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Highly Enantioselective Syntheses of Chiral β-Amino Alcohols in the Presence of Chiral Ti^{IV} Schiff Base Complexes as Catalysts

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Two new chiral Schiff bases **1** and **2** were prepared by condensation of 3,3′-di-*tert*-butyl-5,5′-methylenebis(salicylaldehyde) and 3,3′-dimethyl-5,5′-methylenebis(salicylaldehyde) with (1*R*,2*S*)-(–)-2-aminodiphenylethanol and were characterized by elemental analysis, ^{1}H NMR, ^{13}C NMR, IR, UV/Vis, and CD spectroscopy, optical rotation, and mass spectrometry. Highly enantioselective ring opening reactions of *meso*-stilbene oxide, cyclohexene oxide, cyclooctene oxide, and *cis*-butene oxide with anilines in the presence of several additives were carried out in the presence of Ti^{IV} complexes generated in situ through the interaction of $Ti(OiPr)_4$ with chiral Schiff bases **1** and **2** at 0 °C. Excellent yields (>99%) of chiral β-amino alcohols with high enantioselectivity (*ee*, >99%) were achieved in 10 h when chiral imines were used as additives. The catalyst **1**-$Ti(OiPr)_4$ worked better than the catalyst **2**-$Ti(OiPr)_4$ in terms of reactivity and enantioselecitivity for the epoxide ring opening reactions to produce chiral β-amino alcohols in high optical purity. The chiral catalyst used in this study was recoverable and recyclable several times with retention of its performance.

Introduction

Chiral *syn*- and *anti*-β-amino alcohols are an important class of organic compounds, their structural units being present in numerous natural products, such as antibiotics,[1a–1c] amino sugars,[1d] and β-adrenergic blocking agents.[1e–1h] They play significant roles in the treatment of a wide variety of human disorders and as chiral auxiliaries[2] in organic synthesis. To achieve high enantioselectivity in the production of *syn*- and *anti*-β-amino alcohols through chiral catalytic routes, several approaches exist. These include: a) Sharpless osmium-catalyzed aminohydroxylation of *trans*-alkenes,[3] b) direct addition of α-hydroxy ketones to imines,[4] c) ring opening of *meso*-epoxides with alkyl-/arylamines in the presence of niobium,[5] copper(II),[6] and various lanthanides with (*R*)/(*S*)-BINOL,[7] Cr(Salen),[8] and chiral bipyridine complexes with scandium, indium, and bismuth as catalysts,[9] and d) aminolytic kinetic resolution of racemic terminal and aromatic *trans*-epoxides with anilines.[8,10] Recent developments in asymmetric ring opening reactions of *meso*-epoxides with anilines have prompted us to design novel ligands that display high enantioselectivity and substrate generality over a broad spectrum of reactions. We have also addressed the issues of catalyst recovery and reuse[7f,8b] while designing ligands for ring opening reaction of *meso*- and *trans*-epoxides. Accordingly, here we report the synthesis of new chiral Schiff base ligands obtained by condensation of (1*R*,2*S*)-(–)-2-amino-1,2-diphenylethanol with 3,3′-di-*tert*-butyl-5,5′-methylenebis(salicylaldehyde) and 3,3′-dimethyl-5,5′-methylenebis(salicylaldehyde). Chiral Ti^{IV} Schiff base complexes were generated in situ from these synthesized chiral ligands, in order to catalyze enantioselective ring opening reactions of *meso*-stilbene oxide, cyclohexene oxide, cyclooctene oxide, and *cis*-butene oxide with anilines at 0 °C in the presence of various additives, chiral imines notable among them. Chiral β-amino alcohols were obtained with excellent yields (99%) and enantioselectivities (*ee*, >99%) in 10 h at 0 °C, with the added advantage of catalyst recycling.

Results and Discussion

Chiral Schiff base ligands **1** and **2** were prepared from the corresponding 3,3′-di-*tert*-butyl-5,5′-methylenebis(salicylaldehyde) or 3,3′-dimethyl-5,5′-methylenebis(salicylaldehyde) and (1*R*,2*S*)-(–)-2-amino-1,2-diphenylethanol as shown in Scheme 1 and were characterized by ^{1}H NMR, ^{13}C NMR, IR, UV/Vis, and CD spectroscopy, optical rotation, and mass spectrometry (see data given in the Exp. Sect.).

To begin with, ring opening of *meso*-stilbene oxide with aniline was conducted in the presence of 20 mol-% of **1** with $Ti(OiPr)_4$, as a catalyst generated in situ, at 0 °C in toluene, with the ligand to metal ratios being kept at 1:1, 1:2, and 1:3. The data are presented in Table 1 and Figure 1. It is evident from the reaction profile that the product formation

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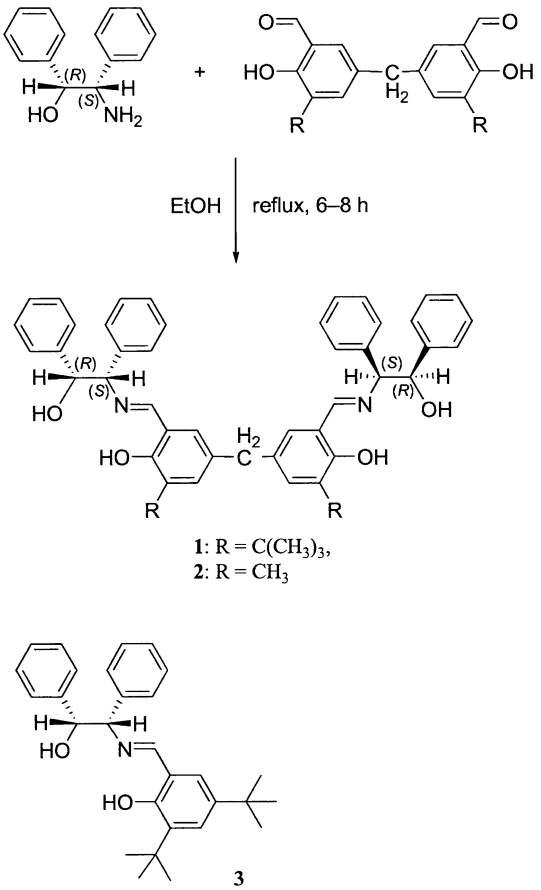


Scheme 1. Synthesis of chiral ligands **1**, **2**, and **3**.

with respect to time (Figure 1) was highest for a 1:1 ligand/metal ratio, followed by 1:2 and then by 1:3, but the enantioselectivity remained the same for all the compositions (Table 1, Entries 1–3). Further, the catalytic reaction was fast in the first 30 minutes for all the three reactions, with product formation then displaying linear behavior to give the highest conversion in 10 h. Such kinetic behavior, with rapid initial product formation, has also been reported for different organic transformations.[11] In view of these results, for our rest of our catalytic experiments we used a 1:1 ligand to metal ratio to provide the catalyst for epoxide ring opening reactions in the preparation of chiral β-amino alcohols.

The chiral catalyst formed from ligand **2** and Ti(O*i*Pr)$_4$ in the above optimized ligand to metal ratio was also generated in situ and evaluated for enantioselective ring opening of *meso*-stilbene oxide with aniline. However, the yields and *ee* values for the chiral *syn*-β-amino alcohol obtained with the same substrate were relatively low after 10 h (Table 1, Entry 4). It has been reported in the literature that the use of additives can improve the reactivity and enantioselectivity of ring opening of *meso*-epoxides with anilines.[7a,7b,7f] Accordingly, when the above reaction was conducted in the presence of 20 mol-% of various additives such as triphenylphosphane, triethylamine, and simple Schiff bases (**a**–**d**; Table 1) there were significant improvements in the yields and *ee* values of the product (Table 1,

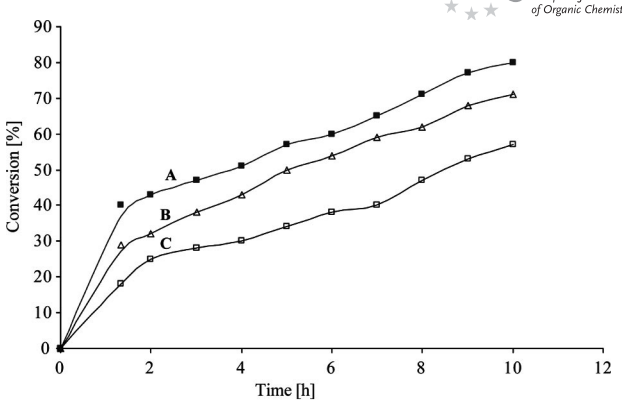


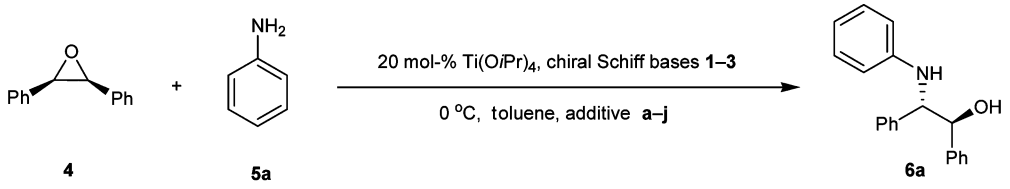
Figure 1. % Conversion of *syn*-β-amino alcohol obtained from ring opening of *meso*-stilbene oxide with aniline vs. time for different M/L ratios: **A**) M/L 1:1, **B**) M/L 1:2, and **C**) M/L 1:3 in toluene at 0 °C.

Entries 5–12). At this point we thought of using the chiral form of a Schiff base (**e**, Table 1) as an additive to see if there was any synergy between the chirality of the catalyst **1**-Ti(O*i*Pr)$_4$ and of the additive (**e**). The results were truly remarkable, as there was an incredible improvement in the *ee* of the product (Table 1, Entries 13, 14). It is to be noted that when we used (*R*)-*N*-benzylidene-1-phenylethanamine – the chiral imine with the opposite configuration – as additive, there was a decrease in the yield together with a significant drop in the *ee* (Table 1, Entry 15). These experiments suggest the existence of synergy between the catalyst and the additive during the transfer of chirality in the ring opening reaction catalytic cycle. Such an observation had also been reported previously for chiral BINOL systems.[12]

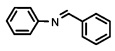
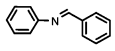
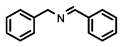
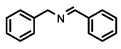
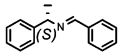
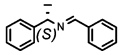
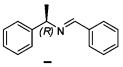
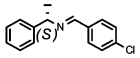
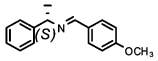
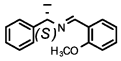
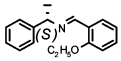
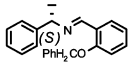
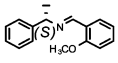
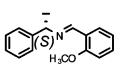
Overall, the complex **1**-Ti(O*i*Pr)$_4$ was distinctly better in all the experiments conducted above, so further trials to improve the catalytic process were conducted with the **1**-Ti(O*i*Pr)$_4$ complex as catalyst. Accordingly, using the base data given in Entry 13 (Table 1) we examined the effects of electronic and steric features of chiral additives (Table 1, **f**–**j**; i.e., 4-chloro-, 4-methoxy-, 2-methoxy-, 2-ethoxy-, and 2-phenoxyimines) in the ring opening of *meso*-stilbene oxide with aniline (Entries 16–20). Of all the substituted chiral imines used, the 2-methoxyimine system (**h**) was found to be the best additive (Table 1, Entry 18, Figure 2). The presence of a bulkier group at the 2-position adversely affected both reactivity and enantioselectivity (Table 1, Entries 19, 20).

For purposes of comparison, the chiral monomeric Schiff base **3** (Scheme 1) was also synthesized by treatment of (1*R*,2*S*)-(–)-2-amino-1,2-diphenylethanol with 3,5-di-*tert*-butylsalicylaldehyde (data given in Exp. Sect.). The complex **3**-Ti(O*i*Pr)$_4$ was also generated in situ by treatment of ligand **3** with Ti(O*i*Pr)$_4$ in 1:1 and 1:0.5 molar ratios, and was used as a catalyst in the ring opening reaction of *meso*-stilbene oxide with aniline in the presence of **h** as an additive under the same reaction conditions. The chiral *syn*-β-amino alcohol was obtained in 75% yield and 64% *ee* in 24 h in the case of the **3**-Ti(O*i*Pr)$_4$ 1:1 system, while with

Table 1. Product yield and *ee* values of asymmetric ring opening[a] of *meso*-stilbene oxide with aniline in the presence of complexes **1**-Ti(O*i*Pr)$_4$, **2**-Ti(O*i*Pr)$_4$, and **3**-Ti(O*i*Pr)$_4$.



4 **5a** **6a**

Entry	Catalyst	Additive	Time [h]	Yield [%][g]	*ee* [%][h]	Configuration of β-amino alcohol[i]
1	**1**-Ti(O*i*Pr)$_4$	none	10	79	60	1*S*,2*S*
2[b]	**1**-Ti(O*i*Pr)$_4$	none	10	69	60	1*S*,2*S*
3[c]	**1**-Ti(O*i*Pr)$_4$	none	10	55	60	1*S*,2*S*
4	**2**-Ti(O*i*Pr)$_4$	none	10	66	50	1*S*,2*S*
5	**1**-Ti(O*i*Pr)$_4$	 **a**	10	89	65	1*S*,2*S*
6	**2**-Ti(O*i*Pr)$_4$	 **a**	10	82	55	1*S*,2*S*
7	**1**-Ti(O*i*Pr)$_4$	 **b**	10	90	68	1*S*,2*S*
8	**2**-Ti(O*i*Pr)$_4$	 **b**	10	80	59	1*S*,2*S*
9	**1**-Ti(O*i*Pr)$_4$	 **c**	10	94	70	1*S*,2*S*
10	**2**-Ti(O*i*Pr)$_4$	 **c**	10	88	59	1*S*,2*S*
11	**1**-Ti(O*i*Pr)$_4$	 **d**	10	92	69	1*S*,2*S*
12	**2**-Ti(O*i*Pr)$_4$	 **d**	10	87	58	1*S*,2*S*
13	**1**-Ti(O*i*Pr)$_4$	 **e**	10	99	94	1*S*,2*S*
14	**2**-Ti(O*i*Pr)$_4$	 **e**	10	92	78	1*S*,2*S*
15[d]	**1**-Ti(O*i*Pr)$_4$	 **e'**	10	80	65	1*S*,2*S*
16	**1**-Ti(O*i*Pr)$_4$	 **f**	10	84	88	1*S*,2*S*
17	**1**-Ti(O*i*Pr)$_4$	 **g**	10	94	86	1*S*,2*S*
18	**1**-Ti(O*i*Pr)$_4$	 **h**	10	99	>99	1*S*,2*S*
19	**1**-Ti(O*i*Pr)$_4$	 **i**	10	70	62	1*S*,2*S*
20	**1**-Ti(O*i*Pr)$_4$	 **j**	10	74	55	1*S*,2*S*
21[e]	**3**-Ti(O*i*Pr)$_4$	 **h**	24	75	64	1*S*,2*S*
22[f]	**3**-Ti(O*i*Pr)$_4$	 **h**	24	86	76	1*S*,2*S*

[a] Chiral ligands **1**, **2**, **3** (0.01 mmol), Ti(O*i*Pr)$_4$ (0.01 mmol), *meso*-stilbene oxide (0.05 mmol), aniline (0.05 mmol), additives (0.01 mmol) in dry toluene (0.4 mL) at 0 °C. [b] Chiral ligand **1** (0.01 mmol), Ti(O*i*Pr)$_4$ (0.02 mmol), *meso*-stilbene oxide (0.05 mmol), aniline (0.05 mmol) in dry toluene (0.4 mL) at 0 °C. [c] Chiral ligand **1** (0.01 mmol), Ti(O*i*Pr)$_4$ (0.03 mmol), *meso*-stilbene oxide (0.05 mmol), aniline (0.05 mmol) in dry toluene (0.4 mL) at 0 °C. [d] Chiral catalyst **1**-Ti(O*i*Pr)$_4$ was used with (*R*)-*N*-benzylidene-1-phenylethanamine (**e**′) as additive for ring opening of *meso*-stilbene oxide with aniline under identical conditions. [e] Chiral catalyst **3**-Ti(O*i*Pr)$_4$ 1:1 system was used under identical reaction conditions. [f] Chiral catalyst **3**-Ti(O*i*Pr)$_4$ 1:1 system was used under identical reaction conditions. [g] Isolated yield after flash chromatography. [h] *ee* determined on Chiralcel OD column. [i] Configuration is determined by comparing optical rotation and HPLC profile with literature values.[7f,9a,5b]

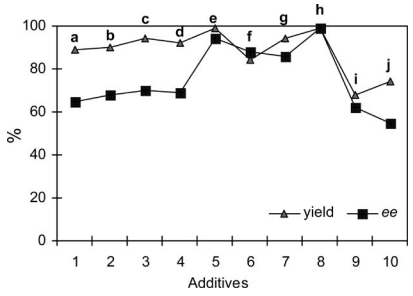


Figure 2. % Yields and *ee* values (%) for ring opening reactions of *meso*-stilbene oxide with aniline in the presence of different additives in 10 h: triphenylphosphane (**a**), triethylamine (**b**), *N*-benzylideneaniline (**c**), *N*-benzylidene-1-phenylmethanamine (**d**), (*S*)-*N*-benzylidene-1-phenylethanamine (**e**), (*S*)-*N*-(4-chlorobenzylidene)-1 phenylethanamine (**f**), (*S*)-*N*-(4-methoxybenzylidene)-1-phenylethanamine (**g**), (*S*)-*N*-(2-methoxybenzylidene)-1-phenylethanamine (**h**), (*S*)-*N*-ethoxybenzylidene-1-phenylethanamine (**i**),(*S*)-*N*-(2-phenoxybenzylidene)-1-phenylethanamine (**j**).

the **3**-Ti(O*i*Pr)$_4$ 1:0.5 system it was 86% yield and 76% *ee* (Table 1, Entries 21, 22). This observation is in line with the trend observed with chiral ligand **1**-Ti(O*i*Pr)$_4$ ratio for the same reaction (Figure 1).

Having established the catalyst and additive, we next studied other reaction parameters (i.e., catalyst loading, additive loading, effect of solvent and temperature) to maximize the yield and *ee* of the *syn*-β-amino alcohol product, using *meso*-stilbene oxide as a representative substrate and aniline as nucleophile in the presence of chiral additive **h**. Figure 3 clearly shows that the best results for the asymmetric ring opening of *meso*-stilbene oxide with aniline were achieved in the presence of 20 mol-% of catalyst and 20 mol-% additive **h** in toluene at 0 °C (Table 2, Entry 1).

Further, we conducted epoxide ring opening reactions at relatively higher scales with *meso*-stilbene oxide (1.0 mM; 980 mg) as representative substrate, together with aniline; these gave results similar to those obtained in the case of a 0.01 mM scale in 14 h (Table 2, Entry 11).

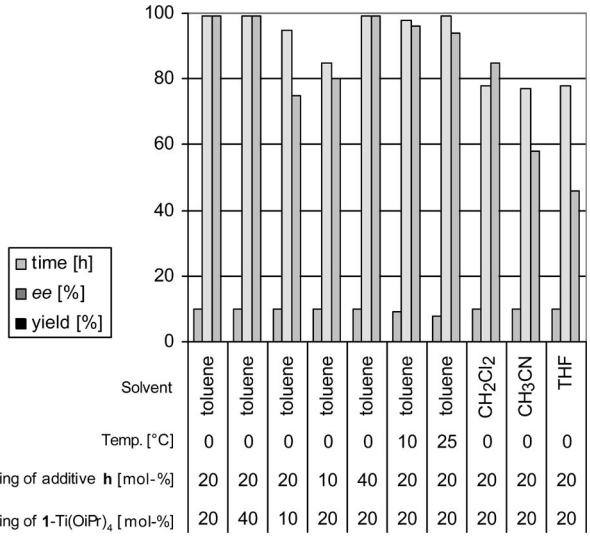
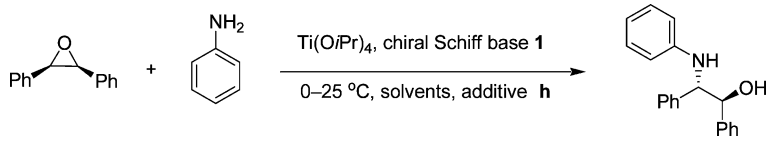


Figure 3. Optimization of reaction conditions for ring opening of *meso*-stilbene oxide with aniline in the presence of 2-MeO imine (**h**) as additive.

We next varied the nucleophiles for the ring opening of *meso*-stilbene oxide as our representative substrate under our optimized reaction conditions, and the results are summarized in Table 3. Among the various nucleophiles used, 4-substituted anilines (4-methoxy-, 4-methyl-, and 4-chloroaniline) afforded amino alcohols with *ee* values above 98%

Table 2. Product yield and *ee* values of enantioselective ring opening[a] of *meso*-stilbene oxide with aniline in the presence of complexes **1**-Ti(O*i*Pr)$_4$ for optimization of the reaction condition.



4 **5a** **6a**

Entry	Catalyst loading [mol-%]	Additive loading [mol-%]	Temp. [°C]	Solvent	Time [h]	Yield[b] [%]	*ee*[c] [%]
1	20	20	0	toluene	10	99	>99
2	40	20	0	toluene	10	99	99
3	10	20	0	toluene	10	95	75
4	20	10	0	toluene	10	85	80
5	20	40	0	toluene	10	99	99
6	20	20	10	toluene	9	98	96
7	20	20	25	toluene	8	99	94
8	20	20	0	CH_2Cl_2	10	78	85
9	20	20	0	CH_3CN	10	77	58
10	20	20	0	THF	10	78	46
[d]11	20	20	0	toluene	14	99	99

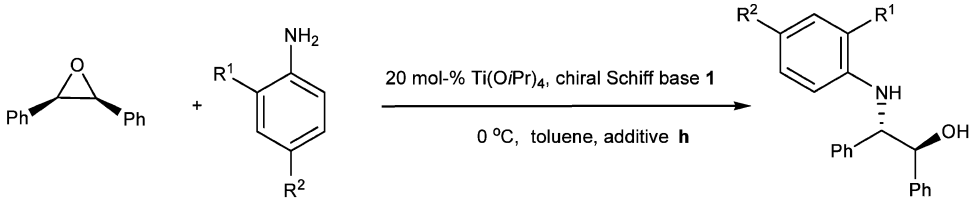
[a] Complex **1**-Ti(O*i*Pr)$_4$ (quantities as mentioned above), *meso*-stilbene oxide (0.05 mmol), aniline (0.05 mmol), 2MeO imine (**h**, quantities as mentioned above) in dry toluene (0.4 mL) at 0 °C. [b] Isolated yield after flash chromatography. [c] *ee* determined on Chiralcel OD column. [d] Reaction conducted at 1 mmol scale of *meso*-stilbene oxide in 2.0 mL of dry toluene, with other ratios and conditions as per Entry 1.

(Table 3, Entries 3–5), though the yields with 4-Cl- and 4-Me-substituted anilines were only 65 and 75%, respectively. On the other hand, 2-methoxyaniline gave only 85% *ee* but a 95% yield (Entry 2) for the corresponding chiral β-amino alcohol, implying that steric interaction arising from *ortho* substitution on the nucleophile disfavors higher enantioselectivity.

The scope of this ring opening reaction protocol was further extended to *cis*-butene oxide with 2- and 4-methoxyaniline as nucleophiles. Excellent enantioselectivity (>99%) and good yields were achieved in the case of 2-methoxyaniline (Table 4, Entry 2). Two representative cyclic epoxides – cyclohexene oxide and cyclooctene oxide – were also screened for ring opening with 2- and 4-methoxyaniline by this protocol. The results in Table 4 show excellent yields (95%, Entries 4–6) of the chiral β-amino alcohol with cyclohexene oxide, while cyclooctene oxide gave only moderate to low yields (Entries 7–9) with both nucleophiles, although the *ee* was better when 2-methoxyaniline was used as nucleophile (Entries 5, 8). It is to be noted that the results obtained in this study are significantly superior to those found for the previously reported copper(II)/Ti^{IV}/lanthanide BINOL and scandium bipyridine systems[6,7e,7f,9a] for similar *meso*-epoxide ring opening reactions. In all catalytic runs, the *R* forms of the chiral Ti^{IV} Schiff base complexes converted all epoxides into predominantly (*S*)-β-amino alcohols, determined by comparison with the HPLC profiles reported in the literature for these products.[7e,7f,9a]

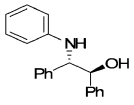
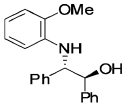
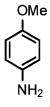
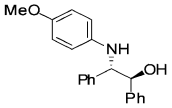
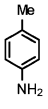
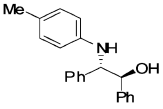
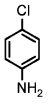
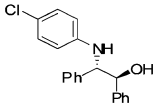
Recyclability experiments were conducted on a 0.1 mmol scale of *meso*-stilbene oxide with complex **1**-Ti(O*i*Pr)$_4$ (20 mol-%) generated in situ, with aniline as nucleophile and in the presence of a chiral additive (**h**) in toluene. After the catalytic run, the amount of the solvent was reduced and the complex was precipitated by addition of excess *n*-hexane. The precipitated catalyst was washed thoroughly with hexane, dried in vacuo, stored under dry and inert atmosphere, and used for the subsequent catalytic run without further purification. The recovered catalyst worked well for the ring opening of *meso*-stilbene oxide, with no additional requirement for a titanium source. However, the

Table 3. Product yields and *ee* values of enantioselective ring opening[a] of *meso*-stilbene oxide with different anilines as nucleophile catalyzed by complex 1-Ti(O*i*Pr)$_4$ in the presence of 2-MeO imine (**h**) as additive under optimized reaction condition.



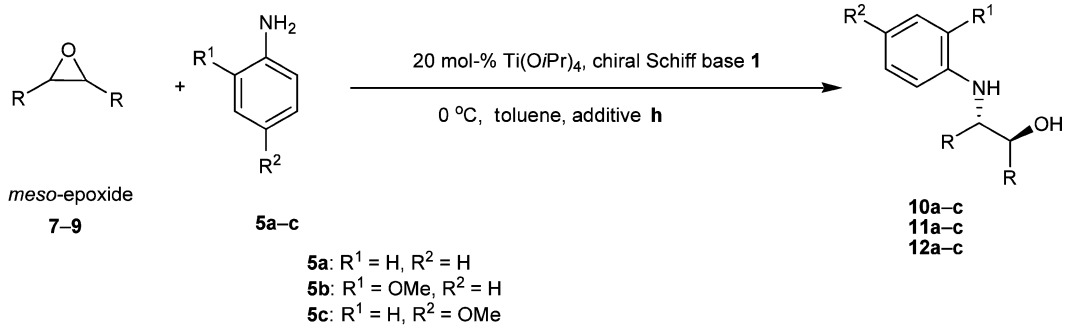
4 **5a–e** **6a–e**

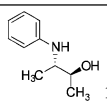
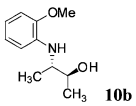
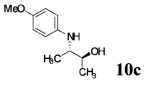
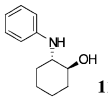
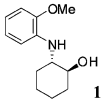
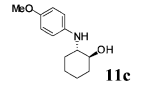
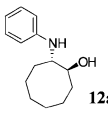
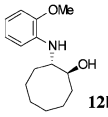
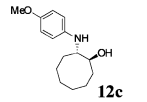
5a: R^1 = H, R^2 = H **5d:** R^1 = H, R^2 = Me
5b: R^1 = OMe, R^2 = H **5e:** R^1 = H, R^2 = Cl
5c: R^1 = H, R^2 = OMe

Entry	Nucleophile	Product	Yield [%][b]	*ee* [%][c]
1			98	>99
2			95	85
3			96	98
4			75	>99
5			65	>99

[a] Chiral ligand **1** (0.01 mmol), Ti(O*i*Pr)$_4$ (0.01 mmol), *meso*-stilbene oxide (0.05 mmol), aniline (0.05 mmol), 2-MeO imine (**h**, 0.01 mmol) in dry toluene (0.4 mL) at 0 °C. [b] Isolated yield after flash chromatography. [c] *ee* determined on Chiralcel OD, OJ, and AD columns.

Table 4. Product yields and *ee* values of enantioselective ring opening[a] of different *meso*-epoxides with different anilines as nucleophile catalyzed by complex **1**-Ti(O*i*Pr)$_4$ in the presence of 2-MeO imine (**h**) as additive under optimized reaction condition.



Entry	*meso*-Epoxides	Nucleophile	Product	Yield [%][b]	*ee* [%][c]	Configuration of β-amino alcohol[d]
1	 **7**		 **10a**	75	68	2*S*,3*S*
2	 **7**		 **10b**	88	>99	2*S*,3*S*
3	 **7**		 **10c**	80	75	2*S*,3*S*
4	 **8**		 **11a**	95	67	1*S*,2*S*
5	 **8**		 **11b**	95	83	1*S*,2*S*
6	 **8**		 **11c**	95	76	1*S*,2*S*
7	 **9**		 **12a**	62	72	1*S*,2*S*
8	 **9**		 **12b**	59	78	1*S*,2*S*
9	 **9**		 **12c**	40	56	1*S*,2*S*

[a] Chiral ligand **1** (0.01 mmol), Ti(O*i*Pr)$_4$ (0.01 mmol), cyclohexene oxide, cyclooctene oxide, *cis*-butene oxide (0.05 mmol), anilines (0.05 mmol), 2-MeO imine (0.01 mmol) in dry toluene (0.4 mL) at 0 °C. [b] Isolated yield after flash chromatography. [c] *ee* determined Chiralcel OD, AD, OJ columns. [d] Configuration determined by comparing optical rotation and HPLC profile with literature values.[7f,5b]

addition of chiral additive was required to produce results corresponding to those obtained with the fresh catalyst. The recycling data as given in Table 5 suggest that the recovered catalyst is stable and worked well for four cycles without loss in performance. The dried solid (soluble in toluene, $CHCl_3$, and CH_3CN) was subjected to elemental analysis,

^{1}H NMR, IR, UV/Vis, and CD spectroscopy, optical rotation measurement, and mass spectrometry (data given in Experimental Section). A similar set of analyses was also carried out for the recovered catalyst (also soluble in the above solvents), and matched well with those for the virgin catalyst generated in situ, suggesting that no major structural changes had taken place during the course of post catalytic workup procedure. To the best of our knowledge, the complex **1**-Ti(O*i*Pr)$_4$ is the most efficient recyclable catalyst for the asymmetric ring opening of *meso*-stilbene oxide and *cis*-butene oxide with various anilines in the presence of chiral 2-MeO-substituted imine **h** as an additive, giving quantitative yields of chiral β-amino alcohols with >99% *ee* (Table 3, Entry 1 and Table 4, Entry 2).

Table 5. Product yield and *ee* values of enantioselective ring opening[a] of *meso*-stilbene oxide with aniline as nucleophile catalyzed by recovered complex 1-Ti(O*i*Pr)$_4$ in the presence of 2-MeO imine (**h**) as additive under optimized reaction condition.

Run	1	2	3	4
Time [h]	10	10	10	10
Yield [%][b]	99	97	95	95
ee [%][c]	>99	>99	>99	>99

[a] Chiral ligand **1** (0.02 mmol), Ti(O*i*Pr)$_4$ (0.02 mmol), *meso*-stilbene oxide (0.1 mmol), anilines (0.1 mmol), 2-MeO imine (0.02 mmol) in dry toluene (1 mL) at 0 °C. [b] Isolated yield after flash chromatography. [c] *ee* is determined by Chiralcel OD columns.

Conclusions

Highly enantioselective β-amino alcohols were obtained from ring opening of *meso*-epoxides with anilines in the presence of chiral additives at 0 °C by use of chiral Ti^{IV} Schiff base complexes generated in situ by the interaction of Ti(O*i*Pr)$_4$ with new chiral Schiff bases prepared by condensation of 3,3′-di-*tert*-butyl-5,5′-methylenebis(salicylaldehyde) and 3,3′-dimethyl-5,5′-methylenebis(salicylaldehyde) with (1*R*,2*S*)-(–)-2-amino-1,2-diphenylethanol. The catalyst **1**-Ti(O*i*Pr)$_4$ worked better than the catalyst **2**-Ti(O*i*Pr)$_4$ in terms of reactivity and enantioselectivity for the epoxide ring opening reactions, producing chiral β-amino alcohols in high optical purity and with the added advantage of recyclability.

Experimental Section

General: Ti(O*i*Pr)$_4$, (1*R*,2*S*)-(–)-2-amino-1,2-diphenylethanol, (*S*)-1-phenylethylamine, (*R*)-1-phenylethylamine, triphenylphosphane, triethylamine, benzaldehyde, 2- and 4-methoxybenzaldehyde, 4-chlorobenzaldehyde, aniline, 2-methoxyaniline, 4-methoxyaniline, 4-chloroaniline, *meso*-stilbene oxide, cyclohexene oxide, cyclooctene oxide, and *cis*-butene oxide were purchased from Aldrich Chemicals and were used as received. 3,5-Di-*tert*-butylsalicylaldehyde,[13] 3,3′-di-*tert*-butyl-5,5′-methylenebis(salicylaldehyde) and 3,3′-dimethyl-5,5′-methylenebis(salicylaldehyde) were synthesized by a previously reported method.[14,15] Various chiral imines used as additives in this study were synthesized by condensation of the appropriate arylaldehydes with (*S*)-1-phenylethylamine by the reported method.[16] The solvents were dried by standard procedures,[17] distilled, and stored under nitrogen. NMR spectra were obtained with a Bruker F113V spectrometer (500 MHz and 125 MHz for ^{1}H and ^{13}C, respectively) and were referenced internally with TMS. FTIR spectra of liquid products (film, KBr plates) were recorded on a Perkin–Elmer Spectrum GX spectrophotometer. CD spectra were recorded in chloroform on a JASCO J-815 CD spectrometer. High-resolution mass spectra were obtained with LC-MS (Q-TOFF) LC (Waters), MS (Micromass) instruments. For the product purification, flash chromatography was performed with silica gel 60–200 mesh purchased from s. d. Fine-Chem. Limited Mumbai (India). Enantiomeric excesses (*ee* values) of the products were determined by HPLC (Shimadzu SCL-10AVP) on Daicel Chiralpak AD, OD and OJ chiral columns with propan-2-ol/hexane as eluent. Optical rotations were measured with a Digipol 781 Automatic Polarimeter (Rudolph Instruments).

Chiral Schiff Base Preparation

Synthesis of Compounds 1, 2, and 3: A solution of 3,3′-di-*tert*-butyl-5,5′-methylenebis(salicylaldehyde)/3,3′-dimethyl-5,5′-methylenebis-(salicylaldehyde)/3,5-di-*tert*-butylsalicylaldehyde (0.54 mmol) in absolute ethanol (15 mL) was added to a pre-cooled solution of (1*R*,2*S*)-(–)-2-amino-1,2-diphenylethanol (1.08:0.54 mmol) in absolute ethanol (15 mL) with vigorous stirring. The resulting reaction mixture was subsequently heated at reflux with stirring for 6–8 h. After completion of the reaction (by TLC), solvent was removed, and the residue was purified by silica gel column chromatography with hexane/ethyl acetate (80:20) as eluent.

Compound 1: Yellow solid; yield 95%; m.p. 120–123 °C. $[\alpha]_D^{27}$ = –208 (*c* = 0.125, CH_3CN). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.60 (s, 18 H), 3.72 (s, 2 H), 4.44 (d, *J* = 5 Hz, 2 H), 5.04 (d, *J* = 5 Hz, 2 H), 6.61 (s, 2 H), 7.10–7.37 (m, 24 H), 8.00 (s, 2 H), 13.47 (br. s, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.3, 34.8, 40.2, 78.36, 80.22, 127.2, 127.9, 128.0, 128.1, 129.9, 130.1, 130.5, 137.2, 139.4, 140.1, 158.5, 166.6 ppm. IR (KBr): $\tilde{\nu}$ = 3448, 3032, 2955, 1647, 1522, 1438, 1265, 1029, 804, 761, 701 cm^{-1}. UV/Vis ($CHCl_3$): λ_{max} (ε) = 240 (19652), 266 (17766), 333 (4768). TOF-MS (ESI+): *m*/*z* = 759 [M + H]$^+$, 781 [M + Na]$^+$. Elemental analysis calcd. for $C_{51}H_{54}N_2O_4$: C 80.71, H 7.17, N 3.69; found C 80.64, H 7.13, N 3.63.

Compound 2: Yellow solid; yield 98%; m.p. 110–115 °C. $[\alpha]_D^{27}$ = –269 (*c* = 0.75, CH_3CN). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.21 (s, 6 H), 3.67 (s, 2 H), 4.44 (d, *J* = 7 Hz, 2 H), 5.02 (d, *J* = 7 Hz, 2 H), 6.63 (s, 2 H), 7.25–7.36 (m, 24 H), 8.00 (s, 2 H), 13.20 (br. s, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.5, 39.7, 69.7, 80.3, 125.3, 125.8, 127.1, 128.0, 129.1, 130.8, 134.2, 139.5, 140.1, 157.4, 166.1 ppm. IR (KBr): $\tilde{\nu}$ = 3449, 2919, 1636, 1560, 1521, 1508, 1438, 1265, 1164, 1040, 759, 695 cm^{-1}. UV/Vis ($CHCl_3$): λ_{max} (ε) = 249 (188000), 266 (215666), 307 (85666), 345 (501666). TOF-MS (ESI+): *m*/*z* = 675 [M + H]$^+$, 698 [M + Na]$^+$. Elemental analysis calcd. for $C_{45}H_{42}N_2O_4$: C 80.09, H 6.27, N 4.15; found C 80.01, H 6.22, N 4.10.

Compound 3: Yellow solid; yield 96%; m.p. 60–65 °C. $[\alpha]_D^{27}$ = –35 (*c* = 0.85, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.24 (s, 9 H), 1.44 (s, 9 H), 4.51 (d, *J* = 6.5 Hz, 1 H), 5.08 (d, *J* = 7 Hz, 1 H), 6.92 (s, 1 H), 7.25–7.37 (m, 12 H), 8.14 (s, 1 H), 13.41 (br. s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.57, 35.22, 78.53, 80.21, 117.96, 126.45, 127.09, 127.66, 128.01, 128.27, 128.44, 128.85, 129.41, 136.71, 139.71, 140.39, 158.07, 167.24 ppm. IR (KBr): $\tilde{\nu}$ = 3413, 3031, 2958, 2870, 1628, 1450, 1389, 1272, 1173, 1029, 822, 762, 700 cm^{-1}. UV/Vis ($CHCl_3$): λ_{max} (ε) = 240 (19652), 266 (17766), 333 (4768). TOF-MS (ESI+): *m*/*z* = 430 [M + H]$^+$.

Elemental analysis calcd. for $C_{29}H_{35}NO_2$: C 81.08, H 8.21, N 3.26; found C 81.01, H 8.19, N 3.22.

Characterization Data for the Complex Generated in situ by Treatment of Ligand 1 with Ti(O*i*Pr)$_4$ in 1:1 Molar Ratio: Yellow solid. $[a]_D^{27}$ = –224 (*c* = 0.142, $CHCl_3$). CD ($CHCl_3$): λ_{max} ($\Delta\varepsilon$) = 290 (+14), 390 (–7), 410 nm (–7). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.17 (s, 18 H), 3.84 (s, 2 H), 5.48 (s, 2 H), 6.28 (s, 2 H), 6.92–7.12 (m, 22 H), 7.69 (s, 2 H), 8.48 (s, 2 H) ppm. IR (KBr): $\tilde{\nu}$ = 3441, 3060, 2922, 1617, 1546, 1452, 1421, 1387, 1289, 1089, 1028, 854, 779, 702, 673, 612, 517 cm^{-1}. UV/Vis ($CHCl_3$): λ_{max} (ε) = 256 (14621), 347 (6253), 361 (5550), 416 (3794). TOF-MS (ESI+): *m*/*z* = 803 (Figure 4). Elemental analysis calcd. for $C_{51}H_{50}N_2O_4Ti$: C 76.11, H 6.51, N 3.48; found C 76.06, H 6.48, N 3.43.

Synthesis of Achiral/Chiral Imines as Additives: A solution of the appropriate aldehyde (5 mmol) in dry MeOH (15 mL) was added to a pre-cooled solution of aniline/benzylamine/(*S*)-(+)-1-phenylethylamine (5 mmol) in dry MeOH (5 mL) with vigorous stirring. The resulting reaction mixture was subsequently heated at reflux with stirring for 6–8 h. After completion of the reaction (by TLC), solvent was removed, and the residue was purified by silica gel column chromatography with hexane/ethyl acetate (80:20) as eluent. Yield 90%. The purified product was characterized by elemental analysis, ^{1}H NMR, ^{13}C NMR, IR, and UV/Vis spectroscopy, optical rotation measurement, and mass spectrometry.

***N*-Benzylideneaniline (c):** Light yellow crystalline solid; m.p. 65–68 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.20–7.24 (m, 3 H), 7.37–7.48 (m, 5 H), 7.89–7.91 (m, 2 H), 8.45 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 120.94, 126.01, 128.85, 128.88, 129.22, 131.46, 134.85, 136.27, 152.16, 160.53 ppm. IR (KBr): $\tilde{\nu}$ = 3060, 2890, 2356, 1828, 1626, 1484, 1450, 1366, 1191, 1072, 978, 868, 759 cm^{-1}. TOF-MS (ESI+): *m*/*z* = 181 [M + H]$^+$, 204 [M + Na]. Elemental analysis calcd. for $C_{13}H_{11}N$: C 86.15, H 6.12, N 7.73; found C 86.09, H 6.08, N 7.68.

***N*-Benzylidene-1-phenylmethanamine (d):** Light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.80 (s, 2 H), 7.23–7.39 (m, 8 H), 7.75–7.77 (m, 2 H), 8.35 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 65.12, 127.12, 128.11, 128.63, 128.74, 130.91, 136.26, 139.41, 162.15 ppm. IR (KBr): $\tilde{\nu}$ = 3028, 2360, 1952, 1702, 1645, 1495, 1452, 1311, 1026, 795, 496 cm^{-1}. TOF-MS (ESI+): *m*/*z* = 196.13 [M + H]$^+$, 218 [M + Na]$^+$. Elemental analysis calcd. for $C_{14}H_{13}N$: C 86.12, H 6.71, N 7.17; found C 86.08, H 6.67, N 7.14.

(*S*)-*N*-Benzylidene-1-phenylethanamine (e): Yellow semisolid. $[a]_D^{27}$ = +146 (*c* = 0.16, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.60 (d, *J* = 7 Hz, 3 H), 4.55 (q, *J* = 6.5 Hz, 1 H), 7.21–7.25 (m, 2 H), 7.32–7.35 (m, 2 H), 7.39–7.43 (m, 6 H), 8.37 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.93, 69.35, 126.74, 126.94, 128.38, 128.53, 128.65, 130.70, 136.46, 145.24, 159.64 ppm. IR (KBr): $\tilde{\nu}$ = 2972, 2847, 1885, 1645, 1493, 1450, 1380, 1296, 1071, 908, 754, 696 cm^{-1}. TOF-MS (ESI+): *m*/*z* = 210 [M + H]$^+$, 232 [M + Na]. Elemental analysis calcd. for $C_{15}H_{15}N$: C 86.08, H 7.22, N 6.69. found. C, 86.02, H 7.19, N 6.62.

(*S*)-*N*-(4-Chlorobenzylidene)-1-phenylethanamine (f): Yellow solid; m.p. 70–75 °C. $[a]_D^{27}$ = +443 (*c* = 0.02, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.59 (d, *J* = 6.5 Hz, 3 H), 4.45 (q, *J* = 6.5 Hz, 1 H), 7.24–7.26 (m, 2 H), 7.34–7.42 (m, 5 H), 7.27 (d, *J* = 8 Hz, 2 H), 8.32 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.83, 69.77, 126.61, 126.94, 128.48, 128.81, 129.46, 134.85, 136.50, 144.94, 158.12 ppm. IR (KBr): $\tilde{\nu}$ = 2972, 2864, 1806, 1640, 1488, 1449, 1378, 1291, 1082, 908, 763, 635 cm^{-1}. TOF-MS (ESI+): *m*/*z* = 244 [M + H]$^+$, 266 [M + Na]. Elemental analysis calcd. for $C_{15}H_{14}ClN$: C 73.92, H, 5.79, N 5.75; found C 73.87, H, 5.74, N 5.70.

(*S*)-*N*-(4-Methoxybenzylidene)-1-phenylethanamine (g): Crystalline solid; m.p. 80–85 °C. $[a]_D^{27}$ = +90 (*c* = 0.71, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.58 (d, *J* = 7 Hz, 3 H), 2.37 (s, 3 H), 4.515 (q, *J* = 6.5 Hz, 1 H), 7.19–7.25 (m, 3 H), 7.30–7.34 (m, 2 H), 7.41–

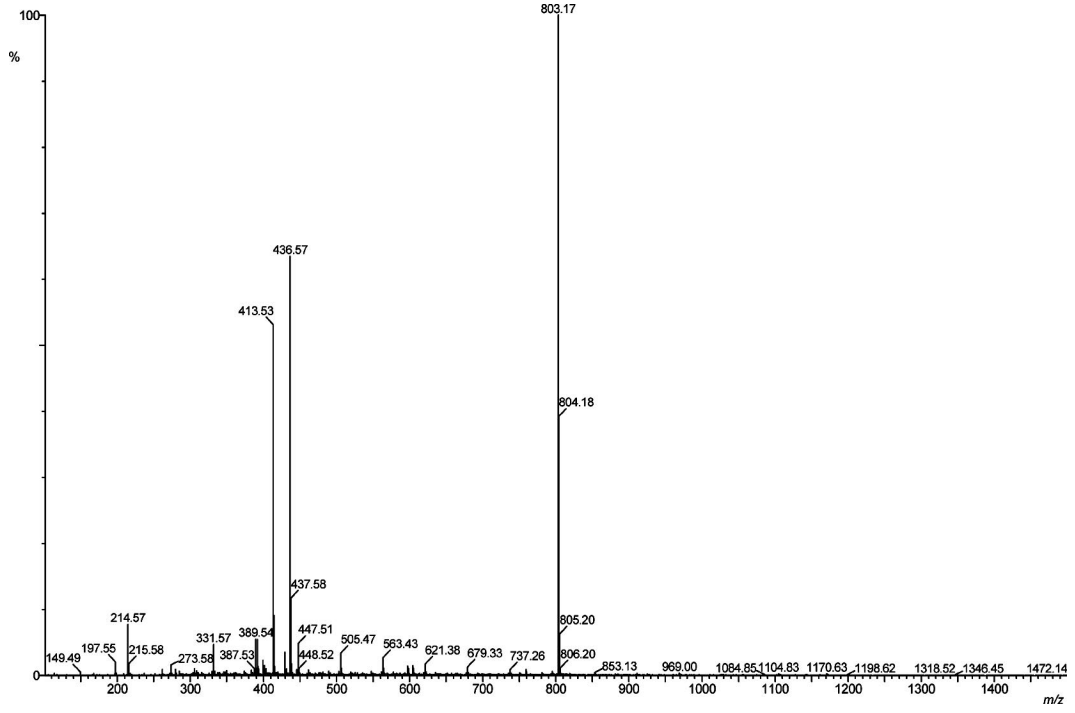


Figure 4. Mass spectrum of complex **1**-Ti(O*i*Pr)$_4$ generated in situ with ligand/metal ratio 1:1.

7.43 (m, 2 H), 7.67 (d, J = 8 Hz, 2 H), 8.33 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.03, 60.74, 69.87, 126.82, 126.95, 128.41, 128.57, 129.43, 133.96, 141.00, 145.47, 159.61 ppm. IR (KBr): $\tilde{\nu}$ = 2972, 2924, 1817, 1642, 1490, 1382, 1288, 1169, 1064, 1019, 973, 907, 823, 761, 468 cm^{-1}. TOF-MS (ESI+): m/z = 239 [M + H]. Elemental analysis calcd. for $C_{16}H_{17}NO$: C 80.30, H 7.16, N 5.85; found C 80.24, H 7.11, N 5.82.

(*S*)-*N*-(2-Methoxybenzylidene)-1-phenylethanamine (h): Pale yellow oil. $[\alpha]_D^{27}$ = +202 (c = 0.04, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.59 (d, J = 6.5 Hz, 3 H), 3.83 (s, 3 H), 4.55 (q, J = 6.5 Hz, 1 H), 6.86–6.96 (m, 2 H), 7.21–7.43 (m, 6 H), 8.05 (br, 1 H), 8.82 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.96, 55.51, 70.13, 110.95, 120.81, 124.86, 126.74, 127.65, 128.42, 128.61, 131.83, 136.02, 145.56, 155.53, 158.78 ppm. IR (KBr): $\tilde{\nu}$ = 2968, 2927, 1879, 1635, 1488, 1379, 1246, 1161, 1046, 835, 761, 468 cm^{-1}. TOF-MS (ESI+): m/z = 239 [M + H]$^+$, 262 [M + Na]. Elemental analysis calcd. for $C_{16}H_{17}NO$: C 80.30, H 7.16, N 5.85; found C 80.26, H 7.12, N 5.80.

(*S*)-*N*-(2-Ethoxybenzylidene)-1-phenylethanamine (i): Light yellow solid; m.p. 80–83 °C. $[\alpha]_D^{27}$ = +13 (c = 0.60, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.40 (t, J = 7 Hz, 3 H), 1.58 (d, J = 6.5 Hz, 3 H), 4.02 (m, 2 H), 4.55 (q, J = 6.5 Hz, 1 H), 6.82 (d, J = 8.5 Hz, 1 H), 6.94 (t, J = 7.5 Hz, 1 H), 7.17–7.44 (m, 6 H), 8.06 (d, J = 8 Hz, 1 H), 8.83 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.93, 25.14, 63.99, 70.15, 112.02, 120.73, 124.97, 125.84, 126.75, 127.70, 128.47, 128.62, 131.84, 145.70, 155.69, 158.29 ppm. IR (KBr): $\tilde{\nu}$ = 2977, 2928, 2885, 1886, 1636, 1487, 1453, 1379, 1290, 1243, 1160, 1118, 1044, 923, 755, 700, 422 cm^{-1}. TOF-MS (ESI+): m/z = 253 [M]$^+$, 254 [M + H]$^+$. Elemental analysis calcd. for $C_{17}H_{19}NO$: C 80.60, H 7.56, N 5.53; found C 80.55, H 7.50, N 5.48.

(*S*)-*N*-(2-Benzyloxybenzylidene)-1-phenylethanamine (j): Pale yellow oil. $[\alpha]_D^{27}$ = +35 (c = 0.85, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.57 (d, J = 7 Hz, 3 H), 4.54 (q, J = 6.5 Hz, 1 H), 5.08 (s, 2 H), 6.93 (d, J = 8 Hz, 1 H), 6.98 (t, J = 7.5 Hz, 1 H), 7.22–7.42 (m, 11 H), 8.08 (d, J = 7 Hz, 1 H), 8.85 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.10, 70.04, 70.49, 112.61, 121.28, 125.38, 126.84, 126.97, 127.46, 127.90, 128.03, 128.53, 128.79, 129.13, 129.40, 131.91, 136.92, 145.57, 155.57, 158.08 ppm. IR (KBr): $\tilde{\nu}$ = 2972, 2926, 1951, 1637, 1600, 1454, 1373, 1242, 1160, 1110, 1022, 911, 732, 701, 618, 531 cm^{-1}. TOF-MS (ESI+): m/z = 315 [M]$^+$, 316 [M + H]$^+$. Elemental analysis calcd. for $C_{22}H_{21}NO$: C 83.78, H 6.71, N 4.44; found C 83.67, H 6.69, N 4.49.

General Procedure for Catalytic Asymmetric Ring-Opening of *meso*-Oxides with Anilines: The chiral Schiff base ligand **1/2/3** (0.01 mmol) was dissolved in dry toluene (0.4 mL) in a 5 mL RBF fitted with a rubber septum and containing a magnetic stirring bar. Ti(O*i*Pr)$_4$ (0.01 mmol) was added at room temperature (27 °C) to the resulting solution, and this was stirred for 1 h, followed by addition of the appropriate additive (**a**–**j**, 0.01 mmol). The reaction mixture was then cooled to 0 °C and the appropriate epoxide (*meso*-stilbene oxide/cyclohexene oxide/cyclooctene oxide/*cis*-butene oxide, 0.05 mmol) was added, with subsequent stirring for 20 min. A solution of the appropriate aniline (0.05 mmol) was then added, and the mixture was allowed to stir for the specified time. The progress of the reaction was checked by TLC with hexane/ethyl acetate (8:2) as mobile phase. After the completion of the reaction, solvent was removed under vacuum, and the product was purified by column chromatography with silica gel 60–200 mesh as stationary phase and hexane/ethyl acetate (8:2) as mobile phase. All products were characterized by appropriate spectroscopic techniques, and data were found to be in agreement with the reported values.[7e,7f,9a,5b]

(1*S*,2*S*)-1,2-Diphenyl-2-(phenylamino)ethanol (6a):[7f,9a] The title compound was isolated by column chromatography (hexane/AcOEt, 90:10) as a white solid; m.p. 100–102 °C; *ee* >99% on HPLC (Chiralpak OD column) mobile phase, 85:15 *n*-hexane/*i*PrOH; flow rate 1 mL min^{-1}, λ = 247 nm, retention time (1*S*,2*S*): 13.77 min, (1*R*,2*R*): 16.97 min. Only one diastereomer was observed by ^{1}H NMR and HPLC analysis. ^{1}H NMR (500 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 (125 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 (in KBr): $\tilde{\nu}$ = 3546, 3407, 3027, 2880, 2849, 1600, 1502, 1451, 1429, 1320, 1033, 752, 695 cm^{-1}. LC-MS: m/z = 290 [M + H]$^+$, 272 (base peak) [M – OH]$^+$, 312 [M + Na]$^+$.

(1*S*,2*S*)-2-(2-Methoxyphenylamino)-1,2-diphenylethanol (6b):[7f,9a] The title compound was isolated by column chromatography (hexane/AcOEt, 90:10) as a white solid; m.p. 93–95 °C; *ee* 85% on HPLC (Chiralpak OJ column) mobile phase 80:20 hexane/*i*PrOH, flow rate 0.5 mL min^{-1}, λ = 254 nm, retention time (1*S*,2*S*): 29.9 min, (1*R*,2*R*): 33.3 min. Only one diastereomer was observed by NMR and HPLC analysis. $[\alpha]_D^{RT}$ = –48 (c = 0.54, CH_2Cl_2). ^{1}H NMR (500 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, 7.2 Hz, 1 H), 6.51–6.70 (m, 3 H), 7.12–7.20 (m, 10 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 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 (in KBr): $\tilde{\nu}$ = 3407, 3062, 3030, 2936, 2835, 1810, 1698, 1601, 1515, 1248, 1027, 846, 740, 700 cm^{-1}. LC-MS: m/z 661 [2 M + Na]$^+$, 320 [M + H]$^+$, 302 (base peak) [M – OH]$^+$, 342 [M + Na]$^+$.

(1*S*,2*S*)-2-(4-Methoxyphenylamino)-1,2-diphenylethanol (6c):[7f,9a] The title compound was isolated by column chromatography (hexane/AcOEt, 90:10) as a yellow solid; m.p. 98–102 °C; *ee* 98% on HPLC (Chiralpak OD column) mobile phase, 85:15 *n*-hexane/*i*PrOH; flow rate 1 mL min^{-1}, λ = 247 nm, retention time (1*S*,2*S*): 18.04 min, (1*R*,2*R*): 20.40 min. Only one diastereomer was observed by NMR and HPLC analysis. ^{1}H NMR (500 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 (125 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 (in KBr): $\tilde{\nu}$ = 3483, 3393, 3026, 2964, 2833, 1807, 1510, 1453, 1254, 1024, 819, 753, 700 cm^{-1}. LC-MS: m/z = 661 [2 M + Na]$^+$, 320 (base peak) [M + H]$^+$, 342 [M + Na]$^+$.

(1*S*,2*S*)-2-(4-Methylphenylamino)-1,2-diphenylethanol (6d):[7f] The title compound was isolated by column chromatography (hexane/AcOEt, 90:10) as a white solid; m.p. 85 °C; *ee* >99% on HPLC (Chiralpak AD column) mobile phase, 85:15 hexane/*i*PrOH; flow rate 1 mL min^{-1}, λ = 247 nm, retention time (1*R*,2*R*): 14.06 min, (1*S*,2*S*): 16.08 min. Only one diastereomer was observed by NMR and HPLC analysis. ^{1}H NMR (500 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 (125 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 (in KBr): $\tilde{\nu}$ = 3399, 3061, 3029, 2859, 2831, 1813, 1616, 1518, 1490, 1259, 1044, 815, 768, 700 cm^{-1}. LC-MS: m/z 304 [M + H]$^+$, 286 (base peak) [M – OH]$^+$.

(1*S*,2*S*)-2-(4-Chlorophenylamino)-1,2-diphenylethanol (6e):[7f] The title compound was isolated by column chromatography (hexane/AcOEt, 90:10) as a white solid; m.p. 95 °C; *ee* >99% on HPLC (Chiralpak AD Column) mobile phase 85:15 hexane/*i*PrOH; flow rate 1 mL min^{-1}, λ = 247 nm, retention time (1*S*,2*S*) 15.58 min, (1*R*,2*R*): 17.37 min. Only one diastereomer was observed by NMR and HPLC analysis. ^{1}H NMR (500 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 (125 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 (in KBr): $\tilde{\nu}$ = 3396, 3063, 3031, 2960, 2929, 2860, 1812, 1722, 1599, 1496, 1268, 1073, 820, 739, 700 cm^{-1}. LC-MS: *m*/*z* 324 [M + H]$^+$, 347 [M + Na]$^+$, 306 [M – OH]$^+$, 289 [M – Cl]$^+$, 271(base peak) [M – OH – Cl]$^+$.

(2*S*,3*S*)-3-(Phenylamino)butan-2-ol (10a):[5b] The title compound was isolated by column chromatography (hexane/AcOEt, 90:10) as an oil; *ee* 68% on HPLC (Chiralpak OD column) mobile phase, 97.56:2.44 hexane/*i*PrOH; flow rate 1 mL min^{-1}, λ = 247 nm, retention time (2*S*,3*S*): 34.56 min, (2*R*,3*R*): 36.21 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.14 (d, *J* = 6.8 Hz, 1 H), 1.25 (d, *J* = 6.8 Hz, 3 H), 2.61 (br. s, 1 H), 3.31 (m, 1 H), 3.62 (m, 2 H), 6.66–6.74 (m, 3 H), 7.15–7.18 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.3, 19.5, 56.1, 71.4, 114.3, 118.2, 129.3, 147.7 ppm. IR (KBr): $\tilde{\nu}$ = 3398, 3053, 2974, 2926, 1922, 1602, 1505, 1439, 1376, 1318, 1254, 1005, 902, 751, 692 cm^{-1}. LC-MS: *m*/*z* 166 [M + H]$^+$,

(2*S*,3*S*)-3-(2-Methoxyphenylamino)butan-2-ol (10b):[5b] The title compound was isolated by column chromatography (hexane/AcOEt, 90:10) as an oil; *ee* >99% on HPLC (Chiralpak OD column) mobile phase, 95:5 hexane/*i*PrOH; flow rate 1 mL min^{-1}, λ = 247 nm, retention time (2*S*,3*S*): 23.34 min, (2*R*,3*R*): 29.31 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.21 (d, *J* = 8.3 Hz, 3 H), 1.33 (d, *J* = 6.0 Hz, 3 H), 2.78 (s, 1 H), 3.40 (m, 1 H), 3.74 (m, 1 H), 3.91 (s, 3 H), 4.13 (s, 1 H), 6.75–6.80 (m, 2 H), 6.85–6.87 (m, 1 H), 6.91–6.96 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.2, 19.4, 55.4, 55.8, 71.4, 109.7, 111.4, 117.2, 121.2, 137.5, 147.5 ppm. IR (KBr): $\tilde{\nu}$ = 3414, 2970, 1602, 1510, 1456, 1249, 1220, 1110, 1025, 902, 737 cm^{-1}. LC-MS: *m*/*z* 196 [M + H]$^+$.

(2*S*,3*S*)-3-(4-Methoxyphenylamino)butan-2-ol (10c):[5b] The title compound was isolated by column chromatography (hexane/AcOEt, 90:10) as an oil; *ee* 75% on HPLC (Chiralpak AD column) mobile phase, 95:5 hexane/*i*PrOH; flow rate 1 mL min^{-1}, λ = 247 nm, retention time (2*S*,3*S*): 48.87 min, (2*R*,3*R*): 49.20 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.18 (d, *J* = 6.4 Hz, 3 H), 1.32 (d, *J* = 6.0 Hz, 3 H), 3.23 (t, *J* = 6.9 Hz, 1 H), 3.63 (t, *J* = 6.6 Hz, 1 H), 3.81 (s, 3 H), 6.71–6.75 (m, 2 H), 6.83–6.86 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.1, 19.4, 55.7, 58.0, 71.4, 114.9, 116.3, 141.0, 152.9 ppm. IR (KBr): $\tilde{\nu}$ = 3394, 2970, 1617, 1512, 1455, 1377, 1236, 1037, 822 cm^{-1}. LC-MS: *m*/*z* 196 [M + H]$^+$.

(1*S*,2*S*)-2-(Phenylamino)cyclohexene-1-ol (11a):[7e,7f,9a] The title compound was isolated by column chromatography (hexane/AcOEt, 90:10) as a white solid; m.p. 58–60 °C; *ee* 67% on HPLC (Chiralpak OD column) mobile phase, 95:5 hexane/*i*PrOH; flow rate 0.4 mL min^{-1}, λ = 247 nm, retention time (1*S*,2*S*): 62.95 min, (1*R*,2*R*): 65.41 min. ^{1}H NMR (500 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, *J* = 10.0, *J* = 10.1 Hz, 1 H), 3.33 (ddd, *J* = 4.2, *J* = 10.4, *J* = 10.5 Hz, 1 H), 6.7–7.2 (m, 2 H), 7.21–7.25 (m, 5 H) ppm. ^{13}C NMR (125 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 (in KBr): $\tilde{\nu}$ = 3354, 2931, 2858, 1602, 1501, 1448, 1320, 1067, 748 cm^{-1}. LC-MS: *m*/*z* = 192 [M + H]$^+$, 214 [M + Na]$^+$.

(1*S*,2*S*)-2-(2-Methoxyphenylamino)cyclohexan-1-ol (11b):[7e,7f] The title compound was isolated by column chromatography (hexane/AcOEt, 90:10) as a white solid; m.p. 68–70 °C; *ee* 83% on HPLC (Chiralpak OJ column) mobile phase, 80:20 hexane/*i*PrOH; flow rate 0.5 mL min^{-1}, λ = 247 nm, retention time (1*S*,2*S*): 17.1 min, (1*R*,2*R*): 19.2 min. $[\alpha]_D^{rt}$ = +49.6 (*c* = 3.0, CH_2Cl_2, 63% *ee*). ^{1}H NMR (500 MHz, $CDCl_3$): 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 (125 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 (11c):[9a,7b,7f] The title compound was isolated by column chromatography (hexane/AcOEt, 85:15) as a white solid; m.p. 62–64 °C; *ee* on HPLC (Chiralpak OD column) mobile phase, 80:20 hexane/*i*PrOH; flow rate 0.5 mL min^{-1}, λ = 247 nm, retention time (1*S*,2*S*): 16.2 min, (1*R*,2*R*): 24.3 min. $[\alpha]_D^{rt}$ = +40.1 (*c* = 3.2, CH_2Cl_2, 48% *ee*). ^{1}H NMR (500 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 (125 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 (in 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}.

(1*S*,2*S*)-2-(Phenylamino)cyclooctan-1-ol (12a):[7b] The title compound was isolated by column chromatography (hexane/AcOEt, 90:10) as a white solid. Melting point 55–56 °C; *ee* 72% on HPLC (Chiralpak OD column) mobile phase, 95:5 hexane/*i*PrOH; flow rate 0.8 mL min^{-1}, λ = 247 nm, retention time (1*S*,2*S*): 27.12 min, (1*R*,2*R*) 29.34 min: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.05–1.45 (m, 4 H), 1.50–2.15 (m, 8 H), 3.40–3.50 (m, 1 H), 3.60–3.70 (m, 1 H), 4.50 (br., 1 H), 6.70–7.20 (m, 6 H) ppm. IR (KBr): $\tilde{\nu}$ = 3315, 3107, 3054, 3027, 2941, 1923, 1690, 1604, 1498, 1465, 1306, 1256 cm^{-1}. LC-MS: *m*/*z* = 218 [M + H]$^+$.

(1*S*,2*S*)-2-(2-Methoxyphenylamino)cyclooctan-1-ol (12b): The title compound was isolated by column chromatography (hexane/AcOEt, 90:10) as an oil; *ee* 78% on HPLC (Chiralpak OJ column) mobile phase, 95:5 hexane/*i*PrOH; flow rate 0.4 mL min^{-1}, λ = 220 nm, retention time (1*S*,2*S*): 40.39 min, (1*R*,2*R*): 42.10 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.27–1.30 (m, 4 H), 1.44–1.70 (m, 8 H), 2.14–2.17 (m, 1 H), 2.90–2.93 (m, 1 H), 3.84 (s, 3 H), 4.47 (br., 1 H), 6.71–7.17 (m, 5 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.43, 25.60, 26.29, 26.49, 26.56, 55.75, 75.75, 110.50, 116.07, 121.38, 147.86, 150.63 ppm. LC-MS: *m*/*z* = 250 [M + H]$^+$.

(1*S*,2*S*)-2-(4-Methoxyphenylamino)cyclooctan-1-ol (12c): The title compound was isolated by column chromatography (hexane/AcOEt, 90:10) as an oil; *ee* 56% on HPLC (Chiralpak OD column) mobile phase, 95:5 hexane/*i*PrOH; flow rate 0.8 mL min^{-1}, λ = 220 nm, retention time (1*S*,2*S*): 27.32 min, (1*R*,2*R*) 39.59 min: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.26–1.29 (m, 4 H), 1.44–1.63 (m, 8 H), 2.12–2.16 (m, 1 H), 2.89–2.91 (m, 1 H), 4.48 (br., 1 H), 3.74 (s, 3 H), 6.66–6.75 (m, 5 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.74, 26.43, 26.70, 55.82, 72.71, 114.91, 116.93, 139.26, 151.53, 153.09, 155.72 ppm. LC-MS: *m*/*z* = 250 [M + H]$^+$.

Recycling of the Catalyst: At the end of the catalytic run (checked on TLC) the solvent was completely removed under reduced pressure. The residue was extracted with hexane to remove the reactants. The remaining solid was further washed with hexane (10 mL), dried under reduced pressure for 1–2 h, and was used as

recovered catalyst for recycling experiments based on asymmetric ring opening of *meso*-stilbene oxide as representative substrate with aniline as nucleophile.

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[1] a) S. Hashiguchi, A. Kawada, H. Natsugari, *J. Chem. Soc. Perkin Trans. 1* **1991**, *1*, 2435–2444; b) Y.-F. Wang, T. Izawa, S. Kobayashi, M. Ohno, *J. Am. Chem. Soc.* **1982**, *104*, 6465–6466; c) S. Knapp, *Chem. Rev.* **1995**, *95*, 1859–1876; d) S. Horri, H. Fukase, T. Matsuo, Y. Kameda, N. Asano, K. Matsui, *J. Med. Chem.* **1986**, *29*, 1038–1046; e) B. G. Main, H. Tucker, in *Medicinal Chemistry: The role of Organic Chemistry in Drug Research of Beta Blockers* (Eds.: S. M. Roberts, B. J. Price), Academic, London, **1985**; f) R. Howe, A. F. Crowther, J. S. Stephenson, B. S. Rao, L. H. Smith, *J. Med. Chem.* **1968**, *11*, 1000–1008; g) A. F. Crowther, L. H. Smith, *J. Med. Chem.* **1968**, *11*, 1009–1013; h) R. Howe, B. S. Rao, *J. Med. Chem.* **1968**, *11*, 1118–1121, and references therein.

[2] a) D. J. Ager, I. Prakash, D. R. Schaad, *Chem. Rev.* **1996**, *96*, 835–875; b) E. L. Eliel, X.-C. He, *J. Org. Chem.* **1990**, *55*, 2114–2119; c) Y. Hayashi, J. J. Rhode, E. J. Corey, *J. Am. Chem. Soc.* **1996**, *118*, 5502–5503; d) C. H. Senanayake, K. Fang, P. Grover, R. P. Bakale, C. P. Vandenbossche, S. A. Wald, *Tetrahedron Lett.* **1999**, *40*, 819–822.

[3] a) G. Li, H. T. Chang, K. B. Sharpless, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 451–454; b) P. O'Brien, *Angew. Chem. Int. Ed.* **1999**, *38*, 326–329.

[4] a) B. List, *J. Am. Chem. Soc.* **2000**, *122*, 9336–9337; b) A. Córdova, W. Notz, G. Zhong, J. M. Betancort, C. F. Barbas, *J. Am. Chem. Soc.* **2002**, *124*, 1842–1843; c) B. M. Trost, L. R. Terrell, *J. Am. Chem. Soc.* **2003**, *125*, 338–339.

[5] a) K. Arai, M. M. Salter, Y. Yamashita, S. Kobayashi, *Angew. Chem. Int. Ed.* **2007**, *46*, 955–957; b) K. Arai, S. Lucarini, M. M. Salter, K. Ohta, Y. Yamashita, S. Kobayashi, *J. Am. Chem. Soc.* **2007**, *129*, 8103–8111.

[6] K. Tanaka, S. Oda, M. Shiro, *Chem. Commun.*, in press (**2008**).

[7] a) A. Sekine, T. Ohshima, M. Shibasaki, *Tetrahedron* **2002**, *58*, 75–82; b) X. L. Hou, J. Wu, L. X. Dai, L. J. Xia, M. H. Tang, *Tetrahedron: Asymmetry* **1998**, *9*, 1747–1752; c) X. L. Fu, S. H. Wu, *Synth. Commun.* **1997**, *27*, 1677–1683; d) F. Carrée, R. Gil, J. Collin, *Tetrahedron Lett.* **2004**, *45*, 7749–7751; e) F. Carrée, R. Gil, J. Collin, *Org. Lett.* **2005**, *7*, 1023–1026; f) R. I. Kureshy, S. Singh, N. H. Khan, S. H. R. Abdi, E. Suresh, R. V. Jasra, *Eur. J. Org. Chem.* **2006**, 1303–1309.

[8] a) G. Bartoli, M. Bosco, A. Carlone, M. Locatelli, M. Massaccesi, P. Melchiorre, L. Sambri, *Org. Lett.* **2004**, *6*, 2173–2176; b) R. I. Kureshy, S. Singh, N. H. Khan, S. H. R. Abdi, S. Agrawal, R. V. Jasra, *Tetrahedron: Asymmetry* **2006**, *17*, 1638–1643.

[9] a) C. Schneider, A. R. Sreekanth, E. Mai, *Angew. Chem. Int. Ed.* **2004**, *43*, 5691–5694; b) E. Mai, C. Schneider, *Chem. Eur. J.* **2007**, *13*, 2729–2741; c) S. Azoulay, K. Manabe, S. Kobayashi, *Org. Lett.* **2005**, *7*, 4593–4595; d) E. Mai, C. Schneider, *Synlett* **2007**, 2136–2138; e) C. Ogawa, S. Azoulay, S. Kobayashi, *Heterocycles* **2005**, *55*, 201–206; f) C. Schneider, *Synthesis* **2006**, 3919–3944; g) I. M. Paster, M. Yus, *Curr. Org. Chem.* **2005**, *9*, 1–29.

[10] a) J. M. Keith, J. F. Larrow, E. N. Jacobsen, *Adv. Synth. Catal.* **2001**, *343*, 5–26; b) H. Label, E. N. Jacobsen, *Tetrahedron Lett.* **1999**, *40*, 7303–7306; c) M. Bandini, P. G. Cozzi, P. Melchiorre, A. Umani-Ronchi, *Angew. Chem. Int. Ed.* **2004**, *43*, 84–87.

[11] a) R. I. Kureshy, N. H. Khan, S. H. R. Abdi, S. Singh, I. Ahmad, R. S. Shukla, R. V. Jasra, *J. Catal.* **2003**, *219*, 1–7; b) R. S. Shukla, S. D. Bhatt, R. B. Thorat, R. V. Jasra, *Appl. Catal. A* **2005**, *294*, 111–118; c) N. H. Khan, S. Agrawal, R. I. Kureshy, S. H. R. Abdi, V. J. Mayani, R. V. Jasra, *Tetrahedron: Asymmetry* **2006**, *17*, 2659–2666.

[12] S. Nakamura, N. Sato, M. Sugimoto, T. Toru, *Tetrahedron: Asymmetry* **2004**, *15*, 1513–1516.

[13] J. F. Larrow, E. N. Jacobsen, Y. Gao, Y. Hong, X. Nie, C. M. Zepp, *J. Org. Chem.* **1994**, *59*, 1939–1942.

[14] R. I. Kureshy, N. H. Khan, S. H. R. Abdi, I. Ahmad, S. Singh, R. V. Jasra, *J. Catal.* **2004**, *221*, 234–240.

[15] N. H. Khan, S. Agrawal, R. I. Kureshy, S. H. R. Abdi, V. J. Mayani, R. V. Jasra, *Tetrahedron: Asymmetry* **2006**, *17*, 2659–2666.

[16] L. De Vitis, S. Florio, C. Granito, L. Ronzini, L. Troisi, V. Capriati, R. Luisi, T. Pilati, *Tetrahedron* **2004**, *60*, 1175–1182.

[17] D. D. Perrin, W. L. F. Armarego, D. R. Perrin, *Purification of Laboratory Chemicals*, Pergamon, New York, **1981**.

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