Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2014, **12**, 1009

Copper(II)-catalyzed enantioselective hydrosilylation of halo-substituted alkyl aryl and heteroaryl ketones: asymmetric synthesis of (*R*)-fluoxetine and (*S*)-duloxetine†

Ji-Ning Zhou, Qiang Fang, Yi-Hu Hu, Li-Yao Yang, Fei-Fei Wu, Lin-Jie Xie, Jing Wu* and Shijun Li*

Received 8th November 2013,
Accepted 3rd December 2013

DOI: 10.1039/c3ob42214c

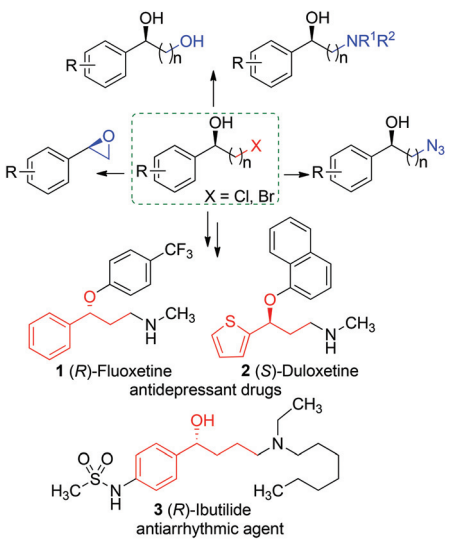
www.rsc.org/obc

A set of reaction conditions has been established to facilitate the non-precious copper-catalyzed enantioselective hydrosilylation of a number of structurally diverse β-, γ- or ε-halo-substituted alkyl aryl ketones and α-, β- or γ-halo-substituted alkyl heteroaryl ketones under air to afford a broad spectrum of halo alcohols in high yields and good to excellent enantioselectivities (up to 99% ee). The developed procedure has been successfully applied to the asymmetric synthesis of antidepressant drugs (*R*)-fluoxetine and (*S*)-duloxetine, which highlighted its synthetic utility.

Introduction

Enantiomerically enriched halo alcohols constitute ubiquitous building blocks for the construction of a variety of structurally versatile compounds, such as chiral diols, amino alcohols, epoxides and azido alcohols (Scheme 1), owing to the versatility conferred by the existence of the halogen that can readily behave as a good leaving group. Also, many biologically active pharmaceuticals or agricultural chemicals have been permitted to be prepared in optically pure form by employing corresponding chiral halo alcohols as the precursors.[1,2] For instance, enantiomerically active γ-halo alcohols can serve as key intermediates in the preparation of (*R*)-fluoxetine **1**[2a,b] or (*S*)-duloxetine **2**,[2c,d] which are important pharmaceuticals for the treatment of psychiatric disorders, such as depression, anxiety, and alcoholism, as well as certain metabolic problems. (*R*)-Ibutilide **3** is a potent class III antiarrhythmic agent, the synthesis of which demands a non-racemic δ-halo alcohol intermediate.[3] Therefore, the development of efficient, economical and practical methodologies for the preparation of structurally diverse chiral halo alcohols has been an appealing objective in organic synthesis for many years.

From both academic and technical points of view, the catalytic asymmetric reduction of halo-substituted ketones as a straightforward approach towards single enantiomer halo alcohols is perhaps among the most attractive, and various strategies have been developed accordingly. In 1987, Corey and co-workers reported the enantioselective borane reduction of α-chloroacetophenone catalyzed by chiral oxazaborolidines to produce (*S*)-2-chlorophenylethanol with up to 97% ee.[4a] Following this significant lead, several catalyst systems for the enantioselective hydroboration of halo ketones have been established.[4b–e] Additionally, some chiral transition metal catalysts, especially those based on rhodium,[5] ruthenium,[5c,6] and iridium,[5c,7] have been exploited and exhibited good to



Scheme 1 Representative examples of biologically active compounds derived from chiral halo alcohols.

College of Material, Chemistry and Chemical Engineering, Hangzhou Normal University, Hangzhou 310036, China. E-mail: jingwubc@hznu.edu.cn, l_shijun@hznu.edu.cn; Fax: (+86)-571-2886-8023

†Electronic supplementary information (ESI) available. See DOI: 10.1039/c3ob42214c

excellent enantioselectivities for the asymmetric transfer hydrogenation of various prochiral α-halo-acetophenone derivatives. Efficient chiral catalysts for the hydrogenation of halo ketones are relatively scarce.[8,9] Noteworthy is the elegant report in 2007 by Noyori *et al.* on the η^6-arene/TsDPEN-Ru(II) catalysts, which allowed for the enantioselective hydrogenation of a series of α-chloro alkyl aryl ketones to chlorohydrins of excellent enantiopurities.[9] With the exception of the need for using noble metal catalysts, the aforementioned studies mainly focused on the stereoselective reduction of α-halo-substituted alkyl aryl ketones, while β-, γ-, and other halo ketonic substrates were seldom involved.

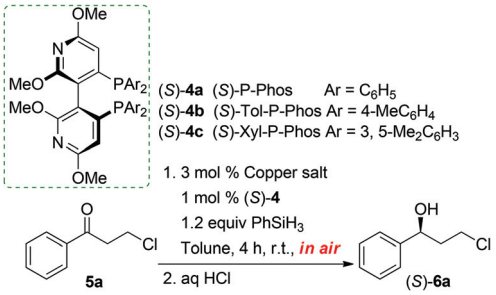
In the past decade, by using stoichiometric amounts of silane as hydride donors, copper-mediated asymmetric reduction of ketones as a desirable tool, leading to a broad range of chiral alcohols, has attracted growing interest, owing to the usage of economically appealing transition metals, the mild reaction conditions, and the operational simplicity.[10,11] Nonetheless, the application of chiral inexpensive metal catalysts in the stereoselective hydrosilylation process for the synthesis of halo alcohols has been relatively unexplored.[12] In 2006, Lipshutz *et al.* described the use of the (DTBM-SEGPHOS)CuH[13] catalyst for effecting the asymmetric hydrosilylation of β-chloropropiophenone in 92% ee at −78 °C.[12c]

Recently, we have established an effective Cu(II)/dipyridylphosphine (Table 1, P-Phos **4a** or Xyl-P-Phos **4c**)[14]/$PhSiH_3$ or PMHS (polymethylhydrosiloxane) system, which was documented to be highly selective (ee up to 99.9%) yet reactive (substrate to ligand ratio up to 100 000) for the catalytic enantioselective hydrosilylation of a diverse assortment of simple ketones[15] as well as 1,4-reduction of β-dehydroamino acid esters[16] under an ambient atmosphere and mild conditions. Herein, we wish to report our endeavors in the application of this catalyst system to the hydrosilylation of a wide range of halo-substituted alkyl aryl and heteroaryl ketones. The reactions proceeded smoothly in air and a broad spectrum of halo alcohols bearing high degrees of enantiopurity became accessible. Furthermore, the developed hydrosilylation methodology has been successfully applied as the key step to the enantioselective synthesis of two frequently used antidepressants, (*R*)-fluoxetine **1**[2b] and (*S*)-duloxetine **2**.[2c,d]

Results and discussion

To initiate our studies, we selected 3-chloro-1-phenylpropan-1-one **5a** as the model substrate and subjected it to a premixed solution of 3 mol% of CuF_2, 1 mol% of (*S*)-**4a** and 1.2 equivalent of hydride resource $PhSiH_3$ in toluene. As shown in entry 1 of Table 1, the reaction was completed in air at room temperature after 4 hours to afford (*S*)-**6a** quantitatively in 88% ee. Next, multifarious Cu(I) or Cu(II) salts were investigated as catalyst precursors in detail (entries 2–13) under a given set of reaction conditions and the results indicated that the extent of conversions or ee values varied considerably as a function of the counter-ion. Consistent with the previous findings,[11c,f]

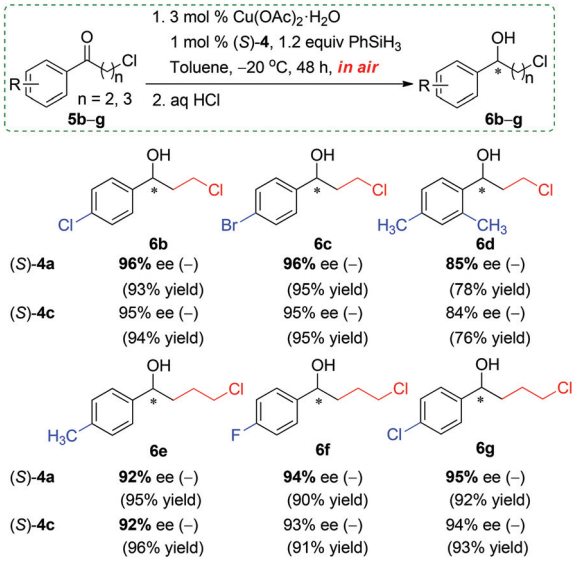
Table 1 Effects of copper salts and chiral ligands on the copper-catalyzed asymmetric hydrosilylation of **5a** in air[a]



Entry	Copper salt	Ligand	Conv[b] (%)	ee[c] (%)
1	CuF_2	(*S*)-**4a**	98	88
2	CuI	(*S*)-**4a**	<5	n.d.[d]
3	CuCl	(*S*)-**4a**	<5	n.d.
4	$CuCl_2$	(*S*)-**4a**	<5	n.d.
5	$CuCl_2{\cdot}2H_2O$	(*S*)-**4a**	<5	n.d.
6	$CuBr_2$	(*S*)-**4a**	13	n.d.
7	Cu(TC)	(*S*)-**4a**	>99	73
8	CuCl + NaBArF	(*S*)-**4a**	99	85
9	$[CuF(PPh_3)_3]{\cdot}2EtOH$	(*S*)-**4a**	95	34
10	$Cu(OTf)_2$	(*S*)-**4a**	<5	n.d.
11	$Cu(acac)_2$	(*S*)-**4a**	<5	n.d.
12	$Cu(OCOCF_3)_2{\cdot}XH_2O$	(*S*)-**4a**	99	80
13	$Cu(OAc)_2{\cdot}H_2O$	(*S*)-**4a**	>99	92
14	$Cu(OAc)_2{\cdot}H_2O$	(*S*)-**4b**	99	88
15	$Cu(OAc)_2{\cdot}H_2O$	(*S*)-**4c**	99	89
16[e]	$Cu(OAc)_2{\cdot}H_2O$	(*S*)-**4a**	99[f]	96
17[e]	$Cu(OAc)_2{\cdot}H_2O$	(*S*)-**4c**	**99**[g]	**99**

[a] Reaction conditions: 51 mg substrate, substrate concentration = 0.1–0.3 M in toluene at 25 °C. [b] The conversions were determined by NMR and GC analysis. [c] The ee values were determined by chiral HPLC analysis. The absolute configuration was determined by comparing the retention times with known data (see the ESI). [d] n.d. = not determined. [e] The reaction was carried out at −20 °C. Reaction time = 48 h. [f] The isolated yield was 94%. [g] The isolated yield was 96%.

the reaction rate largely relied on the choice of halogen in copper salts. Thus, except for the use of CuF_2, all other copper(I) or copper(II) halides such as CuI, CuCl, $CuCl_2$, $CuCl_2{\cdot}2H_2O$ and $CuBr_2$ exhibited disappointing reactivities under otherwise identical conditions (<5% conversion, entries 2–6). With respect to the other investigated copper sources, including Cu(TC), $CuF(PPh_3)_3{\cdot}2EtOH$, $Cu(OTf)_2$ and $Cu(acac)_2$, either poor activities or low to moderate ees were observed. Although promising outcomes were achieved as well by utilizing CuBArF or $Cu(OCOCF_3)_2{\cdot}XH_2O$, $Cu(OAc)_2{\cdot}H_2O$ (entry 13, >99% conv. and 92% ee) appeared to be the most preferable choice because of its substantially low cost and ease of handling. On the other hand, both (*S*)-Tol-P-Phos ((*S*)-**4b**) and (*S*)-Xyl-P-Phos ((*S*)-**4c**) gave comparative levels of activity and asymmetric induction with those of the P-Phos ligand (entries 14 and 15 *vs.* entry 13). Further examination demonstrated that full conversion and up to 99% ee were realized at −20 °C in the presence of (*S*)-**4c** as the chiral ligand simply by prolonging the reaction time to 48 hours (entry 17) and 96% ee was obtained by applying (*S*)-**4a** (entry 16).

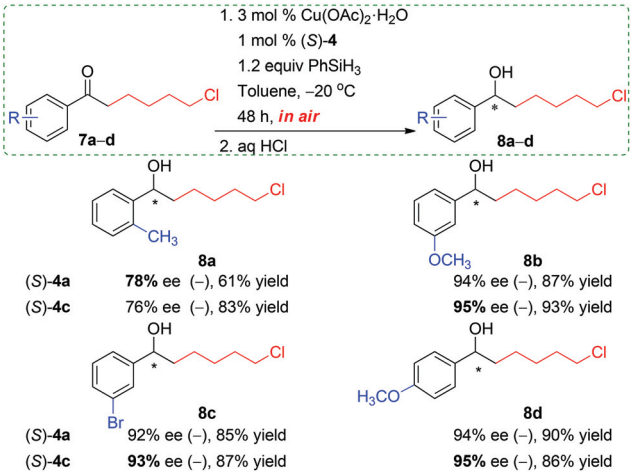


Scheme 2 Cu(II)-catalyzed asymmetric hydrosilylation of β- or γ halo-substituted alkyl aryl ketones **5b–5g** in air.

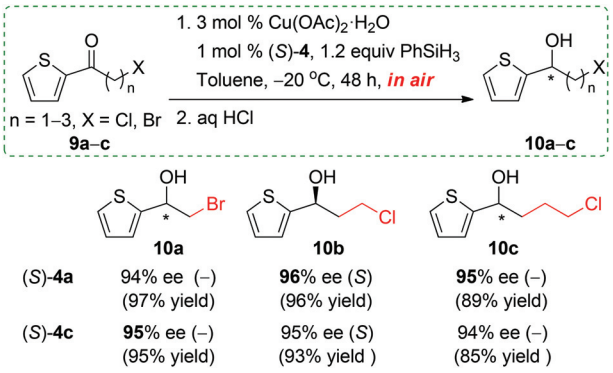
With the optimized conditions in hand, we turned our attention to evaluating the efficiency of the present catalyst system for the asymmetric reduction of a range of other β- or γ halo-substituted alkyl aryl ketones **5b–5g** under an air atmosphere. Gratifyingly, as illustrated in Scheme 2, the complete hydrosilylation of most substrates to the corresponding γ-, or δ-substituted halo alcohols **6b–6g** with good to excellent enantiopurities (84–99% ees) was realized in the presence of (*S*)-**4a** or (*S*)-**4c** as the chiral ligand within 48 h at −20 °C (76–96% yield). The stereoselectivities of the reaction were affected by the positioning of the substituents on the arene ring of ketones. Transformations of substrates with either electron-withdrawing or electron-donating *para*-substituents (**5b**, **5c**, **5e–5g**) proceeded well to furnish the desired alcohols (**6b**, **6c**, **6e–6g**) of 92–96% enantioselectivities in high isolated yields. In contrast, the presence of an *ortho*-substituent (**5d**) resulted in the diminution in enantioselectivities (84–85% ee), possibly due to the bulky group at the *ortho*-position, which blocked the approach of the carbonyl group to the copper hydride.

To access a wide range of halo-substituted alkyl aryl alcohols of high optical purity, we turned to the reactions of several ε-chloro-substituted alkyl aryl ketones **7a–7d**. As the findings in Scheme 3 indicated, the distance between a halo substituent and a carbonyl group did not show a pronounced influence on the outcome of the reactions. Substrates possessing a *meta*- or *para*-substituted electron-rich or electron-deficient arene group all underwent facile reduction under an air atmosphere to give the desired products neatly in consistently high ee values (92–95%, **7b–7d**). Whereas the halo ketone substrate bearing an *ortho*-substituted phenyl group (**7a**) was converted to the corresponding alcohol product of moderate enantiomeric purity (76% or 78% ee).

Despite the wide utility of enantioenriched halo-substituted alkyl heteroaryl alcohols and their derivatives in the



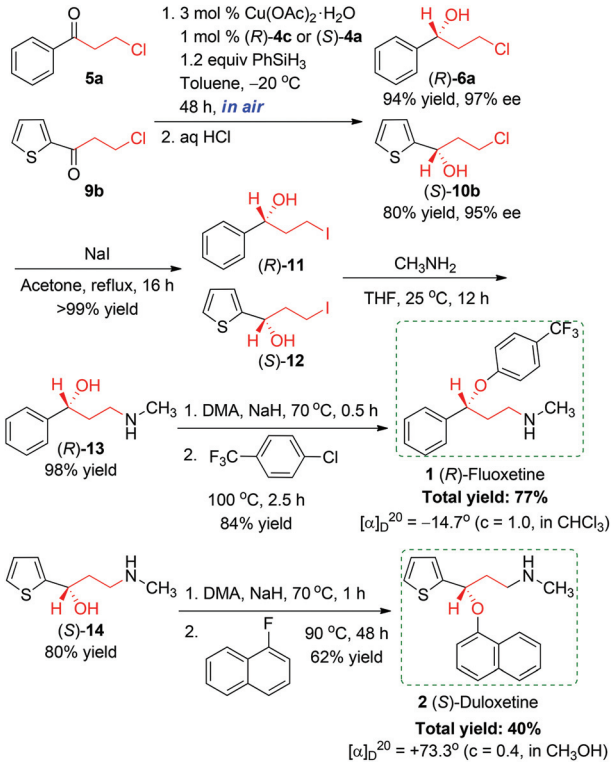
Scheme 3 Cu(II)-catalyzed asymmetric hydrosilylation of ε-halo-substituted alkyl aryl ketones **7a–7d** in air.



Scheme 4 Cu(II)-catalyzed asymmetric hydrosilylation of halo-substituted alkyl heteroaryl ketones **9a–9c** in air.

commercial manufacture of pharmaceuticals,[1,2c,d,4c] the catalytic asymmetric synthesis of halo-substituted alkyl heteroaromatic alcohols has received scant attention and hence remained a challenge. Given the good performance of the present catalyst system in the hydrosilylation of a broad assortment of β-, γ- and ε-halo alkyl aromatic ketones, we were therefore interested in the examination of its general applicability in the stereoselective reduction of halo-substituted alkyl heteroaryl ketones under an air atmosphere and a given set of conditions, and the representative results are summarized in Scheme 4. To our delight, the chiral dipyridylphosphine ligated Cu-H behaved as an efficacious catalyst, rendering high isolated yields (85–97%) and excellent ee values (94–96%) for the reduction of 2-thienyl alkyl ketones with α-, β- or γ-halo substituent (**9a–9c**).

With a practical and economical catalytic method for the highly asymmetric preparation of structurally diverse halo-substituted alcohols available, we turned to applying this methodology to the enantioselective synthesis of significant antidepressant drugs (*R*)-fluoxetine (**1**) and (*S*)-duloxetine (**2**). As the procedure outlined in Scheme 5 indicated, asymmetric



Scheme 5 Asymmetric synthesis of (*R*)-fluoxetine **1** and (*S*)-duloxetine **2**.

hydrosilylation of ketones **5a** and **9b** under the aforementioned optimized conditions proceeded uneventfully in air to furnish the corresponding chloro-substituted alcohols (*R*)-**6a** and (*S*)-**10b** with 97% and 95% ee, respectively. Then, reaction of enantioenriched (*R*)-**6a** or (*S*)-**10b** and saturated sodium iodide in acetone at reflux for 16 h cleanly provided iodo alcohol (*R*)-**11** or (*S*)-**12** (>99% yield). Next, the mixture of iodo alcohol product (*R*)-**11** or (*S*)-**12** and 40% aqueous methylamine in THF was stirred at room temperature for 12 h to afford amine intermediates (*R*)-**13** (98% yield) or (*S*)-**14** (80% yield) after work-up steps. Finally, (*R*)-**13** or (*S*)-**14** reacted with sodium hydride in *N*,*N*-dimethylacetamide (DMA) at 70 °C for 0.5–1 h followed by the treatment of *p*-chlorobenzotrifluoride or 1-fluoronaphthalene to form target chiral product (*R*)-fluoxetine **1** (84% yield) or (*S*)-duloxetine **2** (62% yield).

Conclusion

In summary, the copper-catalyzed asymmetric hydrosilylation of a diverse range of β-, γ- or ε-halo-substituted alkyl aryl ketones and α-, β- or γ-halo substituted alkyl heteroaryl ketones was realized with good to excellent enantioselectivities (up to 99%), leading to a vast array of optically active halo-substituted alcohols, which are important building blocks for the synthesis of numerous biologically active and structurally interesting compounds. The present catalyst system was formed *in situ* from catalytic amounts of copper source $Cu(OAc)_2{\cdot}H_2O$ and optically pure dipyridylphosphine ligand (*S*)-**4** along with the stoichiometric hydride donor $PhSiH_3$ under an air atmosphere. The excellent enantioselectivities and the satisfactory yields observed in these reactions, accompanied by the commercial availability and stability of the ligands and reagents, the mild reaction conditions, as well as the wide substrate scope, make this procedure economical, practical and versatile. In particular, the practical viability of the developed process was evinced by the efficient transformation of enantiomerically enriched halo-substituent alcohol products to the significant antidepressant drugs (*R*)-fluoxetine and (*S*)-duloxetine.

Experimental section

General

^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker advance spectrophotometer (400 or 500 MHz) at room temperature. Chemical shifts (δ) are given in ppm and are referenced to residual solvent peaks. HRMS spectra were recorded at the UCSB mass spectrometry facility using a Micromass VG 70e magnetic sector by the ESI standard methods. Low resolution mass spectra were obtained using an Agilent Technologies 5975C. IR absorption spectra (FT = diffuse reflectance spectroscopy) were recorded for samples loaded as neat films on KBr plates using a Bruker TENSOR27 and only noteworthy absorptions (in cm^{-1}) are listed. Conversions were determined by ^1H NMR and gas chromatographic analyses (Capillary GC, INNOWAX column, 30 m × 0.25 mm, carrier gas, N_2). Enantiomeric excess of the asymmetric hydrosilylation products was determined by chiral HPLC. Gas chromatographic analyses were conducted using a Fuli 9790 with an FID detector. HPLC analyses were performed using an Agilent 1200 with a UV detector. Optical rotations were measured using a Perkin-Elmer Model 341 polarimeter in a 10 cm cell. Optically pure P-Phos (**4a**) and Xyl-P-Phos (**4c**) were purchased from commercial sources. (*S*)-Tol-P-Phos (**4b**) was prepared according to a previously reported procedure.[17] Substrates were prepared and characterized according to the literature procedures.[18,19] All solvents were purified and dried according to standard methods prior to use. Copper salts, phenylsilane, and some ketone substrates were purchased from Aldrich, Alfa Aesar or Acros Organics and used as received without further purification unless otherwise stated.

General procedure for the catalytic asymmetric hydrosilylation reaction in air (Table 1, entry 16, 3-chloro-1-phenylpropan-1-one, 5a)[15b]

$Cu(OAc)_2{\cdot}H_2O$ (1.8 mg, 9.0×10^{-3} mmol) and (*S*)-P-Phos (**4a**, 1.9 mg, 3.0×10^{-3} mmol) were weighed under air and placed in a 25 mL round-bottomed flask equipped with a magnetic stirring bar. Toluene (1.0 mL) was added and the mixture was stirred at room temperature for 20 min. To the solution, phenylsilane (44.9 μL, 3.6×10^{-1} mmol) in toluene (0.5 mL) was added and the mixture was cooled to −20 °C. A solution of

3-chloro-1-phenylpropan-1-one (**5a**, 50.6 mg, 0.3 mmol) in toluene (0.5 mL) was added under vigorous stirring, and the flask was stoppered. The reaction was monitored by TLC. Upon completion, the reaction mixture was treated with 10% HCl (2.0 mL) and the organic product was extracted with ether (3 × 3 mL). The combined extract was washed with water, dried with anhydrous sodium sulfate, filtered through a plug of silica gel and concentrated *in vacuo* to give the crude product. The conversion and the enantiomeric excess of the product (*S*)-3-chloro-1-phenylpropan-1-ol (**6a**) were determined by NMR, GC (Capillary GC, INNOWAX column, 30 m × 0.25 mm, carrier gas, N_2) and chiral HPLC (25 cm × 4.6 mm Chiralcel OD column) analysis to be 99% and 96%, respectively. The pure product was isolated (48 mg, 94% yield) by column chromatography (ethyl acetate–petroleum ether = 1 : 10).

(*S*)-3-Chloro-1-phenylpropan-1-ol (6a).[15b] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.99 (br, 1H), 2.09–2.28 (m, 2H), 3.54–3.60 (m, 1H), 3.72–3.78 (m, 1H), 4.93–4.97 (m, 1H), 7.28–7.39 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.43, 41.79, 71.33, 125.81, 127.97, 128.71, 143.70. IR (thin film): ν_{max} (cm^{-1}) = 3391, 2955, 2925, 2854, 1493, 1455, 1377, 1285, 1135, 1055, 763, 700. MS (EI, *m*/*z*, relative intensity): 172 (M^+, 1), 170 (M^+, 3), 107 (100), 91 (5), 63 (4), 51 (9), 39 (4).

The conversion was determined by capillary GC with a 30 m × 0.25 mm INNOWAX column; 180 °C; isothermal; t_R (**5a**) = 2.62 min; t_R (**6a**) = 13.28 min. The ee value was determined by chiral HPLC analysis with a 25 cm × 4.6 mm Chiralcel OD column (eluent, 2-propanol–hexane 2 : 98; flow rate: 1.0 mL min^{-1}; detection: 254 nm light); t_R (*R*) = 19.6 min; t_R (*S*) = 24.2 min.

(−)-3-Chloro-1-(4-chlorophenyl)propan-1-ol (6b).[20] ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.00–2.24 (m, 3H), 3.51–3.57 (m, 1H), 3.71–3.77 (m, 1H), 4.94 (m, 1H), 7.26–7.35 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.43, 41.54, 70.67, 127.17, 128.81, 133.59, 142.20. IR (thin film): ν_{max} (cm^{-1}) = 3385, 2962, 2925, 1596, 1491, 1430, 1136, 1091, 1055, 925, 827, 736, 699. MS (EI, *m*/*z*, relative intensity): 206 (M^+, 4), 204 (M^+, 6), 169 (1), 167 (1), 141 (100), 133 (1), 77 (49), 63 (5), 51 (8).

The conversion was determined by capillary GC with a 30 m × 0.25 mm INNOWAX column; 200 °C; isothermal; t_R (**5b**) = 2.99 min; t_R (**6b**) = 18.63 min. The ee value was determined by chiral HPLC analysis with a 25 cm × 4.6 mm Chiralcel OD-H column (eluent, 2-propanol–hexane 2 : 98; flow rate: 1.0 mL min^{-1}; detection: 254 nm light); t_R (major) = 18.39 min; t_R (minor) = 22.72 min. $[\alpha]_D^{20}$ = −15.6 (*c* = 1.0 in $CHCl_3$).

(−)-1-(4-Bromophenyl)-3-chloropropan-1-ol (6c).[21] ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.00–2.23 (m, 3H), 3.51–3.57 (m, 1H), 3.70–3.77 (m, 1H), 4.91–4.94 (m, 1H), 7.23–7.50 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.36, 41.57, 70.66, 121.69, 127.53, 131.77, 142.72. IR (thin film): ν_{max} (cm^{-1}) = 3386, 2959, 2924, 1592, 1486, 1407, 1287, 1104, 1070, 927, 823, 729, 663. MS (EI, *m*/*z*, relative intensity): 250 (M^+, 8), 248 (M^+, 6), 217 (1), 215 (3), 185 (100), 157 (17), 105 (6), 91 (5), 77 (57), 63 (7), 51 (12).

The conversion was determined by capillary GC with a 30 m × 0.25 mm INNOWAX column; 180 °C; isothermal; t_R (**5c**) = 7.00 min; t_R (**6c**) = 25.32 min. The ee value was determined by chiral HPLC analysis with a 25 cm × 4.6 mm Chiralcel OD-H column (eluent, 2-propanol–hexane 2 : 98; flow rate: 1.0 mL min^{-1}; detection: 254 nm light); t_R (major) = 20.39 min; t_R (minor) = 24.89 min. $[\alpha]_D^{20}$ = −13.3 (*c* = 1.0 in $CHCl_3$).

(−)-3-Chloro-1-(2,4-dimethylphenyl)propan-1-ol (6d).[22] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.94 (br, 1H), 2.02–2.12 (m, 2H), 2.30 (s, 6H), 3.59–3.64 (m, 1H), 3.77–3.82 (m, 1H), 5.12–5.15 (m, 1H), 6.96–7.34 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.83, 20.96, 40.50, 42.09, 67.37, 125.03, 127.05, 131.31, 134.36, 137.15, 138.95. IR (thin film): ν_{max} (cm^{-1}) = 3392, 2955, 2925, 2855, 1615, 1594, 1456, 1283, 1134, 1052, 821, 738, 698. MS (EI, *m*/*z*, relative intensity): 163 ($[M - Cl]^+$, 3), 91 (100), 77 (37), 41 (11).

The conversion was determined by capillary GC with a 30 m × 0.25 mm INNOWAX column; 180 °C; isothermal; t_R (**5d**) = 3.52 min; t_R (**6d**) = 23.97 min. The ee value was determined by chiral HPLC analysis with a 25 cm × 4.6 mm Chiralcel AD column (eluent, 2-propanol–hexane 2 : 98; flow rate: 1.0 mL min^{-1}; detection: 254 nm light); t_R (major) = 19.28 min; t_R (minor) = 15.93 min. $[\alpha]_D^{20}$ = −40.5 (*c* = 1.0 in $CHCl_3$).

(−)-4-Chloro-1-*p*-tolylbutan-1-ol (6e).[23] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.77–1.93 (m, 5H), 2.34 (s, 3H), 3.53–3.55 (m, 2H), 4.65–4.67 (m, 1H), 7.15–7.36 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.14, 29.02, 36.12, 45.02, 73.79, 125.79, 129.27, 137.50, 141.36. IR (thin film): ν_{max} (cm^{-1}) = 3371, 2955, 2924, 2853, 1431, 1378, 1135, 818, 741, 699. MS (EI, *m*/*z*, relative intensity): 163 ($[M - Cl]^+$, 15), 149 (1), 91 (100), 77 (23), 41 (8).

The conversion was determined by capillary GC with a 30 m × 0.25 mm INNOWAX column; 180 °C; isothermal; t_R (**5e**) = 4.85 min; t_R (**6e**) = 3.34 min. The ee value was determined by chiral HPLC analysis with a 25 cm × 4.6 mm Chiralcel OD-H column (eluent, 2-propanol–hexane 2 : 98; flow rate: 1.0 mL min^{-1}; detection: 254 nm light); t_R (major) = 22.34 min; t_R (minor) = 28.14 min. $[\alpha]_D^{20}$ = −34.2 (*c* = 1.0 in $CHCl_3$).

(−)-4-Chloro-1-(4-fluorophenyl)butan-1-ol (6f).[24] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.77–1.92 (m, 5H), 3.54–3.56 (m, 2H), 4.69–4.70 (m, 1H), 7.02–7.06 (m, 2H), 7.30–7.36 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.87, 36.27, 44.91, 73.29, 115.42 (d, $J_{C,F}$ = 21.3 Hz), 127.45 (d, $J_{C,F}$ = 7.9 Hz), 140.06 (d, $J_{C,F}$ = 2.8 Hz), 162.34 (d, $J_{C,F}$ = 244.1 Hz). IR (thin film): ν_{max} (cm^{-1}) = 3386, 2957, 2926, 1605, 1510, 1445, 1223, 1157, 1067, 837, 726, 651. MS (EI, *m*/*z*, relative intensity): 165 ($[M - Cl]^+$, 2), 125 (100), 109 (8), 97 (42), 77 (14), 63 (2), 63 (6), 41 (6).

The conversion was determined by capillary GC with a 30 m × 0.25 mm INNOWAX column; 180 °C; isothermal; t_R (**5f**) = 9.84 min; t_R (**6f**) = 2.73 min. The ee value was determined by chiral HPLC analysis with a 25 cm × 4.6 mm Chiralcel OD-H column (eluent, 2-propanol–hexane 2 : 98; flow rate: 1.0 mL min^{-1}; detection: 254 nm light); t_R (major) = 18.72 min; t_R (minor) = 21.30 min. $[\alpha]_D^{20}$ = −39.8 (*c* = 1.0 in $CHCl_3$).

(−)-4-Chloro-1-(4-chlorophenyl)butan-1-ol (6g).[25] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.78–1.93 (m, 5H), 3.55–3.59 (m, 2H), 4.70–4.72 (m, 1H), 7.28–7.34 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.75, 36.19, 44.85, 73.21, 127.18, 128.70, 133.38, 142.78. IR (thin film): ν_{max} (cm^{-1}) = 3396, 2956, 2925, 2870, 1596, 1491, 1445, 1297, 1136, 1090, 1014, 830, 728, 699, 649.

MS (EI, *m*/*z*, relative intensity): 183 ([M − Cl]$^+$, 14), 181 ([M − Cl]$^+$, 42), 147 (100), 139 (98), 125 (11), 115 (23), 105 (23), 77 (24), 63 (10), 51 (11).

The conversion was determined by capillary GC with a 30 m × 0.25 mm INNOWAX column; 200 °C; isothermal; t_R (**5g**) = 4.11 min; t_R (**6g**) = 3.40 min. The ee value was determined by chiral HPLC analysis with a 25 cm × 4.6 mm Chiralcel OD-H column (eluent, 2-propanol–hexane 2 : 98; flow rate: 1.0 mL min^{-1}; detection: 254 nm light); t_R (major) = 19.66 min; t_R (minor) = 23.71 min. $[\alpha]_D^{20}$ = –34.3 (*c* = 1.0 in $CHCl_3$).

(−)-6-Chloro-1-*o*-tolylhexan-1-ol (8a). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37–1.53 (m, 4H), 1.67–1.84 (m, 5H), 2.34 (s, 3H), 3.50–3.53 (m, 2H), 4.90–4.94 (m, 1H), 7.12–7.46 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.08, 25.31, 26.81, 32.54, 37.84, 45.04, 70.53, 125.08, 126.30, 127.19, 130.40, 134.39, 142.88. IR (thin film): ν_{max} (cm^{-1}) = 3385, 2936, 2860, 1488, 1461, 1379, 1181, 758, 728, 650. MS (EI, *m*/*z*, relative intensity): 228 (M$^+$, 0.7), 226 (M$^+$, 2), 121 (100), 105 (5), 77 (12), 51 (1), 41 (5). HRMS (ESI) Calcd for $C_{13}H_{19}ClNaO$ 249.1019; Found 249.1012 [M + Na]$^+$.

The conversion was determined by capillary GC with a 30 m × 0.25 mm INNOWAX column; 220 °C; isothermal; t_R (**7a**) = 6.85 min; t_R (**8a**) = 11.80 min. The ee value was determined by chiral HPLC analysis with a 25 cm × 4.6 mm Chiralcel OD-H column (eluent, 2-propanol–hexane 2 : 98; flow rate: 1.0 mL min^{-1}; detection: 254 nm light); t_R (major) = 17.92 min; t_R (minor) = 20.49 min. $[\alpha]_D^{20}$ = –45.8 (*c* = 1.0 in $CHCl_3$).

(−)-6-Chloro-1-(3-methoxyphenyl)hexan-1-ol (8b).[26] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (m, 4H), 1.67–1.79 (m, 4H), 1.97 (br, 1H), 3.49–3.52 (m, 2H), 3.80 (s, 3H), 4.63 (m, 1H), 6.80–7.27 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.09, 26.77, 32.52, 38.80, 45.03, 55.24, 74.41, 111.40, 112.96, 118.20, 129.50, 146.53, 159.78. IR (thin film): ν_{max} (cm^{-1}) = 3407, 2936, 2859, 1601, 1586, 1487, 1456, 1316, 1156, 1045, 877, 785, 746, 700, 649. MS (EI, *m*/*z*, relative intensity): 244 (M$^+$, 11), 242 (M$^+$, 4), 137 (100), 121 (5), 109 (78), 77 (20), 41 (7).

The conversion was determined by capillary GC with a 30 m × 0.25 mm INNOWAX column; 200 °C; isothermal; t_R (**7b**) = 16.92 min; t_R (**8b**) = 25.22 min. The ee value was determined by chiral HPLC analysis with a 25 cm × 4.6 mm Chiralcel OB-H column (eluent, 2-propanol–hexane 5 : 95; flow rate: 1.0 mL min^{-1}; detection: 254 nm light); t_R (major) = 31.10 min; t_R (minor) = 39.12 min. $[\alpha]_D^{20}$ = –15.4 (*c* = 1.0 in $CHCl_3$).

(−)-1-(3-Bromophenyl)-6-chlorohexan-1-ol (8c).[27] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29–1.48 (m, 4H), 1.67–1.81 (m, 4H), 1.90 (br, 1H), 3.50–3.53 (m, 2H), 4.65–4.68 (m, 1H), 7.19–7.25 (m, 2H), 7.39–7.53 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.0, 26.7, 32.5, 38.9, 45.0, 73.8, 122.6, 124.5, 129.0, 130.1, 130.6, 147.1. IR (thin film): ν_{max} (cm^{-1}) = 3405, 2930, 2862, 1600, 1582, 1455, 1322, 1045, 876, 780, 750, 649. MS (EI, *m*/*z*, relative intensity): 292 (M$^+$, 19), 290 (M$^+$, 15), 257 ([M − Cl]$^+$, 1), 255 ([M − Cl]$^+$, 1), 187 (100), 185 (100), 159 (55), 157 (62), 77 (100), 41 (40).

The conversion was determined by capillary GC with a 30 m × 0.25 mm J & W Scientific INNOWAX column; 230 °C; isothermal; t_R (**7c**) = 14.48 min; t_R (**8c**) = 4.01 min. The ee value was determined by chiral HPLC analysis with a 25 cm × 4.6 mm Daicel Chiralcel OB-H column (eluent, 2-propanol–hexane 5 : 95; flow rate: 1.0 mL min^{-1}; detection: 254 nm light); t_R (major) = 14.4 min; t_R (minor) = 18.26 min. $[\alpha]_D^{20}$ = –16.8 (*c* = 1.0 in $CHCl_3$).

(−)-6-Chloro-1-(4-methoxyphenyl)hexan-1-ol (8d).[27] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43–1.47 (m, 4H), 1.72–1.82 (m, 5H), 3.49–3.53 (m, 2H), 3.80 (s, 3H), 4.60–4.63 (m, 1H), 6.87–6.89 (m, 2H), 7.25–7.27 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.18, 26.77, 32.52, 38.73, 45.07, 55.31, 74.09, 113.84, 127.14, 136.90, 159.03. IR (thin film): ν_{max} (cm^{-1}) = 3392, 2935, 2859, 1612, 1585, 1512, 1443, 1247, 1175, 1035, 832, 731, 649. MS (EI, *m*/*z*, relative intensity): 207 ([M − Cl]$^+$, 6), 147 (100), 121 (34), 91 (43), 77 (13), 41 (12).

The conversion was determined by capillary GC with a 30 m × 0.25 mm INNOWAX column; 220 °C; isothermal; t_R (**7d**) = 23.48 min; t_R (**8d**) = 8.98 min. The ee value was determined by chiral HPLC analysis with a 25 cm × 4.6 mm Chiralcel AD-H column (eluent, 2-propanol–hexane 5 : 95; flow rate: 1.0 mL min^{-1}; detection: 254 nm light); t_R (major) = 28.50 min; t_R (minor) = 25.98 min. $[\alpha]_D^{20}$ = –53.5 (*c* = 1.0 in $CHCl_3$).

(−)-2-Bromo-1-(thiophen-2-yl)ethanol (10a).[28] ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.88 (br, 1H), 3.60–3.70 (m, 2H), 5.14–5.17 (m, 1H), 6.98–7.30 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.47, 70.00, 124.73, 125.39, 126.95, 143.78. IR (thin film): ν_{max} (cm^{-1}) = 3406, 2958, 2925, 2854, 1437, 1419, 1378, 1219, 1065, 850, 703, 657. MS (EI, *m*/*z*, relative intensity): 208 (M$^+$, 5), 206 (M$^+$, 5), 126 (2), 113 (100), 85 (37), 45 (14).

The conversion was determined by capillary GC with a 30 m × 0.25 mm INNOWAX column; 180 °C; isothermal; t_R (**9a**) = 8.98 min; t_R (**10a**) = 15.13 min. The ee value was determined by chiral HPLC analysis with a 25 cm × 4.6 mm Chiralcel OJ-H column (eluent, 2-propanol–hexane 5 : 95; flow rate: 1.0 mL min^{-1}; detection: 254 nm light); t_R (major) = 27.63 min; t_R (minor) = 35.83 min. $[\alpha]_D^{20}$ = –32.3 (*c* = 1.0 in $CHCl_3$).

(*S*)-3-Chloro-1-(thiophen-2-yl)propan-1-ol (10b).[29] ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.16–2.36 (m, 3H), 3.55–3.60 (m, 1H), 3.71–3.77 (m, 1H), 5.19–5.21 (m, 1H), 6.97–7.28 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.43, 41.46, 67.15, 124.13, 124.99, 126.80, 147.42. IR (thin film): ν_{max} (cm^{-1}) = 3399, 2955, 2925, 2854, 1458, 1377, 1307, 1135, 1063, 852, 699, 649. MS (EI, *m*/*z*, relative intensity): 179 (M$^+$, 0.7), 177 (M$^+$, 3), 163 (1), 91 (100), 85 (8), 77 (98), 45 (86).

The conversion was determined by capillary GC with a 30 m × 0.25 mm INNOWAX column; 180 °C; isothermal; t_R (**9b**) = 3.69 min; t_R (**10b**) = 16.43 min. The ee value was determined by chiral HPLC analysis with a 25 cm × 4.6 mm Chiralcel OD-H column (eluent, 2-propanol–hexane 2 : 98; flow rate: 1.0 mL min^{-1}; detection: 254 nm light); t_R (*S*) = 28.23 min; t_R (*R*) = 32.22 min. $[\alpha]_D^{20}$ = –32.3 (*c* = 1.0 in $CHCl_3$).

(−)-4-Chloro-1-(thiophen-2-yl)butan-1-ol (10c).[23] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.82–2.03 (m, 4H), 2.13 (br, 1H), 3.56–3.61 (m, 2H), 4.94–4.96 (m, 1H), 6.96–7.27 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.92, 36.44, 44.87, 69.70, 123.92, 124.82, 126.76, 148.23. IR (thin film): ν_{max} (cm^{-1}) = 3414, 3051, 2956, 2925, 2869, 1665, 1443, 1431, 1311, 1134, 1069, 853, 786, 699,

650. MS (EI, *m*/*z*, relative intensity): 154 ([M − Cl]$^+$, 94), 111 (100), 97 (34), 84 (20), 58 (6).

The conversion was determined by capillary GC with a 30 m × 0.25 mm INNOWAX column; 180 °C; isothermal; t_R (**9c**) = 15.54 min; t_R (**10c**) = 4.67 min. The ee value was determined by chiral HPLC analysis with a 25 cm × 4.6 mm Chiralcel OD-H column (eluent, 2-propanol–hexane 2 : 98; flow rate: 1.0 mL min^{-1}; detection: 254 nm light); t_R (major) = 40.84 min; t_R (minor) = 62.85 min. $[\alpha]_D^{20}$ = −21.4 (*c* = 1.0 in $CHCl_3$).

Procedure for the synthesis of (*R*)-fluoxetine (1)[2b]

The nonracemic alcohol (*R*)-**6a** was furnished *via* the copper-catalyzed asymmetric hydrosilylation of **5a** (505.9 mg, 3.0 mmol) under the aforementioned conditions in 94% yield (481 mg) and 97% ee. Then, a solution of (*R*)-3-chloro-1-phenyl-1-propanol (481 mg, 2.8 mmol) in 50 mL of acetone that had been saturated with sodium iodide was refluxed for 16 h. The acetone was removed under reduced pressure. Product isolation (water, ether, water, brine, Na_2SO_4) provided nearly homogeneous product (*R*)-**11** (738.7 mg, >99% yield) as a light red oil that was used without further purification. An analytical sample was prepared by recrystallization from hexane–ether to provide white crystals with mp 55–56 °C.

A solution of (*R*)-3-iodo-1-phenyl-1-propanol (738.7 mg, 2.8 mmol) and methylamine (2.2 mL of a 40% solution in water, 28 mmol) in 15 mL of THF was stirred at room temperature for 12 h. The solvent was removed under reduced pressure and then brine and 2 mL of 2 N sodium hydroxide was added. Product isolation (ether, brine, Na_2SO_4) provided homogeneous (*R*)-3-(methylamino)-1-phenyl-1-propanol ((*R*)-**13**, 453.3 mg, 98% yield) as an oil.

A mixture of (*R*)-3-(methylamino)-1-phenyl-1-propanol (453.3 mg, 2.7 mmol) and sodium hydride (677 mg of a 60% dispersion in oil, 28.2 mmol; oil removed with hexane) in 15 mL of dimethylacetamide was heated to 70 °C for 0.5 h. *p*-Fluorobenzotrifluoride (487.5 mg, 2.7 mmol) was added and the reaction was heated at 93 °C for 2.5 h. After the mixture cooled to room temperature, product isolation (water, ether, water, brine, Na_2SO_4) and flash chromatography [silica gel, methanol/methylene chloride/ammonium hydroxide (10/100/l)] provided homogeneous (*R*)-fluoxetine as an oil (634.7 mg, 84% yield).

(*R*)-Fluoxetine (1).[2b] ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.00–2.04 (m, 1H), 2.18–2.23 (m, 1H), 2.44 (s, 3H), 2.73–2.77 (m, 2H), 5.29–5.32 (m, 1H), 6.89–7.44 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.34, 38.57, 48.15, 78.56, 115.74, 125.76, 126.69, 126.73, 126.81, 127.86, 128.81, 140.95, 160.48. IR (thin film): ν_{max} (cm^{-1}) = 3032, 2927, 2852, 2797, 1615, 1517, 1454, 1328, 1251, 1112, 1068, 1009, 835, 756, 701, 637. MS (EI, *m*/*z*, relative intensity): 309 (M$^+$, 2), 251 (1), 162 (9), 145 (6), 104 (12), 44 (100). $[\alpha]_D^{20}$ = −14.7 (*c* = 1.0 in $CHCl_3$), Literature data: $[\alpha]_D^{23}$ = −13.8 (*c* = 1.0, $CHCl_3$).

Procedure for the synthesis of (*S*)-duloxetine (2)[2c,e]

The nonracemic alcohol (*S*)-**10b** was furnished *via* the copper-catalyzed asymmetric hydrosilylation of **9b** (524 mg, 3.0 mmol) under the aforementioned conditions in 80% yield (423 mg) and 95% ee. Then, a mixture of (*S*)-3-chloro-1-(thiophen-2-yl)-propan-1-ol (423 mg, 2.4 mmol) and NaI in saturated acetone solution (50 mL), protected from light, was refluxed for 16 h. The reaction mixture was filtered to remove the precipitated NaCl and concentrated *in vacuo*. The residue was dissolved in water (30 mL) and extracted with Et_2O (3 × 20 mL). The combined extract was washed with sat NaCl, dried with $MgSO_4$ to yield (*S*)-**12** (642 mg, >99% yield) as a yellow oil. GC purity was 100%, hence (*S*)-**12** was used without further purification.

A solution of (*S*)-**12** (642 mg, 2.4 mmol) in THF (15 mL) was mixed with methylamine (40% aqueous, 2.0 mL, 24 mmol). The mixture was stirred at room temperature under a N_2 atmosphere for 12 h. After the reaction mixture was treated with 5 mol L^{-1} NaOH (2 mL) and then concentrated *in vacuo*, water (15 mL) was added, and the mixture was extracted with Et_2O (3 × 20 mL). The combined extracts were washed with saturated brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography (CH_2Cl_2–MeOH–NH_4OH, 40 : 10 : 1) to yield (*S*)-**14** in 80% yield (328.8 mg).

To NaH (456 mg, 19 mmol) suspended in pentane (6 mL) and dimethylacetamide (8 mL), was added a solution of (*S*)-**14** (328.8 mg, 1.9 mmol) in dimethylacetamide (8 mL), and the mixture was heated to 60–70 °C for 1 h. When the solution became clear, 1-fluoronaphthalene (277.7 mg, 1.9 mmol) was added. The temperature was raised to 90 °C, and the reaction was stirred for an additional 48 h. The mixture was poured into water (40 mL), and extracted with Et_2O (3 × 20 mL). The extract was washed with saturated brine, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2–MeOH–NH_4OH, 100 : 10 : 1) to afford (*S*)-duloxetine (350 mg) in 62% yield.

(*S*)-Duloxetine (2).[2c,e] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.75 (br, 1H), 2.20–2.24 (m, 1H), 2.42 (s, 3H), 2.44–2.48 (m, 1H), 2.80–2.84 (m, 2H), 5.76–5.79 (m, 1H), 6.84–7.05 (m, 3H), 7.19–7.49 (m, 5H), 7.76–7.78 (m, 1H), 8.34–8.36 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.58, 39.00, 48.34, 74.74, 106.98, 120.64, 122.17, 124.62, 124.77, 125.31, 125.78, 126.11, 126.38, 126.63, 127.54, 134.58, 145.21, 153.34. IR (thin film): ν_{max} (cm^{-1}) = 3052, 2927, 2846, 2793, 1595, 1578, 1462, 1397, 1236, 1177, 1064, 791, 771, 731. MS (EI, *m*/*z*, relative intensity): 297 (M$^+$, 1), 144 (94), 115 (100), 89 (14), 72 (9), 28 (8). $[\alpha]_D^{20}$ = +73.3 (*c* = 0.4, CH_3OH). Literature data: $[\alpha]_D^{22}$ = +75 (*c* = 1.0, CH_3OH).

Acknowledgements

We thank the National Natural Science Foundation of China (21172049, 91127010, 21032003, 21072039), the Program for Changjiang Scholars and Innovative Research Team in Chinese University (IRT 1231), the Zhejiang Provincial Natural Science Foundation of China (LZ13B030001), the Public

Welfare Technology and Application Program of Zhejiang Province (2010C31042) and the Special Funds for Key Innovation Team of Zhejiang Province (2010R50017) for generous financial support of this research.

Notes and references

1 For reviews, see: (*a*) B. A. Astelford and L. O. Weigel, in *Chirality in Industry II*, ed. A. N. Collins, Wiley-VCH, New York, 1997, pp. 99–120; (*b*) *Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions*, ed. H.-U. Blaser and E. Schmidt, Wiley-VCH, Weinheim, Germany, 2004; (*c*) M. Breuer, K. Ditrich, T. Habicher, B. Hauer, M. Keβeler, R. Stürmer and T. Zelinski, *Angew. Chem., Int. Ed.*, 2004, **43**, 788–824; (*d*) V. Farina, J. T. Reeves, C. H. Senanayake and J. J. Song, *Chem. Rev.*, 2006, **106**, 2734–2793.

2 For selected examples, see: (*a*) D. W. Robertson, J. H. Krushinski, R. W. Fuller and J. D. Leander, *J. Med. Chem.*, 1988, **31**, 1412–1417; (*b*) E. J. Corey and G. A. Reichard, *Tetrahedron Lett.*, 1989, **30**, 5207–5210; (*c*) H.-L. Liu, B. H. Hoff and T. Anthonsen, *Chirality*, 2000, **12**, 26–29; (*d*) A. Kamal, M. S. Malik, A. A. Shaik and S. Azeeza, *J. Mol. Catal. B: Enzym.*, 2009, **58**, 132–137; (*e*) I. Santiago, A. Mili and L. Anita, *WO* 2006/099433 A1, 2006; (*f*) A. Hashimoto, A. E. Jacobson, R. B. Rothman, C. M. Dersch, C. George, J. L. Flippen-Anderson and K. C. Rice, *Bioorg. Med. Chem.*, 2002, **10**, 3319–3329; (*g*) X. X. Xu, R. Fu, J. Chen, S. W. Che and X. Bai, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 101–104; (*h*) A. F. Harms, W. Hespe, W. T. Nauta, R. F. Rekker, H. Timmerman and J. de Vries, *Drug Des.*, 1976, **6**, 1–80; (*i*) K. Tanaka, M. Katsurada, F. Ohno, Y. Shiga and M. Oda, *J. Org. Chem.*, 2000, **65**, 432–437; (*j*) K. B. Hansen, J. R. Chilenski, R. Desmond, P. N. E. Devine, J. J. Grabowski, R. Heid, M. Kubryk, D. J. Mathre and R. Varsolona, *Tetrahedron: Asymmetry*, 2003, **14**, 3581–3587; (*k*) K. Mizuno, M. Sawa, H. Harada, I. Taoka, H. Yamashita, M. Oue, H. Tsujiuchi, Y. Arai, S. Suzuki, Y. Furutani and S. Kato, *Bioorg. Med. Chem.*, 2005, **13**, 855–868.

3 M. P. Gamble, A. R. C. Smith and M. Wills, *J. Org. Chem.*, 1998, **63**, 6068–6071.

4 Examples of catalytic asymmetric hydroboration of halo ketones, see: (*a*) E. J. Corey, R. K. Bakshi and S. Shibata, *J. Am. Chem. Soc.*, 1987, **109**, 5553–5554; (*b*) E. J. Corey, R. K. Bakshi, S. Shibata, C.-P. Chen and V. K. Singh, *J. Am. Chem. Soc.*, 1987, **109**, 7925–1926; (*c*) E. J. Corey and C. J. Helal, *Angew. Chem., Int. Ed.*, 1998, **37**, 1986–2012; (*d*) B. T. Cho, *Aldrichimica Acta*, 2002, **35**, 3–16; (*e*) J. Y. L. Chung, R. Cvetovich, J. Amato, J. C. McWilliams, R. Reamer and L. DiMichele, *J. Org. Chem.*, 2005, **70**, 3592–3601.

5 Examples of Rh-catalyzed asymmetric transfer hydrogenation of α-halo-acetophenone derivatives, see: (*a*) T. Hamada, T. Torii, K. Izawa, R. Noyori and T. Ikariya, *Org. Lett.*, 2002, **4**, 4373–4376; (*b*) T. Hamada, T. Torii, T. Onishi, K. Izawa and T. Ikariya, *J. Org. Chem.*, 2004, **69**, 7391–7394; (*c*) F. Wang, H. Liu, L. Cun, J. Zhu, J. Deng and Y. Jiang, *J. Org. Chem.*, 2005, **70**, 9424–9429; (*d*) D. S. Matharu, D. J. Morris, A. M. Kawamoto, G. J. Clarkson and M. Wills, *Org. Lett.*, 2005, **7**, 5489–5491.

6 Examples of Ru-catalyzed asymmetric transfer hydrogenation of α-halo-acetophenone derivatives, see: (*a*) D. J. Bayston, C. B. Travers and M. E. C. Polywka, *Tetrahedron: Asymmetry*, 1998, **9**, 2015–2018; (*b*) D. J. Cross, J. A. Kenny, I. Houson, L. Campbell, T. Walsgrovec and M. Wills, *Tetrahedron: Asymmetry*, 2001, **12**, 1801–1806; (*c*) Y. Ma, H. Liu, L. Chen, X. Cui, J. Zhu and J. Deng, *Org. Lett.*, 2003, **5**, 2103–2106; (*d*) D. J. Morris, A. M. Hayes and M. Wills, *J. Org. Chem.*, 2006, **71**, 7035–7044.

7 Example of Ir-catalyzed asymmetric transfer hydrogenation of α-halo-acetophenone derivatives, see: O. Soltani, M. A. Ariger, H. Vázquez-Villa and E. M. Carreira, *Org. Lett.*, 2010, **12**, 2893–2895.

8 For Rh-catalyzed asymmetric hydrogenation of α-halo ketones, see: (*a*) M. Devocelle, A. Mortreux, F. Agbossou and J.-R. Dormoy, *Tetrahedron Lett.*, 1999, **40**, 4551–4554; (*b*) F. Agbossou-Niedercorn and I. Suisse, *Coord. Chem. Rev.*, 2003, **242**, 145–158.

9 For Ru-catalyzed asymmetric hydrogenation of α-halo ketones, see: T. Ohkuma, K. Tsutsumi, N. Utsumi, N. Arai, R. Noyori and K. Murata, *Org. Lett.*, 2007, **9**, 255–257.

10 For reviews, see: (*a*) B. H. Lipshutz, in *Modern Organocopper Chemistry*, ed. N. Krause, Wiley-VCH, Weinheim, 2002, pp. 167–187; (*b*) H. Nishiyama and K. Itoh, in *Transition Metals for Organic Synthesis*, ed. M. Beller and C. Bolm, Wiley-VCH, Weinheim, 2nd edn, 2004, vol. 2, pp. 182–191; (*c*) O. Riant, N. Mostefai and J. Courmarcel, *Synthesis*, 2004, 2943–2958; (*d*) S. Rendler and M. Oestreich, *Angew. Chem., Int. Ed.*, 2007, **46**, 498–504; (*e*) S. Díez-González and S. P. Nolan, *Acc. Chem. Res.*, 2008, **41**, 349–358; (*f*) C. Deutsch, N. Krause and B. H. Lipshutz, *Chem. Rev.*, 2008, **108**, 2916–2927; (*g*) B. H. Lipshutz, *Synlett*, 2009, 509–524; (*h*) C. G. Arena, *Mini-Rev. Org. Chem.*, 2009, **6**, 159–167; (*i*) A. V. Malkov, *Angew. Chem., Int. Ed.*, 2010, **49**, 9814–9815.

11 For selected examples, see: (*a*) H. Brunner and W. Miehling, *J. Organomet. Chem.*, 1984, **275**, C17–C21; (*b*) B. H. Lipshutz, K. Noson and W. Chrisman, *J. Am. Chem. Soc.*, 2001, **123**, 12917–12918; (*c*) S. Sirol, J. Courmarcel, N. Mostefai and O. Riant, *Org. Lett.*, 2001, **3**, 4111–4113; (*d*) B. H. Lipshutz, K. Noson, W. Chrisman and A. Lower, *J. Am. Chem. Soc.*, 2003, **125**, 8779–8789; (*e*) J. Yun and D.-W. Lee, *Tetrahedron Lett.*, 2004, **45**, 5415–5417; (*f*) J. Wu, J. X. Ji and A. S. C. Chan, *Proc. Natl. Acad. Sci. U. S. A.*, 2005, **102**, 3570–3575; (*g*) K. Junge, B. Wendt, D. Addis, S. Zhou, S. Das and M. Beller, *Chem.–Eur. J.*, 2010, **16**, 68–73; (*h*) W. J. Li and S. X. Qiu, *Adv. Synth. Catal.*, 2010, **352**, 1119–1122; (*i*) R. Moser, Ž. V. Bošković, C. S. Crowe and B. H. Lipshutz, *J. Am. Chem. Soc.*, 2010, **132**, 7852–7853; (*j*) X.-C. Zhang, F.-F. Wu, S. Li, J.-N. Zhou,

J. Wu, N. Li, W. Fang, K. H. Lam and A. S. C. Chan, *Adv. Syn. Catal.*, 2011, **353**, 1457–1462; (*k*) A. Albright and R. E. Gawley, *J. Am. Chem. Soc.*, 2011, **133**, 19680–19683; (*l*) K. R. Voigtritter, N. A. Isley, R. Moser, D. H. Aue and B. H. Lipshutz, *Tetrahedron*, 2012, **68**, 3410–3416.

12 (*a*) M. Bandini, P. G. Cozzi, L. Negro and A. Umani-Ronchi, *Chem. Commun.*, 1999, 39–40; (*b*) M. Bandini, F. Bernardi, A. Bottoni, P. G. Cozzi, G. P. Miscione and A. Umani-Ronchi, *Eur. J. Org. Chem.*, 2003, 2972–2984; (*c*) B. H. Lipshutz, A. Lower, R. J. Kucejko and K. Noson, *Org. Lett.*, 2006, **8**, 2969–2972.

13 DTBM-SEGPHOS = (4,4′-bi-1,3-benzodioxol)-5,5′-diylbis-(di(3,5-di-tert-4-me-thoxyphenyl)phos-phane). T. Saito, T. Yokozawa, T. Ishizaki, T. Moroi, N. Sayo, T. Miura and H. Kumobayashi, *Adv. Synth. Catal.*, 2001, **343**, 264–267.

14 J. Wu and A. S. C. Chan, *Acc. Chem. Res.*, 2006, **39**, 711–720.

15 (*a*) X.-C. Zhang, Y. Wu, F. Yu, F.-F. Wu, J. Wu and A. S. C. Chan, *Chem.–Eur. J.*, 2009, **15**, 5888–5891; (*b*) F. Yu, J.-N. Zhou, X.-C. Zhang, Y.-Z. Sui, F.-F. Wu, L.-J. Xie, A. S. C. Chan and J. Wu, *Chem.–Eur. J.*, 2011, **17**, 14234–14240; (*c*) F. Yu, X.-C. Zhang, F.-F. Wu, J.-N. Zhou, W. Fang, J. Wu and A. S. C. Chan, *Org. Biomol. Chem.*, 2011, **9**, 5652–5654; (*d*) Y.-Z. Sui, X.-C. Zhang, J.-W. Wu, S. Li, J.-N. Zhou, M. Li, W. Fang, A. S. C. Chan and J. Wu, *Chem.–Eur. J.*, 2012, **18**, 7486–7492; (*e*) F.-F. Wu, J.-N. Zhou, Q. Fang, Y.-H. Hu, S. Li, X.-C. Zhang, A. S. C. Chan and J. Wu, *Chem. Asian J.*, 2012, **7**, 2527–2530; (*f*) S.-B. Qi, M. Li, S. Li, J.-N. Zhou, J.-W. Wu, F. Yu, X.-C. Zhang, A. S. C. Chan and J. Wu, *Org. Biomol. Chem.*, 2013, **11**, 929–937.

16 (*a*) Y. Wu, S. Qi, F.-F. Wu, X.-C. Zhang, M. Li, J. Wu and A. S. C. Chan, *Org. Lett.*, 2011, **13**, 1754–1757; (*b*) Y.-Z. Sui, Q. Fang, M. Li, Y.-H. Hu, H.-F. Xia, S. Li and J. Wu, *Chin. J. Chem.*, 2012, **30**, 2611–2614.

17 J. Wu, H. Chen, Z.-Y. Zhou, C.-H. Yeung and A. S. C. Chan, *Synlett*, 2001, 1050–1054.

18 A. Kamal, M. S. Malik, A. A. Shaik and S. Azeeza, *Tetrahedron: Asymmetry*, 2008, **19**, 1078–1083.

19 C. R. Smith, E. M. Bunnelle, A. Rhodes and R. Sarpong, *Org. Lett.*, 2007, **9**, 1169–1171.

20 R. Silvestri, M. Artico, G. L. Regina, A. D. Pasquali, G. D. Martino, F. D. D'Auria, L. Nencioni and A. T. Palamara, *J. Med. Chem.*, 2004, **47**, 3924–3926.

21 M. D. Varney, W. H. Romines II, T. Boritzki, S. A. Margosiak, C. Bartlett and E. J. Howland, *J. Heterocycl. Chem.*, 1995, **32**, 1493–1498.

22 J. Früchtel, E. Dupont, T. Goebel, S. Schorderetweber and J. Bouvier, *PCT Int. Appl. WO 2009/071500 A2*, 20090611, 2009.

23 T. Birkinshaw, D. Cheshire and A. Mete, *PCT Int. Appl. WO 01/62713 A1*, 20010830, 2001.

24 N. Khorana, C. Smith, K. Herrick-Davis, A. Purohit, M. Teitler, B. Grella, M. Dukat and R. A. Glennon, *J. Med. Chem.*, 2003, **46**, 3930–3937.

25 G. L. Regina, F. D. D'Auria, A. Tafi, F. Piscitelli, S. Olla, F. Caporuscio, L. Nencioni, R. Cirilli, F. L. Torre, N. R. De Melo, S. L. Kelly, D. C. Lamb, M. Artico, M. Botta, A. T. Palamara and R. Silvestri, *J. Med. Chem.*, 2008, **51**, 3841–3855.

26 R. Perrone, F. Berardi, N. A. Coabufo, M. Leopoldo and V. Tortorella, *J. Med. Chem.*, 2000, **43**, 270–277.

27 J. E. G. Guillemont, I. Dorange, M. M. S. Motte, K. J. L. M. Andries and A. Koul, *PCT Int. Appl. WO 2008/068268 A1*, 20080612, 2008.

28 J. F. Bagli, W. D. Mackay and E. Ferdinandi, *J. Med. Chem.*, 1976, **19**, 876–882.

29 S. Ini, M. Abramov and A. Liberman, *PCT Int. Appl. WO 2006/099433 A1*, 20060921, 2006.