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Total synthesis of Fluoxetine & Duloxetine through an *in situ* imine formation/borylation/transimination and reduction approach

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We report efficient, catalytic, asymmetric total syntheses of both (*R*)-Fluoxetine and (*S*)-Duloxetine from α,β -unsaturated aldehydes conducting five sequential one pot steps (imine formation / copper mediated β -borylation / transimination / reduction / oxidation) followed by the specific ether group formation which deliver to the desired products (*R*)-Fluoxetine in 45% yield (96% e.e.) and (*S*)-Duloxetine in 47% yield (94% e.e.).

ARTICLE

Introduction

Fluoxetine 1 and Duloxetine 2, developed by Eli Lilly,¹ are top-selling pharmaceuticals used for the treatment of major depressive disorder (MDD)² and other conditions.³ Fluoxetine 1 belongs to the selective serotonin reuptake inhibitor (SSRI) class of anti-depressants⁴ and Duloxetine 2 to the serotonin-norepinephrine reuptake inhibitor (SNRI) class.⁵

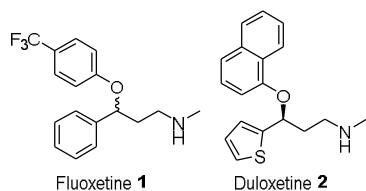


Figure 1 Molecular structure of Fluoxetine 1 and Duloxetine 2.

Due to the success and importance of these drugs, several groups have been interested in their preparation. An original asymmetric approach to Fluoxetine 1 was developed by Brown *et al.*, using the chiral auxiliary diisopinocampheylchloroborane, for the asymmetric reduction of ketone precursors.⁶ Sharpless *et al.* also developed a route to Fluoxetine using an asymmetric epoxidation of an allylic alcohol, followed by ring-opening strategy.⁷ Corey *et al.* achieved an asymmetric reduction using the chiral oxazaborolidine (CBS reduction) in combination with borane to reduce a prochiral ketone in his approach.⁸ In recent years, the advancement of asymmetric catalytic hydrogenation has also proven highly effective for the asymmetric reduction of ketones (e.g. Noyori *et al.*)⁹ and, indeed, other groups have employed this methodology to the synthesis of both Fluoxetine 1 and Duloxetine 2.¹⁰

It is interesting to note that Fluoxetine 1, despite being a chiral compound, is marketed as the racemic HCl-salt (Fig. 1).¹¹ However, studies have revealed evidence of differing pharmacological and pharmacokinetic properties depending on the enantiomer of Fluoxetine 1.¹² This evidence suggests that the (S)-enantiomer of Fluoxetine 1 is more active in the inhibition of serotonin than the (R)-enantiomer.¹² Additionally, one of the major metabolites of Fluoxetine 1, norfluoxetine (demethylated Fluoxetine), is significantly more active as an inhibitor. In contrast, Duloxetine 2 is marketed as a single (S)-enantiomer.¹³

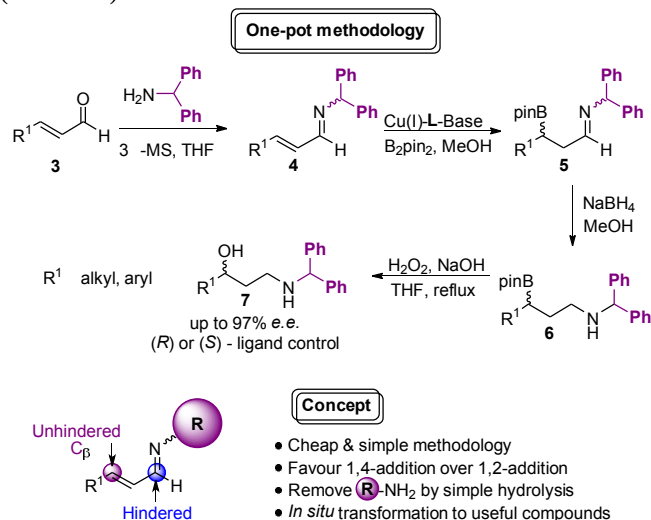
Herein, we report an efficient, catalytic, asymmetric synthesis of Fluoxetine and Duloxetine with key steps that involves: 1) an *in situ* imine formation, 2) a copper-catalysed asymmetric α -borylation protocol that requires a specific bulky amine to block the imine functionality and prevent 1,2 addition versus 1,4 addition of the Cu-Bpin system, 3) a sequential transimination reaction, 4) a reduction of C=N bond and 5) a C-B oxidation protocol. Interestingly, since the asymmetry is induced in the second step by using a cheap chiral ligand (R/S)-dimethyl-BINAP [(R/S)-DM-BINAP]), another key point is the

prevalence of the asymmetric induction along the following synthetic steps towards the target product.

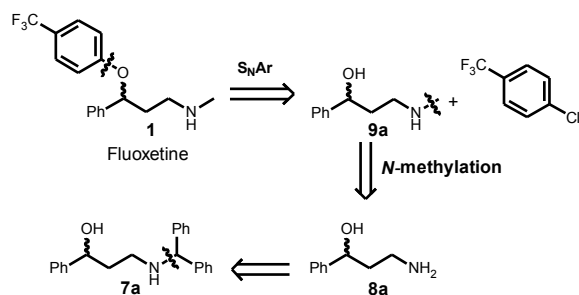
Results and discussion

In recent years we have been interested in the preparation of α -amino alcohols (e.g. 7-)¹⁴ via the α -borylation¹⁵ of α,α -unsaturated imines (e.g. 4-) because such α -amino alcohols have applications as auxiliaries in synthetic and biochemical systems.¹⁶ In this context, we demonstrated a novel protocol for the asymmetric α -borylation of enal-derived α,α -unsaturated aldimines.¹⁷ This methodology owes its success to the sterically bulky *N*-benzhydryl substituent, which favours exclusive 1,4-boron addition (enals are prone to 1,2-boron addition to the carbonyl). The resulting α -boryl imines 5- can be reduced and oxidised in one-pot to yield *N*-benzhydryl α -amino alcohols 7- with e.e. values up to 97% (Scheme 1).

We therefore became interested in applying our one-pot methodology (Scheme 2) to the total synthesis of some pharmaceuticals, such as Fluoxetine 1¹⁸ and Duloxetine 2. By applying our retrosynthetic analysis to Fluoxetine 1, one can clearly see that α -amino alcohol 7a is an appropriate precursor to Fluoxetine 1. Indeed, we considered that a debenzhydrylation, *N*-methylation and, finally, a nucleophilic aromatic substitution would result in the target compound 1 (Scheme 2).



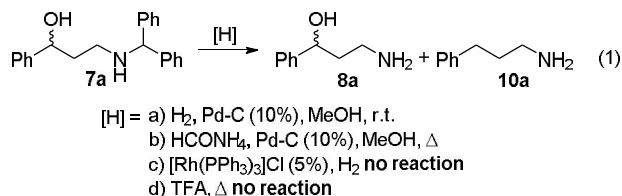
Scheme 1 Asymmetric one-pot methodology towards chiral α -amino alcohols.



Scheme 2 Retrosynthetic analysis of Fluoxetine 1.

Initially, we prepared compound 7a from cinnamaldehyde 3a using CuCl/L0 or CuCl/L1 (L0=PPh₃ and L1=((R)-DM-BINAP) as the catalytic system.¹⁷ Our initial hypothesis to transform 7a into 1 required a debenzhydrylation step using hydrogen over a palladium-on-carbon heterogeneous catalyst [Pd-C (10%)], because this has been employed for standard debenzhydrylation in the literature [see Eqn. (1)].¹⁹ However, using this methodology we encountered significant C-O bond hydrogenolysis,²⁰ *i.e.* cleavage of the benzylic hydroxyl-group, which led to the formation of 10a as a significant product, in addition to the formation of the desired 8a. We therefore considered transfer hydrogenation as a suitable method, due to the practical ease of delivering stoichiometric amounts of hydrogen *in situ* from the decomposition of ammonium formate [see Eqn. (1)]. However, this resulted in the formation of a mixture of 7a, 8a, and 10a. Increased loadings of ammonium formate resulted in 10a being the primary product, with complete *N*-benzhydryl group cleavage. Other milder methods, such as hydrogenation *via* Wilkinson's catalyst and, indeed, refluxing TFA, resulted in no debenzhydrylation. To our disappointment, conventional debenzhydrylation methodologies appeared to be too harsh for substrate 7a due to the presence of the benzylic hydroxyl-group, which appears to undergo facile hydrogenolysis under palladium-catalysed hydrogenation conditions.

In addition to debenzhydrylation, hydrolysis of compound 5a to the analogous aldehyde, with subsequent reductive amination using methylamine/NaBH₄ (to yield 12a) was attempted and indeed did work, but due to the instability of the analogous α -boryl aldehyde the overall conversion in this case was low (<20%) and, hence, we needed to avoid the utilisation of such α -boryl aldehydes as intermediates in subsequent synthesis.



Intrigued by recent reports of transimination²¹ (also known as imine-metathesis²²), we wondered whether treating the α -boryl imine 5a (Scheme 1) with an excess of methylamine, would result in the formation of *N*-methyl imine 11a. More specifically, could the equilibrium between *N*-benzhydryl imine 5a and *N*-methyl imine 11a, on addition of methylamine, be directed towards the formation of 11a as a result of the

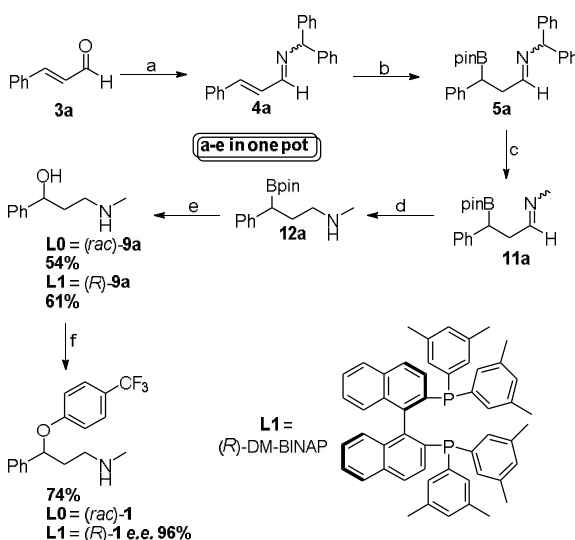
difference in amine nucleophilicity of methylamine and benzhydrylamine (Scheme 3)? If successful, this would bypass the need for forming the parent α -boryl aldehyde²³ simply by the addition of cheap and readily available methylamine.



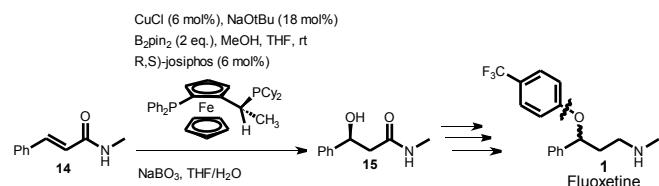
Scheme 3 Proposed transimination through amine exchange.

Continuing with the established one-pot methodology (Scheme 4), we therefore treated the intermediate α -boryl imine 5a with excess methylamine (4 equiv.), followed by *in situ* reduction using NaBH₄/MeOH. Subsequently, solvent removal (to prevent MeOH oxidation to formaldehyde, which in the presence of α -amino alcohols leads to the formation of 1,3-oxazines, as previously reported²⁴) and replacement with THF, followed by B-C oxidation with H₂O₂/NaOH of boronate 12a, gave the known precursor to Fluoxetine, α -amino alcohol 9a [54% yield when using PPh₃ L0 and 61% when using (R)-DM-BINAP L1, see Scheme 4]. This was achieved in five-steps, all of which were conducted in one-pot, without intermediate purification. Next, the addition of NaH to 9a resulted in the *in situ* generation of the analogous Na-alkoxide of 9a which, on addition of 4-chlorobenzotrifluoride at elevated temperature (100 °C, 3 h), gave Fluoxetine (*rac*)-1 in 74% yield [(*R*)-1 in 96% e.e. when using L1] (Scheme 4). Determination of the enantiomeric excess was carried out by chiral HPLC on the Fluoxetine *N*-acyl compound 13a (see ESI), which is consistent with previously reported values of asymmetric induction (previously found to be 97% e.e.).¹⁷

It is important to note that recent work described by Yun *et al.* on the asymmetric α -borylation of α,β -unsaturated amides 14, conducted to the formal synthesis of (S)-Fluoxetine with excellent enantioselectivity (99% e.e.),¹⁸ using in this case copper salts modified with a type of chiral josphos ligand (Scheme 5). The intermediate compound 15 could be reduced using LiAlH₄²⁵ to give 9a in quantitative yields, which could be transformed to Fluoxetine using known procedures (*e.g.* Scheme 4).⁷

Scheme 4 Asymmetric synthesis of (R)-Fluoxetine 1. Conditions: a) Ph₂CHNH₂ (1 equiv.), 3 Å-MS, THF, r.t., 6h; b) CuCl

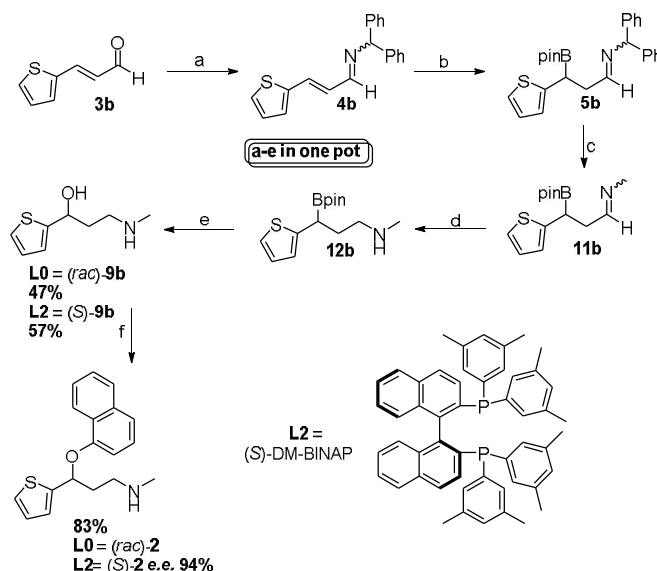
(3%), PPh₃ L0 (6%), NaOtBu (9%), B₂pin₂ (1.1 equiv.), MeOH (2.5 equiv.), r.t., 15h or CuCl (3%), (R)-DM-BINAP L1 (3%), NaOtBu (9%), B₂pin₂ (1.1 equiv.), MeOH (2.5 equiv.), r.t., 15h; c) MeNH₂ (4 equiv.), r.t., 2 h; d) NaBH₄, MeOH, r.t. 3h. Remove solvent *in vacuo*; e) H₂O₂, NaOH, THF, reflux, 1 h; f) NaH (1.1 equiv.), DMA, 70 °C, 30 min. Ar-Cl (1.2 equiv.), 100 °C, 3 h.



Scheme 5 Yun *et al.*'s formal synthesis of Fluoxetine.¹⁸

With these results in hand, we turned our attention to the total synthesis of Duloxetine, which is marketed as the (S)-2 enantiomer. Enal **3b** is not commercially available and therefore had to be prepared *via* reduction of the parent acid (DIBAL-H) to the analogous allylic alcohol, followed by oxidation to the aldehyde (without purification of the intermediate allylic alcohol) using Swern conditions.²⁶

Hence enal **3b** (Scheme 6) was transformed *in situ* to the corresponding *N*-benzhydryl aldimine **4b** in the presence of 3 Å-molecular sieves and THF. After 9 hours, the imine was transferred directly to the pre-catalyst (copper salt, base, ligand and B₂pin₂) mixture, followed by the addition of MeOH, to give the intermediate α -boryl aldimine **5b**. Subsequent transimination was achieved through the addition of methylamine (in THF) which, after *in situ* borohydride reduction gave **12b**. Again, to prevent the unwanted formation of oxazines (through *in situ* formaldehyde formation²⁴), the solvent was removed *in vacuo* prior to C-B oxidation and, hence, oxidation resulted in the formation of the known precursor α -amino alcohol **9b** in good yield [47% yield when using PPh₃ L0 and 57% when using (S)-DM-BINAP L2, see Scheme 6]. Finally, addition of NaH to **9b** resulted in the *in situ* generation of the analogous alkoxide of **9b** which, on addition of 1-fluoronaphthalene at elevated temperature (70 °C, 1.5 h), gave Duloxetine (*rac*)-**2** in 83% yield [(S)-**2** in 94% e.e. when using L2] (Scheme 6). The enantiomeric excess was again determined by chiral HPLC on the *N*-acetamide **13b** of **2** (see ESI).



Scheme 6 Asymmetric synthesis of (S)-Duloxetine 2.

Conditions: a) Ph₂CHNH₂ (1 equiv.), 3 Å-MS, THF, r.t., 8h; b) CuCl (3%), PPh₃ L0 (6%), NaOtBu (9%), B₂pin₂ (1.1 equiv.), MeOH (2.5 equiv.), r.t., 15h or CuCl (3%), (S)-DM-BINAP L2 (3%), NaOtBu (9%), B₂pin₂ (1.1 equiv.), MeOH (2.5 equiv.), r.t., 15h; c) MeNH₂ (4 equiv.), r.t., 2 h; d) NaBH₄, MeOH, r.t. 3h. Remove solvent *in vacuo*; e) H₂O₂, NaOH, THF, reflux, 1 h; f) NaH (1.1 equiv.), DMSO, 50 °C, 1.5 h. Ar-Cl (1.2 equiv.), 70 °C, 1.5 h.

Conclusions

In conclusion, we have developed an efficient, catalytic, asymmetric route to both (R)-Fluoxetine and (S)-Duloxetine (45 and 47% overall yield, 96 and 94% e.e., respectively) through the asymmetric copper mediated α -borylation of α,β -unsaturated imines. Although this strategy involves six steps, the first five-steps are conducted following a one-pot strategy. Importantly, the asymmetric induction provided by CuCl modified with a cheap chiral ligand (R/S)-DM-BINAP L1/L2, is high and is constant along the following transformation towards the targeted pharmaceuticals. Having demonstrated this approach, further applications are underway and will be communicated in due course.

Experimental

General experimental

All reagents were used as received from the supplier without further purification, unless stated. All solvents were used as received from the supplier, except THF (freshly distilled) and methanol (stored over molecular sieves). Molecular sieves, 3 Å 1-2mm beads, were supplied from Alfa Aesar, and stored at 220 °C. Reactions were monitored by TLC analysis using POLTFRAM[®] SIL G/UV₂₅₄ (40 x 80 mm) TLC plates. Flash column chromatography was carried out using Silica gel as supplied from Sigma-Aldrich (230-400 mesh, 40-63 μ m, 60 Å) and monitored using TLC analysis. ¹H NMR spectra were recorded on a Varian-Mercury 500 MHz spectrometer, operating at ambient probe temperature unless specified elsewhere. ¹³C NMR spectra were recorded on a Varian Mercury 500 MHz instrument, operating at 101 MHz, unless specified elsewhere. Deuterated chloroform CDCl₃ was used as solvent for all NMR spectra, unless specified elsewhere. NMR peaks are reported as

singlet (s), doublet (d), triplet (t), quartet (q), broad (br), combinations thereof, or as a multiplet (m). Mass spectra for liquid chromatography mass spectrometry (LCMS) were obtained using a Waters (UK) TQD mass spectrometer (low resolution ESI⁺, electrospray in positive ion mode, ESI⁺), Waters (UK) Xevo QTOF mass spectrometer (low and high resolution ASAP⁺) and a Waters (UK) LCT premier XE (high resolution ESI⁺, electrospray in positive ion mode, ESI⁺) unless stated elsewhere. HPLC analysis was carried out on an Agilent 1100 series instrument, fitted with a Perkin Elmer series 200 degasser. AS-H-CHIRALCEL column (250 x 4.6 mm) fitted with guard cartridge (50 x 4.6 mm) was used to achieve chiral resolution, unless stated elsewhere. Optical rotations were measured using a JASCO P-1020 polarimeter with $[\alpha]_D$ values given in deg cm²g⁻¹.

Experimental procedure

Synthesis of 3-(Methylamino)-1-phenylpropan-1-ol (9a). Benzhydrylamine (0.86 mL, 5.00 mmol) and cinnamaldehyde 3a (0.63 mL, 5.00 mmol) was added to a stirring solution of THF (20 mL) and oven-dried 3 Å-MS (5.0 g) for 6 h, to form the α,β -unsaturated imine 4a *in situ*. After 6 h, an aliquot of the solution containing the *in situ*-formed imine 4a (16.0 mL, 4.00 mmol) was transferred to a Schlenk-tube (under argon) containing CuCl (12.0 mg, 0.12 mmol), PPh₃ (62.9 mg, 0.24 mmol) or (R)-DM-BINAP (88.2 mg, 0.12 mmol), NaOt-Bu (34.6 mg, 0.36 mmol) and B₂pin₂ (1.12 g, 4.4 mmol). After 5 min, MeOH (400 μ L, 10.0 mmol) was added to the solution and the reaction was stirred overnight. Methylamine (8 mL, 16.0 mmol, 2 M THF solution) was added under argon and the resulting solution was stirred for 1.5 h. NaBH₄ (0.46 g, 12.0 mmol) was added, followed by the drop-wise addition of MeOH (8.0 mL). The mixture was stirred for 3 h, followed by the removal of solvent under reduced pressure. THF (20 mL) was added to the resulting residue, followed by NaOH (2.4 mL, w/v 20%) and H₂O₂ (1.1 mL, w/v 35%), and the solution was heated to reflux for 1 h. After cooling, the resulting solution was partitioned between EtOAc and brine. The aqueous layer was extracted further with EtOAc (3x). The organic phase was separated and dried over anhydrous MgSO₄. After filtration the organic phase was removed under reduced pressure to yield a crude product. Purification by silica gel chromatography (DCM : MeOH : NEt₃, 5 : 1 : 1%) gave the pure product as an off colourless oil, which formed an off colourless solid 2 on standing [356 mg, 54% when using PPh₃ and 402 mg, 61% when using (R)-DM-BINAP]: ¹H-NMR (400 MHz, CDCl₃): δ 7.40-7.24 (m, 5H), 4.95 (dd, *J* = 8.7, 3.1 Hz, 1H), 3.65-3.4 (bs, 1H), 2.97-2.83 (m, 2H), 2.46 (s, 3H), 1.93-1.72 (m, 2H); ¹³C-NMR (101 MHz, CDCl₃): δ 145.0, 128.2, 127.0, 125.6, 75.4, 50.3, 36.7, 35.9; LR-MS (ESI⁺) 166.5 [M+H]⁺; HR-MS (ESI⁺) Calculated [C₁₀H₁₅NO+H]⁺ 166.1232, found 166.1228. All spectroscopic values are consistent with those obtained in the literature.²⁷

Synthesis of 3-(Methylamino)-1-(thiophen-2-yl)propan-1-ol (9b). Benzhydrylamine (0.86 mL, 5.00 mmol) and (2E)-3-(thiophen-2-yl)prop-2-enal 3b (0.63 mL, 5.00 mmol) was added to a stirring solution of THF (20 mL) and oven-dried 3 Å-MS (5.0 g) for 6 h, to form the α,β -unsaturated imine 4b *in situ*. After 6 h, an aliquot of the solution containing the *in situ*-formed imine 4b (12.0 mL, 3.0 mmol) was transferred to a Schlenk-tube (under argon) containing CuCl (9.0 mg, 0.09 mmol), PPh₃ (48.0 mg, 0.18 mmol) or (S)-DM-BINAP (66.1 mg, 0.09 mmol), NaOt-Bu (27.0 mg, 0.27 mmol) and B₂pin₂ (0.84 g, 3.3 mmol). After 5 min, MeOH (300 μ L, 7.5 mmol) was

added to the solution and the reaction was stirred overnight. Methylamine (6 mL, 12.0 mmol, 2 M THF solution) was added under argon and the resulting solution was stirred for 1.5 h. NaBH₄ (0.34 g, 9.0 mmol) was added, followed by the drop-wise addition of MeOH (6.0 mL). The mixture was stirred for 3 h, followed by the removal of solvent under reduced pressure. THF (15 mL) was added to the resulting residue, followed by NaOH (1.8 mL, w/v 20%) and H₂O₂ (0.84 mL, w/v 35%), and the solution was heated to reflux for 1 h. After cooling, the resulting solution was partitioned between EtOAc and brine. The aqueous layer was extracted further with EtOAc (3x). The organic phase was separated and dried over anhydrous MgSO₄. After filtration the organic phase was removed under reduced pressure to yield a crude product. Purification by silica gel chromatography (DCM : MeOH : NEt₃, 5 : 1 : 1%) gave the pure product as an off colourless oil, which formed a pale yellow oil 9b on standing [241 mg, 47% when using PPh₃ and 292 mg, 57% when using (S)-DM-BINAP]: ¹H NMR (400 MHz, CDCl₃): δ 7.20 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.06 (dd, *J* = 5.0, 3.4, 1H), 6.93-6.91 (m, 1H), 5.19 (dd, *J* = 8.4, 3.2 Hz, 1H), 4.68-4.32 (bs, 1H), 3.02-2.83 (m, 2H), 2.45 (s, 3H), 2.05-1.86 (m, 2H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 149.7, 126.6, 123.7, 122.3, 71.9, 50.1, 36.8, 35.9 ppm. LRMS (ESI⁺) [M+H]⁺, 171.9. HRMS (ESI⁺) calculated [C₈H₁₃NOS+H]⁺ 172.0796, found 172.0829. All spectroscopic values are consistent with those obtained in the literature.¹³

Synthesis of Fluoxetine, N-methyl-3-phenyl-3-[4-(trifluoromethyl)phenoxy]propan-1-amine (1). 3-(Methylamino)-1-phenylpropan-1-ol 9a (330 mg, 2.00 mmol) was dissolved in dry dimethylacetamide (2.8 mL) and transferred to an oven-dried Schlenk-tube and purged with Argon. NaH (100 mg, 2.2 mmol, 60% in mineral oil) was transferred directly to the solution and heated (70 °C) under Argon for 30-40 min, or until hydrogen evolution had ceased. 4-Chlorobenzotrifluoride (354 μ L, 2.4 mmol) was added under argon, and the resulting solution was heated (100 °C) for 3 h. On cooling, the solution was partitioned between toluene and H₂O and washed (3x H₂O). The organic phase was separated and dried over anhydrous MgSO₄. After filtration the organic phase was removed under reduced pressure to yield a crude product. Purification by silica gel chromatography (DCM : MeOH : NEt₃, 5 : 1 : 1%) gave the pure product as a yellow oil 1, (458 mg, 74%): ¹H-NMR (400 MHz, CDCl₃): δ 7.43 (d, *J* = 8.6 Hz, 2H), 7.39-7.24 (m, 5H), 6.90 (d, *J* = 8.6 Hz, 2H), 5.31 (dd, *J* = 8.2, 4.7 Hz, 1H), 2.79-2.69 (m, 2H), 2.43 (s, 3H), 2.26-1.95 (m, 2H) ppm. ¹³C-NMR (101 MHz, CDCl₃): δ 160.5, 141.0, 128.8, 127.9, 126.8, 126.7, 125.8, 115.8, 78.6, 48.2, 38.6, 29.7 ppm. LR-MS (ESI⁺) 309.3 (57%) [M]⁺; HR-MS (ESI⁺) Calculated [C₁₇H₁₈NOF₃+H]⁺ 310.1419, found 310.1411. = +3.5 (1.0, HCCl₃). Enantiomeric excess was determined by derivatisation to 13a. All spectroscopic values are consistent with those obtained in the literature.²⁷

Synthesis of Duloxetine, Methyl[3-(naphthalene-1-yloxy)-3-(thiophen-2-yl)propyl]amine (2). 3-(Methylamino)-1-(thiophen-2-yl)propan-1-ol 9b (150 mg, 0.87 mmol) was dissolved in dry DMSO (3.0 mL) and transferred to an oven-dried Schlenk-tube and purged with Argon. NaH (43.5 mg, 0.96 mmol, 60% in mineral oil) was transferred directly to the solution and heated (60 °C) under Argon for 1.5 h, or until hydrogen evolution had ceased. 1-Fluoronaphthalene (154 μ L, 1.2 mmol) was added under argon, and the resulting solution was heated (70 °C) for 1.5 h. On cooling, the solution was partitioned between toluene and H₂O and washed (3x H₂O). The organic phase was separated and dried over anhydrous MgSO₄. After filtration the organic phase was removed under reduced pressure to yield a crude product. Purification by silica gel chromatography (DCM : MeOH : NEt₃, 5 : 1 : 1%) gave the

pure product as a yellow oil 2, (214 mg, 83%): ^1H NMR (400 MHz, CDCl_3): δ 8.38–8.33 (m, 1H), 7.80–7.76 (m, 1H), 7.51–7.46 (m, 2H), 7.39 (d, J = 8.3 Hz, 1H), 7.29 (d, J = 7.9 Hz, 1H), 7.21 (dd, J = 5.0, 1.2 Hz, 1H), 7.06 (d, J = 3.5 Hz, 1H), 6.94 (dd, J = 5.0, 3.5 Hz, 1H), 6.86 (d, J = 7.2 Hz, 1H), 5.79 (dd, J = 7.7, 5.3 Hz, 1H), 2.88–2.79 (m, 2H), 2.51–2.40 (m, 2H), 2.44 (s, 3H) ppm. ^{13}C NMR (101 MHz, CDCl_3): δ 153.4, 145.3, 134.6, 127.5, 126.6, 126.3, 126.2, 125.7, 125.2, 124.7, 124.5, 122.1, 122.1, 120.6, 107.0, 74.8, 48.4, 39.1, 36.6 ppm. LRMS (ESI $^+$) $[\text{M}+\text{H}]^+$, 298.0. HRMS (ESI $^+$) calculated $[\text{C}_{18}\text{H}_{19}\text{NOS}+\text{H}]^+$ 298.1266, found 298.1263. = +105.4 (1.0, MeOH). Enantiomeric excess was determined by derivatisation to 13b. All spectroscopic values are consistent with those obtained in the literature.²⁸

Synthesis of (2*E*)-3-(thiophen-2-yl)prop-2-enal (3b). (2*E*)-3-(thiophen-2-yl)prop-2-enoic acid (3.0 g, 19.5 mmol) was dissolved in THF (80 mL) and cooled to -78°C under argon. DIBAL-H (58.5 mL, 1 M THF) was added slowly over 1 hour, and the resulting solution was allowed to react overnight, warming to room temperature. The resulting solution was quenched with a saturated aqueous potassium sodium tartrate solution and allowed to stir for 1 h. After, the resulting solution was partitioned between EtOAc and the aqueous layer was extracted with EtOAc (3x). The organic phase was separated and dried over anhydrous MgSO_4 . After filtration the organic phase was removed under reduced pressure to yield a crude allylic product [(2*E*)-3-(thiophen-2-yl)prop-2-en-1-ol]. In a separate vessel, DMSO (42.9 mmol, 3.0 mL) and DCM (40 mL) were combined under argon and cooled to -78°C . Oxalyl chloride (21.5 mmol, 1.8 mL) was added and the reaction mixture was stirred for 10 min. The crude allylic alcohol [(2*E*)-3-(thiophen-2-yl)prop-2-en-1-ol] was added (in DCM, 12 mL) to the solution at -78°C , and allowed to stir for 10 min. Triethylamine (97.5 mmol, 13.6 mL) was subsequently added, and the solution allowed to warm to room temperature over 1.5 h. After, the resulting solution was partitioned quenched with water and partitioned between EtOAc and the aqueous layer was extracted with EtOAc (3x). The organic phase was separated and dried over anhydrous MgSO_4 . After filtration the organic phase was removed under reduced pressure to yield a crude brown oil. Purification by silica gel chromatography (Hexane : EtOAc, 9 : 1) gave 3b as a yellow oil (996 mg, 37%). ^1H NMR (400 MHz, CDCl_3): δ 9.63 (d, J = 7.7 Hz, 1H), 7.58 (d, J = 15.6 Hz, 1H), 7.51 (d, J = 5.0 Hz, 1H), 7.37 (d, J = 3.7 Hz, 1H), 7.11 (dd, J = 5.1, 3.6 Hz, 1H), 6.52 (dd, J = 15.6, 7.7 Hz, 1H) ppm. ^{13}C NMR (101 MHz, CDCl_3): δ 192.9, 144.4, 139.3, 132.0, 130.4, 128.5, 127.4 ppm. LRMS (ESI $^+$) $[\text{M}+\text{H}]^+$, 138.8. HRMS (ESI $^+$) calculated $[\text{C}_7\text{H}_6\text{OS}+\text{H}]^+$ 139.0218, found 139.0246. All spectroscopic values are consistent with those obtained in the literature.²⁹

Synthesis of *N*-methyl-*N*-[3-phenyl-3-[4-trifluoromethyl]phenoxy]propyl]acetamide (13a). Fluoxetine 1 (200 mg, 0.65 mmol), DCM (4 mL), acetic anhydride (1 mL) and pyridine (1 mL) were combined and allowed to stir over night. The resulting solution was diluted in DCM (30 mL) and washed with HCl (3 x 10 mL, w/v 20%) and water (3 x). The organic layer was separated and dried over anhydrous MgSO_4 . Filtration followed by the removal of solvent under vacuum yielded a crude yellow oil. Purification by silica gel chromatography (Hexane : DCM, 1 : 1 DCM : MeOH, 9 : 1) gave 13a as a yellow oil (220 mg, 96%). IR (neat): ν 3052, 2928, 1636, 1578, 1396, 1093, 771 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 7.42 (d, J = 8.5 Hz, 2H), 7.38–7.27 (m, 5H), 6.89 (d, J = 8.4 Hz, 2H), 5.21 (dd, J = 8.6, 4.3 Hz, 1H), 3.63–3.51 (m, 2H), 2.97 (s, 3H), 2.25–2.09 (m, 2H), 2.04 (s, 3H) ppm. ^{13}C NMR (101 MHz, CDCl_3): δ 170.6, 160.3, 140.7, 129.1, 128.3, 126.9, 126.8, 125.7, 125.5, 115.6, 78.4, 47.1, 37.4, 36.6, 21.1 ppm. LRMS (ESI $^+$) $[\text{M}+\text{H}]^+$, 351.9. HRMS (ESI $^+$) calculated $[\text{C}_{19}\text{H}_{20}\text{NO}_2\text{F}_3+\text{H}]^+$ 352.1524 found

352.1515. Enantiomeric excess was determined by HPLC using an AS-H CHIRALCEL column (250 x 4.6 mm) fitted with guard cartridge (50 x 4.6 mm), 25°C , 1.0 mL/min, 210 nm, hexane : IPA (9 : 1). t_{R} (R) = 23.6 min; t_{R} (S) = 31.9 min.

Synthesis of *N*-methyl-*N*-[3-(naphthalene-1-yloxy)-3-(thiophen-2-yl)propyl]acetamide (13b). Duloxetine 2 (166 mg, 0.56 mmol), DCM (3 mL), acetic anhydride (1 mL) and pyridine (1 mL) were combined and allowed to stir over night. The resulting solution was diluted in DCM (30 mL) and washed with HCl (3 x 10 mL, w/v 20%) and water (3 x). The organic layer was separated and dried over anhydrous MgSO_4 . Filtration followed by the removal of solvent under vacuum yielded a crude yellow oil. Purification by silica gel chromatography (Hexane : DCM, 1 : 1 DCM : MeOH, 9 : 1) gave 13b as a yellow oil (150 mg, 79%). IR (neat): ν 2931, 1636, 1516, 1323, 1245, 1108, 835 cm^{-1} . Observed as a mixture of rotamers, major rotamer: ^1H NMR (400 MHz, CDCl_3): δ 8.40–8.30 (m, 1H), 7.84–7.81 (m, 1H), 7.56–7.51 (m, 2H), 7.44 (d, J = 8.6 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.21 (dd, J = 5.0, 1.2 Hz, 1H), 7.11 (d, J = 3.8 Hz, 1H), 6.97 (dd, J = 5.0, 3.5 Hz, 1H), 6.87 (d, J = 8.5 Hz, 1H), 5.74 (dd, J = 8.0, 4.9 Hz, 1H), 3.82–3.61 (m, 2H), 3.00 (s, 3H), 2.57–2.45 (m, 2H), 2.06 (s, 3H) ppm. ^{13}C NMR (101 MHz, CDCl_3): δ 170.7, 153.1, 144.8, 134.6, 127.7, 126.8, 126.5, 126.1, 125.7, 127.5, 124.9, 124.8, 122.0, 121.1, 106.9, 74.5, 45.1, 36.7, 33.3, 21.9 ppm. LRMS (ESI $^+$) $[\text{M}+\text{Na}]^+$, 361.3. HRMS (ESI $^+$) calculated $[\text{C}_{20}\text{H}_{21}\text{NO}_2\text{S}+\text{H}]^+$ 340.1371, found 340.1377. Enantiomeric excess determined by HPLC using an AS-H CHIRALCEL column (250 x 4.6 mm) fitted with guard cartridge (50 x 4.6 mm), 25°C , 1.0 mL/min, 210 nm, hexane : IPA (85 : 15). t_{R} (S) = 29.2 min; t_{R} (R) = 38.2 min.

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Notes and references

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- (a) D. T. Wong, J. S. Horng, F. P. Bymaster, K. L. Hauser and B. B. Molloy, *Life Sci.*, 1974, 15, 471–479; (b) D. T. Wong, F. P. Bymaster and E. A. Engleman, *Life Sci.*, 1995, 57, 411–441.
- L. Sghendo and J. Mifsud, *J Pharm Pharmacol.*, 2012, 64, 317–325.
- F. S. Messiha, *Neurosci Biobehav Rev.*, 1993, 17, 385–396.
- C. Hiemke and S. Härtter, *Pharmacology & Therapeutics.*, 2000, 85, 11–28.
- C. J. Harmer, G. M. Goodwin and P. J. Cowen, *Am. J. Psychiatry.*, 2004, 161, 1256–1263.
- M. Srebnik, P. V. Ramachandran and H. C. Brown, *J. Org. Chem.*, 1988, 53, 2916–2920.
- Y. Gao and K. B. Sharpless, *J. Org. Chem.*, 1988, 53, 4081–4084.
- E. J. Corey and G. A. Reichard, *Tetrahedron Lett.*, 1989, 30, 5207–5210.
- (a) D. Liu, W. Gao, C. Wang and X. Zhang, *Angew. Chem. Int. Ed.*, 2005, 44, 1687–1689; (b) T. Ohkuma, D. Ishii, H. Takeno and R. Noyori, *J. Am. Chem. Soc.*, 2000, 122, 6519–6511; (c) R. Noyori, T. Ohkuma, M. Kitamura, H. Takaya, N. Sayo, H. Kumobayashi and S.

- Akutagawa, *J. Am. Chem. Soc.*, 1987, 109, 5856-5858; (d) R. Noyori, *Angew. Chem. Int. Ed.*, 2002, 41, 2008-2022.
- 10 (a) P. Motloch, I. Valterová and M. Kotora, *Adv. Synth. Catal.*, 2014, 356, 199-204; (b) Â. de Fátima, A. A. M. Lapis and R. A. Pilli, *J. Braz. Chem. Soc.*, 2005, 16, 495-499; (c) M. Iwata, R. Yazaki, N. Kumagai and M. Shibasaki, *Tetrahedron: Asymmetry*, 2010, 21, 1688-1694.
- 11 D. T. Wong, K. W. Perry and F. P. Bymaster, *Nat. Rev. Drug. Discov.*, 2005, 4, 764-774.
- 12 C. J. Wenthur, M. R. Bennett and C. W. Lindsley, *ACS Chem. Neurosci.*, 2014, 5, 14-23.
- 13 Y. Suzuki, M. Iwata, R. Yazaki, N. Kumagai and M. Shibasaki, *J. Org. Chem.*, 2012, 77, 4496-4500.
- 14 (a) C. Solé, A. Whiting, H. Gulyás and E. Fernández, *Adv. Synth. Catal.*, 2011, 353, 376-384; (b) C. Solé, A. Tatla, J. A. Mata, A. Whiting, H. Gulyás and E. Fernández, *Chem. Eur. J.*, 2011, 17, 14248-14257.
- 15 (a) J. Cid, H. Gulyás, J. J. Carbó and E. Fernández, *Chem. Soc. Rev.*, 2012, 41, 3558-3570. (b) A. D. J. Calow and A. Whiting, *Org. Biomol. Chem.*, 2012, 10, 5485-5497.
- 16 H. -H. Blaser, *Chem. Rev.*, 1992, 92, 935-952.
- 17 A. D. J. Calow, A. Batsanov, A. Pujol, C. Solé, E. Fernández and A. Whiting, *Org. Lett.*, 2013, 15, 4810-4813
- 18 H. Chea, H. -S. Sim, J. Yun, *Adv. Synth. Catal.*, 2009, 351, 855-858.
- 19 (a) S. Ram and L. D. Spicer, *Synth. Commun.*, 1987, 17, 415-418; (b) P. Bucks, *Russ. Chem. Rev.* 1983, 52, 2072-2090.
- 20 (a) S. Rajagopal and A. F. Spatola, *Appl. Catal., A*, 1997, 152, 69-81; (b) R. J. Rahaim and R. E. Maleczka, *Org. Lett.*, 2011, 13, 584-587.
- 21 M. Ciaccia, R. Cacciapaglia, P. Mencarelli, L. Mandolini and S. Di Stefano, *Chem. Sci.*, 2013, 4, 2253-2261.
- 22 G. K. Cantrell and T. Y. Meyer, *Organometallics.*, 1997, 16, 5381-5383.
- 23 This α -boryl aldehyde eliminates to give cinnamaldehyde during column chromatography, as reported in the literature: I. Ibrahim, P. Breistein and A. Córdova, *Angew. Chem. Int. Ed.*, 2011, 50, 12036-12041.
- 24 A. D. J. Calow, A. S. Batsanov, E. Fernández, C. Solé and A. Whiting, *Chem. Commun.*, 2012, 48, 11401-11403.
- 25 H. Kakei, T. Nemoto, T. Ohshima and M. Shibasaki, *Angew. Chem.*, 2004, 116, 321-324.
- 26 K. Omura and D. Swern, *Tetrahedron.*, 1978, 34, 1651-1660.
- 27 G. Wang, X. Liu and G. Zhao, *Tetrahedron: Asymmetry.*, 2005, 16, 1873-1879
- 28 J. Deeter, J. Frazier, G. Staten, M. Staszak and L. Weigel, *Tetrahedron Letters*, 1990, 31, 7101-7104.
- 29 E. Kim, M. Koh, J. Ryu and S. B. Park, *J. Am. Chem. Soc.*, 2008, 130, 12206-12207.

Graphical abstract

Total synthesis of Fluoxetine & Duloxetine through an *in situ* imine formation/borylation/transimination and reduction approach

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Efficient, catalytic, asymmetric total syntheses of both (*R*)-Fluoxetine and (*S*)-Duloxetine from α,β -unsaturated aldehydes are reported.

