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

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,  
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

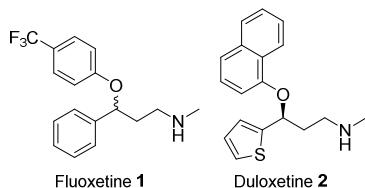
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We report efficient, catalytic, asymmetric total syntheses of both (*R*)-Fluoxetine and (*S*)-Duloxetine from  $\alpha,\beta$ -unsaturated aldehydes conducting five sequential one pot steps (imine formation / copper mediated  $\beta$ -borylation / 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.*).

## Introduction

Fluoxetine **1** and Duloxetine **2**, developed by Eli Lilly,<sup>1</sup> are top-selling pharmaceuticals used for the treatment of major depressive disorder (MDD)<sup>2</sup> and other conditions.<sup>3</sup> Fluoxetine **1** belongs to the selective serotonin reuptake inhibitor (SSRI) class of anti-depressants<sup>4</sup> and Duloxetine **2** to the serotonin-norepinephrine reuptake inhibitor (SNRI) class.<sup>5</sup>



**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.<sup>6</sup> Sharpless *et al.* also developed a route to Fluoxetine using an asymmetric epoxidation of an allylic alcohol, followed by ring-opening strategy.<sup>7</sup> 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.<sup>8</sup> 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.*)<sup>9</sup> and, indeed, other groups have employed this methodology to the synthesis of both Fluoxetine **1** and Duloxetine **2**.<sup>10</sup>

It is interesting to note that Fluoxetine **1**, despite being a chiral compound, is marketed as the racemic HCl-salt (Fig. 1).<sup>11</sup> However, studies have revealed evidence of differing pharmacological and pharmacokinetic properties depending on the enantiomer of Fluoxetine **1**.<sup>12</sup> This evidence suggests that

the (*S*)-enantiomer of Fluoxetine **1** is more active in the inhibition of serotonin than the (*R*)-enantiomer.<sup>12</sup> 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.<sup>13</sup>

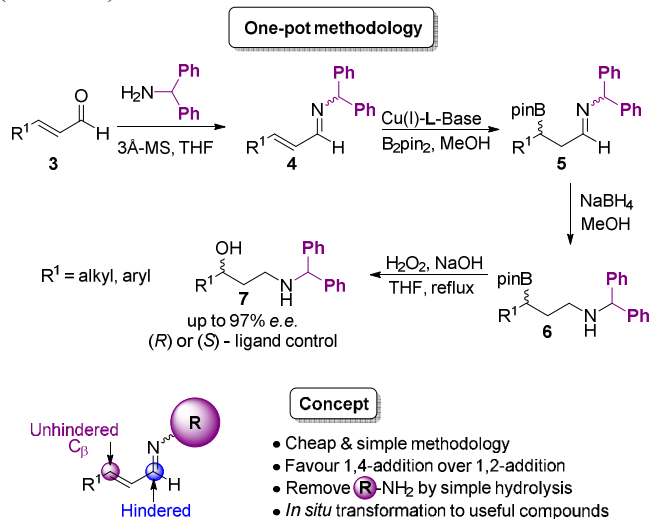
Herein, we report an efficient, catalytic, asymmetric synthesis of Fluoxetine and Duloxetine with key steps that involves: 1) an *in situ* imine formation, 2) a copper-catalysed asymmetric  $\beta$ -borylation protocol that requires a specific bulky amine to block the imine functionality and prevent 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

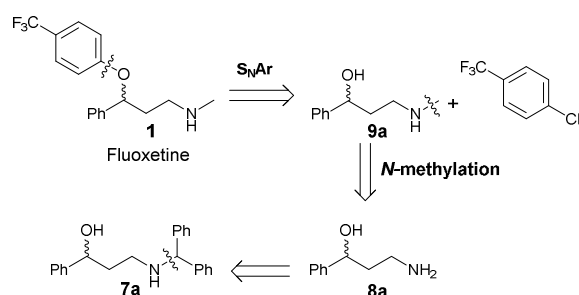
In recent years we have been interested in the preparation of  $\gamma$ -amino alcohols (*e.g.* **7**-)<sup>14</sup> via the  $\beta$ -borylation<sup>15</sup> of  $\alpha,\beta$ -unsaturated imines (*e.g.* **4**-) because such  $\gamma$ -amino alcohols have applications as auxiliaries in synthetic and biochemical systems.<sup>16</sup> In this context, we demonstrated a novel protocol for the asymmetric  $\beta$ -borylation of enal-derived  $\alpha,\beta$ -unsaturated aldimines.<sup>17</sup> 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  $\beta$ -boryl imines **5**- can be reduced and oxidised in one-pot to yield *N*-benzhydryl  $\gamma$ -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 **1**<sup>18</sup> and Duloxetine **2**. By applying our retrosynthetic analysis to Fluoxetine **1**, one can clearly see that  $\gamma$ -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  $\gamma$ -amino alcohols.

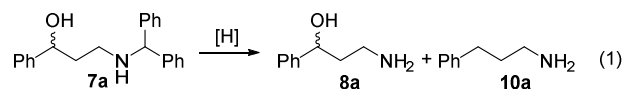


**Scheme 2** Retrosynthetic analysis of Fluoxetine **1**.

Initially, we prepared compound **7a** from cinnamaldehyde **3a** using CuCl/**L0** or CuCl/**L1** (**L0**=PPh<sub>3</sub> and **L1**=(*R,R*)-DM-BINAP) as the catalytic system.<sup>17</sup> 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)].<sup>19</sup> However, using this methodology we encountered significant C-O bond hydrogenolysis,<sup>20</sup> *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 catalysis 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

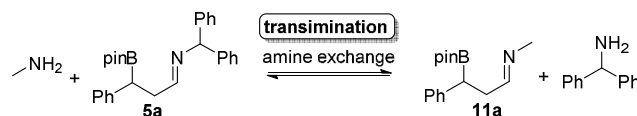
conditions.

In addition to debenzhydrylation, hydrolysis of compound **5a** to the analogous aldehyde, with subsequent reductive amination using methylamine/NaBH<sub>4</sub> (to yield **12a**) was attempted and indeed did work, but due to the instability of the analogous  $\beta$ -boryl aldehyde the overall conversion in this case was low (<20%) and, hence, we needed to avoid the utilisation of such  $\beta$ -boryl aldehydes as intermediates in subsequent synthesis.



- [H] = a) H<sub>2</sub>, Pd-C (10%), MeOH, r.t.  
 b) HCONH<sub>4</sub>, Pd-C (10%), MeOH,  $\Delta$   
 c) [Rh(PPh<sub>3</sub>)<sub>3</sub>]Cl (5%), H<sub>2</sub> **no reaction**  
 d) TFA,  $\Delta$  **no reaction**

Intrigued by recent reports of transimination<sup>21</sup> (also known as imine-metathesis<sup>22</sup>), we wondered whether treating the  $\beta$ -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  $\beta$ -boryl aldehyde<sup>23</sup> simply by the addition of cheap and readily available methylamine.

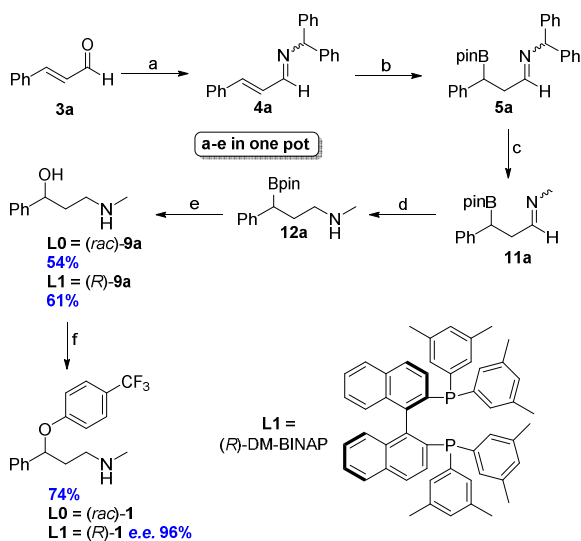


**Scheme 3** Proposed transimination through amine exchange.

Continuing with the established one-pot methodology (Scheme 4), we therefore treated the intermediate  $\beta$ -boryl imine **5a** with excess methylamine (4 equiv.), followed by *in situ* reduction using NaBH<sub>4</sub>/MeOH. Subsequently, solvent removal (to prevent MeOH oxidation to formaldehyde, which in the presence of  $\gamma$ -amino alcohols leads to the formation of 1,3-oxazines, as previously reported<sup>24</sup>) and replacement with THF, followed by B-C oxidation with H<sub>2</sub>O<sub>2</sub>/NaOH of boronate **12a**, gave the known precursor to Fluoxetine,  $\gamma$ -amino alcohol **9a** [54% yield when using PPh<sub>3</sub> **L0** and 61% when using (*R,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,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.*).<sup>17</sup>

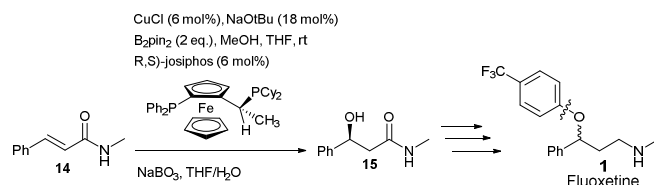
It is important to note that recent work described by Yun *et al.* on the asymmetric  $\beta$ -borylation of  $\alpha,\beta$ -unsaturated amides **14**, conducted to the formal synthesis of (*S*)-Fluoxetine with excellent enantioselectivity (99% *e.e.*),<sup>18</sup> using in this case copper salts modified with a type of chiral josphos ligand (Scheme 5). The intermediate compound **15** could be reduced

using  $\text{LiAlH}_4^{25}$  to give **9a** in quantitative yields, which could be transformed to Fluoxetine using known procedures (*e.g.* Scheme 4).<sup>7</sup>



#### Scheme 4 Asymmetric synthesis of (*R*)-Fluoxetine **1**.

Conditions: a)  $\text{Ph}_2\text{CHNH}_2$  (1 equiv.), 3 Å-MS, THF, r.t., 6h; b)  $\text{CuCl}$  (3%),  $\text{PPh}_3$  **L0** (6%),  $\text{NaOtBu}$  (9%),  $\text{B}_2\text{pin}_2$  (1.1 equiv.), MeOH (2.5 equiv.), r.t., 15h or  $\text{CuCl}$  (3%), (*R*)-DM-BINAP **L1** (3%),  $\text{NaOtBu}$  (9%),  $\text{B}_2\text{pin}_2$  (1.1 equiv.), MeOH (2.5 equiv.), r.t., 15h; c)  $\text{MeNH}_2$  (4 equiv.), r.t., 2 h; d)  $\text{NaBH}_4$ , MeOH, r.t. 3h. Remove solvent *in vacuo*; e)  $\text{H}_2\text{O}_2$ ,  $\text{NaOH}$ , THF, reflux, 1 h; f)  $\text{NaH}$  (1.1 equiv.), DMA, 70 °C, 30 min. Ar-Cl (1.2 equiv.), 100 °C, 3 h.

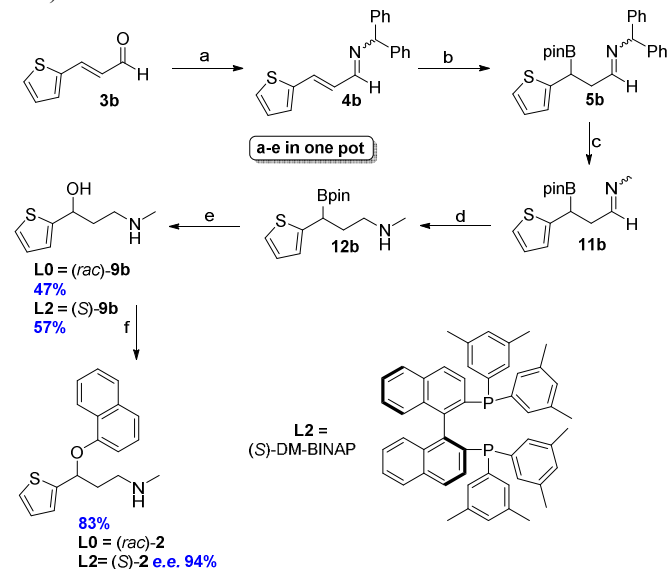


#### Scheme 5 Yun *et al.*'s formal synthesis of Fluoxetine.<sup>18</sup>

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.<sup>26</sup>

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  $\text{B}_2\text{pin}_2$ ) mixture, followed by the addition of MeOH, to give the intermediate  $\beta$ -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 formation<sup>24</sup>), the solvent was removed *in vacuo* prior to C-B oxidation and, hence, oxidation resulted in the formation of the known precursor  $\gamma$ -amino alcohol **9b** in good yield [47% yield when using  $\text{PPh}_3$  **L0** and 57% when using (*S*)-DM-BINAP **L2**, see Scheme 6]. Finally,

addition of  $\text{NaH}$  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)  $\text{Ph}_2\text{CHNH}_2$  (1 equiv.), 3 Å-MS, THF, r.t., 8h; b)  $\text{CuCl}$  (3%),  $\text{PPh}_3$  **L0** (6%),  $\text{NaOtBu}$  (9%),  $\text{B}_2\text{pin}_2$  (1.1 equiv.), MeOH (2.5 equiv.), r.t., 15h or  $\text{CuCl}$  (3%), (*S*)-DM-BINAP **L2** (3%),  $\text{NaOtBu}$  (9%),  $\text{B}_2\text{pin}_2$  (1.1 equiv.), MeOH (2.5 equiv.), r.t., 15h; c)  $\text{MeNH}_2$  (4 equiv.), r.t., 2 h; d)  $\text{NaBH}_4$ , MeOH, r.t. 3h. Remove solvent *in vacuo*; e)  $\text{H}_2\text{O}_2$ ,  $\text{NaOH}$ , THF, reflux, 1 h; f)  $\text{NaH}$  (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  $\beta$ -borylation of  $\alpha,\beta$ -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  $\text{CuCl}$  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, 3Å 1-2mm beads, were supplied from Alfa Aesar, and stored at 220 °C. Reactions were monitored by TLC analysis using POLTRAM<sup>®</sup> SIL G/UV<sub>254</sub> (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  $\mu\text{m}$ , 60  $\text{\AA}$ ) and monitored using TLC analysis.  $^1\text{H}$  NMR spectra were recorded on a Varian-Mercury 500 MHz spectrometer, operating at ambient probe temperature unless specified elsewhere.  $^{13}\text{C}$  NMR spectra were recorded on a Varian Mercury 500 MHz instrument, operating at 101 MHz, unless specified elsewhere. Deuterated chloroform  $\text{CDCl}_3$  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  $\text{ESI}^+$ , electrospray in positive ion mode,  $\text{ESI}^+$ ), Waters (UK) Xevo QTOF mass spectrometer (low and high resolution  $\text{ASAP}^+$ ) and a Waters (UK) LCT premier XE (high resolution  $\text{ESI}^+$ , electrospray in positive ion mode,  $\text{ESI}^+$ ) 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  $[\alpha]_{\text{D}}$  values given in  $\text{deg cm}^2\text{g}^{-1}$ .

### 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  $\text{\AA}$ -MS (5.0 g) for 6 h, to form the  $\alpha,\beta$ -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  $\text{CuCl}$  (12.0 mg, 0.12 mmol),  $\text{PPh}_3$  (62.9 mg, 0.24 mmol) or (*R*)-DM-BINAP (88.2 mg, 0.12 mmol),  $\text{NaOt-Bu}$  (34.6 mg, 0.36 mmol) and  $\text{B}_2\text{pin}_2$  (1.12 g, 4.4 mmol). After 5 min, MeOH (400  $\mu\text{L}$ , 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.  $\text{NaBH}_4$  (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  $\text{H}_2\text{O}_2$  (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  $\text{MgSO}_4$ . After filtration the organic phase was removed under reduced pressure to yield a crude product. Purification by silica gel chromatography (DCM  $\rightarrow$  DCM : MeOH :  $\text{NEt}_3$ , 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  $\text{PPh}_3$  and 402 mg, 61% when using (*R*)-DM-BINAP]:  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  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);  $^{13}\text{C}$ -NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  145.0, 128.2, 127.0, 125.6, 75.4, 50.3, 36.7, 35.9; LR-MS ( $\text{ESI}^+$ ) 166.5  $[\text{M}+\text{H}]^+$ ; HR-MS ( $\text{ESI}^+$ ) Calculated  $[\text{C}_{10}\text{H}_{15}\text{NO}+\text{H}]^+$  166.1232, found 166.1228. All spectroscopic values are consistent with those obtained in the literature.<sup>27</sup>

**Synthesis of 3-(Methylamino)-1-(thiophen-2-yl)propan-1-ol (9b).** Benzhydrylamine (0.86 mL, 5.00 mmol) and (2*E*)-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  $\text{\AA}$ -MS (5.0 g) for 6 h, to form the  $\alpha,\beta$ -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  $\text{CuCl}$  (9.0 mg, 0.09 mmol),  $\text{PPh}_3$  (48.0 mg, 0.18 mmol) or (*S*)-DM-BINAP (66.1 mg, 0.09 mmol),  $\text{NaOt-Bu}$  (27.0 mg, 0.27 mmol) and  $\text{B}_2\text{pin}_2$  (0.84 g, 3.3 mmol). After 5 min, MeOH (300  $\mu\text{L}$ , 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.  $\text{NaBH}_4$  (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  $\text{H}_2\text{O}_2$  (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  $\text{MgSO}_4$ . After filtration the organic phase was removed under reduced pressure to yield a crude product. Purification by silica gel chromatography (DCM  $\rightarrow$  DCM : MeOH :  $\text{NEt}_3$ , 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  $\text{PPh}_3$  and 292 mg, 57% when using (*S*)-DM-BINAP]:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  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.  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  149.7, 126.6, 123.7, 122.3, 71.9, 50.1, 36.8, 35.9 ppm. LRMS ( $\text{ESI}^+$ )  $[\text{M}+\text{H}]^+$ , 171.9. HRMS ( $\text{ESI}^+$ ) calculated  $[\text{C}_8\text{H}_{13}\text{NOS}+\text{H}]^+$  172.0796, found 172.0829. All spectroscopic values are consistent with those obtained in the literature.<sup>13</sup>

**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  $^\circ\text{C}$ ) under Argon for 30–40 min, or until hydrogen evolution had ceased. 4-Chlorobenzotrifluoride (354  $\mu\text{L}$ , 2.4 mmol) was added under argon, and the resulting solution was heated (100  $^\circ\text{C}$ ) for 3 h. On cooling, the solution was partitioned between toluene and  $\text{H}_2\text{O}$  and washed (3x  $\text{H}_2\text{O}$ ). The organic phase was separated and dried over anhydrous  $\text{MgSO}_4$ . After filtration the organic phase was removed under reduced pressure to yield a crude product. Purification by silica gel chromatography (DCM  $\rightarrow$  DCM : MeOH :  $\text{NEt}_3$ , 5 : 1 : 1%) gave the pure product as a yellow oil **1**, (458 mg, 74%):  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  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.  $^{13}\text{C}$ -NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  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 ( $\text{ESI}^+$ ) 309.3 (57%)  $[\text{M}]^+$ ; HR-MS ( $\text{ESI}^+$ ) Calculated  $[\text{C}_{17}\text{H}_{18}\text{NOF}_3+\text{H}]^+$  310.1419, found 310.1411.  $[\alpha]_{\text{D}}^{22} = +3.5$  (1.0,  $\text{HCCl}_3$ ). Enantiomeric excess was determined by derivatisation to **13a**. All spectroscopic values are consistent with those obtained in the literature.<sup>27</sup>

**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 µL, 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 H<sub>2</sub>O and washed (3x H<sub>2</sub>O). The organic phase was separated and dried over anhydrous MgSO<sub>4</sub>. After filtration the organic phase was removed under reduced pressure to yield a crude product. Purification by silica gel chromatography (DCM → DCM : MeOH : NEt<sub>3</sub>, 5 : 1 : 1%) gave the pure product as a yellow oil **2**, (214 mg, 83%): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 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. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): 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<sup>+</sup>) [M+H]<sup>+</sup>, 298.0. HRMS (ESI<sup>+</sup>) calculated [C<sub>18</sub>H<sub>19</sub>NOS+H]<sup>+</sup> 298.1266, found 298.1263. [α]<sub>D</sub><sup>22</sup> = +105.4 (1.0, MeOH). Enantiomeric excess was determined by derivatisation to **13b**. All spectroscopic values are consistent with those obtained in the literature.<sup>28</sup>

**Synthesis of (2E)-3-(thiophen-2-yl)prop-2-enal (3b).** (2E)-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<sub>4</sub>. After filtration the organic phase was removed under reduced pressure to yield a crude allylic product [(2E)-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 [(2E)-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<sub>4</sub>. 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%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 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. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 192.9, 144.4, 139.3, 132.0, 130.4, 128.5, 127.4 ppm. LRMS (ESI<sup>+</sup>) [M+H]<sup>+</sup>, 138.8. HRMS (ESI<sup>+</sup>) calculated [C<sub>7</sub>H<sub>6</sub>OS+H]<sup>+</sup> 139.0218, found 139.0246. All spectroscopic values are consistent with those obtained in the literature.<sup>29</sup>

**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<sub>4</sub>. 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<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 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. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): 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<sup>+</sup>) [M+H]<sup>+</sup>, 351.9. HRMS (ESI<sup>+</sup>) calculated [C<sub>19</sub>H<sub>20</sub>NO<sub>2</sub>F<sub>3</sub>+H]<sup>+</sup> 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<sub>R</sub>* (S) = 23.6 min; *t<sub>R</sub>* (R) = 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<sub>4</sub>. 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<sup>-1</sup>. Observed as a mixture of rotamers, major rotamer: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 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. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): 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<sup>+</sup>) [M+Na]<sup>+</sup>, 361.3. HRMS (ESI<sup>+</sup>) calculated [C<sub>20</sub>H<sub>21</sub>NO<sub>2</sub>S+H]<sup>+</sup> 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<sub>R</sub>* (S) = 29.2 min; *t<sub>R</sub>* (R) = 38.2 min.

## Acknowledgements

A.D.J.C would like to thank the EPSRC for a doctoral training account.

## Notes and references

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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## 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  $\alpha,\beta$ -unsaturated aldehydes are reported.

