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Direct catalytic asymmetric aldol reaction of thioamides: a concise asymmetric synthesis of (*R*)-fluoxetine

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Dedicated to Professor Henri B. Kagan on the occasion of his 80th birthday

ABSTRACT

A direct catalytic asymmetric aldol reaction of aromatic aldehydes and thioamides is described. A soft Lewis acid/hard Brønsted base cooperative catalyst comprising (*R*,*R*)-Ph-BPE/[Cu(CH_3CN)$_4$]PF_6/Li(OC_6H_4-*p*-OMe) promoted the title reaction efficiently, triggered by in situ generation of the active thioamide enolate through a soft–soft interaction of Cu(I) and the thioamide. The aldol product was transformed into (*R*)-fluoxetine, an antidepressant agent.

1. Introduction

The aldol reaction is one of the most fundamental and ubiquitous carbon–carbon bond-forming reactions in both bioorganic transformations and organic synthesis.[1] Due to the synthetic utility of enantioenriched β-hydroxy carbonyl entities produced by enantioselective aldol reactions, the catalytic asymmetric aldol reaction is a subject of intense research.[2] Although a number of methodologies using preactivated enolates have been developed for the catalytic asymmetric aldol reaction, the direct catalytic asymmetric aldol reaction, in which an active enolate is generated in a catalytic manner via proton-transfer and coupled with subsequent asymmetric addition to aldehydes, is attracting increasing attention as a more atom-economical[3] and environmentally benign synthetic methodology.[4–6] The key issue of the direct aldol reaction is efficient catalytic generation of active enolates in situ, thus the aldol donors implemented in the direct aldol reaction have been largely limited to ketones and aldehydes in which the acidity of the α-proton is high enough for deprotonative activation. For further elaboration of synthetically versatile aldol products, the direct aldol reaction with aldol donors in the carboxylic acid oxidation state provides β-hydroxy carboxylates, which offer broader functional group manipulation.[7–9]

In this context, we focused on thioamide functionality as a suitable aldol donor that can be activated through a soft Lewis acid/hard Brønsted base cooperative catalysis.[10] In addition, thioamide functionality in the aldol product serves as a useful handle for subsequent functional group transformations. A catalytic system comprising (*R*,*R*)-Ph-BPE/[Cu(CH_3CN)$_4$]PF_6/LiOAr promoted the direct catalytic asymmetric aldol reaction of aliphatic aldehydes **1** and thioamides **2**, affording β-hydroxy thioamides **3** in high enantioselectivity,[11,12] whereas aromatic aldehydes were not applicable due to retro-reaction and subsequent dehydration to give unsaturated thioamides. Herein, we report the direct catalytic asymmetric aldol reaction of thioamides with aromatic aldehydes. The utility of the reaction is highlighted by a concise enantioselective synthesis of (*R*)-fluoxetine, a widely used antidepressant agent.

2. Results and discussion

Previous studies have reported that soft Lewis acid/hard Brønsted base cooperative catalysts comprising (*R*,*R*)-Ph-BPE/[Cu(CH_3CN)$_4$]PF_6/LiOAr are effective for chemoselective activation of thioamides as a soft Lewis basic pronucleophile through a soft–soft interaction.[11] As for the direct aldol reaction of thioamides, DMF as a Lewis basic solvent is essential for efficient catalytic turnover.[11a,13] A model reaction of benzaldehyde **1a** and *N*,*N*-diallylthioacetamide **2a** under the standard aldol reaction conditions for aliphatic aldehydes with 10 mol % catalyst resulted in moderate enantioselectivity and the time-dependent formation of α,β-unsaturated thioamide **4aa** (Table 1, entries 1–3). When the isolated aldol product **3aa** was again subjected to the reaction conditions, a mixture of **1a**, **2a**, **4aa**, as well as **3aa** was produced (Scheme 1a), whereas the aldol product derived from aliphatic aldehyde **3′** remained unchanged in the same procedure (Scheme 1b), indicating that the aldol product derived from the aromatic aldehyde was more prone to retro-aldol reaction and β-elimination. A THF/DMF mixed solvent system attenuated the Brønsted basicity of Li(OC_6H_4-*p*-OMe) and prevented the β-elimination at −70 °C (entries 4–8). When the reaction was conducted in THF/DMF = 9/1 solvent, catalytic turnover was arrested likely due to product

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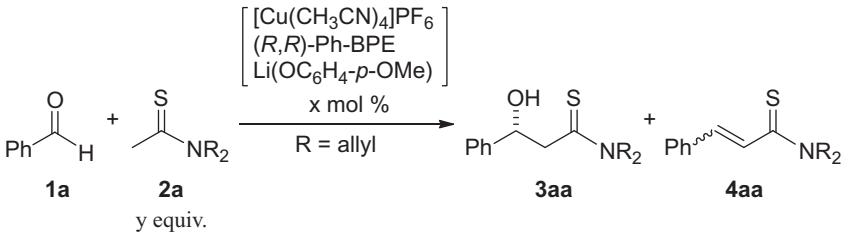
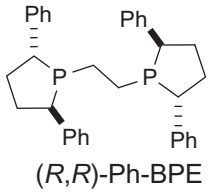
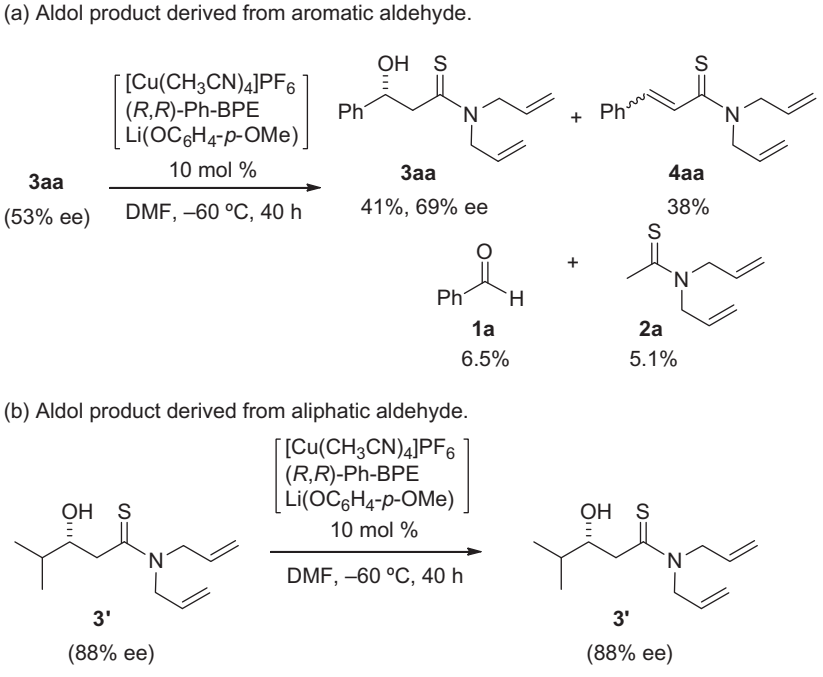
Table 1
Direct catalytic asymmetric aldol reaction of benzaldehyde **1a** and *N*,*N*-diallylthioacetamide **2a**[a]



Entry	*x*	*y*	Solvent	Temp (°C)	Time (h)	Yield[b] (%)		ee (%) (**3aa**)
						3aa	**4aa**	
1	10	1.2	DMF	−60	8	72	9	68
2	10	1.2	DMF	−60	24	73	19	72
3	10	1.2	DMF	−60	40	42	30	66
4	5	1.2	THF/DMF 9/1	−70	20	23	ND[d]	70
5	5	1.2	THF/DMF 1/3	−70	20	80	ND[d]	78
6[c]	5	1.2	THF/DMF 1/3	−70	20	84	7	59
7	5	1.2	THF/DMF 1/7	−70	20	74	ND[d]	83
8	5	1.5	THF/DMF 1/7	−70	20	94	1.7	79

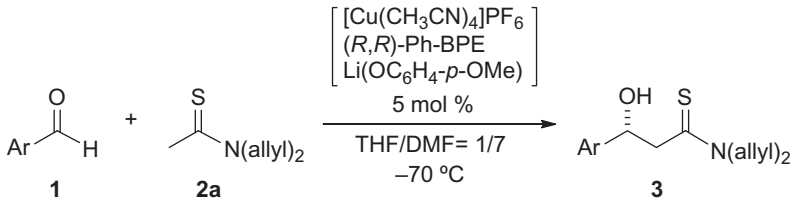


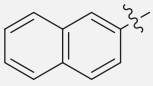
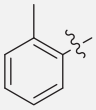
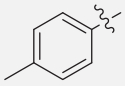
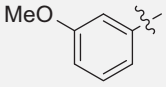
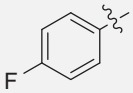
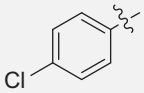
[a] **1a**: 0.2 mmol.
[b] Determined by ^{1}H NMR analysis with 1,2-dimethoxyethane as an internal standard.
[c] Li salt of 2,2,5,7,8-pentamethylchromanol was used as a Brønsted base instead of Li(OC$_6$H$_4$-*p*-OMe).
[d] Not detected.



Scheme 1. Re-subjection of aldol products to aldol reaction conditions in DMF at −60 °C.

Table 2
Direct catalytic asymmetric aldol reaction of aromatic aldehydes **1** and thioamides **2a**[a]



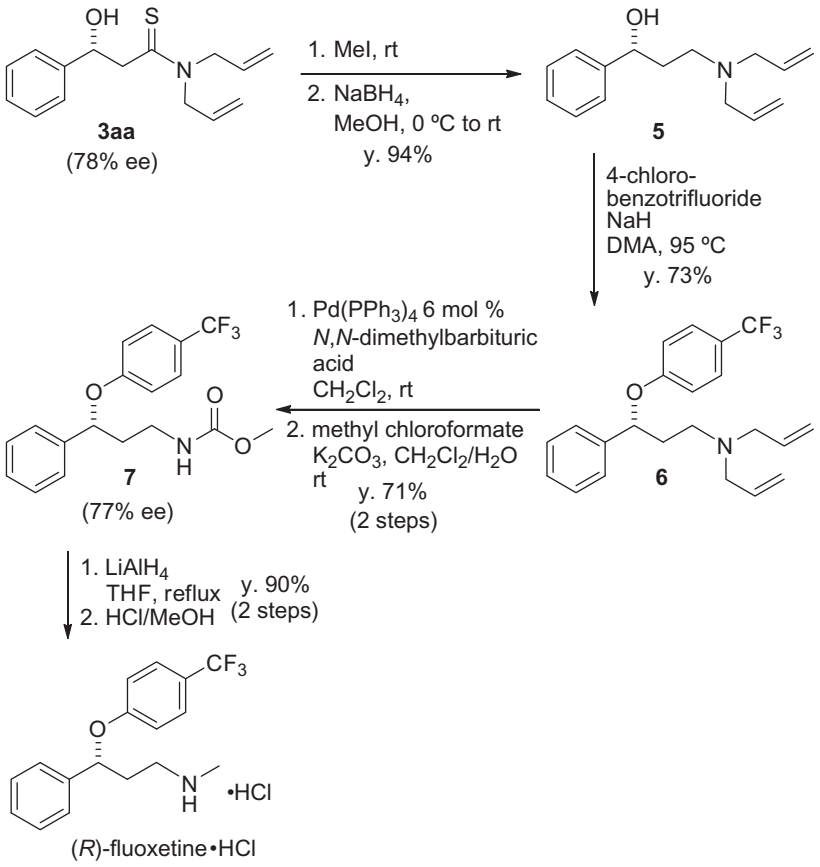
Entry	Aldehyde	Ar	Product	Time (h)	Yield[b] (%)	ee (%)
1[c]		**1a**	**3aa**	20	94 (1.7)	79
2[c]		**1b**	**3ba**	20	96 (3.0)	79
3		**1c**	**3ca**	40	89 (3.6)	67
4		**1d**	**3da**	20	88 (2.1)	79
5		**1e**	**3ea**	40	85 (3.4)	82
6		**1f**	**3fa**	40	96 (3.0)	74
7		**1g**	**3ga**	40	80 (2.2)	71
8		**1h**	**3ha**	40	74 (ND[d])	91

[a] **1**: 0.3 mmol, **2a**: 0.45 mmol.
[b] Isolated yield. Yield of dehydrated product is provided in parentheses (determined by ^{1}H NMR of the crude mixture).
[c] **1**: 0.4 mmol, **2a**: 0.6 mmol.
[d] Not detected.

inhibition, affording **3aa** in only 23% yield. Increasing the DMF content allowed the reaction to proceed smoothly without the formation of **4aa**. The formation of **4aa** was sensitive to the Brønsted basicity of the catalyst, as shown in the reaction using Li salt of 2,2,5,7,8-pentamethylchromanol as a stronger Brønsted base (entry 6). In terms of chemical yield and enantioselectivity, the reaction conditions with THF/DMF = 1/7 and 1.5 equiv of **2a** were optimum (entry 8).[14,15]

Having developed suitable conditions for the catalytic asymmetric aldol reaction of aromatic aldehydes and the thioamides, we next examined the substrate scope of the present catalytic system. Aromatic aldehydes **1b**–**d** bearing non-polar substituents produced the corresponding aldol products in comparable yield and enantioselectivity (entries 1–4), whereas an *ortho* methyl group may negatively affect stereoselection, leading to a marginal loss of enantioselectivity, probably due to the increased steric factors close to the carbonyl group (entry 3). The effect of heteroatom substituents was negligible, affording the aldol product **3ea**–**ga** in comparable yield and enantioselectivity (entries 5–7). The reaction with heteroaromatic aldehyde **1h** proceeded with the highest enantioselectivity (91% ee) albeit with a moderate yield (entry 8) (Table 2).

Fluoxetine (Prozac™, Eli Lilly Co Ltd) is a selective serotonin reuptake inhibitor (SSRI) and widely used for the treatment of depression and anxiety. Although fluoxetine is clinically used as a racemate, accumulating evidence[16] that the (*R*)- and (*S*)-enantiomers of fluoxetine have different pharmacokinetics and bioactivities have led to the catalytic asymmetric synthesis of fluoxetine, largely through catalytic asymmetric hydrogenation,[17] epoxidation,[18] or dihydroxylation.[19] Facile manipulation of the thioamide functionality of the aldol product **3aa** enabled a concise asymmetric synthesis of (*R*)-fluoxetine, in which the stereogenic center was generated concomitantly with C–C bond formation (Scheme 2).[20] Desulfurization of the aldol product **3aa** (78% ee sample) was performed by the activation of thioamide with MeI and subsequent hydride reduction with $NaBH_4$,[21] affording the corresponding diallylamine **5** in 94% yield. Installation of the requisite 4-trifluoromethylphenyl group under basic conditions gave aryl ether **6**.[17–19] A palladium-catalyzed deallylation protocol and the following carbamate formation afforded **7** in 71% yield in two steps.[22] Reduction



Scheme 2. Asymmetric synthesis of (*R*)-fluoxetine.

of **7** with $LiAlH_4$ and subsequent treatment with HCl/MeOH delivered (*R*)-fluoxetine·HCl.[17–19]

3. Conclusion

A direct catalytic asymmetric aldol reaction of aromatic aldehydes and thioamides with a soft Lewis acid/hard Brønsted base cooperative catalyst was developed. Exquisite control of the reaction conditions effectively prevented a retro-reaction as well as dehydration, affording the desired aldol products with moderate to good enantioselectivity. Facile manipulation of the *N*,*N*-diallylthioamide functionality allowed for a concise asymmetric synthesis of (*R*)-fluoxetine. Further efforts will be devoted to the development of a diasteroselective version of the direct catalytic asymmetric aldol reaction of thioamides.

4. Experimental

4.1. General

Catalytic asymmetric aldol reactions were performed in a flame-dried 20 mL test tube with a Teflon-coated magnetic stirring bar unless otherwise noted. The test tubes were fitted with a three-way glass stopcock and the reactions were run under Ar atmosphere. All work-up and purification procedures were carried out with reagent-grade solvents under ambient atmosphere.

Infrared (IR) spectra were recorded on a JASCO FT/IR 410 Fourier transform infrared spectrophotometer. NMR was recorded on JEOL LA-500, JEOL ECX-500 spectrometers. Chemical shifts for proton are reported in 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 ^{19}F NMR, chemical shifts were reported in the scale relative to CF_3COOH as an external reference. NMR data are reported as follows: chemical shifts, multiplicity (s: singlet, d: doublet, dd: doublet of doublets, t: triplet, m: multiplet, br: broad signal), coupling constant (Hz), and integration. Optical rotation was measured using a 1 mL cell with a 0.5 dm path length on a JASCO polarimeter P-1010. ESI mass spectra were measured on Waters-ZQ4000. High-resolution mass spectra (ESI (+)) were measured on JEOL AccuTOF JMS-T100LC. HPLC analysis was conducted on a JASCO HPLC system equipped with Daicel chiral stationary phase columns.

4.2. Direct catalytic asymmetric aldol reaction of aromatic aldehyde and thioamide

4.2.1. Representative procedure for the preparation of (*R*)-*N*,*N*-diallyl-3-hydroxy-3-phenylpropanethioamide 3aa

To a flame-dried 20 mL test tube equipped with a magnetic stirring bar and a three-way glass stopcock were added (*R*,*R*)-Ph-BPE/$[Cu(CH_3CN)_4]PF_6$ solution (0.1 M/THF, 200 μL, 0.02 mmol), dry THF (0.5 mL), dry DMF (3.5 mL), *N*,*N*-diallylthioacetamide **2a** (95.4 μL, 0.60 mmol), and benzaldehyde **1a** (40.6 μL, 0.4 mmol) under Ar at room temperature. The test tube was immersed into the electronically controlled 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, 100 μL, 0.02 mmol) and stirred at −70 °C. After 20 h of stirring, AcOH in THF (0.1 M, 300 μL), satd NH_4Cl aq, and bipyridine (9.4 mg, 0.06 mmol) were added to the reaction mixture (essential to make sure of the dissociation of the aldol product from the Cu

complex) and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with H_2O and brine, then dried over Na_2SO_4. The filtrate was concentrated under reduced pressure and the resulting residue was submitted to ^1H NMR analysis to determine the yield of the dehydrated product. The residue was purified by silica gel column chromatography (SiO_2, eluent: *n*-hexane/CH_2Cl_2 = 1/1–1/10) to give **3aa** as a pale yellow oil (98.7 mg, 0.378 mmol, 94% yield). Enantiomeric excess was determined by HPLC analysis. Pale yellow oil; IR (neat) ν 3390, 1642, 1495, 1411 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42–7.39 (m, 2H), 7.38–7.34 (m, 2H), 7.31–7.26 (m, 1H), 5.89 (dddd, J = 17.4, 10.4, 5.8, 5.8 Hz, 1H), 5.72 (dddd, J = 17.1, 10.4, 4.6, 4.6 Hz, 1H), 5.28–5.23 (m, 1H), 5.29–5.24 (m, 2H), 5.23–5.17 (m, 1H), 5.15–5.10 (m, 1H), 4.74 (dd, J = 15.0, 5.8 Hz, 1H), 4.64 (d, J = 3.1 Hz, 1H), 4.56 (dd, J = 15.0, 6.1 Hz, 1H), 4.18–4.12 (m, 1H), 4.06–4.00 (m, 1H), 2.97–2.94 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 201.8, 143.0, 130.4, 130.4, 128.5, 127.6, 125.9, 118.4, 117.9, 72.3, 55.7, 52.8, 50.1; $[\alpha]_D^{23} = +105.0$ (c 1.2, $CHCl_3$, 79% ee sample); ESI-MS m/z 284 $[M+Na]^+$; HRMS (ESI-TOF) Anal. Calcd for $C_{15}H_{19}NNaOS$ m/z 284.1085 $[M+Na]^+$. Found: 284.1076; HPLC: Daicel CHIRALCEL OZ-H (ϕ 0.46 cm × 25 cm), 2-propanol/*n*-hexane = 1/9, flow rate 1.0 mL/min, detection 254 nm, t_R = 12.4 min (minor), 14.6 min (major).

4.2.2. (*R*)-*N*,*N*-Diallyl-3-hydroxy-3-(naphthalen-2-yl)propanethioamide 3ab

Colorless oil; IR (neat) ν 3388, 1640, 1497, 1411 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.90 (br s, 1H), 7.85–7.82 (m, 3H), 7.52–7.45 (m, 3H), 5.89 (dddd, J = 17.1, 10.4, 5.8, 5.8 Hz, 1H), 5.72 (dddd, J = 17.1, 10.4, 4.6, 4.6 Hz, 1H), 5.50–5.46 (m, 1H), 5.30–5.10 (m, 4H), 4.75 (d, J = 2.8 Hz, 1H), 4.74 (dd, J = 14.6, 5.8 Hz, 1H), 4.57 (dd, J = 14.6, 6.1 Hz, 1H), 4.18–4.12 (m, 1H), 4.06–4.00 (m, 1H), 3.05–3.02 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 201.8, 140.4, 133.3, 132.9, 130.4, 130.3, 128.2, 128.0, 127.7, 126.2, 125.9, 124.6, 124.0, 118.9, 117.9, 72.4, 55.7, 52.8, 50.1; $[\alpha]_D^{23} = +92.4$ (c 1.1, $CHCl_3$, 79% ee sample); ESI-MS m/z 334 $[M+Na]^+$; HRMS (ESI-TOF) Anal. Calcd for $C_{19}H_{21}NNaOS$ m/z 334.1242 $[M+Na]^+$. Found: 334.1233; HPLC: Daicel CHIRALCEL OZ-H (ϕ 0.46 cm × 25 cm), 2-propanol/*n*-hexane = 1/9, flow rate 1.0 mL/min, detection 254 nm, t_R = 16.7 min (minor), 21.5 min (major).

4.2.3. (*R*)-*N*,*N*-Diallyl-3-hydroxy-3-*o*-tolylpropanethioamide 3ac

Colorless oil; IR (neat) ν 3405, 2924, 1641, 1490, 1411 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.56 (dd, J = 7.6, 1.5 Hz, 1H), 7.23 (dd, J = 7.4, 1.5 Hz, 1H), 7.19 (ddd, J = 7.6, 7.4, 1.6 Hz, 1H), 7.15–7.13 (m, 1H), 5.90 (dddd, J = 16.7, 10.1, 6.1, 6.1 Hz, 1H), 5.72 (dddd, J = 17.1, 10.1, 4.6, 4.6 Hz, 1H), 5.56–5.53 (m, 1H), 5.30–5.24 (m, 2H), 5.24–5.20 (m, 1H), 5.15–5.10 (m, 1H), 4.85 (dd, J = 15.0, 5.2 Hz, 1H), 4.49 (d, J = 2.7 Hz, 1H), 4.46 (dd, J = 14.6, 6.2 Hz, 1H), 4.23–4.17 (m, 1H), 4.06–3.99 (m, 1H), 2.89–2.87 (m, 2H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 202.2, 141.1, 134.0, 130.5, 130.4, 130.4, 127.3, 126.3, 125.8, 118.9, 117.7, 69.1, 55.8, 52.7, 48.6, 19.1; $[\alpha]_D^{23} = +92.3$ (c 0.9, $CHCl_3$, 67% ee sample); ESI-MS m/z 298 $[M+Na]^+$; HRMS (ESI-TOF) Anal. Calcd for $C_{16}H_{21}NNaOS$ m/z 298.1242 $[M+Na]^+$. Found: 298.1240; HPLC: Daicel CHIRALCEL OZ-H (ϕ 0.46 cm × 25 cm), 2-propanol/*n*-hexane = 1/9, flow rate 1.0 mL/min, detection 254 nm, t_R = 7.0 min (minor), 10.3 min (major).

4.2.4. (*R*)-*N*,*N*-Diallyl-3-hydroxy-3-*p*-tolylpropanethioamide 3ad

Colorless oil; IR (neat) ν 3389, 2921, 1642, 1495, 1411 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.29 (d, J = 7.6 Hz, 2H), 7.16 (d, J = 7.6 Hz, 2H), 5.89 (dddd, J = 17.1, 10.0, 5.8, 5.8 Hz, 1H), 5.71 (dddd, J = 17.4, 10.4, 4.6, 4.6 Hz, 1H), 5.29–5.10 (m, 5H), 4.73 (dd, J = 14.9, 5.8 Hz, 1H), 4.56 (dd, J = 14.9, 6.1 Hz, 1H), 4.55 (d, J = 2.8 Hz, 1H), 4.20–4.14 (m, 1H), 4.06–4.01 (m, 1H), 2.95–2.94 (m, 2H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 202.0, 140.1, 137.3, 130.5, 130.4, 129.2, 125.8, 118.8, 117.9, 72.1, 55.7, 52.8, 50.2, 21.1; $[\alpha]_D^{23} = +95.0$ (c 1.2, $CHCl_3$, 79% ee sample); ESI-MS m/z 298 $[M+Na]^+$; HRMS (ESI-TOF) Anal. Calcd for $C_{16}H_{21}NNaOS$ m/z 298.1242 $[M+Na]^+$. Found: 298.1240; HPLC: Daicel CHIRALCEL OZ-H (ϕ 0.46 cm × 25 cm), 2-propanol/*n*-hexane = 1/9, flow rate 1.0 mL/min, detection 254 nm, t_R = 16.1 min (minor), 18.2 min (major).

4.2.5. (*R*)-*N*,*N*-Diallyl-3-hydroxy-3-(3-methoxyphenyl)propanethioamide 3ae

Colorless oil; IR (neat) ν 3380, 2932, 1602, 1586, 1411 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28–7.24 (m, 1H), 7.00–6.95 (m, 2H), 6.82 (dd, J = 8.3, 2.8 Hz, 1H), 5.89 (dddd, J = 16.8, 10.1, 6.1, 6.1 Hz, 1H), 5.72 (dddd, J = 17.1, 10.4, 4.6, 4.6 Hz, 1H), 5.29–5.10 (m, 5H), 4.74 (dd, J = 14.7, 5.8 Hz, 1H), 4.66 (d, J = 2.5 Hz, 1H), 4.55 (dd, J = 14.6, 6.1 Hz, 1H), 4.18–4.13 (m, 1H), 4.05–4.00 (m, 1H), 3.81 (s, 3H), 2.97–2.94 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 201.8, 159.7, 144.7, 130.4, 130.4, 129.5, 118.8, 118.1, 117.9, 113.1, 111.3, 72.2, 55.7, 55.2, 52.8, 50.0; $[\alpha]_D^{23} = +88.1$ (c 0.9, $CHCl_3$, 82% ee sample); ESI-MS m/z 314 $[M+Na]^+$; HRMS (ESI-TOF) Anal. Calcd for $C_{16}H_{21}NNaO_2S$ m/z 314.1191 $[M+Na]^+$. Found: 314.1189; HPLC: Daicel CHIRALCEL OZ-H (ϕ 0.46 cm × 25 cm), 2-propanol/*n*-hexane = 1/9, flow rate 1.0 mL/min, detection 254 nm, t_R = 14.3 min (minor), 18.7 min (major).

4.2.6. (*R*)-*N*,*N*-Diallyl-3-(4-fluorophenyl)-3-hydroxypropanethioamide 3af

Colorless oil; IR (neat) ν 3389, 1604, 1509, 1411 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38 (m, 2H), 7.05–7.00 (m, 2H), 5.88 (dddd, J = 17.1, 10.4, 5.8, 5.8 Hz, 1H), 5.72 (dddd, J = 17.1, 10.4, 4.9, 4.9 Hz, 1H), 5.30–5.10 (m, 5H), 4.72 (d, J = 3.1 Hz, 1H), 4.71 (dd, J = 14.4, 6.1 Hz, 1H), 4.55 (dd, J = 15.0, 6.2 Hz, 1H), 4.17–4.12 (m, 1H), 4.06–4.00 (m, 1H), 2.92–2.90 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 201.6, 162.1 ($J^1_{C-F} = 245.0$ Hz), 138.7 ($J^4_{C-F} = 3.1$ Hz), 130.3, 130.3, 127.5 ($J^3_{C-F} = 8.3$ Hz), 118.9, 117.9, 115.2 ($J^2_{C-F} = 21.7$ Hz), 71.6, 55.7, 52.8, 50.0; ^{19}F NMR δ −81.9; $[\alpha]_D^{23} = +92.1$ (c 1.0, $CHCl_3$, 74% ee sample); ESI-MS m/z 302 $[M+Na]^+$; HRMS (ESI-TOF) Anal. Calcd for $C_{15}H_{18}NNaOSF$ m/z 302.0991 $[M+Na]^+$. Found: 302.0989; HPLC: Daicel CHIRALCEL OZ-H (ϕ 0.46 cm × 25 cm), 2-propanol/*n*-hexane = 1/9, flow rate 1.0 mL/min, detection 254 nm, t_R = 10.8 min (minor), 12.9 min (major).

4.2.7. (*R*)-*N*,*N*-Diallyl-3-(4-chlorophenyl)-3-hydroxypropanethioamide 3ag

Colorless oil; IR (neat) ν 3386, 1642, 1492, 1411 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34–7.31 (m, 4H), 5.88 (dddd, J = 17.1, 10.1, 6.1, 6.1 Hz, 1H), 5.72 (dddd, J = 17.1, 10.4, 4.6, 4.6 Hz, 1H), 5.30–5.10 (m, 5H), 4.73 (d, J = 2.8 Hz, 1H), 4.72 (dd, J = 14.7, 6.1 Hz, 1H), 4.57 (dd, J = 9.9, 6.1 Hz, 1H), 4.17–4.12 (m, 1H), 4.06–4.02 (m, 1H), 2.92–2.88 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 201.5, 141.5, 133.2, 130.3, 130.2, 128.6, 127.3, 119.0, 118.0, 71.5, 55.8, 52.8, 49.2; $[\alpha]_D^{23} = +87.2$ (c 1.0, $CHCl_3$, 71% ee sample); ESI-MS m/z 318 $[M+Na]^+$; HRMS (ESI-TOF) Anal. Calcd for $C_{15}H_{18}NNaOSCl$ m/z 318.0695 $[M+Na]^+$. Found: 318.0682; HPLC: Daicel CHIRALCEL OZ-H (ϕ 0.46 cm × 25 cm), 2-propanol/*n*-hexane = 1/9, flow rate 1.0 mL/min, detection 254 nm, t_R = 11.2 min (minor), 13.3 min (major).

4.2.8. (*R*)-*N*,*N*-Diallyl-3-hydroxy-3-(thiophen-2-yl)propanethioamide 3ah

Colorless oil; IR (neat) ν 3387, 1642, 1495, 1411 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.24 (dd, J = 4.8, 1.3 Hz, 1H), 7.00–6.96 (m, 2H), 5.88 (dddd, J = 17.1, 10.1, 6.1, 6.1 Hz, 1H), 5.75 (dddd, J = 17.4, 10.7, 4.6, 4.6 Hz, 1H), 5.61–5.57 (m, 1H), 5.31–5.13 (m, 4H), 4.77 (d, J = 3.1 Hz, 1H), 4.72 (dd, J = 14.7, 5.8 Hz, 1H), 4.58 (dd, J = 14.7, 5.8 Hz, 1H), 4.23–4.17 (m, 1H), 4.12–4.06 (m, 1H), 3.06–3.02 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 201.2, 146.6, 130.4, 130.3, 126.6, 124.5,

123.3, 118.9, 118.1, 68.6, 55.7, 52.9, 49.9; $[\alpha]_D^{23} = +110.0$ (*c* 1.1, $CHCl_3$, 91% ee sample); ESI-MS *m*/*z* 290 $[M+Na]^+$; HRMS (ESI-TOF) Anal. Calcd for $C_{13}H_{17}NNaOS_2$ *m*/*z* 290.0649 $[M+Na]^+$. Found: 290.0646; HPLC: Daicel CHIRALCEL OZ-H (ϕ 0.46 cm × 25 cm), 2-propanol/*n*-hexane = 1/9, flow rate 1.0 mL/min, detection 254 nm, t_R = 14.3 min (minor), 18.7 min (major).

4.3. Preparation of (*R*)-fluoxetine

4.3.1. Preparation of (*R*)-3-(diallylamino)-1-phenylpropan-1-ol 5

The aldol product **3aa** (2.11 g, 8.07 mmol, 78% ee) was placed in a 300 mL pear-shaped flask and stirred with MeI (8.1 mL) at room temperature for 18 h. Then MeI was removed under reduced pressure to give a residue, which was dissolved in MeOH (80 mL) and the resulting solution was cooled to 0 °C. To the solution was added $NaBH_4$ (611 mg, 16.1 mmol) and the resulting solution was stirred at 0 °C for 30 min and at room temperature for 3 h. The reaction was quenched with H_2O, and MeOH was removed under reduced pressure. The aqueous solution was extracted with $CHCl_3$ and the combined organic extracts were dried over Na_2SO_4. Volatiles were removed under reduced pressure and the resulting residue was purified by silica gel column chromatography (SiO_2, eluent: $CHCl_3$/MeOH = 1/0–20/1) to give **5** as a colorless oil (1.75 g, 7.55 mmol, 94% yield). IR (neat) *ν* 3245, 3077, 2926, 2818, 1643, 1451, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39–7.22 (m, 5H), 6.60 (br s, 1H), 5.93–5.85 (m, 2H), 5.23–5.19 (m, 4H), 4.90 (dd, *J* = 9.2, 2.8 Hz, 1H), 3.33 (dd, *J* = 14.0, 5.7 Hz, 2H), 2.99 (dd, *J* = 14.0, 7.7 Hz, 2H), 2.87 (ddd, *J* = 13.1, 10.6, 3.4 Hz, 1H), 2.61 (ddd, *J* = 13.1, 4.9, 3.4 Hz, 1H), 1.91–1.76 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 145.0, 134.4, 128.2, 126.9, 125.6, 118.6, 75.6, 56.6, 52.3, 34.6; $[\alpha]_D^{24} = +31.6$ (*c* 1.2, $CHCl_3$); ESI-MS *m*/*z* 232 $[M+H]^+$; HRMS (ESI-TOF) Anal. Calcd for $C_{15}H_{21}NNaO$ *m*/*z* 254.1521 $[M+Na]^+$. Found: 254.1511.

4.3.2. Preparation of (*R*)-*N*-allyl-*N*-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)prop-2-en-1-amine 6

Into a 20 mL flame-dried test tube were placed **5** (50 mg, 0.216 mmol) and DMA (1.0 mL) and the resulting solution was cooled to 0 °C. Then NaH (13 mg, 0.324 mmol) was added to the solution and the mixture was stirred at 55 °C for 45 min. The solution was cooled to room temperature and 4-chlorobenzotrifluoride (87 μL, 0.648 mmol) was added, then the resulting solution was stirred at 95 °C for 90 min. After cooling to room temperature, additional NaH (13 mg, 0.324 mmol) and 4-chlorobenzotrifluoride (87 μL, 0.648 mmol) were added and the mixture was stirred at 95 °C for 90 min. The reaction was quenched with H_2O at 0 °C, and the resulting mixture was extracted with AcOEt and the combined organic extracts were washed with H_2O and brine, then dried over Na_2SO_4. Volatiles were removed under reduced pressure and the resulting residue was purified by preparative thin layer chromatography (SiO_2, eluent: *n*-hexane/ethyl acetate = 2/1) to give **6** as a pale yellow oil (59 mg, 0.157 mmol, 73% yield). IR (neat) *ν* 3076, 2925, 2808, 1615, 1329 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42 (d, *J* = 8.6 Hz, 2H), 7.33–7.25 (m, 5H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.83–5.74 (m, 2H), 5.28 (dd, *J* = 8.6, 4.6 Hz, 1H), 5.16–5.06 (m, 4H), 3.14–3.03 (m, 4H), 2.67 (ddd, *J* = 13.1, 7.4, 7.4 Hz, 1H), 2.55 (ddd, *J* = 13.1, 7.7, 5.2 Hz, 1H), 2.17–2.10 (m, 1H), 1.99–1.92 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 160.7, 141.3, 135.5, 128.7, 127.7, 126.7 (J_{C-F} = 4.1 Hz), 125.8, 124.6 (J_{C-F} = 307 Hz), 122.6 (J_{C-F} = 31.9 Hz), 117.5, 115.7, 78.3, 56.9, 49.1, 36.3; ^{19}F NMR δ −28.4; $[\alpha]_D^{27}$ +5.0 (*c* 1.4, $CHCl_3$); ESI-MS *m*/*z* 376 $[M+H]^+$; HRMS (ESI-TOF) Anal. Calcd for $C_{22}H_{25}F_3NO$ *m*/*z* 376.1888 $[M+H]^+$. Found: 376.1883.

4.3.3. Preparation of (*R*)-methyl 3-phenyl-3-(4-(trifluoromethyl)-phenoxy)propylcarbamate 7

To a stirred solution of **6** (467 mg, 1.24 mmol) in CH_2Cl_2 (12 mL) were added $Pd(PPh_3)_4$ (87 mg, 0.075 mmol) and *N*,*N*-dimethylbarbituric acid (1.16 g, 7.46 mmol) and the resulting solution was stirred at 35 °C for 4 h. After cooling to room temperature, the mixture was diluted with $CHCl_3$. The solution was washed with satd Na_2CO_3 aq three times to remove barbituric acid, then dried over Na_2SO_4. Volatiles were removed under reduced pressure and the resulting residue was dissolved in CH_2Cl_2 (2.5 mL). To the solution were added methyl chloroformate (124 μL, 1.61 mmol) and K_2CO_3 (857 mg, 6.2 mmol) in H_2O (2.5 mL) and the resulting biphasic solution was stirred at room temperature. After stirring for 90 min, the mixture was extracted with CH_2Cl_2 and the combined organic extracts were dried over Na_2SO_4. Volatiles were removed under reduced pressure and the resulting residue was purified by silica gel column chromatography (SiO_2, eluent: *n*-hexane/ethyl acetate = 30/1–5/1) to give **7** as a pale yellow oil (309 mg, 0.875 mmol, 71% yield (two steps)). Enantiomeric excess was determined by HPLC analysis (77% ee). IR (neat) *ν* 3334, 3065, 2952, 1714, 1328 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.43 (d, *J* = 8.9 Hz, 2H), 7.36–7.26 (m, 5H), 6.89 (d, *J* = 8.9 Hz, 2H), 5.24 (dd, *J* = 8.6, 4.3 Hz, 1H), 4.93 (br s, 1H), 3.65 (s, 3H), 3.41–3.36 (m, 2H), 2.22–2.08 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 160.2, 157.0, 140.3, 128.9, 128.0, 126.8 (J_{C-F} = 3.6 Hz), 125.6, 124.3 (J_{C-F} = 274.6 Hz), 122.9 (J_{C-F} = 33.4 Hz), 115.7, 78.5, 52.0, 38.6, 38.0; ^{19}F NMR δ −28.5; $[\alpha]_D^{27} = +5.8$ (*c* 0.9, $CHCl_3$); ESI-MS *m*/*z* 376 $[M+Na]^+$; HRMS (ESI-TOF) Anal. Calcd for $C_{18}H_{18}F_3NNaO_3$ *m*/*z* 376.1136 $[M+Na]^+$. Found: 376.1132. Daicel CHIRALCEL OZ-H (ϕ 0.46 cm × 25 cm), 2-propanol/*n*-hexane = 1/9, flow rate 1.0 mL/min, detection 254 nm, t_R = 7.1 min (major), 8.3 min (minor).

4.3.4. Preparation of (*R*)-fluoxetine from 7

To a stirred solution of **7** (265 mg, 0.75 mmol) in THF (10 mL) was added $LiAlH_4$ (57 mg, 1.5 mmol) at 0 °C. After refluxing the resulting suspension for 1 h, the mixture was cooled to 0 °C, then MeOH, H_2O, Celite, and ethyl acetate were added and the resulting suspension was stirred at room temperature for 30 min. The suspension was filtered through a pad of Celite and rinsed with ethyl acetate and the filtrate was concentrated to give a free amine, which was treated with 2 M HCl/MeOH (1.5 mL) at room temperature for 5 min. Then MeOH was removed under reduced pressure and the resulting residue was triturated with AcOEt/*n*-hexane to give (*R*)-fluoxetine·HCl as a colorless solid (234 mg, 0.677 mmol, 90% (two steps), $[\alpha]_D^{24} = -11.9$ (*c* 0.9, $CHCl_3$), specific rotation of enantiopure (*R*)-fluoxetine reported in the literature: $[\alpha]_D^{24} = -13.8$ (*c* 1, $CHCl_3$)[16b]). Other spectroscopic data were in full agreement with the literature.

4.4. Determination of absolute configuration

4.4.1. Preparation of (*R*)-3-(*tert*-butyldimethylsilyloxy)-3-phenylpropanal (TBS protection of 3aa, followed by reduction of the thioamide to an aldehyde)

To a stirred solution of **3aa** (127 mg, 0.486 mmol) in CH_2Cl_2 (5 mL) were added 2,6-lutidine (113 μL, 0.972 mmol) and TBSOTf (168 μL, 0.729 mmol) at 0 °C. The resulting solution was stirred at room temperature for 8 h. The reaction was quenched with satd NH_4Cl aq, and the biphasic mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. Volatiles were removed under reduced pressure and the resulting residue was purified by silica gel column chromatography (SiO_2, eluent: *n*-hexane/AcOEt = 1/0–20/1) to give the TBS ether as a pale yellow oil (180 mg, 0.479 mmol, 99% yield). A flame-dried 20 mL pear-shaped flask was charged with $Cp_2Zr(H)Cl$ (82.4 mg, 0.319 mmol) in a dry box under Ar atmosphere. Toluene (1.5 mL) and the TBS ether (60.0 mg, 0.16 mmol) in toluene (3 mL) were added to the flask at room temperature. After stirring for 90 min, the mixture was cooled to −78 °C and silica gel (82 mg) was added to the cooled reaction mixture. After stirring for

30 min at the same temperature, the resulting suspension was stirred at room temperature for 2 h. The suspension was filtered through a short pad of silica gel and rinsed with CH_2Cl_2, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (SiO_2, eluent: *n*-hexane/ether = 20/1–10/1) to give the title compound as a colorless oil (17.0 mg, 0.0642 mmol, 40% yield). The absolute configuration of the aldehyde was determined to be (*R*) $\{[\alpha]_D^{29} = +58.3$ (*c* 0.72, $CHCl_3)\}$ by comparing the reported specific rotation $\{[\alpha]_D = +64.3$ (*c* 1, $CHCl_3)\}$ in the literature,[23] indicating that the absolute configuration of **3aa** was (*R*). The absolute configuration of other aldol products was deduced to be (*R*) by analogy. The tendency of the specific rotation and HPLC analysis are consistent for all the aldol products.

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