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Enantioselective total and formal syntheses of paroxetine (PAXIL) via phosphine-catalyzed enone α-arylation using arylbismuth(V) reagents: a regiochemical complement to Heck arylation

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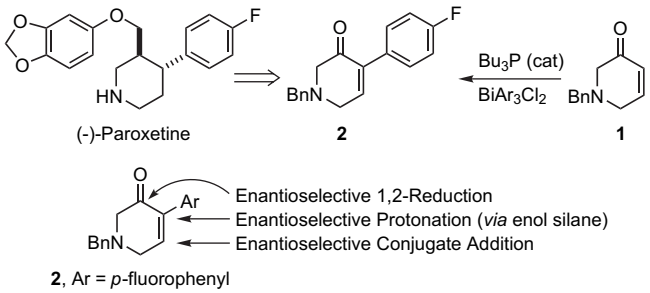
Abstract—Exposure of dihydropyridinone **1** to the arylbismuth(V) reagent (p-F-Ph)$_3$BiCl$_2$ in the presence of substoichiometric quantities of tributylphosphine (10 mol %) results in aryl transfer to the transiently generated (β-phosphonio)enolate to provide the α-arylated enone **2**. This transformation, which represents a regiochemical complement to the Mizoroki–Heck arylation, is used strategically in concise formal and enantioselective total syntheses of the blockbuster antidepressant (−)-paroxetine (PAXIL).

1. Introduction

Nucleophilic or Lewis base catalysis represents a major subset of organocatalytic transformations.[1] As part of an ongoing program in this area, we have developed a family of catalytic transformations that exploit the unique reactivity of enolates derived upon phosphine-conjugate addition to α,β-unsaturated carbonyl compounds.[2–5] These studies encompass a catalytic method for the regiospecific α-arylation of enones and enals, wherein transiently generated (β-phosphonio)enolates or oxaphospholenes are captured by arylbismuth(V) reagents.[5–7] The scope of this process complements corresponding palladium-catalyzed enolate arylations,[8] as strongly basic reagents are not required for enolate generation. Further, the use of enones as enolate precursors enables regiospecific enolate generation. In this account, the synthetic utility of the phosphine-catalyzed enone α-arylation is highlighted through its strategic use in concise formal and enantioselective total syntheses of the blockbuster antidepressant (−)-paroxetine (PAXIL).

Paroxetine, a GlaxoSmithKline product marketed as Paxil/Seroxat, is an enantiomerically enriched *trans*-3,4-disubsituted piperidine used for the treatment of depression, obsessive compulsive disorder, and panic disorder.[9] As one of the leading prescription drugs worldwide, paroxetine has received considerable attention from synthetic chemists, evoking a surprisingly diverse array of strategies for its asymmetric synthesis. To date, approaches to the asymmetric synthesis of paroxetine encompass the physical resolution of racemates,[10] enzyme-catalyzed asymmetric transformations,[11] chiral auxiliary-based approaches,[12] asymmetric deprotonation using chiral bases,[13] catalytic enantioselective transformations,[14] as well as the use of naturally occurring chiral starting materials.[15] We envisioned a concise approach to (−)-paroxetine based on phosphine-catalyzed α-arylation of *N*-benzyl dihydropyridinone **1**, which may be prepared from commercially available *N*-benzyl glycine ethyl ester in only three steps.[16] The resulting α-arylated enone **2** represents an attractive synthetic intermediate *en route* to (−)-paroxetine, as closely related α-aryl enones are amenable to a range of relevant catalytic enantioselective transformations. These include asymmetric conjugate addition, asymmetric 1,2-reduction, as well as asymmetric protonation by way of the enol silane (Scheme 1).[17,18]



Scheme 1. Retrosynthesis of (−)-paroxetine via enone α-arylation.

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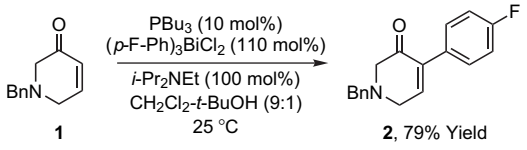
1.1. Formal synthesis of (±)-paroxetine (PAXIL)

Preparation of the arylation substrate, dihydropyridinone **1**, is achieved readily in accordance with the literature procedure.[16] The requisite bismuth reagent $(p\text{-F-Ph})_3BiCl_2$ is prepared by treating *p*-F-PhMgBr with $BiCl_3$ followed by oxidation of the resulting triarylbismuth(III) compound with elemental chlorine.[5,6] Gratifyingly, exposure of dihydropyridinone **1** to $(p\text{-F-Ph})_3BiCl_2$ (110 mol %) in the presence of tributylphosphine (10 mol %) and Hünig's base (100 mol %) at ambient temperature in CH_2Cl_2/^{t}BuOH (9:1) provides the α-arylated dihydropyridinone **2** in 79% isolated yield as a single regioisomer, based on ^{1}H NMR analysis (Scheme 2).



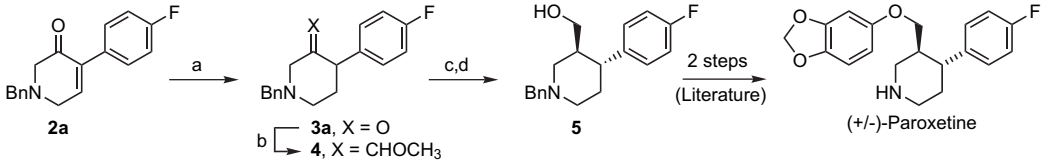
Scheme 2. Catalytic α-arylation of dihydropyridinone **1**.

Subsequent efforts focused on the conversion of aryl enone **2a** to *N*-benzyl aminoalcohol **5**, which has been converted to paroxetine in two steps.[10i,11e,13b,c,15] Conjugate reduction of **2a** using L-Selectride provides the corresponding saturated α-aryl ketone **3a** in 87% yield.[19] Ketone olefination using $Ph_3P{=}CHOMe$[20] affords the enol ether **4** in 65% yield as a single alkene geometrical isomer, as determined by ^{1}H NMR. Acid hydrolysis of enol **4** followed by $NaBH_4$ reduction of the resulting aldehyde provides *N*-benzyl aminoalcohol **5** in 63% yield over the two-step sequence as a single diastereomer, as determined by ^{1}H NMR. Aminoalcohol **5** exhibits spectral properties identical in all respects to previously reported material that has been converted to paroxetine in two steps.[10i,11e,13b,c,15] Hence, the preparation of **5** from dihydropyridinone **1** represents a formal synthesis of (±)-paroxetine (Scheme 3).

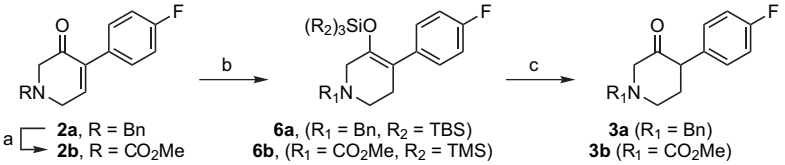
1.2. Enantioselective total synthesis of (−)-paroxetine (PAXIL)

Having completed a formal racemic synthesis of paroxetine, efforts toward an enantioselective total synthesis were made. Here, a potentially effective strategy involves asymmetric protonation[17,18] of enol silanes **6a** or **6b**, which are derived in a single manipulation from enones **2a** and **2b** by way of conjugate reduction with trapping of the resulting enolate in situ using trimethylsilyl chloride or *tert*-butyldimethylsilyl chloride, respectively.[19] However, enol silane **6a** did not react upon exposure to Yamamoto's BINOL/$SnCl_4$ reagent,[17a–c] perhaps due to the presence of the Lewis basic *N*-benzyl amine. Treatment of the carbamoyl-protected enone **6b** to the BINOL/$SnCl_4$ reagent gave the desired α-aryl ketone **3b** in 80% yield, but with very low levels of optical enrichment (10% ee). Yanagisawa's recently reported silver fluoride-catalyzed asymmetric protonation gave a more promising result, providing the α-aryl ketone **3b** in 90% yield and 39% ee (Scheme 4).[17d]

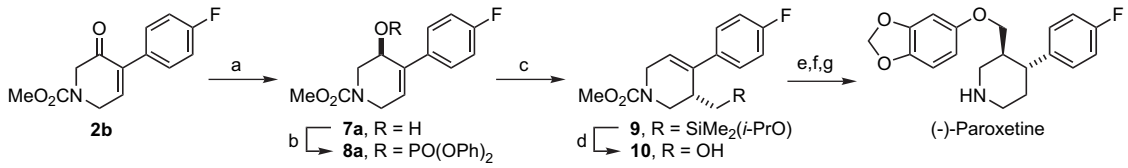
The difficulties encountered in preparing optically enriched aminoketones **3a** or **3b** led us to consider alternative synthetic routes. Accordingly, oxazaborolidine-catalyzed asymmetric 1,2-reduction of enones **2a** and **2b** was explored.[21] The *N*-benzyl-protected enone **2a** gave the corresponding allylic alcohol in 35% yield and 70% ee. It was speculated that the presence of the Lewis basic *N*-benzyl amine of **2a** was incompatible with the Lewis acidic oxazaborolidine catalyst, resulting in diminished yields and selectivities. Gratifyingly, oxazaborolidine-catalyzed asymmetric 1,2-reduction of the corresponding *N*-carbamoyl-protected enone **2b** provides allylic alcohol **7a** in 95% yield and 96% ee. The allylic alcohol **7a** was converted to the diphenyl phosphate **8a** and was subjected to conditions for *anti*-selective copper-mediated S_N2' allylic substitution[22] using $(i\text{-PrO})Me_2SiCH_2Cl$ as a hydroxymethyl anion equivalent.[23] The silicon containing product of allylic substitution **9** was obtained in 96% yield and was subjected to Tamao oxidation to provide the homo-allylic alcohol **10** in 70% yield. As revealed by chiral stationary phase HPLC analysis, compound **10** is obtained in 92% ee. The high fidelity of chirality transfer supports an *anti*-S_N2' mechanism for allylic substitution and the slight decrease in enantiomeric excess is attributed to competitive S_N2 substitution. Stereoselective substrate-directed catalytic homogeneous hydrogenation of the homo-allylic alcohol **10** was accomplished using Crabtree's conditions[24,25] to provide the corresponding saturated alcohol in 69% yield as a single diastereomer, as determined by ^{1}H NMR analysis.



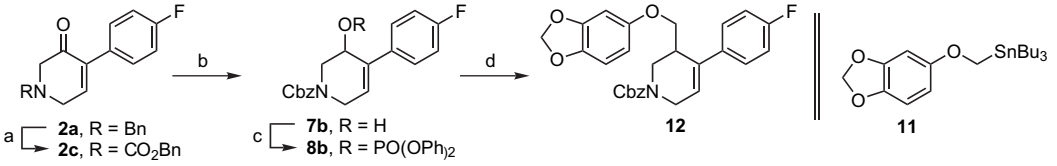
Scheme 3. Conversion of arylation product **2a** to (±)-paroxetine. Conditions: (a) L-Selectride, THF, −78 °C, 87%; (b) Ph_3PCH_2OMeCl, NaHMDS, THF, 0 °C, 65%; (c) 0.1 M H_2SO_4, THF, 50 °C; (d) $NaBH_4$, EtOH, 25 °C, 63% over two steps.



Scheme 4. Attempted asymmetric protonation of enol silanes **6a** and **6b**. Conditions: (a) MeOCOCl, CH_2Cl_2, 25 °C, 86%; (b) Li(s-Bu)$_3$BH, THF, −78 °C, then R_3SiCl, 74% (from **2a** using TBSCl) and 86% (from **2b** using TMSCl); (c) AgF (cat.), *R*-BINAP (cat.), DCM/MeOH (20:1), 90%, 39% ee (refers to the conversion of **6b** to **3b**).



Scheme 5. Enantioselective total synthesis of (−)-paroxetine. Conditions: (a) (*S*)-Me-CBS (cat.), $BH_3 \cdot SMe_2$, CH_2Cl_2, −20 °C, 95%, 96% ee; (b) $(PhO)_2P(O)Cl$, DMAP (cat.), Pyr, CH_2Cl_2, 25 °C, 89%; (c) (*i*-PrO)Me_2SiCH_2Cl, Mg, 25 °C, then CuCN, THF, −30 to 0 °C, 96%; (d) KF, H_2O_2, DMF, 25 °C, 70%, 92% ee; (e) $[Ir(COD)(PCy_3)Pyr]PF_6$, CH_2Cl_2, 25 °C, 69%; (f) DIAD, PPh_3, sesamol, THF, 0–50 °C, 76%; (g) KOH, $(HOCH_2)_2$, 100 °C, then HCl, 92%.



Scheme 6. Enantioselective total synthesis of (−)-paroxetine. Conditions: (a) BnOCOCl, CH_2Cl_2, 25 °C, 89%; (b) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, CH_3OH, 25 °C, 76%; (c) $(PhO)_2P(O)Cl$, DMAP (cat.), Pyr, CH_2Cl_2, 25 °C, 86%; (d) stannane **11**, *n*-BuLi, THF, −78 °C, then CuBr·DMS, THF, −78 to −10 °C, 27%.

The alcohol was converted to the phenolic ether in 76% yield through its reaction with sesamol under Mitsunobu's conditions.[26] Finally, deprotection of methyl carbamate was achieved under basic conditions[27] and the free amine was treated with anhydrous HCl to provide (−)-paroxetine as the hydrochloride salt in 92% yield. (−)-Paroxetine hydrochloride obtained in this manner exhibits spectral properties identical in all respects to previously reported material (Scheme 5).[10–15]

Finally, it is noteworthy that a more concise approach to (−)-paroxetine is potentially achieved via direct *anti*-selective copper-mediated S_N2' allylic substitution using a sesamol-based phenoxymethyl anion. Stimulated by this prospect, the tributylstannylmethyl ether **11** was prepared from sesamol and tributyl(iodomethyl)stannane.[28] Allylic substitution using the phenoxymethyl anion derived cuprate with allylic phosphate **8b** gave the desired phenolic ether in 27% yield. This low yield is attributed to the instability of the intermediate α-alkoxy organolithium reagent, and the resulting organocuprate, with respect to α-elimination, as suggested by the recovery of sesamol. Hence, this strategy was not implemented in the synthesis of (−)-paroxetine (Scheme 6).

2. Conclusion

In summary, the phosphine-catalyzed α-arylation of enones was used strategically in concise formal and total enantioselective syntheses of the blockbuster antidepressant (−)-paroxetine (PAXIL). This methodology complements related Pd-catalyzed enolate arylations in several regards. The use of enones as latent enolates enables regiospecific enolate generation and preservation of the enone moiety in the product facilitates subsequent elaboration of the arylated products. Future studies will focus on the invention of related reagents for aryl transfer under the conditions of nucleophilic catalysis.

3. Experimental

3.1. General

All reactions were performed under an atmosphere of argon, unless otherwise indicated. Anhydrous solvents were transferred by an oven-dried syringe and degassed with argon prior to use. Flasks were flame-dried and cooled under argon. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl. Dichloromethane (DCM) was distilled from calcium hydride. Methanol (MeOH) was distilled from magnesium turnings and iodine. Other solvents and chemical reagents obtained from commercial sources were used without further purification, unless otherwise noted. The literature procedures used to prepare dihydropyridinone **1** from *N*-benzyl glycine ethyl ester are described in Ref. 16.

Analytical thin-layer chromatography (TLC) was carried out by using 0.2-mm commercial silica gel plates (DC-Fertigplatten Kieselgel 60 F_{254}, EMD Chemicals). Solvents for chromatography are listed as volume/volume ratios. Infrared spectra were recorded on a Perkin–Elmer 1420 spectrometer. Samples were prepared as films through evaporation from dichloromethane or chloroform solution on sodium chloride plates. High-resolution mass spectra (HRMS) were obtained on a Karatos MS9 by using chemical ionization in the positive ionization mode. Accurate masses are reported for the molecular ion (M+1) or a suitable fragment ion. Melting points were determined on a Thomas Hoover Uni-melt apparatus in open capillaries and were uncorrected. Enantiomeric purity was determined by chiral stationary phase HPLC analysis. Optical rotations were measured by using an Atago Polax-2L polarimeter. Concentrations are reported in units of g/100 mL.

Proton NMR (^{1}H NMR) spectra were recorded with a Varian Gemini (300 MHz) spectrometer, a Varian Gemini (400 MHz) spectrometer, and a Inova (500 MHz) spectrometer. Chemical shifts (δ) are expressed as parts per million

relative to trimethylsilane (δ=0.00 ppm), referenced to the residual protic solvent. Coupling constants are reported in hertz. Carbon-13 NMR (^{13}C NMR) spectra were recorded on a Varian Gemini 300 (75 MHz) spectrometer, a Varian Gemini 400 (100 MHz) spectrometer, and a Inova 500 (125 MHz) spectrometer. Chemical shifts (δ) are expressed as parts per million relative to trimethylsilane (δ=0.0 ppm), referenced to the center of the triplet at δ=77.0 ppm for deuteriochloroform and δ=39.5 ppm for deuteriodimethylsulfoxide (DMSO). ^{13}C NMR analyses were run routinely with broadband decoupling.

3.2. Preparation of compounds 2a–12

3.2.1. Aryl enone 2a. To 100 mL flask charged with tris-(4-fluorophenyl)bismuth dichloride (12.3 g, 21.7 mmol, 110 mol %) and **1** (3.7 g, 19.7 mmol, 100 mol %) was added CH_2Cl_2/^{t}BuOH (9:1) (36 mL, 0.5 M), followed by tributylphosphine (0.5 mL, 1.98 mmol, 10 mol %) and diisopropylethylamine (3.4 mL, 19.7 mmol, 100 mol %). The reaction mixture was allowed to stir at room temperature until complete consumption of starting material was observed by TLC (3 h), at which point the reaction mixture was evaporated onto silica gel. Purification by column chromatography (SiO_2, 9:1 to 3:2 hexane/ethyl acetate) gives the title compound **2a** (4.39 g, 15.6 mmol) in 79% yield as an off white solid. Mp 66.5–68.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (m, 6H), 7.03 (m, 4H), 3.70 (s, 2H), 3.43 (d, J=3.42 Hz, 2H), 3.33 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.1, 162.5 (d, J=247.5 Hz), 145.2, 137.4, 136.3, 130.8, 130.2 (d, J=8.5 Hz), 129.1, 128.5, 127.6, 114.9 (d, J=21.5 Hz), 61.8, 61.7, 52.6. IR (film): 3063, 3029, 2918, 2803, 2750, 1683, 1601, 1509, 1349, 1223, 1160, 823, 699 cm^{-1}. HRMS: Calcd for $C_{18}H_{17}NOF$ [M+1] 282.12942, found 282.12898.

3.2.2. Aryl enone 2b. Methylchloroformate (2 mL, 24.9 mmol, 200 mol %) was added dropwise to a solution containing **2a** (3.5 g, 12.4 mmol, 100 mol %) in CH_2Cl_2 (20 mL) at room temperature. The reaction mixture was stirred at this temperature for 18 h, at which point the reaction mixture was evaporated onto silica gel and purified via column chromatography (SiO_2, 4:1 to 1:1 hexane/ethyl acetate) to give the title compound **2b** (2.64 g, 10.5 mmol) in 86% yield as a white solid. Mp 110–111 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (dd, J=8.6, 5.5 Hz, 2H), 7.05 (t, J=8.6 Hz, 3H), 4.45 (d, J=2.1 Hz, 2H), 4.29 (s, 2H), 3.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.2, 162.1 (d, J=247.5 Hz), 155.3, 143.4, 137.2, 130.1 (d, J=3.1 Hz), 130.2 (d, J=7.7 Hz), 115.1 (d, J=21.5 Hz), 53.0, 51.9, 43.6. IR (film): 3053, 2981, 2863, 1723, 1673, 1606, 1463, 1403, 1351, 1236, 1103, 953, 842, 809 cm^{-1}. HRMS: Calcd for $C_{13}H_{13}NO_3F$ [M+1] 250.0879, found 250.0882.

3.2.3. Aryl enone 2c. Benzylchloroformate (1.21 g, 7.1 mmol, 200 mol %) and **2a** (1.0 g, 3.5 mmol, 100 mol %) were reacted according to the procedure described for **2b**. The crude product was purified via column chromatography (SiO_2, 4:1 to 1:1 hexane/ethyl acetate) to give compound **2c** (1.03 g, 3.16 mmol) in 89% yield as a white solid. Mp 80–81 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (m, 5H), 7.31 (dd, J=8.9, 5.5 Hz, 2H), 7.04 (t, J=8.9 Hz, 2H), 5.19 (s, 2H), 4.47 (d, J=3.8 Hz, 2H), 4.32 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.1, 162.7 (d, J=247.5 Hz), 154.7, 143.3, 137.2, 135.8, 130.3 (d, J=7.7 Hz), 128.5, 128.2 (d, J=6.9 Hz), 115.1 (d, J=21.5 Hz), 67.8, 51.9, 43.6. IR (film): 3033, 2956, 2829, 1688, 1601, 1509, 1430, 1350, 1231, 1160, 1100, 814 cm^{-1}. HRMS: Calcd for $C_{19}H_{17}NO_3F$ [M+1] 326.1192, found 326.1195.

3.2.4. Aryl ketone 3a. To a solution containing **2a** (0.71 g, 2.53 mmol, 100 mol %) in dry THF (15 mL) at −78 °C was added L-Selectride (1 M in THF, 2.6 mL, 2.53 mmol, 100 mol %) dropwise. The mixture was stirred at −78 °C for 1 h, at which point aqueous NH_4Cl (10% solution, 20 mL) was added. The reaction mixture was transferred to a separatory funnel and was extracted with CH_2Cl_2 (3×30 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated to afford an oily residue. Purification by column chromatography (SiO_2, 9:1 to 3:2 hexane/ethyl acetate) gives compound **3a** (0.609 g, 2.15 mmol) in 87% yield as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (m, 5H), 7.11 (m, 2H), 7.03 (m, 2H), 3.64 (s, 2H), 3.53 (t, J=10.0 Hz, 1H), 3.36 (dd, J=14.1, 1.8 Hz, 1H), 3.06 (dm, J=9.2 Hz, 1H), 2.93 (d, J=13.8 Hz, 1H), 2.58 (m, 1H), 2.21 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.2, 162.2 (d, J=246.2 Hz), 136.9, 133.65, 130.2 (d, J=8.4 Hz), 129.0, 128.4, 127.4, 115.3 (d, J=11.5 Hz), 64.4, 62.5, 54.3, 51.9, 32.7. IR (film): 3062, 3029, 2949, 2801, 1722, 1604, 1511, 1454, 1224, 1098, 833, 740, 700 cm^{-1}. HRMS: Calcd for $C_{18}H_{19}NOF$ [M+1] 284.14507, found 284.14541.

3.2.5. Aryl ketone 3b. A mixture of silver fluoride (2 mg, 0.016 mmol, 10 mol %) and (*R*)-BINAP (5.8 mg, 9.0 μmol, 6 mol %) was dissolved in methanol (0.2 mL) and stirred at room temperature for 10 min in the dark, at which point CH_2Cl_2 (2 mL) was added and the solution was stirred for another 10 min. The solution was cooled to −78 °C and **6b** (50 mg, 0.155 mmol, 100 mol %) in CH_2Cl_2 (2 mL) was added dropwise. The mixture was warmed to −30 °C and stirred at this temperature for 72 h, at which point the mixture was evaporated to dryness. Purification via column chromatography (SiO_2, 4:1 to 1:1 hexane/ethyl acetate) gives the title compound **3b** (35 mg, 0.014 mmol) in 90% yield as a colorless oil. Chiral HPLC (Daicel Chiralpak OJ-H column, 85:15 hexanes/*i*-PrOH, λ=254 nm, 0.5 mL min^{-1}, t_{major}=67.0 min, t_{minor}=97.7 min, ee=39%). ^{1}H NMR (500 MHz, DMSO-d_6 at 100 °C): δ 7.19 (dd, J=8.6, 5.5 Hz, 2H), 7.10 (t, J=11.1 Hz, 2H), 4.14 (A part of AB pattern, d, J=17.4 Hz, 1H), 4.05 (B part of AB pattern, d, J=17.4 Hz, 1H), 3.85 (m, 2H), 3.63 (s, 3H), 3.56 (m, 2H), 2.21 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6 at 100 °C): δ 203.9, 160.7 (d, J=243.1 Hz), 154.7, 133.3 (d, J=3.5 Hz), 129.2 (d, J=8.1 Hz), 114.2 (d, J=1.3 Hz), 53.2, 51.9, 41.7, 29.1. IR (film): 2956, 1700, 1602, 1511, 1449, 1404, 1223, 835, 770 cm^{-1}. HRMS: Calcd for $C_{13}H_{15}NO_3F$ [M+1] 252.1036, found 252.1038.

3.2.6. Enol ether 4. To a vigorously stirred suspension of methoxymethyltriphenylphosphonium chloride[20] (500 mg, 1.76 mmol, 100 mol %) in dry THF (18 mL) was added a solution of NaHMDS (2 M in THF, 3.5 mL, 7.06 mmol, 400 mol %) dropwise. The resulting red solution was stirred at this temperature for 2 h, at which point **3a** (500 mg, 1.76 mmol, 100 mol %) in THF (3 mL) was added dropwise

over 10 min. The reaction mixture was allowed to stir at room temperature for 20 h, at which point aqueous NH_4Cl (1 M, 30 mL) was added. The resulting mixture was extracted with diethyl ether (3×15 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and evaporated to give a yellow oil. Purification of the residue via column chromatography (SiO_2, 9:1 to 4:1 hexane/ethyl acetate) gives the title compound **4** (350 mg, 11.2 mmol) in 65% yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (m, 5H), 7.19 (m, 2H), 6.99 (t, J=8.9 Hz, 2H), 5.14 (s, 1H), 3.83 (d, J=12.3 Hz, 1H), 3.70 (A part of AB pattern, J=13.0 Hz, 1H), 3.50 (B part of AB pattern, J=13.0 Hz, 1H), 3.42 (s, 3H), 3.16 (d, J=10.3 Hz, 1H), 2.90 (d, J=11.6 Hz, 1H), 2.60 (d, J=12.3 Hz, 1H), 2.21 (td, J=11.3, 2.7 Hz, 1H), 1.98 (m, 1H), 1.78 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.4 (d, J=244.4 Hz), 143.2, 137.9, 137.7, 129.8 (d, J=7.6 Hz), 129.4, 128.1, 126.9, 117.5, 114.9 (d, J=21.1 Hz), 63.0, 59.4, 52.8, 51.6, 43.9, 32.7. IR (film): 3029, 2933, 2846, 2798, 1677, 1603, 1509, 1222, 1129, 835, 699 cm^{-1}. HRMS: Calcd for $C_{20}H_{22}NOF$ [M+1] 311.16854, found 311.16756.

3.2.7. Aminoalcohol 5. A solution of the enol ether **4** (50 mg, 0.16 mmol, 100 mol %) in THF (3 mL) was treated with 0.1 M aqueous H_2SO_4 (2.4 mL, 0.24 mmol, 150 mol %). The solution was allowed to reflux for a 12 h period, at which point the heating batch was removed and the reaction was allowed to reach room temperature. Saturated aqueous $NaHCO_3$ (10 mL) was added, and the resulting mixture was extracted with diethyl ether (3×5 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to provide the crude aldehyde (34 mg, 0.11 mmol) in 72% yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.45 (d, J=1.8 Hz, 1H), 7.34 (m, 5H), 7.28 (m, 2H), 7.02 (t, J=8.5 Hz, 2H), 3.62 (s, 2H), 3.18 (dm, J=11.4 Hz, 1H), 2.99 (dm, J=11.4 Hz, 1H), 2.90 (dm, J=18.4 Hz, 1H), 2.77 (dd, J=9.0, 7.0 Hz, 1H), 2.12 (t, J=11.1 Hz, 2H), 1.89 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.0, 161.6 (d, J=244.7 Hz), 138.6, 137.8, 129.1, 128.8 (d, J=7.9 Hz), 128.3, 127.2, 115.5 (d, J=21.4 Hz), 63.1, 54.4, 53.5, 53.0, 43.1, 34.1. IR (film): 2938, 2806, 1721, 1603, 1510, 1465, 1224, 1160, 833, 699 cm^{-1}. HRMS: Calcd for $C_{19}H_{21}NOF$ [M+1] 298.1607, found 298.1601.

This crude aldehyde was dissolved in ethanol (2 mL) and treated with $NaBH_4$ (6 mg, 0.16 mmol, 100 mol %), and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was treated with 2 N aqueous sodium hydroxide (10 mL) and extracted with CH_2Cl_2 (3×5 mL), the combined organic extracts were dried over $MgSO_4$, filtered, and evaporated in vacuo to give an oily residue. Purification of the residue via column chromatography (SiO_2, 9:1 to 3:2 hexane/ethyl acetate) gives the title compound **5** (30 mg, 0.10 mmol) in 63% yield over two steps as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (m, 5H), 7.17 (m, 2H), 6.98 (t, J=8.6 Hz, 2H), 3.60 (A part of AB pattern, J=13.2 Hz, 1H), 3.56 (B part of AB pattern, J=13.2 Hz, 1H), 3.37 (dd, J=11.3, 3.0 Hz, 1H), 3.21 (m, 2H), 2.98 (d, J=11.0 Hz, 1H), 2.33 (m, 1H), 1.98 (m, 3H), 1.79 (m, 3H). IR (film): 3427, 2934, 2848, 2799, 1604, 1510, 1222, 1130, 836, 739, 700 cm^{-1}. HRMS: Calcd for $C_{19}H_{23}NOF$ [M+1] 300.17637, found 300.17487.

3.2.8. Enol silane 6a. To a solution containing **2a** (0.1 g, 0.35 mmol, 100 mol %) in dry THF (2 mL) at −78 °C was added L-Selectride (1 M in THF, 0.36 mL, 0.35 mmol, 100 mol %) dropwise. The mixture was stirred at this temperature for 1 h, at which point TBSCl (59 mg, 0.39 mmol, 110 mol %) in THF (1 mL) was added dropwise. The reaction mixture was allowed to stir at this temperature for an addition 1 h and then left to warm to room temperature. Removal of the volatiles in vacuo affords an oily residue, which upon purification by column chromatography (SiO_2, 9:1 hexane/ethyl acetate) gives **6a** (104 mg, 2.62 mmol) in 74% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (m, 7H), 6.95 (t, J=8.7 Hz, 2H), 3.63 (s, 2H), 2.99 (s, 2H), 2.63 (t, J=5.6 Hz, 2H), 2.43 (m, 2H), 0.74 (s, 9H), −0.19 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.1 (d, J=243.5 Hz), 140.8, 130.1 (d, J=7.6 Hz), 129.3, 128.3, 114.6 (d, J=21.1 Hz), 62.2, 56.3, 50.1, 29.2, 25.5, 17.9, −4.2. IR (film): 2928, 2856, 1669, 1601, 1509, 1471, 1222, 837, 780 cm^{-1}. HRMS: Calcd for $C_{24}H_{33}NOFSi$ [M+1] 398.2315, found 398.2313.

3.2.9. Enol silane 6b. Aryl enone **2b** (200 mg, 0.80 mmol, 100 mol %), L-Selectride (1 M in THF, 0.8 mL, 0.80 mmol, 100 mol %), and chlorotrimethylsilane (0.12 mL, 0.880 mmol, 110 mol %) were reacted according to the procedure described for **8a**. The crude product was purified via Kugelrohr distillation to give **6b** (230 mg, 0.71 mmol) in 86% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (dd, J=8.2 Hz, 2H), 6.98 (t, J=8.7 Hz, 2H), 3.91 (s, 2H), 3.73 (s, 3H), 3.60 (s, 2H), 2.43 (s, 2H), −0.04 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.0, 161.2 (d, J=245.0 Hz), 155.8, 140.8, 135.2, 129.8 (d, J=7.6 Hz), 114.5 (d, J=21.4 Hz), 52.6, 46.8, 41.0, 28.5, 0.3. IR (film): 2957, 1707, 1601, 1510, 1448, 1410, 1253, 1226, 1106, 844, 767 cm^{-1}. HRMS: Calcd for $C_{16}H_{23}NO_3FSi$ [M+1] 324.1431, found 324.1437.

3.2.10. Allylic alcohol 7a. To a dry 50 mL flask, a solution of (*S*)-2-methyl-CBS-oxazaborolidine catalyst (1 M in toluene, 0.4 mL, 0.04 mmol, 10 mol %) and a solution of borane dimethyl sulfide complex (2 M in THF, 2 mL, 4.0 mmol, 100 mol %) were added successively at room temperature. The resulting solution was cooled to −20 °C and **2b** (1.0 g, 4.0 mmol, 100 mol %) in dichloromethane (18 mL) was added dropwise over 1 h, the reaction mixture was stirred at this temperature for 1 h. Methanol (15 mL) was added dropwise to the reaction mixture and the reaction mixture was allowed to warm to room temperature. The solution was evaporated to dryness. Purification of the residue via column chromatography (SiO_2, 9:1 to 1:1 hexane/ethyl acetate) gives **7a** (0.96 g, 3.85 mmol) in 95% yield as a white solid. Mp 104–105 °C. $[\alpha]_D^{25}$ +70 (*c* 1.6, CH_2Cl_2). Chiral HPLC (Daicel Chiralpak OJ-H column, 70:30 hexanes/*i*-PrOH, λ=254 nm, 0.5 mL min^{-1}, t_{major}=35.2 min, t_{minor}=39.2 min, ee=96%). ^{1}H NMR (500 MHz, DMSO-d_6 at 100 °C): δ 7.52 (dd, J=8.9, 5.5 Hz, 2H), 7.10 (t, J=12.0 Hz, 2H), 6.08 (t, J=3.5 Hz, 1H), 4.79 (d, J=6.6 Hz, 1H), 4.46 (m, 1H), 4.23 (dd, J=19.0, 2.7 Hz, 1H), 3.86 (dd, J=13.3, 3.8 Hz, 1H), 3.84 (dt, J=17.2, 2.0 Hz, 1H), 3.65 (s, 3H), 3.34 (dd, J=13.3, 3.3 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6 at 100 °C): δ 161.0 (d, J=244.1 Hz), 155.1, 136.4, 135.2 (d, J=3.05 Hz), 127.2 (d, J=8.1 Hz), 122.6, 114.2 (d, J=20.8 Hz), 63.0, 51.5, 47.9, 42.9. IR (film): 3412, 2957,

2921, 2851, 1693, 1601, 1511, 1470, 1448, 1411, 1231, 1130, 1062, 818, 767 cm^{-1}. HRMS: Calcd for $C_{18}H_{17}NOF$ [M+1] 250.0879, found 250.0880.

3.2.11. Allylic alcohol 7b. To a solution containing $CeCl_3 \cdot 7H_2O$ (1.09 g, 2.71 mmol, 100 mol %) and **2c** (0.88 g, 2.71 mmol, 100 mol %) in methanol (20 mL) was added $NaBH_4$ (0.10 g, 2.7 mmol, 100 mol %) in small portions over 2 min at room temperature. The mixture was allowed to stir for 5 min, at which point water (30 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3×20 mL). The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford an oily residue. Purification via column chromatography (SiO_2, 3:1 hexane/ethyl acetate) gives **7b** (0.68 g, 2.07 mmol) in 76% yield as a white solid. Mp 106–108 °C. ^1H NMR (500 MHz, DMSO-d_6 at 100 °C): δ 7.53 (dd, J=8.8, 5.5 Hz, 2H), 7.36 (m, 5H), 7.11 (t, J=8.9 Hz, 2H), 6.09 (t, J=3.5 Hz, 1H), 5.15 (s, 2H), 4.86 (t, J=5.4 Hz, 1H), 4.49 (m, 1H), 4.29 (dd, J=19.1, 3.7 Hz, 1H), 3.92 (dd, J=13.2, 3.7 Hz, 1H), 3.89 (d, J=16.5 Hz, 1H), 3.39 (dd, J=13.2, 3.1 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6 at 100 °C): δ 161.0 (d, J=244.1 Hz), 154.5, 136.6, 136.4, 135.2 (d, J=3.05 Hz), 127.8, 127.2 (d, J=7.6 Hz), 127.1, 126.9, 122.6, 114.2 (d, J=21.4 Hz), 71.6, 63.0, 47.9, 43.0. IR (film): 3414, 3033, 2915, 1691, 1510, 1432, 1360, 1229, 1125, 1070, 819, 698 cm^{-1}. HRMS: Calcd for $C_{19}H_{19}NO_3F$ [M+1] 328.1349, found 328.1349.

3.2.12. Allylic alcohol derived from 2a. To a solution of **2a** (0.1 g, 0.355 mmol, 100 mol %) in CH_2Cl_2 (3.5 mL) and isopropyl alcohol (30 μL, 0.355 mmol, 100 mol %) at −20 °C was added dropwise a solution of $BH_3 \cdot SMe_2$ (2 M in THF, 0.45 mL, 0.889 mmol, 250 mol %). The mixture was allowed to stir at −20 °C for 1 h, at which point a solution containing both (*S*)-2-methyl-CBS-oxazaborolidine (2 M in toluene, 36 μL, 0.035 mmol, 10 mol %) and $BH_3 \cdot SMe_2$ (2 M in THF 30 μL) was added in one portion. The reaction mixture was allowed to stir at −20 °C for 30 min. The temperature was increased to −15 °C over 45 min, at which point MeOH (10 mL) was added carefully and the reaction mixture allowed to stir for an additional 15 min. The reaction mixture was placed in heating bath at 50 °C and CH_2Cl_2 and $BH_3 \cdot SMe_2$ were removed via distillation. To the remaining solution was added MeOH (5 mL) and the resulting mixture was allowed to stir at 65 °C for 1 h (to cleave the N–B complex). The heating bath was removed and reaction mixture was allowed to reach ambient temperature. The solvent was removed in vacuo and the resulting residue was purified via column chromatography (SiO_2, 3:2 to 1:1 hexane/ethyl acetate) to provide the allylic alcohol (36 mg, 0.13 mmol) in 35% yield as a white solid. Mp 76–77 °C. Chiral HPLC (Daicel Chiralpak OJ-H column, 98:2 hexanes/*i*-PrOH, λ=254 nm, 1 mL min^{-1}, t_{major}=43.9 min, t_{minor}=31.7 min, ee=70%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.48 (dd, J=8.7, 5.5 Hz, 2H), 7.33 (m, 5H), 6.99 (t, J=8.9 Hz, 2H), 6.09 (t, J=3.5 Hz, 1H), 6.02 (dd, J=4.8, 3.4 Hz, 1H), 4.37 (s, 1H), 3.65 (s, 2H), 3.35 (dd, J=17.4, 4.4 Hz, 1H), 3.04 (dd, J=10.6, 2.0 Hz, 1H), 2.84 (d, J=17.4 Hz, 1H), 2.75 (br s, 1H), 2.49 (dd, J=11.6, 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.1 (d, J=246.0 Hz), 137.6, 137.0, 135.2 (d, J=3.1 Hz), 129.0, 128.3, 127.3, 127.1 (d, J=7.7 Hz), 124.5, 115.2 (d, J=21.5 Hz), 66.1, 62.2, 57.7, 53.0. IR (film): 3408, 3061, 3029, 2917, 2804, 1602, 1509, 1454, 1230, 1162, 1054, 822, 699. HRMS: Calcd for $C_{18}H_{19}NOF$ [M+1] 284.14506, found 284.14320.

3.2.13. Diphenyl phosphate 8a. Chlorodiphenylphosphate (0.9 mL, 4.2 mmol, 150 mol %) was added dropwise to a solution containing **7a** (0.71 g, 2.8 mmol, 100 mol %), pyridine (0.45 mL, 5.6 mmol, 200 mol %), and DMAP (0.51 g, 4.2 mmol, 150 mol %) at room temperature. After stirring for 2 h at this temperature, the reaction mixture was transferred to a separatory funnel, washed with aqueous $CuSO_4$ (2 M, 3×20 mL), dried ($MgSO_4$), filtered, and evaporated to afford an oily residue. Purification via column chromatography (SiO_2, 9:1 to 4:1 dichloromethane/ethyl acetate) gives **8a** (1.21 g, 2.42 mmol) in 89% yield as a white solid. Mp 99–100 °C. $[\alpha]_D^{23}$ +36 (*c* 3.33, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ 7.34 (m, 4H), 7.18 (m, 6H), 6.94 (t, J=8.4 Hz, 2H), 6.88 (d, J=7.94 Hz, 2H), 6.22 (s, 1H), 5.62 (s, 1H), 4.55 (dd, J=14.6, 2.8 Hz, 2H), 3.91 (d, J=18.2 Hz, 1H), 3.76 (s, 1H), 3.61 (s, 2H), 3.50 (d, J=14.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.5 (d, J=247.3 Hz), 155.9, 150.4, 150.0, 133.4, 129.0 (d, J=16.0 Hz), 127.8, 127.7, 125.2, 125.1, 119.8, 119.7, 115.4 (d, J=21.4 Hz), 71.7, 52.7, 46.4, 43.5. IR (film): 3063, 3033, 2962, 2840, 1706, 1590, 1512, 1488, 1446, 1410, 1283, 1232, 1190, 1130, 1009, 956, 825, 767 cm^{-1}. HRMS: Calcd for $C_{25}H_{24}NO_7FP$ [M+1] 500.1274, found 500.1278.

3.2.14. Diphenyl phosphate 8b. Chlorodiphenylphosphate (0.5 mL, 2.31 mmol, 150 mol %), **7b** (500 mg, 1.54 mmol, 100 mol %), pyridine (0.25 mL, 3.08 mmol, 200 mol %), and DMAP (0.28 g, 2.3 mmol, 150 mol %) were reacted according to the procedure described for **8a**. The crude product was purified via column chromatography (SiO_2, 9:1 to 4:1 dichloromethane/ethyl acetate) to give **8b** (0.74 g, 1.323 mmol) in 86% yield as a white solid. Mp 59–61 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.24 (m, 17H), 6.91 (t, J=8.4 Hz, 2H), 6.88 (d, J=7.94 Hz, 2H), 6.20 (s, 1H), 5.62 (s, 1H), 5.2 (s, 1H), 4.60 (dd, J=14.4, 3.0 Hz, 2H), 3.92 (d, J=19.5 Hz, 1H), 3.76 (s, 1H), 3.52 (dd, J=14.1, 2.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.5 (d, J=247.3 Hz), 155.3, 150.4, 150.0, 136.3, 133.4, 129.0 (d, J=16.0 Hz), 128.4, 127.8, 127.7, 125.2, 125.0, 119.8, 115.4 (d, J=21.4 Hz), 71.7, 67.4, 46.4, 43.6. IR (film): 3065, 2951, 1706, 1590, 1511, 1489, 1429, 1283, 1230, 1190, 1010, 957, 825, 766, 689 cm^{-1}. HRMS: Calcd for $C_{31}H_{28}NO_6FP$ [M+1] 560.163, found 560.1638.

3.2.15. Silane 9. To a slurry of CuCN (0.43 g, 4.81 mmol, 200 mol %) in THF (10 mL) was added a solution of (*i*-PrO)Me_2SiCH_2MgCl (1 M in THF, 4.80 mL, 4.81 mmol, 200 mol %) at −18 °C (ice/NaCl). After stirring at this temperature for 40 min, the reaction mixture was cooled to −50 °C and **8a** (1.20 g, 2.40 mmol, 100 mol %) in THF (10 mL) was added dropwise. The reaction mixture was allowed to warm to 0 °C over 40 min, at which point aqueous NH_4Cl (10% solutions, 40 mL) was added. The resulting mixture was extracted with CH_2Cl_2 (3×10 mL) and the combined organic extracts were dried ($MgSO_4$), filtered, and evaporated to afford an oily residue. Purification of the residue via column chromatography (SiO_2, 3:2 hexane/ethyl acetate) gives **9** (0.84 g, 2.306 mmol) in 96% yield as a colorless oil. $[\alpha]_D^{23}$ +72 (*c* 3.6, CH_2Cl_2). ^1H NMR (300 MHz,

$CDCl_3$): δ 7.29 (m, 2H), 6.99 (t, J=8.7 Hz, 2H), 5.76 (s, 1H), 4.28 (m, 1H), 3.95 (m, 2H), 3.87 (d, J=18.8 Hz, 1H), 3.71 (s, 3H), 3.28 (dd, J=13.2, 3.3 Hz, 1H), 2.87 (s, 1H), 1.12 (2d, J=6.2 Hz, 6H), 0.68 (2d, J=10.8 Hz, 1H), 0.55 (2s, 1H), 0.09 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.1 (d, J=246.0 Hz), 156.6, 141.6, 135.9, 127.6 (d, J=7.3 Hz), 119.5, 115.1 (d, J=21.1 Hz), 64.9, 52.4, 46.3, 43.8, 32.3, 25.8, 19.5, −0.78. IR (film): 3081, 2956, 2889, 1706, 1601, 1510, 1448, 1412, 1375, 1335, 1250, 1231, 1191, 1118, 1025, 958, 880, 836, 813 cm^{-1}. HRMS: Calcd for $C_{19}H_{27}NO_3FSi$ [M−1] 364.1744, found 364.1745.

3.2.16. Homo-allyl alcohol 10. To a solution of **9** (0.82 g, 2.24 mmol, 100 mol %) in DMF (12 mL) at room temperature were added potassium fluoride (0.52 g, 8.98 mmol, 400 mol %) and 30% aqueous hydrogen peroxide (3 mL, 26.9 mmol, 1200 mol %). The reaction mixture was allowed to stir at room temperature for 18 h, at which point H_2O (60 mL) was added. The resulting mixture was extracted with diethyl ether (3×20 mL), and the combined organic extracts were washed with saturated aqueous $Na_2S_2O_3$ (20 mL) dried ($MgSO_4$), and evaporated to afford a colorless oil. Purification via column chromatography (SiO_2, 4:1 to 1:1 hexane/ethyl acetate) gives **10** (0.41 g, 1.54 mmol) in 70% yield as a colorless oil. $[\alpha]_D^{23}$ +84 (c 3.06, CH_2Cl_2). Chiral HPLC (Daicel Chiralpak OJ-H column, 90:10 hexanes/i-PrOH, λ=254 nm, 0.4 mL min^{-1}, t_{major}=31.0 min, t_{minor}=45.9 min, ee=92%). ^{1}H NMR (500 MHz, DMSO-d_6 at 100 °C): δ 7.43 (dd, J=8.8, 2.1 Hz, 2H), 7.12 (t, J=8.9 Hz, 2H), 6.00 (t, J=2.4 Hz, 1H), 4.27 (s, 1H), 4.18 (m, 2H), 3.82 (dt, J=19.1, 2.8 Hz, 1H), 3.65 (s, 3H), 3.32 (dt, J=10.6, 3.8 Hz, 1H), 3.18 (m, 2H), 2.83 (dd, J=4.2, 2.1 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6 at 100 °C): δ 161.0 (d, J=2.44.1 Hz), 155.3, 135.7 (d, J=3.0 Hz), 135.0, 126.9 (d, J=8.1 Hz), 121.9, 114.4 (d, J=21.4 Hz), 60.3, 51.5, 43.1, 41.5. IR (film): 3426, 3056, 2954, 2876, 1686, 1601, 1510, 1448, 1412, 1375, 1228, 1131, 1091, 1039, 953, 836, 814, 768, 735 cm^{-1}. HRMS: Calcd for $C_{14}H_{17}NO_3F$ [M+1] 266.1192, found 266.1199.

3.2.17. Conversion of 10 to paroxetine hydrochloride. A solution containing **10** (300 mg, 1.13 mmol, 100 mol %) in CH_2Cl_2 (11 mL) was cooled to −78 °C, evacuated and filled with Ar(g). This process was repeated twice. The solution was allowed to warm to room temperature and Crabtree's catalyst (45 mg, 0.056 mmol, 5 mol %) was added as a solid in one portion. The mixture was purged with H_2(g) for 5 min and allowed to stir under 1 atm of hydrogen for 20 h. The reaction mixture was evaporated onto silica gel. Purification via column chromatography (SiO_2, 4:1 to 3:2 hexane/ethyl acetate) gives the saturated alcohol (210 mg, 0.78 mmol) in 69% yield. $[\alpha]_D^{23}$ −40 (c 2.0, CH_2Cl_2). ^{1}H NMR (500 MHz, DMSO-d_6 at 100 °C): δ 7.23 (dd, J=7.9, 6.1 Hz, 2H), 7.06 (t, J=8.9 Hz, 2H), 4.30 (dd, J=13.3, 2.5 Hz, 1H), 4.09 (d, J=5.6 Hz, 1H), 4.07 (d, J=15.7 Hz, 1H), 3.64 (s, 3H), 3.18 (m, 1H), 3.02 (m, 1H), 2.83 (t, J=13.0 Hz, 1H), 2.66 (t, J=11.4 Hz, 1H), 2.53 (td, J=11.6, 3.2 Hz, 1H), 1.72 (m, 2H), 1.57 (qd, J=12.6, 4.4 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6 at 100 °C): δ 160.3 (d, J=244.1 Hz), 154.7, 139.8 (d, J=3.0 Hz), 128.5 (d, J=7.6 Hz), 114.3 (d, J=21.4 Hz), 60.8, 51.5, 46.7, 43.6, 43.0, 42.8, 33.2. IR (film): 3435, 3009, 2918, 2853, 1697, 1603, 1510, 1476, 1451, 1413, 1279, 1223, 1159, 1129, 1064, 1014, 832, 767 cm^{-1}. HRMS: Calcd for $C_{14}H_{19}NO_3F$ [M+1] 268.1349, found 268.1350.

The saturated alcohol (100 mg, 0.37 mmol, 100 mol %) was dissolved in THF (3 mL) and PPh_3 (120 mg, 0.45 mmol, 120 mol %) was added. The solution was cooled to 0 °C and DIAD was added dropwise. The solution was allowed to stir at 0 °C for 10 min, at which point sesamol (100 mg, 0.75 mmol, 200 mol %) in THF (1 mL) was added dropwise and the reaction mixture was allowed to stir for another 10 min at 0 °C. The reaction mixture was heated to 50 °C and was allowed to stir at this temperature for 2 h, at which point the reaction mixture was allowed to reach ambient temperature. The reaction mixture was evaporated to dryness, and the residue was dissolved in CH_2Cl_2 (5 mL). In order to remove excess sesamol, the organic layer was washed with aqueous NaOH (2 M, 2×10 mL) and the aqueous extracts were back-extracted with CH_2Cl_2 (10 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated onto silica gel. Purification via column chromatography (SiO_2, 4:1 hexane/ethyl acetate) gives the phenolic ether (110 mg, 2.84 mmol) in 76% yield as a pale yellow oil. $[\alpha]_D^{23}$ −13 (c 1.5, CH_2Cl_2). ^{1}H NMR (500 MHz, DMSO-d_6 at 100 °C): δ 7.27 (dd, J=8.6, 5.6 Hz, 2H), 7.06 (t, J=8.9 Hz, 2H), 6.9 (d, J=8.5 Hz, 1H), 6.40 (d, J=2.4 Hz, 1H), 6.18 (dd, J=8.3, 2.4 Hz, 1H), 5.89 (s, 2H), 4.31 (dd, J=13.4, 3.0 Hz, 1H), 4.09 (dt, J=13.3, 2.0 Hz, 1H), 3.64 (s, 3H), 3.41 (m, 2H), 2.89 (td, J=12.8, 2.8 Hz, 1H), 2.82 (t, J=11.6 Hz, 1H), 2.70 (td, J=5.8 Hz, 1H), 2.05 (m, 1H), 1.73 (dd, J=13.2, 3.1 Hz, 1H), 1.67 (qd, J=12.1, 4.4 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6 at 100 °C): 160.5 (d, J=242.6 Hz), 154.7, 153.6, 147.4, 141.0, 139.7 (d, J=3.0 Hz), 128.6 (d, J=8.1 Hz), 114.5 (d, J=21.4 Hz), 107.3, 105.9, 100.4, 97.6, 69.0, 51.6, 46.4, 43.5, 42.9, 40.6, 32.9. IR (film): 3008, 2916, 1701, 1510, 1488, 1450, 1412, 1276, 1223, 1185, 1132, 1037, 937, 832, 765 cm^{-1}. HRMS: Calcd for $C_{21}H_{23}NO_5F$ [M+1] 388.1560, found 388.1561.

To a reaction vessel charged with the phenolic ether (50 mg, 0.13 mmol, 100 mol %) and KOH (94 mg, 1.68 mmol %, 1300 mol %) were added ethylene glycol (1.5 mL), and water (0.6 mL). The mixture was heated to 100 °C for 20 h and then cooled to room temperature, diluted with water (10 mL), and extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were washed with H_2O (2×5 mL), dried ($MgSO_4$), filtered, and evaporated to provide an oily residue. The residue was dissolved in ether (5 mL) and the resulting solution was treated with 4 M HCl in dioxane (5 mL) to give a white solid. The white solid was filtered, washed with ether, and dried to afford (45 mg, 0.12 mmol) paroxetine hydrochloride in 92% yield. Mp 132–134 °C. Lit[10i] 136–138 °C. $[\alpha]_D^{23}$ −85 (c 1.0, CH_3OH). Lit[10i] −86.5. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (dd, J=8.2, 5.5 Hz, 2H), 7.00 (t, J=8.5 Hz, 2H), 6.61 (d, J=8.2 Hz, 1H), 6.32 (d, J=2.73 Hz, 1H), 6.10 (dd, J=8.5, 2.4 Hz, 1H), 5.88 (s, 2H), 3.73 (dd, J=21.5, 14.4 Hz, 2H), 3.60 (d, J=8.2 Hz, 1H), 3.48 (dd, J=9.9, 4.4 Hz, 1H), 3.17 (t, J=10.9 Hz, 1H), 2.04 (m, 1H), 2.90 (t, J=11.3 Hz, 1H), 2.64 (m, 1H), 2.38 (q, J=13.3 Hz, 2H), 2.03 (d, J=6.3 Hz, 1H). IR (film): 3401, 2925, 1605, 1510, 1224, 1185, 1037, 831 cm^{-1}.

3.2.18. Phenolic ether 12. To a stirred solution of **11** (240 mg, 0.54 mmol, 300 mol %) in THF (3 mL) at −78 °C

was added *n*-BuLi (2.5 M in hexanes, 0.18 mL, 0.45 mmol, 250 mol %) dropwise. The reaction mixture was allowed to stir at −78 °C for 1 h, at which point $CuBr \cdot SMe_2$ (110 mg, 0.54 mmol, 300 mol %) in Me_2S (0.5 mL) was added dropwise. The reaction mixture was allowed to stir an additional 30 min at −78 °C, at which point **8b** (100 mg, 0.18 mmol, 100 mol %) in Me_2S (0.5 mL) was added. The reaction mixture was allowed to continue stirring at −78 °C for an additional 1 h period, at which point the reaction mixture was allowed to warm to −10 °C and aqueous NH_4Cl (10% solution, 10 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3×5 mL) and the combined organic extracts were dried ($MgSO_4$), filtered, and evaporated to afford an oily residue. Purification of the residue via column chromatography (SiO_2, 3:2 hexane/ethyl acetate) gives the title compound **12** (22 mg, 0.05 mmol) in 27% yield. ^{1}H NMR (500 MHz, DMSO-d_6 at 100 °C): δ 7.45 (dd, J=8.8, 5.5 Hz, 2H), 7.29 (s, 5H), 7.13 (t, J=8.8 Hz, 2H), 6.68 (d, J=8.4 Hz, 1H), 6.41 (d, J=2.4 Hz, 1H), 6.22 (dd, J=8.5, 2.3 Hz, 1H), 6.10 (t, J=3.4 Hz, 1H), 5.89 (s, 2H), 5.08 (AB pattern, J=12.6 Hz, 2H), 4.33 (d, J=13.3 Hz, 2H), 3.90 (d, J=19.2 Hz, 1H), 3.72 (d, J=5.1 Hz, 2H), 3.29 (d, J=3.4 Hz, 2H), 3.20 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6 at 100 °C): 161.2 (d, J=244.6 Hz), 154.5, 153.5, 147.4, 141.0, 136.5, 135.4, 134.1, 127.7, 127.1, 127.1 (d, J=8.1 Hz), 126.8, 123.2, 114.6 (d, J=21.4 Hz), 107.3, 106.0, 100.4, 97.7, 68.1, 65.8, 43.1, 41.8, 36.9. IR (NaCl): 3033, 2962, 2877, 1701, 1602, 1508, 1465, 1431, 1260, 1224, 1184, 1129, 1037, 814 cm^{-1}. HRMS: Calcd for $C_{27}H_{25}NO_5F$ [M+1] 462.1717, found 462.1711.

Supplementary data

Scanned images of ^{1}H NMR and ^{13}C NMR spectra. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.05.092.

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