Tetrahedron 68 (2012) 5522–5532

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of chiral β-amino acid derivatives by asymmetric hydrosilylation with an imidazole derived organocatalyst

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ARTICLE INFO

Article history:
Received 31 January 2012
Received in revised form 3 April 2012
Accepted 23 April 2012
Available online 30 April 2012

Keywords:
Hydrosilylation
Asymmetric synthesis
β-amino acid
Organocatalyst

ABSTRACT

The organocatalysed asymmetric hydrosilylation of a number of *N*-aryl and alkyl β-substituted enamino esters proceeds in generally good yield and enantioselectivity. Crucial to obtaining high yield and selectivity was the addition of benzoic acid as an additive and under these conditions, both *N*-alkyl and *N*-aryl substituents were well tolerated. β-Aryl and alkyl substituents were evaluated and a model proposed to account for the experimental observations based upon enamine tautomerisation and conformational preferences of the reactive ketimine intermediate.

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1. Introduction

Optically active β-amino acids and their derivatives are key building blocks for the synthesis of β-peptides, β-lactams and related biologically active compounds, with a wide variety of methods having been reported for their preparation.[1] Catalytic methods include the use of transition-metals, organocatalysts, and biocatalysts, and more recently, several groups have reported the use of chiral Lewis-bases for the trichlorosilane mediated asymmetric reduction of β-enamino esters.[2] These advances stem from efforts from a number of research groups to extend the substrate scope of such catalysts derived from formamides, picolinoylamides, phosphine oxides and sulfoxides as activators of trichlorosilane for the catalytic asymmetric reduction of ketimines.[3]

Malkov and Kočovský first reported the reduction of β-enamino esters and nitriles in 2008 using the commercially available Sigamide® chiral formamide catalyst.[4] The addition of acetic acid was deemed essential to buffer the reaction medium and promote isomerisation to the reactive ketimine tautomer. Using these conditions, a range of β-aryl and alkyl *N*-*p*-methoxyphenyl enamines were reduced in excellent yield with an enantiomeric excess ranging from 59 to 90%. α-Substituted substrates were also found to react with exceptional levels of diastereoselectivity. Later that year,[5] Zhang published similar findings with 2-picolinamide catalysts, although it was not until their follow-up work in 2011 that the applicability to α-substituted substrates was comprehensively demonstrated and observations were made of the need to use unpurified solvent to facilitate generation of HCl needed to promote tautomerisation. Nakajima's group was the first to use Lewis basic bis-phosphine oxides and pyridine-*N*-oxides to affect competitive 1,4- and 1,2-reduction pathways of structurally related *N*-acyl-β-enamino ketones in up to 81% ee.[6] Subsequent work by Benaglia has demonstrated the use of phosphinamide catalysts for the reduction of β-aryl *N*-benzyl and *N*-*p*-methoxybenzyl β-enamino esters in generally good yield, with an enantiomeric excess of up to 83%, which could be increased further by the use of an additional stereodirecting group in the substrate.[7] A recent report by the same group has examined the use of picolinamide catalysts to effect the same transformation with similar results. Interestingly, neither Nakajima nor Benaglia report the use of additives to augment the yield and/or selectivity. However, recent work from Sun has shown that additives, in particular precisely measured quantities of water, are essential for ensuring high yields and ees in the reduction of *N*-alkyl β-enamino esters promoted by sulfonamide catalysts.[8]

We recently reported the development of an imidazole-based organocatalyst able to catalyse the asymmetric reduction of a variety of ketimines in excellent yields and enantioselectivities at very low catalyst loading,[9] and more recently reported the extension of this catalyst to the direct reductive amination of ketones with both aromatic and aliphatic amines.[3c] Herein, we describe the application to the reduction of β-enamino esters with this catalyst.

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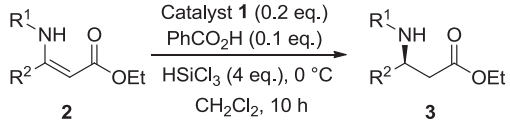
doi:10.1016/j.tet.2012.04.084

2. Results and discussion

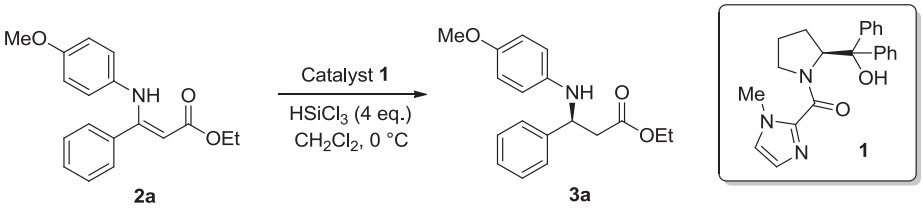
β-Enamino ester **2a** was used as a model substrate for initial evaluation of the reduction conditions (Scheme 1). Under the initial reaction conditions, the process suffered from poor reproducibility in terms of both yields and enantioselectivity, however, this problem could not be overcome by addition of acetic acid or water as noted by other groups (Table 1, entries 1–3). Sub-stoichiometric amounts of other Brønsted acids including salicylic acid, benzoic acid and phenol were then investigated in the presence of 10 mol % catalyst (Table 1, entries 4–11). High reactivity was observed when 0.2 equiv of salicylic acid was used as an additive but low enantioselectivity was observed (Table 1, entry 4). Using 0.2 equiv of benzoic acid or phenol also improved the reactivity slightly and gave good enantioselectivity (Table 1, entries 5 and 6). However, further increasing the amount of benzoic acid additive to 0.3 equiv rendered a sharp decrease in enantioselectivity (Table 1, entry 7). Higher enantioselectivity could be achieved when using less equivalents of additive, but this did lead to a drop in yield (Table 1, entries 8–10). The optimum ratio of catalyst to additive was found to be 0.2 equiv of catalyst **1** with 0.1 equiv of benzoic acid as an additive (Table 1, entry 11). Using these conditions, product **2a** was isolated in 76% yield and 91% ee after 10 h at 0 °C (Table 1, entry 11).

There appears to be a tentative correlation between the enantioselectivity of these reactions with the pK_a of the aniline or amine, since the more basic species generally provide products with higher enantioselectivity. Thus, electron donating nitrogen substituents are likely to facilitate the rate of equilibration of the enamine to its reactive ketimine tautomer and any subsequent isomerisation. Since it is well recognized that the enantioselectivities obtained in trichlorosilane processes are independent of the ratio of the initial ketimine geometries, facile equilibration is a prerequisite for high selectivity (Fig. 1).



Scheme 2. Application of optimized conditions.

The ketimine tautomer then adopts a preferred conformation that places the nitrogen substituent *anti* to the aryl ring, which maximizes the conjugation between the aryl and C=N π-systems. This conformation must also locate the ester functionality at 90° to the sp^2 system to minimize interactions between this group and both the nitrogen substituent and aryl ring. Such a conformation that then places the ester remote from the catalyst is important, since Sun demonstrated that the selectivity in these processes is independent of the size of the ester functionality.[8] Molecular modelling of a simple representative iminium ion supports this hypothesis, clearly showing a low-energy conformation with these key features (Fig. 2). Note that the face selectivity in this proposed model is then analogous to that proposed for the reduction of acetophenone derivatives by Matsumura.[10]



Scheme 1. Initial substrate for optimization studies in Table 1.

Table 1
Optimization of initial reaction conditions for Scheme 1 [a]

Entry	**1** (equiv)	Additive (equiv)	Time (h)	Yield[b] (%)	ee[c] (%)
1	0.1	None	10	55	84
2	0.1	AcOH (1)	10	90	42
3	0.1	H_2O (1)	10	74	51
4	0.1	Salicylic acid (0.2)	10	87	65
5	0.1	PhCOOH (0.2)	10	68	85
6	0.1	PhOH (0.2)	10	70	83
7	0.1	PhCOOH (0.3)	10	83	75
8	0.1	PhCOOH (0.1)	10	60	88
9	0.1	PhCOOH (0.1)	24	62	88
10	0.1	PhCOOH (0.05)	10	58	91
11	0.2	PhCOOH (0.1)	10	76	91

[a] Compound **2a** (0.5 mmol), $HSiCl_3$ (2 mmol), CH_2Cl_2 (1 mL) at 0 °C.
[b] Refers to isolated product.
[c] Determined by chiral phase HPLC.

With optimized conditions in-hand, a representative series of β-enamino esters were prepared by standard methods and used in this reaction. In the first instance, a series of differentially *N*-substituted β-phenyl enamine substrates were examined (Scheme 2, Table 2, entries 1–8). Most delivered the desired product with enantioselectivities over 85% (entries 1–3, 5, 7 and 8), notably including *N*-methyl and *N*-benzyl substrates. The absolute configuration of the products was confirmed by comparison with literature specific rotations where possible or by structural analogy. Two anomalies were observed with *p*-fluorophenyl (entry 4) and *o*-methoxyphenyl (entry 6). Since high enantioselectivities can be obtained with nitrogen protecting groups of varied size (Me vs Ph), the origin of the selectivity is more likely to lie in electronic factors.

Table 2
Substrate scope of reaction described in Scheme 2

Entry	R^1	R^2	Product	Yield[a] (%)	ee[b] (%)
1	4-$MeOC_6H_4$	Ph	**3a**	76	91
2	Ph	Ph	**3b**	64	85
3	4-MeC_6H_4	Ph	**3c**	69	87
4	4-FC_6H_4	Ph	**3d**	59	71
5	2-MeC_6H_4	Ph	**3e**	53	86
6	2-$MeOC_6H_4$	Ph	**3f**	41	13
7	$PhCH_2$	Ph	**3g**	57	93
8	Me	Ph	**3h**	59	94
9	4-$MeOC_6H_4$	4-MeC_6H_4	**3i**	75	92
10	4-$MeOC_6H_4$	4-$MeOC_6H_4$	**3j**	70	91
11	4-$MeOC_6H_4$	2-Thienyl	**3k**	66	90
12	4-$MeOC_6H_4$	4-$NO_2C_6H_4$	**3l**	50	82
13	4-$MeOC_6H_4$	2-MeC_6H_4	**3m**	27	3
14	4-$MeOC_6H_4$	$PhCH_2$	**3n**	56	30
15	4-$MeOC_6H_4$	Me	**3o**	63	20
16	4-$MeOC_6H_4$	*i*-Pr	**3p**	44	56

[a] Refers to isolated product.
[b] Determined by chiral phase HPLC, except entry 15 where integration of signals in the ^1H NMR spectrum after addition of mandelic acid was employed.

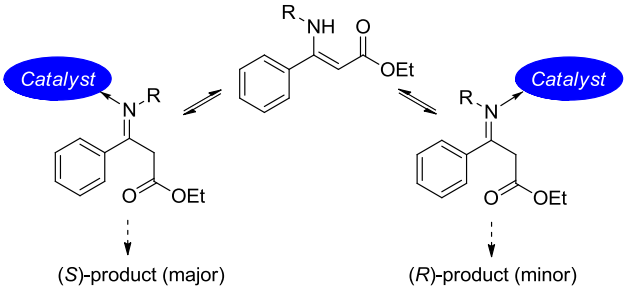


Fig. 1. Effect of the *N*-substituent on selectivity.

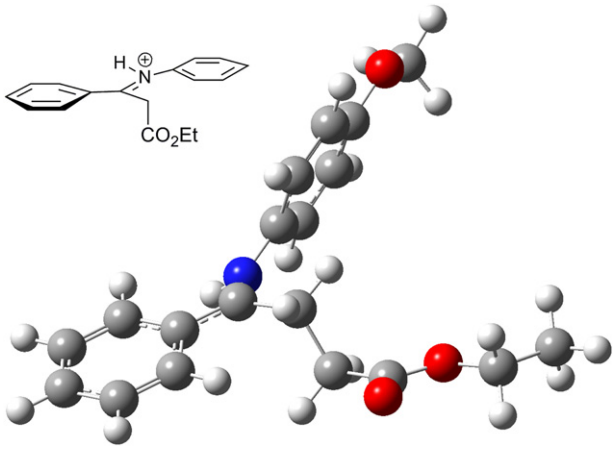
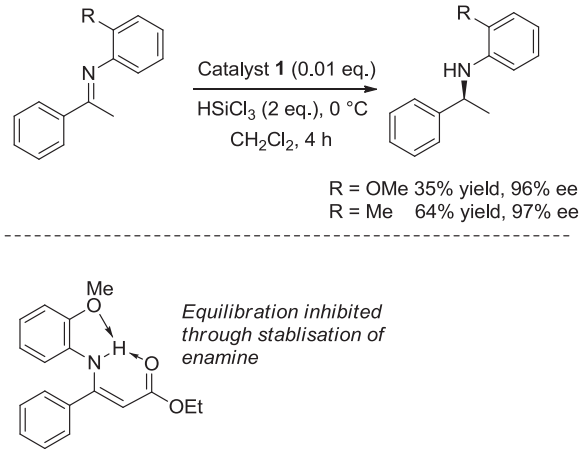


Fig. 2. Modelled low-energy conformer of reaction intermediate.

The exception to this hypothesis is then the *o*-methoxyphenyl derivative (entry 6), which despite having similar basicity to the *p*-methoxyphenyl derivative delivers the lowest enantioselectivity. It is also interesting to note the reduction of the corresponding ketimine proceeds with excellent selectivity, although in low yield, whilst the analogous 2-methyl derivative provides product with both good yield and selectivity (Scheme 3). This evidence strongly supports a synergistic role of the oxygen atom and the adjacent carbonyl group, perhaps through stabilisation of the enamine tautomer, thus inhibiting the rate of the tautomerisation process. It is important to note that only one other report has investigated the role of the nitrogen protecting group in this type of reaction, and high enantioselectivities were obtained in all cases.[5b] However,



Scheme 3. Reduction of 2-substituted *N*-aryl ketimines/enamines.

since no additives were employed in this work, their role in influencing the data cannot be ruled out.

Since the *N*-*p*-methoxyphenyl group delivered one of the best yields and enantioselectivities, it was then used to probe the effect of varying the substituent in the β-position (Table 2, entries 9–16). In general, nearly all β-aryl substituents gave good yield and enantioselectivity (Table 2, entries 9–12), except for the *o*-methylphenyl derivative (Table 2, entry 13). In this case, the conversion obtained is inline with that observed for the background reaction, and this, coupled with the low ee, indicates that the catalyst cannot bind to this substrate due to the steric requirements of the *o*-methyl group (Fig. 3).

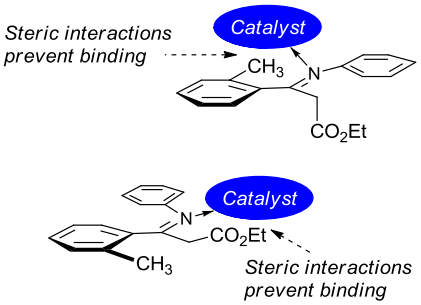


Fig. 3. Possible steric interaction preventing catalyst binding with substrate (Table 2, entry 13).

All of the three β-alkyl substituents evaluated (Table 2, entries 14–16) gave low enantioselectivities, which improved slightly with increasing steric bulk. With the smaller groups, such as methyl and benzyl, there is essentially no difference in the size of the two alkyl groups to dictate a preference for one ketimine geometry. Only when the size differential starts to increase, as with the *iso*-propyl group, is there sufficient bias of one ketimine geometry to facilitate selectivity.

In summary, catalyst **1** can facilitate the reduction of a range of *N*-alkyl and *N*-aryl enamino esters with generally good yield and enantioselectivity. With the information provided from this study and observations noted by other groups, it seems likely that the key stereocontrol event in this reaction is the equilibration of the enamine to a preferred ketimine form. Here stereoselective reduction may then occur on the basis of classic large versus small steric discrimination of the substituents such as in the model proposed by Matsumura (Fig. 4).[10] More detailed mechanistic studies are currently being carried out and will be the subject of a future publication.

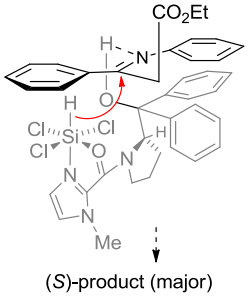


Fig. 4. Possible model for the observed selectivity applying Matsumura's model.

3. Experimental

3.1. General experimental

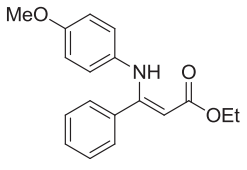
Unless stated otherwise, all solvents were obtained from a Grubbs dry solvent system and glassware were flame dried and cooled under vacuum before use. Petroleum ether refers to the

boiling fraction between 40 and 60 °C. All chemicals were used as received without further purification unless otherwise stated. Analytical thin layer chromatography (TLC) was performed using Merck 60 F_{254} precoated silica gel plates. Subsequent to elution, plates were visualized using UV radiation (254 nm); further visualization was possible by staining with a basic solution of potassium permanganate or silica supported iodine. Flash chromatography was performed using silica gel 40–63 μ 60 Å (Fluorochem Limited). Silica gel chromatography columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 400 MHz or 250 MHz spectrometer at ambient temperature unless otherwise stated. Chemical shifts for ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-*d* (δ 7.26, singlet). Coupling constants (*J*) are reported in hertz. Data for ^{13}C NMR are reported as δ in parts per million downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-*d* (δ 77.0, triplet). Mass spectra (*m*/*z*) were recorded on a 'Waters'-LCT for Electrospray (ES). Infrared spectra were recorded on a Perkin–Elmer 1600 FT-IR as thin film from a solution in dichloromethane or chloroform. Specific rotations were performed at room temperature on an Optical Activity Ltd. AA-10 automatic polarimeter at 589 nm (Na D-line) at 20 °C and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Melting points were measured on a Gallenkamp apparatus and are uncorrected. Elemental analysis was performed on a Perkin–Elmer 2400 CHNS/O Series II apparatus. Enantioselectivities were determined by high performance liquid chromatography (HPLC) analysis employing a Gilson HPLC chain with an ABI Analytical Spectroflow 783 UV detector at λ 254 nm unless specified otherwise, using a mixture of hexane and ipa (propan-2-ol) as the mobile phase and Chiralcel OD-H, Chiralcel OJ, Kromasil 3-Cellucoat OD, Phenomenex Lux 3 μm Amylase-2 or Phenomenex Lux 3 μm Cellulose-1 column as the stationary phase. Mobile phase flow, unless specified otherwise, was 1.0 mL/min. Absolute configuration of the products was determined by comparison with compounds previously published. Catalyst **1** was prepared by established literature methods.[9]

3.2. General procedure A for the preparation of β-enamino esters

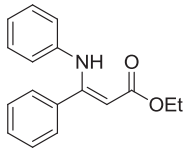
A mixture of β-ketoester (10 mmol), amine (1.1–1.5 equiv, specified for each compound) and *p*-TsOH (0.1 mmol) in ethanol (25 mL) was heated at reflux for overnight. The mixture was then cooled to room temperature and the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel with eluents as noted to give the β-enamino ester.

3.2.1. (*Z*)-Ethyl 3-(4-methoxyphenylamino)-3-phenylacrylate **2a**.[4b]



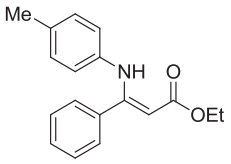
Obtained by general procedure A using 1.0 equiv amine, and purified using 5% EtOAc/petroleum ether eluent, followed by recrystallization from EtOAc/petroleum ether as a yellow solid (1.80 g, 60%); mp 102–105 °C (lit.[4b] 96–98 °C); R_f (10% EtOAc/petroleum ether) 0.60; δ_H (250 MHz, $CDCl_3$) 1.33 (t, 3H, *J* 7.1, CH_3CH_2), 3.72 (s, 3H, OCH_3), 4.22 (q, 2H, *J* 7.1, CH_2), 4.95 (s, 1H, CHCO), 6.65 (app. s, 4H, 4×ArCH), 7.24–7.37 (m, 5H, 5×ArCH), 10.25 (br s, 1H, NH); δ_C (63 MHz, $CDCl_3$) 14.6 (CH_3), 55.3 (OCH_3), 59.2 (OCH_2), 89.6 (C=CH), 113.9 (2×ArCH), 124.3 (2×ArCH), 128.3 (2×ArCH), 128.4 (2×ArCH), 129.2 (ArCH), 133.6 (ArC), 136.1 (ArC), 155.9 (ArC), 159.9 (C=CH), 170.3 (CO). Data were in accordance with the literature.

3.2.2. (*Z*)-Ethyl 3-phenyl-3-(phenylamino)acrylate **2b**.[11]



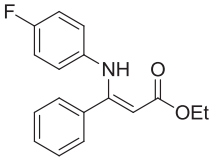
Obtained by general procedure A using 1.2 equiv amine, and purified using 100% petroleum ether eluent as a white solid (1.00 g, 34%); mp 72–74 °C (lit.[11] 65–66 °C); R_f (10% EtOAc/petroleum ether) 0.90; δ_H (250 MHz, $CDCl_3$) 1.34 (t, 3H, *J* 7.2, CH_3CH_2), 4.22 (q, 2H, *J* 7.2, CH_2), 5.01 (s, 1H, CH), 6.65–6.70 (m, 2H, 2×ArCH), 6.89–6.96 (m, 1H, ArCH), 7.07–7.13 (m, 2H, 2×ArCH), 7.26–7.38 (m, 5H, 5×ArCH), 10.32 (br s, 1H, NH); δ_C (63 MHz, $CDCl_3$) 14.6 (CH_3), 59.3 (CH_2), 91.3 (C=CH), 122.2 (2×ArCH), 123.0 (ArCH), 128.3 (2×ArCH), 128.4 (2×ArCH), 128.6 (2×ArCH), 129.4 (ArCH), 136.1 (ArC), 140.1 (ArC), 159.1 (C=CH), 170.1 (CO). ^{1}H NMR data were in accordance with the literature.

3.2.3. (*Z*)-Ethyl 3-phenyl-3-(4-methylphenylamino)acrylate **2c**.[12]



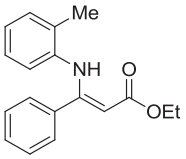
Obtained by general procedure A using 1.2 equiv amine, and purified using 100% petroleum ether eluent, followed by recrystallization from petroleum ether as a white solid (1.51 g, 53% yield); mp 72–74 °C (not reported in literature); R_f (20% EtOAc/petroleum ether) 0.60; δ_H (400 MHz, $CDCl_3$) 1.34 (t, 3H, *J* 7.1, CH_3CH_2), 2.23 (s, 3H, CH_3), 4.23 (q, 2H, *J* 7.1, CH_2), 4.98 (s, 1H, CH), 6.59 (d, 2H, *J* 7.6, 2×ArCH), 6.90 (d, 2H, *J* 7.6, 2×ArCH), 7.28–7.38 (m, 5H, 5×ArCH), 10.28 (br s, 1H, NH); δ_C (100 MHz, $CDCl_3$) 14.6 (CH_3), 20.7 (CH_3), 59.2 (OCH_2), 90.4 (C=CH), 122.4 (2×ArCH), 128.3 (2×ArCH), 128.4 (2×ArCH), 129.2 (2×ArCH), 129.3 (ArCH), 132.6 (ArC), 136.2 (ArC), 137.8 (ArC), 159.4 (C=CH), 170.2 (CO). Data were in accordance with the literature.

3.2.4. (*Z*)-Ethyl 3-(4-fluorophenylamino)-3-phenylacrylate **2d**.[13]



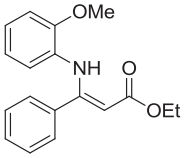
Obtained by general procedure A using 1.5 equiv amine, and purified using a 5%→25% diethyl ether/petroleum ether gradient eluent, followed by recrystallization from diethyl ether/petroleum ether as a white solid (1.67 g, 59% yield); mp 75–77 °C (not reported in literature); R_f (25% diethyl ether/petroleum ether) 0.70; δ_H (400 MHz, $CDCl_3$) 1.34 (t, 3H, *J* 7.1, CH_3CH_2), 4.23 (q, 2H, *J* 7.1, CH_2), 5.02 (s, 1H, CH), 6.64–6.68 (m, 2H, 2×ArCH), 6.78–6.82 (m, 2H, 2×ArCH), 7.28–7.38 (m, 5H, 5×ArCH), 10.26 (br s, 1H, NH); δ_C (100 MHz, $CDCl_3$) 14.5 (CH_3), 59.3 (CH_2), 91.0 (C=CH), 115.3 (d, J_{C-F} 22.7, 2×ArCH), 124.0 (d, J_{C-F} 7.9, 2×ArCH), 128.3 (2×ArCH), 128.5 (2×ArCH), 129.5 (ArCH), 135.7 (ArC), 136.5 (ArC), 159.0 (d, J_{C-F} 242.8, ArCF), 159.3 (C=CH), 170.2 (CO); δ_F (235 MHz, $CDCl_3$) −119.9. Data were in accordance with the literature, although ^{19}F NMR not reported, or J_{C-F} values and multiplicities in ^{13}C NMR data.

3.2.5. (Z)-Ethyl 3-phenyl-3-(2-methylphenylamino)acrylate ***2e***.[14]



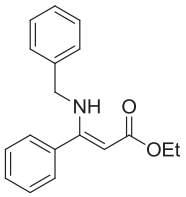
Obtained by general procedure A using 1.5 equiv amine, and purified using a 5%→20% diethyl ether/petroleum ether gradient eluent, followed by recrystallization from diethyl ether/petroleum ether as a light yellow solid (1.16 g, 41%); mp 103–105 °C (not reported in literature); R_f (25% diethyl ether/petroleum ether) 0.70; δ_H (400 MHz, $CDCl_3$) 1.35 (t, 3H, *J* 7.1, CH_3CH_2), 2.45 (s, 3H, CH_3), 4.24 (q, 2H, *J* 7.1, OCH_2), 5.06 (s, 1H, C*H*), 6.35 (d, 1H, *J* 7.8, ArC*H*), 6.83 (td, 1H, *J* 7.8, 1.2, ArC*H*), 6.88 (td, 1H, *J* 7.4, 1.0, ArC*H*), 7.16 (d, 1H, *J* 7.4, ArC*H*), 7.26–7.35 (m, 5H, 5×ArC*H*), 10.17 (br s, 1H, N*H*); δ_C (100 MHz, $CDCl_3$) 14.6 (CH_3CH_2), 18.2 (CH_3C), 59.3 (CH_2), 90.8 (C=*C*H), 123.5 (ArCH), 123.9 (ArCH), 125.8 (ArCH), 128.1 (2×ArCH), 128.3 (2×ArCH), 129.4 (ArCH), 130.2 (ArC), 130.4 (ArCH), 136.2 (ArC), 139.0 (ArC), 159.8 (*C*=CH), 170.3 (*C*O). Data were in accordance with the literature, although ^{13}C NMR signals below 128 ppm have been omitted.

3.2.6. (Z)-Ethyl 3-(2-methoxyphenylamino)-3-phenylacrylate ***2f***.[14]



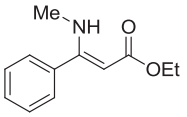
Obtained by general procedure A using 1.2 equiv amine, and purified using a 5% EtOAc/petroleum ether eluent, followed by recrystallization from petroleum ether as yellow crystals (1.21 g, 40%); mp 90–91 °C (lit.[14] 105 °C); R_f (20% EtOAc/petroleum ether) 0.60; δ_H (400 MHz, $CDCl_3$) 1.34 (t, 3H, *J* 7.1, CH_3CH_2), 3.93 (s, 3H, OCH_3), 4.24 (q, 2H, *J* 7.1, CH_2), 5.02 (s, 1H, C*H*), 6.25 (dd, 1H, *J* 7.5, 1.0, ArC*H*), 6.52–6.56 (m, 1H, ArC*H*), 6.84–6.91 (m, 2H, 2×ArC*H*), 7.28–7.40 (m, 5H, 5×ArC*H*), 10.29 (br s, 1H, N*H*); δ_C (100 MHz, $CDCl_3$) 14.6 (CH_3CH_2), 55.7 (OCH_3), 59.3 (CH_2), 91.6 (C=CH), 110.5 (ArCH), 120.0 (ArCH), 121.8 (ArCH), 122.9 (ArCH), 128.0 (2×ArCH), 128.4 (2×ArCH), 129.4 (ArCH), 129.6 (ArC), 136.4 (ArC), 150.5 (ArC), 158.4 (*C*=CH), 169.9 (*C*O). Data were in accordance with the literature.

3.2.7. (Z)-Ethyl 3-(benzylamino)-3-phenylacrylate ***2g***.[8]



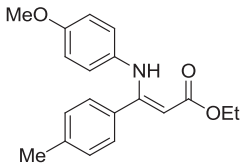
Obtained by general procedure A using 1.5 equiv amine, and purified using a 5%→10% diethyl ether/petroleum ether gradient eluent, followed by recrystallization from petroleum ether/diethyl ether as a white solid (1.17 g, 42% yield); mp 71–72 °C (lit.[8] 66–67 °C); δ_H (400 MHz, $CDCl_3$) 1.33 (t, 3H, *J* 7.1, CH_3CH_2), 4.21 (q, 2H, *J* 7.1, OCH_2), 4.32 (d, 2H, *J* 6.5, NCH_2), 4.75 (s, 1H, C*H*), 7.22–7.44 (m, 10H, 10×ArC*H*), 9.00 (br s, 1H, N*H*); δ_C (100 MHz, $CDCl_3$) 14.7 (CH_3), 48.4 (NCH_2), 58.8 (OCH_2), 86.6 (C=*C*H), 126.9 (2×ArCH), 127.3 (ArCH), 127.9 (2×ArCH), 128.5 (2×ArCH), 128.7 (2×ArCH), 129.3 (ArCH), 136.1 (ArC), 139.4 (ArC), 164.7 (C=*C*H), 170.4 (*C*O). Data were in general accordance with the literature, although no signals above 140 ppm were reported in the ^{13}C NMR data.

3.2.8. (Z)-Ethyl 3-(methylamino)-3-phenylacrylate ***2h***.[15]



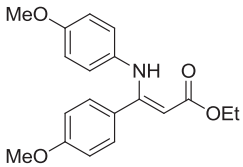
Obtained by general procedure A using methanaminium acetate (2.0 equiv), and purified using a 3%→20% EtOAc/petroleum ether gradient eluent as light yellow oil (1.22 g, 55%); R_f (50% EtOAc/petroleum ether) 0.50; ν_{max} (thin film, cm^{-1}) 3296, 2978, 1650, 1613, 1595, 1574; δ_H (400 MHz, $CDCl_3$) 1.30 (t, 3H, *J* 7.1, CH_3CH_2), 2.79 (d, 3H, *J* 5.2, NCH_3), 4.16 (q, 2H, *J* 7.1, CH_2), 4.62 (s, 1H, C*H*), 7.28–7.43 (m, 5H, 5×ArC*H*), 8.52 (br s, 1H, N*H*); δ_C (100 MHz, $CDCl_3$) 14.6 (CH_3), 31.4 (CH_3N), 58.6 (CH_2), 84.8 (C=CH), 127.8 (2×ArCH), 128.3 (2×ArCH), 129.1 (ArCH), 135.9 (ArC), 165.6 (*C*=CH), 170.6 (C=O); *m*/*z* (TOF ES^+) 206.1172 (MH^+, $C_{12}H_{16}NO_2$ requires 206.1181). Only bp, ν_{max} and signal of δ_H 4.61 ppm are reported in the literature.

3.2.9. (Z)-Ethyl 3-(4-methoxyphenylamino)-3-(4-methylphenyl)acrylate ***2i***.



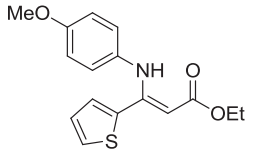
Obtained by general procedure A using 1.06 equiv amine, and purified using a 10%→20% diethyl ether/petroleum ether gradient eluent, followed by recrystallization from diethyl ether/petroleum ether as yellow crystals (1.27 g, 41% yield); mp 78–80 °. Found C 73.24, H 6.62, N 4.43; $C_{19}H_{21}NO_3$ requires C 73.29, H 6.80, N 4.50; R_f (25% diethyl ether/petroleum ether) 0.50; ν_{max} (thin film, cm^{-1}) 3251, 2978, 1653, 1615, 1513; δ_H (400 MHz, $CDCl_3$) 1.34 (t, 3H, *J* 7.1, CH_3CH_2), 2.34 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 4.22 (q, 2H, *J* 7.1, CH_2), 4.94 (s, 1H, C*H*), 6.65–6.69 (m, 4H, 4×ArC*H*), 7.09 (d, 2H, *J* 8.0, 2×ArC*H*), 7.23 (d, 2H, *J* 8.0, 2×ArC*H*), 10.23 (br s, 1H, N*H*); δ_C (100 MHz, $CDCl_3$) 14.6 (CH_3), 21.3 (CH_3), 55.3 (OCH_3), 59.1 (CH_2), 89.3 (C=*C*H), 113.9 (2×ArCH), 124.2 (2×ArCH), 128.3 (2×ArCH), 129.0 (2×ArCH), 133.1 (ArC), 133.7 (ArC), 139.3 (ArC), 155.8 (ArC), 160.0 (C=*C*H), 170.4 (*C*O); *m*/*z* (TOF ES^+) 312 (100, MH^+), 266 (10).

3.2.10. (Z)-Ethyl 3-(4-methoxyphenyl)-3-(4-methoxyphenylamino) acrylate ***2j***.[4a]



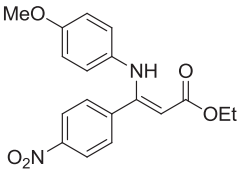
Obtained by general procedure A using 1.5 equiv amine, and purified using a 10%→20% diethyl ether/petroleum ether gradient eluent as a brown, sticky oil (1.63 g, 50% yield); R_f (20% diethyl ether/petroleum ether) 0.40; δ_H (400 MHz, $CDCl_3$) 1.33 (t, 3H, *J* 7.1, CH_3CH_2), 3.74 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.20 (q, 2H, *J* 7.1, OCH_2), 4.93 (s, 1H, C*H*), 6.65–6.69 (m, 4H, 4×ArC*H*), 6.80 [$(AX)_2$, 2H, 2×ArC*H*], 7.26 [$(AX)_2$, 2H, 2×ArC*H*], 10.21 (br s, 1H, N*H*); δ_C (100 MHz, $CDCl_3$) 14.6 (CH_3), 55.2 (OCH_3), 55.3 (OCH_3), 59.1 (CH_2), 88.9 (C=*C*H), 113.7 (2×ArCH), 113.9 (2×ArCH), 124.3 (2×ArCH), 128.2 (ArC), 129.8 (2×ArCH), 133.8 (ArC), 155.7 (ArC), 159.7 (ArC), 160.4 (C=*C*H), 170.4 (*C*O). Data were in accordance with the literature, although a solid is reported rather than an oil.

3.2.11. (Z)-Ethyl 3-(4-methoxyphenylamino)-3-(2-thienyl)acrylate ***2k***.[4b]



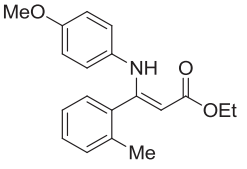
Obtained by general procedure A using 1.5 equiv amine, and purified using a 5%→20% diethyl ether/petroleum ether gradient eluent, followed by recrystallization from petroleum ether as yellow crystals (1.36 g, 45% yield); mp 54–56 °C (lit.[4b] 52–53 °C); R_f (20% EtOAc/petroleum ether) 0.70; δ_H (400 MHz, $CDCl_3$) 1.34 (t, 3H, *J* 7.1, C*H*$_3$CH$_2$), 3.77 (s, 3H, OC*H*$_3$), 4.22 (q, 2H, *J* 7.1, CH$_3$O), 5.15 (s, 1H, C*H*), 6.73 [(AX)$_2$, 2H, 2×ArC*H*], 6.83 [(AX)$_2$, 2H, 2×ArC*H*], 6.92 (dd, 1H, *J* 5.0, 3.7, ArC*H*), 7.01 (dd, 1H, *J* 3.7, 1.2, ArC*H*), 7.30 (dd, 1H, *J* 5.0, 1.2, ArC*H*), 10.05 (br s, 1H, N*H*); δ_C (100 MHz, $CDCl_3$) 14.6 (*C*H$_3$), 55.4 (OCH$_3$), 59.3 (OCH$_2$), 89.5 (*C*H), 114.0 (2×ArCH), 125.3 (2×ArCH), 127.1 (ArCH), 127.6 (ArCH), 129.0 (ArCH), 133.5 (Ar*C*), 137.6 (Ar*C*), 153.0 (Ar*C*), 156.5 (C=*C*H), 170.1 (*C*O). Data were in accordance with the literature.

3.2.12. (Z)-Ethyl 3-(4-methoxyphenylamino)-3-(4-nitrophenyl)acrylate ***2l***.



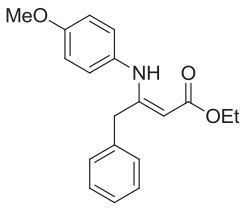
Obtained by general procedure A using 1.5 equiv amine, and purified by slow cooling of the reaction mixture, filtration and washing with diethyl ether as yellow needle-like crystals (2.80 g, 82% yield); mp 126–128 °C. Found C 63.29, H 5.26, N 8.17; $C_{18}H_{18}N_2O_5$ requires C 63.15, H 5.30, N 8.18; ν_{max} (thin film, cm^{-1}) 3258, 2979, 1658, 1615, 1591, 1514; δ_H (400 MHz, $CDCl_3$) 1.35 (t, 3H, *J* 7.1, C*H*$_3$CH$_2$), 3.73 (s, 3H, OC*H*$_3$), 4.24 (q, 2H, *J* 7.1, C*H*$_2$), 5.00 (s, 1H, C*H*), 6.64–6.69 (m, 4H, 4×ArC*H*), 7.51 (d, 2H, *J* 7.5, 2×ArC*H*), 8.14 (d, 2H, *J* 7.5, 2×ArC*H*), 10.17 (br s, 1H, N*H*); δ_C (100 MHz, $CDCl_3$) 14.5 (*C*H$_3$), 55.3 (OCH$_3$), 59.6 (*C*H$_2$), 91.3 (C=*C*H), 114.2 (2×ArCH), 123.6 (2×ArCH), 124.8 (2×ArCH), 129.3 (2×ArCH), 132.7 (Ar*C*), 142.7 (Ar*C*), 148.0 (Ar*C*), 156.4 (Ar*C*), 157.2 (C=*C*H), 169.8 (*C*O); *m*/*z* (TOF ES$^+$) 343.1290 (MH$^+$, $C_{18}H_{19}N_2O_5$ requires 343.1294).

3.2.13. (Z)-Ethyl 3-(4-methoxyphenylamino)-3(2-methylphenyl)acrylate ***2m***.[4b]



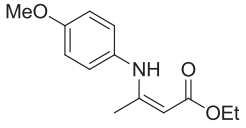
Obtained by general procedure A using 2.0 equiv amine, and purified using a 5%→20% diethyl ether/petroleum ether gradient eluent, followed by recrystallization from diethyl ether/petroleum ether as a white solid (0.43 g, 11%); mp 58–61 °C (lit.[4b] 51–53 °C); R_f (20% EtOAc/petroleum ether) 0.40; δ_H (400 MHz, $CDCl_3$) 1.34 (t, 3H, *J* 7.1, C*H*$_3$CH$_2$), 2.13 (s, 3H, C*H*$_3$), 3.71 (s, 3H, OC*H*$_3$), 4.22 (q, 2H, *J* 7.1, CH$_2$CH$_3$), 4.72 (s, 1H, C*H*), 6.57–6.62 (m, 4H, 4×ArC*H*), 7.08 (d, 1H, *J* 7.4, ArC*H*), 7.18–7.23 (m, 1H, ArC*H*), 7.24–7.27 (m, 1H, ArC*H*), 7.32 (dd, 1H, *J* 7.4, 1.5, ArC*H*), 10.51 (br s, 1H, N*H*); δ_C (100 MHz, $CDCl_3$) 14.6 (*C*H$_3$), 19.5 (*C*H$_3$), 55.3 (OCH$_3$), 59.1 (*C*H$_2$), 88.1 (C=*C*H), 113.9 (2×ArCH), 122.9 (2×ArCH), 125.8 (ArCH), 129.0 (ArCH), 130.3 (2×ArCH), 133.1 (Ar*C*), 135.5 (Ar*C*), 135.9 (Ar*C*), 155.8 (Ar*C*), 160.2 (C=*C*H), 170.5 (*C*O). Data were in accordance with the literature.

3.2.14. (Z)-Ethyl 3-(4-methoxyphenylamino)-4-phenylbut-2-enoate ***2n***.



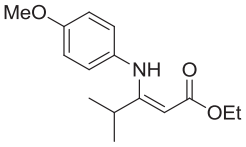
Obtained by general procedure A using 1.5 equiv amine, and purified using a 5%→10% diethyl ether/petroleum ether gradient eluent, followed by recrystallization from diethyl ether/petroleum ether as white needle-like crystals (1.17 g, 56% yield), mp 70–72 °C. Found C 73.52, H 6.78, N 4.47; $C_{19}H_{21}NO_3$ requires C 73.29, H 6.80, N 4.50; R_f (25% diethyl ether/petroleum ether) 0.40; ν_{max} (thin film, cm^{-1}) 3028, 2977, 1651, 1613, 1514; δ_H (400 MHz, $CDCl_3$) 1.30 (t, 3H, *J* 7.1, C*H*$_3$CH$_2$), 3.52 (s, 2H, C*H*$_2$), 3.81 (s, 3H, OC*H*$_3$), 4.16 (q, 2H, *J* 7.1, OC*H*$_2$), 4.62 (s, 1H, C*H*), 6.81 [(AX)$_2$, 2H, 2×ArC*H*], 6.96 [(AX)$_2$, 2H, 2×ArC*H*], 7.03–7.06 (m, 2H, 2×ArC*H*), 7.18–7.26 (m, 3H, 3×ArC*H*), 10.15 (br s, 1H, N*H*); δ_C (100 MHz, $CDCl_3$) 14.6 (*C*H$_3$), 38.7 (*C*H$_2$), 55.4 (OCH$_3$), 58.8 (OCH$_2$), 86.1 (C=*C*H), 114.1 (2×ArCH), 126.6 (ArCH), 127.8 (2×ArCH), 128.4 (2×ArCH), 128.9 (2×ArCH), 131.8 (Ar*C*), 137.0 (Ar*C*), 157.8 (Ar*C*), 162.4 (C=*C*H), 170.7 (*C*O); *m*/*z* (TOF ES$^+$) 312.1610 (MH$^+$, $C_{19}H_{22}NO_3$ requires 312.1600).

3.2.15. (Z)-Ethyl 3-(4-methoxyphenylamino)but-2-enoate ***2o***.[16]



Obtained by general procedure A using 1.5 equiv amine and heating at reflux for 3 h, and purified using a 20% diethyl ether/petroleum ether eluent, followed by recrystallization from petroleum ether as white needle-like crystals (1.55 g, 66% yield), mp 42–44 °C (lit.[17] 44.5–45.5 °C); R_f (25% diethyl ether/petroleum ether) 0.30; δ_H (400 MHz, $CDCl_3$) 1.31 (t, 3H, *J* 7.2, C*H*$_3$ CH$_2$), 1.91 (s, 3H, C*H*$_3$), 3.83 (s, 3H, OC*H*$_3$), 4.17 (q, 2H, *J* 7.2, C*H*$_2$), 4.67 (s, 1H, CH), 6.69 [(AX)$_2$, 2H, 2×ArC*H*], 7.05 [(AX)$_2$, 2H, 2×ArC*H*], 10.17 (br s, 1H, N*H*); δ_C (100 MHz, $CDCl_3$) 14.6 (*C*H$_3$), 20.1 (*C*H$_3$), 55.4 (OCH$_3$), 58.6 (CH$_2$), 84.7 (C=*C*H), 114.2 (2×ArCH), 126.8 (2×ArCH), 132.1 (Ar*C*), 157.5 (Ar*C*), 160.0 (*C*=CH), 170.5 (*C*O). Data were in accordance with the literature.

3.2.16. (Z)-Ethyl 3-(4-methoxyphenylamino)-4-methylpent-2-enoate ***2p***.[4b]



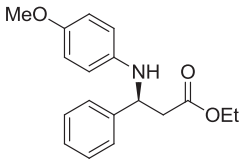
Obtained by general procedure A using 1.5 equiv amine, and purified using a 5% diethyl ether/petroleum ether eluent to remove excess amine. The resulting mixture was distilled under reduced pressure to remove excess volatiles, and the residue solidified on

standing to provide product as a white solid (1.10 g, 42% yield); mp 37–39 °C (lit.[4b] 36–38 °C); δ_H (400 MHz, $CDCl_3$) 1.08 [d, 6H, *J* 6.8, $CH(CH_3)_2$], 1.32 (t, 3H, *J* 7.1, CH_3), 2.73 (hept, 1H, *J* 6.8, C*H*), 3.83 (s, 3H, CH_3), 4.17 (q, 2H, *J* 7.1, CH_2), 4.73 (s, 1H, C*H*=C), 6.89 [$(AX)_2$, 2H, 2×ArC*H*], 7.05 [$(AX)_2$, 2H, 2×ArC*H*], 10.19 (br s, 1H, N*H*); δ_C (100 MHz, $CDCl_3$) 14.6 (CH_3), 22.0 (2×CH_3), 28.4 (CH), 55.4 (OCH_3), 58.7 (CH_2), 80.3 (C=*C*H), 114.3 (2×ArCH), 127.8 (2×ArCH), 131.8 (Ar*C*), 157.7 (Ar*C*), 171.1 (C=*C*H), 171.3 (*C*O). Data were in accordance with the literature.

3.3. General procedure B for the reduction of β-enamino esters

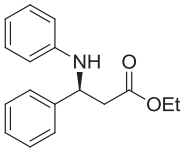
β-Ketoester (0.5 mmol), catalyst **1** (0.1 mmol), benzoic acid (0.05 mmol) and dry dichloromethane (1 mL) were added into a 20 mL Schlenk tube. The mixture was stirred until complete dissolution, then cooled to 0 °C and trichlorosilane (0.2 mmol) was added by syringe. The resulting mixture was left to stir for 10 h at 0 °C. The reaction mixture was diluted with CH_2Cl_2 (20 mL), quenched with water (2 mL) and followed by addition of aqueous sodium hydroxide (1 M, 20 mL). This mixture was stirred until the precipitate was completely dissolved and no gas was evolved. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2×20 mL). The combined organic phases were washed with brine (20 mL) and dried over $MgSO_4$. Filtration and concentration gave the crude product, which was purified by chromatography on silica gel using a 2–20% solution of diethyl ether in petroleum ether.

3.3.1. (S)-Ethyl 3-(4-methoxyphenylamino)-3-phenylpropanoate **3a**.[4b]



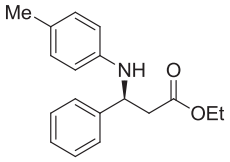
Obtained by general procedure B as a white solid (114 mg, 76% yield, 91% ee); mp 68–70 °C (lit.[4b] 51–53 °C); $[\alpha]_D$ −5.7 (*c* 0.7, $CHCl_3$) 91% ee; lit.[4b] $[\alpha]_D$ −5.6 (*c* 1.0, in $CHCl_3$) 92.3% ee; R_f (25% diethyl ether/petroleum ether) 0.30; δ_H (400 MHz, $CDCl_3$) 1.22 (t, 3H, *J* 7.1, CH_3CH_2), 2.75–2.85 (m, 2H, CH_2), 3.72 (s, 3H, OCH_3), 4.09–4.16 (m, 2H, OCH_2), 4.33 (br s, 1H, N*H*), 4.77 (t, 1H, *J* 6.7, NC*H*), 6.55 [$(AX)_2$, 2H, 2×ArC*H*], 6.72 [$(AX)_2$, 2H, 2×ArC*H*], 7.24–7.28 (m, 1H, ArC*H*), 7.32–7.40 (m, 4H, 4×ArC*H*); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 43.0 (CH_2), 55.7 (NCH), 56.0 (OCH_3), 60.8 (OCH_2), 114.8 (2×ArCH), 115.2 (2×ArCH), 126.3 (2×ArCH), 127.4 (ArCH), 128.7 (2×ArCH), 141.0 (Ar*C*), 142.5 (Ar*C*), 152.3 (Ar*C*), 171.3 (*C*O). Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 μm Cellulose-1) 5% ipa in hexane@1 mL min^{-1}, t_R=13.3 min (minor), 17.7 min (major). Data were in accordance with the literature.

3.3.2. (S)-Ethyl 3-phenyl-3-(phenylamino)propanoate **3b**.[16]



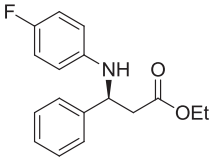
Obtained by general procedure B as a white solid (86 mg, 64% yield, 85% ee); mp 74–76 °C (no literature mp reported); $[\alpha]_D$ 0 (*c* 1.0, $CHCl_3$) 85% ee; lit.[16] $[\alpha]_D$ −1.3 (*c* 1.0, $CHCl_3$) 92.3% ee; R_f (25% diethyl ether/petroleum ether) 0.40; δ_H (400 MHz, $CDCl_3$) 1.22 (t, 3H, *J* 7.2, CH_3CH_2), 2.81 (dd, 1H, *J* 14.8, 6.8, CHH), 2.85 (dd, 1H, *J* 14.8, 6.8, CHH), 4.07–4.19 (m, 2H, OCH_2), 4.65 (br s, 1H, N*H*), 4.86 (t, 1H, *J* 6.8, NC*H*), 6.59 (d, 2H, *J* 7.8, 2×ArC*H*), 6.69 (t, 1H, *J* 7.4, ArC*H*), 7.12 (t, 2H, *J* 7.4, 2×ArC*H*), 7.23–7.29 (m, 1H, ArC*H*), 7.33–7.37 (m, 2H, 2×ArC*H*), 7.40–7.42 (m, 2H, 2×ArC*H*); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 42.9 (CH_2), 55.0 (NCH), 60.8 (OCH_2), 113.7 (2×ArCH), 117.8 (ArCH), 126.3 (2×ArCH), 127.5 (ArCH), 128.8 (2×ArCH), 129.2 (2×ArCH), 142.2 (Ar*C*), 146.8 (Ar*C*), 171.1 (*C*O). Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 μm Cellulose-1) 5% ipa in hexane@1 mL min^{-1}, t_R=12.2 min (major), 12.8 min (minor). Data were in accordance with the literature.

3.3.3. (S)-Ethyl 3-phenyl-3-(4-methylphenylamino)propanoate **3c**.



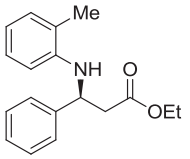
Obtained by general procedure B as a white solid (98 mg, 69% yield, 87% ee); mp 58–60 °C; $[\alpha]_D$ −5.7 (*c* 0.7, $CHCl_3$) 87% ee. Found C 76.09, H 7.38, N 4.72; $C_{18}H_{21}NO_2$ requires C 76.29, H 7.47, N 4.94; R_f (25% diethyl ether/petroleum ether) 0.40; ν_{max} (thin film, cm^{-1}) 3392, 2981, 1728, 1618, 1520; δ_H (400 MHz, $CDCl_3$) 1.22 (t, 3H, *J* 7.2, CH_3CH_2), 2.22 (s, 3H, CH_3), 2.80 (dd, 1H, *J* 14.7, 7.0, CHH), 2.84 (dd, 1H, *J* 14.7, 7.0, CHH), 4.08–4.19 (m, 2H, OCH_2), 4.48 (br s, 1H, N*H*), 4.83 (t, 1H, *J* 7.0, NC*H*), 6.52 (d, 2H, *J* 7.5, 2×ArC*H*), 6.95 (d, 2H, *J* 7.5, 2×ArC*H*), 7.25–7.29 (m, 1H, ArC*H*), 7.33–7.37 (m, 2H, 2×ArC*H*), 7.40–7.42 (m, 2H, 2×ArC*H*); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 20.4 (CH_3), 43.0 (CH_2), 55.3 (NCH), 60.8 (OCH_2), 113.9 (2×ArCH), 126.3 (2×ArCH), 127.0 (ArCH), 127.4 (Ar*C*), 128.8 (2×ArCH), 129.7 (2×ArCH), 142.5 (Ar*C*), 144.6 (Ar*C*), 171.2 (*C*O); *m*/*z* (TOF ES^+) 284 (MH^+, 100). Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 μm Cellulose-1) 5% ipa in hexane@1 mL min^{-1}, t_R=9.5 min (minor), 11.7 min (major).

3.3.4. (S)-Ethyl 3-phenyl-3-(4-fluorophenylamino)propanoate **3d**.



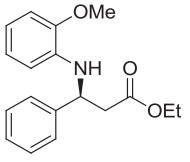
Obtained by general procedure B as a white solid (84 mg, 59% yield, 71% ee); mp 50–52 °C; $[\alpha]_D$ +10 (*c* 1.2, $CHCl_3$) 71% ee. Found C 70.75, H 6.29, N 4.77; $C_{17}H_{18}FNO_2$ requires C 71.06, H 6.31, N 4.87; R_f (25% diethyl ether/petroleum ether) 0.50; ν_{max} (thin film, cm^{-1}) 3393, 2982, 1727, 1510; δ_H (400 MHz, $CDCl_3$) 1.22 (t, 3H, *J* 7.2, CH_3CH_2), 2.78 (dd, 1H, *J* 14.8, 7.9, CHH), 2.83 (dd, 1H, *J* 14.8, 5.5, CHH), 4.10–4.17 (m, 2H, CH_2), 4.51 (br s, 1H, N*H*), 4.75–4.79 (m, 1H, NC*H*), 6.49–6.52 (m, 2H, 2×ArC*H*), 6.80–6.84 (m, 2H, 2×ArC*H*), 7.25–7.39 (m, 5H, 5×ArC*H*); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 42.9 (CH_2), 55.7 (NCH), 60.8 (OCH_2), 114.6 (d, J_{C-F} 7.5, 2×ArCH), 115.6 (d, J_{C-F} 22.3, 2×ArCH), 126.3 (2×ArCH), 127.5 (ArCH), 128.8 (2×ArCH), 142.1 (Ar*C*), 143.2 (Ar*C*), 156.0 (d, J_{C-F} 235.4, ArCF), 171.2 (*C*O); δ_F (235 MHz, $CDCl_3$) −127.6; *m*/*z* (TOF ES^+) 288.1393 (MH^+, $C_{17}H_{19}FNO_2$ requires 288.1400). Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 μm Cellulose-1) 5% ipa in hexane@1 mL min^{-1}, t_R=9.4 min (minor), 11.7 min (major).

3.3.5. (S)-Ethyl 3-(2-methylphenylamino)-3-phenylpropanoate ***3e***.



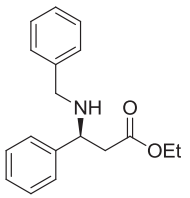
Obtained by general procedure B as a colourless oil (75 mg, 53% yield, 86% ee); $[\alpha]_D$ +25.3 (*c* 1.5, $CHCl_3$) 73% ee. Found C 76.35, H 7.83, N 4.94; $C_{18}H_{23}NO_2$ requires C 76.29, H 7.47, N 4.94; R_f (15% diethyl ether/petroleum ether) 0.60; ν_{max} (thin film, cm^{-1}) 3419, 2980, 1728, 1606, 1588; δ_H (400 MHz, $CDCl_3$) 1.23 (t, 3H, *J* 7.1, CH_3CH_2), 2.28 (s, 3H, CH_3), 2.84 (dd, 1H, *J* 14.5, 7.7, CHH), 2.89 (dd, 1H, *J* 14.5, 5.5, CHH), 4.11–4.17 (m, 2H, OCH_2), 4.65 (br s, 1H, NH), 4.88 (dd, 1H, *J* 7.7, 5.5, NCH), 6.41 (d, 1H, *J* 8.0, ArCH), 6.65 (t, 1H, *J* 7.3, ArCH), 6.99 (t, 1H, *J* 8.0, ArCH), 7.08 (d, 1H, *J* 7.3, ArCH), 7.25–7.29 (m, 1H, ArCH), 7.33–7.42 (m, 4H, 4×ArCH); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 17.6 (CH_3), 43.2 (CH_2), 55.0 (NCH), 60.9 (OCH_2), 111.2 (ArCH), 117.3 (ArCH), 122.3 (ArC), 126.2 (2×ArCH), 127.0 (ArCH), 127.4 (ArCH), 128.8 (2×ArCH), 130.1 (ArCH), 142.3 (ArC), 144.8 (ArC), 171.3 (CO); *m*/*z* (TOF ES^+) 284.1644 (MH^+, $C_{18}H_{22}NO_2$ requires 284.1651). Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 μm Cellulose-1) 5% ipa in hexane@1 mL min^{-1}, t_R=10.1 min (major), 13.8 min (minor).

3.3.6. (S)-Ethyl 3-(2-methoxyphenylamino)-3-phenylpropanoate ***3f***.[18]



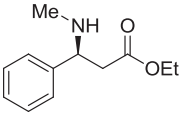
Obtained by general procedure B as a colourless oil (61 mg, 41% yield, 13% ee); $[\alpha]_D$ +3.0 (*c* 2.3, $CHCl_3$) 13% ee; lit.[18] $[\alpha]_D$ −19 (*c* 1.2, $CHCl_3$) 83% ee for *R* isomer; R_f (20% diethyl ether/petroleum ether) 0.60; δ_H (400 MHz, $CDCl_3$) 1.22 (t, 3H, *J* 7.2, CH_3CH_2), 2.83 (dd, 1H, *J* 14.6, 6.7, CHH), 2.88 (dd, 1H, *J* 14.6, 6.7, CHH), 3.90 (s, 3H, OCH_3), 4.07–4.19 (m, 2H, OCH_2), 4.87 (q, 1H, *J* 6.7, NCH), 5.10 (d, 1H, *J* 6.7, NH), 6.45 (d, 1H, *J* 7.7, ArCH), 6.65 (td, 1H, *J* 7.7, 1.5, ArCH), 6.74 (td, 1H, *J* 7.7, 1.4, ArCH), 6.79 (dd, 1H, *J* 7.8, 1.2, ArCH), 7.24–7.28 (m, 1H, ArCH), 7.73–7.36 (m, 2H, 2×ArCH), 7.40–7.42 (m, 2H, 2×ArCH); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 43.3 (CH_2), 54.9 (NCH), 55.5 (OCH_3), 60.7 (OCH_2), 109.5 (ArCH), 111.2 (ArCH), 116.9 (ArCH), 121.2 (ArCH), 126.3 (2×ArCH), 127.4 (ArCH), 128.7 (2×ArCH), 136.8 (ArC), 142.5 (ArC), 146.9 (ArC), 171.0 (CO). Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 μm Cellulose-1) 5% ipa in hexane@1 mL min^{-1}, t_R=15.3 min (minor), 19.3 min (major). Data were in accordance with the literature.

3.3.7. (S)-Ethyl 3-(benzylamino)-3-phenylpropanoate ***3g***.[8]



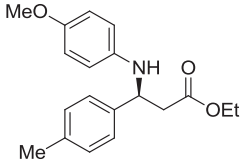
Obtained by general procedure B as a colourless oil (81 mg, 57% yield, 93% ee); $[\alpha]_D$ −41 (*c* 1.5, acetone) 93% ee; lit.[8] +34 (*c* assumed to be 1, $CHCl_3$) for *R* isomer; R_f (20% diethyl ether/petroleum ether) 0.20; δ_H (400 MHz, $CDCl_3$) 1.21 (t, 3H, *J* 7.1, CH_3CH_2), 2.12 (br s, 1H, NH), 2.64 (dd, 1H, *J* 15.5, 5.2, CHH), 2.74 (dd, 1H, *J* 15.5, 8.8, CHH), 3.57 (d, 1H, *J* 13.2, NCHH), 3.67 (d, 1H, *J* 13.2, NCHH), 4.09–4.15 (m, 3H, NCH and OCH_2), 7.23–7.40 (m, 10H, 10×ArCH); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 43.2 (CH_2), 51.4 (NCH_2), 58.9 (NCH), 60.5 (OCH_2), 126.9 (ArCH), 127.2 (2×ArCH), 127.5 (ArCH), 128.3 (2×ArCH), 128.4 (2×ArCH), 128.6 (2×ArCH), 140.3 (ArC), 142.6 (ArC), 171.8 (CO). Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 μm Cellulose-1) 5% ipa in hexane@1 mL min^{-1} at λ 210 nm, t_R=6.8 min (minor), 9.6 min (major). NMR data have only been previously reported in acetone-d_6.

3.3.8. (S)-Ethyl 3-(methylamino)-3-phenylpropanoate ***3h***.



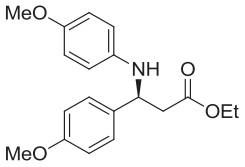
Obtained by general procedure B, except purified using a 20%→100% diethyl ether/petroleum ether gradient eluent, as a colourless oil (61 mg, 59% yield, 94% ee); $[\alpha]_D$ −25 (*c* 1.3, $CHCl_3$) 94% ee; R_f (diethyl ether) 0.10; ν_{max} (thin film, cm^{-1}) 3345, 2978, 1731, 1453; δ_H (400 MHz, $CDCl_3$) 1.22 (t, 3H, *J* 7.1, CH_3CH_2), 1.70 (br s, 1H, NH), 2.29 (s, 3H, NCH_3), 2.63 (dd, 1H, *J* 15.5, 5.4, CHH), 2.73 (dd, 1H, *J* 15.5, 8.5, CHH), 3.98 (dd, 1H, *J* 8.5, 5.4, NCH), 4.12 (q, 2H, *J* 7.1, OCH_2), 7.28–7.36 (m, 5H, 5×ArCH); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3CH_2), 34.4 (CH_3), 42.8 (CH_2), 60.5 (OCH_2), 61.5 (NCH), 127.1 (2×ArCH), 127.4 (ArCH), 128.5 (2×ArCH), 142.4 (ArC), 171.9 (CO); *m*/*z* (TOF ES^+) 208.1345 (MH^+, $C_{12}H_{18}NO_2$ requires 208.1338). Enantiomeric excess was determined by comparison of the integrals in the ^1H NMR spectrum in $CDCl_3$ of the diastereomeric salts formed by addition of excess L-mandelic acid. Compound reported in the literature, but with no NMR data.

3.3.9. (S)-Ethyl 3-(4-methoxyphenylamino)-3-(4-methylphenyl)propanoate ***3i***.



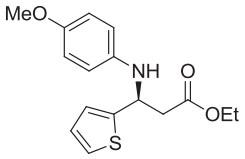
Obtained by general procedure B as a colourless oil (118 mg, 75%, yield, 92% ee); $[\alpha]_D$ −19.4 (*c* 0.62 in $CHCl_3$) 92% ee. Found C 72.94, H 7.75, N 4.43; $C_{19}H_{23}NO_3$ requires C 72.82, H 7.40, N 4.47; R_f (20% diethyl ether/petroleum ether) 0.30; ν_{max} (thin film, cm^{-1}) 3386, 2983, 1731, 1513, 1239; δ_H (400 MHz, $CDCl_3$) 1.22 (t, 3H, *J* 7.1, CH_3CH_2), 2.23 (s, 3H, CH_3), 2.78 (d, 2H, *J* 6.8, CH_2), 3.72 (s, 3H, OCH_3), 4.07–4.18 (m, 2H, OCH_2), 4.28 (br s, 1H, NH), 4.74 (t, 1H, *J* 6.8, NCH), 6.54 [$(AX)_2$, 2H, 2×ArCH], 6.72 [$(AX)_2$, 2H, 2×ArCH], 7.14 (d, 2H, *J* 7.8, 2×ArCH), 7.27 (d, 2H, *J* 7.8, 2×ArCH); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 21.1 (CH_3), 43.0 (CH_2), 55.7 (NCH & CH_3O), 60.7 (OCH_2), 114.8 (2×ArCH), 115.2 (2×ArCH), 126.2 (2×ArCH), 129.4 (2×ArCH), 137.0 (ArC), 139.5 (ArC), 141.2 (ArC), 152.3 (ArC), 171.3 (CO); *m*/*z* (TOF ES^+) 314.1750 (MH^+, $C_{19}H_{24}NO_3$ requires 314.1756). Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 μm Cellulose-1) 5% ipa in hexane@1 mL min^{-1}, t_R=11.6 min (minor), 12.8 min (major).

3.3.10. (S)-Ethyl 3-(4-methoxyphenylamino)-3-(4-methoxyphenyl) propanoate ***3j***.[4b]



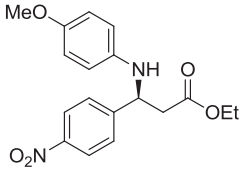
Obtained by general procedure B as a colourless oil (115 mg, 70% yield, 91% ee); $[\alpha]_D$ −20 (*c* 1.0, $CHCl_3$) 91% ee; lit.[4b] $[\alpha]_D$ −17.9 (*c* 1.0 in $CHCl_3$) 88% ee; R_f (20% diethyl ether/petroleum ether) 0.20; δ_H (400 MHz, $CDCl_3$) 1.22 (t, 3H, *J* 7.1, CH_3CH_2), 2.74–2.83 (m, 2H, CH_2), 3.72 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.09–4.17 (m, 2H, OCH_2), 4.28 (br s, 1H, NH), 4.73 (t, 1H, *J* 6.8, NCH), 6.55 [$(AX)_2$, 2H, 2×ArCH], 6.73 [$(AX)_2$, 2H, 2×ArCH], 6.88 [$(AX)_2$, 2H, 2×ArCH], 7.30 [$(AX)_2$, 2H, 2×ArCH]; δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 43.0 (CH_2), 55.2 (NCH), 55.4 (OCH_3), 55.7 (OCH_3), 60.7 (OCH_2), 114.1 (2×ArCH), 114.8 (2×ArCH), 115.2 (2×ArCH), 127.4 (2×ArCH), 134.5 (ArC), 141.1 (ArC), 152.3 (ArC), 158.8 (ArC), 171.3 (CO). Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 μm Cellulose-1) 5% ipa in hexane@1 mL min^{-1}, t_R=12.9 min (minor), 14.1 min (major). Data were in accordance with the literature.

3.3.11. (S)-Ethyl 3-(4-methoxyphenylamino)-3-(thienyl)propanoate ***3k***.[4b]



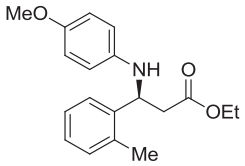
Obtained by general procedure B as a colourless oil (110 mg, 66% yield, 90% ee); $[\alpha]_D$ −15 (*c* 1.0, $CHCl_3$) 90% ee; lit.[4b] −9.1 $[\alpha]_D$ (*c* 1.0) 70% ee; R_f (20% diethyl ether/petroleum ether) 0.20; δ_H (400 MHz, $CDCl_3$) 1.25 (t, 3H, *J* 7.1, CH_3CH_2), 2.90 (dd, 1H, *J* 15.2, 6.5, CHH), 2.94 (dd, 1H, *J* 15.2, 6.5, CHH), 3.75 (s, 3H, OCH_3), 4.16 (q, 2H, *J* 7.1, OCH_2), 4.23 (br s, 1H, NH), 5.09 (t, 1H, *J* 6.5, NCH), 6.67 [$(AX)_2$, 2H, 2×ArCH], 6.78 [$(AX)_2$, 2H, 2×ArCH], 6.94–7.19 (m, 2H, 2×ArCH), 7.20 (dd, 1H, *J* 5.0, 1.2, 2×ArCH); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 42.6 (CH_2), 52.3 (NCH), 55.7 (OCH_3), 60.8 (OCH_2), 114.8 (2×ArCH), 115.8 (2×ArCH), 123.8 (ArCH), 124.2 (ArCH), 126.8 (ArCH), 140.6 (ArC), 147.3 (ArC), 152.9 (ArC), 170.9 (CO). Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 μm Cellulose-1) 10% ipa in hexane@1 mL min^{-1}, t_R=10.6 min (minor), 13.0 min (major). Data were in accordance with the literature.

3.3.12. (S)-Ethyl 3-(4-methoxyphenylamino)-3-(4-nitrophenyl)propanoate ***3l***.



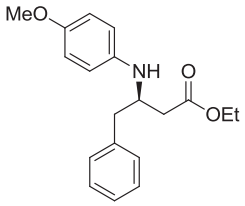
Obtained by general procedure B as an orange oil (87 mg, 50% yield, 82% ee); $[\alpha]_D$ −23 (*c* 0.8, $CHCl_3$) 82% ee; R_f (20% diethyl ether/petroleum ether) 0.40; ν_{max} (thin film, cm^{-1}) 3386, 2983, 1730, 1514; δ_H (400 MHz, $CDCl_3$) 1.22 (t, 3H, *J* 7.2, CH_3CH_2), 2.81 (dd, 1H, *J* 15.1, 6.5, CHH), 2.84 (dd, 1H, *J* 15.1, 6.5, CHH), 3.71 (s, 3H, OCH_3), 4.14 (q, 2H, *J* 7.2, OCH_2), 4.48 (br s, 1H, NH), 4.86 (t, 1H, *J* 6.5, NCH), 6.49 [$(AX)_2$, 2H, 2×ArCH], 6.72 [$(AX)_2$, 2H, 2×ArCH], 7.58 [$(AX)_2$, 2H, 2×ArCH], 8.19 [$(AX)_2$, 2H, 2×ArCH]; δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 42.3 (CH_2), 55.5 (NCH), 55.6 (OCH_3), 61.1 (OCH_2), 114.9 (2×ArCH), 115.2 (2×ArCH), 124.0 (2×ArCH), 127.4 (2×ArCH), 140.2 (ArC), 147.3 (ArC), 150.3 (ArC), 152.7 (ArC), 170.6 (CO); *m*/*z* (TOF ES^+) 345.1435 (MH^+, $C_{18}H_{21}N_2O_5$ requires 345.1450). Enantiomeric excess was determined by chiral phase HPLC (Chiralpak IA) 10% ipa in hexane@1 mL min^{-1}, t_R=27.9 min (minor), 30.5 min (major).

3.3.13. (S)-Ethyl 3-(4-methoxyphenylamino)-3-(2-methylphenyl)propanoate ***3m***.[4b]



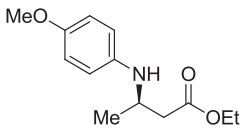
Obtained by general procedure B as a light yellow oil (42 mg, 27% yield, 3% ee); $[\alpha]_D$ 0 (*c* 1.0, $CHCl_3$) 3% ee; lit.[4b] $[\alpha]_D$ +1.4 (*c* 1.0, $CHCl_3$) 79% ee; R_f (20% diethyl ether/petroleum ether) 0.40; δ_H (400 MHz, $CDCl_3$) 1.23 (t, 3H, *J* 7.2, CH_3CH_2), 2.48 (s, 3H, CH_3), 2.68 (dd, 1H, *J* 14.8, 8.4, CHH), 2.77 (dd, 1H, *J* 14.8, 5.1, CHH), 3.72 (s, 3H, OCH_3), 4.08–4.19 (m, 2H, OCH_2), 4.27 (br, s, 1H, NH), 4.96 (dd, 1H, *J* 8.4, 5.1, NCH), 6.48 [$(AX)_2$, 2H, 2×ArCH], 6.72 [$(AX)_2$, 2H, 2×ArCH], 7.15–7.21 (m, 3H, 3×ArCH), 7.40–7.44 (m, 1H, ArCH); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 19.1 (CH_3), 41.3 (CH_2), 52.4 (NCH), 55.7 (OCH_3), 60.8 (OCH_2), 114.8 (2×ArCH), 114.9 (2×ArCH), 125.2 (ArCH), 126.6 (ArCH), 127.2 (ArCH), 130.8 (ArCH), 135.0 (ArC), 140.2 (ArC), 141.1 (ArC), 152.3 (ArC), 171.3 (CO). Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 μm Cellulose-1) 5% ipa in hexane@1 mL min^{-1}, t_R=10.2 min (minor), 15.6 min (major). Data were in accordance with the literature.

3.3.14. (S)-Ethyl 3-(4-methoxyphenylamino)-4-phenylbutanoate ***3n***.



Obtained by general procedure B as a light yellow oil (88 mg, 56% yield, 30% ee); $[\alpha]_D$ +2.3 (*c* 1.3, $CHCl_3$) 30% ee; R_f (25% diethyl ether/petroleum ether) 0.20; ν_{max} (thin film, cm^{-1}) 3371, 2981, 2934, 1728, 1512; δ_H (400 MHz, $CDCl_3$) 1.26 (t, 3H, *J* 7.1, CH_3CH_2), 2.44 (dd, 1H, *J* 15.3, 6.3, CHH), 2.51 (dd, 1H, *J* 15.3, 6.0, CHH), 2.87 (dd, 1H, *J* 13.6, 7.2, CHH), 2.97 (dd, 1H, *J* 13.6, 5.1, CHH), 3.64 (br s, 1H, NH), 3.78 (s, 3H, OCH_3), 4.01–4.07 (m, 1H, NCH), 4.14 (q, 2H, *J* 7.1, OCH_2), 6.66 [$(AX)_2$, 2H, 2×ArCH], 6.82 [$(AX)_2$, 2H, 2×ArCH], 7.19–7.33 (m, 5H, 5×ArCH); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 38.3 (CH_2), 40.0 (CH_2), 52.6 (NCH), 55.8 (OCH_3), 60.5 (OCH_2), 115.0 (2×ArCH), 115.5 (2×ArCH), 126.6 (ArCH), 128.5 (2×ArCH), 129.5 (2×ArCH), 137.9 (ArC), 140.9 (ArC), 152.5 (ArC), 172.0 (CO); *m*/*z* (TOF ES^+) 314.1749 (MH^+, $C_{19}H_{24}NO_3$ requires 314.1756). Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 μm Cellulose-1) 10% ipa in hexane@1 mL min^{-1}, t_R=8.7 min (major), 9.8 min (minor).

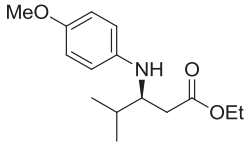
3.3.15. (S)-Ethyl 3-(4-methoxyphenylamino)butanoate ***3o***.[16]



Obtained by general procedure B as a light yellow oil (75 mg, 63% yield, 20% ee); $[\alpha]_D$ 0 (*c* 1.0, $CHCl_3$) 20% ee; lit.[16] $[\alpha]_D$ −4.0 (*c* 0.5, MeOH) 93.8% ee; R_f (20% diethyl ether/petroleum ether) 0.10; δ_H (400 MHz,

$CDCl_3$) 1.27 (d, 3H, *J* 6.4, CH_3), 1.28 (t, 3H, *J* 7.2, CH_3CH_2), 2.42 (dd, 1H, *J* 15.0, 6.8, C*H*H), 2.62 (dd, 1H, *J* 15.0, 6.8, C*H*H), 3.51 (br s, 1H, N*H*), 3.77 (s, 3H, OCH_3), 3.83–3.91 (m, 1H, NC*H*), 4.16 (q, 2H, *J* 7.2, OCH_2), 6.64 [$(AX)_2$, 2H, 2×ArC*H*], 6.80 [$(AX)_2$, 2H, 2×ArC*H*]; δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 20.7 (CH_3), 41.0 (CH_2), 47.3 (NCH), 55.7 (OCH_3), 60.4 (OCH_2), 114.9 (2×ArCH), 115.5 (2×ArCH), 141.0 (ArC), 152.4 (ArC), 172.0 (CO). Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 μm Cellulose-1) 5% ipa in hexane@1 mL min^{-1}, t_R=10.2 min (minor), 10.9 min (major). Data were in accordance with the literature.

3.3.16. Ethyl 3-(4-methoxyphenylamino)-4-methylpentanoate ***3p***.[4b]

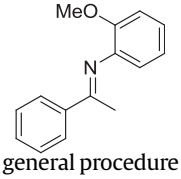


Obtained by general procedure B as a light yellow oil (58 mg, 44% yield, 56% ee); $[\alpha]_D$ +20 (*c* 1.0, $CHCl_3$) 56% ee; lit.[4b] $[\alpha]_D$ +21.3 (*c* 1.0, $CHCl_3$) 59% ee; R_f (25% diethyl ether/petroleum ether) 0.30; δ_H (400 MHz, $CDCl_3$) 0.95 (d, 3H, *J* 6.8, CH_3CH), 1.00 (d, 3H, *J* 6.8, CH_3CH), 1.23 (t, 3H, *J* 7.1, CH_3CH_2), 1.86–1.98 [m, 1H, $(CH_3)_2CH$], 2.43 (dd, 1H, *J* 14.8, 7.3, C*H*H), 2.52 (dd, 1H, *J* 14.8, 5.3, C*H*H), 3.46 (br s, 1H, N*H*), 3.61–3.65 (m, 1H, NC*H*), 3.76 (s, 3H, OCH_3), 4.10 (q, 2H, *J* 7.1, OCH_2), 6.63 [$(AX)_2$, 2H, 2×ArC*H*], 6.78 [$(AX)_2$, 2H, 2×ArC*H*]; δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 18.6 (CH_3), 18.7 (CH_3), 31.7 (CH), 36.9 (CH_2), 55.8 (OCH_3), 57.2 (NCH), 60.4 (OCH_2), 114.9 (2×ArCH), 115.0 (2×ArCH), 141.9 (ArC), 152.1 (ArC), 172.4 (CO). Enantiomeric excess was determined by chiral phase HPLC (Phenomenex Lux 3 μm Cellulose-1) 5% ipa in hexane@1 mL min^{-1}, t_R=9.1 min (minor), 9.9 min (major). Data were in accordance with the literature.

3.4. General procedure C for the preparation of ketimines

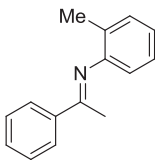
Activated 4 Å molecular sieves (20 g), toluene (40 mL), ketone (50 mmol) and amine (60 mmol) were introduced into a 100 mL flask. The mixture was stirred at room temperature for 24 h and filtered. The imines were purified by distillation under reduced pressure to remove volatiles, leaving the pure product as residue.

3.4.1. 2-Methoxy-N-(1-phenylethylidene)benzenamine ***4a***.[19]



Prepared according to general procedure C as a yellow oil (44%); δ_H (250 MHz, $CDCl_3$) 2.20 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 6.80 (dd, 1H, *J* 7.5, 1.7, ArC*H*), 6.94–7.01 (m, 2H, 2×ArC*H*), 7.07–7.14 (m, 1H, ArC*H*), 7.44–7.49 (m, 3H, 3×ArC*H*), 8.01–8.05 (m, 2H, 2×ArC*H*); δ_C (63 MHz, $CDCl_3$) 17.8 (CH_3), 55.7 (OCH_3), 111.8 (ArCH), 120.7 (ArCH), 121.1 (ArCH), 124.3 (ArCH), 127.4 (2×ArCH), 128.4 (2×ArCH), 130.5 (ArCH), 139.6 (ArC), 140.8 (ArC), 149.1 (ArC), 167.0 (C=N). Data were in accordance with the literature, except a yellow solid was previously noted.

3.4.2. 2-Methyl-N-(1-phenylethylidene)benzenamine ***4b***.[20]

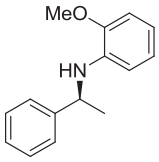


Prepared according to general procedure C, followed by recrystallisation from diethyl ether/petroleum ether 40–60 °C as a yellow solid (48%), mp 49–50 °C (not reported in literature); δ_H (400 MHz, $CDCl_3$) 2.13 (3H, s, CH_3), 2.20 (3H, s, CH_3), 6.88 (dd, 1H, *J* 7.8, 1.0, ArC*H*), 7.03 (ddd, 1H, *J* 8.7, 7.6, 1.2, ArC*H*), 7.19–7.25 (m, 2H, 2×ArC*H*), 7.46–7.51 (m, 3H, 3×ArC*H*), 8.02–8.05 (m, 2H, 2×ArC*H*); δ_C (63 MHz, $CDCl_3$) 17.5 (CH_3), 17.8 (CH_3), 118.5 (ArCH), 123.3 (ArCH), 126.4 (ArCH), 127.2 (2×ArCH), 128.4 (2×ArCH), 130.4 (ArCH), 130.5 (ArCH), 139.5 (2×ArC), 150.4 (ArC), 164.9 (C=N). Data were in accordance with the literature.

3.5. General procedure D for the reduction of ketimines

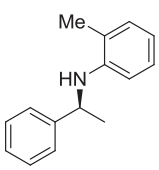
Imine (1 mmol), catalyst **1** (0.01 mmol) and dry CH_2Cl_2 (0.5 mL or 1 mL) were introduced into an oven-dried 25 mL two-necked flask or an oven-dried carousel tube. The mixture was stirred until complete dissolution, then cooled to 0 °C and trichlorosilane (2 mmol, 0.2 mL) was added by syringe over 5–10 s. The reaction mixture was left to stir for the desired time. Aqueous hydrochloric acid (1 M, ca. 2 mL) was added, which led to gas evolution and precipitation, followed by CH_2Cl_2 (20 mL) and aqueous sodium hydroxide (1 M, 20 mL). This mixture was stirred until the precipitate was completely dissolved. The organic phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2×20 mL). The combined organic phases were washed with brine (20 mL) and dried over $MgSO_4$. Filtration and concentration gave the product that could be purified by chromatography column on silica gel using a 2–10% solution of diethyl ether or ethyl acetate in petroleum ether. Racemic samples of compound were obtained by this procedure, using *N*-formylpyrrolidine (0.1 mmol) as catalyst.

3.5.1. (S)-2-Methoxy-N-(1-phenylethyl)aniline ***5a***.[19]



Prepared according to general procedure D (80 mg, 35%, 96% ee) as a white solid, mp 78–80 °C (not reported in literature); $[\alpha]_D$ +78.3 (*c* 0.6, ethyl acetate) 96% ee; lit.[19] $[\alpha]_D$ −32.3 (*c* 1.03, $CHCl_3$) 97% ee for *R* isomer; R_f (5% EtOAc/petroleum ether) 0.80; δ_H (400 MHz, $CDCl_3$) 1.57 (d, 3H, *J* 6.8, CH_3), 3.91 (s, 3H, OCH_3), 4.49 (q, 1H, *J* 6.8, NC*H*), 4.68 (br s, 1H, N*H*), 6.36 (dd, 1H, *J* 7.6, 1.6, ArC*H*), 6.63 (td, 1H, *J* 7.6, 1.9, ArC*H*), 6.70 (td, 1H, *J* 7.5, 1.6, ArC*H*), 6.77 (dd, 1H, *J* 7.8, 1.9, ArC*H*), 7.20–7.41 (m, 5H, 5×ArC*H*); δ_C ($CDCl_3$, 100 MHz) 25.3 (CH_3), 54.3 (NCH), 55.5 (CH_3O), 109.4 (ArCH), 111.2 (ArCH), 116.4 (ArCH), 121.3 (ArCH), 126.0 (2×ArCH), 126.9 (ArCH), 128.7 (2×ArCH), 137.3 (ArC), 145.6 (ArC), 146.7 (ArC). Enantiomeric excess was determined by chiral phase HPLC (Kromasil 3-Cellucoat OD-H), 0.2% ipa in hexane@1 mL min^{-1}, t_R=7.5 min (major), 10.6 min (minor). Data were in accordance with the literature.

3.5.2. (S)-2-Methyl-N-(1-phenylethyl)aniline ***5b***.[21]



Prepared according to general procedure D (135 mg, 64%, 97% ee) as a white solid, mp 42–44 °C (not reported in literature); $[\alpha]_D$ +60.8 (*c* 1.09, $CHCl_3$) 97% ee; lit.[21] $[\alpha]_D$ +14 (*c* 0.5, $CHCl_3$) 25% ee; R_f (5% EtOAc/petroleum ether) 0.60; δ_H (400 MHz, $CDCl_3$) 1.59 (d, 3H, *J* 6.7, CH_3), 2.26 (s, 3H, ArCH_3), 3.88 (br s, 1H, N*H*), 4.56 (q, 1H, *J* 6.7, NC*H*),

6.39 (d, 1H, *J* 8.1, ArC*H*), 6.62 (t, 1H, *J* 7.2, ArC*H*), 6.98 (t, 1H, *J* 7.7, ArC*H*), 7.01 (d, 1H, *J* 7.2, ArC*H*), 7.25 (t, 1H, *J* 7.1, ArC*H*), 7.33–7.40 (m, 4H, 4×ArC*H*); δ_C (100 MHz, $CDCl_3$) 17.7 (ArCH_3), 25.4 (CH_3), 53.4 (NCH), 111.1 (ArCH), 116.9 (ArCH), 121.6 (Ar*C*), 125.9 (2×ArCH), 126.9 (ArCH), 127.1 (ArCH), 128.7 (2×ArCH), 130.1 (ArCH), 145.2 (Ar*C*), 145.4 (Ar*C*). Enantiomeric excess was determined by chiral phase HPLC (Kromasil 3-Cellucoat OD-H), 3% ipa in hexane@1 mL min^{-1}, t_R=4.1 min (major), 7.0 min (minor). Data were in accordance with the literature.

3.6. Molecular modelling

All electronic structure calculations were performed using the SMP version of the Gaussian 09 program package (rev. A2)[22] with the B3LYP functional method.[23] Gaussian was compiled using the Portland Compiler version 8.0-6 with the Gaussian-supplied version of BLAS[24] and ATLAS[25] on the EMT64 architecture. In all calculations we used the 6-311G** basis set on all atoms.[26] All calculations were run in vacuo on the enantiomeric series to that depicted in this manuscript. All minimum energy structures found have indeed zero imaginary frequencies.

Acknowledgements

We would like to thank the University of Sheffield for support.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2012.04.084.

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