to produce β-hydroxypropionate derivatives.[15] We felt an extension of this methodology to include chiral glycine enolate synthons would prove extremely useful in the synthesis of β-substituted α-phenylserine derivatives.[16] Evaluation of the enolate precursors (**3a–d**) using standard kinetic (*Z*)-boron enolate generation conditions was undertaken and our early work established that the dibenzyl protected analogue (**3b**) provided the best results. A selection of the experiments using dibutylboron triflate for enolate generation, followed by condensation with benzaldehyde (Scheme 4, (i)), are outlined in Table 2.

It was observed that two of the four possible diastereomeric compounds predominated in the mixtures formed. These two diastereomers were at first assigned as the *syn* and *anti* 2(*R*) derivatives, however NMR analysis indicated



Scheme 3. *Reagents and conditions*: (i) NaH, THF, 0°C then RBr.



Scheme 4. Bu_2BOTf mediated aldol condensation of (**3b**) with benzaldehyde. *Reagents and conditions*: (i) Bu_2BOTf, 1.0 M in CH_2Cl_2 (5.0 equiv.), NEt_3 (10 equiv.), CH_2Cl_2, −78°C, 5 min, then RCHO, −78–0°C, 2 h.; pH 7 buffer, MeOH, $H_2O_{2(aq)}$, (ii) 9-BBNOTf, 0.5 M in hexanes (5.0 equiv.), NEt_3 (10 equiv.), CH_2Cl_2, 0°C, 1 h, then RCHO, 2 h.; pH 7 (phosphate buffer). MeOH, $H_2O_{2(aq)}$ 0°C, 1 h.

Table 2. Condensation of **3b** with benzaldehyde for the formation of *syn*-aldol products **12a**,**b**

Enolate formation temperature (°C)	Enolate formation time (min)	Ratio of diastereomers of **12**[a] **12a**:**12b**	Diastereomeric excess (%)	Yield[b] (%)
−78	5	13:1	94	65 (87)
−78	60	0:1	>95	33
−2	45	0:1	>95	68
0	30	5:14	47	56
−88	30[c]	4:32[d]	62	25

[a] Assignments made on ^1H NMR coupling constants.
[b] Isolated yields after purification. Values in brackets based on ^1H NMR of crude material.
[c] Reaction performed using 2,6-lutidine as base.
[d] A trace quantity of trans isomer could be identified in the crude ^1H NMR spectrum.

Table 3. Aldol products derived from (**3b**) using 9-BBNOTf

Product	**Aldehyde**	Yield (%)	Non-Evans *syn*(**a**):Evans *syn* (**b**)	Diastereomeric excess[a] (%)
12	Benzaldehyde[b]	84	0:1	>95
13	4-Methoxyaldehyde[c]	63	37:22	2
13	4-Methoxyaldehyde[b]	66	1:32	94
14	2-Fluorobenzaldehyde[c]	63	32:31	0
14	2-Fluorobenzaldehyde[b]	62	0:1	>95
15	4-Nitrobenzaldehyde[c]	42	39:57	19
15	4-Nitrobenzaldehyde[b]	72	0:1	>95
16	Butyraldehyde[b]	69	0:1	>95
17	Furfuraldehyde[b]	65	6:94	88

[a] Diastereomeric excess of >95% assigned on the basis of only a single diastereomer apparent in the ^{1}H NMR spectra.
[b] Enolate generated at 0°C.
[c] Enolate generated at −78°C.

(**12a**) to have a 2′(*S*) configuration and further NMR and related crystallographic studies (on **13** and **14**) confirmed the structures of the two *syn* products (**12a**,**b**). These results illustrate that allowing enolisation to occur with short reaction times and at low temperature, increased the ratio of the so-called 'non-Evans' *syn* product (**12a**). The use of longer times for enolisation resulted in the formation of the 2′(*R*) i.e. the 'Evans' *syn* isomer as the major product. These experiments were found to be of a capricious nature and further work was unable to identify a general procedure using di-*n*-butylboron triflate for the selective formation of either *syn* isomer. A more general procedure was identified using 9-BBN triflate as a reagent for the enolate generation (Scheme 4, (ii)).[17] The results of the aldol condensation of a series of aldehydes with the glycine enolate equivalent (**3b**) using 9-BBNOTf are shown (Table 3).

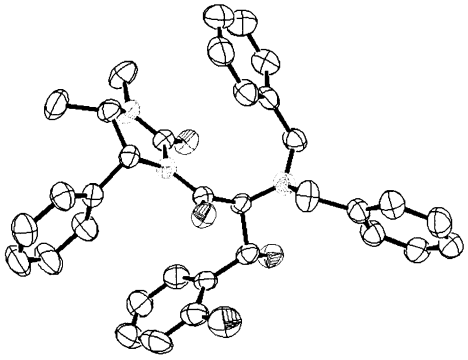
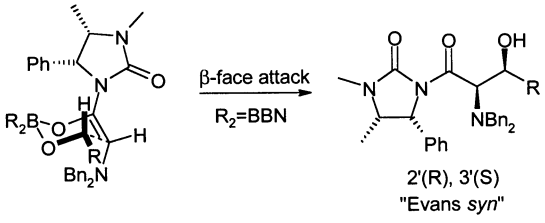


Figure 3. X-ray crystal structure of non-Evans *syn* aldol product **14a**.



Scheme 5. Origin of 'Evans *syn*' stereoselectivity.

Stereochemical assignments were made by comparison of ^{1}H NMR chemical shifts and coupling constants of H2′ and H3′ to the 4″-methoxy derivatives (**13a**) and (**13b**).[18] X-ray crystallographic analysis of 'non-Evans' *syn* adducts **13a** (not shown) and **14a** (below) established the accuracy of NMR assignments (Fig. 3).

Assuming (*Z*)-boron enolate generation under the reaction conditions, the stereoselectivity observed for the BBN enolates can be explained by invoking a chair-like transition state. The chiral auxiliary adopts a conformation so as to minimise the dipole–dipole repulsive energy between its carbonyl group and the enolate oxygen. This orientation of the steric control element hinders approach of the aldehyde from the α face and directs attack from above (Scheme 5).[19]

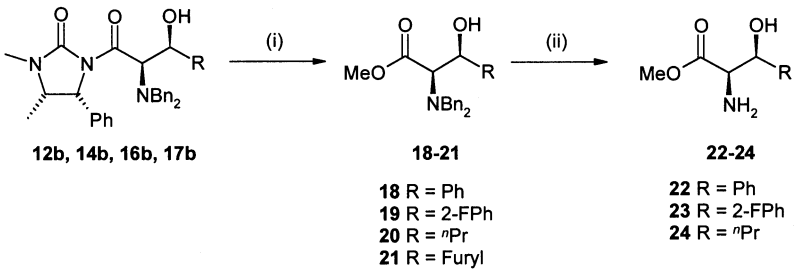
The cleavage of the chiral auxiliary for a selection of the aldol products was achieved using sodium methoxide (Table 4).[20] Hydrogenation of the resultant compounds afforded the β-hydroxy-α-amino esters with no observed racemisation at either the 2 or 3 positions (Scheme 6).

A drawback of this cleavage method was that those compounds bearing an electron withdrawing aryl substituent were found to produce significant amounts of the retro-aldol products on treatment with NaOMe. This pathway resulted in poor yields of the desired methyl ester (**19**).

Table 4. Auxiliary cleavage using sodium methoxide

Imide substrate	Methyl ester	Auxiliary recovery (%)	Yield[a] (%)	Diastereomeric excess[b] (%)
12b	**18**	93	57	>95
14b	**19**	35	16 (29)	>95
16b	**20**	81	77 (86)	>95
17b	**21**	78	46 (59)	>95

[a] Values in brackets represent yields based on recovered starting material.
[b] Diastereomeric excess of >95% assigned on the basis of only a single diastereomer apparent in the ^{1}H NMR spectra.



Scheme 6. Formation of β-hydroxy-α-amino acid methyl esters (**22**–**24**). *Reagents and conditions*: (i) NaOMe, MeOH, (ii) $Pd(OH)_2/C$, H_2, MeOH.

Attempted cleavage of (**15a**) was found to produce retro-aldol product only. Employment of a less basic cleavage protocol would be required for such sensitive substrates.[†]

Hydrogenation of the methyl esters (**18**–**21**) was achieved in approaching quantitative yields using Pearlmanns catalyst to afford the corresponding β-hydroxy-α-amino acid methyl esters (**22**–**24**) (Scheme 6).[21,22]

3. Conclusions

In conclusion, the imidazolidinone derivative (**3b**) offers a new chiral glycine enolate equivalent for the chemical syntheses of natural and non-natural amino acid derivatives. The asymmetric alkylation of (**5**) with activated alkyl bromides has been demonstrated, and the principle of increasing proton acidity at the α-position to achieve disubstitution has been attained. The simplicity of the 9-BBN mediated experimental procedures, the excellent levels of optical purity obtained and the uniformity of the chemical yields make this an attractive procedure for the preparation of β-hydroxy-α-amino acid derivatives. The intriguing observation that the stereoselectivity can be influenced by the reaction conditions offers some interesting possibilities for the further development of (**3b**) as a synthon in the production of stereodefined hydroxyamino acids.

4. Experimental

4.1. General procedures

All reactions were performed using oven-dried apparatus under a dry nitrogen atmosphere at room temperature (unless otherwise stated). Tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone ketyl prior to use. Dichloromethane, toluene and dimethyl formamide were distilled from CaH_2. Methanol was distilled from magnesium. The term petrol refers to distilled petroleum ether with boiling temperatures of 40–60°C. Chromatographic purification of compounds was carried out on normal phase Merck no. 9385 (230–400 mesh) silica gel. Analytical thin-layer chromatography (TLC) was performed on E. Merck silica gel 60F-254 pre-coated plates and the spots were visualised with a UV lamp and anisaldehyde, ninhydrin or permanganate dips. The term in vacuo refers to solvent removal via a Buchi rotary evaporator at water aspirator pressure followed by evaporation at 0.5 mm for several hours. All melting points are uncorrected. IR spectra were recorded using either a Perkin–Elmer FT-IR 298 or 2000 FT spectrometers by placing the neat compound onto a sodium chloride disc. NMR spectra were measured using Bruker 300 MHz and Varian Unity Plus 400 MHz machines with coupling constants (*J*) being quoted to the nearest 0.5 Hz. Mass spectra were recorded on a Fisons autospec or Micromass Platform instruments. High resolution spectra were performed at the National Service Centre, University College, Swansea on a Thermoquest Finnigan MAT900XT Spectrometer. Optical rotation measurements were recorded on a Perkin–Elmer 241 polarimeter (cont. Na 589).

4.1.1. 1-(2′-Bromo)ethanoyl-3,4(*S*)-dimethyl-5(*R*)-phenylimidazolidin-2-one (2). 1,5(*S*)-dimethyl-4(*R*)-phenylimidazolidin-2-one (2.14 g, 11.20 mmol) and 2,6-lutidine (1.08 g, 1.28 mL, 11.0 mmol) were stirred in CH_2Cl_2 (50 mL) at −78°C for 15 min before the addition of freshly distilled bromoacetylbromide (2.02 g, 0.96 mL, 10.5 mmol). The reaction mixture was slowly warmed to 23°C over ca. 2 h and stirred for a further 24 h. The mixture was concentrated in vacuo and partitioned with CH_2Cl_2 (3×100 mL) and saturated $NH_4Cl_{(aq)}$ solution (100 mL). The combined organic extracts were then washed with water (100 mL), dried ($MgSO_4$), filtered and concentrated to afford *1-(2′-Bromo)ethanoyl-3,4*(S)*-dimethyl-5*(R)*-phenylimidazolidin-2-one* (**2**) as a clear oil which solidified on cooling (3.16 g, >99%) R_f 0.50 (30% EtOAc/petrol) $[\alpha]_D^{27}=-101.6$ (*c* 0.39, MeOH); ν_{max} 2979, 2937, 1729, 1605 cm^{-1}; δ_H ($CDCl_3$) 0.72 (d, *J*=6.5 Hz, 3H, 4Me), 2.78 (s, 3H, NMe), 3.78 (m, 1H, H4), 4.37 (d, *J*=12.0 Hz, 1H, H2), 4.45 (d, *J*=12.0 Hz, 1H, H2′), 5.15 (d, *J*=8.5 Hz, 1H, H5), 6.99 (d, *J*=8.0 Hz, 1.5, 2H, ArH), 7.20 (m, 3H, ArH); δ_C ($CDCl_3$) 15.4, 28.7, 29.3, 54.5, 59.9, 127.4, 128.8, 129.0, 136.1, 155.4, 165.6; *m/z* (EI^+) 337 (M^+), 246, 232; $C_{13}H_{15}N_2O_2Br$ requires 310.0317 (M^+) found 310.0317.

4.1.2. 1-[2′-(Phenylmethyl)amino]ethanoyl-3,4(*S*)-dimethyl-5(*R*)-phenylimidazolidin-2-one (2b). To a stirred solution of 1-(2′-bromo)ethanoyl-3,4(*S*)-dimethyl-5(*R*)-phenylimidazolidin-2-one (**2**) (3.15 g, 10.7 mmol) in THF (30 mL) was added benzylamine (4.11 g, 38.6 mmol). The reaction was stirred for 17 h before being concentrated in vacuo. The residue was partitioned with EtOAc (3×100 mL) and water (3×100 mL). The subsequent organic layer was then washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated to afford *1-[2′-(phenylmethyl)amino]*

[†] Compound **21** was found to be unstable preventing a HRMS spectrum of the pure sample being obtained.

*ethanoyl-3,4(*S*)-dimethyl-5(*R*)-phenylimidazolidin-2-one* **(2b)** as a clear oil (3.60 g, >99%) R_f 0.3 (eluent 10% MeOH/CH_2Cl_2) $[\alpha]_D^{27}=-41.1$ (*c* 2.72, CH_2Cl_2); ν_{max} 2979, 2937, 1729, 1605 cm^{-1}; δ_H ($CDCl_3$) 0.76 (d, *J*=6.5 Hz, 3H, 4Me), 2.80 (s, 3H, NMe), 3.80 (m, 2H, 2′CH_2), 4.10 (m, 2H, H5, NH), 3.90 (m, 2H, NCH_2Ph), 5.28 (d, *J*=8.5 Hz, 1H, H4), 7.14–7.38 (m, 10H, ArH); δ_C ($CDCl_3$) 15.4, 28.5, 54.7, 57.0, 57.8, 59.3, 126.3, 127.2, 127.4, 128.4, 128.5, 128.9, 129.5, 137.0, 139.6, 156.1, 171.3; *m/z* (EI^+) 337 (M^+), 246, 232; $C_{20}H_{23}N_3O_2$ requires 337.1786 (M^+) found 337.1790.

4.1.3. Preparation of 1-[2′-(*N*-phenylmethyl-*N*-*tert*-butoxycarbonyl)amino]ethanoyl-3,4(*S*)-dimethyl-5(*R*)-phenylimidazolidin-2-one (3a). To a stirred solution of the 1-[2′-(phenylmethyl)amino]ethanoyl-3,4(*S*)-dimethyl-5(*R*)-phenylimidazolidin-2-one (**2b**) (2.63 g, 7.8 mmol) in THF (20 mL) was added di-*tert*-butoxycarbonyl anhydride (3.49 g, 16.0 mmol, 2 equiv.). The solution was stirred for 5 min before the addition of DMAP (cat. 10 mg). The reaction was stirred for 46 h then concentrated in vacuo. The residue was partitioned with EtOAc (3×100 mL) and water (3×100 mL). The organic phase was further washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated. The product was then subjected to column chromatography (eluent 20% EtOAc/petrol) and recrystallised (EtOAc) to afford *1-[2′-(*N*-phenylmethyl-*N*-tert-butoxycarbonyl)amino]ethanoyl-3,4(*S*)-dimethyl-5(*R*)-phenylimidazolidin-2-one* **(3a)** as translucent crystals (1.61 g, 49%) R_f 0.5 (eluent 20% EtOAc/petrol); $[\alpha]_D^{23}=-52.0$ (*c* 1.19, $CHCl_3$) mp 144°C; ν_{max} 2977, 1732, 1703 cm^{-1}; δ_H (DMSO, 393 K) 0.72 (d, *J*=6.5 Hz, 3H, 4Me), 1.32 (s, 9H, ^{t}Bu), 2.72 (s, 3H, NMe), 3.93–4.08 (m, 1H, H4), 4.33 (s, 2H, H2′), 4.49 (s, 2H, NCH_2Ph), 5.28 (d, *J*=8.5 Hz, 1H, H5), 7.12–7.37 (m, 10H, ArH); δ_C ($CDCl_3$) 15.4, 28.7, 28.8, 50.8, 52.0, 54.7, 59.0, 127.6, 128.0, 128.1, 128.3, 128.4, 129.0, 129.1, 129.2, 129.3, 137.8, 138.9, 156.1, 156.2, 168.7; *m/z* (EI^+) 437 (M^+), 381 ($M^+-{}^t$Bu), 364, 337 (M^+−Boc) $C_{25}H_{31}N_3O_4$ requires 437.2315 (M^+) found 437.2315; $C_{25}H_{31}N_3O_4$ requires (%) C 68.63, H 7.14, N 9.60; found (%) C 68.61, H 7.15, N 9.59.

4.1.4. 1-[2′-*N*,*N*-Di(methylphenyl)amino]ethanoyl-3,4(*S*)-dimethyl-5(*R*)-phenylimidazolidin-2-one (3b). To a solution of 1-(2′-bromo)-ethanoyl-3,4(*S*)-dimethyl-5(*R*)-phenylimidazolidin-2-one (**2**) (4.20 g, 13.5 mmol) in THF (90 mL) was added dibenzylamine (3 equiv., 40.5 mmol, 7.79 mL). The reaction was stirred for 17 h then filtered and concentrated. The residue was partitioned with EtOAc (3×100 mL) and washed with saturated $NaHCO_{3(aq)}$ (2×100 mL) and water (2×100 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (eluent 30% EtOAc/petrol) to afford *1-[2′-*N,N*-di(methylphenyl)amino]ethanoyl-3,4(*S*)-dimethyl-5(*R*)-phenylimidazolidin-2-one* **(3b)** as a hygroscopic white solid (2.33 g, 74%) R_f 0.4 (eluent 30% EtOAc/petrol) mp 116–118°C; $[\alpha]_D^{27}=-49.1$ (*c* 1.59, CH_2Cl_2); ν_{max} 3580, 1730, 1690 cm^{-1}; δ_H ($CDCl_3$) 0.62 (d, *J*=6.5 Hz, 3H, 4Me), 2.61 (s, 3H, NMe), 3.71 (m, 5H, NCH_2 and H4), 3.85 (s, 2H, H2′), 5.15 (d, *J*=8.5 Hz, 1H, H5), 7.00–7.27 (m, 15H, ArH); δ_C ($CDCl_3$) 15.5, 28.6, 53.5, 54.8, 57.9, 59.3, 127.3, 127.5, 128.6, 128.6, 128.7, 128.9, 129, 129.3, 140.1, 140.5, 156.2, 171.6; *m/z* (EI^+) 427 (M^+), 336 (M^+−Bn), 210, 91; $C_{27}H_{29}N_3O_2$ requires 427.2260 (M^+) found 427.2260.

4.1.5. Preparation of 1-[2′-(*N*-formyl)amino]ethanoyl-3,4(*S*)-dimethyl-5(*R*)-phenylimidazolidin-2-one (3c). To a stirred solution of 1-(2′-bromo)ethanoyl-3,4(*S*)-dimethyl-5(*R*)-phenylimidazolidin-2-one (**2**) (0.61 g, 2.0 mmol) in THF (5 mL) was added formamide (1.00 mL, 51.1 mmol) and 2,6-lutidine (0.50 mL, 4.3 mmol). The reaction was heated at reflux for 16 h before the removal of solvent in vacuo. The residue was partitioned with CH_2Cl_2 (20 mL) and $NH_4Cl_{(aq)}$ (2×20 mL). The organic phase was further washed with water (20 mL) and brine (20 mL) then dried ($MgSO_4$), filtered and concentrated. Chromatography afforded *1-[2′-(*N*-formyl)amino]ethanoyl-3,4(*S*)-dimethyl-5(*R*)-phenylimidazolidin-2-one* (**3c**) as a white solid (0.48 g, 25%) R_f 0.3 (eluent 30% EtOAc/petrol); $[\alpha]_D^{27}=-113.7$ (*c* 1.15, $CHCl_3$) mp 171–172°C; ν_{max} 2977, 2918, 1731, 1700, 1427, 1397, 1165 cm^{-1}; δ_H ($CDCl_3$) 0.77 (d, *J*=6.5 Hz, 3H, 4Me), 2.79 (s, 3H, NMe), 3.95 (m, 1H, H4), 5.22 (2d, *J*=17.0 Hz, *J*=10.0 Hz, 2H, H2′, NH), 5.35 (d, *J*=17.0 Hz, 1H, H5), 5.40 (d, *J*=17.0 Hz, 1H, H2′), 7.08–7.55 (m, 5H, ArH), 8.10 (s, 1H, NCHO); δ_C ($CDCl_3$) 15.3, 28.5, 55.3, 59.4, 63.4, 127.3, 128.7, 129.0, 136.2, 155.9, 160.6, 166.0; *m/z* (FAB^+) 277 (MH_2^+), 231 (MH_2^+−NH[CHO]), 189 (χ_c^+), 147.

4.1.6. Preparation of 1-[2′-(*N*,*N*-bis-diformyl)amino]-ethanoyl-3,4(*S*)-dimethyl-5(*R*)-phenylimidazolidin-2-one (3d). To a flask charged with 1-(2′-bromo)ethanoyl-3,4(*S*)-dimethyl-5(*R*)-phenylimidazolidin-2-one (**2**) (1.05 g, 3.38 mmol) in THF (40 mL) was added sodium diformylamide (1 equiv., 334 mg, 3.38 mmol) and reaction heated to reflux for 12 h. The solvent was removed in vacuo and the remaining residue redissolved in CH_2Cl_2 (30 mL), washed with $NH_4Cl_{(aq)}$ (2×20 mL), dried (Na_2SO_4), filtered and concentrated to afford after chromatography (eluent 5% MeOH/$CHCl_3$) *1-[2′-(*N*,*N*-bis-diformyl)amino]ethanoyl-3,4(*S*)-dimethyl-5(*R*)-phenylimidazolidin-2-one* (**3d**) as a white solid (427 mg, 43%) R_f 0.3 (5% MeOH/$CHCl_3$) mp 174–175°C; $[\alpha]_D^{27}=-95.0$ (*c* 0.65, CH_2Cl_2); ν_{max} 2893, 2346, 1722, 1685, 1602, 1536 cm^{-1}; δ_H ($CDCl_3$) 0.74 (d, *J*=6.5 Hz, 3H, 4Me), 2.78 (s, 3H, NMe), 3.92 (m, 1H, H4), 4.98 (d, *J*=17.5 Hz, 1H, H2′), 5.06 (d, *J*=17.5 Hz, 1H, H2′), 5.23 (d, *J*=9.5 Hz, 1H, H5), 7.13–7.28 (m, 5H, ArH), 8.77 (s, 2H, CHO); δ_C ($CDCl_3$) 15.4, 28.6, 42.8, 50.0, 59.8, 127.2, 128.7, 129.1, 136.1, 155.9, 163.5, 163.8; *m/z* (EI^+) 303 (M^+), 275 (M^+−CO), 191 (χ_cH^+), 132; $C_{15}H_{17}N_3O_4$ requires 304.1297 (MH^+) found 304.1298.

4.2. General procedure for alkylations and acylation of 1-[2′-di(phenylmethyl)amino]ethanoyl-3,4(*S*)-dimethyl-5(*R*)-phenylimidazolidin-2-one (4–9)

To a cold (0°C) solution of secondary amine (1.5 mmol, 0.30 mL) in THF (5 mL) was added *n*-BuLi (1.5 mmol, 0.60 mL, 2.5 M solution in hexanes). The resulting solution was stirred for 30 min before being transferred dropwise via a double headed needle to a solution, at an internal temperature of −78°C, of 1-[2′-di(phenylmethyl)amino]-ethanoyl-3,4(*S*)-dimethyl-5(*R*)-phenylimidazolidin-2-one (**3b**) (1.01 mmol, 0.42 g) in THF (5 mL). The solution was

stirred for 15 min at that temperature before the addition of alkylating or acylating agent (1.10 mmol, 1.5 equiv.). The mixture was warmed to 23°C over a 2 h period, then concentrated in vacuo and partitioned with $NH_4Cl_{(aq)}$ (2×30 mL) and CH_2Cl_2 (4×20 mL). Column chromatography (15% EtOAc/petrol) afforded the desired adducts.

4.2.1. Preparation of 1-[2′(*R*)-diphenylmethyl)amino-3′-phenyl]propionoyl-3,4(*S*)-dimethyl-5(*R*)-phenylimidazolidin-2-one (4). Prepared according to the general procedure (dicyclohexylamine base) on a 1 mmol scale to afford the desired compound which was subsequently recrystallised (EtOAc) to afford *1-[2′(*R*)-diphenylmethyl)amino-3′-phenyl]propionoyl-3,4(*S*)-dimethyl-5(*R*)-phenylimidazolidin-2-one* (**4**) as translucent crystals (0.31 g, 59%) R_f 0.6 (eluent 20% EtOAc/petrol) mp 169°C; $[\alpha]_D^{23}=-22.3$ (*c* 1.02, $CHCl_3$); ν_{max} 2893, 2346, 1722, 1685, 1602, 1536 cm^{-1}; δ_H ($CDCl_3$) 0.72 (d, *J*=6.5 Hz, 3H, 4Me), 2.65 (s, 3H, NMe), 2.76 (dd, *J*=14.0, 5.5 Hz, 1H, H3′), 3.12 (dd, *J*=14.0, 5.5 Hz, 1H, H3′), 3.64 (d, *J*=14.5 Hz, 2H, $PhCH_2$), 3.80 (m, 1H, H4), 3.85 (d, *J*=14.5 Hz, 2H, $PhCH_2$), 5.15 (d, *J*=8.5 Hz, 1H, H5), 5.32 (m, 1H, H2′), 6.91–7.26 (m, 20H, ArH); δ_C ($CDCl_3$) 15.4, 28.5, 35.6, 54.4, 55.0, 59.5, 61.1, 126.5, 127.1, 127.2, 128.3, 128.5, 128.4, 128.7, 128.9, 129.0, 129.1, 130.0, 137.0, 138.5, 140.5, 155.4, 174.5; *m/z* (FAB^+) 518 (MH^+), 426 (MH^+-Bn), 300, 208; $C_{34}H_{35}N_3O_2$ requires (%) C 78.89, H 6.81, N 8.11; found (%) C 78.77, H 6.84, N 8.10; HPLC (spherisorb S5 chiral column, λ=254 nm) flow rate=0.25 mL min^{-1}, eluent 30% IPA/*n*-hexane, rt, 68.3 min, area >99%.

4.2.2. Preparation of 1-[2′(*R*)-(diphenylmethyl)amino]-pent-4′,5′-enoyl-3,4(*S*)-dimethyl-5(*R*)-phenylimidazolidin-2-one (5). Prepared according to the general procedure (*N-i*-propyl-*N*-cyclohexylamine base) on a 1.2 mmol scale to afford the desired compound which was subsequently recrystallised to afford *1-[2′(*R*)-(diphenylmethyl)amino]-pent-4′,5′-enoyl-3,4(*S*)-dimethyl-5(*R*)-phenylimidazolidin-2-one* (5) as translucent crystals (0.27 g, 48%) R_f 0.5 (eluent 20% EtOAc/petrol) mp 157–158°C; $[\alpha]_D^{27}=-14.1$ (*c* 0.32, CH_2Cl_2); ν_{max} 3437, 3028, 2919, 1729, 1683, 1392 cm^{-1}; δ_H ($CDCl_3$) 0.82 (d, *J*=6.5 Hz, 3H, 4Me), 2.48–2.78 (m, 2H, H3′), 2.80 (s, 3H, NMe), 3.82 (m, 3H, H4 and $PhCH_2$), 4.11 (d, *J*=14.5 Hz, 2H, $PhCH_2$), 5.13 (m, 3H, H2′, H5′), 5.23 (d, *J*=8.5 Hz, 1H, H5), 5.97 (m, 1H, H4′), 7.12–7.52 (m, 15H, ArH); δ_C ($CDCl_3$) 15.4, 28.5, 34.7, 54.4, 55.2, 59.6, 60.1, 117.4, 127.2, 127.3, 128.5, 129.0, 129.2, 135.7, 137.1, 140.8, 155.5, 174.4; *m/z* (FAB^+) 468 (MH^+), 426 ($MH^+-C_3H_5$), 336, 250; $C_{30}H_{33}N_3O_2$ requires 468.2651 (MH^+) found 468.2638.

4.2.3. Preparation of 1-[2′(*R*)-(diphenylmethyl)amino-4′-oxo-4′-phenyl]butanoyl-3,4(*S*)-dimethyl-5(*R*)-phenylimidazolidin-2-one (6). Prepared according to the general procedure (*N-i*-propyl-*N*-cyclohexylamine base, 1.5 equiv.) on a 0.6 mmol scale, in the presence of anhydrous LiCl (6 equiv.) to afford *1-[2′(*R*)-(diphenylmethyl)amino]-4′-oxo-4′-phenylbutanoyl-3,4(*S*)-dimethyl-5(*R*)-phenylimidazolidin-2-one* (**6**) as a clear gum (72 mg, 23%) R_f 0.4 (eluent 25% EtOAc/petrol); $[\alpha]_D^{25}=-33.1$ (*c* 0.54, $CHCl_3$); ν_{max} 3063, 3029, 2918, 2850, 1730, 1681, 1392 cm^{-1}; δ_H ($CDCl_3$) 0.72 (d, *J*=6.5 Hz, 3H, 4Me), 2.75 (s, 3H, NMe), 2.95 (dd, *J*=16.0, 8.0 Hz, 1H, H3′), 3.51 (dd, *J*=16.0, 7.5 Hz, 1H, H3′), 3.72 (m, 3H, H4 and $PhCH_2$), 3.89 (d, *J*=14.0 Hz, 2H, CH_2Ph), 5.05 (d, *J*=8.5 Hz, 1H, H5), 5.61 (t, *J*=7.5 Hz, 1H, H2′), 7.09 (s, 10H, ArH), 7.18–7.47 (m, 8H, ArH), 7.85 (d, *J*=8.0 Hz, 2H, ArH); δ_C ($CDCl_3$) 18.2, 26.6, 37.8, 52.5, 53.3, 56.5, 58.0, 125.2, 126.5, 126.7, 126.8, 127.0, 127.0, 127.2, 131.2, 134.8, 138.3, 153.8, 170.5, 197.4; *m/z* (EI^+) 545 (M^+), 454 (M^+-Bn), 348 (M^+-NBn_2), 328, 264, 243; $C_{35}H_{35}N_3O_3$ requires 454.2130 (M^+-Bn) found 454.2130.

4.2.4. Preparation of 1-[2′(*R*)-di(phenylmethyl)amino-3′-oxo-3′-(4″-bromo)phenyl]propionoyl-3,4(*S*)-dimethyl-5(*R*)-phenylimidazolidin-2-one (7). Prepared according to the general procedure (*N-i*-propyl-*N*-cyclohexylamine base, 1.5 equiv.) on a 0.9 mmol scale, in the presence of anhydrous LiCl (6 equiv.) to afford after chromatography *1-[2′(*R*)-di(phenylmethyl)amino-3′-oxo-3′-(4″-bromo)phenyl]propionoyl-3,4(*S*)-dimethyl-5(*R*)-phenylimidazolidin-2-one* (**7**) as a white solid (54 mg, 9%) R_f 0.5 (30% EtOAc/petrol); δ_H ($CDCl_3$) 0.69 (d, *J*=6.5 Hz, 3H, 4Me), 2.66 (s, 3H, NMe), 2.77 (dd, *J*=14.0, 5.5 Hz, 1H, H3′), 3.15 (dd, *J*=14.0, 5.5 Hz, 1H, H3′), 3.65 (d, *J*=14.05 Hz, 2H, $PhCH_2$), 3.80 (m, 1H, H4), 3.90 (d, *J*=14.0 Hz, 2H, $PhCH_2$), 5.16 (d, *J*=8.5 Hz, 1H, H5), 5.30 (m, 1H, H2′), 6.90–7.27 (m, 19H, ArH); δ_C ($CDCl_3$) 15.3, 28.5, 35.1, 54.4, 55.0, 59.5, 61.0, 120.3, 127.1, 127.2, 128.4, 129.0, 131.5, 131.8, 136.9, 137.6, 140.4, 155.4, 173.9.

4.2.5. Preparation of 1-[2′-(*R*,*S*)-di(phenylmethyl)-amino-3′-oxo-3′-phenyl]propionoyl-3,4(*S*)-dimethyl-5(*R*)-phenylimidazolidin-2-one (8a,b). Prepared according to the general procedure (*N-i*-propyl-*N*-cyclohexylamine base, 1.5 equiv.) on a 0.9 mmol scale, in the presence of anhydrous LiCl (6 equiv.) to afford after chromatography *1-N-[2′-(R,S)-di(phenylmethyl)amino-3′-oxo-3′-phenyl]-propionoyl-3,4(*S*)-dimethyl-5(*R*)-phenylimidazolidin-2-one* (**8a**,**b**) (452 mg, 91%, de 2′*S* 43%). Recrystallisation (ether/petrol) afforded pure 2′(*S*) diastereomer (166 mg, 33%) and enrichment of the mother liquor in the 2′(*R*) diastereomer. Slow dropwise addition of benzoyl chloride caused a reduced yield of product with an increase in selectivity (**8a**) (83%, >95% de) *1-[2′-(*R*)-di(phenylmethyl)amino-3′-oxo-3′-phenyl]propionoyl-3,4(*S*)-dimethyl-5(*R*)-phenylimidazolidin-2-one* (**8a**) R_f 0.4 (eluent 30% EtOAc/petrol); $[\alpha]_D^{23}=+11.1$ (*c* 0.94, CH_2Cl_2) mp 159–160°C; ν_{max} 1723, 1693, 1562, 1495, 1288, 1029 cm^{-1}; δ_H ($CDCl_3$) 0.69 (d, *J*=6.5 Hz, 3H, 4Me), 2.58 (s, 3H, NMe), 3.71 (d, *J*=14.0 Hz, 2H, CH_2N), 3.88 (m, 3H, H4 and CH_2N), 5.36 (d, *J*=9.0 Hz, 1H, H5), 5.93 (s, 1H, H2′), 6.93–7.64 (m, 20H, ArH); δ_C ($CDCl_3$) 16.0, 28.9, 55.5, 56.4, 60.1, 68.3, 127.9, 128.2, 129.0, 129.0, 129.3, 130.0, 130.3, 133.6, 136.6, 137.1, 140.2, 156.3, 170.5, 197.5; *m/z* (EI^+) 532 (MH^+), 441, 428, 336, 314; $C_{34}H_{33}N_3O_3$ requires 531.252; found 532.260 (MH^+).

4.2.6. Preparation of 1-[2′-(*R*)-di(phenylmethyl)amino-3′-oxo-3′-(4″-iodo)-phenyl]propionoyl-3,4(*S*)-dimethyl-5(*R*)-phenylimidazolidin-2-one (9). Prepared according to the general procedure (*N-i*-propyl-*N*-cyclohexylamine base, 1.5 equiv.) on a 0.4 mmol scale, in the presence of anhydrous LiCl (6 equiv.) to afford after chromatography *1-[2′-(*R*)-di(phenylmethyl)amino-3′-oxo-3′-(4-iodo)-phenyl]propionoyl-3,4(*S*)-dimethyl-5(*R*)-phenylimidazolidin-2-one* (**9**)

as a white solid (106 mg, 37%, de >95%) R_f 0.4 (eluent 30% EtOAc/petrol) mp 93–94°C; $[\alpha]_D^{30}=+126.9$ (*c* 0.25, CH_2Cl_2); ν_{max} 2917, 2850, 1724, 1694, 1582, 1393 cm^{-1}; δ_H (DMSO) 0.68 (d, *J*=6.5 Hz, 3H, 4Me), 2.57 (s, 3H, 3Me), 3.71 (d, *J*=14.0 Hz, 2H, CH_2N), 3.88 (m, 3H, H4 and CH_2N), 5.36 (d, *J*=9.0 Hz, 1H, H5), 5.82 (s, 1H, H2′), 6.94–7.65 (m, 19H, ArH); δ_C ($CDCl_3$) 15.6, 28.6, 55.1, 56.0, 59.6, 67.4, 101.1, 127.7, 127.7, 128.6, 128.7, 128.9, 129.6, 131.3, 136.0, 136.1, 137.9, 139.7, 155.8, 169.6, 195.7; *m/z* (EI^+) 657 (M^+), 566 (M^+-Bn), 467, 426 ($M^+-COPhI$), 376, 336; $C_{34}H_{32}N_3O_3I$ requires 657.1488; found 657.1488.

4.2.7. Preparation of 1-[2′(*R*,*S*)-di(phenylmethyl)amino-2′(*R*,*S*)-phenylmethyl-3′-oxo-3′-phenyl]propionoyl-3,4(*S*)-dimethyl-5(*R*)-phenylimidazolidin-2-one (10). To a solution of 1-[2′(*R*,*S*)-di(phenylmethyl)amino-3′-oxo-3′-phenyl]-propionoyl-3,4(*S*)-dimethyl-5(*R*)-phenylimidazolidin-2-one (**8a**) (157 mg, 0.29 mmol) in THF (2 mL) was added NaH (60% dispersion in mineral oil, 3 equiv., 42 mg). The solution was stirred at 0°C for 30 min before the addition of benzyl bromide (3 equiv., 0.85 mmol, 100 μl). TLC analysis (eluent 30% EtOAc/petrol) indicated no reaction. NaH (3 equiv.) was then added and the reaction stirred for 30 min then heated to reflux for 1 h. After this period TLC showed the reaction was complete. The reaction was quenched with water (2 mL) and basified to pH 9 with $NaHCO_3$. Extraction with CH_2Cl_2 (3×20 mL) followed by drying (Na_2SO_4), filtration and concentration afforded, after chromatography, *1-[2′*(R,S)*-di(phenylmethyl)amino-2′*(R,S)*-phenylmethyl-3′-oxo-3′-phenyl]propionoyl-3,4*(S)*-dimethyl-5*(R)*-phenylimidazolidin-2-one* (**10**) as a white solid (139 mg, 77%, dr 59:41, de 18%) R_f 0.3 (eluent 15% EtOAc/petrol) mp 159–160°C; ν_{max} 3580, 1730, 1690 cm^{-1}; δ_H ($CDCl_3$) 0.56 and 0.61 (d, *J*=6.5 Hz, 3H, 4Me), 2.48 and 2.63 (s, 3H, NMe), 3.51–3.78 (m, 5H, H4′, $2NCH_2Ph$), 4.25–4.47 (m, 2H, CH_2Ph), 5.21–5.27 (d, 1H, H5), 6.89–7.36 (m, 25H, ArH); δ_C ($CDCl_3$) 14.7, 15.6, 16.4, 22.1, 28.1, 28.8, 25.2, 54.0, 56.4, 58.2, 59.9, 60.4, 61.0, 71.8, 127.2, 127.7, 127.9, 128.0, 128.3, 128.6, 128.9, 129.9, 130.0, 134.7, 134.8, 137.6, 138.0, 138.1, 139.2, 139.4, 139.7, 150.0, 154.3, 154.6, 155.2, 166.6, 167.2; *m/z* (EI^+) 621 (M^+), 530 (M−Bn), 426, 334, 312, 279, 248; $C_{41}H_{39}N_3O_3$ requires 621.299 (M^+) found 621.299; $C_{41}H_{39}N_3O_3$ requires (%) C 79.20, H 6.32, N 6.75; found (%) C 79.35, H 6.37, N 6.69.

4.2.8. Preparation of 1-[2′(*R*,*S*)-di(phenylmethyl)amino-2′(*R*,*S*)-phenylmethyl-3″-oxo-3′-phenyl]pent-4′,5′-enoyl]-3,4(*S*)-dimethyl-5(*R*)-phenylimidazolidin-2-one (11). To a flask containing NaH (31 mg, 8 equiv., 60% dispersion in mineral oil), freshly washed with petrol and dried in vacuo, was added a solution of 1-[2′(*R*,*S*)-di(phenylmethyl)-amino-3′-oxo-3′-phenyl]propionoyl-3,4(*S*)-dimethyl-5(*R*)-phenylimidazolidin-2-one (**8a**) (50 mg, 94 μmol) in THF (3 mL). The reaction was stirred at 25°C for 30 min before the addition of allyl bromide (2.6 equiv., 0.19 mmol, 17 μL). TLC indicated reaction completion after 60 h (eluent 30% EtOAc/petrol). Chromatography afforded *1-[2′*(R,S)*-di(phenylmethyl)amino-2′*(R,S)*-phenylmethyl-3″oxo-3′-phenyl]pent-4′,5′-enoyl]-3,4*(S)*-dimethyl-5*(R)*-phenylimidazolidin-2-one* (**11**) (40 mg, 74% dr 61:39, de 22%) R_f 0.6 (eluent 30% EtOAc/petrol); ν_{max} 2921, 2854, 1736, 1657, 1259 cm^{-1}; δ_H ($CDCl_3$) 0.70, 0.77 (d, *J*=6.5 Hz, 3H, 4Me), 2.63, 2.74 (s, 3H, NMe), 3.37–4.01 (m, 7H, H3′, H4, $PhCH_2$), 5.01 (m, 2H, H5′, H5), 5.34 (m, 1H, H5′), 5.72 (m, 1H, H4′), 6.77–7.39 (m, 20H, ArH) *m/z* (CI^+) 574, 572 (MH^+), 208, 198, 191, 106; $C_{37}H_{37}N_3O_3$ requires 572.2913 (MH^+) found 572.2906.

4.3. General procedure for boron aldol condensations

Method A: To a solution (−78°C) of 1-[2′-di(phenylmethyl) amino]ethanoyl-3,4(*S*)-dimethyl-5(*R*)-phenylimidazolidin-2-one (**3b**) (0.7 mmol, 0.32 g) in CH_2Cl_2 (4 mL) was added dropwise, over 1 min, freshly distilled di-*n*-butylboron triflate (1.0 M in CH_2Cl_2, 0.35 mL, 5 equiv.) and NEt_3 (7.0 mmol, 0.56 mL, 10 equiv.). The mixture was stirred at that temperature for 5 min before addition of aldehyde (1.40 mmol, 150 μL, 2.0 equiv.). After 1 h the reaction was slowly warmed to 0°C and stirred for a further 1 h. The reaction was quenched by the sequential addition of aqueous pH 7 phosphate buffer (4.5 mL), methanol (10 mL), and $H_2O_{2(aq)}$ (30%, 4.5 mL). After 1 h at 0°C the mixture was concentrated and the residue partitioned between Et_2O (20 mL) and water (20 mL). The organic phase was washed with cold $HCl_{(aq)}$ (5%, 20 mL), saturated $NaHCO_3$ (20 mL) and brine (20 mL). The organic phase was dried (Na_2SO_4) and concentrated to afford, after chromatography, the desired aldol adduct.

Method B: To a solution (0°C) of 1-[2′-di(phenylmethyl)-amino]ethanoyl-3,4(*S*)-dimethyl-5(*R*)-phenylimidazolidin-2-one (**3b**) (0.59 mmol, 0.25 g) in CH_2Cl_2 (4 mL) was added 9-BBN triflate (0.5 M in hexanes, 5.85 mL, 5 equiv.). After 15 min NEt_3 (5.9 mmol, 0.82 mL, 10 equiv.) was added. The mixture was stirred at that temperature for 1 h and then aldehyde (0.7 mmol, 1.2 equiv.) was added. After 30 min the reaction was warmed to 23°C and stirred for 3 h. The reaction was quenched by the sequential addition of aqueous pH 7 phosphate buffer (4.5 mL), methanol (10 mL), and $H_2O_{2(aq)}$ (30%, 4.5 mL). After 1 h at 0°C the mixture was concentrated and the residue partitioned between CH_2Cl_2 (20 mL) and water (20 mL). The organic phase was washed with saturated $NaHCO_3$ (20 mL) and brine (20 mL). The organic phase was dried (Na_2SO_4) and concentrated to afford, after chromatography, the desired aldol adduct.

4.3.1. Preparation of 1-[3′(*R*)-hydroxy-2′(*S*)-di(phenylmethyl)amino-3-phenyl]propionoyl-3,4(*R*)-dimethyl-5(*S*)-phenylimidazolidin-2-one (12a). Prepared according to method A on a 0.7 mmol scale (see Table 1) to afford, after chromatography, *1-[3′*(R,S)*-hydroxy-2′*(S,R)*-di(phenylmethyl)amino-3′-phenyl]propionoyl-3,4*(R)*-dimethyl-5*(S)*-phenylimidazolidin-2-one* (**12a**,**b**) as a pale foam—241 mg, combined yield 65%, dr 97 (**12a**):3 (**12b**). *1-[3′*(R)*-hydroxy-2′*(S)*-di(phenylmethyl)amino-3-phenyl]propionoyl-3,4*(R)*-dimethyl-5*(S)*-phenylimidazolidin-2-one* (**12a**): R_f 0.4 (eluent 30% EtOAc/petrol); δ_H ($CDCl_3$) 0.61 (d, *J*=6.5 Hz, 3H, 4Me), 2.65 (s, 3H, NMe), 3.60 (m, 1H, H4), 3.80 (d, *J*=14.5 Hz, 2H, CH_2Ph), 4.20 (d, *J*=14.5 Hz, 2H, CH_2Ph), 4.83 (d, *J*=9.5 Hz, 1H, H3′), 4.99 (d, *J*=8.5 Hz, 1H, H2′), 5.66 (d, *J*=9.5 Hz, 1H, H5), 6.50 (br. s, 1H, OH), 7.09–7.32 (m, 20H, ArH); δ_C ($CDCl_3$) 15.2, 28.6, 54.0, 55.5, 60.0, 67.8, 72.7, 127.7, 127.7, 128.3, 128.7, 128.9, 129.1, 129.7, 137.4, 139.9, 140.1, 155.2, 171.3; *m/z* (FAB^+) 534 (MH^+), 426

(M^+−PhCHO), 316, 191; $C_{34}H_{35}N_3O_3$ requires 534.2757 (MH^+) found 534.2743.

4.3.2. Preparation of 1-[3′(*S*)-hydroxy-2′(*R*)-di(phenylmethyl)amino-3-phenyl]propionoyl-3,4(*R*)-dimethyl-5(*S*)-phenylimidazolidin-2-one (12b). Prepared according to method B, on a 0.5 mmol scale, to afford after chromatography *1-[3′*(S)*-hydroxy-2′*(R)*di(phenylmethyl)amino-3-phenyl]propionoyl-3,4*(R)*-dimethyl-5*(S)*-phenylimidazolidin-2-one* (**12b**) as a white foam (271 mg, 84%) R_f 0.4 (eluent 30% EtOAc/petrol) mp 63–64°C; $[\alpha]_D^{20}$=−10.6 (*c* 0.81, CH_2Cl_2); ν_{max} 3447, 1728, 1674, 1494, 1453, 1421, 1391 cm^{-1}; δ_H ($CDCl_3$) 0.52 (d, *J*=6.5 Hz, 3H, 4Me), 2.40 (s, 3H, NMe), 3.02 (m, 1H, H4), 3.47 (d, *J*=14.0 Hz, 2H, CH_2Ph), 3.77 (br. s, 1H, OH), 3.99 (d, *J*=14.0 Hz, 2H, CH_2Ph), 4.70 (d, *J*=6.5 Hz, 1H, H3′), 4.76 (d, *J*=7.0 Hz, 1H, H2′), 5.39 (d, *J*=8.5 Hz, 1H, H5), 7.11–7.40 (m, 20H, ArH); δ_C ($CDCl_3$) 15.2, 28.5, 53.8, 55.2, 59.8, 66.2, 72.1, 126.3, 126.9, 127.6, 128.0, 128.2, 128.4, 128.7, 128.7, 128.8, 128.9, 129.1, 129.5, 136.1, 139.3, 139.8, 154.8, 169.8; *m/z* (ES^+) 557 ($MHNa^{2+}$), 556 (MNa^+), 534 (MH^+), 429 (MH^+−PhCHO), 428 (M^+−PhCHO), 199; $C_{34}H_{35}N_3O_3$ requires 534.2757 (MH^+) found 534.2743.

4.3.3. Preparation of 1-[3′(*R*,*S*)-hydroxy-2′(*S*,*R*)-di(phenylmethyl)amino-3′-(4″-methoxy)phenyl]propionoyl-3,4-dimethyl-5(*S*)-phenylimidazolidin-2-one (13a,b,c). Prepared according to method A on a 0.3 mmol scale to afford, after chromatography (eluent 15% EtOAc/petrol), *1-[3′*(R,S)*-hydroxy-2′*(S,R)*-di(phenylmethyl)amino-3′-(4″-methoxy)phenyl]propionoyl-3,4-dimethyl-5*(S)*-phenylimidazolidin-2-one* as a mixture of diastereomers (**13a**,**b**) as a pale foam (202 mg, combined yield 68%, dr 37:22:4). Further chromatography (eluent 15% EtOAc/petrol) and recrystallisation (EtOAc/petrol) provided *1-[3′(S)-hydroxy-2′(R)-di(phenylmethyl)amino-3-(4″-methoxy)phenyl]propionoyl-3,4(R)-dimethyl-5(S)-phenylimidazolidin-2-one* (**13a**) as a pale foam: R_f 0.4 (eluent 30% EtOAc/petrol) mp 75–76°C; $[\alpha]_D^{20}$=−149.0 (*c* 0.91, CH_2Cl_2); ν_{max} 3445, 3029, 1728, 1673, 1613, 1514, 1389, 1249 cm^{-1}; δ_H ($CDCl_3$) 0.54 (d, *J*=6.5 Hz, 3H, 4Me), 2.60 (s, 3H, NMe), 3.47–4.14 (m, 6H, OH, H4, $2CH_2Ph$), 3.75 (s, 3H, OMe), 4.92 (d, *J*=8.5 Hz, 1H, H5), 5.58 (d, *J*=9.5 Hz, 1H, H3′), 5.66 (d, *J*=9.5 Hz, 1H, H2′), 6.67 (br. s, 2H, ArH), 6.85–7.23 (m, 17H, ArH); δ_C ($CDCl_3$) 17.3, 30.7, 56.0, 57.4, 57.8, 61.9, 68.3, 73.8, 116.2, 129.7, 130.1, 130.5, 130.9, 131.3, 131.7, 132.2, 133.5, 138.2, 142.1, 157.0, 161.8, 172.0; *m/z* (FAB^+) 564 (MH^+), 426 ($M-MeOC_6H_4CHO$), 336, 231; $C_{35}H_{37}N_3O_4$ requires (%) C 74.58, H 6.62, N 7.45; found (%) C 74.32, H 6.58, N 7.41.

4.3.4. Preparation of 1-[3′(*S*)-hydroxy-2′(*R*)-di(phenylmethyl)amino-3-(4″-methoxy)phenyl]propionoyl-3,4(*R*)-dimethyl-5(*S*)-phenylimidazolidin-2-one (13b). Prepared according to method B on a 0.5 mmol scale to afford after chromatography (eluent 15% EtOAc/petrol) *1-[3′*(S)*-hydroxy-2′*(R)*-di(phenylmethyl)amino-3-(4″-methoxy)phenyl]propionoyl-3,4*(R)*-dimethyl-5*(S)*-phenylimidazolidin-2-one* (**13b**) as a pale foam (211 mg, 66%, de 94%) R_f 0.3 (eluent 30% EtOAc/petrol) mp 153–155°C; $[\alpha]_D^{20}$=−8.91 (*c* 0.13, CH_2Cl_2); ν_{max} 3439, 1728, 1674, 1612, 1513, 1391, 1249 cm^{-1}; δ_H ($CDCl_3$) 0.60 (d, *J*=6.5 Hz, 3H, 4Me), 2.49 (s, 3H, NMe), 3.17 (dq, *J*=6.5 Hz, 8.5, 1H, H4), 3.48 (d, *J*=14.0 Hz, 2H, CH_2Ph), 3.68 (s, 3H, OMe), 3.74 (br. s, 1H, OH), 3.80 (d, *J*=14.0 Hz, 2H, CH_2Ph), 4.74 (d, *J*=9.5 Hz, 1H, H3′), 4.88 (d, *J*=8.5 Hz, 1H, H5), 5.40 (d, *J*=9.5 Hz, 1H, H2′), 6.73 (d, *J*=9.0 Hz, 2H, ArH), 7.04–7.31 (m, 17H, ArH); δ_C ($CDCl_3$) 15.2, 28.5, 53.9, 55.3, 55.7, 59.8, 60.8, 67.6, 71.9, 113.6, 127.5, 127.7, 128.6, 128.8, 129.0, 129.4, 129.6, 132.0, 137.3, 139.8, 155.0, 159.7, 171.2; *m/z* (FAB^+) 564 (MH^+), 426 ($M-MeOC_6H_4CHO$), 336, 231; $C_{35}H_{37}N_3O_4$ requires 564.2862 (MH^+) found 564.2865.

4.3.5. Preparation of 1-[3′(*R*)-hydroxy-2′(*S*)-di(phenylmethyl)amino-3-(2″-fluoro)phenyl]propionoyl-3,4(*R*)-dimethyl-5(*S*)-phenylimidazolidin-2-one (14a,b). Prepared according to method A on a 0.5 mmol scale to afford *1-[3′*(R,S)*-hydroxy-2′*(R,S)*-di(phenylmethyl)amino-3-(2″-fluoro)phenyl]propionoyl-3,4*(R)*-dimethyl-5*(S)*-phenylimidazolidin-2-one* (**14a**,**b**) as a mixture of the *syn* diastereomers. Chromatography (eluent 15% EtOAc/petrol) afforded (**14a**) and (**14b**) as pale foams (184 mg, 63%, dr 32:31). *1-[3′(R)-hydroxy-2′(S)-di(phenylmethyl)amino-3-(2″-fluoro)phenyl]-propionoyl-3,4(R)-dimethyl-5(S)-phenylimidazolidin-2-one* (**14a**) R_f 0.4 (eluent 30% EtOAc/petrol); $[\alpha]_D^{33}$=−231.6 (*c* 0.11, CH_2Cl_2); ν_{max} 3452, 2922, 1731, 1678, 1494, 1391 cm^{-1}; δ_H ($CDCl_3$) 0.56 (d, *J*=7.0 Hz, 3H, 4Me), 2.51 (s, 3H, NMe), 3.53 (m, 1H, H4), 3.76 (d, *J*=14.0 Hz, 2H, CH_2Ph), 4.12 (d, *J*=14.0 Hz, 2H, CH_2Ph), 4.82 (d, *J*=8.5 Hz, 1H, H5), 5.01 (d, *J*=9.5 Hz, 1H, H3′), 5.61 (d, *J*=9.5 Hz, 1H, H2′), 6.42 (br. s, 2H, ArH), 6.63–7.36 (m, 17H, ArH); δ_C ($CDCl_3$) 15.2, 28.5, 53.9, 55.2, 59.8, 64.9, 65.7, 115.9, 116.2, 124.3, 126.7, 127.3, 127.5, 127.6, 128.0, 128.6, 128.7, 128.8, 129.0, 129.1, 129.3, 129.5, 129.7, 129.8, 130.8, 136.2, 139.8, 140.0, 154.9, 169.5; *m/z* (FAB^+) 552 (MH^+), 426 ($M-FC_6H_4CHO$), 334, 136; $C_{34}H_{34}N_3O_3F$ requires 552.2662 (MH^+) found 552.2688.

4.3.6. Preparation of 1-[3′(*S*)-hydroxy-2′(*R*)-di(phenylmethyl)amino-3-(2″-fluoro)phenyl]propionoyl-3,4(*R*)-dimethyl-5(*S*)-phenylimidazolidin-2-one (14b). Prepared according to method B on a 0.5 mmol scale to afford after chromatography (eluent 15% EtOAc/petrol) *1-[3′*(S)*-hydroxy-2′*(R)*-di(phenylmethyl)amino-3-(2″-fluoro)phenyl]-propionoyl-3,4*(R)*-dimethyl-5*(S)*-phenylimidazolidin-2-one* (**14b**) as a pale foam (200 mg, 62%, de >95%) R_f 0.3 (eluent 30% EtOAc/petrol); $[\alpha]_D^{20}$=+9.2 (*c* 0.82, CH_2Cl_2); ν_{max} 3444, 2918, 1730, 1678, 1493, 1391 cm^{-1}; δ_H ($CDCl_3$) 0.64 (d, *J*=7.0 Hz, 3H, 4Me), 2.35 (s, 3H, NMe), 3.20 (dq, *J*=6.8, 8.5 Hz, 1H, H4), 3.43 (d, *J*=14.0 Hz, 2H, CH_2Ph), 3.65 (m, 3H, OH and CH_2Ph), 4.91 (d, *J*=8.5 Hz, 1H, H5), 5.09 (d, *J*=10.0 Hz, 1H, H3′), 5.61 (d, *J*=10.0 Hz, 1H, H2′), 6.64–7.36 (m, 19H, ArH); δ_C ($CDCl_3$) 17.2, 30.5, 56.2, 57.3, 62.1, 62.9, 67.5, 68.1, 116.8, 117.1, 126.5, 126.6, 129.3, 129.4, 129.7, 129.8, 130.7, 130.8, 130.9, 131.1, 131.6, 132.5, 132.6, 139.4, 141.7, 157.1, 172.7; *m/z* (FAB^+) 552 (MH^+), 426 ($M-FC_6H_4CHO$), 334, 136; $C_{34}H_{34}N_3O_3F$ requires 552.2662 (MH^+) found 552.2688; $C_{34}H_{34}N_3O_3F$ requires (%) C 74.03, H 6.21, N 7.61; found (%) C 73.24, H 6.42, N 7.16.

4.3.7. Preparation of 1-[3′(*R*,*S*)-hydroxy-2′(*S*,*R*)-di(phenylmethyl)amino-3-(4″-nitro)phenyl]propionoyl-3,4(*R*)-dimethyl-5(*S*)-phenylimidazolidin-2-one (15a,b).

Prepared according to method A on a 0.5 mmol scale to afford, after chromatogaphy (eluent 15% EtOAc/petrol), *1-[3′(*R,S*)-hydroxy-2′(*R,S*)-di(phenylmethyl)amino-3-(4″-nitro)-phenyl]propionoyl-3,4(*R*)-dimethyl-5(*S*)-phenylimidazolidin-2-one* (**15a**,**b**) as a pale foam (110 mg, 42%, dr 39:57).

Comparison of this spectrum to (**15b**) reveals the NMR data for the minor product *1-[3′(*R*)-hydroxy-2′(*S*)-di(phenylmethyl)amino-3-(2″-nitro)-phenyl]propionoyl-3,4(*R*)-dimethyl-5(*S*)-phenylimidazolidin-2-one* (**15a**) δ_H ($CDCl_3$) 0.58 (d, J=6.5 Hz, 3H, 4Me), 2.60 (s, 3H, NMe), 3.45 (m, 1H, H4), 3.55 (m, 2H, CH_2Ph), 4.09 (d, J=14.5 Hz, 2H, CH_2Ph), 4.84 (d, J=9.5 Hz, 1H, H3′), 4.91 (d, J=8.0 Hz, 1H, H5), 5.20 (d, J=9.5 Hz, 1H, H2′), 6.48 (br. s, 2H, ArH), 7.03–7.35 (m, 15H, ArH), 7.92 (d, J=9.0 Hz, 2H, ArH); δ_C ($CDCl_3$) 14.9, 28.4, 53.9, 55.3, 60.0, 66.3, 71.2, 123.8, 127.3, 127.8, 128.6, 128.6, 128.7, 128.8, 128.9, 129.3, 129.5, 136.0, 139.0, 147.3, 147.8, 154.7, 169.3.

4.3.8. Preparation of 1-[3′(*S*)-hydroxy-2′(*R*)-di(phenylmethyl)amino-3-(4″-nitro)phenyl]propionoyl-3,4(*R*)-dimethyl-5(*S*)-phenylimidazolidin-2-one (15b). Prepared according to method B on a 0.5 mmol scale to afford after chromatography (eluent 15% EtOAc/petrol) *1-[3′(*S*)-hydroxy-2′(*R*)-di(phenylmethyl)amino-3-(4″-nitro)phenyl]-propionoyl-3,4(*R*)-dimethyl-5(*S*)-phenylimidazolidin-2-one* (**15b**) as a hygroscopic yellow foam (244 mg, 72%, de >95%) R_f 0.4 (eluent 30% EtOAc/petrol); $[\alpha]_D^{31}$=+9.0 (*c*, 0.1); ν_{max} 3437, 2918, 1729, 1676, 1603, 1522 cm^{-1}; δ_H ($CDCl_3$) 0.69 (d, J=6.5 Hz, 3H, 4Me), 2.56 (s, 3H, NMe), 3.38 (d, J=14.0 Hz, 2H, CH_2Ph), 3.42 (m, 1H, H4), 3.91 (d, J=14.0 Hz, 2H, CH_2Ph), 4.89 (d, J=9.5 Hz, 1H, H3′), 5.09 (d, J=9.0 Hz, 1H, H5), 5.36 (d, J=9.5 Hz, 1H, H2′), 7.08–7.41 (m, 17H, ArH), 8.04 (d, J=6.5 Hz, 2H, ArH); δ_C ($CDCl_3$) 15.4, 28.7, 53.9, 55.3, 59.6, 67.0, 71.1, 123.5, 127.8, 128.0, 128.9, 129.0, 129.1, 129.1, 129.6, 137.1, 139.4, 147.9, 148.1, 154.9, 170.1; *m/z* (CI^+) 579 (MH^+), 429, 428 ($M-NO_2PhCHO$), 338, 336; $C_{34}H_{34}N_4O_5$ requires 579.2607 (MH^+) found 579.2600.

4.3.9. Preparation of 1-[3′(*S*)-hydroxy-2′(*R*)-di(phenylmethyl)amino-4′-methyl]pentanoyl-3,4(*R*)-dimethyl-5(*S*)-phenylimidazolidin-2-one (16b). Prepared according to method B on a 0.5 mmol scale to afford after chromatography (eluent 15% EtOAc/petrol) *1-[3′(*S*)-hydroxy-2′(*R*)-di(phenylmethyl)amino-4′-methyl]pentanoyl-3,4(*R*)-dimethyl-5(*S*)-phenylimidazolidin-2-one* (**16b**) as a pale foam (201 mg, 69%, de >95%) R_f 0.5 (eluent 30% EtOAc/petrol) mp 115–116°C; $[\alpha]_D^{20}$=+41.7 (*c* 0.89, CH_2Cl_2); ν_{max} 3436, 3029, 2957, 1728, 1673, 1494, 1454, 1421, 1389 cm^{-1}; δ_H ($CDCl_3$) 0.86 (t, J=7.0 Hz, 3H, H6′), 0.89 (d, J=6.5 Hz, 3H, 4Me), 1.32–1.58 (m, 4H, H4′, H5′), 2.87 (s, 3H, NMe), 3.32 (br. s, 1H, OH), 3.34 (d, J=14.0 Hz, 2H, CH_2Ph), 3.85 (d, J=14.0 Hz, 2H, CH_2Ph), 3.92 (m, 2H, H3′, H4), 5.11 (d, J=9.5 Hz, 1H, H2′), 5.44 (d, J=9.0 Hz, 1H, H5), 7.11–7.44 (m, 15H, ArH); δ_C ($CDCl_3$) 15.2, 16.3, 20.3, 29.6, 36.5, 54.7, 56.1, 60.5, 66.4, 69.0, 129.0, 129.3, 129.5, 129.6, 130.1, 138.2, 140.6, 156.3, 171.8; *m/z* (AP^+) 500 (MH^+), 482 (MH^+-H_2O), 428; $C_{31}H_{37}N_3O_3$ requires 500.2913 (MH^+) found 500.2910.

4.3.10. Preparation of 1-[3′(*S*)-hydroxy-2′(*R*)-di(phenylmethyl)amino-3′-furyl]propionoyl-3,4(*R*)-dimethyl-5(*S*)-phenylimidazolidin-2-one (17b). Prepared according to method B on a 0.5 mmol scale to afford after chromatography (eluent 15% EtOAc/petrol) *1-[3′(*S*)-hydroxy-2′(*R*)-di(phenylmethyl)amino-3′-furyl]propionoyl-3,4(*R*)-dimethyl-5(*S*)-phenylimidazolidin-2-one* (**17b**) as a pale foam (198 mg, 65%, de >95%) R_f 0.3 (eluent 30% EtOAc/petrol) mp 58–60°C; $[\alpha]_D^{20}$=+34.1 (*c* 0.32, CH_2Cl_2); ν_{max} 3446, 1729, 1674, 1391, 1072 cm^{-1}; δ_H ($CDCl_3$) 0.63 (d, J=7.0 Hz, 3H, 4Me), 2.62 (s, 3H, NMe), 3.37 (d, J=14.0 Hz, 2H, NCH_2), 3.50 (m, 1H, H4), 3.56 (br. s, 1H, OH), 3.75 (d, J=14.0 Hz, 2H, NCH_2), 4.77 (d, J=10.0 Hz, 1H, H3′), 5.01 (d, J=8.5 Hz, 1H, H5), 5.50 (d, J=10.0 Hz, 1H, H2′), 6.10–6.15 (m, 2H, ArH), 6.99–7.24 (m, 16H, ArH); δ_C ($CDCl_3$) 15.4, 28.8, 54.1, 55.3, 59.9, 65.1, 65.6, 108.6, 110.6, 127.6, 128.0, 128.8, 129.0, 129.5, 137.3, 139.6, 142.7, 153.4, 155.4, 170.3; *m/z* (CI^+) 525 (MH_2^+), 524 (MH^+), 429, 428, 233; $C_{32}H_{33}N_3O_4$ requires 524.2549 (MH^+) found 524.2554.

4.4. General procedure for the transesterification of boron aldol derivatives (12b, 14b, 16b, 17b)

To a solution of the aldol products, in MeOH, was added freshly prepared NaOMe (1.02 equiv., unless stated) and the mixture stirred until all starting material consumed. The reaction was quenched with water (25 mL) and the MeOH removed in vacuo. The residue was extracted with CH_2Cl_2 (3×25 mL) and the combined organic extracts dried (Na_2SO_4), filtered and concentrated. Column chromatography afforded the desired methyl esters.

4.4.1. Preparation of 2(*R*)-di(phenylmethyl)amino-3(*S*)-hydroxy-3-phenylpropionoic acid, methyl ester (18). Prepared according to the general procedure on a 0.27 mmol scale, in MeOH (10 mL), to afford (**18**) as a clear gum (58 mg, 57%) R_f 0.4 (eluent 10% EtOAc/petrol); $[\alpha]_D^{33}$=+102.2 (*c* 1.25, MeOH); ν_{max} 3434, 2951, 2851, 1733, 1642, 1495, 1454 cm^{-1}; δ_H ($CDCl_3$) 3.33 (d, J=10.0 Hz, 1H, H3), 3.37 (d, J=13.0 Hz, 2H, NCH_2), 3.55 (s, 3H, OMe), 4.06 (d, J=13.0 Hz, 2H, CH_2N), 4.13 (br. s, 1H, OH), 4.87 (d, J=10.0 Hz, 1H, H2), 7.05–7.70 (m, 15H, ArH); δ_C ($CDCl_3$) 51.7, 55.2, 68.0, 69.9, 127.7, 128.1, 128.4, 128.6, 128.7, 128.8, 129.1, 129.3, 129.7, 138.3, 140.8, 170.4; *m/z* (FAB^+) 376 (MH^+), 268, 91; $C_{24}H_{25}NO_3$ requires 376.1912 (MH^+) found 376.1910.

4.4.2. Preparation of 2(*R*)-di(phenylmethyl)amino-3(*S*)-hydroxy-3-(2′-fluoro)phenylpropionic acid, methyl ester (19). Prepared according to the general procedure on a 0.39 mmol scale, in MeOH (10 mL), to afford (**19**) as a clear gum (25 mg, 16%) R_f 0.3 (eluent 10% EtOAc/petrol); $[\alpha]_D^{33}$=+76.3 (*c* 1.08, MeOH); ν_{max} 3436, 3030, 2951, 2925, 2851, 1735, 1642, 1494, 1455 cm^{-1}; δ_H ($CDCl_3$) 3.46, (d, J=13.5 Hz, 2H, NCH_2), 3.55 (d, J=9.5 Hz, 1H, H3), 3.59 (s, 3H, OMe), 3.98 (br. s, 1H, OH), 4.06 (d, J=13.0 Hz, 2H, CH_2N), 5.19 (d, J=10.0 Hz, 1H, H2), 6.83–7.31 (m, 14H, ArH); δ_C ($CDCl_3$) 51.8, 55.3, 64.5, 66.3, 115.7, 116.0, 124.5, 124.6, 127.6, 127.7, 128.0, 129.1, 129.4, 129.5, 129.7, 129.8, 129.9, 138.4, 170.6; *m/z* (FAB^+) 394 (MH^+), 334, 268, 91; $C_{24}H_{24}NO_3F$ requires 394.1825 (MH^+) found 394.1818.

4.4.3. Preparation of 2(*R*)-(diphenylmethyl)amino-3(*S*)-hydroxyhexanoic acid, methyl ester (20). Prepared according to the general procedure on a 0.24 mmol scale, in MeOH (10 mL), to afford (**20**) as a clear oil (63 mg, 77%) R_f 0.9 (eluent 30% EtOAc/petrol); $[\alpha]_D^{33}=+87.8$ (*c* 0.9, MeOH); ν_{max} 3434, 2957, 1733, 1495, 1454 cm^{-1}; δ_H ($CDCl_3$) 0.79 (t, *J*=7.0 Hz, 3H, 6Me), 1.04–1.47 (m, 4H, H4, H5), 3.05 (d, *J*=9.5 Hz, 1H, H2), 3.31 (d, *J*=13.5 Hz, 2H, CH_2N), 3.49 (s, 1H, OH), 3.74 (s, 3H, OMe), 3.84 (ddd, *J*=9.5, 2.0 Hz, 1H, H3), 3.95 (d, *J*=−13.5 Hz, 2H, NCH_2), 7.16–7.28 (m, 10H, ArH); δ_C ($CDCl_3$) 14.5, 19.4, 36.4, 51.8, 55.2, 66.2, 67.0, 128.0, 129.0, 129.6, 138.5, 171.2; *m/z* (CI^+) 342 (MH^+), 270, 198, 106; $C_{21}H_{27}NO_3$ requires 342.2069 (MH^+) found 342.2068.

4.4.4. Preparation of 2(*R*)-di(phenylmethyl)amino-3(*S*)-hydroxy-3-furylpropionic acid, methyl ester (21). Prepared according to the general procedure on a 0.17 mmol scale, in MeOH (10 mL), to afford (**21**) as a red oil (27 mg, 46%) R_f 0.7 (eluent 30% EtOAc/petrol); $[\alpha]_D^{33}=+70.9$ (*c* 1.27, MeOH); ν_{max} 3473, 3029, 2923, 2852, 1734, 1603, 1496 cm^{-1}; δ_H ($CDCl_3$) 3.42 (d, *J*=13.5 Hz, 2H, NCH_2), 3.62 (s, 3H, OMe), 3.68 (d, *J*=10.0 Hz, 1H, H3), 3.88 (br. s, 1H, OH), 3.99 (d, *J*=13.5 Hz, 2H, CH_2N), 4.92 (d, *J*=10.0 Hz, 1H, H2), 6.17 (m, 2H, H5, H6), 7.18–7.31 (m, 11H, ArH); δ_C ($CDCl_3$) 52.0, 55.2, 63.8, 64.9, 108.7, 110.6, 126.3, 128.1, 129.1, 129.7, 138.2, 143.0, 153.0, 170.2; *m/z* (FAB^+) 366, 268, 91.

4.5. General procedure for the hydrogenation of di(phenylmethyl)amino esters (22–24)

To a solution of the methyl esters in MeOH (0.5 mL) was added Pearlmann's catalyst ($Pd(OH)_2$ wet, 10% w/w). The mixture was stirred under an atmosphere of H_2 for 3 h then filtered through a pad of celite and washed with MeOH (10 mL). The filtrate was concentrated to afford the amino acid methyl esters **22** and **23**[22] in 100 and 96%, respectively.

4.5.1. Preparation of 2(*R*)-amino-3(*S*)-hydroxy-3-(2″-fluoro)phenylpropanoic acid, methyl ester (23). Prepared according to the general procedure on a 0.04 mmol scale to afford *2(*R*)-amino-3(*S*)-hydroxy-3-(2″-fluoro)phenylpropanoic acid, methyl ester* (**23**) as a clear oil (9 mg, 98%); ν_{max} 3411 (br. s) 2957, 2926, 2854, 1728, 1641 cm^{-1}; δ_H ($CDCl_3$) 2.91 (br. s, 3H, NH_2, OH), 3.58 (d, *J*=4.0 Hz, 1H, H3), 3.66 (s, 3H, OMe), 5.21 (d, *J*=3.5 Hz, 1H, H2), 6.91–7.48 (m, 4H, ArH); δ_C ($CDCl_3$) 56.7, 63.8, 70.4, 126.4, 128.2, 128.4, 130.1, 153.7, 166.9, 204.2; *m/z* (FAB^+) 214 (MH^+), 136, 69; $C_{10}H_{12}NO_3F$ requires 214.0879 (MH^+) found 214.0878.

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