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Facile Enantioselective Ring-Opening Reaction of *meso* Epoxides with Anilines Using (*S*)-(–)-BINOL-Ti Complex as a Catalyst

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The catalytic enantioselective ring-opening reaction of *meso*-stilbene oxide and cyclohexene oxide with anilines was catalyzed by (*S*)-(–)-BINOL-Ti complexes at ambient temperature to obtain β-amino alcohols in high yield (95%) and enantioselectivity (*ee*, 78%). The enantiomeric excess (*ee*) of the product was further improved to 98% by a single recrystallization step. The absolute configuration of representative β-amino alcohols was determined by single-crystal X-ray diffraction analysis. The catalyst recovered after first use was recycled four times with retention in its performance.

Introduction

The catalytic enantioselective ring-opening reaction of epoxides is an attractive and powerful method in asymmetric synthesis.[1,2] A number of valuable products could be synthesized when reagents such as trialkylsilyl azide,[3–6] trimethylsilyl cyanide,[7–10] aryllithium,[11] halides[12–14] and alkylamines,[15] alcohols/phenols,[16,17] thiols,[18,19] as well as carboxylic acid[20] were used as nucleophiles for ring-opening reactions of epoxides. A catalytic asymmetric ring opening of *meso*-epoxide with aromatic amines is of particular interest because it has wider applications in the synthesis of pharmaceutically active compounds.[21] However, until now, this area has been scarcely studied.[15] Nevertheless, various lanthanides[21,22–25] with (*R*)/(*S*)-BINOL, Cr(Salen)[26] and Sc(bipyridine)[27] have been employed as catalysts for ring-opening of *meso* epoxide with alkyl/arylamines to generate β-amino alcohols. Herein, we report the opening of *meso*-stilbene oxide and cyclohexene oxide with aniline and substituted anilines, catalyzed by the recoverable (*S*)-BINOL-Ti complex to get enantio-enriched *syn*-β-amino alcohols and *trans*-β-amino alcohols in high yield (up to 95%) with 78% enantiomeric excess at ambient temperature. The catalyst was recovered after the first use and was recycled four times with the retention in its performance.

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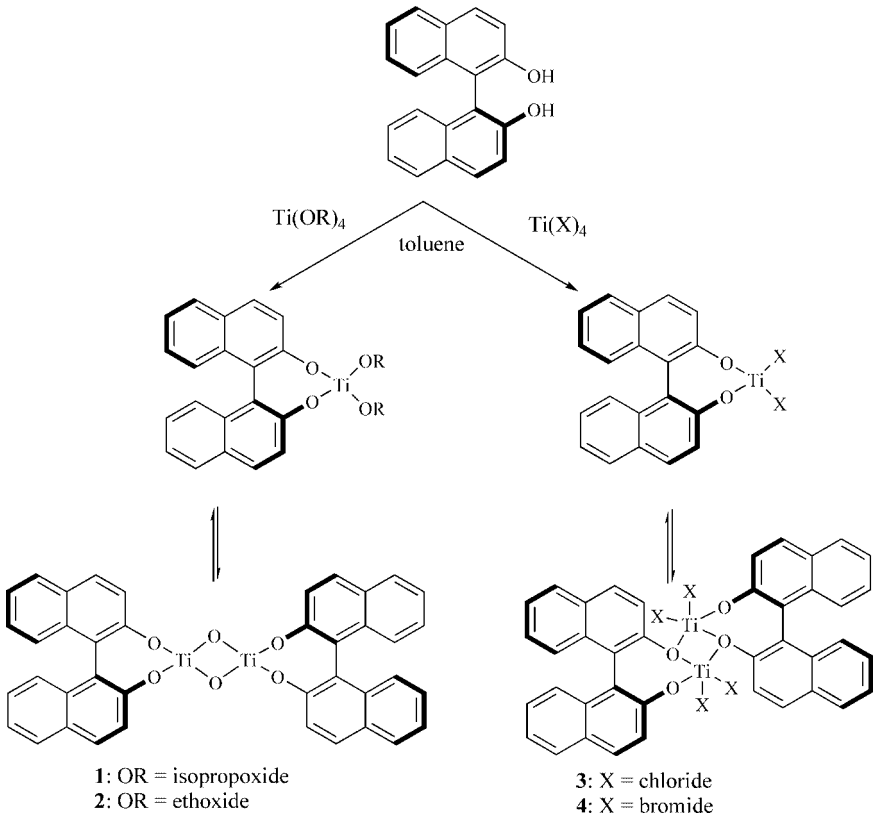
Results and Discussion

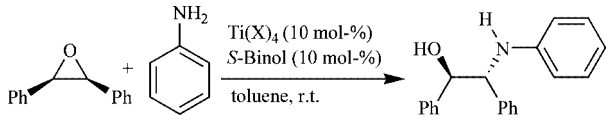
The enantioselective ring-opening reaction of *meso*-stilbene oxide with aniline was carried out by using complexes **1**–**4** generated in situ by the interaction of equimolar quantities of (*S*)-BINOL and an appropriate Ti source such as $Ti(OiPr)_4$, $Ti(OC_2H_5)_4$, $TiBr_4$ and $TiCl_4$ in toluene (Scheme 1). NMR and MS data for these complexes suggest the existence of catalytically active dimeric species, which are in equilibrium with the corresponding monomeric species. This observation is in agreement with previous reports.[28,29] The complexes **1** and **2** were found to be better catalysts to yield *syn*-β-amino alcohol in excellent yields (85–90%) with good enantioselectivity (*ee*, 63–67%) (Table 1, Entries 1, 2) than the complexes **3** and **4** (yield, 20–40%; *ee*, 35–51%) (Table 1, Entries 3, 4). The use of complexes **3** and **4** affected the rearrangement of the epoxide into 2-phenylacetophenone, which further decomposes to give benzaldehyde as major side product.

The complex **1** was further explored for carrying out the ring-opening reaction of *meso*-stilbene oxide with substituted anilines under identical reaction conditions. The result was 72–95% isolated yield of respective *syn*-β-amino alcohols with *ee* in the range of 64–78% (Table 2, Entries 5, 7–11). The product **7a** was recrystallized from toluene/hexane solvent mixture where the racemic product (Figure 1) preferentiallycrystallized out first leaving behind a solution with 98% *ee* for (1*R*,2*R*)-1,2-diphenyl-2-(phenylamino)ethanol. The above solution was treated with di-



Scheme 1. Synthesis of catalyst **1**–**4**.

Table 1. Asymmetric catalytic ring opening of *meso*-stilbene oxide with aniline using complexes **1**–**4**.



5 **6a** **7a**

Entry	Catalyst	Time [h]	Yield of **7a** [%][a]	*ee* [%][b]
1	**1**	7	90	67
2	**2**	8	85	63
3	**3**	5	20[c]	35
4	**4**	5	40[c]	51

[a] Isolated yield after chromatographic separation. [b] Determined by HPLC. [c] Epoxide was completely consumed and rest of the material was benzaldehyde.

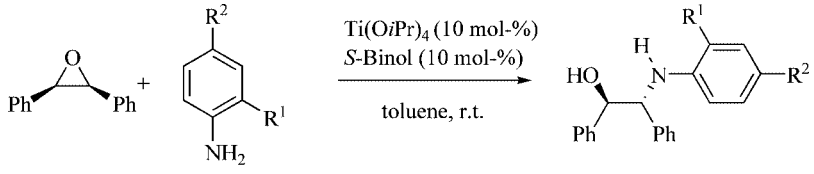
lute HCl, and the solid obtained was recrystallized from methanol/water (1:1) to yield crystals of **7a·HCl** with (1*R*,2*R*) configuration (Figure 2).

Further, it has been reported in the literature[21] that the use of additives improves the *ee* of amino alcohols. Therefore, we next examined the influence of *N*-, *O*- and *P*-coordinated additives such as triethylamine, pyridine, pyridine *N*-oxide, 4-(phenylpropyl)pyridine *N*-oxide, 1,4-bis(diphenylphosphanyl)butane and triphenylphosphane on the enantioselective ring opening of *meso*-stilbene oxide with aniline under identical reaction conditions, and the results are given in Table 3. Of all additives used, P-containing 1,4-diphenylphosphanylbutane and triphenylphosphane exhibited the best enantioselectivity (71% and 78% *ee*, respectively) (Entries 16, 17), which is significantly higher than the *ee* obtained for the reaction conducted in the absence of an additive (Table 1, Entry 1). However, other additives adversely affected the activity and selectivity (Table 3, Entries 12–15).

Furthermore, ring-opening reaction of epoxides has been reported to be solvent-dependent.[15,21] The ring opening of *meso*-stilbene oxide with aniline using (*S*)-(BINOL)-Ti in the presence of different solvents suggests that toluene (Table 4, Entry 18) is the solvent of choice. In case of other solvents CH_2Cl_2 (Entry 19) worked better than solvents having a heteroatom such as THF (Entry 20) and CH_3CN (Entry 21).[15,21]

We have also used the catalyst **1** for the ring opening of cyclohexene oxide (**8**) with different anilines **6a**–**c**, where *trans*-amino alcohols were obtained in excellent yields with moderate enantioselectivity (Table 5). The catalyst **1** was found to be very active for the ring opening of cyclohexene oxide with aniline in the presence of triphenylphosphane (TPP) (Table 5, Entry 23) giving 92% isolated yield and 39% *ee* in 2 h. These results are significantly superior as compared to the report where lanthanide iodobinapthol-ate[25] was used as a catalyst for a similar reaction which gave 55% yield with 20% *ee* in 18 h. The absolute configuration was determined by comparing the optical rotation and the HPLC profile with literature. Details are given in the Experimental Section.

Table 2. Asymmetric catalytic ring-opening of *meso*-stilbene oxide with anilines using complex **1**.



5 **6** **7a-f**

6a: $R^1 = H$, $R^2 = H$ **6d**: $R^1 = H$, $R^2 = Cl$
6b: $R^1 = H$, $R^2 = OMe$ **6e**: $R^1 = Cl$, $R^2 = H$
6c: $R^1 = OMe$, $R^2 = H$ **6f**: $R^1 = H$, $R^2 = Me$

Entry	Amines	Time [h]	Isolated yield **7a–f** [%][a]	*ee* [%][b]
5 (6)	**6a**	7	90	67 (98)[c]
7	**6b**	20	72	78
8	**6c**	8	90	64
9	**6d**	5	95	65
10	**6e**	5	95	67
11	**6f**	10	80	71

[a] Isolated yield after chromatographic separation. [b] Determined by HPLC. [c] Value in parenthesis refers to *ee* after recrystallization.

Table 3. Effect of additives on catalytic asymmetric ring opening of *meso*-stilbene oxide with aniline using complex **1**.

Entry	Additives	Time (h)	Isolated yield **7a** [%][a]	*ee* [%][b]
12	triethylamine	24	10	0
13	pyridine	24	30	27
14	pyridine *N*-oxide	24	10	23
15	4-(phenylpropyl)pyridine *N*-oxide	20	30	30
16	1,4-bis(diphenylphosphanyl)butane	7	90	71
17	triphenylphosphane	7	90	78

[a] Isolated yield after chromatographic separation. [b] Determined by HPLC.

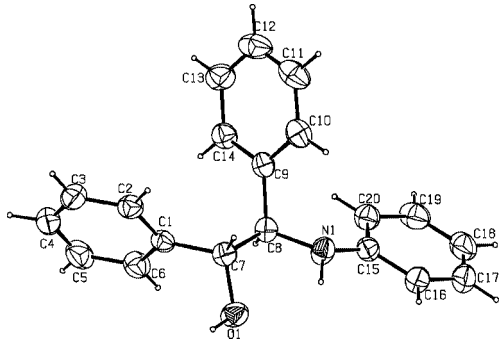


Figure 1. ORTEP diagram (40% probability factor for the thermal ellipsoid) with atom-numbering scheme for racemic 1,2-diphenyl-2-(phenylamino)ethanol.

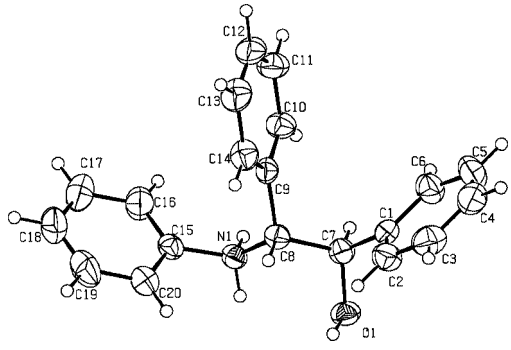


Figure 2. ORTEP diagram (40% probability factor for the thermal ellipsoid) of the cationic part of compound (1*R*,2*R*)-diphenyl-2-(phenylamino)ethanol hydrochloride with atom-numbering scheme.

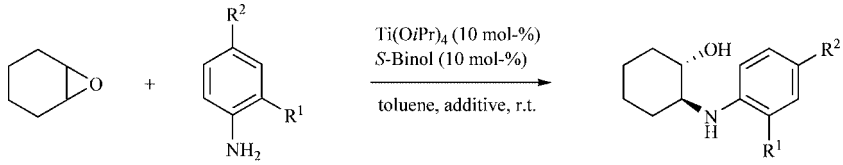
The recycling experiments were conducted with the (*S*)-BINOL-Ti complex **1**. The recovered catalyst was characterized by MS, NMR and elemental analysis, and the data correspond to the fresh complex. The recovered catalyst was used for subsequent catalytic runs for the ring opening of *meso*-stilbene oxide with aniline that showed essentially the same performance for four catalytic runs (Table 6).

Table 4. Effect of different solvent on asymmetric ring opening of *meso*-stilbene oxide with aniline using complex **1**.

Entry	Solvent	Time [h]	Isolated yield **7a** [%][a]	*ee* [%][b]
18	toluene	7	90	67
19	CH_2Cl_2	7	80	50
20	THF	7	75	29
21	CH_3CN	20	15	13

[a] Isolated yield after chromatographic separation. [b] Determined by HPLC.

Table 5. Effect of additives on catalytic asymmetric ring opening of cyclohexene oxide with aniline.



8 **6a**: R^1 = H, R^2 = H; **6b**: R^1 = H, R^2 = OMe; **6c**: R^1 = OMe, R^2 = H **9a-c**

Entry	Temp. (°C)	Additive	Amine	Time [h]	Isolated yield **9a**–**c** [%][a]	*ee* [%][b]
22	25	–	**6a**	3 h	90	21
23	25	TPP	**6a**	2 h	92	39
24	25	TPP	**6b**	3 h	93	48
25	25	TPP	**6c**	4 h	95	63

[a] Isolated yield after chromatographic separation. [b] Determined by HPLC.

Table 6. Asymmetric catalytic aminolysis of *meso*-stilbene oxide by aniline with recycled complex **1**.

Run	1	2	3	4
Time (h)	7	7	7	7
Isolated yield	85	75	70	60
ee	67	65	64	64

Determination of the Absolute Configuration of β-Amino Alcohols

As there is no X-ray crystal structure determination of the absolute configuration of **7a** available in the literature, an attempt was made to get suitable crystals for X-ray diffraction studies of the product **7a** (Table 2, Entry 6). A plate-like crystal of **7a** was obtained from toluene/hexane (1:1) solution. This compound crystallized in the centrosymmetric space group $P2_1/c$, and the established crystal structure of the compound showed the presence of a racemic mixture with equimolar amounts of *R*,*R* and *S*,*S* with respect to the chiral center C7 and C8, thus confirming *rac*-1,2-diphenyl-2-(phenylamino)ethanol. An ORTEP[30] diagram of the compound with atom-numbering scheme is shown in Figure 1. Block crystals with different morphology were obtained from the same crystallization experiment, as a second crop after three days. In an attempt to derive the absolute configuration at the C7 and C8 asymmetric carbon atom, we converted the compound (1*R*,2*R*)-1,2-diphenyl-2-(phenylamino)ethanol to its hydrochloride salt. The ORTEP diagram of the cationic part of the compound with an atom-numbering scheme is depicted in Figure 2. This compound crystallizes in the chiral space group $P2_1$, and the established crystal structure revealed the configuration as (1*R*,2*R*) with respect to the chiral carbon atoms C7 and C8, respectively.

Conclusion

In conclusion, we have developed a highly regio-, diastereo-, and enantioselective ring-opening reaction of *meso*-stilbene oxide with anilines at room temperature catalyzed by the recyclable (*S*)-(–)-(BINOL)-Ti complex to give the respective *syn*-β-amino alcohols in 95% isolated yield with 78% *ee*. The commercial availability of the BINOL ligand and Ti(O*i*Pr)$_4$ as well as the recycling of the catalyst (4 runs) make this protocol suitable for industrial use.

Experimental Section

General: The solvents were dried by standard procedures, distilled and stored under nitrogen. All melting points reported are uncorrected. NMR spectra were obtained with a Bruker F113V spectrometer (200 MHz and 50 MHz for ^{1}H and ^{13}C, respectively) and are referenced internally with TMS. FTIR spectra were recorded with a Perkin–Elmer Spectrum GX spectrophotometer in KBr window. High-resolution mass spectra were obtained with a LC-MS (Q-TOFF) LC (Waters), MS (Micromass) instruments. Product purification was performed by flash chromatography using silica gel 60–200 mesh purchased from s. d. Fine-Chem. Limited Mumbai (India). Enantiomeric excesses (*ee*) were determined by HPLC (Shimadzu SCL-10AVP) using Daicel Chiralpak AD, OD and OJ chiral columns (wavelengths 243 nm) with 2-propanol/hexane as eluent. Optical rotations were measured with a Digipol 781 Automatic Polarimeter Rudolph Instruments. $TiCl_4$, $TiBr_4$, Ti(OEt)$_4$, Ti(O*i*Pr)$_4$, aniline, 2-methoxyaniline, 4-methoxyaniline, 2-chloroaniline, 4-chloroaniline and 4-methylaniline as well as *meso*-stilbene oxide were purchased from Aldrich Chemicals and were used as received.

General Procedure for Asymmetric Catalytic Aminolysis of *meso*-Stilbene Oxide: To a 5-mL round-bottom flask fitted with a rubber septum and equipped with a magnetic stirring bar, *S*-BINOL (0.025 mmol) and Ti(O*i*Pr)$_4$ (0.025 mmol) were added in dry toluene (0.5 mL) at room temperature (27 °C). The reaction mixture was stirred at 27 °C for 30 min. To the above mixture, were added *meso*-stilbene oxide and anilines all at once in equimolar amount (0.25 mmol), and the reaction was stirred for the specified time. The progress of the reaction was checked by TLC using hexane/ethyl acetate (8:2) as mobile phase. The reaction mixture was concentrated and hexane/diethyl ether (9:1) was used for the precipitation of the catalyst. The catalyst was filtered off, dried under vacuum and kept for further use. The filtrate containing the prod-

uct was concentrated and purified by column chromatography using silica gel 60–200 mesh as stationary phase and hexane/ethyl acetate (8:2) as mobile phase. All products were characterized by ^{1}H and ^{13}C NMR spectroscopy.

Crystal Data Collection and Refinement: The diffraction experiments for all the three crystals were carried out with a Bruker AXS SMART APEX CCD diffractometer at room temparature (300 K). The SMART[31] program was used for collecting frames of data, indexing reflection, and determination of lattice parameters. SAINT[31] program for integration of the intensity of reflections and scaling, SADABS[32] program for absorption correction, and SHELXTL[33] program for space group, structure determination and least-squares refinements on F^2. The structures were solved by direct methods. H atoms bonded to nitrogen atoms in both compounds were found on difference Fourier maps, while the remaining H atoms were placed on idealized positions. The final refinement was performed by full-matrix least-squares.

CCDC-266779 and -283380 contain the supplementary crystallographic data for **7a** and **7a**·hydrochloride. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

(1*R*,2*R*)-1,2-Diphenyl-2-(phenylamino)ethanol (7a):[26,27] The title compound was isolated by column chromatography (hexane/AcOEt, 90:10) as a white solid. M.p. 114–116 °C. The *ee* was determined with HPLC (Chiralpak OD column), mobile phase: *n*-hexane/*i*PrOH (85:15); flow rate: 1 mL/min, λ = 247 nm, R_t (1*R*,2*R*): 12.7 min, (1*S*,2*S*): 17.1 min. Only one diastereomer was observed by ^{1}H NMR and HPLC analysis. $[\alpha]_D^{27}$ = +32.7 (*c* = 4, $CHCl_3$, 77% *ee*). LC-MS: *m*/*z* = 290 $[M + H]^+$, 272 (base peak) $[M – OH]^+$, 312 $[M + Na]^+$. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.38 (br. s, OH), 4.40 (br. s, NH), 4.51 (d, *J* = 5.8 Hz, 1 H), 4.85 (d, *J* = 5.8 Hz, 1 H), 6.50–6.53 (m, 2 H), 6.59–6.67 (m, 1 H), 7.01–7.09 (m, 2 H), 7.21–7.25 (m, 10 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 64.8, 78.1, 114.2, 117.9, 126.6, 127.3, 127.5, 128.2, 128.5, 129.0, 140.0, 140.6, 147.0 ppm. IR (KBr): $\tilde{\nu}$ = 3546, 3407, 3027, 2880, 2849, 1600, 1502, 1451, 1429, 1320, 1033, 752, 695 cm^{-1}.

(1*R*,2*R*)-1,2-Diphenyl-2-(phenylamino)ethanol Hydrochloride (7a·HCl): The compound **7a** (0.05 mmol) was dissolved in MeOH (4 mL) and 1 N HCl (4 mL) was added, then refluxed for 30 min. The resulting solution was filtered through 0.2-mμ filter and kept for crystallization. After 24 h we obtained the single crystal of **7a**·HCl. M.p. 212–215 °C. $[\alpha]_D^{27}$ = –26.1 (*c* = 0.75, MeOH, 98% *ee*). LC-MS: *m*/*z* = 290 $[M + H]^+$. IR (KBr): $\tilde{\nu}$ = 3367, 3058, 3033, 2915, 2863, 2737, 2650, 2526, 2372, 1970, 1580, 1497, 1455, 1371, 1341, 1205, 1064, 1019, 960, 767, 748, 698 cm^{-1}.

(1*R*,2*R*)-2-(4-Methoxyphenylamino)-1,2-diphenylethanol (7b):[26,27] The title compound was isolated by column chromatography (hexane/AcOEt, 85:15) as a yellow solid. M.p. 98–102 °C. The *ee* was determined with HPLC using (Chiralpak OD column), hexane/*i*PrOH (90:10); flow rate 0.8 mL/min, λ = 243 nm, R_t (1*S*,2*S*): 29.3 min, (1*R*,2*R*): 35.3 min. Only one diastereomer was observed by NMR and HPLC analysis. $[\alpha]_D^{27}$ = +30.7 (*c* = 1, $CHCl_3$, 78% *ee*). LC-MS: *m*/*z* = 661 $[2M + Na]^+$, 320 (base peak) $[M + H]^+$, 342 $[M + Na]^+$. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.64 (s, 3 H), 4.38 (d, *J* = 6.4 Hz, 1 H), 4.85 (d, *J* = 6.4 Hz, 1 H), 6.47–6.51 (m, 2 H), 6.62–6.66 (m, 2 H), 7.01–7.09 (m, 2 H), 7.15–7.22 (m, 10 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 55.7, 66.2, 78.1, 114.7, 115.8, 126.7, 127.3, 127.8, 127.9, 128.5, 128.7, 140.3, 140.7, 141.4, 152.6 ppm. IR (KBr): $\tilde{\nu}$ = 3483, 3393, 3026, 2964, 2833, 1807, 1510, 1453, 1254, 1024, 819, 753, 700 cm^{-1}.

(1*R*,2*R*)-2-(2-Methoxyphenylamino)-1,2-diphenylethanol (7c):[26] The title compound was isolated by column chromatography (hexane/AcOEt, 90:10) as a white solid. M.p. 80 °C. The *ee* was determined with HPLC (Chiralpak OJ column), mobile phase: hexane/*i*PrOH (80:20), flow rate 0.5 mL/min, λ = 254 nm, R_t (1*S*,2*S*): 29.9 min, (1*R*,2*R*): 33.3 min. Only one diastereomer was observed by NMR and HPLC analysis. $[\alpha]_D^{27}$ = +43.5 (*c* = 1.2, $CHCl_3$, 64% *ee*). LC-MS: *m*/*z* = 661 $[2M + Na]^+$, 320 $[M + H]^+$, 302 (base peak) $[M – OH]^+$, 342 $[M + Na]^+$. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.73 (br. s, OH), 3.79 (s, 3 H), 4.43 (d, *J* = 6.2 Hz, 1 H), 4.79 (d, *J* = 6.4 Hz, 1 H), 5.19 (br. s, NH), 6.32 (dd, *J* = 1.6 Hz, 7.2 Hz, 1 H), 6.51–6.70 (m, 3 H), 7.12– 7.20 (m, 10 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 55.6, 64.9, 78.3, 109.6, 111.7, 117.1, 121.0, 126.7, 127.3, 127.7, 128.0, 128.3, 131.1, 140.2, 140.7, 140.6, 147.3 ppm. IR (KBr): $\tilde{\nu}$ = 3407, 3062, 3030, 2936, 2835, 1810, 1698, 1601, 1515, 1248, 1027, 846, 740, 700 cm^{-1}.

(1*R*,2*R*)-2-(4-Chlorophenylamino)-1,2-diphenylethanol (7d): The title compound was isolated by column chromatography (hexane/AcOEt, 85:15) as a white solid. M.p. 95 °C. The *ee* was determined with HPLC (Chiralpak AD Column), mobile phase: hexane/*i*PrOH (80:20), flow rate 0.5 mL/min, λ = 254 nm and R_t(1*S*,2*S*) 21.2 min, (1*R*,2*R*): 24.7 min. Only one diastereomer was observed by NMR and HPLC analysis. $[\alpha]_D^{27}$ = +40.6 (*c* = 1.2, $CHCl_3$, 77% *ee*). LC-MS: *m*/*z* = 324 $[M + H]^+$, 347 $[M + Na]^+$, 306 $[M – OH]^+$, 289 $[M – Cl]^+$, 271 (base peak) $[M – OH – Cl]^+$. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.38 (br. s, 1 H), 4.47 (d, *J* = 5.6 Hz, 1 H), 4.70 (br. s, 1 H, NH), 4.86 (d, *J* = 5.6 Hz, 1 H), 6.41 (d, *J* = 8.8 Hz, 2 H), 6.98 (d, *J* = 8.0 Hz, 2 H), 7.15–7.30 (m, 10 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 64.7, 77.9, 126.4, 127.2, 127.6, 128.0, 128.3, 128.6, 139.8, 140.1, 140.4, 145.8 ppm. IR (KBr): $\tilde{\nu}$ = 3396, 3063, 3031, 2960, 2929, 2860, 1812, 1722, 1599, 1496, 1268, 1073, 820, 739, 700 cm^{-1}.

(1*R*,2*R*)-2-(2-Chlorophenylamino)-1,2-diphenylethanol (7e): The title compound was isolated by column chromatography (hexane/AcOEt, 85:15) as a white solid. M.p. 92 °C. The *ee* was determined with HPLC (Chiralpak OJ column), mobile phase: hexane/*i*PrOH (80:20); flow rate 0.5 mL/min, λ = 254 nm, R_t (1*R*,2*R*) 27.9 min, (1*S*,2*S*): 30.1 min. Only one diastereomer was observed by NMR and HPLC analysis. $[\alpha]_D^{27}$ = +25.3 (*c* = 1.2, $CHCl_3$, 77% *ee*). LC-MS: *m*/*z* = 324 $[M + H]^+$, 347 $[M + Na]^+$, 306 (base peak) $[M – OH]^+$, 289 $[M – Cl]^+$, 271 $[M – OH – Cl]^+$. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.34 (d, *J* = 2.6 Hz, OH), 4.55 (d, *J* = 5.2 Hz, 1 H), 4.90 (dd, *J* = 2.4 Hz, 5.0 Hz, 1 H), 5.41 (d, *J* = 4.6 Hz, NH), 6.29–6.90 (m, 4 H), 7.16–7.27 (m, 10 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 64.7, 77.8, 126.4, 127.2, 127.5, 128.0, 128.3, 128.7, 139.9, 140.1, 140.3, 145.7 ppm. IR (KBr): $\tilde{\nu}$ = 3395, 3062, 3031, 2960, 2929, 2860, 1811, 1722, 1595, 1496, 1268, 1027, 846, 740, 700 cm^{-1}.

(1*R*,2*R*)-2-(4-Methylphenylamino)-1,2-diphenylethanol (7f): The title compound was isolated by column chromatography (hexane/AcOEt, 85:15) as a white solid. M.p. 85 °C. The *ee* was determined with HPLC (Chiralpak AD column), mobile phase: hexane/*i*PrOH (80:20); flow rate 0.5 mL/min λ = 254 nm, R_t (1*R*,2*R*): 21.2 min, (1*S*,2*S*): 24.7 min. Only one diastereomer was observed by NMR and HPLC analysis. $[\alpha]_D^{27}$ = +22.6 (*c* = 1, $CHCl_3$, 77% *ee*). LC-MS: *m*/*z* = 304 $[M + H]^+$, 286 (base peak) $[M – OH]^+$. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.15 (s, 3 H), 4.45 (d, *J* = 6.2 Hz, 1 H), 4.81 (d, *J* = 6.2 Hz, 1 H), 6.42–6.46 (m, 2 H), 6.84–6.88 (m, 2 H), 7.19–7.23 (m, 10 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.3, 65.2, 78.0, 114.4, 126.5, 127.2, 127.6, 128.1, 128.3, 129.5, 139.3, 139.5.4, 146.5 ppm. IR (KBr): $\tilde{\nu}$ = 3399, 3061, 3029, 2859, 2831, 1813, 1616, 1518, 1490, 1259, 1044, 815, 768, 700 cm^{-1}.

(1*S*,2*S*)-2-(Phenylamino)cyclohexen-1-ol (9a):[22,25,27] The title compound was isolated by column chromatography (hexane/AcOEt,

90:10) as a white solid. M.p. 58–60 °C. The *ee* was determined with HPLC (Chiralpak OD column), mobile phase: 85:15 hexane/*i*PrOH; flow rate 1 mL/min, λ = 247 nm, R_t. (1*S*,2*S*): 10.1 min, (1*R*,2*R*): 10.7 min. $[a]_D^{27}$ = +31.9 (*c* = 3.3, $CHCl_3$, 39% *ee*). LCMS: *m*/*z* 192 $[M + H]^+$, 214 $[M + Na]^+$. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.03–1.41 (m, 4 H), 1.71–1.77 (m, 2 H), 2.09–2.15 (m, 2 H), 2.89 (m, 2 H), 3.13 (ddd, *J* = 3.9 Hz, *J* = 10.0 Hz, *J* = 10.1 Hz, 1 H), 3.33 (ddd, *J* = 4.2 Hz, *J* = 10.4 Hz, *J* = 10.5 Hz, 1 H), 6.7–7.2 (m, 2 H), 7.21–7.25 (m, 5 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.2, 24.9, 31.5, 33.1, 60.1, 74.4, 114.3, 118.3, 129.3, 147.8 ppm. IR (KBr): $\tilde{\nu}$ = 3354, 2931, 2858, 1602, 1501, 1448, 1320, 1067, 748 cm^{-1}.

(1*S*,2*S*)-2-(2-Methoxyphenylamino)cyclohexan-1-ol (9b):[25] The title compound was isolated by column chromatography (hexane/AcOEt, 90:10) as a white solid. M.p. 68–70 °C. The *ee* was determined with HPLC (Chiralpak OJ column), mobile phase: hexane/*i*PrOH (80:20); flow rate 0.5 mL/ min, λ = 247 nm, R_t (1*S*,2*S*): 17.1 min, (1*R*,2*R*): 19.2 min. $[a]_D^{27}$ = +49.6 (*c* = 3.0, CH_2Cl_2, 63% *ee*).^1H NMR (200 MHz, $CDCl_3$): ^1H NMR ($CDCl_3$): δ = 0.97–1.15 (m, 1 H), 1.24–1.50 (m, 3 H), 1.68–1.78 (m, 2 H), 2.04–2.16 (m, 2 H), 2.85 (br. s, 1 H), 3.07–3.19 (m, 1 H), 3.34–3.46 (m, 1 H), 3.83 (s, 3 H), 6.63–6.89 (m, 4 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.2, 25.0, 31.5, 33.0, 55.4, 55.6, 74.5, 109.7, 111.4, 117.2, 121.2, 137.5, 147.5 ppm. IR (in KBr): $\tilde{\nu}$ = 3616, 3429, 3067, 2964, 1602, 1511, 1456, 1430, 1341, 1247, 1180, 1121, 1050, 1030, 977, 945 cm^{-1}.

(1*S*,2*S*)-2-(4-Methoxyphenylamino)cyclohexan-1-ol (9c):[21,25] The title compound was isolated by column chromatography (hexane/AcOEt, 85:15) as a white solid. M.p. 62–64 °C. The *ee* was determined with HPLC (Chiralpak OD column), mobile phase: hexane/*i*PrOH (80:20); flow rate 0.5 mL/min, λ = 247 nm. R_t (1*S*,2*S*): 16.2 min, (1*R*,2*R*): 24.3 min. $[a]_D^{27}$ = +40.1 (*c* = 3.2, CH_2Cl_2, 48% *ee*). ^1H NMR (200 MHz, $CDCl_3$): δ = 0.85–1.10 (m, 1 H), 1.12–1.40 (m, 3 H), 1.60–1.80 (m, 2 H), 2.0–2.18 (m, 2 H), 2.92–3.04 (m, 1 H), 2.60 (br. s, 1 H), 3.24–3.55 (m, 1 H), 3.73 (s, 3 H), 6.66 (d, *J* = 8.8 Hz, 2 H), 6.76 (d, *J* = 8.8 Hz, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.2, 25.0, 31.4, 33.0, 55.6, 61.6, 74.3, 114.7, 116.3, 141.5, 152.8 ppm. IR (KBr): $\tilde{\nu}$ = 3677, 3529, 3366, 3021, 3013, 2938, 2861, 2836, 1612, 1512, 1465, 1450, 1401, 1296, 1239, 1221, 1180, 1136, 1067, 1038 cm^{-1}.

Crystal Structure Analysis of 7a: $C_{20}H_{19}NO$, *M*r = 289.36, monoclinic, space group: $P2_1/c$, *a* = 7.8784(6), *b* = 18.5946(15), *c* = 10.9515(9) Å, β = 94.907(2)°, *V* = 1598.5(2) $Å^3$, $\rho_{calcd.}$ = 1.202 g·cm^{-3}, *Z* = 4, *F*(000) = 616, crystal dimensions: 0.16 × 0.12 × 0.08 mm. A total of 9579 reflections was collected at 273(2) K using a Bruker Smart Apex CCD diffractometer with θ range of 2.16–28.29°, 3713 reflections were unique (R_{int} = 0.0146). The structure was solved by direct methods. Full-matrix least-squares refinement was based on F^2, with all non-hydrogen atoms anisotropic and hydrogen atoms isotropic. The refinement converged R_1 = 0.0431, wR_2 = 0.1119 for all data; final GOF: 1.039; largest peak/hole in the final difference Fourier map: 0.171/–0.116 e·$Å^{-3}$.

Crystal Structure Analysis of (1*R*,2*R*)-(–)-7a·HCl: $C_{20}H_{20}ClNO$, *M*r = 325.82, monoclinic, space group: $P2_1$, *a* = 11.452(4), *b* = 6.789(2), *c* = 11.502(4) Å, β = 98.107(6)°, *V* = 885.2(5) $Å^3$, ρcalcd. = 1.222 g·cm^{-3}, *Z* = 2, *F*(000) = 344, crystal dimensions: 0.20 × 0.14 × 0.080 mm. A total of 10535 reflections was collected at 273(2) K with a Bruker SMART Apex CCD diffractometer with θ range of 1.79–28.26°, 3740 reflections were unique (R_{int} = 0.0230). The structure was solved by direct methods. Full-matrix least-squares refinement was based on F^2, with all non-hydrogen atoms anisotropic and hydrogen atoms isotropic. The refinement converged at R_1 = 0.0458, wR_2 = 0.1081 for all data; final GOF: 1.081; largest peak/hole in the final difference Fourier map: 0.331/–0.187 e·$Å^{-3}$ and absolute structure parameter 0.10(8).

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