# Opening of Diaryl Epoxides: *ortho*-Fluorophenyl and 2-Pyridyl Epoxides

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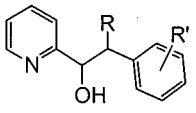
**Keywords:** Epoxides / Asymmetric synthesis / Ring opening

Opening of epoxides with $LiAlH_4$, $MgBr_2{\cdot}2OEt_2$ (solution in $Et_2O$), $MgBr_2{\cdot}OEt_2$ (suspension in $Et_2O$), and NaBr/Amberlyst-15 has been studied. While 2-pyridyl epoxide **1** opens with complete regioselectivity, *ortho*-fluorophenyl epoxide **2** does not, but affords mixtures. Moreover, while the *anti* isomer (100–80%) is in all cases the *major* product with epoxide **1**, epoxide **2** affords the *anti* isomer as *major* product with $MgBr_2$ and the *syn* isomer as *major* product with NaBr/Amberlyst-15.

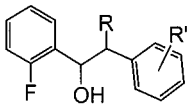


## Introduction

During investigation of a short route towards type **I** chiral aromatic alcohols[1] possessing an extra heteroatom, and as an application of our asymmetric synthesis of *trans* diaromatic epoxides (which has been shown to give almost total enantioselectivities),[2] opening of *trans* diaryl epoxides was considered.

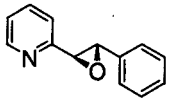



Type I

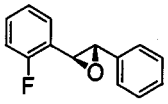



Type II

Here we present the opening of racemic *trans*-2-pyridyl epoxide **1**,[3] and also of racemic *trans-ortho*-fluorophenyl epoxide **2**,[4] in order to prepare type **II** ligands that have not yet been studied.




*trans*-**1**




*trans*-**2**

$LiAlH_4$, which had provided fully regioselective opening of epoxide **1**,[3] was tested on epoxide **2**. Metal bromides, for production of halohydrins (in which the halogen can be easily replaced by important functional groups such as nitrogen), were also studied; the reagents used were: prepared $MgBr_2{\cdot}2OEt_2$ (≈ 4 M solution in $Et_2O$),[5] the commercially available and crystalline $MgBr_2{\cdot}OEt_2$ (as a suspension in $Et_2O$),[6,7] and NaBr/Amberlyst-15 (as a suspension in acetone).[7]

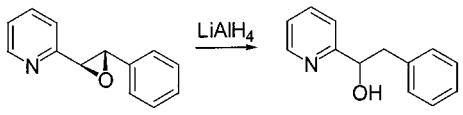
It should be noted that, while the magnesium atom is involved in the reaction during both $MgBr_2$ openings (either with prepared $MgBr_2{\cdot}2OEt_2$ or with commercial $MgBr_2{\cdot}OEt_2$, making an aqueous workup necessary (to generate the hydroxyl group), the bromohydrin is formed directly during NaBr/amberlyst-15 opening (sodium is trapped by the resin, proton is provided) and no workup is necessary. One could therefore say that, overall, HBr is provided to the substrate; this is denoted below as '*HBr*', rather than NaBr/amberlyst-15.

All the isomer ratios were determined on unpurified crude reaction products (to avoid enrichment). All isomers were fully characterised, either after isolation or on mixtures, as described below.

## Results

### Opening of the *trans* Phenyl-2-pyridyloxirane 1

The *trans* epoxide **1** has already been shown[3] to be regioselectively opened by $LiAlH_4$, to give the pyridyl alcohol **3** as the sole product (Scheme 1).




*trans* **1** **3** 100%

Scheme 1

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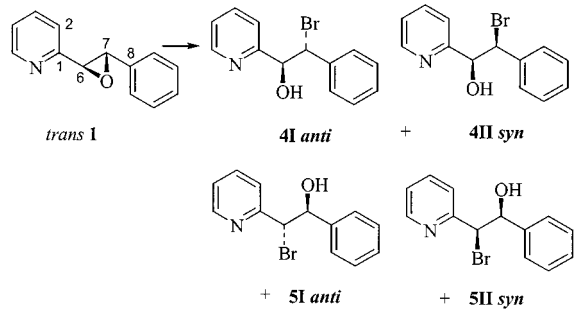
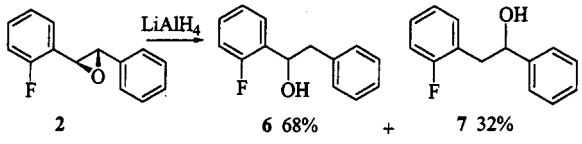
Two pairs of regioisomers, **4I/4II** and **5I/5II**, would, in principle, be expected upon cleavage of **1** with bromide reagents (Scheme 2).




Scheme 2

As shown in Table 1, formation of a single regioisomer − **4** − was observed in all cases (with either $MgBr_2$ or '*HBr*'), in diastereomeric ratios ranging from 80:20 to > 98:2. When freshly prepared (a few minutes) $MgBr_2{\cdot}2(OEt_2)$ (≈ 4 M ethereal solution) was used, only one diastereomer − **4I** (> 98%) − was obtained, in almost quantitative yield (Table 1, entry 1), while $MgBr_2{\cdot}OEt_2$ provided a small amount of diastereomer **II** (**4II**, 8%). It is worth noting that use of older solutions of $MgBr_2{\cdot}2(OEt_2)$ (one day) resulted in a slower reaction and an almost equimolar mixture of **4I** and **4II** (56:44), but that **5** was never observed.



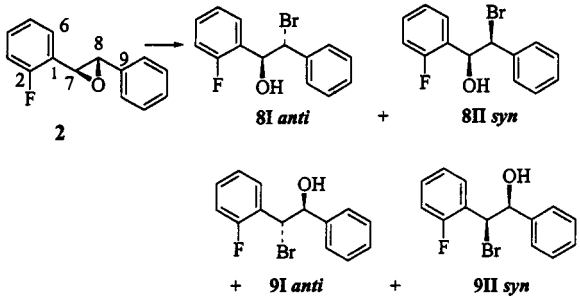

Scheme 3

Interestingly, '*HBr*' also provided **4** as the only regioisomer, but with a lower diastereoselectivity than seen with $MgBr_2$.

### Opening of the *trans* 2-Fluorophenyl(phenyl)oxirane 2

Ring-opening of fluoro epoxide **2** with $LiAlH_4$ in $Et_2O$ (Scheme 3) gave a mixture of the two possible regioisomers, **6** and **7**, in 68:32 ratio.

Two pairs of regioisomers, **8I/8II** and **9I/9II**, would also be expected upon cleavage of epoxide **2** by bromine reagents, Scheme 4.




Scheme 4

As shown in Table 2 (lines 1 and 2), $MgBr_2$ − either prepared [$MgBr_2{\cdot}2(OEt_2)$, ≈ 4 M solution in $Et_2O$] or commercial [$MgBr_2{\cdot}1(OEt_2)$ suspension] − provided the two *anti* isomers **8I** and **9I** (out of the four possible isomers) in the ratio ≈ 4:1 in favour of the regioisomer **8I**. On the other hand, '*HBr*'-opening gave, in quantitative yield, a mixture of all four isomers, with the *syn* bromohydrin **8II** as the *major* compound, Table 2 (line 3).

Table 1. Opening of *trans*-phenyl-2-pyridylepoxide **1**

| Bromide | Conv.[a] (%) | Product ratios[a] **4I** | **4II** | **5I** | **5II** | Regioselectivity **4/5** | Reaction condition |
|---|---|---|---|---|---|---|---|
| $MgBr_2{\cdot}2(Et_2O)$[b] | quant. | >98[c] | – | – | – | 100:0 | $Et_2O$, 0 °C; 1 h |
| $MgBr_2{\cdot}1(Et_2O)$[d] | 90 | 92 | 8 | – | – | 100:0 | $Et_2O$, 0 °C → 20 °C; 18 h |
| NaBr/Amberlyst-15 | 87 | 80 | 20 | – | – | 100:0 | acetone, 25 °C; 48 h |

[a] Determined by $^1H$ NMR spectroscopy of the crude product of the reaction. [b] 3 M solution in $Et_2O$, freshly prepared from of Mg and 1,2-dibromoethane in diethyl ether.[5] [c] Isolated yield. [d] Commercial (Aldrich).

Table 2. Bromide cleavage of *trans*-2-fluorophenyl-phenylepoxide **2**

| Bromide | Conv.[a] (%) | Product ratios[a] **8I** | **8II** | **9I** | **9II** | Regioselectivity **8/9** | Reaction condition |
|---|---|---|---|---|---|---|---|
| $MgBr_2{\cdot}2\ (Et_2O)$[b] | 98 | 84 | – | 16 | – | 84:16 | $Et_2O$, 0 °C → 20 °C; 18 h |
| $MgBr_2{\cdot}1\ (Et_2O)$[c] | 83 | 82 | – | 18 | – | 82:18 | $Et_2O$, 0 °C; 3 h |
| NaBr/Amberlyst-15 | quant. | 13 | 62 | 10 | 15 | 75:25 | acetone, 25 °C; 12 h |

[a] Determined by $^1H$ NMR spectroscopy of the crude product of the reaction. [b] 3 M solution in $Et_2O$, freshly prepared from Mg and 1,2-dibromoethane in diethyl ether.[5] [c] Commercial (Aldrich).

### Characterisation of the Bromohydrins 4I and 4II

The structure **4** was assigned to the *major* isomer **I** by long-range $^1H/^{13}C$ NMR correlation, which identified a correlation between the pyridyl ring C2 carbon[8] and the proton at C6 (Figure 1), assigned to CH(OH) from the presence of a coupling constant with the OH proton (dd). No correlation was observed with the proton at C7 assigned to CHBr (d).

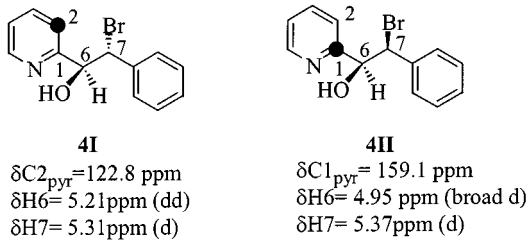


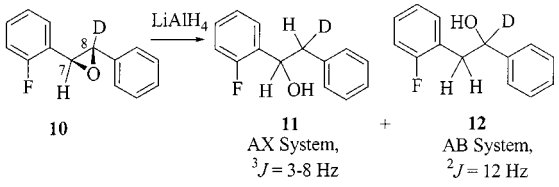

Figure 1. NMR data used for the assignment of the structure of **4I** and **4II**

In the case of the *minor* isomer **II**, a correlation was observed between the pyridyl ring C1 carbon and the proton at C6 (br. d), while no correlation was found between C1 and the proton at C7 (d).

The two isomers obtained were thus both assigned as structure **4**, showing that regioisomer **5** was not formed. The stereochemistry was determined by alkaline ring-closure.[9] A 4:1 mixture of **4I/4II** gave a 4:1 *trans*/*cis* mixture of the corresponding pyridyl epoxide, indicating that the *major* **4I** isomer was *anti*, as shown in Scheme 2, and **4II** was *syn*.

### Characterisation of Alcohols 6 and 7

The structure **6** was assigned to the *major* (68%) regioisomer (and **7** to the *minor* one) by comparison of the $^1H$ NMR spectra of mixtures obtained by $LiAlH_4$ reduction either from epoxide **2** or from epoxide **10** monodeuterated at C8[10] (Scheme 5).

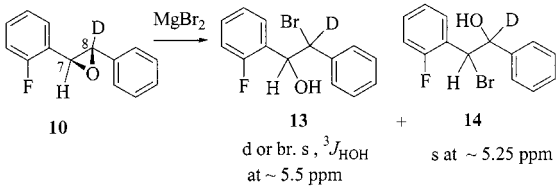



Scheme 5

In the $^1H$ NMR, the ABX system of the *major* regioisomer obtained from epoxide **2** showed the CH(OH) signal (X part) at δ = 5.29[11] (after $D_2O$ exchange: dd, $^3J$ = 7.5 and 5 Hz) and the $CH_2$ signals (AB part) at δ = 3.15 (dd, $^2J$ = 12.0, $^3J$ = 5.0 Hz) and δ = 2.95 (dd, $^2J$ = 12.0, $^3J$ = 7.5 Hz), while in the $^1H$ NMR of the *major* regioisomer obtained from epoxide **10**, the AX system exhibited a signal at δ = 5.28 (d, $^3J$ = 4.0 Hz, after $D_2O$ exchange), which was assigned to CH(OH), and one at δ = 3.15 (d, $^3J$ = 4.0 Hz), assigned to CH(D). It was thus concluded that the hydroxyl group was at C7 (Scheme 5), and that the structure of the *major* regioisomer obtained from epoxide **2** was **6**. As a consequence, structure **7** was assigned to the *minor* regioisomer, consistently with the absence of the CH(OH) signal at δ = 5.0 and with the presence of an AB system at δ = 3.09 (d, $^2J$ = 12.0 Hz) and δ = 3.15 (d, $^2J$ = 12.0 Hz).

### Characterisation of Bromohydrins 8I, 8II, 9I, and 9II

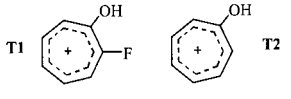
The structure of the *major* isomer (Table 2, entries 1 and 2) obtained from $MgBr_2$-opening of epoxide **2** was assigned as **8** by comparison of the $^1H$ NMR spectrum of the 84:16 mixture (d, δ = 5.12: CHBr; dd, δ = 5.40: CHOH[11]) to that of the mixture obtained on opening epoxide **10** (deuterated at C8)[10] with prepared $MgBr_2{\cdot}2(OEt_2)$ (Scheme 6). The $^1H$ NMR spectrum of the *major* isomer obtained from epoxide **10** exhibited a broad singlet at δ = 5.45 (corresponding to the δ = 5.40 signal observed in the *major* isomer obtained from epoxide **2** and assigned to C*H*OH) and no signal at δ ≈ 5.12 (where the C*H*Br signal would be expected). Structure **13** was thus assigned to the *major* isomer obtained from **10** and, as a consequence, structure **8** to the *major* isomer obtained from **2**.




Scheme 6

$LiAlH_4$ reduction of the above 84:16 mixture (in which the *major* isomer (84%) was assigned the structure **8**) afforded both regioisomers **6** (corresponding to **8**) and **7** (corresponding to **9**) in ≈ 4:1 ratio. It could thus be concluded that the *minor* isomer was the regioisomer **9**. A GC-MS analysis confirmed the regiochemistry, allowing us to assign the structure **8** to the *major* isomer (main peak: *m*/*z* = 125, **T1**) and the structure **9** to the *minor* product (main peak: *m*/*z* = 107, **T2**). The *anti* stereochemistries of both **8** and **9** were then determined by alkaline ring-closure[9] of the 82:18 mixture of **8** and **9**, which gave only the *trans* fluoro epoxide **2** (> 95%, NMR) as the crude product. Both isomers, *major* and *minor,* were thus assigned as *anti*: **8I** and **9I** (Scheme 3).

The *major* isomer obtained with '*HBr*' (Table 2, line 3) was assigned structure **8** by long-range $^1H/^{13}C$ NMR correlation, which revealed, for this isomer, a correlation between the phenyl ring C9[12] (Scheme 4) and proton CHBr at C8. This isomer, being different from **8I** (different NMR spectra), could therefore only be *syn* (**8II**), which was also confirmed by GC-MS analysis (main peak: *m*/*z* = 125, **T1**) and by alkaline ring-closure.[9] The 13:62:10:15 mixture of bromohydrins gave ≈3:1 *cis*/*trans* mixture of the corresponding fluoro epoxide.



## Discussion and Conclusion

### Regioselectivity

As shown in Figure 2 (Tables 1 and 2), while the 2-pyridyl epoxide **1** opened with complete regioselectivity, the *ortho*-fluorophenyl epoxide **2** did not, but afforded mixtures with all three reagents used: $LiAlH_4$, $MgBr_2$, and '*HBr*'.

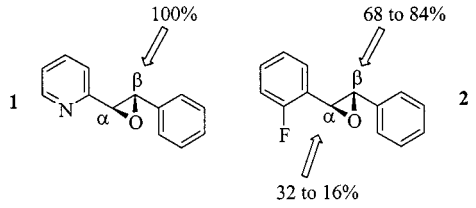



Figure 2. Regioselectivity of ring opening

Although participation of a neighbouring fluorine atom has been observed during opening of epoxides with organoaluminium reagents,[13] such assistance is not strong enough in the case of epoxide **2** and $MgBr_2$. It also appears that, although the bite angle[14] is more favourable in the case of epoxide **2** (six-membered ring) than in epoxide **1** (five-membered ring) for small cations such as magnesium (Figure 3), the complexing ability of fluorine when attached to a carbon is not enough to provide full regioselectivity, while the complexing ability of nitrogen is enough to overcome the effect of the bite angle and direct the approach of the reagent (through formation of a five-membered Mg-chelate), resulting in complete regioselectivity in the case of epoxide **1** (100% β-opening). A directed approach through Mg-chelation has also been postulated with functionalized epoxides.[6,7d]

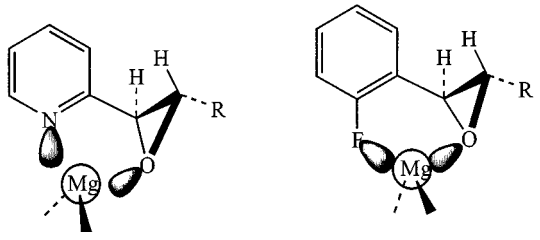



Figure 3. 5- and 6-membered chelates

Observation of 100% β-opening of pyridyl epoxide **1** with '*HBr*' (NaBr/Amberlyst-15) is less straightforward, as it is difficult to envisage such a strong role/chelation of sodium under these conditions (surface of a resin providing $H^+$). One could thus postulate a contribution of a carbenium ion (or a partial plus-charge) that is more reactive when α to a phenyl group than when α to a pyridyl group, which may be due to formation of a 'charged' pyridinium ion ($H^+$ provided by the resin), thus resulting in Br fixation only at the β-position.

Such a driving force being absent in epoxide **2**, α-opening is also obtained with '*HBr*'.

### Diastereoselectivity

The diastereoselectivities observed for β- and α-opening are listed in Table 3.

Table 3. Diastereoselectivities obtained for α- and β-opening of epoxides **1** and **2**

| Compound | Bromide | β-Opening *anti* **I**/*syn* **II** | α-Opening *anti* **I**/*syn* **II** |
|---|---|---|---|
| | $MgBr_2$ | 100:0 | – |
| **4** | $MgBr_2$ | 92:8 | – |
| | '*HBr*' | 80:20 | – |
| | $MgBr_2$ | 100:0 | 100:0 |
| **8** | $MgBr_2$ | 100:0 | 100:0 |
| | '*HBr*' | 17:**83** | 40:**60** |

The obtainment of the *anti* isomer corresponds to an $S_N2$ reaction at the centre undergoing substitution, in agreement with previous results,[6a–6c] and so the results obtained with $MgBr_2$ (Table 3, lines 1, 2, 4, 5) are not surprising.

The results observed in the case of epoxide **2** for '*HBr*' opening (NaBr/Amberlyst-15), in which the *syn*[15] isomers **8II** and **9II** were *major* products (Table 3, line 6), can be compared to literature results[16] in which mainly *syn* isomers (explained by frontal approach)[16] were obtained through opening of *trans* and/or *cis* stilbene oxide with dry HCl in benzene. The obtaining of the *syn* isomer as the *major* product thus suggests the same kind of approach for NaBr/amberlyst-15-opening ('*HBr*' addition) of epoxide **2**.

The results observed with epoxide **1** for '*HBr*'-opening, in which the *anti* isomer was the *major* product, may be compared to HBr delivery from grafted phosphonium salts,[17] which gave a 1:1 mixture of *trans*/*cis* addition with stilbene, and also to previous results with NaBr/Amberlyst-15 and functionalised epoxides, which provided *trans* isomers.[7]

Other studies to provide more insight into NaBr/resin reagents are underway.

## Experimental Section

**General:** 1D and 2D $^1H$ and $^{13}C$ NMR spectra (pulse programmes: coloc for long range and hxco for direct) were recorded on a Bruker Avance 400 with $C_6D_6$ or $CDCl_3$ as solvents. Chemical shifts (δ) are given in ppm downfield from TMS as internal standard. TLC was performed on Merck glass plates with 60 $F_{254}$ silica gel. Merck silica gel was used for chromatographic purification. MS spectra were recorded on a Hewlett Packard 6890 chromatograph equipped with a HP 5973 mass detector. Crystalline $MgBr_2$:1($OEt_2$) and Amberlyst-15 were purchased from Aldrich.

**General Procedure for the Synthesis of Racemic Epoxides 1 and 2:**[18] NaOH (7.1 mL of. 50% aqueous solution) was added dropwise at 0 °C to a stirred solution of benzyldimethylsulfonium chloride (1.3 equiv., 10.5 mmol), 2-pyridinecarboxyaldehyde (for **1**), or 2-fluorobenzaldehyde (for **2**) (1 equiv.), and tetrabutylammonium hydrogensulfate (0.05 equiv.) in $CH_2Cl_2$ (15 mL). After 5 h, the organic layer was separated and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 10 mL). The organic phases were combined and dried

with $Na_2SO_4$. After evaporation, the crude product was analysed by NMR and found to be a ≈ 7:3 mixture of *trans*/*cis* epoxide (as seen on $^1H$ NMR spectra).

***trans*-2-Phenyl-1-(2-pyridyl)oxirane (1):**[2b] This compound was obtained in a yield of 63% after chromatographic purification ($CHCl_3/Et_2O$, 7:3). $^1H$ NMR ($CDCl_3$/TMS): δ = 4.05 (br. s, 2 H), 7.25 (m, 2 H), 7.35 (m, 5 H), 7.70 (td, $^3J$ = 7.0, $^4J$ = 2.0 Hz, 1 H), 8.60 (dd, $^3J$ = 5.0, $^4J$ = 2.0 Hz, 1 H). $^{13}C$ NMR ($CDCl_3$/TMS): δ = 61.8, 62.9, 120.2, 123.3, 125.8, 128.5, 128.6, 136.9, 149.6, 136.8, 156.4.

***trans*-1-(*o*-Fluorophenyl)-2-phenyloxirane (2):**[10] This compound was obtained in a yield of 51% after chromatographic purification (hexane/$CH_2Cl_2$ 7:3). $^1H$ NMR ($CDCl_3$/TMS): δ = 3.9 (d, $^3J$ = 2.0 Hz, 1 H), 4.3 (d, $^3J$ = 2.0 Hz, 1 H), 7.25 (m, 9 H). $^{13}C$ NMR ($CDCl_3$/TMS): δ = 57.15 (d, $^3J_{C,F}$ = 6 Hz), 62.4, 115.4 (d, $^3J_{C,F}$ = 20 Hz), 124.5 (d, $J_{C,F}$ = 4 Hz), 124.7 (d, $^2J_{C,F}$ = 12.5 Hz), 125.8, 126.1 (d, $J_{C,F}$ = 4 Hz), 128.7, 128.8, 129.7 (d, $J_{C,F}$ = 8 Hz), 136.8, 161.6 (d, $^1J_{C,F}$ = 245 Hz). $C_{14}H_{11}FO$ (214.2): found C 78.60, H 5.23; calcd. C 78.48, H 5.17.

***trans*-(*R,R*)-[2-$^2$H]-1-(*o*-Fluorophenyl)-2-phenyloxirane (10):**[10] $^1H$ NMR ($CDCl_3$/TMS): δ = 4.3 (br. s, 1 H), 7.25 (m, 9 H).

**General Procedure for Opening of Epoxides with $MgBr_2$:** Either commercial $MgBr_2{\cdot}Et_2O$ or freshly prepared 4 M $MgBr_2{\cdot}2Et_2O$ in $Et_2O$ (4 equiv.)[3] was added at 0 °C, all at once, to a solution of the desired epoxide (1 equiv.) in anhydrous $Et_2O$ (5 mL). The mixture was stirred at the desired temperature, and the reaction was monitored by TLC. After completion of the reaction, the mixture was poured into ice (or into a saturated $NH_4Cl$ solution in $H_2O$, in the case of $MgBr_2{\cdot}2Et_2O$) and the precipitate was filtered off. The filtrate was washed with $H_2O$ and dried with $Na_2SO_4$, the solvent was evaporated under vacuum, and the crude product was analysed by NMR.

**General Procedure for Opening of Epoxides with NaBr/Amberlyst-15:** NaBr (2 equiv.) and Amberlyst-15 (1 equiv.)[7d] were added to a cold (−30 °C), stirred solution of epoxide (1 equiv.) in acetone (10 mL). The mixture was stirred at the desired temperature, and the reaction was monitored by TLC, until completion. The mixture was then filtered, and the filtrate was evaporated under vacuum. The residue was dissolved in EtOAc, and the resulting organic layer was dried with $Na_2SO_4$, the solvent was evaporated under vacuum, and the crude product was analysed by NMR.

***anti*-2-Bromo-2-phenyl-1-(2-pyridyl)ethanol (4I):** $^1H$ NMR (400 MHz, $C_6D_6$): δ = 4.15 (br. d, 1 H, OH), 5.21 (dd, $^3J_{H,OH}$ = 8, $^3J_{H,H}$ = 6 Hz, 1 H, C*H*OH), 5.31 (d, $^3J$ = 6.0 Hz, 1 H, C*H*Br) 6.47 (m, 1 H, C4*H*), 6.8−7.0 (m, 6 H), 7.26 (≈d, $^3J$ = 5.0 Hz, 2 H), 8.18 (≈d, $^3J$ = 4.0 Hz, C5*H*). $^{13}C$ NMR (100 MHz, $C_6D_6$): δ = 58.7 (*C*HBr), 77.4 (*C*HOH), 122.7/122.8 (*C*2H and *C*4H, pyridyl), 128.3/128.4/129.3 (CH, phenyl), 136.0 (*C*3H, pyridyl), 138.7 (*C*8, phenyl), 148.6 (*C*5H, pyridyl), 159.0 (*C*1, pyridyl).

***syn*-2-Bromo-2-phenyl-1-(2-pyridyl)ethanol (4II):** Characterisation in the mixture: **4I/4II** = 4:1. $^1H$ NMR (400 MHz, $C_6D_6$), overlapped with **4I** signals but: δ = 4.95 (br. d, $^3J$ = 4.0 Hz, 1 H, C*H*OH), 5.37 (d, $^3J$ = 4.0 Hz, 1 H, C*H*Br). $^{13}C$ NMR (100 MHz, $C_6D_6$): overlapped with **4I** but: δ = 61.5 (*C*HBr), 76.5 (*C*HOH), 121.8 (*C*2H, pyridyl), 136.2 (*C*3H, pyridyl), 140.0 (*C*8, phenyl), 148.4 (*C*5H, pyridyl), 159.1 (*C*1, pyridyl). $C_{14}H_{12}BrFO$ (295.2): found C 57.04, H 4.11, calcd. C 56.94, H 4.06. $C_{13}H_{12}BrNO$ (278.1): found C 56.04, H 4.41; calcd: calcd. C 56.13, H 4.34.

***anti*-2-Bromo-1-(*o*-fluorophenyl)-2-phenylethanol (8I) and *anti*-2-Bromo-2-(*o*-fluorophenyl)-1-phenylethanol (9I):** Characterisation by $^1H$ NMR of the mixture: **8I/9I** = 4:1. $^1H$ NMR (400 MHz, $C_6D_6$): δ = 4.96 (dd, $^3J_1$ = 6, $^3J_2$ = 5 Hz, 1 H, C*H*OH, **9I**, 20%), 5.12 (d, $^3J$ = 6.0 Hz, 1 H, C*H*Br, **8I**, 80%), 5.40 (dd, $^3J_1$ = 6, $^3J_2$ = 5 Hz, 1 H, C*H*OH, **8I**, 80%), 5.50 (d, $^3J$ = 6.0 Hz, 1 H, C*H*Br, **9I**, 20%), 6.6−7.2 (m, 9 H, C*H* arom., **8I**+**9I**). MS *major*: **8I** (*m*/*z*,%): 296 $[M + 2]^+$ (1), 294 $[M^+]$ (1), 125 (100). MS *minor*: **9I** (*m*/*z*,%): 296 $[M + 2]^+$ (1), 294 $[M^+]$ (1), 107 (100).

***syn*-2-Bromo-1-(*o*-fluorophenyl)-2-phenylethanol (8II):** Characterisation as the major product of the mixture: **8I/8II/9I/9II** = 13:62:10:15. $^1H$ NMR (400 MHz, $C_6D_6$), overlapping signals but: 4.95 (br. d, CHOH, 1 H, **9I**, 10%), 5.11 (d, $^3J$ = 5.0 Hz, 1 H, C*H*Br, **8II**, 62%), 5.14 (d, 1 H, CHBr, **8I**, 13%), 5.23 (dd, $^3J_1$ = 5, $^3J_2$ = 3 Hz, 1 H, CHOH, **8II**, 62%), 5.40 (dd, 1 H, CHOH, **8I**, 13%), 5.2 (br. d, 1 H, CHOH, **9II**, 15%), 5.50 (d,, 1 H CHBr, **9I**, 10%), 5.76 (d, 1 H, CHBr, **9II**, 15%). $^{13}C$ NMR (100 MHz, $C_6D_6$), **8II**: 63.1 (*C*HBr), 72.0 (*C*HOH), 115.2 (d, $^2J_{C,F}$ = 22 Hz, *C*3H), 124.2 (*C*5H), 126.0 (d, $^2J_{C,F}$ = 22 Hz, *C*1), 127.2, 128.3 (d, $^3J_{C,F}$ = 4.5 Hz, *C*4H or *C*6H) 128.5, 128.6, 128.7, 128.7 (d, $^3J_{C,F}$ = 4.5 Hz, *C*4H or *C*6H), 129.7, 138.8 (*C*9) 160.0 (d, $^1J_{C,F}$ = 245 Hz, *C*2). MS: **8II** (*m*/*z*,%): 296 $[M + 2]^+$ (1), 294 $[M^+]$ (1), 125 (100).

**Reduction of Epoxide 2:** $LiAlH_4$ (1 M in diethyl ether, 1.5 equiv.) was added dropwise and under argon to a solution of ***trans*-2** (214 mg, 1 mmol, 1 equiv.) in anhydrous $Et_2O$ (5 mL). The mixture was stirred at room temperature for 2 h and monitored by TLC. After usual workup the organic layer was dried with $Na_2SO_4$, the solvent was evaporated under vacuum, and the crude product was analysed by NMR: 220 mg of a 68:32 mixture of **6** and **7** was obtained, with a conversion of 88%.

**1-(*o*-Fluorophenyl)-2-phenylethanol (6) and 2-(*o*-Fluorophenyl)-1-phenylethanol (7):** $^1H$ NMR (400 MHz, $CDCl_3$ + 1 drop of $D_2O$), δ = 2.96 (A part of ABX system, $^3J_{AX}$ = 7.5, $^2J_{AB}$ = 12 Hz, 1 H, **6**, 68%), 3.06 (AB part of ABX system, 2 H, **7**, 32%), 3.15 (B part of ABX system, $^3J_{BX}$ = 5, $^2J_{AB}$ = 12 Hz, 1 H, **6**, 68%), 5.0 (X part of ABX system, dd, $^3J$ = 7.5, $^3J$ = 5.0 Hz, 1 H, **7**, 32%), 5.25 (X part of ABX system, dd, $^3J$ = 7.5, $^3J$ = 5.0 Hz, 1 H, **6**, 68%), 7.3 (m, H arom). $C_{14}H_{13}FO$ (216.3): found C 77.51, H 6.11; calcd. C 77.75, H 6.05.

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[2] [2a] A. Solladié-Cavallo, A. Diep-Vohuule, *J. Org. Chem.* **1995**, *60*, 3494. [2b] A. Solladié-Cavallo, A. Diep-Vohuule, V. Sunjic, V. Vinkovic, *Tetrahedron: Asymm* **1996**, *7*, 1783. [2c] A. Solladié-Cavallo, L. Bouérat, M. Roje, *Tetrahedron Lett.* **2000**, *41*, 7309.

[3] The (*R,R*)-epoxide **1** can be obtained with up to 99.2% *ee.* by the chiral sulfonium method; see: A. Solladié-Cavallo, M. Roje, T. Isarno, V. Sunjic, V. Vinkovic, *Eur. J. Org. Chem.* **2000**, 1077. Obtainment of pyridyl epoxide **1** by classical epoxidation methods is not possible because of oxidation of the pyridyl group.

[4] The (*R,R*)-epoxide **2** can be obtained with up to 99.9% *ee* by the chiral sulfonium method (cf. ref.[2b]).

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[8] The pyridyl C2 was assigned by direct $^1H/^{13}C$ NMR correlation experiments and reference to *Carbon-13 Nuclear Magnetic Resonance for Organic Chemists*, (Ed.: Levy and Nelson, Wiley Interscience, NY, **1972**.

[9] The mixture of bromohydrins was stirred at room temperature in anhydrous THF, in the presence of 1 equiv. of NaH, until disappearance of starting material. The crude product was neutralised with sat. sol. $NH_4Cl$ in ice, extracted with $Et_2O$, and analysed by $^1H$ NMR.

[10] T. Isarno, PhD Dissertation, Strasbourg, February **2000**. Deuterated (80% $^2H$) (*R*,*R*)-epoxide **10** was synthesized in ≈ 50% yield, from 2-fluorobenzaldehyde and a chiral deuterated benzyl sulfonium salt as described in ref. [3].

[11] The CH(OH) signals were assigned, in all cases, from the presence of a $^3J_{H-OH}$ coupling constant (resulting in an extra splitting or in broadening), which disappears upon addition of $D_2O$.

[12] The phenyl C9 (cf. Scheme 4 for numbering) was assigned by direct $^1H/^{13}C$ NMR experiments and comparison with spectra of known compounds: *Carbon-13 Nuclear Magnetic Resonance for Organic Chemists*, (Ed.: Levy and Nelson, Wiley Interscience, New York, **1972**.

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[15] However, the obtainment of the *syn* isomer implies a retention at the opening-centre and could come either from a 'front' mechanism, from a double $S_N2$ (due to Br exchange after opening) or from an $S_N1$.

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Received December 7, 2001
[O01579]