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Preparation of polymer-supported Ru-TsDPEN catalysts and use for enantioselective synthesis of (*S*)-fluoxetine

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Polymer-supported chiral ligands **9** and **17** were prepared based on Noyori's (1*S*,2*S*)- or (1*R*,2*R*)-*N*-(*p*-tolylsulfonyl)-1,2-diphenylethylenediamine. The combination with $[RuCl_2(p\text{-cymene})]_2$ has been shown to exhibit high activities and enantioselectivities for heterogeneous asymmetric transfer hydrogenation of aromatic ketones (**19a–c**) with formic acid–triethylamine azeotrope as the hydrogen donor, whereby affording the respective optically active alcohols **20a–c**, the key precursors of chiral fluoxetine. As exemplified by ligand **17** for substrate **19c**, the catalysts can be recovered and reused in three consecutive runs with no significant decline in enantioselectivity. The procedure avoids the plausible contamination of fluoxetine by the toxic transition metal species.

Introduction

Fluoxetine (Prozac™, Eli Lilly Co.) and analogues belong to the first selective serotine (5-HT) reuptake inhibitors (SSRIs), and have been widely used in the treatment of anxiety and depression that show little effect on noradrernegic or dopaminergic systems.[1] A recent report also revealed that fluoxetine can ameliorate primary negative symptoms in chronic schizophrenia patients who are treated with typical antipsychotics.[2] Although fluoxetine is currently used therapeutically as a racemate, it has been demonstrated that the two enantiomers have quite different bioactivities and rates of metabolism. Thus, whilst the stereospecificity of the (*S*)-enantiomer for anti-depressant efficacy has been claimed,[3] Lily submitted also an approval application for (*R*)-fluoxetine in the US for the treatment of bulimia in 1995.[4] Due to its potential medicinal significance, considerable efforts have been devoted to the synthesis of optically active fluoxetine during the past decade. These syntheses relied on the production of the suitable chiral alcohol intermediates. Representative procedures for this subject include enzymatic resolution,[5] asymmetric reduction of the prochiral ketones,[6] dihydroxylation or Sharpless epoxidation of styrene,[7] and carbonyl-ene reaction of benzaldehyde.[8]

One of the most attractive chemical methods to obtain optically active secondary alcohols is the asymmetric transfer hydrogenation of prochiral ketones due to its high enantioselectivity, high product yield, and green chemistry.[9] Amongst the various types of chiral catalysts, Noyori's (1*S*,2*S*)- or (1*R*,2*R*)-*N*-(*p*-tolylsulfonyl)-1,2-diphenylethylenediamine (TsDPEN) in combination with $[RuCl_2(p\text{-cymene})]_2$ has been recognized as the most efficient one giving products with up to 99% ee for most aromatic ketones including those bearing neighboring functional groups at the α or β position of the carbonyl group.[6i]

In recent years, covalent immobilization of chiral catalysts which allow for feasible recycling of catalyst with low leaching level of metals have aroused considerable research efforts.[10] In comparison to the solution counterparts, using polymer-supported catalysis can facilitate the catalyst separation from the reaction mixture, simplify the recovery and recycling of the often expensive and even toxic catalysts, and eventually be prospective to meet the need for more environmentally benign chemistry. However, in view of practical use, the advantages gained by covalent attachment to a support should be outweighed by the added complexity associated with synthesizing the appropriately modified ligands.

A few papers have appeared describing the chiral supported Ru-TsDPEN complex, including the use of polystyrene, dendrimer and silica as the support.[11] The reactivity of the Ru-TsDPEN catalysts seemed to be influenced by the sulfonamide group, tending to decrease with increasing electron-withdrawing ability of sulfonamide group.[12] Several RSO_2-DPEN ligands for transfer hydrogenation have been reported with R = Ar, CF_3, R_2N.[13] In an attempt to develop readily accessible and hence more appealing catalyst candidates for production of intermediates used in the synthesis of fluoxetine, we have prepared two novel polystyrene-bound chiral Ru-TsDPEN catalysts and tested the efficacy in the heterogeneous asymmetric transfer hydrogenation of several functionalized aromatic ketones. The resulting secondary alcohols are useful in the synthesis of optically active fluoxetine.

Results and discussion

Two polystyrene-supported TsDPEN-derived ligands **9** and **17** were synthesized according to Scheme 1 and Scheme 2, respectively. As shown in Scheme 1, 4-hydroxybenzenesulfonic acid sodium salt dihydrate **1** was dehydrated using a Dean Stark apparatus, which was then allowed to react with ethyl bromoacetate affording the benzenesulfonic acid sodium salt **2** using K_2CO_3 as base. Upon treatment with excess thionyl chloride in the presence of catalytic amount of DMF, the salt **2** was further transformed into the corresponding benzenesulfonyl chloride **3**. The commercially available (1*S*,2*S*)-diamine **4** was then sulfonylated with **3** to provide **5**. *N*-protection of **5** with di-*tert*-butyl dicarbonate led to the *N*-Boc derivative **6**. Basic saponification of **6** gave the free acid **7**, which is ready to be coupled to a solid support. Immobilization onto aminomethylated polystyrene (1.07 mmol g^{-1}, DVB 1%) to provide ligand **8** was readily achieved under the standard peptide coupling conditions using DCC, pentafluorophenol and DMAP. Deprotection of the *N*-Boc group occurred readily with 50% TFA in dichloromethane in 98% yield whereby affording the ligand **9** with a polystyrene backbone.

Next, we expected to relieve the electron-withdrawing effect of the sulfamido group by lengthening the linkage. However, the standard Williamson ether reaction proved to be unsuccessful using ethyl 3-bromopropionate in place of ethyl bromoacetate. An alternative way has been devised which is depicted by Scheme 2. By screening the protecting group, benzyl group appeared to be more appropriate for protecting the hydroxyl group of sodium 4-hydroxybenzenesulfonate salt. Conversion of the sodium salt **10** to the corresponding benzenesulfonyl chloride **11** occurred with $SOCl_2$ as for **3**. TsDPEN-derived

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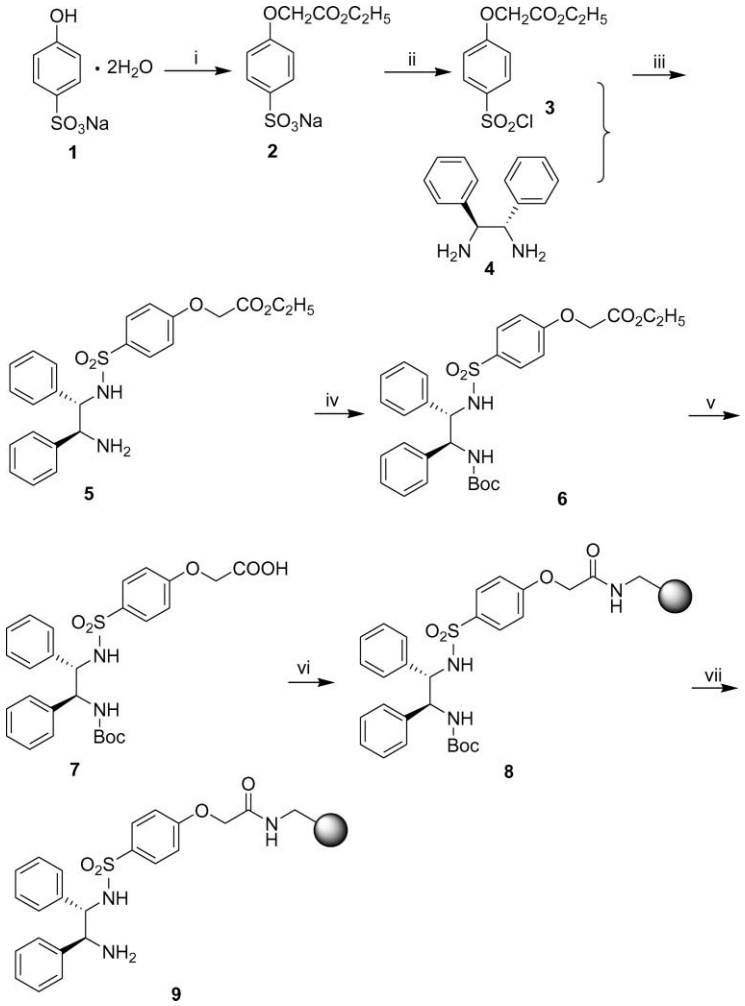
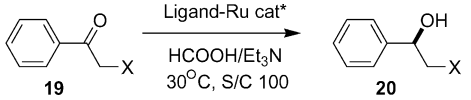


Scheme 1 Preparation of the supported ligand **9**. *Reagents and conditions*: (i) Dean Stark; then $BrCH_2CO_2Et$, K_2CO_3, dibenzo-18-crown-6, acetone, 95%; (ii) $SOCl_2$, DMF (cat.), 71%; (iii) Et_3N, CH_2Cl_2, 55%; (iv) $(Boc)_2O$, DIPEA, CH_2Cl_2, 98%; (v) NaOH, H_2O, 95%; (vi) aminomethylated polystyrene, DCC, pentafluorophenol, DMAP; (vii) TFA, CH_2Cl_2.

ligand **12** was synthesized by reacting the (1*S*,2*S*)-diamine **4** with **11**. Consecutive *N*-Boc protection of the amino group and deprotection of the benzyl group with hydrogen in the presence of 10% Pd/C provided the phenol **14**, which was etherified with 3-bromopropanoic acid using Cs_2CO_3 as a base that diminished the plausible formation of *N*-alkylated byproduct. Immobilization onto the aminomethylated polystyrene and deprotection of the *N*-Boc group provided ligand **17** having one more carbon between the polymer backbone and the binding sites.

The ruthenium catalysts Ru-**9** and Ru-**17** were formed *in situ* by mixing the ligands with $[RuCl_2(p\text{-cymene})]_2$ giving orange–red beads for each polymer. The effectiveness of the catalysts were evaluated in the asymmetric transfer hydrogenation of fluoxetine precursors **19a–c**. For comparison, the known supported chiral ligand **18** bearing a *para* electron-withdrawing carboxyl group on the benzene ring was also prepared and used in the reaction. Table 1 shows the results for the ruthenium catalyzed prochiral ketones using a 5 : 2 formic acid–triethylamine azeotrope as the hydrogen donor. All reactions were performed with 1 mol% catalyst in dichloromethane at 35 °C. The three catalysts all displayed remarkably high catalytic activity and good enantioselectivity, affording the corresponding optically active alcohols. The absolute configuration of the key intermediate was determined from the sign of rotation of the isolated product. One notable feature of this asymmetric transfer hydrogen is the keto-carbonyl group selectivity and the neighboring ester, amido or cyano groups did not interfere with the reduction. It can also be seen that the electronic character and the spacer length between the supporter and the benzene ring has only a subtle effect on the reduction outcome (entries 1–3 and 7–9).

Table 1 Asymmetric transfer hydrogenation of aromatic ketones **19a–c**[a]

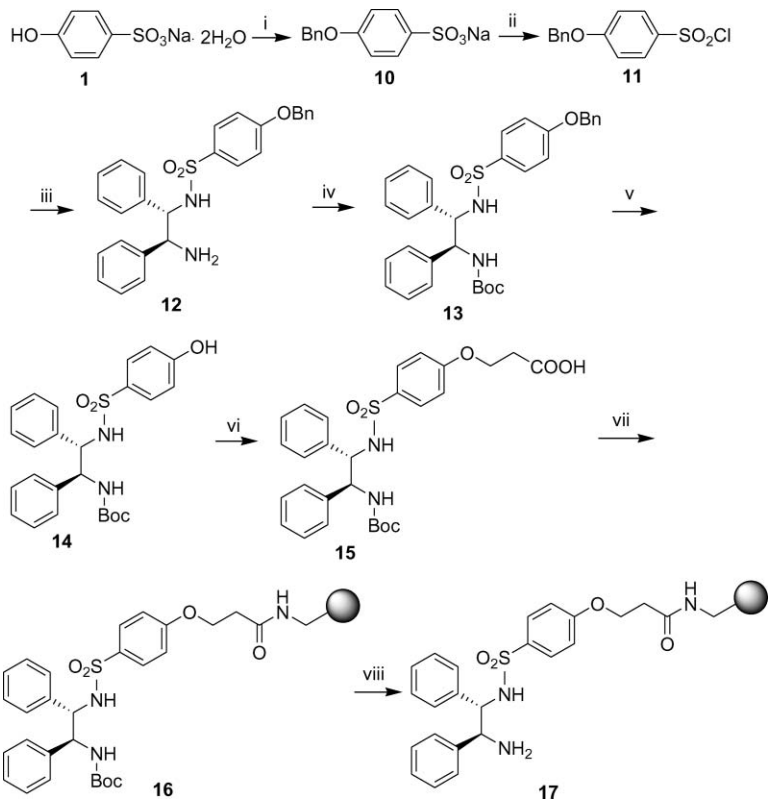


19,20 **a**: X = $CO_2C_2H_5$; **b**: X = $CONHCH_3$; **c**: X = CN

Entry	Ketone	Ligand	Time (h)	Conversion[b] (%)	Ee[c] (%)
1	**19a**	**18**	24	97	95
2	**19a**	**9**	24	97	94
3	**19a**	**17**	20	95	96
4	**19b**	**18**	22	85	91
5	**19b**	**9**	22	93	86
6	**19b**	**17**	22	95	88
7	**19c**	**18**	22	97	95
8	**19c**	**9**	17	98	95
9	**19c**	**17**	17	98	97
10	**19c**	**17** (2nd use)	28	92[d]	93
11	**19c**	**17** (3rd use)	60	81[d]	93
12	**19c**	**12**	18	>99	97

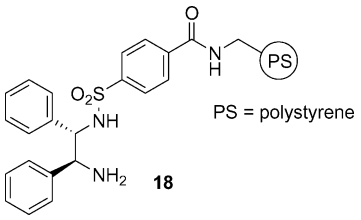
[a] Ketone : chiral ligand : [Ru] = 100 : 1.2 : 1, ketone = 0.5 mol L^{-1}, acid : triethylamine azeotrope : CH_2Cl_2 = 1 : 1. [b] Isolated yield. [c] Enantiomeric excesses were determined by HPLC on a Daciel Chiralcel OD column. [d] Based on GC analysis.

However, for *N*-methyl-3-oxo-3-phenylpropanamide (**19b**), the catalyst Ru-**17** gave more promising result (entries 4–6). The best result (97% ee at 98% conversion) was obtained using



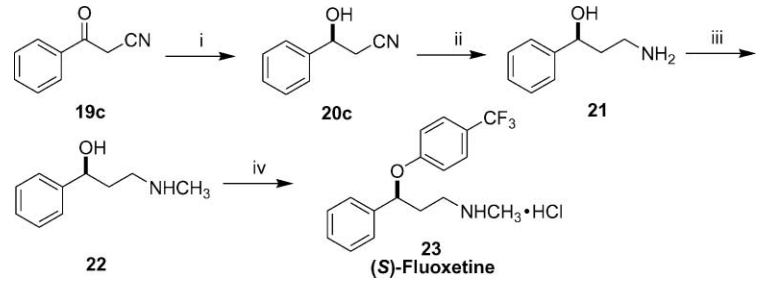
Scheme 2 Preparation of the supported ligand **17**. *Reagents and conditions*: (i) Dean Stark; then BnBr, K_2CO_3, dibenzen-18-crown-6, acetone, 99%; (ii) $SOCl_2$, DMF (cat.), 85%; (iii) **4**, Et_3N, CH_2Cl_2, 65%; (iv) $(Boc)_2O$, DIPEA, CH_2Cl_2, 95%; (v) Pd/C, H_2, CH_3OH, 99%; (vi) Cs_2CO_3, 3-bromopropionic acid, acetone, 67%; (vii) aminomethylated polystyrene, DCC, pentafluorophenol, DMAP; (viii) TFA, CH_2Cl_2.

Ru-**17** for 2-cyanoacetophenone **19c** (entry 9). For comparison, the homogenous ligand **12** was also used for the reduction of **19c**. Under the similar condition, (*S*)-2-cyano-1-phenyl-1-ethanol was obtained in 99% conversion rate and 97% ee (entry 12).



After reduction the visual appearance of the polymer is unchanged with the bead remaining orange to red in color. The catalyst was easily recovered from the mixture by filtration and solvent washing under nitrogen. The recycling reactions for the substrate **19c** were attempted with the recovered catalysts Ru-**17**. As shown in Table 1 (entry 10), the catalyst can be successfully reused but with a slight drop in activity and enantioselectivity. A third use performed well with nearly the same enantioselectivity as in the second run, but still shows a drop in activity, and a prolonged time (60 hours) was requested to achieve 81% conversion (entry 11). Addition of more $[RuCl_2(p\text{-cymene})]_2$ to the polymer supported ligand cannot regenerate the catalytic activity. The cause of the activity drop is unclear at the present.

All of the three resulting alcohols (*S*)-**20a–c** are appropriate intermediates for the construction of optically active fluoxetine according to known procedures.[5] Thus, reduction of (*S*)-**20c** with Ru-**17** under our asymmetric transfer hydrogenation conditions afforded **20c**. The alcohol **20c** was then reduced with $BH_3{\cdot}Me_2S$ in dry THF to provide optically active 3-amino-1-phenyl-1-propanol (*S*)-**21**, which was transformed to the *N*-methylated derivative (*S*)-**22** by sequential treatment with methyl chloroformate and reduction with lithium aluminium hydride. Finally, 4-chlorobenzontrifluoride was subjected to aromatic nucleophilic substitution with sodium alkoxide of (*S*)-**22**, generated by action with NaH. By this procedure, (*S*)-fluoxetine hydrochloride **23** was obtained as a white solid in 75% overall yield for four steps, and in 97% ee, as well as 98% chemical purity (Scheme 3). We found that there was no ruthenium contamination of the product down to the level of detection of the analytical apparatus (Graphite Furnace Atomic Absorption, less than 0.04 ppm).



Scheme 3 Synthesis of (*S*)-fluoxetine. *Reagents and conditions*: (i) ligand **17**, $[RuCl_2(p\text{-cymene})]_2$, HCOOH–$Et_3N$, CH_2Cl_2, 98%; (ii) $BH_3{\cdot}Me_2S$, THF, 92%; (iii) methyl chloroformate, K_2CO_3, CH_2Cl_2; then $LiAlH_4$, THF; two steps: 92%; (iv) NaH, 4-chlorobenzotrifluoride, DMSO, then satd. HCl of Et_2O, 90%.

Conclusion

This work presents the successful reductive transformation of three aromatic ketones **19a–c** *via* asymmetric hydrogen transfer reaction to optically active alcohols, which are suitable intermediates for the synthesis of fluoxetine, a very important antidepressant. The real synthesis of (*S*)-fluoxetine was exemplified by using the product (*S*)-2-cyano-1-phenyl-1-ethanol (**20c**) in 75% overall yield and 97% ee. Immobilization of the chiral ligand onto polymer bead allows the simple recovery and reuse of the expensive chiral Ru-catalyst and decreases the potentially toxic transition metal species contaminating the product, thus rendering the procedure to be green and practical.

Experimental

General

The NMR data were acquired on a Bruker 500 or a Varian 400 spectrometer. ^{1}H and ^{13}C chemical shifts (δ) are reported in ppm relative to TMS as internal standard. Coupling constants (J) are given in Hz. The reactions were monitored by thin layer chromatography coated with silica gel. Ee % values were determined by HPLC on a Daciel Chiralcel OD column. Absolute configuration was determined by comparison with the known specific rotation values.

Preparation of ligand 9

Sodium 4-((ethoxycarbonyl)methoxy)benzenesulfonate (2). 4-Hydroxybenzenesulfonic acid sodium salt dihydrate (2.32 g, 0.01 mol) was dehydrated by distillation with benzene and dissolved in 20 mL of acetone. Ethyl bromoacetate (2.00 g, 0.012 mol), K_2CO_3 (2.76 g, 0.02 mol) and dibenzo-18-crown-6 (68 mg, 0.2 mmol) were added, and the mixture was heated at reflux for 48 h. After cooling to room temperature, the crystals were collected by filtration, washed with acetone (2 × 60 mL), and dried under reduced pressure to yield **2** as a white powder (2.68 g, 95%). Mp > 300 °C; IR (KBr): ν 3070, 2866, 1730, 1598, 1495, 1451 cm^{-1}.

Ethyl (4-chlorosulfonyl)phenoxyacetate (3). To the sodium salt **2** (2.68 g, 0.095 mol) was added dropwise a solution of DMF (69 mg, 0.95 mmol) in $SOCl_2$ (15 mL) at 0 °C. The resulting mixture was stirred at 60 °C for 2 h. At the end of this time, the mobile, nearly homogeneous reaction mixture was poured over 100 g of ice with vigorous stirring. The aqueous layer was extracted with EtOAc (3 × 50 mL). The organic phases were combined, washed with 50 mL of ice water, dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc–hexane, 1 : 9, v/v) provided **3** as a colorless vicious liquid (1.87 g, 67%). IR (neat): ν 3093, 2938, 1720, 1586, 1492, 1368, 1262 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 1.32 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 4.30 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 4.74 (s, 2 H, CH_2CO), 7.06 (d, J = 8.7 Hz, 2 H, C_6H_4), 7.99 (d, J = 8.7 Hz, 2 H, C_6H_4).

(1*S*,2*S*)-*N*-((4-Ethoxycarbonyl)methoxybenzenesulfonyl)-1,2-diphenylethylenediamine (5). To a solution of (1*S*,2*S*)-diphenylethylenediamine (212 mg, 1.0 mmol) and Et_3N (101 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) was added dropwise a solution of **3** (279 mg, 1.0 mmol) in CH_2Cl_2 (20 mL) over 1 h. The mixture was stirred at room temperature for 4 h, and washed with satd. aq. $NaHCO_3$ (20 mL). The organic phase was separated and dried over Na_2SO_4 and concentrated. The product was purified by silica gel chromatography (gradient elution: CH_2Cl_2 to CH_2Cl_2–EtOAc–Et_3N (1 : 2 : 0.01, v/v/v)) to yield **5** as a white powder (250 mg, 55%). Mp 121–123 °C; IR (KBr): ν 3209, 3010, 2880, 1729, 1589, 1453 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.21 (t, J = 7.0 Hz, 3 H, CH_2CH_3), 3.94 (d, J = 7.5 Hz, 1 H, CH), 4.17 (q, J = 7.0 Hz, 2 H, CH_2CH_3), 4.29 (d, J = 7.5 Hz, 1 H, CH), 4.78 (s, 2 H, CH_2CO), 6.77 (d, J = 8.7 Hz, 2 H, C_6H_4), 6.92–7.12 (m, 10 H, 2 × C_6H_5), 7.33 (d, J = 8.7 Hz, 2 H, C_6H_4).

(1*S*,2*S*)-*N*-Boc-*N*′-((4-ethoxycarbonyl)methoxybenzenesulfonyl)-1,2-diphenylethylenediamine (6). A solution of **5** (454 mg, 1.0 mmol), $(Boc)_2O$ (262 mg, 1.2 mmol), and DIPEA (258 mg, 2 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature for 4 h. The solution was washed with 5% aq. HCl. The organic phase was separated, dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (CH_2Cl_2–EtOAc, 1 : 1) to give **6** as a white powder (544 mg, 98%). Mp 131–133 °C; IR (KBr): ν 3033, 2934, 1710, 1627, 1593, 1450, 1320 cm^{-1}; δ_H (500 MHz, DMSO-d_6): 1.21 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 1.29 (s, 9H, $C(CH_3)_3$), 4.20 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 4.64 (s, 2 H, 2 × CH), 4.71 (s, 2 H, CH_2CO), 6.80 (d, J = 8.8 Hz, 2 H, C_6H_4), 7.08–7.25 (m, 10 H, 2 × C_6H_5), 7.35 (d, J = 8.8 Hz, 2H, C_6H_4), 8.10 (s, 1 H, NHCO).

(1*S*,2*S*)-*N*-Boc-*N*′-(4-carboxymethoxybenzenesulfonyl)-1,2-diphenylethylenediamine (7). A solution of **6** (555 mg, 1.0 mmol) and NaOH (160 mg, 4.0 mmol) in 4 mL of CH_3OH–H_2O (1 : 1, v/v) was stirred at reflux for 6 h. The resulting mixture was diluted with 10 mL H_2O and acidified with citric acid, and then extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with 10 mL of brine, dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography using hexane–EtOAc (1 : 2, v/v) as the eluent yielded **7** as a colorless crystal (501 mg, 95%). Mp 142–143 °C; IR (KBr): ν 3390, 2921, 2851, 1685, 1592, 1316 cm^{-1}; δ_H (500 MHz, DMSO-d_6): 1.23 (s, 9 H, $C(CH_3)_3$), 4.61–4.64 (m, 2H, CH_2CO and CH), 4.81 (s, 1 H, CH), 6.67 (d, J = 8.7 Hz, 2 H, C_6H_4), 7.04–7.18 (m, 10 H, 2 × C_6H_5), 7.30 (d, J = 8.7 Hz, 2 H, C_6H_4), 8.05 (s, 1 H, NHCO).

The polymer-bound ligand 8

A solution of **7** (527 mg, 1.0 mmol), DCC (1.03 g, 5 mmol), pentafluorophenol (920 mg, 5 mmol), DMAP (cat.) and the aminomethylated polystyrene (930 mg, 1.07 mmol g^{-1}) in dry CH_2Cl_2 (20 mL) was stirred at room temperature for 24 h under N_2. The polymer was filtered, rinsed sequentially with CH_2Cl_2 and acetone and dried at 50 °C *in vacuo* to yield the product as pale yellow beads. Elemental analysis Found: N, 2.90 requires N, 2.91%; IR (KBr): ν 3058, 2922, 2850, 1671, 1601, 1492, 1451, 1366 cm^{-1}.

The polymer-bound ligand 9

The polymer-bound ligand **8** (500 mg) was added in batches to a solution of TFA–CH_2Cl_2 (1 : 1, v/v, 10 mL). The mixture was stirred at room temperature for 40 min. The polymer was filtrated, rinsed sequentially with CH_2Cl_2 and CH_2Cl_2–Et_3N (1 : 4, v/v), and dried at 50 °C *in vacuo* to yield the deprotected ligand **9** as pale yellow beads. Elemental analysis Found: N, 3.04 requires N, 3.13%; IR (KBr): ν 3025, 2922, 2851, 1664, 1601, 1493, 1452, 1382 cm^{-1}.

Preparation of ligand 17

Sodium 4-(benzyloxy)benzenesulfonate (10). As described for the sodium salt **2** using benzyl bromide. The salt **10** was obtained as a white powder in 99% yield. Mp > 300 °C; IR (KBr): ν 3063, 2864, 1599, 1499, 1453, 1241 cm^{-1}.

4-(Benzyloxy)benzenesulfonyl chloride (11). As described for **3**. The crude product **11** was purified by chromatography (CH_2Cl_2–hexane, 1 : 4, v/v) to yield a white powder in 86% yield. Mp 102–103 °C; IR (KBr): ν 3094, 2938, 1587, 1492, 1368, 1262, 1163 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 5.18 (s, 2 H, CH_2), 7.12 (d, J = 9.2 Hz, 2 H, C_6H_4), 7.42–7.43 (m, 5 H, C_6H_5), 7.99 (d, J = 9.2 Hz, 2 H, C_6H_5).

(1*S*,2*S*)-*N*-((4-Benzyloxy)benzenesulfonyl)-1,2-diphenylethylenediamine (12). As described for the ligand **5**. The crude product was purified by chromatography (gradient elution: from pure CH_2Cl_2 to CH_2Cl_2–EtOAc–Et_3N (1 : 3 : 0.01, v/v/v) to provide a white powder in 65% yield. Mp 141–142 °C; IR (KBr): *v* 3290, 3028, 2988, 1591, 1519, 1450, 1319, 1450, 1390, 1151 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 4.11 (d, $J = 5.1$ Hz, 1 H, CH), 4.36 (d, $J = 5.1$ Hz, 1 H, CH), 5.05 (s, 2 H, CH_2), 6.71 (d, $J = 8.8$ Hz, 2 H, C_6H_4), 6.72–7.16 (m, 10 H, 2 × C_6H_5), 7.33 (d, $J = 8.8$ Hz, 2 H, C_6H_4), 7.41–7.42 (m, 5 H, $C_6H_5CH_2$).

(1*S*,2*S*)-*N*-Boc-*N*′-((4-benzyloxy)benzenesulfonyl)-1,2-diphenylethylenediamine (13). As described for the ligand **6**. The crude product was purified by chromatography (CH_2Cl_2–hexane, 1 : 2, v/v) to yield a white powder (95%). IR (KBr): *v* 3031, 2960, 1690, 1590, 1516, 1453, 1319, 1450 cm^{-1}; Mp 145–146 °C; δ_H (500 MHz, $CDCl_3$): 1.47 (s, 9 H, $C(CH_3)_3$), 4.55 (m, 1 H, CH), 4.78 (m, 1 H, CH), 5.20 (s, 2 H, CH_2), 6.76 (d, $J = 8.8$ Hz, 2 H, C_6H_4), 6.78–7.16 (m, 10 H, 2 × C_6H_5), 7.34 (s, 1 H, NHCO), 7.38–7.40 (m, 5 H, $C_6H_5CH_2$), 7.45 (d, $J = 8.8$ Hz, 2 H, C_6H_4).

(1*S*,2*S*)-*N*-Boc-*N*′-(4-hydroxybenzenesulfonyl)-1,2-diphenylethylenediamine (14). A solution of **13** (559 mg, 1 mmol) and 10% Pd/C (11 mg, 0.1 mmol) in 20 mL methanol was stirred at room temperature for 24 h under an atmosphere of H_2. Upon completion of the reaction, the mixture was filtered, and the cake was washed with methanol. The combined methanol solution was evaporated *in vacuo* and the residue was purified by chromatography using CH_2Cl_2 as eluent to yield a white powder (464 mg, 99%). Mp 132 °C (dec.); IR (KBr): *v* 3381, 3033, 2978, 1688, 1590, 1517, 1452, 1319, 1450 cm^{-1}; δ_H (500 MHz, DMSO-d_6): 1.25 (s, 9 H, $C(CH_3)_3$), 4.60 (m, 1 H, CH), 4.79 (m, 1 H, CH), 6.50 (d, $J = 8.7$ Hz, 2 H, C_6H_4), 7.02–7.24 (m, 10 H, 2 × C_6H_5), 7.25 (s, 1 H, NHCO), 7.95 (d, $J = 8.7$ Hz, 2 H, C_6H_4), 10.07 (br, 1 H, OH).

(1*S*,2*S*)-*N*-Boc-*N*′-((4-carboxyethoxybenzenesulfonyl)-1,2-diphenylethylenediamine (15). A solution of **14** (469 mg, 1 mmol), 3-bromopropionic acid (153 mg, 1 mmol) and Cs_2CO_3 (652 mg, 2 mmol) in 10 mL of acetone was heated at reflux for 24 h. The volatiles were removed *in vacuo* and the residue was triturated with CH_2Cl_2. The extracts were filtered, dried over Na_2SO_4, after evaporation of the solvent under reduced pressure, a pale yellow foam was obtained which was purified by chromatography (CH_2Cl_2–hexane, 1 : 2, v/v) to yield a white crystal (362 mg, 67%). Mp 161–163 °C; IR (KBr): *v* 3381, 2923, 2852, 1687, 1590, 1454, 1318, 1288 cm^{-1}; δ_H (500 MHz, DMSO-d_6): 1.27 (s, 9 H, $C(CH_3)_3$), 2.67 (t, $J = 5.8$ Hz, 2 H, CH_2COOH), 4.14 (t, $J = 5.8$ Hz, 2 H, OCH_2), 4.61 (m, 1 H, CH), 4.79 (m, 1 H, CH), 6.68 (d, $J = 8.6$ Hz, 2 H, C_6H_4), 7.07–7.19 (m, 10 H, 2 × C_6H_5), 7.29 (d, $J = 8.6$ Hz, 2 H, C_6H_4), 8.04 (s, 1 H, NHCO), 12.41 (br, 1 H, COOH).

The polymer-bound ligand 16

16 was prepared as described for the polymer **8**. Elemental analysis Found: N, 2.71 requires N, 2.88%; IR (KBr) 3059, 2923, 2853, 1669, 1602, 1494, 1451, 1367, 1165, 1090 cm^{-1}.

The polymer-bound ligand 17

17 was prepared as described for the polymer **9**. Elemental analysis Found: N, 3.01 requires N, 3.06%; IR (KBr): *v* 3058, 2924, 2855, 1671, 1601, 1492, 1450, 1369, 1163 cm^{-1}.

General procedure for the asymmetric transfer hydrogenation

A suspension of $[RuCl_2(p\text{-cymene})]_2$ (3.1 mg, 0.005 mmol) and the polymer ligand (0.012 mmol) in CH_2Cl_2 (1 mL) was stirred for 1 h at room temperature under an atmosphere of argon. The appropriate ketone (1.0 mmol) and HCOOH–Et_3N azeotrope (1.0 mL) were sequentially added, and the mixture was stirred for the appropriate period of time (see Table 1) at 35 °C. After completion of the reaction, the suspension was diluted with CH_2Cl_2 (20 mL) and filtered immediately. The filtrates were washed with satd. aq. $NaHCO_3$ and dried over $MgSO_4$. The volatiles were removed *in vacuo* and the residue was purified by chromatography on silica gel using CH_2Cl_2 as eluent.

The recovered catalyst was washed with CH_2Cl_2 four times and reused in the hydrogen transfer reaction by reloading formic acid–triethylamine azeotrope (1.0 mL) and the ketone (1.0 mmol).

Preparation of (*S*)-fluoxetine hydrochloride

(*S*)-2-Cyano-1-phenyl-1-ethanol (20c). A solution of $[RuCl_2(p\text{-cymene})]_2$ (90 mg, 0.15 mmol) and the ligand **17** (494 mg, 0.36 mmol) in CH_2Cl_2 (30 mL) was stirred for 1 h at room temperature under argon. 2-Cyanoacetophenone (4.35 g, 30.0 mmol) and HCOOH–Et_3N azeotrope (30 mL) were added and then stirred for 18 h at 35 °C. After addition of CH_2Cl_2 (50 mL), the organic phase was separated, washed with satd. aq. $NaHCO_3$, and dried over $MgSO_4$. The volatiles were removed *in vacuo* and the residue purified by chromatography (CH_2Cl_2) to yield a colorless vicious liquid (4.33 g, 98%). $[\alpha]_D^{20}$ −53.2 (*c* 2.60, C_2H_5OH) (lit.,[6i] $[\alpha]_D^{20}$ −52.5 (*c* 2.60, C_2H_5OH)); δ_H (500 MHz, $CDCl_3$): 2.54 (br, 1 H, OH), 2.77–2.79 (m, 2 H, CH_2CN), 5.07 (t, $J = 6.1$ Hz, 1 H, *CH*OH), 7.33–7.57 (m, 5 H, C_6H_5).

(*S*)-3-Amino-1-phenyl-1-propanol (21). A solution of borane–dimethyl sulfide complex (1.76 g, 2.2 mL, 23 mmol) in anhyd THF (10 mL) was added dropwise to a solution of (*S*)-**20** (4.30 g, 29 mmol) in dry THF (10 mL) at 0 °C with stirring under N_2. The mixture was heated at 70 °C for 4 h. After cooling to 0 °C 20 mL of water was carefully added to quench the reaction and extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by chromatography (EtOAc–methanol, 1 : 1) afforded a white solid (4.03 g, 92%). Mp 53–55 °C (lit.[6e] 56 °C); $[\alpha]_D^{20}$ −44.1 (*c* 1, CH_3OH) (lit.[14] $[\alpha]_D^{20}$ −43.7 (*c* 1, CH_3OH)); δ_H (500 MHz, $CDCl_3$): 1.72–1.85 (m, 2 H, CH_2NH_2), 2.91–3.13 (m, 2 H, CH_2CH), 5.01 (dd, $J = 3.0, 8.6$ Hz, 1 H, *CH*OH), 7.25–7.57 (m, 5 H, C_6H_5).

(*S*)-3-Methylamino-1-phenyl-1-propanol (22). To a solution of (*S*)-**21** (4.03 g, 27 mmol) and methyl chloroformate (3.00 g, 32 mmol) in CH_2Cl_2 (15 mL) was added K_2CO_3 (14.9 g, 108 mmol) in H_2O (15 mL) at 0 °C with stirring. The mixture was warmed to room temperature, stirred further for 30 min. After the reaction, 10 mL of water were added, the mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residual was dissolved in 10 mL of THF and the resulting solution was directly used in the next reduction step. *Reduction*: To a suspension of $LiAlH_4$ (1.03 g, 27 mmol) in anhyd. THF (20 mL) was added dropwise a solution of the above formamide intermediate in 10 mL of THF at 0 °C with stirring under N_2. Then the mixture was heated at reflux for 8 h. After cooling to 0 °C, 4 mL of degassed water was carefully added to quench the reaction. The resulting mixture was filtered off, and the organic layers were separated, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography on silica gel chromatography (CH_2Cl_2–methanol, 1 : 1) yielded **22** as a colorless vicious liquid (4.10 g, 92%). $[\alpha]_D^{20}$ −37.5 (*c* 1, $CHCl_3$) (lit.[6c] $[\alpha]_D^{20}$ −38.2 (*c* 1.07, $CHCl_3$)); δ_H (500 MHz, $CDCl_3$): 1.83 (m, 2 H, CH_2NH), 2.44 (s, 3 H, CH_3), 2.87 (m, 2 H, CH_2CH), 4.92 (dd, $J = 3.0, 8.5$ Hz, 1 H, *CH*OH), 7.31–7.42 (m, 5 H, C_6H_5).

(*S*)-Fluoxetine hydrochloride (23). 60% NaH (1.19 g, 30 mmol) was added in three batches into a solution of (*S*)-**22** (4.10 g, 25 mmol) in DMSO (20 mL) at 0 °C with stirring. After the mixture was vigorously stirred at 70 °C for 30 min, a

solution of 4-chlorobenzontrifluoride (4.5 g, 25 mmol) in DMSO (5 mL) was added to the mixture and then heated at 90 °C for 2 h. The resulting mixture was cooled to 0 °C, water (20 mL) was added carefully and extracted with Et_2O (2 × 20 mL). The Et_2O extracts were combined and dried over $MgSO_4$ and concentrated to about 10 mL. A satd. solution of HCl in Et_2O was added dropwise into the solution to provide (*S*)-fluoxetine hydrochloride as colorless crystals (7.79 g, 90%). Mp 144–145 °C (lit.[8] 138–140 °C); $[a]_D^{20}$ +13.5 (*c* 1, $CHCl_3$) (lit.[15] $[a]_D^{20}$ +13.9 (*c* 1.01, $CHCl_3$)); δ_H (500 MHz, $CDCl_3$): 2.50 (m, 2 H, CH_2N^+), 2.64 (s, 3 H, CH_3), 3.21 (m, 2 H, CH_2CH), 5.51 (dd, $J = 6.2$ Hz, 1 H, CHC_6H_5), 6.91 (d, $J = 8.5$ Hz, 2 H, C_6H_4), 7.21–7.53 (m, 7 H, C_6H_5+C_6H_4).

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