

Regio- and Stereoselective Ring-Opening Reactions of Epoxides with Indoles and Pyrroles in 2,2,2-Trifluoroethanol

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Dedicated to Professor Emanuel Vogel on the occasion of his 80th birthday

Abstract: Aliphatic and aromatic epoxides react regio- and stereoselectively with indoles and pyrroles in 2,2,2-trifluoroethanol without the use of a catalyst or any other additive. While aromatic epoxides are selectively attacked at the benzylic position, aliphatic epoxides react at the less-substituted position. Chiral epoxides react with > 99 % *ee* (*ee* = enantiomeric excess).

Keywords: C–C coupling • electrophilic substitution • enantioselectivity • heterocycles • regioselectivity

Introduction

Indoles and pyrroles are key motifs in many pharmacologically and biologically active compounds, and the synthesis of optically active indolyl and pyrrolyl derivatives has been the topic of numerous investigations.^[1] Many methods for the stereoselective ring opening of epoxides with *N*-, *O*- and *S*-nucleophiles have been developed^[2] including enzymatic processes,^[3] but regio- and stereoselective reactions with carbon nucleophiles are rare.^[4–8] Apart from reactions with trimethylsilyl cyanide^[4] and strong nucleophiles, such as phenyllithium,^[5] dialkyl zinc compounds,^[6] or enolates,^[7] reactions with electron-rich arenes, for example, indoles and pyrroles, have been reported.^[8–14]

As the nucleophilicity of indoles and pyrroles is not sufficient for a direct attack at ordinary epoxides, activation of the C–O bond is generally needed. The use of strong Lewis acids is problematic, because they may trigger isomerizations of the epoxides with formation of carbonyl compounds. Thus, Ranu and Jana reported a selective synthesis of benzylic aldehydes and ketones by treatment of the corresponding epoxides with indium(III) chloride.^[9a] On the other hand, the InBr₃-catalyzed reaction of indoles with optically pure styrene oxide gave 2-(1*H*-indol-3-yl)-2-phenylethanol in good yields and 99 % *ee* (*ee* = enantiomeric excess),^[9b] and InCl₃ has been successfully employed as a catalyst for the reactions of indoles with racemic styrene oxide in CH₂Cl₂. Under the same conditions, aliphatic epoxides gave mixtures of regioisomeric products with favored attack at the less-substituted oxirane position.^[9c] High enantioselectivities but lower yields (up to 64 %) were obtained when the reaction of 1-methylindole with enantiopure styrene oxide was catalyzed by a polymer-supported indium Lewis acid (Amberlyst-In).^[9d]

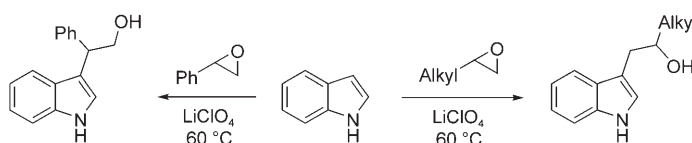
To avoid undesired isomerizations, most investigations of the reactions of indoles with epoxides employed mild Lewis acids. Thus, LiClO₄ has been reported to catalyze the reactions of aliphatic and aromatic epoxides with indoles to give high yields of 3-substituted indoles (Scheme 1); the stereochemistry of these reactions was not investigated.^[10a,b]

Somewhat lower yields of these substitution products were obtained when the reactions of indoles with styrene oxide were catalyzed by nanocrystalline titanium(IV) oxide.^[10c]

Aliphatic and aromatic epoxides were reported to react with indole, pyrrole, furan, and thiophene in the presence of

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Scheme 1. Reactions of indole with aliphatic and aromatic epoxides catalyzed by LiClO₄ under solvent-free conditions (60 °C).^[10a]

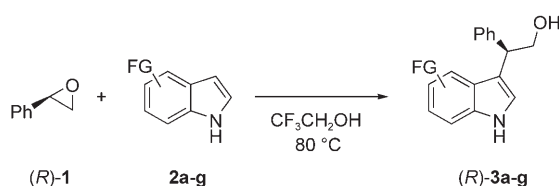
Table 1. Reactions of (*R*)-styrene oxide ((*R*)-**1**) with indole (**2a**) and 1,2-dimethylindole (**2b**) in different solvents (1M solutions) to yield compounds (*R*)-**3a** or (*R*)-**3b**.

Entry	Solvent ^[a]	<i>Y</i> ^[b]	<i>N</i> ^[c]	<i>t</i> [h]	<i>T</i> [°C]	Yield 3 [%] ^[d]	<i>ee</i> [%] ^[e]
Reactions with indole (2a)							
1	EtOH	−2.40	7.44	72	80	— ^[f]	—
2	MeOH	−1.12	7.54	72	70	— ^[g]	—
3	MeCN/H ₂ O 90:10	—	4.56	72	90	— ^[h]	—
4	acetone/H ₂ O 80:20	−0.70	5.77	72	RT	— ^[h]	—
5	acetone/H ₂ O 80:20	−0.70	5.77	72	60	9	> 99
6	EtOH/H ₂ O 40:60	2.62	5.81	72	RT	16	> 99
7	EtOH/H ₂ O 40:60	2.62	5.81	72	80	45	> 99
8	CF ₃ CH ₂ OH	2.53	1.23	48	RT	65 ^[i]	> 99
9	CF ₃ CH ₂ OH	2.53	1.23	10	80	79	> 99
Reactions with 1,2-dimethylindole (2b)							
10	EtOH	−2.40	7.44	72	80	— ^[f]	—
11	MeOH	−1.12	7.54	72	70	— ^[g]	—
12	MeCN/H ₂ O 90:10	—	4.56	72	90	— ^[h]	—
13	acetone/H ₂ O 80:20	−0.70	5.77	72	RT	7	> 99
14	acetone/H ₂ O 80:20	−0.70	5.77	14	60	17	> 99
15	EtOH/H ₂ O 40:60	2.62	5.81	72	RT	29	> 99
16	EtOH/H ₂ O 40:60	2.62	5.81	12	80	54	> 99
17	CF ₃ CH ₂ OH	2.53	1.23	24	RT	77	> 99
18	CF ₃ CH ₂ OH	2.53	1.23	3	80	90	> 99

[a] Solvent mixtures are given as v/v. [b] Ionizing powers *Y* taken are *Y*_{Br} from reference [15]. [c] Solvent nucleophilicities are taken from reference [19]. [d] Isolated yields of **3a** (entries 1–9) or **3b** (entries 10–18) after column chromatography. [e] Enantiomeric excess determined by chiral HPLC from the reaction mixtures and isolated compounds by comparing their retention times to those reported in the literature (see also the Experimental Section). [f] Trace amounts of **4c** have been detected in GCMS. [g] Trace amounts of **4b** have been detected in GCMS. [h] No conversion. [i] Trace amounts of **4d** have been detected in GCMS.

while slow ring opening was observed in 80% aqueous acetone (*Y* = −0.70). The increased yields obtained in 40% aqueous ethanol reflect the higher ionizing power *Y* of this solvent (*Y* = 2.62). The excellent yields obtained in 2,2,2-trifluoroethanol are due to its high ionizing power (*Y* = 2.53) and low solvent nucleophilicity,^[19] which explains the absence of side products which were observed in ethanol or methanol.

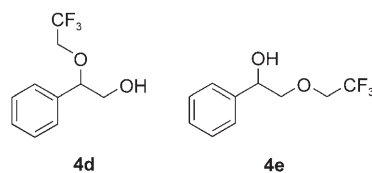
Variation of the nucleophiles: The conditions of experiments 9 and 18 (Table 1), that is, heating of equimolar amounts of heteroarenes and styrene oxide (**1**) in CF₃CH₂OH at 80 °C, were then employed for screening the scope of nucleophiles for this reaction (Scheme 4).



Scheme 4. Reactions of indoles **2a–g** with (*R*)-styrene oxide ((*R*)-**1**). FG = functional group.

The reactions of the indoles **2a–e** (*N* > 5)^[20] gave exclusively the (*R*)-2-(1*H*-indol-3-yl)-2-phenylethanol **3a–e** in good yields with a high enantiomeric excess (Table 2). Exclusive substitution at the 3-position of the indole skeleton was observed. When indoles bearing electron-withdrawing

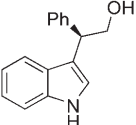
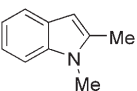
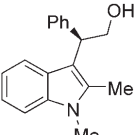
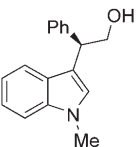
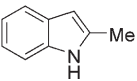
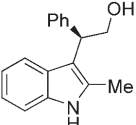
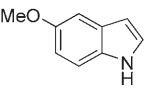
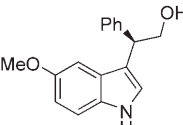
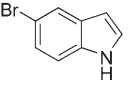
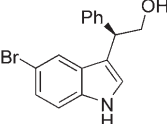
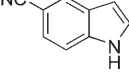
groups were used, the yields of the substitution products **3** decreased. 5-Bromoindole (**2f**) with *N* = 4.38^[20] gave only 45% of **3f** accompanied by 19% of the trifluoroethyl ether **4d**, which is formed by nucleophilic attack of 2,2,2-trifluoroethanol at the benzylic position of **1**. The nucleophilicity of 5-cyanoindole (**2g**) is so low (*N* = 2.83)^[20] that it does not act as a nucleophile at all and, again, the only reaction product obtained after 72 h at 80 °C was 17% of the ether **4d**. In line with these findings, the even weaker nucleophile anisole (*N* = −1.18)^[21] did not react with styrene oxide (**1**) under these conditions. When CF₃CH₂OH acted as a nucleophile, styrene oxide (**1**) was also regioselectively attacked at the benzylic position to yield ether **4d**.



Evidence for the constitution of **4d** comes from ¹³C NMR and mass spectroscopy. A 2:1 mixture of **4d** and **4e** is formed by heating styrene oxide (**1**) in CF₃CH₂OH/CF₃CH₂ONa for 11 h at 80 °C. Both ethers show only very small *M*⁺ peaks, *m/z*: 220, but PhCHOCH₂CF₃⁺ (*m/z*: 189) appears only in the spectrum of **4d**, whereas PhCHOH⁺ (*m/z*: 107) was found in the spectrum of **4e**.

Both fragments are typical for each compound. Another argument for the differentiation of **4d** and **4e** is given by

Table 2. Reactions of (*R*)-styrene oxide ((*R*)-**1**) with indoles **2a–g** in CF₃CH₂OH (80 °C).

Indole	<i>N</i> ^[a]	<i>t</i> [h]	Product 3	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
2a 	5.55	4	3a 	67	> 99
2b 	6.54	3	3b 	90	> 99
2c 	5.75	4	3c 	73	> 99
2d 	6.91	3	3d 	72	> 99
2e 	6.22	3	3e 	72	> 99
2f 	4.38	72	3f 	45 ^[d]	> 99
2g 	2.83	72	3g –	– ^[e]	–

[a] Nucleophilicities of the indoles taken from ref. [20]; [b] Isolated yields of **3** after column chromatography. [c] Enantiomeric excess determined by chiral HPLC from the reaction mixtures and isolated compounds. [d] 19% of ether **4d** has been detected; conversion was not complete. [e] 17% of **4d** has been detected along with the starting materials.

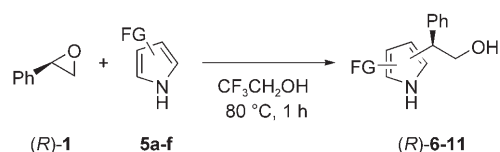
the chemical shifts in the carbon NMR spectra. While the benzylic carbon of **4d** absorbs at $\delta = 84.6$ ppm and the methylene group at $\delta = 67.1$ ppm, **4e** shows the corresponding peaks at $\delta = 72.9$ and 78.0 ppm. This is in line with the shifts in 1-phenylethane-1,2-diol (**4a**) in which the benzylic proton absorbs at $\delta = 74.7$ ppm and the CH₂ group at $\delta = 67.9$ ppm.^[22] The ratio of 2:1 (**4d/4e**) was derived from the peak areas in GCMS and the ¹H NMR spectroscopic integrals.

Reactions of pyrroles: As the pyrroles **5a–f** are somewhat more nucleophilic than the analogously substituted indoles, their reactions with styrene oxide (**1**) in CF₃CH₂OH at 80 °C were faster (Scheme 5, Table 3).

An equimolar mixture of the parent pyrrole (**5a**) and (*R*)-**1** gave a 2:1 mixture of the two regioisomers (*R*)-**6a** and (*R*)-**6b** in 68% yield within 1 h (Table 3, entry 1). Monitoring the reaction via GCMS revealed a change of the **6a/6b** ratio during the reaction. After 15 min only the 2-isomer **6a**

was detectable by GC. The ratio **6a/6b** decreased to 5.5:1 after 30 min, to 2.7:1 after 45 min and, finally, to 2.0:1 after 1 h. Attempts to elucidate the mechanism of the rearrangement of **6a** into **6b** have not been made. The bisalkylated pyrrole, 2-[5-(2-hydroxy-1-phenylethyl)-1*H*-pyrrol-2-yl]-2-phenylethanol,^[13a] was obtained in 17% yield as a side product. Bisalkylation was suppressed when styrene oxide (**1**) was combined with five equivalents of pyrrole (**5a**).

1-Methylpyrrole (**5b**) reacted with (*R*)-**1** within 1 h to give a 1:1 mixture of (*R*)-**7a** and (*R*)-**7b**, which did not change during the reaction (entry 2). Pyrroles **5c** and **5d**, in which the 2- and 5-positions of the pyrrole ring are blocked by methyl groups, gave the 3-substitution products *rac*-**8** with *rac*-**1** and (*R*)-**9** with (*R*)-**1** in 30 and 74% yields, respectively. 2,4-Dimethylpyrrole (**5e**) and 3-ethyl-2,4-dimethylpyrrole (**5f**), the strongest nucleophiles in the series of alkyl-substituted pyrroles, reacted with *rac*-**1** within 1 h to give *rac*-**10** and *rac*-**11** in 55 and 56% yields, respectively. The fact that in all reactions with pyrroles only

Scheme 5. Reactions of pyrroles **5a–f** with (*R*)-styrene oxide ((*R*)-**1**).

moderate yields of substitution products are observed is probably due to the high tendency of pyrroles to oligomerize or polymerize leading to nonvolatile distillation residues. The isolated products showed high enantiomeric excesses (> 99% *ee* in all examined cases).

All reactions described in Tables 2 and 3, which were investigated stereochemically, were performed with racemic and optically pure styrene oxide (**1**). Because the two enantiomers obtained with racemic styrene oxide (*rac*-**1**) were separable by chiral HPLC, we can conclude that the substi-

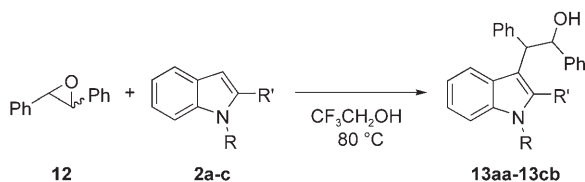
Table 3. Reactions of (*R*)-styrene oxide ((*R*)-**1**) with pyrroles **5a–f** in CF₃CH₂OH at 80 °C (1 h).

Entry	Pyrrole	Product	Yield [%] ^[a]	ee [%] ^[b]
1	5a	6a/b	68 ^[c]	> 99
2	5b	7a/b	55	> 99
3	5c	8	30	n.d. ^[d]
4	5d	9	74	> 99
5	5e	10	55	n.d. ^[d]
6	5f	11	56	n.d. ^[d]

[a] Isolated yields after column chromatography. [b] Enantiomeric excess determined by chiral HPLC from reaction products and isolated compounds. [c] 17 % of 2-[5-(2-hydroxy-1-phenylethyl)-1*H*-pyrrol-2-yl]-2-phenylethanol has been isolated as a side product. [d] Not determined; reaction was only studied with *rac*-**1**.

tution products obtained with enantiopure styrene oxide ((*R*)-**1**) had an *ee* value of more than 99 %.

Reactions with stilbene oxides: Analogous reactions with *cis*- and *rac-trans*-stilbene oxide (**12**) were studied with the indoles **2a–c** (Scheme 6).



Scheme 6. Reaction of indoles **2a–c** with *trans*- and *cis*-stilbene oxide (**12**) in CF₃CH₂OH at 80 °C.

In all cases, the reactions with *trans*-**12** gave considerably better yields than with *cis*-**12**; indole (**2a**) did not react with *cis*-**12**, and the starting materials have been recovered (Table 4, entry 2). Both diastereomers of stilbene oxide re-

acted stereospecifically with **2b** and **2c**, and the NMR spectra of the resulting triarylethanols showed that the diastereomers obtained from *trans*-**12** differed from those obtained from *cis*-**12**. In diastereomer **13ba**, obtained from *trans*-**12** and 1,2-dimethylindole (**2b**), the two benzylic protons absorb as doublets (*J* = 9.9 Hz) at δ = 4.49 and 5.76 ppm, while the corresponding resonances of the diastereomer **13bb** are at δ = 4.55 (d, *J* = 8.9 Hz) and δ = 5.76 ppm (dd, *J* = 8.9, 3.6 Hz). The additional 3.6 Hz splitting of the δ = 5.76 ppm resonance in CD₃CN is due to coupling with the OH proton (δ = 3.05 ppm, d, *J* = 3.6 Hz). Analogous spectra were observed for the products obtained from the reactions of the stilbene oxides with 1-methylindole (**2c**).

Reactions with other aromatic epoxides: *rac*-(*p*-Methoxyphenyl)oxirane (**14**) reacted with 1,2-dimethylindole (**2b**) in 2,2,2-trifluoroethanol within 4 h to give *rac*-**15** in 69 % yield (Scheme 7).

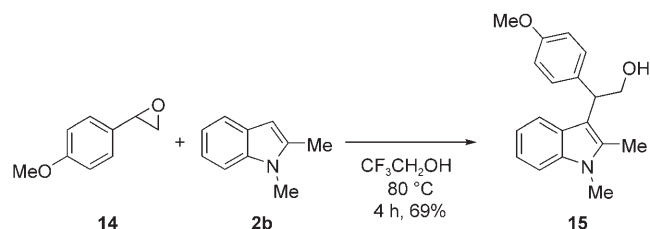
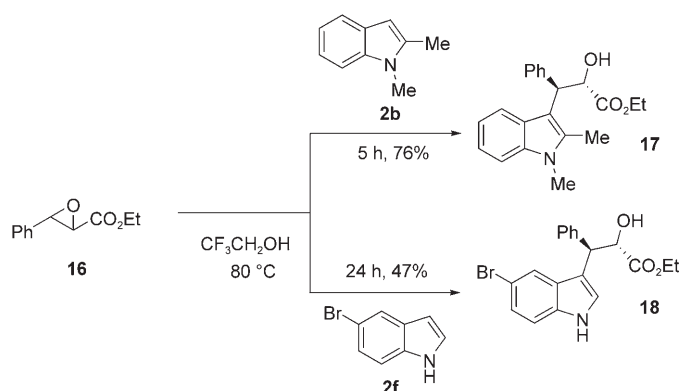
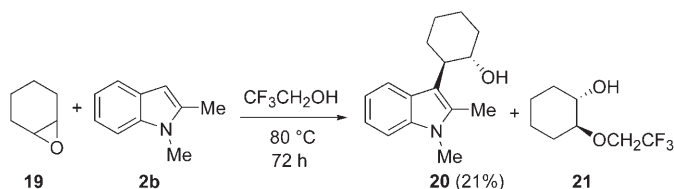
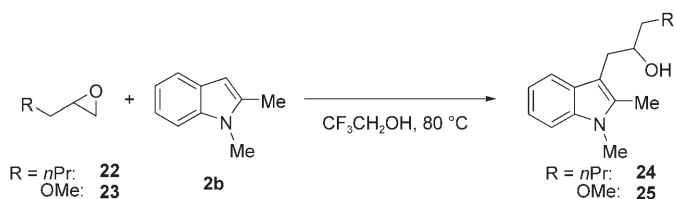
rac-3-Phenylloxirane-2-carboxylic acid ethyl ester (**16**), which was used as a 8:1 mixture of *trans* and *cis* isomers, turned out to be particularly reactive and gave better yields with 5-bromoindole (**2f**) than styrene oxide (Scheme 8). NMR spectroscopic and GCMS analysis of the products revealed that only one of the potential diastereomers of *rac*-**17** and *rac*-**18** was formed. With the assumption that, again, back-side attack of the nucleophile at the epoxide takes place, we conclude that an exclusive reaction with the major isomer (*trans*-**16**) took place while the *cis*-isomer was not attacked.

Reactions with aliphatic epoxides: 1,2-Dimethylindole (**2b**) was used as a probe to examine reactions with aliphatic epoxides. Cyclohexene oxide (**19**) gave only 21 % of *rac*-**20** after 72 h, whereas 2-(2,2,2-trifluoroethoxy)cyclohexanol (*rac*-**21**) was formed as the major product (Scheme 9). The yield of **20** increased to 31 % when the reaction mixture was heated for one week and an additional 1.5 equivalents of **19** was added after 3 and 5 d. Again, back-side attack at the epoxide is observed, and *rac*-**20** is formed as the only diastereomer. The *trans* configuration of **20** can be determined by an analysis of the coupling constants of the axial proton of

Table 4. Reactions of indoles **2a–c** with *trans*- and *cis*-stilbene oxide (**12**) in CF₃CH₂OH at 80 °C.

Entry	Indole	Stilbene oxide	<i>t</i> [h]	Product 13	Yield [%] ^[a]
1	2a	<i>rac-trans</i> - 12	42	<i>rac</i> - 13aa	37
2	2a	<i>cis</i> - 12	42	–	– ^[b]
3	2b	<i>rac-trans</i> - 12	9	<i>rac</i> - 13ba	66
4	2b	<i>cis</i> - 12	24	<i>rac</i> - 13bb	17
5	2c	<i>rac-trans</i> - 12	29	<i>rac</i> - 13ca	69
6	2c	<i>cis</i> - 12	29	<i>rac</i> - 13cb	19

[a] Isolated yields after column chromatography. [b] No conversion observed.

Scheme 7. Reaction of *rac*-(*p*-methoxyphenyl)oxirane (**14**) with 1,2-dimethylindole (**2b**).Scheme 8. Reactions of *rac*-3-phenyloxirane-2-carboxylic acid ethyl ester (**16**) with 1,2-dimethylindole (**2b**) and 5-bromoindole (**2f**).Scheme 9. Reaction of cyclohexene oxide (**19**) with 1,2-dimethylindole (**2b**).Scheme 10. Reactions of *rac*-1,2-epoxyhexane (*rac*-**22**) and *rac*-glycidyl methyl ether (*rac*-**23**) with 1,2-dimethylindole (**2b**) in CF₃CH₂OH at 80 °C.

tion of **22** should show the ¹H and ¹³C NMR spectroscopic resonances of the CH₂OH group at lower field. Analogous NMR arguments allowed us to identify **25** as a secondary alcohol, which was formed in 51 % yield when glycidyl methyl

the CHOH group. It shows two axial–axial couplings of 10.4 Hz and one axial–equatorial coupling of 4.1 Hz, indicating that the OH group and the indolyl group occupy equatorial positions on the cyclohexane ring.

The monosubstituted aliphatic epoxides *rac*-**22** and *rac*-**23** were selectively attacked at the less-substituted position (Scheme 10).

rac-1,2-Epoxyhexane (*rac*-**22**) gave 32 % of alcohol **24** after 10 h as well as 28 % of 1-(2,2,2-trifluoroethoxy)-hexan-2-ol (determined by GCMS). The constitution of compound **24** is derived from its ¹H NMR spectrum with a multiplet for CHOH at δ = 3.84 ppm and two dd at δ = 2.74 and 2.94 ppm for the diastereotopic protons at C-1 and from the ¹³C NMR spectrum in which all CH₂ groups resonate at δ < 38 ppm. The regioisomeric primary alcohol arising from nucleophilic attack at the higher substituted posi-

ether (*rac*-**23**) was heated with 1,2-dimethylindole (**2b**) for 48 h in CF₃CH₂OH.

Conclusion

Aromatic and aliphatic epoxides can be attacked nucleophilically by electron-rich arenes when the ring-opening reaction is electrophilically assisted by 2,2,2-trifluoroethanol. The high stereoselectivities of the reactions (>99% *ee*) indicate the operation of S_N2-type processes. This is also the case for styrene oxides, in which nucleophilic attack occurs regioselectively at the benzylic position, that is, at the position which is usually favored in S_N1-type reactions. The principle of electrophilic solvent assistance of S_N2-type reactions demonstrated in this work should systematically be explored also for other types of S_N2 reactions.

Experimental Section

General: All solvents were distilled prior to use. Water was purified with Millipore MilliQplus. All starting materials were commercially available and used as received, 1-methylindole (**2c**), 2,5-dimethylpyrrole (**5c**), and 2,4-dimethylpyrrole (**5e**) were distilled. 1,2-Dimethylindole (**2b**) was recrystallized from methanol prior to use. 2-(4-Methoxyphenyl)oxirane (**14**) was synthesized according to a literature procedure.^[24] ¹H NMR spectra were recorded on a Bruker ARX 300 or Varian Inova 400. Chemical shifts refer to TMS or the solvent resonance as the internal standards (CDCl₃: δ = 7.26 ppm, CD₃CN: δ = 1.94 ppm). Multiplicities are given as s = singlet, d = doublet, t = triplet, q = quartet, br = broad, and m = multiplet. ¹³C NMR spectra were recorded on Bruker ARX 300 or Varian VXR 400 spectrometers with broad-band proton decoupling. Chemical shifts refer to TMS or the solvent as internal standards (CDCl₃: δ = 77.0 ppm, CD₃CN: δ = 1.32, 118.3 ppm). Spin multiplicities are derived from DEPT135 spectra. GCMS spectra were recorded on an Agilent 5973 MSD spectrometer (HP-5MS capillary column with 30 m length, 0.25 mm diameter, 1.0 mL min⁻¹ flow rate, injector, split, He carrier gas, quadrupole mass spectrometer). Chromatographic purification was carried out with Merck silica gel 60 (mesh 40–63 μm) by common or flash-column chromatography. MPLC separation was done on a Büchi Sepacore System (pump manager C-615, C-605 pumps, C-660 fraction collector and C-635 photometer). HPLC analysis was performed on a Waters HPLC system (550 pumps, degasser, PDA, single injector). Chiralpak IB was used as a stationary phase (0.46 cm ID × 25 cm length) at 20 °C and calibrated with flavanone prior to use. Eluents, flow rate, detection, and retention times are listed. In some cases, Chiralcel OD-H (0.46 cm ID × 25 cm length) was used as a chiral column. Kugelrohr distillations were performed by using a Büchi GKR-50 Kugelrohr oven. The boiling points refer to the oven temperature. Optical rotations were measured by using a Perkin-Elmer polarimeter 343 over a path length of 10 cm with the sample temperature maintained at 20 °C in the solvent indicated.

General reaction procedure: The epoxide (3.0 mmol) was added all at once to a solution of the nucleophile (3.0 mmol) in the corresponding solvent (3 mL), and the resulting mixture was stirred for the specified time at room temperature or under reflux. Three different workup techniques were used.

Workup A: When the reaction was finished, the solvent was removed in vacuo and the crude product was purified by Kugelrohr distillation and/or column chromatography.

Workup B: When the product precipitated from the reaction mixture it was filtered off, washed with cold EtOH (3 × 5 mL), and recrystallized from EtOH.

Workup C: When aqueous solvent mixtures were used, Et₂O (10 mL) and then H₂O (10 mL) were added and the aqueous phase was extracted with Et₂O (3 × 10 mL). The combined organic phases were dried (MgSO₄), and after evaporation of the solvent in vacuo, the crude product was purified by Kugelrohr distillation and/or column chromatography.

(R)-2-(1H-Indol-3-yl)-2-phenylethanol (3a):^[9c,10b,c,12,13] Indole (**2a**, 351 mg, 3.00 mmol) and (*R*)-styrene oxide ((*R*)-**1**, 342 μL, 3.00 mmol) were stirred in CF₃CH₂OH (3 mL) at 80 °C (10 h) to yield after column chromatography (silica gel, hexanes/ethyl acetate 2:1) **3a** as a colorless solid (477 mg, 67%). *R*_f = 0.211; [α]_D²⁰ = +12.8 (*c* = 1.60 in CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ = 1.64 (brs, 1H; OH), 4.16 (dd, *J* = 7.1, 11 Hz, 1H; 1-H), 4.23 (dd, *J* = 6.7, 11 Hz, 1H; 1-H), 4.47 (t, *J* = 6.9 Hz, 1H; 2-H), 7.04 (ddd, *J* = 0.9, 7.1, 7.9 Hz, 1H; ArH), 7.07 (d, *J* = 2.2 Hz, 1H; ArH), 7.15–7.24 (m, 2H; ArH), 7.28–7.34 (m, 5H; ArH), 7.44 (d, *J* = 7.9 Hz, 1H; ArH), 8.09 ppm (brs, 1H; NH); ¹³C NMR (100 MHz, CDCl₃): δ = 45.6 (d; 2-C), 66.4 (t; 1-C), 111.1 (d; 7'-C), 116.0 (s; 3'-C), 119.4 (d; 4'-C), 119.5 (d; 5'-C), 121.9 (d; 6'-C), 122.3 (d; Ph), 125.8 (d; 2'-C), 128.3 (s; 3a'-C), 128.6 (d; Ph), 128.7 (d; Ph), 136.5 (s; 7a'-C), 141.6 ppm (s; Ph), signal assignments are based on gHMBC and gHSQC experiments; GCMS (*t* = 12.6 min): *m/z* (%): 237 (13) [*M*⁺], 207 (18), 206 (100), 204 (17), 178 (13); Chiral HPLC: OD-H (isocratic, heptane/isopropanol 85:15, 0.5 mL min⁻¹, UV at 215 nm, *t*(S) = 28.7 min, *t*(R) = 37.8 min); IB (isocratic, heptane/isopropanol 95:5 containing 0.01% diethylamine, 1.0 mL min⁻¹, UV at 275 nm, *t*(S) = 40.5 min, *t*(R) = 47.9 min), >99% *ee*.

(R)-2-(1,2-Dimethyl-1H-indol-3-yl)-2-phenylethanol (3b):^[9d] 1,2-Dimethylindole (**2b**, 726 mg, 5.00 mmol) and (*R*)-styrene oxide ((*R*)-**1**, 571 μL, 5.00 mmol) were stirred in CF₃CH₂OH (5 mL) at 80 °C (4 h) to yield after column chromatography (silica gel, hexanes/ethyl acetate 1:1) **3b** as a yellow oil (1.19 g, 90%). *R*_f = 0.565; [α]_D²⁰ = -77.0 (*c* = 1.45 in CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ = 1.53 (brs, 1H; OH), 2.29 (s, 3H; 2'-Me), 3.59 (s, 3H; NMe), 4.26 (d, *J* = 7.6 Hz, 2H; 1-H), 4.43 (t, *J* = 7.6 Hz, 1H; 2-H), 6.93 (ddd, *J* = 1.1, 7.0, 8.0 Hz, 1H; ArH), 7.05–7.12 (m, 2H; ArH), 7.15–7.27 (m, 5H), 7.39 ppm (d, *J* = 8.0 Hz, 1H; ArH); ¹³C NMR (75.5 MHz, CDCl₃): δ = 10.7 (q), 29.6 (q), 45.4 (d), 65.1 (t), 108.9 (d), 109.3 (s), 119.1 (d), 119.2 (d), 120.7 (d), 126.2 (d), 127.9 (s), 128.4 (d), 135.2 (s), 136.9 (s), 141.9 ppm (s); GCMS (*t* = 13.5 min): *m/z* (%): 265 (18) [*M*⁺], 235 (20), 234 (100), 218 (10); Chiral HPLC: OD-H (isocratic, heptane/isopropanol 85:15, 0.5 mL min⁻¹, UV at 215 nm, *t*(S) = 24.3 min, *t*(R) = 29.0 min); IB (isocratic, heptane/isopropanol 95:5 containing 0.01% diethylamine, 1.0 mL min⁻¹, UV at 275 nm, *t*(S) = 11.7 min, *t*(R) = 26.3 min), >99% *ee*.

2-Methoxy-2-phenylethanol (4b):^[25] GCMS: (*t* = 7.1 min): *m/z* (%): 152 (5) [*M*⁺], 135 (7) [*M*⁺ - H₂O], 121 (100) [*M*⁺ - CH₂OH], 91 (8).

2-Ethoxy-2-phenylethanol (4c):^[26] GCMS (*t* = 7.9 min): *m/z* (%): 165 (5) [*M*⁺], 135 (100) [*M*⁺ - CH₂OH], 91 (6).

2-Phenyl-2-(2,2,2-trifluoroethoxy)ethanol (4d) and 1-phenyl-2-(2,2,2-trifluoroethoxy)ethanol (4e): A solution of *rac*-styrene oxide (*rac*-**1**, 571 μL, 5.00 mmol) in CF₃CH₂OH (5 mL) was cooled to 0 °C and sodium hydride (204 mg, 5.10 mmol) was added in portions. The reaction mixture was then allowed to come to room temperature and was heated to 80 °C for 10 h. The mixture was poured onto saturated NaCl solution (20 mL) and the aqueous phase was extracted with Et₂O (3 × 30 mL). The combined organic layers were washed with H₂O (30 mL) and dried (MgSO₄). After removal of the solvent in vacuo, the crude product was purified by Kugelrohr distillation (5 × 10⁻² mbar, 131–140 °C) to yield a 2:1 mixture of **4d** and **4e** as a colorless liquid (561 mg, 51%). ¹H NMR (300 MHz, CDCl₃): δ = 2.55 (brs; 1H; OH of **4d** and **4e**), 3.59–3.99 (m, 4H; two CH₂ of **4d** and **4e**), 4.54 (dd, *J* = 3.6, 8.3 Hz, 0.66H; CH of **4d**), 4.89 (dd, *J* = 3.2, 8.6 Hz, 0.34H; CH of **4e**), 7.27–7.40 ppm (m, 5H; ArH of **4d** and **4e**); ¹³C NMR (75.5 MHz, CDCl₃): δ = 66.2 (q, *J*_{CF} = 34 Hz), 67.1 (t), 68.8 (q, *J*_{CF} = 34 Hz), 72.9 (d), 78.0 (t), 84.6 (d), 123.9 (q, *J*_{CF} = 288 Hz), 126.2 (d), 126.9 (d), 128.1 (d), 128.2 (d), 128.6 (d), 128.9 (d), 136.7 (s), 139.7 ppm (s); ¹⁹F NMR (282 MHz, CDCl₃): δ = -74.59 (t, *J* = 8.8 Hz, 3F of **4e**), -74.46 ppm (t, *J* = 8.8 Hz, 3F of **4d**); GCMS: **4e** (*t* = 6.2 min): *m/z* (%): 189 (100); **4d** (*t* = 6.5 min): *m/z* (%): 107 (100), 79 (59), 77 (37).

(R)-2-(1-Methyl-1H-indol-3-yl)-2-phenylethanol (3c):^[10c,12,13a] 1-Methylindole (**2c**, 384 μL, 3.00 mmol) and (*R*)-styrene oxide ((*R*)-**1**, 342 μL,

3.00 mmol) were stirred in $\text{CF}_3\text{CH}_2\text{OH}$ (3 mL) at 80 °C (4 h) to yield after column chromatography (silica gel, hexanes/ethyl acetate 1:1) **3c** as a yellow oil (550 mg, 73 %). R_f =0.659; $[\alpha]_D^{20}$ =+3.9 (c =1.66 in CHCl_3); ^1H NMR (300 MHz, CDCl_3): δ =1.82 (brs, 1H; OH), 3.73 (s, 3H; NMe), 4.14 (dd, J =7.1, 11 Hz, 1H; 1-H), 4.21 (dd, J =6.7, 11 Hz, 1H; 1-H), 4.46 (t, J =6.9 Hz, 1H; 2-H), 6.93 (s, 1H; ArH), 7.03 (ddd, J =1.2, 6.9, 8.0 Hz, 1H; ArH), 7.17–7.35 (m, 7H; ArH), 7.45 ppm (td, J =0.9, 8.0 Hz, 1H; ArH); ^{13}C NMR (75.5 MHz, CDCl_3): δ =32.7 (q), 45.6 (d), 66.4 (t), 109.2 (d), 114.4 (s), 119.0 (d), 119.4 (d), 121.8 (d), 126.6 (d), 126.7 (d), 127.4 (d), 128.2 (s), 128.6 (d), 137.2 (s), 141.8 ppm (s); GCMS (t =12.0 min): m/z (%): 251 (13) [M^+], 221 (18), 220 (100), 204 (11); Chiral HPLC: OD-H (isocratic, heptane/isopropanol 85:15, 0.5 mL min $^{-1}$, UV at 215 nm, $t(S)$ =22.7 min, $t(R)$ =45.3 min), IB (isocratic, heptane/isopropanol 90:10 containing 0.01 % diethylamine, 1.0 mL min $^{-1}$, UV at 275 nm, $t(S)$ =13.6 min, $t(R)$ =23.3 min): >99 % ee.

(R)-2-(2-Methyl-1H-indol-3-yl)-2-phenylethanol (3d):^[9c,10b,c,12,13] 2-Methylindole (**2d**, 394 mg, 3.00 mmol) and (*R*)-styrene oxide ((*R*)-**1**, 342 μL , 3.00 mmol) were stirred in $\text{CF}_3\text{CH}_2\text{OH}$ (3 mL) at 80 °C (4 h) to yield after column chromatography (silica gel, hexanes/ethyl acetate 1:1) **3d** as a yellow oil (536 mg, 72 %). R_f =0.479; ^1H NMR (300 MHz, CDCl_3): δ =2.03 (s, 3H, Me), 2.56 (s, 1H; OH), 4.16 (d, J =7.6 Hz, 2H; 1-H), 4.31 (t, J =7.6 Hz, 1H; 2-H), 6.90–7.14 (m, 7H; ArH), 7.20–7.22 (m, 2H; ArH), 7.37 (d, J =7.8 Hz, 1H; ArH), 7.99 ppm (s, 1H; NH); ^{13}C NMR (75.5 MHz, CDCl_3): δ =11.6 (q), 30.4 (d), 64.6 (t), 109.6 (d), 110.4 (d), 117.2 (d), 119.0 (d), 120.5 (d), 125.9 (d), 127.7 (d), 128.1 (d), 128.9 (s), 133.0 (s), 135.2 (s), 141.6 ppm (s); GCMS (t =13.3 min): m/z (%): 251 (15) [M^+], 221 (19), 220 (100), 204 (8), 178 (7); Chiral HPLC: IB (isocratic, heptane/isopropanol 90:10 containing 0.01 % diethylamine, 1.0 mL min $^{-1}$, UV at 275 nm, $t(S)$ =18.4 min, $t(R)$ =21.1 min): >99 % ee.

(R)-2-(5-Methoxy-1H-indol-3-yl)-2-phenylethanol (3e):^[10c,13] 5-Methoxyindole (**2e**, 442 mg, 3.00 mmol) and (*R*)-styrene oxide ((*R*)-**1**, 342 μL , 3.00 mmol) were stirred in $\text{CF}_3\text{CH}_2\text{OH}$ (3 mL) at 80 °C (3 h) to yield after column chromatography (hexanes/ethyl acetate 1:1) **3e** as a beige solid (577 mg, 72 %). R_f =0.420; ^1H NMR (300 MHz, CDCl_3): δ =2.51 (brs, 1H; OH), 3.61 (s, 3H; OMe), 4.00 (dd, J =7.2, 11 Hz, 1H; diastereotopic 1-H), 4.07 (dd, J =6.8 Hz, 1H, 1H; diastereotopic 1-H), 4.30 (t, J =6.9 Hz, 1H; 2-H), 6.73–6.82 (m, 3H; ArH), 7.00–7.24 (m, 6H; ArH), 8.37 ppm (brs, 1H; NH); ^{13}C NMR (75.5 MHz, CDCl_3): δ =45.3 (d), 55.5 (q), 66.0 (t), 101.0 (d), 111.7 (d), 111.8 (d), 115.0 (s), 122.7 (d), 126.3 (d), 127.2 (s), 128.1 (d), 128.2 (d), 131.5 (s), 141.7 (s), 153.4 ppm (s); GCMS (t =17.2 min): m/z (%): 267 (16) [M^+], 237 (18), 236 (100), 204 (13); Chiral HPLC: IB (isocratic, heptane/isopropanol 90:10 containing 0.01 % diethylamine, 1.0 mL min $^{-1}$, UV at 275 nm, $t(S)$ =31.5 min, $t(R)$ =33.4 min): >99 % ee.

(R)-2-(5-Bromo-1H-indol-3-yl)-2-phenylethanol (3f):^[9b,d,13b] 5-Bromoin-dole (**2f**, 588 mg, 3.00 mmol) and (*R*)-styrene oxide ((*R*)-**1**, 342 μL , 3.00 mmol) were stirred in $\text{CF}_3\text{CH}_2\text{OH}$ (3 mL) at 80 °C (72 h) to yield **3f** as colorless crystals (427 mg, 45 %). ^1H NMR (300 MHz, CDCl_3): δ =1.80 (brs, 1H; OH), 4.09 (dd, J =7.1, 11 Hz, 1H; diastereotopic 1-H), 4.16 (dd, J =6.6, 11 Hz, 1H; diastereotopic 1-H), 4.41 (t, J =6.7 Hz, 1H; 2-H), 7.11 (s, 1H; ArH), 7.20–7.43 (m, 7H; ArH), 7.58 (s, 1H; ArH), 8.28 ppm (brs, 1H; NH); ^{13}C NMR (75.5 MHz, CDCl_3): δ =45.4 (d), 66.4 (t), 112.6 (d), 112.8 (s), 115.8 (s), 121.8 (d), 123.1 (d), 125.1 (d), 126.9 (d), 128.2 (d), 128.7 (d), 128.8 (s), 135.0 (s), 141.2 ppm (s); GCMS (t =21.1 min): m/z (%): 317 (12), 315 (12), 287 (15), 286 (99), 285 (17), 284 (100), 204 (39), 176 (10); Chiral HPLC: IB (isocratic, heptane/isopropanol 98:2 containing 0.01 % diethylamine, 1.0 mL min $^{-1}$, UV at 275 nm, $t(S)$ =45.3 min, $t(R)$ =53.8 min): >99 % ee.

(R)-2-Phenyl-2-(1H-pyrrol-2-yl)ethanol (6a) and (R)-2-phenyl-2-(1H-pyrrol-3-yl)ethanol (6b):^[13] Pyrrole (**5a**, 119 μL , 1.00 mmol) and (*R*)-styrene oxide ((*R*)-**1**, 114 μL , 1.00 mmol) were stirred in $\text{CF}_3\text{CH}_2\text{OH}$ (1 mL) at 80 °C (1 h) to yield after column chromatography (silica gel, hexanes/ethyl acetate 1:2) a 2:1 mixture of **6a** and **6b** as a yellow oil (127 mg, 68 %). **6a**: R_f =0.313, **6b**: R_f =0.373; ^1H NMR (200 MHz, CDCl_3): δ =2.73 (brs, 1H), 3.02 (brs, 2H), 3.87–4.17 (m, 9H), 5.90–5.93 (m, 2H), 6.02–6.09 (m, 3H), 6.57–6.61 (m, 1H), 6.62–6.71 (m, 3H), 7.18–7.40 (m, 15H), 9.08 (brs, 3H); GCMS: **6a** (t =10.8 min): m/z (%): 187 (100) [M^+], 156 (100), 128 (12); **6b** (t =10.4 min): m/z (%): 187 (8) [M^+], 156

(100), 128 (17); Chiral HPLC: OD-H (isocratic, heptane/isopropanol 85:15, 0.5 mL min $^{-1}$, UV at 215 nm, **6a**: $t(S)$ =38.7 min, $t(R)$ =41.1 min): >99 % ee; **6b**: $t(S)$ =25.9 min, $t(R)$ =31.0 min: >99 % ee.

(R)-2-Phenyl-2-(1-methyl-1H-pyrrol-2-yl)ethanol (7a) and (R)-2-phenyl-2-(1-methyl-1H-pyrrol-3-yl)ethanol (7b):^[13] 1-Methylpyrrole (**5b**, 119 μL , 1.00 mmol) and (*R*)-styrene oxide ((*R*)-**1**, 114 μL , 1.00 mmol) were stirred in $\text{CF}_3\text{CH}_2\text{OH}$ (1 mL) at 80 °C (1 h) to yield after column chromatography (silica gel, hexanes/ethyl acetate 1:1) a 1:1 mixture of **7a** and **7b** as a yellow oil (111 mg, 55 %) which was separated by column chromatography. R_f =0.420 (**7a**), 0.391 (**7b**); ^1H NMR (300 MHz, CDCl_3): **7a**: δ =1.78 (brs, 1H; OH), 3.33 (s, 3H; NMe), 3.89–4.20 (m, 3H; 1-H, 2-H), 6.14–6.18 (m, 2H; ArH), 6.59 (t, J =2.4 Hz, 1H; ArH), 7.14–7.32 ppm (m, 5H); **7b**: δ =1.78 (brs, 1H; OH), 3.60 (s, 3H; NMe), 3.94–4.10 (m, 3H; 1-H, 2-H), 6.03 (t, J =2.1 Hz, 1H; ArH), 6.43 (s, 1H; ArH), 6.56 (t, J =2.1 Hz, 1H; ArH), 7.20–7.31 ppm (m, 5H; ArH); ^{13}C NMR (75.5 MHz, CDCl_3): **7a**: δ =33.7 (q), 46.5 (d), 66.4 (t), 105.5 (d), 106.8 (d), 122.4 (d), 126.9 (d), 128.2 (d), 128.7 (d), 131.6 (s), 140.2 ppm (s); **7b**: δ =41.8 (q), 47.2 (d), 67.3 (t), 107.8 (d), 120.1 (s), 122.3 (d), 123.8 (d), 126.7 (d), 128.3 (d), 128.7 (d), 142.8 ppm (s); GCMS: **7a** (t =10.7 min): m/z (%): 201 (9) [M^+], 170 (100); **7b** (t =10.4 min): m/z (%): 201 (11) [M^+], 170 (100); Chiral HPLC: OD-H (isocratic, heptane/isopropanol 85:15, 0.5 mL min $^{-1}$, UV at 215 nm, **7a**: $t(S)$ =17.2 min, $t(R)$ =10.5 min: >99 % ee; **7b**: $t(S)$ =9.2 min, $t(R)$ =12.6 min): >99 % ee.

rac-2-(2,5-Dimethyl-1H-pyrrol-3-yl)-2-phenylethanol (8):^[13a] 2,5-Dimethylpyrrole (**5c**, 119 μL , 1.00 mmol) and (*rac*)-styrene oxide (*rac*-**1**, 114 μL , 1.00 mmol) were stirred in $\text{CF}_3\text{CH}_2\text{OH}$ (1 mL) at 80 °C (1 h) to yield after column chromatography (silica gel, hexanes/ethyl acetate 1:1) **8** as an orange oil (65 mg, 30 %). R_f =0.311; ^1H NMR (400 MHz, CD_3CN): δ =2.07 (s, 3H; 2'-Me), 2.12 (s, 3H; 5'-Me), 2.44 (brs, 1H; OH), 3.88–3.97 (m, 3H; 1-H, 2-H), 5.64 (s, 1H; 4'-H), 7.12–7.27 (m, 5H; ArH), 8.43 ppm (brs, 1H; NH); ^{13}C NMR (100 MHz, CD_3CN): δ =11.0 (q), 12.7 (q), 46.6 (d), 66.9 (t), 105.2 (d), 127.4 (d), 128.5 (d), 128.9 (d), 129.2 (s), 130.6 (s), 138.3 (s), 145.4 ppm (s); GCMS (t =9.0 min): m/z (%): 215 (12) [M^+], 185 (15), 184 (100).

(R)-2-Phenyl-2-(1,2,5-trimethyl-1H-pyrrol-3-yl)ethanol (9): 1,2,5-Trimethylpyrrole (**5d**, 238 μL , 2.00 mmol) and (*R*)-styrene oxide ((*R*)-**1**, 228 μL , 2.00 mmol) were stirred in $\text{CF}_3\text{CH}_2\text{OH}$ (2 mL) at 80 °C (1 h) to yield after column chromatography (silica gel, hexanes/ethyl acetate 3:1) **9** as a yellow oil (339 mg, 74 %). R_f =0.313; ^1H NMR (400 MHz, CD_3CN): δ =2.09 (s, 3H), 2.14 (s, 3H), 2.49 (brs, 1H; OH), 3.31 (s, 3H; NMe), 3.82–3.97 (m, 3H; 1-H, 2-H), 5.71 (s, 1H; 4'-H), 7.13–7.17 (m, 1H; ArH), 7.22–7.29 ppm (m, 4H; ArH); ^{13}C NMR (100 MHz, CD_3CN): δ =10.1 (q), 12.4 (q), 30.4 (q), 46.8 (d), 66.9 (t), 104.6 (d), 119.3 (s), 124.9 (s), 126.6 (d), 127.7 (s), 128.9 (d), 129.0 (d), 145.5 ppm (s); GCMS: (t =9.4 min): m/z (%): 229 (14) [M^+], 198 (100), 196 (7), 182 (7), 181 (6); Chiral HPLC: IB (isocratic, heptane/isopropanol 90:10 containing 0.01 % diethylamine, 1.0 mL min $^{-1}$, UV at 275 nm, $t(S)$ =31.5 min, $t(R)$ =36.6 min): >99 % ee. HR-EIMS: calcd for $\text{C}_{15}\text{H}_{19}\text{NO}$: 229.1467; found: 229.1473.

rac-2-(3,5-Dimethyl-1H-pyrrol-2-yl)-2-phenylethanol (10): 2,4-Dimethylpyrrole (**5e**, 119 μL , 1.00 mmol) and (*rac*)-styrene oxide (*rac*-**1**, 114 μL , 1.00 mmol) were stirred in $\text{CF}_3\text{CH}_2\text{OH}$ (1 mL) at 80 °C (1 h) to yield after column chromatography (silica gel, hexanes/ethyl acetate 1:1) **10** as a yellow oil (118 mg, 55 %). R_f =0.298; ^1H NMR (400 MHz, CD_3CN): δ =1.90 (s, 3H; 3'-Me), 2.13 (s, 3H; 5'-Me), 2.80 (brs, 1H; OH), 3.93–4.01 (m, 2H; 1-H), 4.11–4.14 (m, 1H; 2-H), 5.52 (s, 1H; 4'-H), 7.16–7.31 (m, 5H; ArH), 8.59 ppm (brs, 1H; NH); ^{13}C NMR (100 MHz, CD_3CN): δ =11.2 (q), 12.8 (q), 45.9 (d), 65.7 (t), 108.5 (d), 115.2 (s), 126.4 (s), 127.0 (d), 127.1 (s), 128.9 (d), 129.3 (d), 143.6 ppm (s); GCMS (t =8.5 min): m/z (%): 215 (12) [M^+], 185 (15), 184 (100).

rac-2-(4-Ethyl-3,5-dimethyl-1H-pyrrol-2-yl)-2-phenylethanol (11): 3-Ethyl-2,4-dimethylpyrrole (**5f**, 246 mg, 2.00 mmol) and (*rac*)-styrene oxide (*rac*-**1**, 229 μL , 2.00 mmol) were stirred in $\text{CF}_3\text{CH}_2\text{OH}$ (2 mL) at 80 °C (1 h) to yield after column chromatography (silica gel, hexanes/ethyl acetate 2:1) **11** as a yellow oil (272 mg, 56 %). R_f =0.331; ^1H NMR (400 MHz, CD_3CN): δ =0.98–1.03 (m, 3H; CH_2CH_3), 1.88 (s, 3H; 3'-Me), 2.09 (s, 3H; 5'-Me), 2.29–2.35 (m, 2H; CH_2CH_3), 3.79 (s, 1H; OH), 3.94 (dd, J =6.8, 11 Hz, 1H; 1-H), 3.99 (dd, J =6.6, 11 Hz, 1H; 1-H), 4.13 (dd,

$J=6.7, 6.7$ Hz, 1H; 2-H), 7.24–7.32 (m, 5H; ArH), 8.40 ppm (brs, 1H; NH); ^{13}C NMR (100 MHz, CD_3CN): $\delta=9.26$ (q), 10.8 (q), 16.1 (q), 18.1 (t), 45.9 (d), 65.6 (t), 113.9 (s), 126.7 (s), 127.0 (d), 128.9 (d), 129.2 (s), 129.3 (d), 143.7 ppm (s); GCMS ($t=9.2$ min): m/z (%): 243 (15) [M^+], 213 (21), 212 (100), 196 (8), 181 (9).

rac-2-(1H-Indol-3-yl)-1,2-diphenylethanol (13aa):^[9c,10c,12] Indole (**2a**, 234 mg, 2.00 mmol) and *trans*-stilbene oxide (*rac-trans*-**12**, 392 mg, 2.00 mmol) were stirred in $\text{CF}_3\text{CH}_2\text{OH}$ (2 mL) at 80°C (42 h) to yield after column chromatography (silica gel, hexanes/ethyl acetate 2:1) **13aa** as a pale-yellow oil (231 mg, 37%). $R_f=0.517$; ^1H NMR (400 MHz, CD_3CN): $\delta=3.24$ (d, $J=4.3$ Hz, 1H; OH), 4.63 (d, $J=8.7$ Hz, 1H; 2-H), 5.46 (dd, $J=4.3, 8.7$ Hz, 1H; 1-H), 6.94–7.50 (m, 15H; ArH), 9.06 ppm (brs, 1H; NH); ^{13}C NMR (100 MHz, CD_3CN): $\delta=50.9$ (d), 76.6 (d), 110.9 (d), 116.8 (s), 119.2 (d), 119.3 (d), 122.0 (d), 122.5 (d), 126.6 (d), 126.8 (d), 127.0 (s), 127.4 (d), 128.0 (d), 128.3 (d), 129.4 (d), 135.9 (s), 140.2 (s), 142.8 ppm (s); GCMS ($t=26.0$ min): m/z (%): 313 (1) [M^+], 207 (28), 206 (100), 204 (13), 178 (10), 77 (4).

rac-2-(1,2-Dimethyl-1H-indol-3-yl)-1,2-diphenylethanol (13ba): 1,2-Dimethylindole (**2b**, 291 mg, 2.00 mmol) and *trans*-stilbene oxide (*rac-trans*-**12**, 392 mg, 2.00 mmol) were stirred in $\text{CF}_3\text{CH}_2\text{OH}$ (2 mL) at 80°C (9 h) to yield **13ba** as colorless crystals (450 mg, 66%). ^1H NMR (300 MHz, CDCl_3): $\delta=2.02$ (s, 3H; 2'-Me), 2.26 (s, 1H; OH), 3.42 (s, 3H; NMe), 4.49 (d, $J=9.9$ Hz, 1H; 2-H), 5.76 (d, $J=9.9$ Hz, 1H; 1-H), 6.99–7.33 (m, 11H; ArH), 7.58–7.60 (m, 2H; ArH), 7.69–7.71 ppm (m, 1H; ArH); ^{13}C NMR (75.5 MHz, CDCl_3): $\delta=10.2$ (q), 29.4 (q), 52.1 (d), 74.9 (d), 108.6 (d), 111.2 (s), 118.7 (d), 119.6 (d), 120.1 (d), 126.3 (d), 126.4 (d), 126.6 (s), 127.2 (d), 127.7 (d), 128.5 (d), 128.8 (d), 133.6 (s), 136.7 (s), 142.0 (s), 143.1 ppm (s); GCMS ($t=25.2$ min): m/z (%): 341 (1) [M^+], 235 (20), 234 (100), 218 (8).

rac-2-(1,2-Dimethyl-1H-indol-3-yl)-1,2-diphenylethanol (13bb): 1,2-Dimethylindole (**2b**, 294 mg, 2.00 mmol) and *cis*-stilbene oxide (*cis*-**12**, 392 mg, 2.00 mmol) were stirred in $\text{CF}_3\text{CH}_2\text{OH}$ (2 mL) at 80°C (24 h) to yield after column chromatography (silica gel, hexanes/ethyl acetate 2:1) **13bb** as colorless crystals (116 mg, 17%). $R_f=0.484$; ^1H NMR (400 MHz, CD_3CN): $\delta=2.34$ (s, 3H; 2'-Me), 3.05 (d, $J=3.6$ Hz, 1H; OH), 3.63 (s, 3H; NMe), 4.55 (d, $J=8.9$ Hz, 1H; 2-H), 5.76 (dd, $J=3.6, 8.9$ Hz, 1H; 1-H), 6.98–7.05 (m, 2H; ArH), 7.09–7.14 (m, 3H; ArH), 7.17–7.26 (m, 3H; ArH), 7.30–7.36 (m, 5H; ArH), 7.81 ppm (d, $J=8.0$ Hz, 1H; ArH); ^{13}C NMR (100 MHz, CD_3CN): $\delta=10.8$ (q), 30.0 (q), 52.7 (d), 75.8 (d), 109.8 (d), 111.3 (s), 119.5 (d), 120.6 (d), 121.1 (d), 126.6 (d), 127.8 (s), 128.0 (d), 128.2 (d), 128.7 (d), 128.8 (d), 129.5 (d), 136.3 (q), 137.9 (s), 144.2 (s), 145.2 ppm (s); GCMS ($t=26.8$ min): m/z (%): 341 (1) [M^+], 235 (20), 234 (100), 218 (8).

rac-2-(1-Methyl-1H-indol-3-yl)-1,2-diphenylethanol (13ca): 1-Methylindole (**2c**, 260 μL , 2.00 mmol) and *trans*-stilbene oxide (*rac-trans*-**12**, 392 mg, 2.00 mmol) were stirred in $\text{CF}_3\text{CH}_2\text{OH}$ (2 mL) at 80°C (29 h) to yield after column chromatography (silica gel, hexanes/ethyl acetate 3:1) **13ca** as an orange oil (452 mg, 69%). $R_f=0.435$; ^1H NMR (300 MHz, CDCl_3): $\delta=2.33$ (brs, 1H; OH), 3.36 (s, 3H; NMe), 4.52 (d, $J=6.3$ Hz, 1H; 2-H), 5.33 (d, $J=6.3$ Hz, 1H; 1-H), 6.87–6.92 (m, 2H; ArH), 7.03–7.15 (m, 10H; ArH), 7.18–7.22 (m, 2H; ArH), 7.27 ppm (ddd, $J=0.7, 1.8, 7.8$ Hz, 1H; ArH); ^{13}C NMR (75.5 MHz, CDCl_3): $\delta=32.3$ (q), 50.8 (d), 76.3 (d), 108.9 (d), 115.2 (s), 118.6 (d), 119.1 (d), 121.3 (d), 126.4 (d), 126.5 (d), 127.1 (d), 127.2 (d), 127.3 (s), 127.8 (d), 128.0 (d), 129.3 (d), 136.6 (s), 140.4 (s), 142.9 ppm (s); GCMS ($t=22.6$ min): m/z (%): 327 (1) [M^+], 221 (20), 220 (100), 204 (8), 178 (5).

rac-2-(1-Methyl-1H-indol-3-yl)-1,2-diphenylethanol (13cb):^[14] 1-Methylindole (**2c**, 260 μL , 2.00 mmol) and *cis*-stilbene oxide (*cis*-**12**, 397 mg, 2.00 mmol) were stirred in $\text{CF}_3\text{CH}_2\text{OH}$ (2 mL) at 80°C (29 h) to yield after column chromatography (silica gel, hexanes/ethyl acetate 2:1) **13cb** as white crystals (124 mg, 19%). $R_f=0.543$; ^1H NMR (300 MHz, CD_3CN): $\delta=2.53$ (brs, 1H; OH), 3.77 (s, 3H; NMe), 4.56 (d, $J=8.1$ Hz, 1H; 2-H), 5.31 (d, $J=8.1$ Hz, 1H; 1-H), 7.00–7.28 (m, 14H; ArH), 7.44 ppm (brd, $J=7.8$ Hz, 1H; ArH); ^{13}C NMR (75.5 MHz, CD_3CN): $\delta=32.8$ (q), 52.2 (d), 77.7 (d), 109.2 (d), 113.7 (s), 119.1 (d), 119.5 (d), 121.9 (d), 126.2 (d), 126.8 (d), 127.2 (d), 127.3 (d), 127.9 (d), 128.0 (s), 128.1 (d), 128.6 (d), 137.1 (s), 141.9 (s), 142.5 ppm (s); GCMS ($t=22.6$ min): m/z (%): 327 (1) [M^+], 221 (20), 220 (100), 204 (8), 178 (5).

rac-2-(1,2-Dimethyl-1H-indol-3-yl)-2-(4-methoxyphenyl)ethanol (15): 1,2-Dimethylindole (**2b**, 436 mg, 3.00 mmol) and 2-(4-methoxyphenyl)oxirane (**14**, 451 mg, 3.00 mmol) were stirred in $\text{CF}_3\text{CH}_2\text{OH}$ (3 mL) at 80°C (4 h) to yield after column chromatography (silica gel, hexanes/ethyl acetate 2:1) **15** as a yellow oil (611 mg, 69%). $R_f=0.415$; ^1H NMR (300 MHz, CDCl_3): $\delta=1.61$ (brs, 1H; OH), 2.36 (s, 3H; 2'-Me), 3.66 (s, 3H; NMe), 3.75 (s, 3H; OMe), 4.29 (d, $J=8.4$ Hz, 2H; 1-H), 4.45 (t, $J=7.8$ Hz, 1H; 2-H), 6.80 (d, $J=6.3$ Hz, 2H; ArH), 7.00 (dd, $J=8.1, 8.1$ Hz, 1H; ArH), 7.14 (dd, $J=8.1, 8.1$ Hz, 1H; ArH), 7.22–7.28 (m, 3H; ArH), 7.46 ppm (d, $J=8.1$ Hz, 1H; ArH); ^{13}C NMR (75.5 MHz, CDCl_3): $\delta=10.6$ (q), 29.6 (q), 44.6 (d), 55.2 (q), 65.3 (t), 108.8 (d), 109.5 (s), 113.8 (d), 119.1 (d), 119.3 (d), 120.6 (d), 126.6 (s), 128.8 (d), 133.9 (s), 135.0 (s), 136.9 (s), 157.9 ppm (s); GCMS ($t=19.7$ min): m/z (%): 295 (11) [M^+], 277 (11), 265 (21), 264 (100), 262 (8), 220 (9).

rac-Ethyl-3-(1,2-dimethyl-1H-indol-3-yl)-2-hydroxy-3-phenylpropanoate (17): 1,2-Dimethylindole (**2b**, 290 mg, 2.00 mmol) and *trans*-ethyl-2-phenylglycidate (**16**, 343 μL , 2.00 mmol) were stirred in $\text{CF}_3\text{CH}_2\text{OH}$ (2 mL) at 80°C (5 h) to yield after column chromatography (silica gel, hexanes/ethyl acetate 2:1) **17** as colorless crystals (513 mg, 76%). $R_f=0.349$; ^1H NMR (300 MHz, CDCl_3): $\delta=0.87$ (t, $J=7.1$ Hz, 3H; OCH_2CH_3), 2.32 (s, 3H; 2'-Me), 2.78 (d, $J=7.3$ Hz, 1H; OH), 3.62 (s, 3H; NMe), 3.93, 3.95 (2 $\times$ q, $J=7.1$ Hz, 2H; diastereotopic OCH_2CH_3), 4.70 (d, $J=6.6$ Hz, 1H; 3-H), 5.01 (dd, $J=6.6, 7.3$ Hz, 1H; 2-H), 6.98–7.04 (m, 1H; ArH), 7.09–7.27 (m, 5H; ArH), 7.42 (d, $J=7.7$ Hz, 2H; ArH), 7.59 ppm (d, $J=7.7$ Hz, 1H; ArH); ^{13}C NMR (75.5 MHz, CDCl_3): $\delta=10.8$ (q), 13.6 (q), 29.5 (q), 47.1 (d), 61.2 (t), 73.5 (d), 108.5 (d), 110.5 (s), 119.0 (d), 119.5 (d), 120.6 (d), 126.3 (d), 127.0 (s), 128.2 (d), 128.6 (d), 134.1 (s), 136.6 (s), 140.6 (s), 174.1 ppm (s); GCMS ($t=17.4$ min): m/z (%): 337 (3) [M^+], 235 (19), 234 (100), 218 (7).

rac-Ethyl-3-(5-bromo-1H-indol-3-yl)-2-hydroxy-3-phenylpropanoate (18): 5-Bromoindole (**2f**, 980 mg, 5.00 mmol) and *trans*-ethyl-2-phenylglycidate (**16**, 858 μL , 5.00 mmol) were stirred in $\text{CF}_3\text{CH}_2\text{OH}$ (5 mL) at 80°C (24 h) to yield after column chromatography (silica gel, hexanes/ethyl acetate 1:1) **18** as a yellow oil (912 mg, 47%). $R_f=0.614$; ^1H NMR (600 MHz, CDCl_3): $\delta=1.27$ (t, $J=7.2$ Hz, 3H; OCH_2CH_3), 2.90 (d, $J=6.6$ Hz, 1H; OH), 4.20 (q, $J=7.2$ Hz, 2H; OCH_2CH_3), 4.69–4.71 (m, 1H; 3-H), 4.86–4.89 (m, 1H; 2-H), 7.17–7.29 (m, 7H; ArH), 7.47 (s, 1H; ArH), 7.49 (s, 1H; ArH), 8.20 ppm (brs, 1H; NH); ^{13}C NMR (150 MHz, CDCl_3): $\delta=14.2$ (q), 46.0 (d), 61.9 (t), 73.8 (d), 112.5 (d), 112.7 (s), 115.9 (s), 121.5 (d), 124.2 (d), 124.9 (d), 127.3 (d), 128.3 (d), 128.7 (s), 129.1 (d), 134.6 (s), 138.1 (s), 173.4 ppm (s); GCMS ($t=7.8$ min): m/z (%): 212 (34), 211 (12), 210 (100), 175 (51), 165 (49), 147 (80), 137 (31), 129 (29), 102 (90), 77 (15), 75 (17), 51 (17); HR-EIMS: calcd for $\text{C}_{19}\text{H}_{18}^{35}\text{BrNO}_3$: 388.0538; found: 388.0531.

rac-2-(1,2-Dimethyl-1H-indol-3-yl)cyclohexanol (20):^[23] 1,2-Dimethylindole (**2b**, 436 mg, 3.00 mmol) and cyclohexene oxide (**19**, 304 μL , 3.00 mmol) were stirred in $\text{CF}_3\text{CH}_2\text{OH}$ (3 mL) at 80°C (72 h) to yield after column chromatography (silica gel, hexanes/ethyl acetate 4:1) **20** as white crystals (153 mg, 21%). When this reaction was repeated, and another 3.00 mmol (304 μL) of **19** were added after 72 h and 1.50 mmol (152 μL) of **19** after 160 h, **20** was obtained in 31% yield. $R_f=0.297$; ^1H NMR (300 MHz, CDCl_3): $\delta=1.15$ –2.21 (m, 9H), 2.40 (s, 3H; 2'-Me), 2.61–2.75 (m, 1H; 2-H), 3.66 (s, 3H; NMe), 4.06 (td, $J=4.1, 10$ Hz, 1H; 1-H), 7.00–7.28 (m, 3H; ArH), 7.68 ppm (d, $J=8.0$ Hz, 1H; ArH); ^{13}C NMR (75.5 MHz, CDCl_3): $\delta=10.7$ (q), 25.2 (t), 26.6 (t), 29.6 (q), 31.5 (t), 34.3 (d), 35.7 (t), 73.7 (d), 108.9 (d), 109.1 (s), 110.5 (d), 118.7 (d), 120.6 (d), 132.3 (s), 137.0 (s), 137.1 ppm (s); GCMS ($t=10.9$ min): m/z (%): 243 (86) [M^+], 184 (78), 171 (19), 158 (100), 144 (12), 115 (7).

rac-2-(2,2,2-Trifluoroethoxy)cyclohexanol (21): GCMS ($t=7.9$ min): m/z (%): 198 (5) [M^+], 180 (17), 152 (32), 139 (10), 98 (68), 81 (100), 70 (17), 55 (12), 41 (20).

rac-1-(1,2-Dimethyl-1H-indol-3-yl)hexan-2-ol (24): 1,2-Dimethylindole (**2b**, 436 mg, 3.00 mmol) and 1,2-epoxyhexane (**22**, 362 μL , 3.00 mmol) were stirred in $\text{CF}_3\text{CH}_2\text{OH}$ (3 mL) at 80°C (48 h) to yield after column chromatography (silica gel, hexanes/ethyl acetate=3:1) **24** as a pale-yellow oil (236 mg, 32%). $R_f=0.610$; ^1H NMR (300 MHz, CDCl_3): $\delta=0.92$ (t, $J=6.9$ Hz, 3H; 6-H), 1.32–1.62 (m, 6H; 3-H, 4-H, 5-H), 2.37 (s, 3H; 2'-Me), 2.74 (dd, $J=8.7, 14$ Hz, 1H; 1-H), 2.94 (dd, $J=4.2, 14$ Hz,

1H; 1-H), 3.65 (s, 3H; NMe), 3.79–3.89 (m, 1H; 2-H), 7.04–7.26 (m, 3H; ArH), 7.51 ppm (d, $J = 7.8$ Hz, 1H; ArH); ^{13}C NMR (75.5 MHz, CDCl_3): $\delta = 10.5$ (q), 14.1 (q), 22.8 (t), 28.2 (t), 29.5 (q), 32.9 (t), 36.6 (t), 71.1 (d), 107.1 (s), 108.5 (d), 118.1 (d), 118.9 (d), 120.7 (d), 127.9 (s), 134.4 (s), 136.7 ppm (s); GCMS ($t = 10.2$ min): m/z (%): 245 (15) [M^+], 159 (13), 158 (100), 143 (5).

rac-1-(1,2-Dimethyl-1H-indol-3-yl)-3-methoxypropan-2-ol (25): 1,2-Dimethylindole (**2b**, 436 mg, 3.00 mmol) and glycidyl methyl ether (**23**, 265 mg, 3.00 mmol) were stirred in $\text{CF}_3\text{CH}_2\text{OH}$ (3 mL) at 80°C (48 h) to yield after column chromatography (silica gel, hexanes/ethyl acetate 1:1) **25** as a colorless oil (357 mg, 51%). $R_f = 0.404$; ^1H NMR (300 MHz, CDCl_3): $\delta = 2.29$ (s, 3H; 2'-Me), 2.62 (brs, 1H; OH), 2.88 (d, $J = 6.9$ Hz, 2H; 1-H), 3.23–3.36 (m, 5H; 3-H, NMe), 3.52 (s, 3H; OMe), 3.95–4.03 (m, 1H; 2-H), 7.01–7.18 ppm (m, 3H; ArH), 7.49 ppm (d, $J = 7.8$ Hz, 1H; ArH); ^{13}C NMR (75.5 MHz, CDCl_3): $\delta = 10.2$ (q), 28.6 (t), 29.4 (q), 58.9 (q), 70.8 (d), 75.9 (t), 106.4 (s), 108.5 (d), 117.9 (d), 118.8 (d), 120.6 (d), 127.9 (s), 134.2 (s), 136.5 ppm (s); GCMS ($t = 9.6$ min): m/z (%): 233 (21) [M^+], 159 (11), 158 (100).

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