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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 $InBr_3$-catalyzed reaction of indoles with optically pure styrene oxide gave 2-(1*H*-indol-3-yl)-2-phenylethanols in good yields and 99% *ee* (*ee* = enantiomeric excess),[9b] and $InCl_3$ has been successfully employed as a catalyst for the reactions of indoles with racemic styrene oxide in CH_2Cl_2. 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, $LiClO_4$ 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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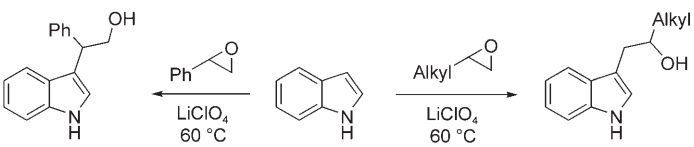
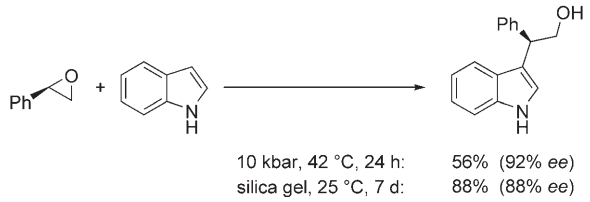


Scheme 1. Reactions of indole with aliphatic and aromatic epoxides catalyzed by $LiClO_4$ under solvent-free conditions (60 °C).[10a]

10 mol% $[ZrCl_2Cp_2]$ (Cp = cyclopentadienyl) to give good yields of substitution products. The NMR spectra, which were claimed to indicate the regioselective 3-attack at these heteroarenes, have not been published, however. Because enantiopure epoxides were not used in this study, the stereochemical course of these reactions could not be derived.[10d]

Ytterbium(III) triflate was found to be the most efficient Lewis acid to catalyze the regio- and stereoselective reaction of indole with glycidyl phenyl ether at 10 kbar.[11]

At elevated pressure (10 kbar) indole reacts with aromatic epoxides in acetonitrile even without a catalyst to give moderate yields of 2-(1*H*-indol-3-yl)-2-phenylethanols.[12] Later studies on the stereochemistry of the reaction of (*R*)-styrene oxide with indole in acetonitrile at 10 kbar and 42 °C showed that the substitution product was formed in 56% yield and 92% *ee* (Scheme 2). Addition of silica gel increased the yield but resulted in a slight decrease in stereoselectivity.[13a]



Scheme 2. High pressure and silica-gel assisted reaction of indole with optically pure (*R*)-styrene oxide.[12,13a]

Also the HBF_4-silica-gel-supported reactions of styrene oxide with indoles and pyrroles in CH_2Cl_2 were reported to give substitution products in good yields, but the stereochemistry was not investigated; aliphatic epoxides did not react.[13b]

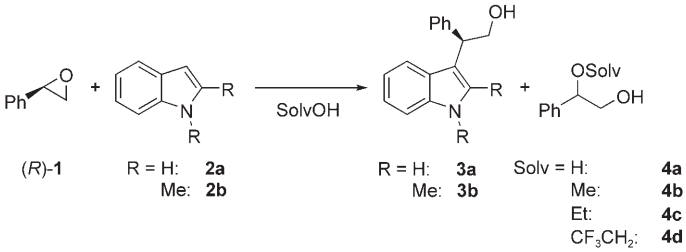
Enantioselective addition of 2-methylindole to aromatic epoxides catalyzed by [Cr(salen)] complexes resulted in kinetic resolution and formation of 3-substituted indoles in moderate yields but with high enantiomeric excesses.[14]

The well-known ionizing power of fluorinated alcohols[15] was previously employed by Bégué[16] to assist the ring opening of epoxides in their reactions with aromatic amines. We report now that 2,2,2-trifluoroethanol is also a suitable solvent for the noncatalyzed reactions of epoxides with indoles and pyrroles.

Abstract in German: *Aliphatische und aromatische Epoxide reagieren regio- und stereoselektiv mit Indolen und Pyrrolen in 2,2,2-Trifluorethanol ohne Zusatz eines Katalysators oder eines anderen Additivs. Während aromatische Epoxide selektiv an der benzylischen Position angegriffen werden, reagieren aliphatische Epoxide an der sterisch weniger gehinderten Position. Die Reaktion chiraler Epoxide liefert sehr hohe Enantiomerenüberschüsse (>99% ee).*

Results and Discussion

Screening of the reaction conditions: Winstein's investigations on the rates of nucleophilic substitutions have shown that the heterolyses of C–X bonds are assisted by protic solvents with a high ionizing power *Y*.[17] To examine whether electrophilic assistance by protic solvents can also enable the attack of electron-rich arenes at epoxides, we studied the reactions of (*R*)-(+)-styrene oxide [(*R*)-**1**] with the parent indole (**2a**) and 1,2-dimethylindole (**2b**) in various solvents (Scheme 3).



Scheme 3. Reactions of (*R*)-styrene oxide ((*R*)-**1**) with indole (**2a**) and 1,2-dimethylindole (**2b**) in different solvents.

Table 1 (entries 1–3) shows that indole (**2a**) did not react with styrene oxide (**1**) in methanol, ethanol, or 90% aqueous acetonitrile at 70–90 °C. In the latter case, no conversion of **1** took place, while in methanol and ethanol small amounts of the corresponding 2-alkoxy-2-phenylethanols **4b** and **4c** were obtained (<3% GCMS). Previously, we discovered that indoles are allylated and benzylated in 80% aqueous acetone in good yields when allyl and benzyl halides were stirred with the indoles in this solvent.[18] Under these conditions, no conversion of indole (**2a**) was observed at room temperature (entry 4), but at 60 °C, the reaction of **2a** with (*R*)-**1** gave 9% of (*R*)-**3a** with high enantiomeric excess (>99% *ee*, entry 5). Better yields of **3a** have been obtained in 40% aqueous ethanol (16% at room temperature and 45% at 80 °C, entries 6 and 7).

Best chemical yields (up to 79%, entries 8 and 9) with high enantiomeric excesses (>99% *ee*) were observed when the reactions were performed in 2,2,2-trifluoroethanol.

1,2-Dimethylindole (**2b**) reacted similarly, but gave somewhat better yields. Again, nucleophilic attack of **2b** at *rac*-**1** was not observable in methanol, ethanol, and acetonitrile/water (90:10 v/v, entries 10–12). When using 80% aqueous acetone as the solvent, 7% of (*R*)-**3b** was isolated after 72 h at room temperature (entry 13); at 60 °C the yield increased to 17% after 14 h (>99% *ee* in both cases, entry 14). As with **2a**, higher yields of (*R*)-**3b** were obtained in ethanol/water (40:60 v/v, entries 15 and 16) and even 90% of enantiopure (*R*)-**3b** has been obtained when 2,2,2-trifluoroethanol was used as the solvent (entries 17 and 18).

The yields correlate with Winstein's solvent ionizing power *Y*.[15,17] No reactions took place in poorly ionizing solvents, such as ethanol ($Y = -2.40$) or methanol ($Y = -1.12$)

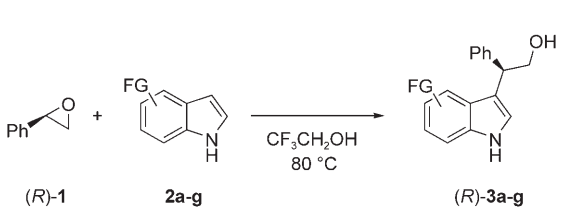
Table 1. Reactions of (*R*)-styrene oxide ((*R*)-**1**) with indole (**2a**) and 1,2-dimethylindole (**2b**) in different solvents (1 M solutions) to yield compounds (*R*)-**3a** or (*R*)-**3b**.

Entry	Solvent[a]	Y[b]	N[c]	t [h]	T [°C]	Yield **3** [%][d]	*ee* [%][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_2O 90:10	–	4.56	72	90	–[h]	–
4	acetone/H_2O 80:20	−0.70	5.77	72	RT	–[h]	–
5	acetone/H_2O 80:20	−0.70	5.77	72	60	9	>99
6	EtOH/H_2O 40:60	2.62	5.81	72	RT	16	>99
7	EtOH/H_2O 40:60	2.62	5.81	72	80	45	>99
8	CF_3CH_2OH	2.53	1.23	48	RT	65[i]	>99
9	CF_3CH_2OH	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_2O 90:10	–	4.56	72	90	–[h]	–
13	acetone/H_2O 80:20	−0.70	5.77	72	RT	7	>99
14	acetone/H_2O 80:20	−0.70	5.77	14	60	17	>99
15	EtOH/H_2O 40:60	2.62	5.81	72	RT	29	>99
16	EtOH/H_2O 40:60	2.62	5.81	12	80	54	>99
17	CF_3CH_2OH	2.53	1.23	24	RT	77	>99
18	CF_3CH_2OH	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.

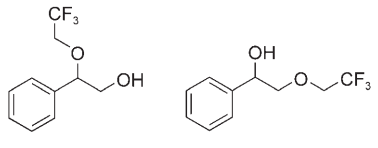
Variation of the nucleophiles: The conditions of experiments 9 and 18 (Table 1), that is, heating of equimolar amounts of heteroarenes and styrene oxide (**1**) in CF_3CH_2OH at 80°C, were then employed for screening the scope of nucleophiles for this reaction (Scheme 4).



(*R*)-**1** **2a-g** (*R*)-**3a-g**

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-phenylethanols **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 CF_3CH_2OH acted as a nucleophile, styrene oxide (**1**) was also regioselectively attacked at the benzylic position to yield ether **4d**.

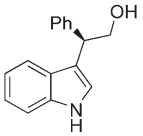
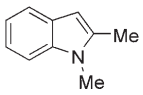
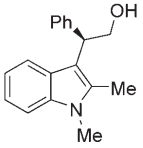
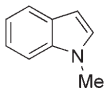
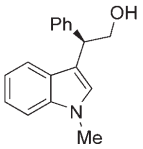
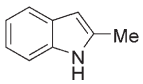
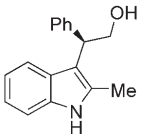
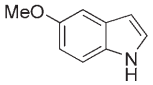
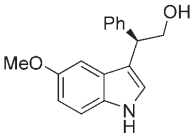
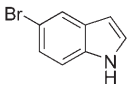
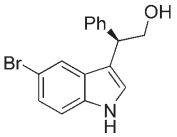
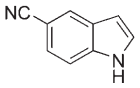


4d **4e**

Evidence for the constitution of **4d** comes from ^{13}C NMR and mass spectroscopy. A 2:1 mixture of **4d** and **4e** is formed by heating styrene oxide (**1**) in CF_3CH_2OH/CF_3CH_2ONa for 11 h at 80°C. Both ethers show only very small M^+ peaks, m/z: 220, but $PhCHOCH_2CF_3^+$ (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 CF_3CH_2OH (80 °C).

	Indole	N[a]	t [h]	Product **3**	Yield [%][b]	*ee* [%][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]	–

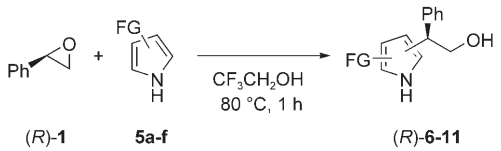
[a] Nucleophilicities of the indoles taken from ref. [20]; [b] Isolated yields of **3** after column chromatography. [c] Enantiomeric excess determined by chiral HPLC from the reaction mixtures and isolated compounds. [d] 19% of ether **4d** has been detected; conversion was not complete. [e] 17% of **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 CH_2 group at $\delta = 67.9$ ppm.[22] The ratio of 2:1 (**4d**/**4e**) was derived from the peak areas in GCMS and the ^{1}H 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 CF_3CH_2OH 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 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).



(*R*)-**1** **5a-f** (*R*)-**6-11**

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

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-

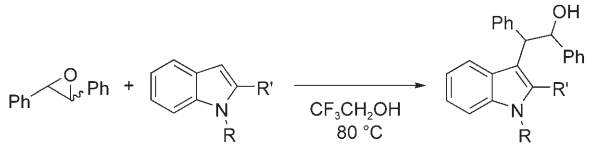
Table 3. Reactions of (*R*)-styrene oxide ((*R*)-**1**) with pyrroles **5a–f** in CF_3CH_2OH at 80 °C (1 h).

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).



12 **2a-c** **13aa-13cb**

Scheme 6. Reaction of indoles **2a–c** with *trans*- and *cis*-stilbene oxide (**12**) in CF_3CH_2OH at 80 °C.

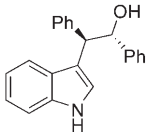
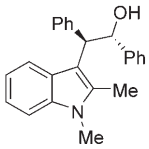
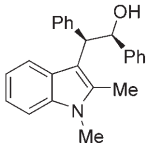
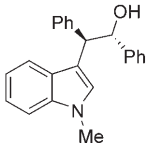
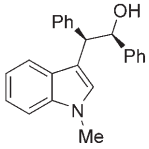
In all cases, the reactions with *trans*-**12** gave considerably better yields than with *cis*-**12**; indole (**2a**) did not react with *cis*-**12**, and the starting materials have been recovered (Table 4, entry 2). Both diastereomers of stilbene oxide reacted stereospecifically with **2b** and **2c**, 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 $\delta=4.49$ and 5.76 ppm, while the corresponding resonances of the diastereomer **13bb** are at $\delta=4.55$ (d, $J=8.9$ Hz) and $\delta=5.76$ ppm (dd, $J=8.9$, 3.6 Hz). The additional 3.6 Hz splitting of the $\delta=5.76$ ppm resonance in CD_3CN is due to coupling with the OH proton ($\delta=3.05$ 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-Phenyloxirane-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 CF_3CH_2OH at 80 °C.

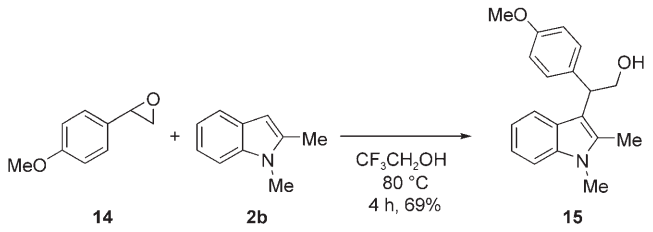
Entry	Indole	Stilbene oxide	*t* [h]	Product **13**		Yield [%][a]
1	**2a**	*rac-trans*-**12**	42	*rac*-**13aa**		37
2	**2a**	*cis*-**12**	42	–	–	–[b]
3	**2b**	*rac-trans*-**12**	9	*rac*-**13ba**		66
4	**2b**	*cis*-**12**	24	*rac*-**13bb**		17
5	**2c**	*rac-trans*-**12**	29	*rac*-**13ca**		69
6	**2c**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

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

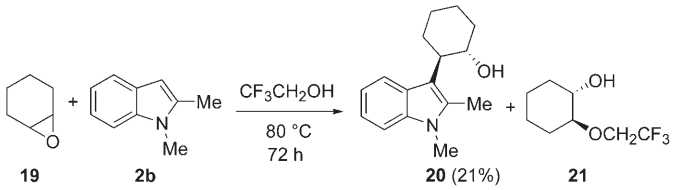
the C*H*OH group. It shows two axial–axial couplings of 10.4 Hz and one axial-equatorial coupling of 4.1 Hz, indicating that the OH group and the indolyl group occupy equatorial positions on the cyclohexane ring.

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

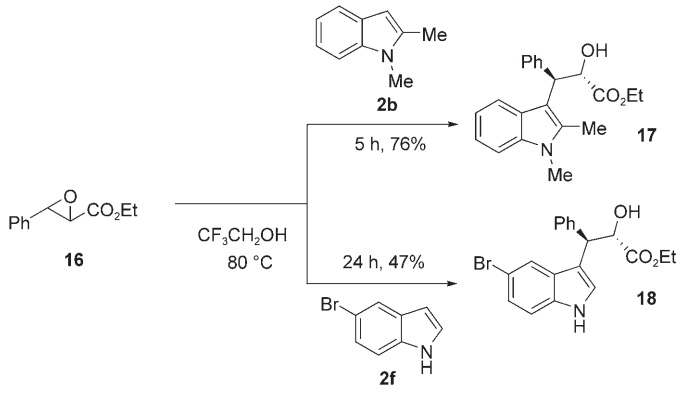
rac-1,2-Epoxyhexane (*rac*-**22**) gave 32% of alcohol **24** after 10 h as well as 28% of 1-(2,2,2-trifluoroethoxy)-hexan-2-ol (determined by GCMS). The constitution of compound **24** is derived from its ^{1}H NMR spectrum with a multiplet for C*H*OH at $\delta = 3.84$ ppm and two dd at $\delta = 2.74$ and 2.94 ppm for the diastereotopic protons at C-1 and from the ^{13}C NMR spectrum in which all CH_2 groups resonate at $\delta < 38$ ppm. The regioisomeric primary alcohol arising from nucleophilic attack at the higher substituted position of **22** should show the ^{1}H and ^{13}C NMR spectroscopic resonances of the CH_2OH 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



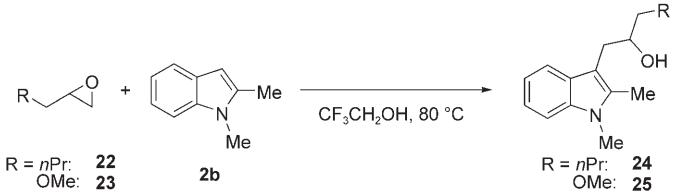
Scheme 7. Reaction of *rac*-(*p*-methoxyphenyl)oxirane (**14**) with 1,2-dimethylindole (**2b**).



Scheme 9. Reaction of cyclohexene oxide (**19**) 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 10. Reactions of *rac*-1,2-epoxyhexane (*rac*-**22**) and *rac*-glycidyl methyl ether (*rac*-**23**) with 1,2-dimethylindole (**2b**) in CF_3CH_2OH at 80 °C.

ether (*rac*-**23**) was heated with 1,2-dimethylindole (**2b**) for 48 h in CF_3CH_2OH.

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 stereoselectivites 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] ^{1}H 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 ($CDCl_3$: $\delta=7.26$ ppm, CD_3CN: $\delta=1.94$ ppm). Multiplicities are given as s=singlet, d=doublet, t=triplet, q=quartet, br=broad, and m=multiplet. ^{13}C 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 ($CDCl_3$: $\delta=77.0$ ppm, CD_3CN: $\delta=1.32$, 118.3 ppm). Spin multiplicities are derived from DEPT135 spectra. GCMS spectra were recorded on an Agilent 5973 MSD spectrometer (HP-5MS capillar column with 30 m length, 0.25 mm diameter, 1.0 mL min^{-1} flow rate, injector, split, He carrier gas, quadrupol 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, Chiracel 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, Et_2O (10 mL) and then H_2O (10 mL) were added and the aqueous phase was extracted with Et_2O (3×10 mL). The combined organic phases were dried ($MgSO_4$), and after evaporation of the solvent in vacuo, the crude product was purified by Kugelrohr distillation and/or column chromatography.

(*R*)-2-(1*H*-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 CF_3CH_2OH (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%). $R_f=0.211$; $[\alpha]_D^{20}=+12.8$ ($c=1.60$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.64$ (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); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=45.6$ (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-1*H*-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 CF_3CH_2OH (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%). $R_f=0.565$; $[\alpha]_D^{20}=-77.0$ ($c=1.45$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.53$ (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); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=10.7$ (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^+-H_2O], 121 (100) [M^+-CH_2OH], 91 (8).

2-Ethoxy-2-phenylethanol (4c):[26] GCMS ($t=7.9$ min): *m*/*z* (%): 165 (5) [M^+], 135 (100) [M^+-CH_2OH], 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 CF_3CH_2OH (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 Et_2O (3×30 mL). The combined organic layers were washed with H_2O (30 mL) and dried ($MgSO_4$). 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%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=2.55$ (brs; 1H; OH of **4d** and **4e**), 3.59–3.99 (m, 4H; two CH_2 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**); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=66.2$ (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); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta=-74.59$ (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-1*H*-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 CF_3CH_2OH (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 $CHCl_3$); ^{1}H 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-1*H*-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 CF_3CH_2OH (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; ^{1}H 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-1*H*-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 CF_3CH_2OH (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; ^{1}H 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-1*H*-indol-3-yl)-2-phenylethanol (3f):[9b,d,13b] 5-Bromoindole (**2f**, 588 mg, 3.00 mmol) and (*R*)-styrene oxide ((*R*)-**1**, 342 μL, 3.00 mmol) were stirred in CF_3CH_2OH (3 mL) at 80 °C (72 h) to yield **3f** as colorless crystals (427 mg, 45 %). ^{1}H 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-(1*H*-pyrrol-2-yl)ethanol (6a) and (*R*)-2-phenyl-2-(1*H*-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 CF_3CH_2OH (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; ^{1}H 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-1*H*-pyrrol-2-yl)ethanol (7a) and (*R*)-2-phenyl-2-(1-methyl-1*H*-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 CF_3CH_2OH (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**); ^{1}H 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/iso-propanol 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-1*H*-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 CF_3CH_2OH (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; ^{1}H 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-1*H*-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 CF_3CH_2OH (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; ^{1}H 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/*iso*-propanol 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 $C_{15}H_{19}NO$: 229.1467; found: 229.1473.

***rac*-2-(3,5-Dimethyl-1*H*-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 CF_3CH_2OH (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; ^{1}H 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-1*H*-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 CF_3CH_2OH (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; ^{1}H 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): δ=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-(1*H*-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 CF_3CH_2OH (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; ^{1}H NMR (400 MHz, CD_3CN): δ=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): δ=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-1*H*-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 CF_3CH_2OH (2 mL) at 80°C (9 h) to yield **13ba** as colorless crystals (450 mg, 66%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=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, $CDCl_3$): δ=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-1*H*-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 CF_3CH_2OH (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; ^{1}H NMR (400 MHz, CD_3CN): δ=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): δ=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 (s), 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-1*H*-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 CF_3CH_2OH (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; ^{1}H NMR (300 MHz, $CDCl_3$): δ=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, $CDCl_3$): δ=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-1*H*-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 CF_3CH_2OH (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; ^{1}H NMR (300 MHz, CD_3CN): δ=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): δ=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-1*H*-indol-3-yl)-2-(4-methoxyphenyl)ethanol (15)**: 1,2-Dimethyl-indole (**2b**, 436 mg, 3.00 mmol) and 2-(4-methoxyphenyl)oxirane (**14**, 451 mg, 3.00 mmol) were stirred in CF_3CH_2OH (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; ^{1}H NMR (300 MHz, $CDCl_3$): δ=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, $CDCl_3$): δ=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-1*H*-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 CF_3CH_2OH (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; ^{1}H NMR (300 MHz, $CDCl_3$): δ=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×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, $CDCl_3$): δ=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-1*H*-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 CF_3CH_2OH (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; ^{1}H NMR (600 MHz, $CDCl_3$): δ=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, $CDCl_3$): δ=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 $C_{19}H_{18}{}^{35}BrNO_3$: 388.0538; found: 388.0531.

***rac*-2-(1,2-Dimethyl-1*H*-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 CF_3CH_2OH (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; ^{1}H NMR (300 MHz, $CDCl_3$): δ=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, $CDCl_3$): δ=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-1*H*-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 CF_3CH_2OH (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; ^{1}H NMR (300 MHz, $CDCl_3$): δ=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-1*H*-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 CF_3CH_2OH (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%). $R_f=0.404$; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=2.29$ (s, 3H; 2′-Me), 2.62 (br s, 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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[1] a) R. J. Sundberg, *The Chemistry of Indoles*, Academic Press, New York, **1970**; b) R. A. Jones in *Comprehensive Heterocyclic Chemistry, Vol. 4*,, Pergamon Press, Oxford, **1984**, Chapter 3.05; c) A. R. Katritzky, R. Taylor, *Adv. Heterocycl. Chem.* **1990**, *47*, 87–137.

[2] Reviews: a) L. P. C. Nielsen, E. N. Jacobsen in *Aziridines and Epoxides in Organic Synthesis* (Ed.: A. K. Yudin), Wiley-VCH, Weinheim, **2006**, pp. 229–269; b) C. Schneider, *Synthesis* **2006**, 3919–3944, c) R. E. Parker, N. S. Isaacs, *Chem. Rev.* **1959**, *59*, 737–799, d) D. Amantini, F. Fringuelli, O. Piermatti, S. Tortoioli, L. Vaccaro, *ARKIVOC* **2002**, *11*, 293–311, e) I. M. Pastor, M. Yus, *Curr. Org. Chem.* **2005**, *9*, 1–29.

[3] For reviews of enzymatic-catalyzed reactions see: a) K. Faber, *Biotransformations in Organic Chemistry*, Springer, New York, **2004**, b) M. S. Smit, *Trends Biotechnol.* **2004**, *22*, 123–129; c) U. T. Bornscheuer, R. J. Kazlauskas, *Hydrolases in Organic Synthesis*, 2nd ed., Wiley-VCH, Weinheim, **2005**.

[4] a) M. Hayashi, M. Tamura, N. Oguni, *Synlett* **1992**, 663–664; b) B. M. Cole, K. D. Shimizu, C. A. Krueger, J. P. A. Harrity, M. L. Snapper, A. H. Hoveyda, *Angew. Chem.* **1996**, *108*, 1776–1779; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1668–1671; c) K. D. Shimizu, B. M. Cole, C. A. Krueger, K. W. Kuntz, M. L. Snapper, A. H. Hoveyda, *Angew. Chem.* **1997**, *109*, 1782–1785; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1704–1707; d) S. E. Schaus, E. N. Jacobsen, *Org. Lett.* **2000**, *2*, 1001–1004; e) Z. Palkulski, K. M. Pietrusiewicz, *Tetrahedron: Asymmetry* **2004**, *15*, 41–45.

[5] N. Oguni, Y. Miyagi, K. Itoh, *Tetrahedron Lett.* **1998**, *39*, 9023–9026.

[6] a) M. Pineschi, *New J. Chem.* **2004**, *28*, 657–665; b) F. Badalassi, P. Crotti, F. Macchia, M. Pineschi, A. Arnold, B. L. Feringa, *Tetrahedron Lett.* **1998**, *39*, 7795–7798; c) F. Bertozzi, P. Crotti, F. Macchia, M. Pineschi, A. Arnold, B. L. Feringa, *Tetrahedron Lett.* **1999**, *40*, 4893–4896; d) F. Bertozzi, P. Crotti, F. Macchia, M. Pineschi, B. L. Feringa, *Angew. Chem.* **2001**, *113*, 956–958; *Angew. Chem. Int. Ed.* **2001**, *40*, 930–932.

[7] P. Crotti, V. Di Bussolo, L. Favero, F. Macchia, M. Pineschi, *Gazz. Chim. Ital.* **1997**, *127*, 273–275.

[8] Reviews: a) M. Bandini, A. Melloni, S. Tommasi, A. Umani-Ronchi, *Synlett* **2005**, 1199–1222; b) M. Bandini, A. Melloni, A. Umani-Ronchi, *Angew. Chem.* **2004**, *116*, 560–566; *Angew. Chem. Int. Ed.* **2004**, *43*, 550–556; c) M. Pineschi, *Eur. J. Org. Chem.* **2006**, 4979–4988.

[9] a) B. C. Ranu, U. Jana, *J. Org. Chem.* **1998**, *63*, 8212–8216; b) M. Bandini, P. G. Cozzi, P. Melchiorre, A. Umani-Ronchi, *J. Org. Chem.* **2002**, *67*, 5386–5389; c) J. S. Yadav, B. V. S. Reddy, S. Abraham, G. Sabitha, *Synlett* **2002**, 1550–1552; d) M. Bandini, M. Fagioli, A. Melloni, A. Umani-Ronchi, *Adv. Synth. Catal.* **2004**, *346*, 573–578.

[10] a) N. Azizi, S. Mehrazma, M. R. Saidi, *Can. J. Chem.* **2006**, *84*, 800–803; b) J. S. Yadav, B. V. S. Reddy, G. Parimala, *J. Chem. Res. Synop.* **2003**, 78–81; c) M. L. Kantam, S. Laha, J. Yadav, B. Sreedhar, *Tetrahedron Lett.* **2006**, *47*, 6213–6216; d) M. L. Kantam, K. Aziz, P. R. Likhar, *Catal. Lett.* **2004**, *98*, 117–121.

[11] H. Kotsuki, M. Teraguchi, N. Shimomoto, M. Ochi, *Tetrahedron Lett.* **1996**, *37*, 3727–3730.

[12] H. Kotsuki, M. Nishiuchi, S. Kobayashi, H. Nishizawa, *J. Org. Chem.* **1990**, *55*, 2969–2972.

[13] a) H. Kotsuki, K. Hayashida, T. Shimanouchi, H. Nishizawa, *J. Org. Chem.* **1996**, *61*, 984–990; b) B. P. Bandgar, A. V. Patil, *Tetrahedron Lett.* **2007**, *48*, 173–176.

[14] M. Bandini, P. G. Cozzi, P. Melchiorre, A. Umani-Ronchi, *Angew. Chem.* **2004**, *116*, 86–89; *Angew. Chem. Int. Ed.* **2004**, *43*, 84–87.

[15] T. W. Bentley, G. Llewellyn, *Prog. Phys. Org. Chem.* **1990**, *17*, 121–158.

[16] U. Das, B. Crousse, V. Kesavan, D. Bonnet-Delpon, J.-P. Bégué, *J. Org. Chem.* **2000**, *65*, 6749–6751.

[17] S. G. Smith, A. H. Fainberg, S. Winstein, *J. Am. Chem. Soc.* **1961**, *83*, 618–625.

[18] M. Westermaier, H. Mayr, *Org. Lett.* **2006**, *8*, 4791–4794.

[19] S. Minegishi, S. Kobayashi, H. Mayr, *J. Am. Chem. Soc.* **2004**, *126*, 5174–5181.

[20] S. Lakhdar, M. Westermaier, F. Terrier, R. Goumont, T. Boubaker, A. R. Ofial, H. Mayr, *J. Org. Chem.* **2006**, *71*, 9088–9095.

[21] a) H. Mayr, B. Kempf, A. R. Ofial, *Acc. Chem. Res.* **2003**, *36*, 66–77; b) H. Mayr, J. Bartl, G. Hagen, *Angew. Chem.* **1992**, *104*, 1689–1691; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1613–1615.

[22] A. Closson, M. Johansson, J.-E. Bäckvall, *Chem. Commun.* **2004**, 1494–1495.

[23] K. Freter, *J. Org. Chem.* **1972**, *37*, 2010–2015.

[24] Y. Tsuchiya, T. Kumamoto, T. Ishikawa, *J. Org. Chem.* **2004**, *69*, 8504–8505.

[25] H. Takeuchi, H. Kishioka, K. Kitajima, *J. Phys. Org. Chem.* **1995**, *8*, 121–126.

[26] M. Moghadam, S. Tangestaninejad, V. Mirkhami, R. Shaibani, *Tetrahedron* **2004**, *60*, 6105–6112.

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