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Concise Enantioselective Synthesis of Duloxetine via Direct Catalytic Asymmetric Aldol Reaction of Thioamide

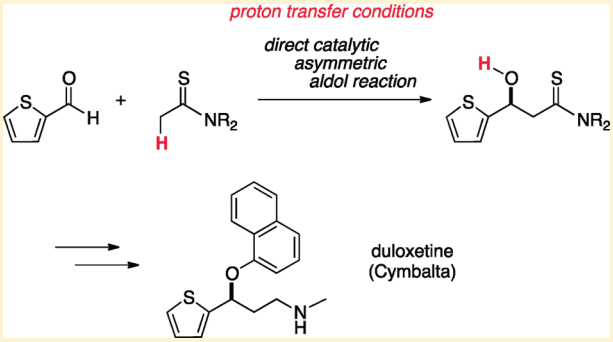
Yuta Suzuki,[†,‡] Mitsutaka Iwata,[†] Ryo Yazaki,[‡] Naoya Kumagai,*[,†] and Masakatsu Shibasaki*[,†]

[†]Institute of Microbial Chemistry, Tokyo, 3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141-0021, Japan

[‡]Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Supporting Information

ABSTRACT: Direct catalytic asymmetric aldol reaction of thioamide offers a new entry to the concise enantioselective synthesis of duloxetine. The direct aldol protocol was scalable (>20 g) to afford the aldol product in 92% ee after $LiAlH_4$ reduction, and 84% of the chiral ligand was recovered after recrystallization. The following four steps of transformation delivered duloxetine.



Duloxetine [(*S*)-*N*-methyl-3-(1-naphthalenyloxy)-2-thiophenepropanamine (**1**)], marketed as Cymbalta, functions as a dual serotonin and norepinephrine reuptake inhibitor in presynaptic cells (Figure 1).[1] It was approved by the U.S.

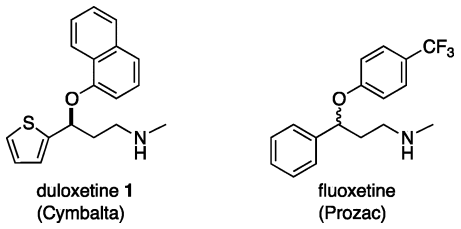


Figure 1. Structure of duloxetine (**1**) and fluoxetine.

Food and Drug Administration in August 2004 and is prescribed for the treatment of major depressive disorders as well as stress urinary incontinence. In contrast to the preceding drug fluoxetine (Prozac), which is an approved racemate, **1** is marketed in enantiomerically pure form,[2] and the development of its scalable and enantioselective synthesis is of broad interest. Commonly explored synthetic approaches are optical resolution,[3] dynamic kinetic resolution,[4] catalytic asymmetric reduction,[5] and catalytic asymmetric hydrogenation.[6] Although the catalytic asymmetric C−C bond-forming reaction is rarely implemented,[7] it allows for construction of the requisite carbon framework concomitant with the introduction of chirality. Herein we envisioned that our direct aldol technology would provide a viable approach for concise enantioselective synthesis of duloxetine (**1**) based on catalytic asymmetric C−C bond formation.

The direct catalytic asymmetric aldol reaction is the most advanced form of the conventional aldol reaction, in which bench stable aldol donor and acceptor are assembled by the actions of an asymmetric catalyst.[8,9] The need of preactivation/preformation of active enolate is obviated, and the overall process proceeds through proton transfer, generating the aldol product in an enantiomerically enriched form without the formation of any waste. Our studies in this field based on cooperative catalysis[10] revealed that thioamides **2** are particularly suitable aldol donors amenable to chemoselective activation to catalytically generate active enolate.[11−13] Given the feasibility of diverse functional group transformation of a thioamide functionality,[12] the aldol product **4** derived from thiophene-2-carboxaldehyde (**3**) was anticipated to give γ-amino alcohol **5**, allowing for an rapid and efficient access to the carbon framework of **1** with the requisite *S* secondary alcohol (Scheme 1).

We previously developed a soft Lewis acid/hard Brønsted base cooperative catalyst comprising $[Cu(CH_3CN)_4]PF_6$, (*S*,*S*)-Ph-BPE, and $Li(OC_6H_4$-*p*-OMe), in which chemoselective activation of thioamide by a soft−soft interaction of Cu^+ and sulfur atom allowed for the exclusive generation of thioamide enolate in the presence of aldehyde.[11b−e] First, we set out to identify the best thioamide **2** (aldol donor) for the direct catalytic asymmetric aldol reaction with aldehyde **3** (aldol acceptor). Use of a thioamide bearing an *N*-methyl substituent streamlines the synthesis of **1**, and reactions with thioamides **2a**−**c** and **3** were initially examined under the standard direct aldol conditions (Table 1).[11c] The use of *N*-methylthioacetamide (**2a**) allowed for direct access to the *N*-Me secondary amine moiety of **1**, but the aldol reaction with **2a** failed, presumably because the acidic thioamide N−H prevented the

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Scheme 1. Efficient Access to Duloxetine (1) via Direct Catalytic Asymmetric Aldol Reaction

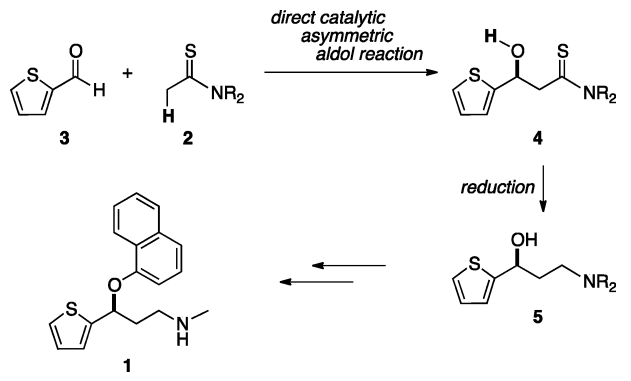
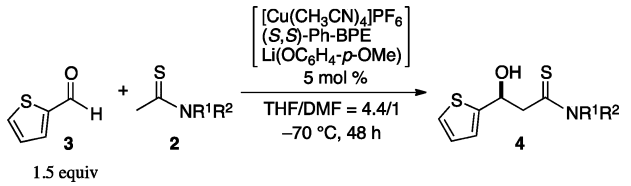
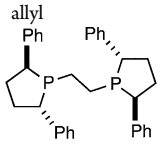


Table 1. Direct Catalytic Asymmetric Aldol Reaction of Thioamides 2a–d[a]



	2					
entry	R^1	R^2		product	yield[b] (%)	ee (%)
1	Me	H	**2a**	**4a**	–	–
2	Me	Bn	**2b**	**4b**	17	72
3	Me	C_6H_4-*p*-OMe	**2c**	**4c**	43	73
4	allyl	allyl	**2d**	**4d**	71	93



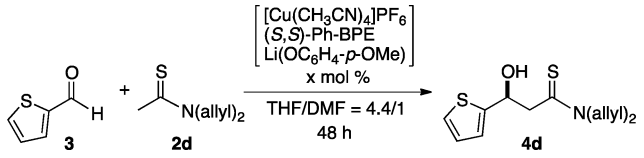
(*S*,*S*)-Ph-BPE

[a] **3**: 0.3 mmol. **2**: 0.2 mmol. [b] Determined by ^{1}H NMR analysis with toluene as an internal standard.

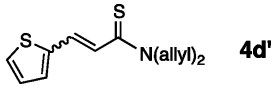
formation of the thioamide enolate (Table 1, entry 1). The next candidates were substituted thioamides **2b** and **2c**, whose *N*-substituent can undergo facile deprotection to provide the –NHMe terminus, but these showed insufficient reactivity (Table 1, entries 2, 3). Although product **4d** required a deprotection/methylation sequence for the synthesis of **1**, the preferable reactivity and enantioselectivity led us to focus on the further optimization using **2d** (Table 2). The use of thioamide **2d** in excess to aldehyde **3** resulted in a lower yield (Table 2, entry 2). The aldol reaction is highly sensitive to the reaction temperature, and a higher reaction temperature significantly increased the formation of the unfavorable dehydrated product **4d′** (Table 2, entry 3). The more advanced form of the cooperative catalyst mesitylcopper/HOC_6H_4-*p*-OMe,[11e] which does not require preparation of $Li(OC_6H_4$-*p*-OMe), did not improve the reaction efficiency (Table 2, entry 4). The amount of thioamide **2d** can be reduced to 1.2 equiv to close to the ideal 1:1 stoichiometry of thioamide **2d** and aldehyde **3** (Table 2, entry 5). Slightly increasing the catalyst loading improved the yield to a level suitable for the large-scale production of **4d** (Table 2, entry 6).

The remaining issue to be resolved before the large-scale demonstration of the direct aldol reaction was the recovery of (*S*,*S*)-Ph-BPE. To develop a cost-effective synthetic scheme for

Table 2. Further Optimization Using 2d[a]



entry	stoichiometry **3**/**2d**	X	temp (°C)	yield[b] (%)	ee (%)
1	1.5/1	5	–70	71 (trace)	93
2[c]	1/1.5	5	–70	63 (trace)	91
3	1.5/1	5	–60	50 (20)	92
4[d]	1.5/1	5	–70	68 (trace)	92
5	1.2/1	5	–70	68 (trace)	92
6	1.2/1	7.5	–70	74 (trace)	92



4d′

[a] **3**: 0.3 mmol. **2d**: 0.2 mmol. [b] Determined by ^{1}H NMR analysis with toluene as an internal standard. Yield of dehydrated product **4d′** is shown in parentheses. [c] **3**: 0.2 mmol. **2d**: 0.3 mmol. [d] Mesitylcopper/HOC_6H_4-*p*-OMe was used instead of $[Cu(CH_3CN)_4]PF_6$/$Li(OC_6H_4$-*p*-OMe).

duloxetine (**1**), it is imperative to recycle the expensive (*S*,*S*)-Ph-BPE. Trials for the recovery of (*S*,*S*)-Ph-BPE after the aldol reaction failed, likely because of the tight complexation of (*S*,*S*)-Ph-BPE and Cu^+. Attempts to liberate free (*S*,*S*)-Ph-BPE by adding chelating agent, acids, and bases were unsuccessful.[14] We then turned our attention to proceeding without purification at this stage, on the basis of the following hypotheses: (1) subsequent $LiAlH_4$ reduction of the crude sample of the aldol reaction would lead to easier isolation of the reduced aldol product, and (2) Cu^+ would be reduced to Cu(0), and free (*S*,*S*)-Ph-BPE would be liberated.[15] Upon confirmation of the validity of this two-step protocol with 89% recovery of (*S*,*S*)-Ph-BPE in small scale trials, we performed a 23.9 g scale reaction of the direct aldol/$LiAlH_4$ reduction. The aldol reaction was quenched by AcOH/THF after 48 h of stirring at –70 °C, and the concentrated ether extracts were taken up with dry THF for the subsequent $LiAlH_4$ reduction. A small aliquot of the extract was purified and analyzed by chiral stationary phase HPLC to determine the enantioselectivity of the aldol reaction (92% ee). $LiAlH_4$ reduction was conducted at –78 °C, and short pad column chromatography on silica gel delivered the recovered (*S*,*S*)-Ph-BPE in 84% (after recrystallization) and γ-amino alcohol **5d** in 56% yield (2 steps). Removal of allyl groups on nitrogen under Pd catalysis and treatment with methyl chloroformate gave carbamate **6**. Reduction with $LiAlH_4$ under reflux conditions in THF afforded *N*-methylated γ-amino alcohol **7** and ether formation by ipso substitution with 1-fluoronaphthalene furnished duloxetine (**1**) (Scheme 2).

In conclusion, we developed a concise enantioselective synthetic route to duloxetine (**1**) based on the direct catalytic asymmetric aldol reaction. The major drawback of the use of costly chiral bisphosphine ligands was eliminated by its efficient recovery after $LiAlH_4$ reduction. The subsequent four-step sequence efficiently afforded duloxetine (**1**), a dual serotonin and norepinephrine reuptake inhibitor.

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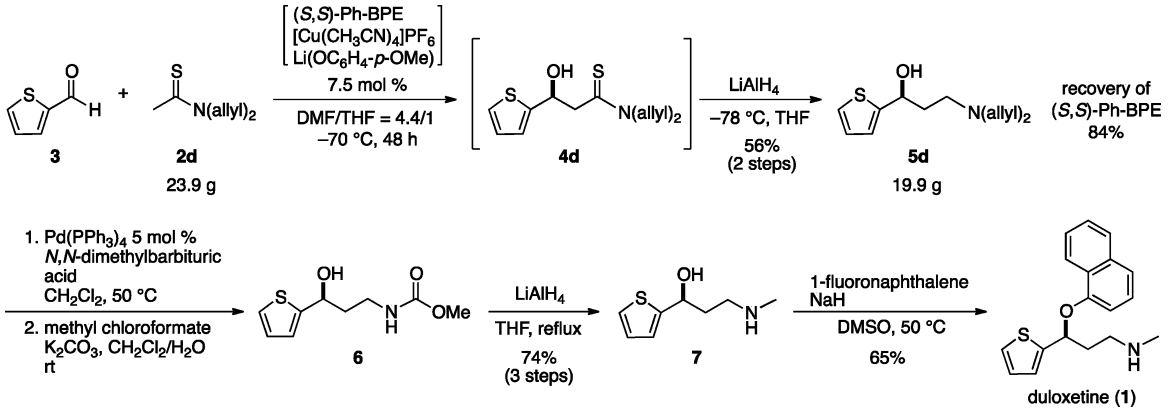
Scheme 2. Enantioselective Synthesis of Duloxetine (1)



EXPERIMENTAL SECTION

The direct catalytic asymmetric aldol reaction was performed in a glass test tube with a Teflon-coated magnetic stirring bar unless otherwise noted. The flasks or test tubes were fitted with a 3-way glass stopcock, and reactions were run under Ar atmosphere. Air- and moisture-sensitive liquids were transferred via a gastight syringe and a stainless-steel needle. All workup and purification procedures were carried out with reagent-grade solvents under ambient atmosphere. Flash chromatography was performed using silica gel 60 (230−400 mesh). Chemical shifts for proton are reported as δ in units of parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CDCl_3$: δ 7.26 ppm). For ^{13}C NMR, chemical shifts were reported in the scale relative to NMR solvent ($CDCl_3$: 77.0 ppm) as an internal reference. For ^{31}P NMR, chemical shifts were reported in the scale relative to H_3PO_4 (0.0 ppm in D_2O) as an external reference. NMR data are reported as follows: chemical shifts, multiplicity (s: singlet, d: doublet, dd: doublet of doublets, t: triplet, q: quartet, sep: septet, m: multiplet, br: broad signal), coupling constant (Hz), and integration. Optical rotation was measured using a 2 mL cell with a 1.0 dm path length. HPLC analysis was conducted with chiral-stationary-phase columns (0.46 cm ϕ × 25 cm).

***N*-Benzyl-*N*-methylethanethioamide (2b).** Pale yellow solid: mp 80−81 °C; IR (KBr) ν 2964, 2360, 1503, 1235, 953 cm^{-1}; ^1H NMR (399.78 MHz, $CDCl_3$) δ 7.33−7.03 (m, 5H, rotamer A + B), 5.25 (s, 2H, rotamer A), 4.75 (s, 2H, rotamer B), 3.37 (s, 3H, rotamer B), 3.08 (s, 3H, rotamer A), 2.65 (s, 3H, rotamer B), 2.63 (s, 3H, rotamer A); ^{13}C NMR (100.53 MHz, $CDCl_3$) δ 200.8, 200.4, 135.4, 134.6, 129.0, 128.6, 127.9, 127.8, 127.7, 126.1, 58.2, 57.9, 42.7, 39.1, 32.9, 32.4; HRMS (ESI TOF (+)) calcd. for $C_{10}H_{14}NS$ *m*/*z* 180.0841 $[M + H]^+$, found 180.0841.

***N*-(4-Methoxyphenyl)-*N*-methylethanethioamide (2c).** Pale yellow solid: mp 44 °C; IR (KBr) ν 2958, 2360, 1511, 1248, 1030 cm^{-1}; ^1H NMR (399.78 MHz, $CDCl_3$) δ 7.05 (d, *J* = 9.0 Hz, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 3.79 (s, 3H), 3.66 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100.53 MHz, $CDCl_3$) δ 201.4, 159.0, 138.5, 126.1, 114.8, 55.4, 45.7, 33.6; HRMS (ESI TOF (+)) calcd. for $C_{10}H_{14}ONS$ *m*/*z* 196.0791 $[M + H]^+$, found 196.0791.

2d is reported in ref 11b, and spectroscopic data of **2d** used in this study was fully consistent with the reported data.

(*S*)-*N*-Benzyl-3-hydroxy-*N*-methyl-3-(thiophen-2-yl)-propanethioamide (4b). To a flame-dried 3 L flask equipped with a magnetic stirring bar and a three-way glass stopcock were added (*S*,*S*)-Ph-BPE (5.1 mg, 0.01 mmol), $[Cu(CH_3CN)_4]PF_6$ (3.7 mg, 0.01 mmol), dry THF (350 μL), and dry DMF (1.75 mL). After stirring for 20 min at room temperature, *N*-benzyl-*N*-methylethanethioamide (**2b**) (35.9 mg, 0.2 mmol) and 2-thiophenecarboxaldehyde (**3**) (27.4 μL, 0.3 mmol) were added. The flask was immersed into the cooling bath at −70 °C. To the solution was added $Li(OC_6H_4$-*p*-OMe) (0.2 M/THF, 50 mL, 0.01 mmol), and the mixture was stirred at −70 °C. After 48 h of stirring, AcOH in THF (0.1 M, 150 μL), and NH_4Cl aq were added to the reaction mixture, and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with 1 N HCl 3 times and with brine and then dried over Na_2SO_4. The residue obtained after filtration/concentration was purified by silica gel column chromatography (acetone/*n*-hexane = 1/9) yielding aldol product **4b** (9.9 mg, 0.034 mmol, yield 17%) as a colorless oil. Enantiomeric excess was determined by HPLC analysis. Colorless oil: IR (KBr) ν 3377, 2930, 2245, 1502, 700 cm^{-1}; ^1H NMR (399.78 MHz, $CDCl_3$) δ 7.40−6.89 (m, 8H, rotamer A + B), 5.67−5.61 (m, 1H, rotamer A), 5.62−5.56 (m, 1H, rotamer B), 5.35 (d, *J* = 14.4 Hz, 1H, rotamer A), 5.30 (d, *J* = 14.4 Hz, 1H, rotamer A), 5.04 (d, *J* = 3.2 Hz, 1H, rotamer A), 5.02 (d, *J* = 3.2 Hz, 1H, rotamer B), 4.87 (d, *J* = 16.5 Hz, 1H, rotamer B), 4.72 (d, *J* = 16.5 Hz, 1H, rotamer B), 3.45 (s, 3H, rotamer B), 3.15−3.07 (m, 2H, rotamer A + B), 3.10 (s, 3H, rotamer A); ^{13}C NMR (100.53 MHz, $CDCl_3$) δ 200.5, 200.3, 146.3, 146.3, 134.6, 134.0, 128.9, 128.5, 127.8, 127.6, 127.5, 126.4, 125.9, 124.2, 124.1, 123.1, 123.0, 68.3, 68.2, 57.7, 56.9, 53.3, 50.2, 49.8, 42.7, 38.8; HRMS (ESI TOF (+)) calcd. for $C_{15}H_{17}ONNaS_2$ *m*/*z* 314.0644 $[M + Na]^+$, found 314.0642; $[\alpha]_D^{24}$ −74.0 (*c* 0.26, $CHCl_3$, 72% ee); HPLC [Daicel CHIRALCEL OD-H, detection at 254 nm, 9:1 *n*-hexane/^{i}PrOH, flow rate = 1.0 mL/min, t_R = 18.7 min (major), t_R = 25.7 min (minor)].

Preparation of $Li(OC_6H_4$-*p*-OMe)/THF. A flame-dried 10 mL pear-shaped flask equipped with a magnetic stirring bar and 3-way stopcock was charged with *p*-methoxyphenol (12.4 mg, 0.10 mmol) and dried under vacuum for 30 min. Ar was backfilled to the flask, and dry THF (440 μL) was added via a syringe and a stainless steel needle. ^{n}BuLi (60 μL, 0.1 mmol, 1.65 M in *n*-hexane) was then added at 0 °C, and the resulting solution was stirred at the same temperature for 60 min to give colorless 0.2 M $Li(OC_6H_4$-*p*-OMe) solution in THF, which was stored at room temperature in the dark and used within a day.

(*S*)-3-Hydroxy-*N*-(4-methoxyphenyl)-*N*-methyl-3-(thiophen-2-yl)propanethioamide (4c). The above-mentioned procedure for direct aldol reaction was applied. Colorless liquid: IR (KBr) ν 3380, 2926, 1509, 1249, 704 cm^{-1}; ^1H NMR (399.78 MHz, $CDCl_3$) δ 7.17 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.01−6.88 (m, 5H), 6.79 (d, *J* = 3.4 Hz, 1H), 5.48−5.43 (m, 1H), 4.89 (d, *J* = 3.0 Hz, 1H), 3.82 (s, 3H), 3.71 (s, 3H), 2.86−2.82 (m, 2H); ^{13}C NMR (100.53 MHz, $CDCl_3$) δ 201.8, 159.4, 146.7, 137.7, 126.5, 124.3, 123.1, 115.1, 68.7, 55.5, 51.2, 45.7; HRMS (ESI TOF (+)) calcd. for $C_{15}H_{17}NO_2S_2$ *m*/*z* 330.0593 $[M + Na]^+$, found 330.0591; $[\alpha]_D^{24}$ −53.9 (*c* 0.84, $CHCl_3$, 73% ee); HPLC [Daicel CHIRALCEL OZ-H, detection at 254 nm, 9:1 *n*-hexane/^{i}PrOH, flow rate = 1.0 mL/min, t_R = 28.1 min (major), t_R = 33.3 min (minor)].

(*S*)-3-(Diallylamino)-1-(thiophen-2-yl)propan-1-ol (5d) (Large-Scale Reaction). To a flame-dried 3 L flask equipped with a magnetic stirring bar and a three-way glass stopcock were added (*S*,*S*)-Ph-BPE (5.70 g, 11.25 mmol), $[Cu(CH_3CN)_4]PF_6$ (4.19 g, 11.25 mmol), dry THF (188 mL), and dry DMF (1313 mL). After stirring for 20 min at room temperature, *N*,*N*-diallylthioacetamide **2d** (23.9 mL,150 mmol) and 2-thiophencarboxaldehyde (**3**) (18 mL, 180

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mmol) were added. The flask was immersed into the cooling bath at −70 °C with 2-propanol as medium. To the solution was added Li(OC$_6$H$_4$-*p*-OMe) (0.2 M/THF, 56.3 mL, 11.25 mmol), and the mixture was stirred at −70 °C. After 48 h of stirring, AcOH in THF (0.1 M, 169 mL), and NH_4Cl aq were added to the reaction mixture, and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with 1 N HCl 3 times and with brine and then dried over Na_2SO_4 . The filtrate was concentrated under reduced pressure, and the resulting residue was submitted to ^{1}H NMR analysis to estimate the yield of the product **4d** (59% yield) and dehydrated byproduct **2d′** (20% yield). Enantiomeric excess was determined by HPLC analysis (92% ee). The resulting crude mixture was directly used for the following reaction. To a flame-dried 1 L flask equipped with dropping funnel was charged $LiAlH_4$ (17.1 g, 450 mmol) and dry THF (300 mL), and the mixture was cooled to −78 °C. A THF (300 mL) solution of the crude mixture was slowly added through a dropping funnel, and the reaction mixture was additionally stirred for 10 min at room temperature. After the flask was cooled to −78 °C, saturated aqueous solution of Rochelle salt was slowly added through dropping funnel, and then the reaction mixture was stirred for additional 30 min at room temperature. Resulting mixture was extracted with $CHCl_3$ three times, and the combined organic phase was dried over Na_2SO_4. Volatiles were removed under reduced pressure, and the resulting residue was immediately passed through a short-pad of silica gel (*n*-hexane/CH_2Cl_2 = 3/1 for (*S*,*S*)-Ph-BPE; *n*-hexane/AcOEt = 3/1 for product **5d**) to isolate (*S*,*S*)-Ph-BPE (partial decomposition of (*S*,*S*)-Ph-BPE should be involved when the crude sample was applied to usual silica gel column chromatography). The obtained (*S*,*S*)-Ph-BPE was then recrystallized with AcOEt and MeOH to give pure (*S*,*S*)-Ph-BPE as a white solid (4.77 g, 84% recovery). Roughly separated crude product mixture was purified again by silica gel column chromatography (*n*-hexane/AcOEt = 3/1) to give desired amine **5d** as a red oil (19.9 g, 83.8 mmol, 56%, 2 steps): IR (KBr) ν 2979, 1708, 1633, 1178, 754 cm^{-1}; ^{1}H NMR (399.78 MHz, $CDCl_3$) δ 7.20 (dd, J = 5.0, 1.1 Hz, 1H), 6.96 (dd, J = 5.0, 3.6 Hz, 1H), 6.93−6.90 (m, 1H), 5.92−5.80 (m, 2H), 5.23−5.19 (m, 2H), 5.19−5.16 (m, 2H), 5.17−5.12 (m, 1H), 3.29 (dd, J = 14.0, 6.1 Hz, 2H), 2.99 (dd, J = 14.0, 7.6 Hz, 2H), 2.85 (ddd, J = 13.0, 9.6, 3.7 Hz, 1H), 2.67 (ddd, J = 13.0, 5.3, 3.4 Hz, 1H), 2.04−1.87 (m, 2H); ^{13}C NMR (100.53 MHz, $CDCl_3$) δ 149.4, 134.2, 126.4, 123.7, 122.2, 118.7, 72.0, 56.5, 51.8, 34.4; HRMS (ESI TOF (+)) calcd. for $C_{18}H_{20}NOS$ m/z 298.1260 [M + H]$^+$, found 298.1261; $[\alpha]_D^{23}$ −99.8 (c 0.41, $CHCl_3$).

Recovered (*S*,*S*)-Ph-BPE. Spectral data: ^{1}H NMR (399.78 MHz, $CDCl_3$) δ 7.26−6.96 (m, 20H), 3.53−3.44 (m, 2H), 2.88−2.81 (m, 2H), 2.41−2.30 (m, 2H), 2.23−2.15 (m, 2H), 2.06−1.94 (m, 2H), 1.79−1.69 (m, 2H), 0.93−0.82 (m, 2H), 0.55−0.43 (m, 2H); ^{13}C NMR (100.53 MHz, $CDCl_3$) δ 144.7−144.6 (m), 138.3 (m), 128.5 (s), 128.3 (s), 127.9−127.8 (m), 127.2 (m), 125.8 (s), 125.7 (s), 50.7−50.5 (m), 46.2−46.1 (m), 37.4 (s), 31.9 (s), 21.5−21.4 (m); ^{31}P NMR (161.83 MHz, $CDCl_3$) δ 14.2.

(*S*)-3-(Methylamino)-1-(thiophen-2-yl)propan-1-ol (7). To a stirred solution of **5d** (870 mg, 3.67 mmol, 92% ee) in CH_2Cl_2 (20 mL) were added $Pd(PPh_3)_4$ (219 mg, 0.18 mmol) and *N*,*N*-dimethylbarbituric acid (2.96 g, 18.33 mmol), and the resulting solution was stirred at 50 °C (bath temp.) 6 h. After cooling to rt, the mixture was diluted with $CHCl_3$. The solution was washed with saturated Na_2CO_3 three times to remove barbituric acid and then dried over Na_2SO_4. Volatiles were removed under reduced pressure to give crude primary amine as a red oil. To a CH_2Cl_2 (7 mL) solution of the crude mixture were added methyl chloroformate (426 μL, 5.50 mmol, 1.5 equiv) and 2.5 M K_2CO_3 aq (7 mL, 18.33 mmol, 5 equiv), and the mixture was stirred for 2.5 h at room temperature. Resulting mixture was diluted with H_2O, and the biphasic mixture was extracted with CH_2Cl_2 three times. The combined organic phase was washed with brine and dried over Na_2SO_4. Volatiles were removed under reduced pressure to give crude carbamate as a red oil. A flame-dried 100 mL flask was charged with the crude carbamate (3.58 mmol; a small portion was used for the following experiments). To the flask was added $LiAlH_4$ (402 mg, 10.60 mmol) suspended in 35 mL of dry THF. The suspension was heated to reflux and stirred for 48 h. Ethylenediamine (600 μL), 600 μL of 1 N NaOH aq, and 1 mL of H_2O were subsequently added with 10 min intervals. The gray mixture was filtered through a pad of Celite, and the filtrate was washed with THF. The organic solvent was removed under reduced pressure. The crude mixture was diluted with H_2O and extracted with CH_2Cl_2 three times. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (CH_2Cl_2 100%, then (8 M NH_3 in MeOH)/CH_2Cl_2 = 1/15) yielding amino alcohol **7** (449 mg, 2.870 mmol, 74% (3 steps), from **5d**) as a colorless oil that crystallized upon standing. Pale yellow solid: mp 59 °C; IR (KBr) ν 3297, 2852, 2361, 1073, 700 cm^{-1}; ^{1}H NMR (399.78 MHz, $CDCl_3$) δ 7.14 (dd, J = 5.0, 1.1 Hz, 1H), 6.90 (dd, J = 5.0, 3.4 Hz, 1H), 6.87−6.84 (m, 1H), 5.08−5.02 (m, 1H), 4.15 (br, 2H), 2.84−2.68 (m, 2H), 2.32 (s, 3H), 1.94−1.78 (m, 2H); ^{13}C NMR (100.53 MHz, $CDCl_3$) δ 149.6, 126.2, 123.4, 122.1, 70.7, 49.5, 37.0, 35.6; HRMS (ESI TOF (+)) calcd. for $C_8H_{14}NOS$ m/z 172.0791 [M + H]$^+$, found 172.0791; $[\alpha]_D^{24}$ −9.1 (c 0.55, $CHCl_3$, 92% ee).

Duloxetine (1). To a solution of **7** (54.1 mg, 0.32 mmol, 92% ee sample) dissolved in 2.1 mL of dry DMSO was added NaH (60% in mineral oil, 19.0 mg, 0.47 mmol). The mixture was stirred at room temperature for 1 h followed by the addition of 1-fluoronaphthalene (56.7 μL, 0.44 mmol). After stirring at 50 °C for 1 h, the mixture was cooled to room temperature, and 5 mL of 1 N NaOH aq was added. The product was extracted with AcOEt three times, and the combined organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography ((8 M NH_3 in MeOH)/CH_2Cl_2 = 1/20) to afford duloxetine (61.1 mg, 0.21 mmol, 65%) as a pale yellow oil: IR (KBr) ν 3052, 2924, 2851, 1397, 1094 cm^{-1}; ^{1}H NMR (399.78 MHz, $CDCl_3$) δ 8.40−8.34 (m, 1H), 7.81−7.76 (m, 1H), 7.52−7.47 (m, 1H), 7.40 (d, J = 8.5 Hz, 1H), 7.31−7.25 (m, 1H), 7.21 (dd, J = 5.0, 1.1 Hz, 1H), 7.08−7.05 (m, 1H), 6.94 (dd, J = 5.0, 3.4 Hz, 1H), 6.87 (d, J = 7.6 Hz, 1H), 5.81 (dd, J = 7.8, 5.2 Hz, 1H), 2.86−2.80 (m, 2H), 2.52−2.40 (m, 4H), 2.29−2.18 (m, 1H); ^{13}C NMR (100.53 MHz, $CDCl_3$) δ 153.1, 144.9, 134.3, 127.2, 126.3, 126.1, 125.8, 125.5, 125.0, 124.5, 124.4, 121.9, 120.3, 106.7, 74.5, 48.0, 38.7, 36.3; HRMS (ESI TOF (+)) calcd. for $C_{18}H_{20}NOS$ m/z 298.1260 [M + H]$^+$, found 298.1261; $[\alpha]_D^{25}$ 107.0 (c 0.08, MeOH).

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR charts and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: nkumagai@bikaken.or.jp; mshibasa@bikaken.or.jp.

Notes

The authors declare no competing financial interest.

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