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Chelation-controlled diastereoselective construction of *N*-aryl-, *N*-acyl/tosylhydrazono β-substituted aspartate derivatives via Barbier-type reaction

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ABSTRACT

An entry into the stereoselective synthesis of several *N*-substituted-β-vinyl aspartate and β-alkyl aspartate derivatives having two contiguous stereocenters via the indium-mediated Barbier-type addition of alkyl 4-bromocrotonates or α-halo esters with *N*-aryl (including *N*-PMP) α-imino- and *N*-acyl/tosylhydrazono esters is reported. The formation of β-alkyl aspartate derivatives with exclusively syn stereochemistry in alcohol media revealed the involvement of a chelation-controlled TS. The synthesis of functionalized 1,4-diols, *cis* piperidine-2,3-dicarboxylate derivative and β-ethyl aspartic acid hydrochloride was performed using the *N*-substituted β-vinyl aspartates obtained in this work. The stereochemistry of representative products was unambiguously established from the single crystal X-ray structure analyses.

1. Introduction

The synthesis and biological evaluation of non-proteinogenic amino acids, peptides and peptidomimetics are a renowned area of research in chemical biology and drug discovery.[1,2] In this line, the β-alkyl aspartates[3] and *N*-substituted β-alkyl aspartates[4] are an important class of non-proteinogenic amino acids and they exhibit diverse biological and biochemical actions. Furthermore, the β-alkyl aspartic acid derivatives have significantly attracted the attention of synthetic chemists due to their occurrence as unusual amino acids in microorganisms, constituents of various peptides, useful building blocks of various biologically active natural products and pharmaceutical agents.[3–5] For example, the (2*R*,3*S*)-3-methyl aspartic acid occurs as a component of certain members of the highly toxic microcystin and nodularin families of natural products and cyclic peptides (which are known to be powerful inhibitors of several serine and threonine phosphatases).[5] Further, the pharmacological activity of various β-alkyl aspartate molecules has been recognized by the medicinal chemists for the synthesis of new drug molecules directed towards a wide range of therapeutic areas (Fig. 1).[3–7]

(2*R*,3*S*)-3-methylaspartic acid

L–β–*threo*-benzyl-Asp
(EAATs Blocker)

Fig. 1. Examples of biologically active β-alkyl aspartic acids.

A survey of the literature revealed that the importance of β-substituted aspartates in amino acid/peptide chemistry continues to flourish, which in turn has inspired the development of several new methodologies,[6,7] such as (a) the alkylation of unsubstituted-aspartates, (b) hydrogenation of tetrasubstituted aminoacrylates, (c) cycloaddition chemistry, (d) lactone ring opening and (e) Mannich-type reactions, etc. for the stereoselective synthesis of β-alkyl aspartate derivatives. Notably, a theme based on the direct Barbier-type stereoselective addition of allylic metals

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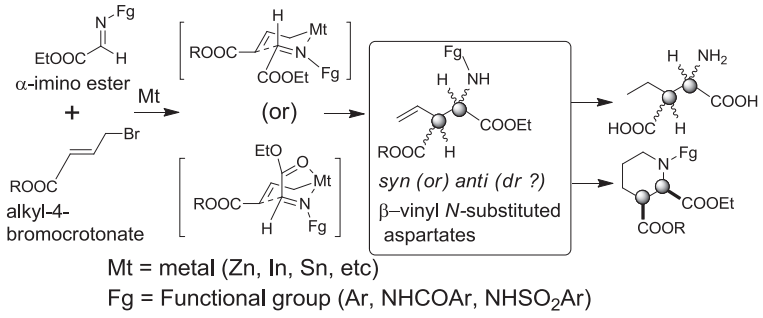
having an ester group at the γ-position with C=N systems, especially, *N*-aryl α-imino- and *N*-acyl/tosylhydrazono esters leading to the β-alkyl aspartates has not been explored[8] (Scheme 1). Markedly, the *N*-aryl α-amino acids are the core structural units in various medicinal agents.[2] Therefore, the development of new synthetic methods leading to the *N*-aryl α-amino acid derivatives will be very useful.

2. Results and discussion

At the outset, we carried out the indium-mediated addition of α-imino ester **1a** with ethyl 4-bromocrotonate (**2a**) under various reaction conditions. A mixture of α-imino ester **1a**, ethyl 4-bromocrotonate (**2a**, *E*-geometry) and indium powder in dry DMF was stirred at 30 °C for 12 h, which furnished the γ-adduct **3a** (70%,



Scheme 1. Theme of this work. Diastereoselective construction of β-alkyl aspartic acid derivatives.

Recent works on the indium-based stereoselective allylation of carbonyls and imine systems (aldimines, ketimines, hydrazones, oximes and sulfonimines) have significantly drawn the attention of organic chemists and have been recognized as the versatile C–C bond forming process.[9–14] This protocol has an advantage of using indium powder and allylic halides directly; thereby circumventing the prior synthesis of allylic metal reagents and the reactions can be carried out in an aqueous or alcoholic media.

The indium-mediated addition of simple as well as γ-substituted allylic reagents to C=N systems furnishing the γ,δ-unsaturated amino acid derivatives is an interesting area of study. Kang and co-workers have shown the addition of γ,γ′-dimethyl allylic indium to *N*-aryl α-imino esters for the synthesis of γ,δ-unsaturated β,β′-dimethyl *N*-aryl α-amino acid derivatives having only one chiral centre. There exists some exceptional reports on the In-mediated stereoselective addition of γ-substituted allylic halides to C=N bond systems, such as oxime ethers,[11] sulfonimines,[12] acylhydrazones[13] and imines derived from alkyl as well as aryl amines,[14] leading to homoallylic amines with two adjoining stereocenters. In this line, recently, we have reported[10] the In-mediated addition of γ-substituted allylic halides (e.g., cinnamyl-, crotyl- and cyclohexenyl bromides) to *N*-aryl α-imino- and α-hydrazono esters and the diastereoselective construction of γ,δ-unsaturated β-substituted *N*-aryl α-amino acid derivatives.

In continuation of our research program on the synthesis of unnatural amino acids[10] with multiple stereocenters, we envisaged the addition of alkyl 4-bromocrotonates or α-halo esters with *N*-aryl α-imino- and *N*-acyl/tosylhydrazono esters and indium metal for the production of several examples of *N*-aryl- and *N*-acyl/tosylhydrazono β-vinyl aspartate derivatives (γ,δ-unsaturated β-substituted *N*-aryl α-amino acid derivatives) having contiguous stereocenters.

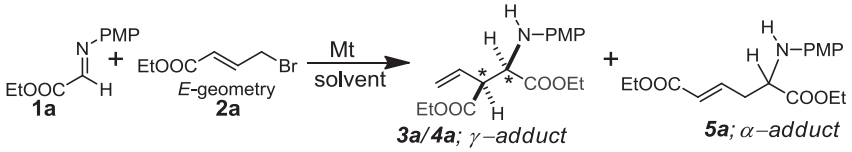
A review of literature revealed that there exists limited and only few exceptional examples on the indium-mediated stereoselective addition of alkyl 4-bromocrotonates to chiral imines of trifluoropyruvate[8e] and glyoxylic acid oxime ether[11c] leading to the corresponding aspartic acid derivatives (γ,δ-unsaturated β-substituted *N*-aryl α-amino acid derivatives). We herein report an easy entry into the diastereoselective synthesis of several examples of *N*-aryl- and *N*-acyl/tosylhydrazono β-vinyl aspartate derivatives having contiguous stereocenters, via the addition of alkyl 4-bromocrotonates or α-halo esters with *N*-aryl α-imino- and *N*-acyl/tosylhydrazono esters mediated by indium metal (Scheme 1).

dr 90:10) and the α-adduct **5a** (25%, Table 1, entry 1) with moderate regioselectivity. A similar trend was observed when the reaction was carried out in dry THF or 1,4-dioxane or toluene (Table 1, entries 2–4). The reaction of α-imino ester **1a**, ethyl 4-bromocrotonate (**2a**) and indium powder in 1,2-DCE or MeOH or DMSO selectively gave the γ-adduct **3a** in 25–63% yields (Table 1, entries 5–7). The reaction in THF-water mixture gave the γ-adduct (syn isomer) **3a** in 46% (dr 98:2, Table 1, entry 8).

Successively, we tried the reaction of **1a** with **2a** in EtOH as the solvent. We observed that the In-mediated addition reactions underwent smoothly in EtOH (Table 1, entries 11–20). The reaction in EtOH at rt (30 °C) gave the γ-adduct **3a** (syn isomer) in 91% yield (Table 1, entry 12) with very high diastereoselectivity and regioselectivity. Further, the reaction of α-imino ester **1a**, ethyl 4-bromocrotonate (**2a**) and indium powder in EtOH at −5 °C or in the presence of NaI as an additive at rt (30 °C) gave the γ-adduct **3a** in 95% yield (dr >95:5, Table 1, entries 14 and 16). Employing other metals, e.g., Sn, Bi and Zn gave the γ-adduct **3a** in 65, 65 and 25% yields (dr >95:5), respectively (Table 1, entries 21–23).

The scope and generality of the direct Barbier-type addition of alkyl 4-bromocrotonates with various *N*-aryl (including *N*-PMP) α-imino- and *N*-acyl/tosylhydrazono esters using indium metal is shown in Table 2 and Scheme 2. The indium-employed addition of ethyl 4-bromocrotonate with α-imino esters synthesized from electron-withdrawing- and donating-group containing anilines in ethanol afforded the respective β-vinyl aspartate derivatives **3b–k** (γ-adducts) having two contiguous stereocenters (syn isomers, dr >95:5, Table 2, entries 1–10). The treatment of methyl 4-bromocrotonate with α-imino esters **1h** and **1e** gave the carboxyl group differentiated (orthogonally protected) β-vinyl aspartate derivatives **3l** and **3m** (syn isomers, dr >95:2, entries 11 and 12, Table 2). Consequently, the addition of the ethyl 4-bromocrotonate with *N*-acylhydrazono esters **1l** and **1m** using indium metal powder in EtOH furnished the functionalized β-vinyl aspartate derivatives **3n** (81%, dr 90:10) and **3o** (50%, dr 70:30, Scheme 2). Treatment of *N*-biphenyl α-imino ester with ethyl- and methyl 4-bromocrotonates (**2a**,**b**) gave the corresponding *N*-biphenyl β-vinyl aspartates **3p** and **3q** in very high yields (dr >95:5, Scheme 2). Next, the addition of ethyl 4-bromocrotonate to hydrazono ester **1o** prepared from ethyl pyruvate gave the adduct **3r** in 46% yield (Scheme 2). In this case, a moderate diastereoselectivity was observed, perhaps due to the involvement of less rigid cyclic TS. Further, the treatment of the α-imino ester **1p** derived from 2-hydroxyaniline afforded the aspartic acid derivative **3s** in 59%

Table 1
Optimization of the reaction conditions for the diastereoselective addition of **2a** with α-imino ester **1a**[a]



Entry	Mt	Solvent (mL)	*T* (°C)	*t* (h)	**3a**/**4a** Yield (%) (dr=*syn*/*anti*)	**5a** Yield (%)
1	In	DMF (1)	30	12	70 (90:10)	25
2	In	THF (1)	30	12	40 (70:30)	25
3	In	Dioxane (1)	30	24	30 (82:18)	13
4	In	Toluene (1)	30	24	31 (81:19)	25
5	In	DCE (1)	30	24	25 (76:24)	ND
6	In	MeOH (1)	30	12	60 (69:31)	ND
7	In	DMSO (0.5)	30	12	63 (85:15)	ND
8	In	THF (1)/H_2O (1)	30	12	46 (98:02)	ND
9	In	EtOH (1)/H_2O (1)	30	12	53 (98:02)	ND
10	In	DMF (1)/H_2O (1)	30	12	60 (98:02)	ND
11	In	EtOH (1)	30	03	66 (>95:05)	ND
12	In	EtOH (1)	30	06	91 (>95:05)	ND
13	In	EtOH (1)	30	24	90 (>95:05)	ND
14	In	EtOH (1)	−5	06	95 (>95:05)	ND
15	In	EtOH (1)	80	06	51 (>93:05)	ND
16	In	EtOH (1)	30	06	95 (>95:05)[b]	ND
17	In	EtOH (1)	30	06	92 (>95:05)[c]	ND
18	In	EtOH (1)	30	06	77 (94:06)[d]	ND
19	In	EtOH (1)	30	06	91 (>95:05)[e]	ND
20	In	EtOH (1)	30	06	84 (>95:05)[f]	ND
21	Sn	EtOH (1)	30	06	65 (>95:05)	23
22	Zn	EtOH (1)	30	06	25 (>95:05)	ND
23	Bi	EtOH (1)	30	06	65 (>95:05)	ND

[a] All the reactions were done using **1a** (0.25 mmol), **2a** (0.75 mmol) and indium powder (0.5 mmol). Isolated yields are given.
[b] 20 mol % of NaI was added as an additive.
[c] 20 mol % of KI was added as an additive.
[d] 20 mol % of I_2 was added as an additive.
[e] 20 mol % of MeCOOH was added as an additive.
[f] The reaction was carried out using **1a** (0.5 mmol), **2a** (1.0 mmol) and indium powder (0.75 mmol). ND=Not detected.

yield. In this case also a moderate diastereoselectivity (dr 76:24) was observed, probably due to the presence of hydroxyl group in the aromatic ring affecting the chelation-assisted TS. Interestingly, the In-mediated addition of **2a** or **2b** with the α-imino ester **1q** derived from 4-acetylaniline afforded the corresponding products **3t** and **3u** (syn isomers) with very high diastereoselectivity (dr 95:5) and chemoselectivity. In these reactions, the acetyl group was not affected and the addition took place selectively at C=N bond of the α-imino ester **1q**, which afforded the corresponding products **3t** and **3u** (Scheme 2).

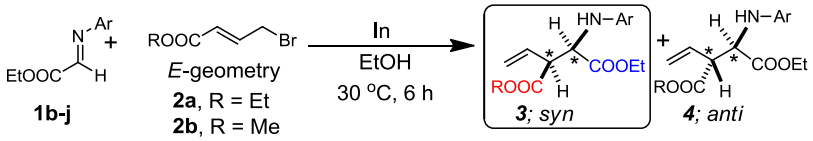
Next, we carried out the three component Barbier-type reactions of ethyl glyoxalate (**6**), amines 7 and ethyl 4-bromo crotonate (**2a**) using indium metal (Table 3). The one-pot In-mediated direct three component reactions of ethyl glyoxalate, various aryl amines or *p*-toluenesulfonyl hydrazine and ethyl 4-bromo crotonate in EtOH exclusively afforded the respective β-alkyl aspartate derivatives **3a**, **3d**, **3h** and **3v** (γ-adducts, Table 3, entries 1–4) with very high regioselectivity and diastereoselectivity (dr >95:5, syn isomers).

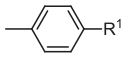
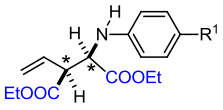
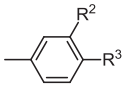
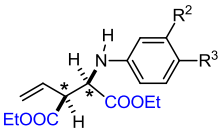
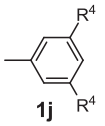
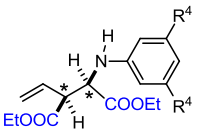
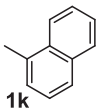
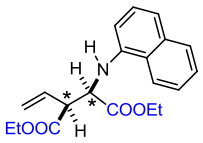
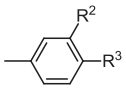
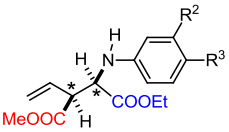
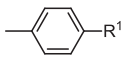
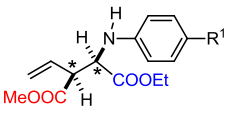
The stereochemistry of representative products **3p**, **3q** and **3v** (syn stereochemistry) was unambiguously established from the single crystal X-ray structure analyses. The stereochemistry of other adducts listed in Tables 1–3 and Scheme 2 was assigned based on the X-ray structure analyses of the compounds **3p**, **3q** and **3v** (Fig. 2).[15d] The exclusive formation of the syn products **3a**–**v** in the In-mediated reaction of the α-imino esters **1** with **2a**,**b** could be explained via a chelation-controlled TS[9u,10,15e,f] in alcoholic media (Scheme 3).[9v] It is well-known that the allylic indium reagents are tolerant to aqueous and alcoholic media[9,10] and in all the reactions listed in Tables 1–3 and Scheme 2, the alcoholic media contributes for the rapid quenching of the transient indium amide, which is formed after the addition of allylic indium reagent. Further, the observed very high stereoselectivity (>95:5) in these reactions, revealed that the allylation process was kinetically controlled.

Next, the indium-mediated Reformatsky-type addition of α-halo esters with *N*-aryl α-imino ester using indium metal was explored (Table 4). The aspartate derivative **9a** was obtained in 65% yield in the reaction of α-halo ester **2c** with the *N*-PMP α-imino ester **1a** in DMF in the presence of indium metal (Table 4, entry 1). Employing other metals, such as Zn, Sn and Bi gave the product **9a** in 41, 38 and <5% yields, respectively (Table 4, entries 2–4). The product **9b** was obtained in 40% by using the α-halo ester **2d** (Table 4, entry 5).

In this line, the In-mediated addition of **2c** with other α-imino esters gave the aspartic acid derivatives **9c**–**e** in good yields (Table 4, entries 6–8). Furthermore, the treatment of the substituted α-halo ester **2e** with the α-imino ester **1a** in THF/DMF gave the β,β-dimethyl aspartate derivative **10a** (Table 5, entries 1 and 2). The indium-mediated reaction of the α-halo esters **2f** and **2g** with **1a** furnished the β,β-difluoro- and β-fluoro aspartates **10b** and **10c**,[15a] respectively (Table 5, entries 3 and 4). The reaction of ethyl 2-bromobutyrate (**2h**) with the *N*-PMP α-imino ester **1a** gave the product **10d**[15b] in 62% yield (dr 65:35, Table 5, entry 5). Similarly, the reaction of ethyl 2-bromooctanoate (**2i**) or ethyl 2-bromopentanoate (**2j**) with the *N*-PMP α-imino ester **1a** gave the corresponding products **10e**[15c] (35%, dr 80:20) and **10f** (50%, dr 60:40) in low yields (Table 5, entries 6 and 7). In some of these cases, relatively low diastereoselectivity was observed. This is perhaps due to the involvement of a less rigid cyclic TS. However, the addition of α-bromo γ-butyrolactone (**2k**) with **1a** in the presence of indium metal furnished the functionalized β-substituted aspartates **10g** (67%, dr 73:27) and **10h** (72%, dr 82:18, Scheme 4 and Fig. 3) with relatively good diastereoselectivity.

Table 2
Diastereoselective addition of **2** with α-imino ester **1** and synthesis of *N*-aryl β-vinyl aspartic acid esters



Entry	–Fg	2	Product	Yield[a] (%) (dr=*syn*/*anti*)
1		**2a**		**3b**; R^1=H, 83 (>95:05)
2		**2a**		**3c**; R^1=Me, 84 (>95:05)
3		**2a**		**3d**; R^1=Cl, 94 (>95:05)
4		**2a**		**3e**; R^1=Br, 87 (>95:05)
5	**1b-f**	**2a**		**3f**; R^1=COOEt, 90 (>95:05)
6		**2a**		**3g**; R^2=Me, R^3=Me, 70 (>95:05)
7		**2a**		**3h**; R^2=Cl, R^3=Cl, 96 (>95:05)
8	**1g-i**	**2a**		**3i**; R^2=Me, R^3=Br, 69 (>95:05)
9	 **1j**	**2a**		**3j** R^4=Cl, 48 (>95:05)
10	 **1k**	**2a**		**3k**; 58 (>95:05)
11	 **1h**	**2b**		**3l**; R^2=Cl, R^3=Cl, 72 (>95:05)
12	 **1e**	**2b**		**3m**; R^1=Br, 72 (>95:05)

[a] All the reactions were carried out using **1** (0.5 mmol), **2** (1.5 mmol) and indium powder (1.0 mmol). Isolated yields are given.

Successively, we focused our attention to show the usefulness of this synthetic methodology. In this line, initially we carried out the catalytic hydrogenation of the compound **3a** (syn isomer), which gave the *N*-PMP β-ethyl aspartate derivative **10d′** (syn isomer, Scheme 5). Additionally, the hydrogenation of the compounds **3h** and **3l** afforded the *N*-aryl β-ethyl aspartate derivatives **11a** and **11b** (syn isomers, Scheme 5). The reduction of the ester group of the representative compounds **3a**, **3d**, **3h** and **3f** furnished the corresponding functionalized 1,4-diols **12a**–**d** bearing two contiguous stereocenters (Scheme 5).

Finally, we extended the utility of this synthetic protocol for constructing the *cis* piperidine-2,3-dicarboxylate (pipecolic acid) derivative bearing two contiguous stereocenters (Scheme 6). N-Allylation of the compound **3a**, followed by the RCM reaction[16] of the compound **13** and hydrogenation of the compound **14** gave the *cis* piperidine-2,3-dicarboxylate derivative **15**[17] (Scheme 6). Later, we carried out the removal of the PMP protecting group followed by hydrolysis that gave an unnatural amino acid, β-ethyl aspartic acid hydrochloride **16** (Scheme 6).

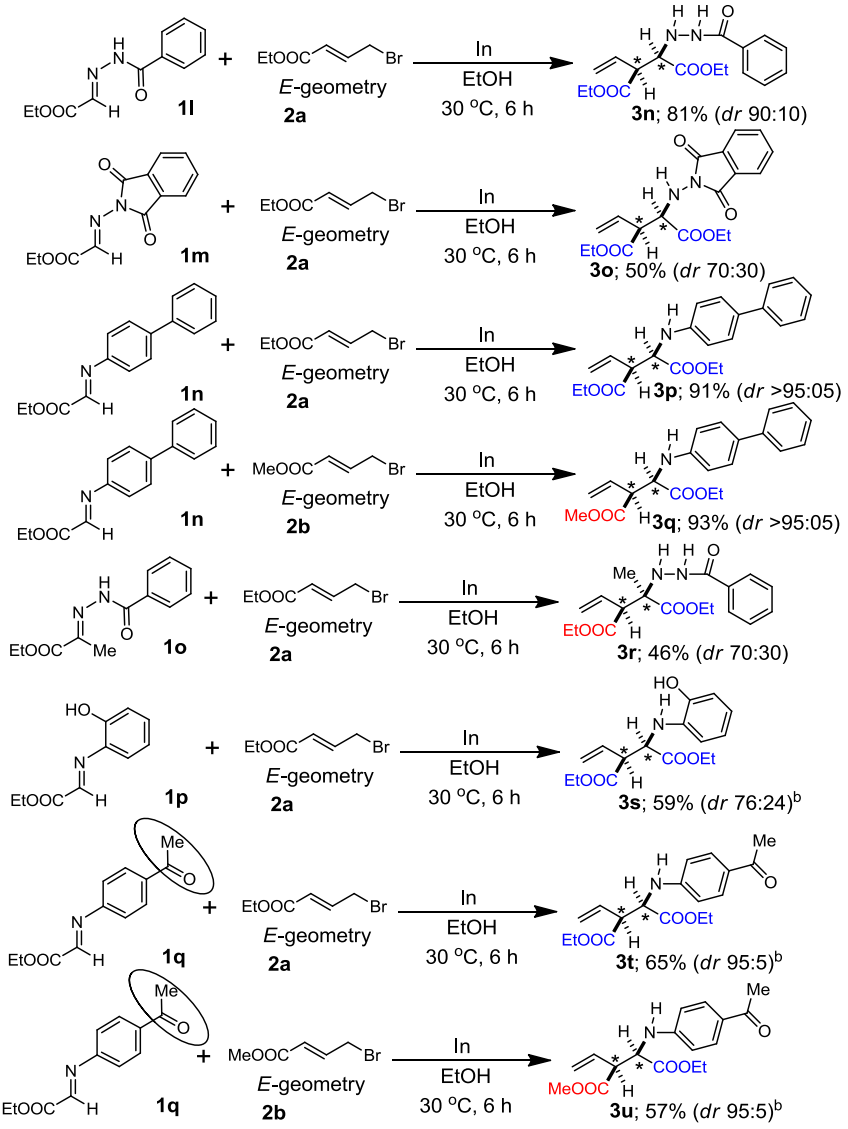
3. Summary

In summary, we have reported an entry into the chelation-controlled stereoselective synthesis of several examples of *N*-aryl-, *N*-acyl/*N*-tosylhydrazono-β-vinyl aspartate and β-alkyl aspartate derivatives. We have shown synthesis of functionalized 1,4-diols, *cis* piperidine-2,3-dicarboxylate derivative and β-ethyl aspartic acid hydrochloride by using the *N*-substituted β-vinyl aspartates obtained in this method. Further studies are in progress to explore the potential applications of the *N*-substituted β-vinyl aspartates obtained in this work.

4. Experimental section

4.1. General

Melting points are uncorrected. IR spectra were recorded as thin films or KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on 400 MHz and 100 MHz spectrometers, respectively, with TMS as an internal or external standard. Column chromatography was carried out on silica gel (100–200 mesh). Reactions were carried out in dry solvent under nitrogen atmosphere wherever required. Solutions were dried using anhydrous sodium sulfate. Reagents were added to the reaction flask with the help of a syringe. Thin layer chromatography (TLC) was performed on silica plates or neutral Al_2O_3 and components were visualized by observation under iodine. Isolated yields of all the products were reported (yields were not optimized) and total yield of both the diastereomers is reported. Ratios of



[a] All the reactions were done using **1** (0.5 mmol), **2** (1.5 mmol) and indium powder (1.0 mmol). Isolated yields are given. [b] The reaction was performed using **1** (0.25 mmol), **2** (0.75 mmol) and indium powder (0.5 mmol).

Scheme 2. Diastereoselective addition of **2** with α-imino ester **1** and the synthesis of β-vinyl aspartic acid esters **3n**–**u**.

diastereomers were determined from the ^{1}H and ^{13}C NMR spectra of crude reaction mixtures or after isolation. In all the reactions, only the major diastereomer was isolated in pure form (in some exceptional cases, the product was isolated as mixture of diastereomers). The stereochemistry of major isomers was assigned based on the X-ray structure analysis of representative compounds. In all the reactions during the column chromatography, we focused to isolate the required aspartic acid derivatives in pure form and other minor impurities/by-products could not be isolated in pure form.

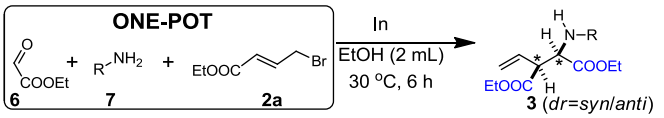
4.2. Procedure A: In-mediated addition of 4-bromocrotonate (2a or 2b) to α-imino esters 1

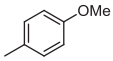
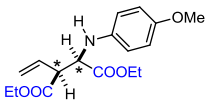
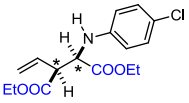
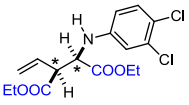
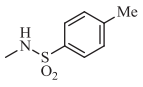
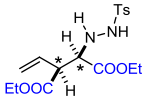
To a vigorously stirring solution of α-imino ester **1** (0.5 mmol, 1 equiv) and *E*-ethyl-4-bromocrotonate or methyl-4-bromo crotonate (**2**, 1.5 mmol, 3 equiv) in EtOH (2 mL) was added indium powder (1 mmol, 2 equiv). The mixture was allowed to stir vigorously for 6 h at 30 °C. After this period, the reaction mixture was quenched with 2 mL of water and transferred to a separating funnel and extracted using ethyl acetate (3×15 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Then the solvent was evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on silica gel (EtOAc/Hexane as eluent) gave the product **3** (see Tables 1 and 2 and Scheme 2 for individual entries).

4.3. Procedure B: one-pot synthesis of *N*-aryl α-amino esters (3a, 3d, 3h, 3v)

Ethyl glyoxylate **6** (0.5 mmol, 1 equiv) and the respective amines **7** (0.5 mmol, 1 equiv) were dissolved in EtOH (2 mL) and stirred for 30 min at rt. To the resulting solution, *E*-ethyl-4-bromocrotonate (**2a**, 1.5 mmol, 3 equiv) and indium powder (1 mmol, 2 equiv) was added successively while stirring the reaction mixture

Table 3
One-pot diastereoselective and regioselective synthesis of *N*-aryl β-vinyl aspartic acid derivatives[a]



Entry	R	Product	Yield[a] (%) (*syn*/*anti*)
1			**3a**; 80 (dr >95:05)
2			**3d** 95 (dr >95:05)
3			**3h**; 74 (dr >95:05)
4			**3v**; 54 (dr >95:05)

[a] All the reactions were done using **6** (0.5 mmol), **7** (0.5 mmol), **2a** (1 mmol) and In (0.75 mmol) and isolated yields are given.

vigorously. The stirring was continued for 6 h at 30 °C. After this period, the reaction mixture was quenched with 2 mL of water and transferred to a separating funnel and extracted using ethyl acetate (3×15 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was then evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on silica gel (EtOAc/Hexane as eluent) gave the corresponding products **3a**, **3d**, **3h**, **3v** (see Table 3 for individual entries).

4.4. Procedure C: In-mediated addition of α-halo esters (2c–k) to α-imino esters 1

To a vigorously stirring solution of α-imino ester **1** (0.5 mmol, 1 equiv) and α-halo ester (**2c**–**k**, 1.5 mmol, 3 equiv) in THF/DMF (1 mL) was added indium powder (1 mmol, 2 equiv). The mixture was allowed to stir vigorously at 30 °C for given time. After this period, the reaction mixture was quenched with 2 mL of water and transferred to a separating funnel and extracted using ethyl acetate (3×15 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Then the solvent was evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on silica gel (EtOAc/Hexane as eluent) gave the product **10** (see Tables 4 and 5 and Scheme 4 for individual entries).

4.5. Procedure D: hydrogenation of *N*-aryl α-amino esters 3a, 3h and 3l

A dry flask containing *N*-aryl α-amino ester **3** (0.5 mmol, 1 equiv) in dry THF (4 mL) was charged with Pd–C (10 mol %) and the contents are allowed to stir under H_2 (1 atm) at rt. After disappearance of starting material (check by TLC) reaction mixture was filtered through Celite pad and the Celite pad was washed with EtOAc (20 mL). The solvent was removed by rotary evaporation and product was purified by column chromatography on silica gel (EtOAc/Hexane as eluent) to afford the corresponding product **10d′**/**11a**/**11b** (Scheme 5).

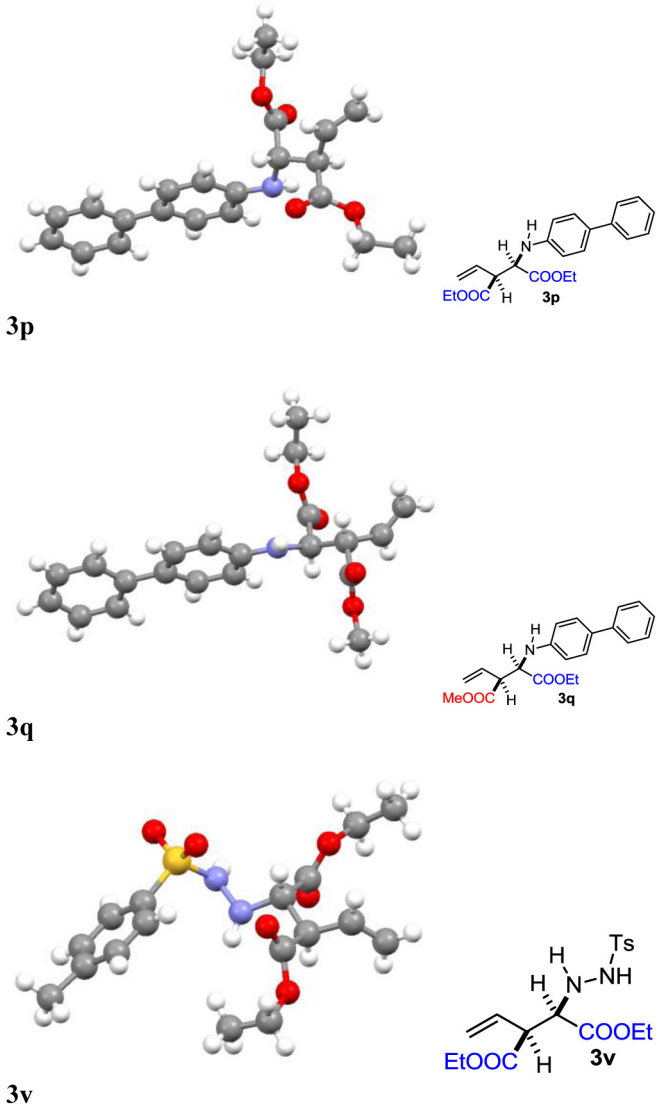
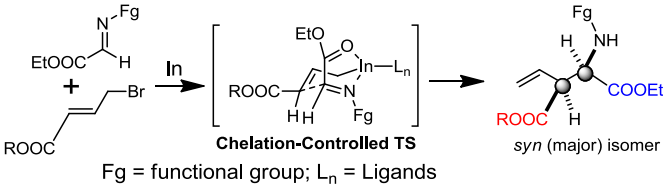


Fig. 2. X-ray structures of **3p**, **3q** and **3v**.

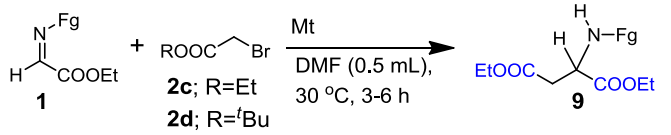


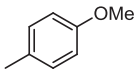
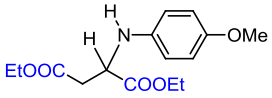
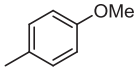
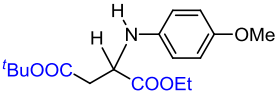
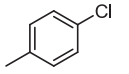
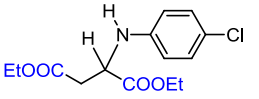
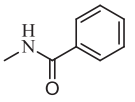
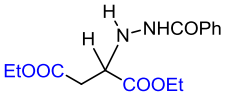
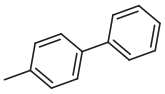
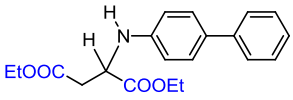
Scheme 3. Plausible mechanism for the formation of syn isomer via chelation-controlled TS.

4.6. Procedure E: reduction of *N*-aryl α-amino esters 3a, 3d, 3h and 3f to *N*-aryl β-amino alcohols 12a–d

A dry flask was charged with dry THF (4 mL) and the respective *N*-aryl α-amino ester **3** (0.5 mmol) under nitrogen atmosphere at 0 °C. To this solution was added $LiAlH_4$ (2 mmol) in portions and allowed to stir overnight at rt EtOH (few drops) and 5% aq NaOH solution (1–2 mL) were then added sequentially. The resulting white suspension was filtered through Celite pad and rinsed with THF (20 mL). Filtrate was dried over anhydrous Na_2SO_4 and the solvent was removed by rotary evaporation and product was purified by column chromatography on silica gel (EtOAc/Hexane as eluent) to afford the respective *N*-aryl β-amino alcohols **12** (Scheme 5).

Table 4
Indium-mediated addition of α-halo esters with α-imino esters and synthesis of aspartic acid esters[a]



Entry	–Fg	Mt	Product	Yield[a] (%)
1		In		**9a**; 65
2		Zn		**9a**; 41
3		Bi		**9a**; <5
4		Sn		**9a**; 38
5		In		**9b**; 40[b]
6		In		**9c**; 69
7		In		**9d**; 60[c]
8		In		**9e**; 67[c]

[a] All the reactions were done using **1** (0.25 mmol), **2** (0.75 mmol) and indium powder (0.5 mmol). Isolated yields are given.
[b] The reaction was carried out at 80 °C.
[c] The reaction was carried out at 0 °C for an initial 1 h then at 30 °C for 10 h.

4.7. Procedure F: N-allylation of *N*-aryl α-amino ester 3a

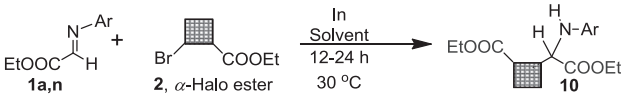
To the *N*-aryl α-amino ester **3a** (1 mmol, 1 equiv) in MeCN (5 mL) was added allyl bromide (6 equiv), NaI (0.1 equiv) and activated K_2CO_3 (3 equiv). The resulting reaction mixture was refluxed for 24 h. After completion of the reaction as indicated by the TLC, the reaction mixture was cooled to rt; water (5–6 mL) was added and the resulting reaction was transferred to a separating flask and extracted using ethyl acetate (3×15 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Then the solvent was evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on silica gel (EtOAc/Hexane as eluent) gave the products **13** (see Scheme 6).

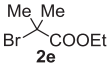
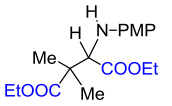
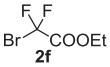
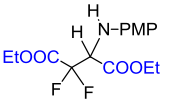
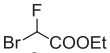
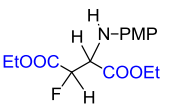
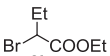
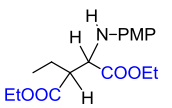
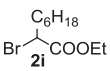
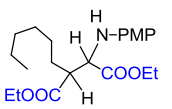
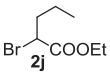
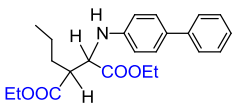
4.8. Procedure G: synthesis of 14 by RCM of the compound 13

To the respective compound **13** (0.5 mmol, 1 equiv) in dry DCM (2 mL) was added Grubbs II generation catalyst (0.05–0.1 equiv), the resulting reaction mixture was stirred overnight at rt. After completion of the reaction as indicated by the TLC, the reaction mixture was subjected to rotary evaporation. Purification of the resulting crude reaction mixture by column chromatography on silica gel (EtOAc/Hexane as eluent) gave the products **14** (see Scheme 6).

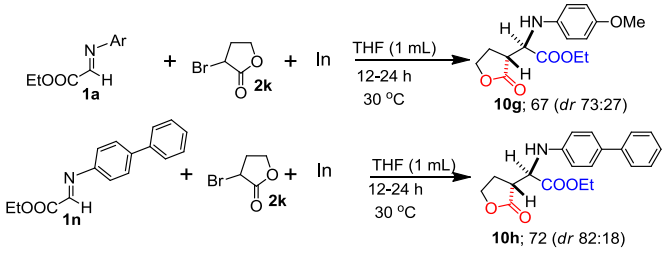
4.8.1. (2R,3S*)-Diethyl 2-((4-methoxyphenyl)amino)-3-vinylsuccinate (**3a**).* Following the general procedure A described above, **3a** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=10:90) as colourless liquid (146 mg, 91%): R_f

Table 5
Indium-mediated addition of α-halo esters with α-imino esters and synthesis of β-substituted aspartic acid esters



Entry	1	Solvent	α-Halo ester	Product	Yield[a] (%) (dr)
1	**1a**	DMF (0.5 mL)	 **2e**		**10a**; 78
2	**1a**	THF (1 mL)			**10a**; 85
3	**1a**	THF (1 mL)	 **2f**		**10b**; 40[b]
4	**1a**	THF (1 mL)	 **2g**		**10c**; 59 (60:40)[b]
5	**1a**	THF (1 mL)	 **2h**		**10d**; 62 (65:35)
6	**1a**	THF (1 mL)	 **2i**		**10e**; 35 (80:20)[c]
7	**1a**	THF (1 mL)	 **2j**		**10f**; 50 (60:40)

[a] The reactions were done using **1a** (0.5 mmol), **2** (1.5 mmol) and In (1 mmol). Isolated yields are given.
[b] The reaction was done at 75 °C.
[c] Indium was first allowed to react with **2i** for 2 h, then the organoindium was added to **1a** slowly.



Scheme 4. In-mediated addition of α-bromo γ-butyrolactone (**2k**) with **1a** and synthesis of β-substituted aspartic acid esters. The reactions were done using **1** (0.5 mmol), **2** (1.5 mmol) and In (1 mmol).

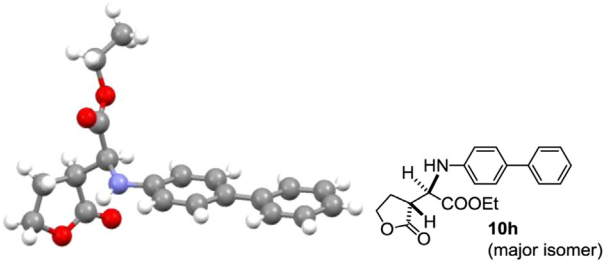
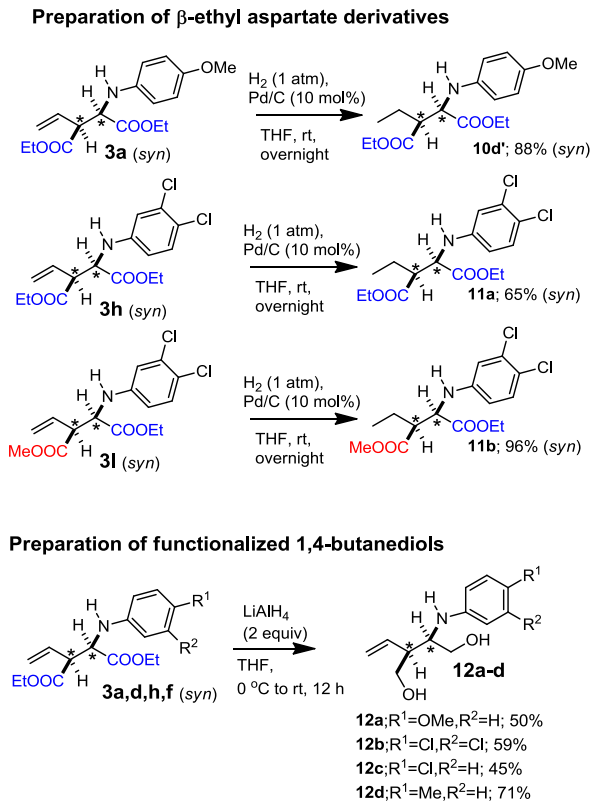


Fig. 3. X-ray structure of **10h** (major isomer).

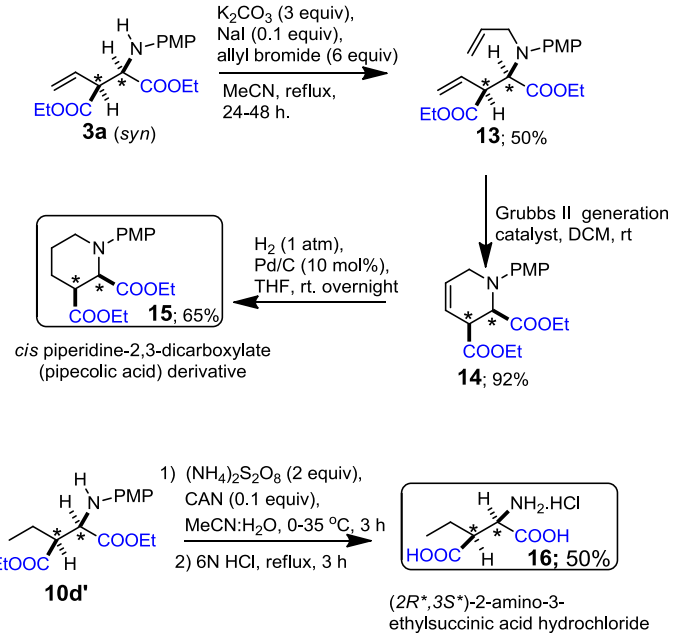


Scheme 5. Scope and functional group transformations. Synthesis of β-ethyl aspartate derivatives and 1,4-diols.

131.4, 120.6, 115.9, 114.8, 61.3, 61.2, 60.0, 55.7, 53.1, 14.2, 14.2; HRMS: (ESI) *m/z* found 344.1471 for $C_{17}H_{23}NO_5Na$ (MNa^+), requires 344.1474.

*4.8.2. (E)-Diethyl 5-((4-methoxyphenyl)amino)hex-2-enedioate (**5a**).* Following the general procedure A described above, **5a** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=11:89) as colourless liquid (40 mg, 25%): R_f (20% EtOAc/Hexane) 0.60; IR (thin film): ν_{max} 3364, 2985, 1730, 1518 and 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 6.96–6.88 (m, 1H, CH=C*H*), 6.77 (d, *J*=8.9 Hz, 2H, Ar*H*), 6.61 (d, *J*=8.9 Hz, 2H, Ar*H*), 5.91 (d, *J*=15.6 Hz, 1H, CH=C*H*), 4.22–4.13 (m, 6H, N*H*, NHC*H*, OCH_2), 3.74 (s, 3H, OCH_3), 2.72–2.66 (m, 2H, CH_2), 1.30–1.22 (m, 6H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 173.0, 165.9, 153.0, 142.9, 140.2, 124.6, 115.4, 114.9, 61.4, 60.4, 56.8, 55.7, 35.5, 14.2, 14.1. MS (CI): *m/z* 322 (100%, MH^+).

4.8.3. (2R,3S*)-Diethyl 2-(phenylamino)-3-vinylsuccinate (**3b**).* Following the general procedure A described above, **3b** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=09:91) as colourless liquid (120 mg, 83%): R_f (20% EtOAc/Hexane) 0.65; IR (thin film): ν_{max} 3386, 2983, 1732, 1604 and 1029 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.18 (dd, J_1=8.6 Hz, J_2=7.4 Hz, 2H, Ar*H*), 6.76 (t, *J*=7.4 Hz, 1H, Ar*H*), 6.69 (d, *J*=8.6 Hz, 2H, Ar*H*), 5.94–5.85 (m, 1H, C*H*), 5.28–5.18 (m, 2H, CH_2), 4.52 (t, *J*=6.4 Hz, 1H, NHC*H*), 4.41 (d, *J*=7.8 Hz, 1H, N*H*), 4.23–4.12 (m, 4H, OCH_2), 3.52 (dd, J_1=9.3 Hz, J_2=6.4 Hz, 1H, C*H*), 1.27 (t, *J*=7.1 Hz, 3H, CH_2CH_3), 1.23 (t, *J*=7.2 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 171.3, 171.1, 146.1, 131.2, 129.4, 120.7, 118.9, 114.1, 61.4, 61.3, 58.6, 52.8, 14.2, 14.2; HRMS: (ESI) *m/z* found 292.1539 for $C_{16}H_{22}NO_4$ (MH^+), requires 292.1549.



Scheme 6. Diastereoselective synthesis of *cis* piperidine-2,3-dicarboxylate derivative and β-ethyl aspartic acid hydrochloride.

(20% EtOAc/Hexane) 0.63; IR (thin film): ν_{max} 3365, 2984, 1731, 1515 and 1035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 6.78 (d, *J*=9.0 Hz, 2H, Ar*H*), 6.68 (d, *J*=9.0 Hz, 2H, Ar*H*), 5.96–5.86 (m, 1H, C*H*), 5.29–5.20 (m, 2H, CH_2), 4.42 (d, *J*=6.8 Hz, 1H, NHC*H*), 4.23–4.13 (m, 4H, OCH_2), 3.75 (s, 3H, OCH_3), 3.49 (dd, J_1=9.3 Hz, J_2=6.8 Hz, 1H, C*H*), 1.29 (t, *J*=7.2 Hz, 3H, CH_2CH_3), 1.24 (t, *J*=7.1 Hz, 3H, CH_2CH_3), 1.30–1.24 (m, 1H, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 171.7, 171.2, 153.1, 140.2,

4.8.4. (2R,3S*)-Diethyl 2-((4-methylphenyl)amino)-3-vinylsuccinate (**3c**).* Following the general procedure A described above, **3c** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=10:90) as colourless liquid (128 mg, 84%): R_f (20% EtOAc/Hexane) 0.65; IR (thin film): ν_{max} 3376, 2984, 1731, 1519 and 1031 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.02 (d, *J*=8.4 Hz, 2H, Ar*H*), 6.64 (d, *J*=8.4 Hz, 2H, Ar*H*), 5.96–5.87 (m, 1H, C*H*), 5.30–5.20

(m, 2H, CH_2), 4.51 (br s, 1H, NH), 4.29 (br s, 1H, NHCH), 4.24–4.14 (m, 4H, OCH_2), 3.52 (dd, J_1=9.3 Hz, J_2=6.8 Hz, 1H, CH), 2.26 (s, 3H, ArCH_3), 1.29 (t, J=7.2 Hz, 3H, CH_2CH_3), 1.25 (t, J=7.1 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 171.5, 171.2, 143.8, 131.3, 129.9, 128.2, 120.6, 114.4, 61.3, 61.2, 59.1, 53.0, 20.4, 14.2, 14.2; HRMS: (ESI) m/z found 306.1698 for $C_{17}H_{24}NO_4$ (MH^+), requires 306.1705.

4.8.5. (2R,3S*)-Diethyl 2-((4-chlorophenyl)amino)-3-vinylsuccinate (**3d**).* Following the general procedure A described above, **3d** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=10:90) as colourless liquid (153 mg, 94%): R_f (20% EtOAc/Hexane) 0.64; IR (thin film): ν_{max} 3378, 2983, 1731, 1502 and 1030 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.26 (d, J=8.5 Hz, 2H, ArH), 6.56 (d, J=8.5 Hz, 2H, ArH), 5.91–5.82 (m, 1H, CH), 5.28–5.18 (m, 2H, CH_2), 4.45 (br s, 2H, NH, NHCH), 4.22–4.12 (m, 4H, OCH_2), 3.49 (dd, J_1=9.1 Hz, J_2=5.0 Hz, 1H, CH), 1.28–1.21 (m, 6H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 171.0, 145.2, 132.1, 131.0, 120.9, 115.6, 110.6, 61.6, 61.4, 58.6, 52.6, 14.2, 14.2; HRMS: (ESI) m/z found 326.1151 for $C_{16}H_{21}ClNO_4$ (MH^+), requires 326.1159.

4.8.6. (2R,3S*)-Diethyl 2-((4-bromophenyl)amino)-3-vinylsuccinate (**3e**).* Following the general procedure A described above, **3e** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=9:91) as colourless liquid (161 mg, 87%): R_f (20% EtOAc/Hexane) 0.65; IR (thin film): ν_{max} 3374, 2983, 1732, 1477 and 1027 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.26 (d, J=8.9 Hz, 2H, ArH), 6.57 (d, J=8.9 Hz, 2H, ArH), 5.92–5.83 (m, 1H, CH), 5.28–5.18 (m, 2H, CH_2), 4.46 (br s, 2H, NH, NHCH), 4.22–4.13 (m, 4H, OCH_2), 3.50 (dd, J_1=9.2 Hz, J_2=5.5 Hz, 1H, CH), 1.28–1.21 (m, 6H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 171.0, 145.2, 132.1, 131.0, 120.9, 115.6, 110.6, 61.6, 61.4, 58.5, 52.6, 14.2, 14.2; HRMS: (ESI) m/z found 370.0658 for $C_{16}H_{21}BrNO_4$ (MH^+), requires 370.0654.

4.8.7. (2R,3S*)-Diethyl 2-((4-(ethoxycarbonyl)phenyl)amino)-3-vinylsuccinate (**3f**).* Following the general procedure A described above, **3f** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=11:89) as colourless liquid (163 mg, 90%): R_f (20% EtOAc/Hexane) 0.63; IR (thin film): ν_{max} 3371, 2983, 1731, 1526 and 1031 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.90 (d, J=8.9 Hz, 2H, ArH), 6.67 (d, J=8.9 Hz, 2H, ArH), 5.92–5.83 (m, 1H, CH), 5.32–5.19 (m, 2H, CH_2), 4.93 (d, J=9.5 Hz, 1H, NH), 4.59 (dd, J_1=9.5 Hz, J_2=5.9 Hz, 1H, NHCH), 4.32 (q, J=7.1 Hz, 2H, OCH_2), 4.25–4.15 (m, 4H, OCH_2), 3.56 (dd, J_1=9.5 Hz, J_2=5.9 Hz, 1H, CH), 1.36 (t, J=7.1 Hz, 3H, CH_2CH_3), 1.31–1.23 (m, 6H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 171.0, 170.6, 166.6, 149.9, 131.5, 130.8, 121.0, 120.3, 112.6, 61.7, 61.4, 60.3, 57.7, 52.3, 14.4, 14.2, 14.1; HRMS: (ESI) m/z found 364.1756 for $C_{19}H_{26}NO_6$ (MH^+), requires 364.1760.

4.8.8. (2R,3S*)-Diethyl 2-((3,4-dimethylphenyl)amino)-3-vinylsuccinate (**3g**).* Following the general procedure A described above, **3g** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=10:90) as colourless liquid (112 mg, 70%): R_f (20% EtOAc/Hexane) 0.65; IR (thin film): ν_{max} 3375, 2982, 1732, 1512 and 1030 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.94 (d, J=8.1 Hz, 1H, ArH), 6.53 (d, J=2.5 Hz, 1H, ArH), 6.47 (dd, J_1=8.1 Hz, J_2=2.5 Hz, 1H, ArH), 5.95–5.86 (m, 1H, CH), 5.28–5.23 (m, 2H, CH_2), 4.49 (dd, J_1=10.0 Hz, J_2=6.6 Hz, 1H, NHCH), 4.24–4.13 (m, 5H, NH, OCH_2), 3.50 (dd, J_1=10.0 Hz, J_2=6.6 Hz, 1H, CHCH), 2.20 (s, 3H, ArCH_3), 2.10 (s, 3H, ArCH_3), 1.28 (t, J=7.2 Hz, 3H, CH_2CH_3), 1.24 (t, J=7.2 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 171.6, 171.2, 144.2, 137.4, 131.4, 130.4, 127.0, 120.5, 116.1, 111.5, 61.3, 61.2, 59.1, 53.1, 20.0, 18.8, 14.2, 14.2; HRMS: (ESI) m/z found 320.1870 for $C_{18}H_{26}NO_4$ (MH^+), requires 320.1862.

4.8.9. (2R,3S*)-Diethyl 2-((3,4-dichlorophenyl)amino)-3-vinylsuccinate (**3h**).* Following the general procedure A described above, **3h** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=10:90) as colourless liquid (173 mg, 96%): R_f (20% EtOAc/Hexane) 0.64; IR (thin film): ν_{max} 3383, 2982, 1731, 1595 and 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.18 (d, J=8.7 Hz, 1H, ArH), 6.76 (d, J=2.8 Hz, 1H, ArH), 6.51 (dd, J_1=8.7 Hz, J_2=2.8 Hz, 1H, ArH), 5.90–5.80 (m, 1H, CH), 5.28–5.19 (m, 2H, CH_2), 4.58 (d, J=9.9 Hz, 1H, NH), 4.39 (dd, J_1=9.9 Hz, J_2=6.1 Hz, 1H, NHCH), 4.21–4.13 (m, 4H, OCH_2), 3.50 (dd, J_1=9.3 Hz, J_2=6.1 Hz, 1H, CH), 1.28–1.21 (m, 6H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 170.9, 170.8, 145.8, 132.9, 130.9, 130.8, 121.4, 121.0, 115.2, 113.5, 61.7, 61.5, 58.4, 52.5, 14.2, 14.1.

4.8.10. (2R,3S*)-Diethyl 2-((4-bromo-3-methylphenyl)amino)-3-vinylsuccinate (**3i**).* Following the general procedure A described above, **3i** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=10:90) as colourless liquid (133 mg, 69%): R_f (20% EtOAc/Hexane) 0.64; IR (thin film): ν_{max} 3376, 2983, 1732, 1479 and 1027 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.27 (d, J=8.6 Hz, 1H, ArH), 6.57 (d, J=2.8 Hz, 1H, ArH), 6.39 (dd, J_1=8.6 Hz, J_2=2.8 Hz, 1H, ArH), 5.91–5.82 (m, 1H, CH), 5.27–5.18 (m, 2H, CH_2), 4.42 (br s, 2H, NH, NHCH), 4.21–4.12 (m, 4H, OCH_2), 3.49 (dd, J_1=9.2 Hz, J_2=5.8 Hz, 1H, CH), 2.29 (s, 3H, ArCH_3), 1.28–1.21 (m, 6H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 171.1, 171.0, 145.5, 138.5, 132.8, 131.1, 120.8, 116.5, 113.3, 113.0, 61.5, 61.4, 58.6, 52.7, 23.1, 14.2, 14.2; HRMS: (ESI) m/z found 384.0810 for $C_{17}H_{23}BrNO_4$ (MH^+), requires 384.0810.

4.8.11. (2R,3S*)-Diethyl 2-((3,5-dichlorophenyl)amino)-3-vinylsuccinate (**3j**).* Following the general procedure A described above, **3j** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=10:90) as colourless liquid (86 mg, 48%): R_f (20% EtOAc/Hexane) 0.64; IR (thin film): ν_{max} 3375, 2984, 1730, 1594 and 1029 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.73 (s, 1H, ArH), 6.56 (s, 2H, ArH), 5.91–5.82 (m, 1H, CH), 5.31–5.22 (m, 2H, CH_2), 4.69 (d, J=9.7 Hz, 1H, NH), 4.40 (dd, J_1=9.7 Hz, J_2=6.0 Hz, 1H, NHCH), 4.23–4.17 (m, 4H, OCH_2), 3.52 (dd, J_1=9.1 Hz, J_2=6.0 Hz, 1H, CH), 1.30–1.24 (m, 6H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 170.9, 170.6, 148.0, 135.6, 130.8, 121.1, 118.5, 112.1, 61.8, 61.5, 58.1, 52.4, 14.2, 14.1; HRMS: (ESI) m/z found 360.0766 for $C_{16}H_{20}Cl_2NO_4$ (MH^+), requires 360.0769.

4.8.12. (2R,3S*)-Diethyl 2-(naphthalen-1-ylamino)-3-vinylsuccinate (**3k**).* Following the general procedure A described above, **3k** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=10:90) as colourless liquid (99 mg, 58%): R_f (20% EtOAc/Hexane) 0.64; IR (thin film): ν_{max} 3420, 2983, 1734, 1531 and 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.89–7.87 (m, 1H, ArH), 7.79–7.76 (m, 1H, ArH), 7.47–7.43 (m, 2H, ArH), 7.34–7.23 (m, 2H, ArH), 6.67 (d, J=7.1 Hz, 1H, ArH), 6.02–5.93 (m, 1H, CH), 5.28–5.18 (m, 3H, CH_2, NH), 4.68 (d, J=6.0 Hz, 1H, NHCH), 4.26–4.15 (m, 4H, OCH_2), 3.66 (dd, J_1=9.2 Hz, J_2=6.0 Hz, 1H, CH), 1.28 (t, J=7.1 Hz, 3H, CH_2CH_3), 1.22 (t, J=7.2 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 171.5, 171.3, 141.4, 134.4, 131.2, 128.6, 126.4, 126.0, 125.1, 123.9, 120.8, 120.2, 118.9, 105.8, 61.6, 61.4, 58.6, 52.4, 14.2; HRMS: (ESI) m/z found 342.1693 for $C_{20}H_{24}NO_4$ (MH^+), requires 342.1705.

4.8.13. (2R,3S*)-1-Ethyl 4-methyl 2-((3,4-dichlorophenyl)amino)-3-vinylsuccinate (**3l**).* Following the general procedure A described above, **3l** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=10:90) as colourless liquid (124 mg, 72%): R_f (20% EtOAc/Hexane) 0.65; IR (thin film): ν_{max} 3375, 2985, 1730, 1597 and 1020 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.22 (d, J=8.7 Hz, 1H, ArH), 6.79 (d, J=2.8 Hz, 1H, ArH), 6.54 (dd, J_1=8.7 Hz, J_2=2.8 Hz, 1H, ArH), 5.92–5.82 (m, 1H, CH), 5.32–5.22 (m, 2H, CH_2), 4.57 (d, J=9.9 Hz, 1H, NH), 4.42 (dd, J_1=9.9 Hz, J_2=6.0 Hz, 1H, NHCH), 4.22–4.16 (m, 2H, OCH_2), 3.76 (s, 3H, OCH_3), 3.55 (dd, J_1=9.2 Hz,

J_2=6.0 Hz, 1H, C*H*), 1.26 (t, J=7.2 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 171.4, 170.7, 145.8, 133.0, 130.8, 130.7, 121.5, 121.1, 115.3, 113.6, 61.8, 58.4, 52.4, 52.3, 14.1; HRMS: (ESI) m/z found 346.0600 for $C_{15}H_{18}Cl_2NO_4$ (MH^+), requires 346.0613.

4.8.14. (2R,3S*)-1-Ethyl 4-methyl 2-((4-bromophenyl)amino)-3-vinylsuccinate (**3m**).* Following the general procedure A described above, **3m** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=9:91) as colourless liquid (128 mg, 72%): R_f (20% EtOAc/Hexane) 0.65; IR (thin film): ν_{max} 3374, 2984, 1730, 1497 and 1021 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.28 (d, J=8.9 Hz, 2H, Ar*H*), 6.59 (d, J=8.9 Hz, 2H, Ar*H*), 5.92–5.83 (m, 1H, C*H*), 5.31–5.19 (m, 2H, CH_2), 4.47 (d, J=3.0 Hz, 2H, N*H*, NHC*H*), 4.22–4.14 (m, 2H, OCH_2), 3.75 (s, 3H, OCH_3), 3.54 (td, J_1=9.2 Hz, J_2=3.0 Hz, 1H, C*H*), 1.25 (t, J=7.2 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 171.5, 170.9, 145.1, 132.1, 130.8, 121.1, 115.7, 110.7, 61.6, 58.5, 52.4, 14.2; HRMS: (ESI) m/z found 356.0486 for $C_{15}H_{19}BrNO_4$ (MH^+), requires 356.0497.

4.8.15. (2R,3S*)-Diethyl 2-(2-benzoylhydrazinyl)-3-vinylsuccinate (**3n**).* Following the general procedure A described above, **3n** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=20:80) as colourless solid (134 mg, 81%): R_f (30% EtOAc/Hexane) 0.45; mp 87–89 °C; IR (thin film): ν_{max} 3264, 2981, 1721, 1451 and 1160 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.96 (s, 1H, N*H*), 7.23 (d, J=7.0 Hz, 2H, Ar*H*), 7.51 (t, J=7.0 Hz, 1H, Ar*H*), 7.43 (t, J=7.0 Hz, 2H, Ar*H*), 5.98–5.89 (m, 1H, C*H*), 5.39–5.27 (m, 3H, CH_2, N*H*), 4.24–4.16 (m, 4H, 2 OCH_2), 4.01 (d, J=7.5 Hz, 1H, NHC*H*), 3.61 (t, J=7.5 Hz, 1H, C*H*), 1.26 (t, J=7.2 Hz, 6H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 171.3, 170.9, 166.9, 132.5, 132.0, 131.3, 128.7, 127.0, 120.4, 64.8, 61.5, 61.4, 51.5, 14.1, 14.1; HRMS: (ESI) m/z found 335.1590 for $C_{17}H_{23}N_2O_5$ (MH^+), requires 335.1607.

4.8.16. (2R,3S*)-Diethyl 2-((1,3-dioxoisoindolin-2-yl)amino)-3-vinylsuccinate (**3o**)[#].* Following the general procedure A described above, **3o** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=22:78) as colourless oil (90 mg, 50%): R_f (30% EtOAc/Hexane) 0.43; IR (thin film): ν_{max} 3297, 2984, 1730, 1468 and 1031 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.85 (dd, J_1=5.5 Hz, J_2=3.1 Hz, 2H, Ar*H*), 7.75 (dd, J_1=5.5 Hz, J_2=3.1 Hz, 2H, Ar*H*), 5.94–5.85 (m, 1H, C*H*), 5.41–5.28 (m, 3H, CH_2, N*H*), 4.30–4.14 (m, 5H, NHC*H*, OCH_2), 3.54 (t, J=8.6 Hz, 1H, C*H*), 1.32 (t, J=7.1 Hz, 3H, CH_2CH_3), 1.26 (t, J=7.1 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 171.9, 171.1, 166.9, 135.3, 135.3, 131.8, 131.0, 124.5, 121.9, 65.3, 62.7, 62.5, 53.4, 15.0, 15.0; HRMS: (ESI) m/z found 361.1393 for $C_{18}H_{21}N_2O_6$ (MH^+), requires 361.1400. [#]The compound was isolated with traces of minor isomer and the NMR values given here for the major isomer.

4.8.17. (2R,3S*)-Diethyl 2-([1,1′-biphenyl]-4-ylamino)-3-vinylsuccinate (**3p**).* Following the general procedure A described above, **3p** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=10:90) as colourless solid (167 mg, 91%): R_f (20% EtOAc/Hexane) 0.62; mp 75–77 °C; IR (KBr): ν_{max} 3349, 2985, 1720, 1527 and 1174 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.53 (d, J=7.5 Hz, 2H, Ar*H*), 7.45 (d, J=8.6 Hz, 2H, Ar*H*), 7.39 (t, J=7.5 Hz, 2H, Ar*H*), 7.27 (t, J=7.5 Hz, 1H, Ar*H*), 6.77 (d, J=8.6 Hz, 2H, Ar*H*), 5.96–5.87 (m, 1H, C*H*), 5.30–5.21 (m, 2H, CH_2), 4.57–4.52 (m, 2H, N*H*, NHC*H*), 4.24–4.15 (m, 4H, OCH_2), 3.56 (dd, J_1=9.2 Hz, J_2=5.8 Hz, 1H, C*H*), 1.31–1.23 (m, 6H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 171.3, 171.1, 145.5, 141.0, 131.8, 131.1, 128.7, 128.1, 126.4, 126.3, 120.8, 114.3, 61.5, 61.4, 58.6, 52.8, 14.2, 14.2; HRMS: (ESI) m/z found 368.1850 for $C_{22}H_{26}NO_4$ (MH^+), requires 368.1862.

4.8.18. (2R,3S*)-1-Ethyl 4-methyl 2-([1,1′-biphenyl]-4-ylamino)-3-vinylsuccinate (**3q**).* Following the general procedure A described above, **3q** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=10:90) as colourless solid (164 mg, 93%): R_f (20% EtOAc/Hexane) 0.63; mp 72–74 °C; IR (KBr): ν_{max} 3375, 2956, 1723, 1528 and 1019 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.49 (d, J=8.6 Hz, 2H, Ar*H*), 7.42 (d, J=8.6 Hz, 2H, Ar*H*), 7.35 (t, J=7.4 Hz, 2H, Ar*H*), 7.23 (t, J=7.4 Hz, 1H, Ar*H*), 6.74 (d, J=8.6 Hz, 2H, Ar*H*), 5.92–5.83 (m, 1H, C*H*), 5.27–5.17 (m, 2H, CH_2), 4.57–4.48 (m, 2H, N*H*, NHC*H*), 4.19–4.10 (m, 2H, OCH_2), 3.71 (s, 3H, OCH_3), 3.55 (dd, J_1=9.3 Hz, J_2=5.9 Hz, 1H, C*H*), 1.21 (t, J=7.1 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 171.7, 171.2, 145.5, 141.0, 131.8, 131.0, 128.7, 128.1, 126.4, 126.3, 121.2, 114.3, 61.6, 58.6, 52.6, 52.4, 14.2; HRMS: (ESI) m/z found 354.1704 for $C_{21}H_{24}NO_4$ (MH^+), requires 354.1705.

4.8.19. (2R,3S*)-Diethyl 2-(2-benzoylhydrazinyl)-2-methyl-3-vinylsuccinate (**3r**)[#].* Following the general procedure A described above, **3r** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=21:79) as colourless oil (80 mg, 46%): R_f (30% EtOAc/Hexane) 0.46; IR (thin film): ν_{max} 3287, 2984, 1731, 1461 and 1029 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.39 (s, 1H, N*H*), 7.76 (d, J=7.1 Hz, 2H, Ar*H*), 7.53–7.42 (m, 3H, Ar*H*), 6.15–6.06 (m, 1H, C*H*), 5.41–5.28 (m, 3H, CH_2, N*H*), 4.22–4.09 (m, 4H, OCH_2), 3.75–3.68 (m, 1H, C*H*), 1.41 (s, 3H, CH_3), 1.28–1.22 (m, 6H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 174.0, 172.2, 166.0, 132.9, 131.7, 130.8, 128.7, 126.9, 121.5, 65.8, 61.7, 61.4, 55.7, 20.1, 14.1, 14.0; HRMS: (ESI) m/z found 371.1578 for $C_{18}H_{24}N_2O_5Na$ (MNa^+), requires 371.1583. [#]The compound was isolated with traces of minor isomer and the NMR values given here for the major isomer.

4.8.20. (2R,3S*)-Diethyl 2-(2-hydroxyphenylamino)-3-vinylsuccinate (**3s**).* Following the general procedure A described above, **3s** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=11:89) as colourless liquid (90 mg, 59%): R_f (20% EtOAc/Hexane) 0.58; IR (thin film): ν_{max} 3419, 2983, 1731, 1516 and 1195 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.82 (m, 4H, Ar*H*), 6.23 (br s, 1H, O*H*), 5.91–5.82 (m, 1H, C*H*), 5.28–5.23 (m, 2H, CH_2), 4.26–4.11 (m, 6H, N*H*, NHC*H*, OCH_2), 3.47 (t, J=8.5 Hz, 1H, C*H*), 1.28 (t, J=7.2 Hz, 3H, CH_2CH_3), 1.20 (t, J=7.1 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 172.3, 172.0, 147.6, 133.8, 131.2, 122.3, 120.8, 120.8, 118.5, 115.6, 60.6, 61.4, 60.8, 53.6, 14.2, 14.1; HRMS: (ESI) m/z found 330.1300 for $C_{16}H_{21}NO_5Na$ (MNa^+), requires 330.1317.

4.8.21. (2R,3S*)-Diethyl 2-(4-acetylphenylamino)-3-vinylsuccinate (**3t**).* Following the general procedure A described above, **3t** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=09:91) as colourless liquid (103 mg, 65%): R_f (20% EtOAc/Hexane) 0.64; IR (thin film): ν_{max} 3379, 2985, 1732, 1599 and 1035 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.83 (d, J=8.8 Hz, 2H, Ar*H*), 6.67 (d, J=8.8 Hz, 2H, Ar*H*), 5.91–5.82 (m, 1H, C*H*), 5.29–5.19 (m, 2H, CH_2), 5.05 (d, J=9.4 Hz, 1H, N*H*), 4.59 (dd, J_1=9.4 Hz, J_2=5.8 Hz, 1H, NHC*H*), 4.23–4.16 (m, 4H, OCH_2), 3.56 (dd, J_1=9.2 Hz, J_2=5.8 Hz, 1H, C*H*), 2.50 (s, 3H, CH_3), 1.29–1.23 (m, 6H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 196.4, 170.9, 170.5, 150.2, 130.8, 128.0, 121.0, 112.5, 61.8, 61.5, 57.6, 52.3, 26.1, 14.1, 14.1; HRMS: (ESI) m/z found 334.1648 for $C_{18}H_{24}NO_5$ (MH^+), requires 334.1654.

4.8.22. (2R,3S*)-1-Ethyl 4-methyl 2-(4-acetylphenylamino)-2-methyl-3-vinylsuccinate (**3u**).* Following the general procedure A described above, **3u** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=09:91) as colourless liquid (91 mg, 57%): R_f (20% EtOAc/Hexane) 0.64; IR (thin film): ν_{max} 3367, 2985, 1731, 1600 and 1276 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.80 (d, J=8.8 Hz, 2H, Ar*H*), 6.63 (d, J=8.8 Hz, 2H, Ar*H*), 5.86–5.77 (m, 1H, C*H*), 5.27–5.15 (m, 2H, CH_2), 4.97 (d, J=9.5 Hz, 1H, N*H*), 4.57 (dd, J_1=9.5 Hz, J_2=5.6 Hz, 1H, NHC*H*), 4.20–4.11 (m, 2H, OCH_2), 3.71 (s, 3H, OCH_3), 3.56 (dd, J_1=9.2 Hz, J_2=5.6 Hz, 1H, C*H*), 2.47 (s, 3H,

CH_3), 1.21 (t, J=7.1 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 196.5, 171.4, 170.4, 150.1, 130.8, 130.5, 128.1, 121.3, 112.5, 61.9, 57.5, 52.5, 52.1, 26.1, 14.1; HRMS: (ESI) m/z found 320.1480 for $C_{17}H_{22}NO_5$ (MH^+), requires 320.1498.

4.8.23. (2R,3S*)-Diethyl 2-(2-tosylhydrazinyl)-3-vinylsuccinate (**3v**).* Following the general procedure B described above, **3v** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=19:81) as colourless solid (103 mg, 54%): R_f (20% EtOAc/Hexane) 0.33; mp 107–109 °C; IR (KBr): ν_{max} 3261, 2987, 1722, 1320 and 1161 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.76 (d, J=8.3 Hz, 2H, ArH), 7.28 (d, J=8.3 Hz, 2H, ArH), 6.54 (s, 1H, NH), 5.86–5.77 (m, 1H, CH), 5.21–5.17 (m, 2H, CH_2), 4.35 (dd, J_1=10.3 Hz, J_2=2.9 Hz, 1H, NH), 4.19–4.13 (m, 2H, OCH_2), 4.09 (q, J=7.0 Hz, 2H, OCH_2), 3.78 (dd, J_1=10.3 Hz, J_2=5.5 Hz, 1H, NHCH), 3.45 (dd, J_1=8.8 Hz, J_2=5.5 Hz, 1H, CH), 2.41 (s, 3H, ArCH_3), 1.25–1.19 (m, 6H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 172.1, 170.9, 144.0, 134.9, 131.4, 129.5, 128.3, 119.9, 65.1, 61.7, 61.4, 51.2, 21.6, 14.1, 14.0; HRMS: (ESI) m/z found 385.1410 for $C_{17}H_{25}N_2O_6S$ (MH^+), requires 385.1433.

*4.8.24. Diethyl 2-(4-methoxyphenylamino)succinate (**9a**).* Following the general procedure C described above, **9a** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=10:90) as colourless liquid (94 mg, 65%): R_f (20% EtOAc/Hexane) 0.56; IR (thin film): ν_{max} 3368, 2983, 1730, 1512 and 1029 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.77 (d, J=9.0 Hz, 2H, ArH), 6.65 (d, J=9.0 Hz, 2H, ArH), 4.34 (t, J=6.0 Hz, 1H, NHCH), 4.22–4.13 (m, 4H, OCH_2), 3.73 (s, 3H, OCH_3), 2.82 (d, J=6.0 Hz, 2H, CH_2CH), 1.27–1.22 (m, 6H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 172.7, 170.6, 153.1, 140.4, 115.8, 114.8, 61.5, 61.0, 55.7, 55.0, 37.7, 14.2, 14.1; HRMS: (ESI) m/z found 296.1509 for $C_{15}H_{22}NO_5$ (MH^+), requires 296.1498.

*4.8.25. 4-tert-Butyl 1-ethyl 2-(4-methoxyphenylamino)succinate (**9b**).* Following the general procedure C described above, **9b** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=10:90) as colourless liquid (64 mg, 40%): R_f (20% EtOAc/Hexane) 0.57; IR (thin film): ν_{max} 3385, 2979, 1731, 1514 and 1155 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.75 (d, J=8.9 Hz, 2H, ArH), 6.62 (d, J=8.9 Hz, 2H, ArH), 4.26 (t, J=5.9 Hz, 1H, NHCH), 4.19–4.12 (m, 2H, OCH_2), 3.71 (s, 3H, OCH_3), 2.71 (d, J=5.9 Hz, 2H, CH_2CH), 1.42 (s, 9H, C(CH_3)$_3$), 1.23–1.20 (m, 4H, NH, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 172.8, 169.8, 153.0, 140.6, 115.7, 114.9, 114.8, 81.4, 61.4, 55.7, 55.1, 38.8, 28.1, 28.1, 14.2; HRMS: (ESI) m/z found 324.1791 for $C_{17}H_{26}NO_5$ (MH^+), requires 324.1811.

*4.8.26. Diethyl 2-(4-chlorophenylamino)succinate (**9c**).* Following the general procedure C described above, **9c** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=10:90) as colourless liquid (104 mg, 69%): R_f (20% EtOAc/Hexane) 0.58; IR (thin film): ν_{max} 3382, 2982, 1732, 1498 and 1202 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.04 (d, J=8.8 Hz, 2H, ArH), 6.51 (d, J=8.8 Hz, 2H, ArH), 4.29 (t, J=5.8 Hz, 1H, NHCH), 4.15–4.04 (m, 4H, OCH_2), 2.76 (dd, J_1=5.8 Hz, J_2=3.2 Hz, 2H, CH_2CH), 1.16 (t, J=7.1 Hz, 6H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 172.1, 170.5, 145.0, 129.2, 123.3, 114.9, 61.7, 61.1, 53.6, 37.3, 14.1, 14.1; HRMS: (ESI) m/z found 300.0999 for $C_{14}H_{19}NO_4Cl$ (MH^+), requires 300.1003.

*4.8.27. Diethyl 2-(benzamido)succinate (**9d**).* Following the general procedure C described above, **9d** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=20:80) as colourless oil (92 mg, 60%): R_f (20% EtOAc/Hexane) 0.31; IR (thin film): ν_{max} 3291, 2928, 1733, 1529 and 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.09 (br s, 1H, NH), 7.76–7.74 (m, 2H, ArH), 7.54–7.50 (m, 1H, ArH), 7.43 (t, J=7.7 Hz, 2H, ArH), 5.45 (br s, 1H, NH), 4.28–4.14 (m, 4H, OCH_2), 4.08–4.04 (m, 1H, NHCH), 2.87 (d, J=5.3 Hz, 2H, CH_2CH), 1.30–1.24 (m, 6H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 171.7, 170.8, 167.1, 132.5, 132.0, 128.7, 127.0, 61.6, 61.1, 59.3, 35.6, 14.1; HRMS: (ESI) m/z found 331.1266 for $C_{15}H_{20}N_2O_5Na$ (MNa^+), requires 331.1270.

*4.8.28. Diethyl 2-([1,1′-biphenyl]-4-ylamino)succinate (**9e**).* Following the general procedure C described above, **9e** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=09:91) as yellow colour liquid (114 mg, 67%): R_f (20% EtOAc/Hexane) 0.60; IR (thin film): ν_{max} 3395, 2982, 1734, 1609 and 1229 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.51–7.49 (m, 2H, ArH), 7.42 (d, J=8.6 Hz, 2H, ArH), 7.36 (t, J=7.5 Hz, 2H, ArH), 7.23 (t, J=7.5 Hz, 1H, ArH), 6.72 (d, J=8.6 Hz, 2H, ArH), 4.46 (t, J=5.7 Hz, 1H, NHCH), 4.31–4.16 (m, 3H, NH, OCH_2), 4.14 (q, J=7.2 Hz, 2H, OCH_2), 2.86 (dd, J_1=5.8 Hz, J_2=2.5 Hz, 2H, CH_2CH), 1.24 (dt, J_1=7.1 Hz, J_2=2.5 Hz, 6H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 172.3, 170.6, 145.7, 141.0, 131.6, 128.7, 128.1, 126.4, 126.3, 114.0, 61.7, 61.1, 53.5, 37.5, 14.2; HRMS: (ESI) m/z found 364.1525 for $C_{20}H_{23}NO_4Na$ (MNa^+), requires 364.1525.

*4.8.29. Diethyl 3-((4-methoxyphenyl)amino)-2,2-dimethylsuccinate (**10a**).* Following the general procedure C described above, **10a** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=9:91) as colourless liquid (137 mg, 85%): R_f (20% EtOAc/Hexane) 0.61; IR (thin film): ν_{max} 3371, 2982, 1728, 1512 and 1238 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.75 (d, J=9.0 Hz, 2H, ArH), 6.68 (d, J=9.0 Hz, 2H, ArH), 4.24 (br s, 1H, NH), 4.24–4.10 (m, 5H, NHCH, OCH_2), 3.72 (s, 3H, OCH_3), 1.29–1.24 (m, 9H, CH_3, CH_2CH_3), 1.20 (t, J=7.2 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 175.6, 172.2, 153.1, 141.4, 116.1, 114.7, 64.7, 61.2, 61.0, 55.7, 45.9, 22.5, 21.6, 14.2, 14.1; HRMS: (ESI) m/z found 324.1797 for $C_{17}H_{26}NO_5$ (MH^+), requires 324.1811.

*4.8.30. Diethyl 2,2-difluoro-3-((4-methoxyphenyl)amino)succinate (**10b**).* Following the general procedure C described above, **10b** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=11:89) as colourless liquid (66 mg, 40%): R_f (20% EtOAc/Hexane) 0.55; IR (thin film): ν_{max} 3363, 2988, 1745, 1514 and 1199 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.77 (d, J=9.1 Hz, 2H, ArH), 6.71 (d, J=9.1 Hz, 2H, ArH), 4.64 (dd, J_1=15.8 Hz, J_2=10.0 Hz, 1H, NHCH), 4.63–4.19 (m, 5H, NH, OCH_2), 3.73 (s, 3H, OCH_3), 1.32 (t, J=7.1 Hz, 3H, CH_2CH_3), 1.26 (t, J=7.1 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.5 (J_{C-F}=3.2 Hz), 162.4 (J_{C-F}=30.7 Hz), 154.0, 139.6, 116.7, 114.8, 63.4, 62.6, 61.6 (J_{C-F}=23.2 Hz), 61.3 (J_{C-F}=23.0 Hz), 55.7, 14.0, 13.9; HRMS: (ESI) m/z found 332.1300 for $C_{15}H_{20}F_2NO_5$ (MH^+), requires 332.1310.

*4.8.31. Diethyl 2-fluoro-3-((4-methoxyphenyl)amino)succinate (**10c**).* Following the general procedure C described above, **10c** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=11:89) as colourless liquid (92 mg, 59%): R_f (20% EtOAc/Hexane) 0.55; IR (thin film): ν_{max} 3369, 2963, 1746, 1515 and 1033 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.75–6.69 (m, 2H, ArH), 6.64–6.60 (m, 2H, ArH), 5.40–5.14 (m, 1H, NHCH), 4.57–4.45 (m, 1H, CHF), 4.31–4.14 (m, 4H, OCH_2), 3.68 (s, 3H, OCH_3), 1.30–1.18 (m, 6H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 169.6 (J_{C-F}=2.3 Hz), 168.4 (J_{C-F}=6.7 Hz), 167.1 (J_{C-F}=8.4 Hz), 166.9 (J_{C-F}=4.2 Hz), 153.7, 153.4, 140.3, 139.6, 116.7, 115.8, 115.0, 114.7, 90.0 (J_{C-F}=80.0 Hz), 88.1 (J_{C-F}=81.8 Hz), 62.3, 62.2, 62.1, 62.0, 60.6 (J_{C-F}=19.7 Hz), 60.2 (J_{C-F}=21.5 Hz), 55.7, 55.6, 14.1, 14.0; HRMS: (ESI) m/z found 314.1391 for $C_{15}H_{21}FNO_5$ (MH^+), requires 314.1404. ^{13}C data given here for the mixture of diastereomers.

4.8.32. (2S,3R*)-Diethyl 2-ethyl-3-((4-methoxyphenyl)amino)succinate (**10d′**).* Following the general procedure C described above,

10d′ (minor isomer) was obtained after purification by silica gel column chromatography (EtOAc/Hexane=9:91) as colourless liquid (100 mg, 62%): R_f (20% EtOAc/Hexane) 0.63; IR (thin film): ν_{max} 3379, 2976, 1731, 1515 and 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 6.69 (d, J=9.0 Hz, 2H, Ar*H*), 6.56 (d, J=9.0 Hz, 2H, Ar*H*), 4.17–4.01 (m, 6H, N*H*, NHC*H*, OCH_2), 3.66 (s, 3H, OCH_3), 2.77–2.66 (m, 1H, C*H*), 1.75–1.66 (m, 1H, C*H*), 1.57–1.47 (m, 1H, C*H*), 1.19 (t, J=7.1 Hz, 3H, CH_2CH_3), 1.14 (t, J=7.1 Hz, 3H, CH_2CH_3), 0.88 (t, J=7.4 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 173.2, 172.8, 152.9, 140.7, 115.5, 114.8, 61.2, 60.8, 59.6, 55.7, 49.9, 22.0, 14.3, 14.2, 12.0; HRMS: (ESI) m/z found 324.1809 for $C_{17}H_{26}NO_5$ (MH^+), requires 324.1811. The major isomer **10d** could not be separated from the minor isomer.

4.8.33. (2S,3R*)-Diethyl 2-hexyl-3-((4-methoxyphenyl)amino)succinate (**10e**)[#].* Following the general procedure C described above, **10e** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=9:91) as colourless liquid (65 mg, 35%): R_f (20% EtOAc/Hexane) 0.64; IR (thin film): ν_{max} 3374, 2925, 1732, 1515 and 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 6.69 (d, J=9.0 Hz, 2H, Ar*H*), 6.56 (d, J=9.0 Hz, 2H, Ar*H*), 4.17 (d, J=6.1 Hz, 1H, NHC*H*), 4.12–3.87 (m, 5H, N*H*, OCH_2), 3.66 (s, 3H, OCH_3), 2.77–2.72 (m, 1H, C*H*), 1.81–1.72 (m, 1H, CH_2), 1.58–1.50 (m, 1H, CH_2), 1.21–1.12 (m, 14H, CH_2, CH_2CH_3), 0.82–0.77 (m, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 173.0, 172.5, 153.0, 140.8, 115.7, 114.8, 61.3, 60.9, 59.9, 55.7, 48.5, 31.6, 29.1, 28.0, 27.6, 22.6, 14.2, 14.2, 14.1; HRMS: (ESI) m/z found 380.2450 for $C_{21}H_{34}NO_5$ (MH^+), requires 380.2437. [#]The compound was isolated with minor isomer and the NMR values given here for the major isomer.

*4.8.34. Diethyl 2-([1,1′-biphenyl]-4-ylamino)-3-propylsuccinate (**10f**).* Following the general procedure C described above, **10f** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=10:90) as colourless liquid (96 mg, 50%): R_f (20% EtOAc/Hexane) 0.63; IR (thin film): ν_{max} 3384, 2962, 1732, 1528 and 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.52–7.50 (m, 2H, Ar*H*), 7.42 (d, J=8.6 Hz, 2H, Ar*H*), 7.37 (t, J=7.4 Hz, 2H, Ar*H*), 7.25 (t, J=7.4 Hz, 1H, Ar*H*), 6.71 (d, J=8.6 Hz, 2H, Ar*H*), 4.39 (br s, 2H, N*H*, NHC*H*), 4.21–4.13 (m, 4H, OCH_2), 2.90–2.85 (m, 1H, C*H*), 1.90–1.81 (m, 1H, CH_2), 1.65–1.57 (m, 1H, CH_2), 1.48–1.30 (m, 2H, CH_2), 1.28–1.22 (m, 6H, CH_2CH_3), 0.92 (t, J=7.2 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 172.9, 172.1, 146.1, 141.0, 131.6, 128.7, 128.0, 126.4, 126.3, 114.1, 61.5, 61.0, 58.4, 48.3, 30.3, 20.9, 14.2, 14.2, 14.0; HRMS: (ESI) m/z found 384.2180 for $C_{23}H_{30}NO_4$ (MH^+), requires 384.2175.

4.8.35. (R)-Ethyl 2-((4-methoxyphenyl)amino)-2-((R*)-2-oxotetrahydrofuran-3-yl)acetate (**10g**).* Following the general procedure C described above, **10g** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=13:87) as colourless liquid (98 mg, 67%): R_f (20% EtOAc/Hexane) 0.60; IR (thin film): ν_{max} 3368, 2916, 1739, 1597 and 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 6.76–6.70 (m, 4H, Ar*H*), 4.37–4.31 (m, 2H, N*H*, NHC*H*), 4.23–4.11 (m, 1H, CH_2), 4.21 (t, J=8.2 Hz, 1H, OCH_2), 4.14 (q, J=7.1 Hz, 2H, OCH_2), 3.68 (s, 3H, OCH_3), 3.06 (dt, J_1=9.6 Hz, J_2=3.5 Hz, 1H, C*H*), 2.27–2.21 (m, 2H, CH_2), 1.19 (t, J=7.1 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 177.0, 172.4, 153.8, 140.6, 117.3, 114.7, 66.8, 61.9, 59.1, 55.7, 42.7, 23.7, 14.2; HRMS: (ESI) m/z found 294.1338 for $C_{15}H_{20}NO_5$ (MH^+), requires 294.1341.

4.8.36. (R)-Ethyl 2-([1,1′-biphenyl]-4-ylamino)-2-((R*)-2-oxotetrahydrofuran-3-yl)acetate (**10h**).* Following the general procedure C described above, **10h** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=14:86) as yellow solid (122 mg, 72%): R_f (20% EtOAc/Hexane) 0.62; mp 113–115 °C; IR (KBr): ν_{max} 3351, 2984, 1757, 1530 and 1025 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.51 (d, J=8.5 Hz, 2H, Ar*H*), 7.43 (d, J=8.6 Hz, 2H, Ar*H*), 7.37 (t, J=7.5 Hz, 2H, Ar*H*), 7.25 (t, J=7.5 Hz, 1H, Ar*H*), 6.88 (d, J=8.6 Hz, 2H, Ar*H*), 4.64–4.56 (m, 2H, N*H*, NHC*H*), 4.42–4.37 (m, 1H, OCH_2), 4.26 (t, J=8.3 Hz, 1H, OCH_2), 4.21 (q, J=7.1 Hz, 2H, OCH_2), 3.15 (dt, J_1=9.7 Hz, J_2=3.4 Hz, 1H, C*H*), 2.35–2.29 (m, 2H, CH_2), 1.25 (t, J=7.1 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 176.4, 170.9, 145.9, 140.9, 132.1, 128.7, 128.2, 126.4, 114.0, 66.7, 62.3, 56.4, 42.5, 24.9, 14.1; HRMS: (ESI) m/z found 340.1535 for $C_{20}H_{22}NO_4$ (MH^+), requires 340.1549.

4.8.37. (2S,3R*)-Diethyl 2-ethyl-3-((4-methoxyphenyl)amino)succinate (**10d′**).* Following the general procedure D described above, **10d′** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=10:90) as colourless liquid (142 mg, 88%). Characterization data (has been given above) same as the product obtained in Table 5.

4.8.38. (2R,3S*)-Diethyl 2-(3,4-dichlorophenylamino)-3-ethylsuccinate (**11a**).* Following the general procedure D described above, **11a** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=10:90) as colourless liquid (117 mg, 65%): R_f (20% EtOAc/Hexane) 0.64; IR (thin film): ν_{max} 3380, 2978, 1731, 1599 and 1193 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.20 (d, J=8.7 Hz, 1H, Ar*H*), 6.75 (d, J=2.8 Hz, 1H, Ar*H*), 6.51 (dd, J_1=8.7 Hz, J_2=2.8 Hz, 1H, Ar*H*), 4.73 (d, J=9.8 Hz, 1H, NHC*H*), 4.22–4.16 (m, 5H, N*H*, OCH_2), 2.85–2.79 (m, 1H, C*H*), 1.86–1.75 (m, 1H, CH_2), 1.65–1.55 (m, 1H, CH_2), 1.29–1.23 (m, 6H, CH_2CH_3), 0.97 (t, J=7.3 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 173.1, 171.8, 146.3, 132.9, 130.7, 121.0, 114.8, 113.3, 61.6, 61.0, 57.8, 49.2, 22.1, 14.2, 14.2, 12.0; HRMS: (ESI) m/z found 384.0728 for $C_{16}H_{21}NO_4Cl_2Na$ (MNa^+), requires 384.0745.

4.8.39. (2R,3S*)-1-Ethyl 4-methyl 2-(3,4-dichlorophenylamino)-3-ethylsuccinate (**11b**).* Following the general procedure D described above, **11b** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=10:90) as colourless liquid (166 mg, 96%): R_f (20% EtOAc/Hexane) 0.65; IR (thin film): ν_{max} 3382, 2970, 1735, 1599 and 1201 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.11 (d, J=8.7 Hz, 1H, Ar*H*), 6.66 (d, J=2.8 Hz, 1H, Ar*H*), 6.42 (dd, J_1=8.7 Hz, J_2=2.8 Hz, 1H, Ar*H*), 4.61 (d, J=8.2 Hz, 1H, NHC*H*), 4.14–4.07 (m, 3H, N*H*, OCH_2), 3.64 (s, 3H, OCH_3), 2.78–2.73 (m, 1H, C*H*), 1.75–1.66 (m, 1H, CH_2), 1.56–1.46 (m, 1H, CH_2), 1.16 (t, J=7.1 Hz, 3H, CH_2CH_3), 0.87 (t, J=7.4 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 173.6, 171.7, 146.3, 132.9, 130.7, 121.1, 114.9, 113.3, 61.7, 57.8, 52.1, 49.1, 22.0, 14.2, 12.0; HRMS: (ESI) m/z found 370.0570 for $C_{15}H_{19}NO_4Cl_2Na$ (MNa^+), requires 370.0589.

4.8.40. (2R,3S*)-2-((4-Methoxyphenyl)amino)-3-vinylbutane-1,4-diol (**12a**).* Following the general procedure E described above, **12a** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=30:70) as colourless oil (59 mg, 50%): R_f (20% EtOAc/Hexane) 0.18; IR (thin film): ν_{max} 3377, 2930, 1513, 1241 and 1038 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 6.78 (d, J=9.0 Hz, 2H, Ar*H*), 6.69 (d, J=9.0 Hz, 2H, Ar*H*), 5.75–5.66 (m, 1H, C*H*), 5.23–5.18 (m, 2H, CH_2), 3.81–3.74 (m, 2H, OCH_2), 3.74 (s, 3H, OCH_3), 3.68 (dd, J_1=11.0 Hz, J_2=5.0 Hz, 2H, OCH_2), 3.56 (dd, J_1=11.0 Hz, J_2=5.0 Hz, 1H, NHC*H*), 3.48–3.44 (m, 1H, C*H*), 2.60–2.52 (m, 1H, C*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 153.2, 141.0, 136.0, 119.0, 116.8, 115.0, 64.8, 61.8, 59.1, 55.7, 48.5; HRMS: (ESI) m/z found 238.1449 for $C_{13}H_{20}NO_3$ (MH^+), requires 238.1443. (OH protons could not be detected perhaps due to the rapid exchange among each other.)

4.8.41. (2R,3S*)-2-((3,4-Dichlorophenyl)amino)-3-vinylbutane-1,4-diol (**12b**).* Following the general procedure E described above, **12b** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=30:70) as colourless oil (81 mg, 59%): R_f (20%

EtOAc/Hexane) 0.18; IR (thin film): ν_{max} 3379, 2923, 1596, 1511 and 1038 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.16 (d, J=8.7 Hz, 1H, Ar*H*), 6.74 (d, J=2.8 Hz, 1H, Ar*H*), 6.51 (dd, J_1=8.7 Hz, J_2=2.8 Hz, 1H, Ar*H*), 5.78–5.69 (m, 1H, C*H*), 5.25–5.18 (m, 2H, CH_2), 3.77–3.67 (m, 3H, NHC*H*, OCH_2), 3.62–3.52 (m, 2H, OCH_2), 2.82 (br s, 1H, C*H*), 2.56–2.49 (m, 1H, C*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 147.1, 135.7, 132.9, 130.8, 120.4, 119.3, 115.0, 113.7, 63.6, 62.1, 56.3, 48.7; HRMS: (ESI) m/z found 276.0548 for $C_{12}H_{16}NO_2Cl_2$ (MH^+), requires 276.0558. (OH protons could not be detected perhaps due to the rapid exchange among each other.)

4.8.42. (2R,3S*)-2-(4-Chlorophenylamino)-3-vinylbutane-1,4-diol (**12c**).* Following the general procedure E described above, **12c** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=31:69) as colourless oil (54 mg, 45%): R_f (20% EtOAc/Hexane) 0.17; IR (thin film): ν_{max} 3373, 2926, 1599, 1496 and 1048 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.08 (d, J=8.8 Hz, 2H, Ar*H*), 6.57 (d, J=8.8 Hz, 2H, Ar*H*), 5.74–5.65 (m, 1H, C*H*), 5.21–5.14 (m, 2H, CH_2), 3.75–3.63 (m, 3H, NHC*H*, OCH_2), 3.58–3.50 (m, 2H, OCH_2), 2.85 (br s, 1H, C*H*), 2.55–2.48 (m, 1H, C*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 146.0, 135.8, 129.3, 122.9, 119.2, 115.4, 63.9, 62.1, 56.8, 48.8; HRMS: (ESI) m/z found 242.0951 for $C_{12}H_{17}ClNO_2$ (MH^+), requires 242.0948. (OH protons could not be detected perhaps due to the rapid exchange among each other.)

4.8.43. (2R,3S*)-2-(p-Tolylamino)-3-vinylbutane-1,4-diol (**12d**).* Following the general procedure E described above, **12d** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=29:71) as colourless oil (78 mg, 71%): R_f (20% EtOAc/Hexane) 0.19; IR (thin film): ν_{max} 3369, 2923, 1617, 1518 and 1256 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 6.98 (d, J=8.0 Hz, 2H, Ar*H*), 6.62 (d, J=8.0 Hz, 2H, Ar*H*), 5.75–5.66 (m, 1H, C*H*), 5.22–5.17 (m, 2H, CH_2), 3.75 (dd, J_1=10.9 Hz, J_2=6.8 Hz, 1H, NHC*H*), 3.71–3.65 (m, 2H, OCH_2), 3.58–3.51 (m, 2H, OCH_2), 2.57–2.50 (m, 1H, C*H*), 2.23 (s, 3H, ArCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 144.9, 136.0, 130.0, 128.2, 119.0, 115.0, 64.5, 62.0, 57.7, 48.8, 20.4; HRMS: (ESI) m/z found 222.1498 for $C_{13}H_{20}NO_2$ (MH^+), requires 222.1494. (OH protons could not be detected perhaps due to the rapid exchange among each other.)

4.8.44. (2R,3S*)-Diethyl 2-(allyl(4-methoxyphenyl)amino)-3-vinylsuccinate (**13**).* Following the general procedure F described above, **13** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=08:92) as colourless liquid (90 mg, 50%): R_f (20% EtOAc/Hexane) 0.64; IR (thin film): ν_{max} 2983, 1730, 1513, 1154 and 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 6.91 (d, J=9.0 Hz, 2H, Ar*H*), 6.75 (d, J=9.0 Hz, 2H, Ar*H*), 5.84–5.75 (m, 1H, C*H*), 5.66–5.57 (m, 1H, C*H*), 5.27 (d, J=17.1 Hz, 1H, CH_2), 5.18 (d, J=10.2 Hz, 1H, CH_2), 5.07 (d, J=17.1 Hz, 1H, CH_2), 5.00 (d, J=10.2 Hz, 1H, CH_2), 4.46 (d, J=11.2 Hz, 1H, NC*H*), 4.09–3.91 (m, 5H, C*H*, OCH_2), 3.83–3.73 (m, 2H, NCH_2), 3.71 (s, 3H, OCH_3), 1.17–1.12 (m, 6H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 171.4, 169.3, 154.0, 142.1, 135.6, 131.9, 120.4, 120.3, 116.5, 114.0, 66.9, 61.0, 60.6, 55.4, 51.7, 49.5, 14.3, 14.1; HRMS: (ESI) m/z found 362.1959 for $C_{20}H_{28}NO_5$ (MH^+), requires 362.1967.

4.8.45. (2R,3S*)-Diethyl 1-(4-methoxyphenyl)-1,2,3,6-tetrahydro pyridine-2,3-dicarboxylate (**14**).* Following the general procedure G described above, **14** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=10:90) as colourless oil (153 mg, 92%): R_f (20% EtOAc/Hexane) 0.63; IR (thin film): ν_{max} 2983, 1736, 1512, 1248 and 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 6.90 (d, J=9.3 Hz, 2H, Ar*H*), 6.85 (d, J=9.3 Hz, 2H, Ar*H*), 6.25–6.21 (m, 1H, C*H*), 5.92–5.87 (m, 1H, C*H*), 5.04 (d, J=5.0 Hz, 1H, NC*H*), 4.22 (q, J=7.1 Hz, 2H, OCH_2), 4.12–3.95 (m, 2H, OCH_2), 3.79–3.75 (m, 2H, NCH_2), 3.77 (s, 3H, OCH_3), 3.67 (br s, 1H, C*H*), 1.30 (t, J=7.2 Hz, 3H, CH_2CH_3), 1.11 (t, J=7.1 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 170.6, 170.0, 153.2, 143.4, 125.8, 122.1, 116.6, 114.5, 61.0, 60.9, 59.0, 55.6, 45.6, 43.7, 14.2, 14.1; HRMS: (ESI) m/z found 334.1660 for $C_{18}H_{24}NO_5$ (MH^+), requires 334.1654.

4.8.46. (2R,3S*)-Diethyl 1-(4-methoxyphenyl)piperidine-2,3-dicar boxylate (**15**).* Following the general procedure D described above, **15** was obtained after purification by silica gel column chromatography (EtOAc/Hexane=10:90) as colourless liquid (109 mg, 65%): R_f (20% EtOAc/Hexane) 0.63; IR (thin film): ν_{max} 2940, 1732, 1512, 1242 and 1037 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 6.93 (d, J=9.1 Hz, 2H, Ar*H*), 6.83 (d, J=9.1 Hz, 2H, Ar*H*), 4.82 (d, J=5.0 Hz, 1H, NC*H*), 4.18 (q, J=7.1 Hz, 2H, OCH_2), 4.07–3.98 (m, 2H, OCH_2), 3.76 (s, 3H, OCH_3), 3.32–3.19 (m, 2H, OCH_2), 2.93–2.88 (m, 1H, NCH_2), 2.07–2.02 (m, 1H, NCH_2), 1.89–1.75 (m, 2H, CH_2), 1.72–1.62 (m, 1H, C*H*), 1.28 (t, J=7.1 Hz, 3H, CH_2CH_3), 1.10 (t, J=7.1 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 172.3, 170.4, 153.5, 144.7, 118.6, 114.3, 61.7, 60.6, 60.5, 55.6, 44.5, 44.3, 24.5, 22.0, 14.2, 14.1; HRMS: (ESI) m/z found 336.1807 for $C_{18}H_{26}NO_5$ (MH^+), requires 336.1811.

4.8.47. (2R,3S*)-2-Amino-3-ethylsuccinic acid hydrochloride (**16**)*.* To the *N*-aryl α-amino ester **10d′** (0.2 mmol, 1 equiv) in MeCN (2 mL) was added aqueous solution of both $(NH_4)_2S_2O_8$ (2 equiv) and ammonium ceric (III) nitrate (0.1 equiv) at 0 °C. The resulting reaction mixture was stirred for 3 h at 35 °C. After this period, the reaction mixture was washed with DCM (2 mL) and treated with Na_2CO_3 to obtain the pH 7. Then, the product was extracted using DCM (5×1 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum, which gave a crude mixture. To this crude reaction mixture 6 N HCl (5 mL) was added and refluxed for 3 h. After completion of the reaction, the reaction mixture was cooled to rt and the solvent was removed under vacuum that gave the product as colourless viscous liquid (20 mg, 50%): IR (thin film): ν_{max} 3562, 3060–2575, 1715 and 1273 cm^{-1}; ^1H NMR (400 MHz, D_2O): δ_H 4.17 (d, J=4.0 Hz, 1H, NHC*H*), 3.07–3.02 (m, 1H, C*H*), 1.80–1.71 (m, 1H, CH_2), 1.59–1.52 (m, 1H, CH_2), 0.91 (t, J=8.0 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, D_2O): δ_C 175.7, 53.1, 46.2, 21.1, 11.0; MS (CI): m/z 162 (100, MH^+), 144 (12), 101 (10%). HRMS: (ESI) m/z found 162.0777 for $C_6H_{12}NO_4$ (MH^+), requires 162.0766. *(OH protons could not be detected perhaps due to the rapid exchange among each other.) *The NMR values given here for the major isomer and the NMR spectrum were having some traces of minor diastereomer.

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Supplementary data

Supplementary data (copy of ^1H, ^{13}C NMR, charts of all the compounds and X-ray structure data of the compounds **3p**, **3q**, **3v** and **10h**). Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.05.130.

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