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Enantioselective introduction of fluoride into organic compounds First asymmetric ring opening of epoxides by hydrofluorinating reagents

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Abstract

The first enantioselective epoxide ring opening with hydrofluorinating agents mediated by chiral non-racemic Lewis acids is reported. The reaction of cyclohexene oxide (**1**) with KHF_2/18-crown-6 is *trans*-diastereoselective and proceeds with 55% ee to form (*R,R*)-(−)-2-fluorocyclohexanol (**2**) in the presence of Jacobsen's (*S,S*)-(+)-(salen)chromium chloride complex **A**. From racemic epoxides such as styrene oxide (**9**) or phenyl glycidether (**13**), mainly or exclusively the products with fluorine in primary position are formed with 90 or 62% ee, respectively. In all cases minor amounts of corresponding chlorohydrins are formed.

Keywords: Fluorohydrins; Epoxide ring opening; Enantioselectivity; (Salen)chromium complex; Hydrofluorination

1. Introduction

Fluorine substituted organic compounds gain a growing interest because of their unique properties due to the influence of the electronegative fluorine substituent on the acidity of neighboring positions and the dipole moment of the molecule [1]. In order to restrict the biological activity exclusively on desired properties and to exclude side effects or toxicity, it is necessary to selectively synthesize only one isomer of a chiral compound [2–4]. However, apart from a fluorodehydroxylation using an enantiopure DAST analog (maximum 16% ee) [5] there is at present only the electrophilic α-fluorination of carbonyl enolates available for asymmetric fluorination [6]. Alternatively chiral non-racemic fluorine compounds can be synthesized from optically active precursors [7] or by racemate cleavage using classical or lipase-catalyzed deracemization of functionalized fluoroorganics [8].

We present here the first results on asymmetric ring opening of *meso*- and racemic epoxides with hydrofluorinating reagents mediated by enantiopure Lewis acidic metal complexes. Enantioselective ring opening of *meso*- or racemic epoxides by nucleophilic reagents is one of the most powerful methods in the asymmetric synthesis of 1,2-disubstituted compounds [9]. This type of reaction has been successfully accomplished with many different nucleophiles such as carbon nucleophiles, thiols, phenols, carboxylic acids, aromatic amines, azide, cyanide and chloride, bromide or iodide mediated or catalyzed by different Lewis acids [9,10]. No results on the application of fluoride have been published as yet.

On the other hand, there are many papers on the diastereo- and regioselective ring opening of epoxides with hydrofluorinating reagents [11–13]. Reactions of terminal epoxides with HF in the presence of silicon fluorides [14] or with Olah's reagent (Py·9HF) to form fluorohydrins bearing a secondary fluorine proceed via an S_N1-like way [15–17], though there is no evidence for the formation of a free carbocation as the intermediate [18]. The regioselectivity, however, can be strongly influenced by substituent effects [19,20]. This method has also been used for the synthesis of optically active fluorohydrins from enantiopure epoxides, although with poor yield [21]. In contrast applying more nucleophilic reagents such as trialkylamine hydrogenfluorides [11,22], tetrabutylammonium dihydrogentrifluoride [23] or potassium hydrogendifluoride [24–26] in S_N2-like reactions, products with fluorine attached to the primary position are formed. For these reactions relatively high reaction temperature is necessary leading sometimes to rearrangements or oligomerization as competitive processes. However, during our investigations of ring opening of α-alkylstyrene oxides which are very sensitive to acidic

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conditions or high temperatures we observed that ring opening with triethylamine tris(hydrogenfluoride) ($Et_3N{\cdot}3HF$) can be catalyzed by $BF_3{\cdot}OEt_2$ [27].

2. Results and discussion

Acknowledging the literature results [26–28] first the catalytic ring opening of cyclohexene oxide (**1**) was examined. This epoxide has been reacted with $Et_3N{\cdot}3HF$ without solvent to give about 90% of *trans*-1,2-fluorocyclohexanol (**2**) after 3 h at 100°C. Some amount of higher molecular weight material was also formed. The reaction proceeded even at room temperature when 20 mol% of $BF_3{\cdot}OEt_2$ was added to a methylene chloride solution of the epoxide and $Et_3N{\cdot}3HF$. Under these conditions only traces of oligomeric material was detected.

On the other hand, using Olah's reagent the ring opening occurred very fast even at −78°C. After 15 min at this temperature the epoxide was completely consumed, but a substantial amount of high molecular weight material was produced. Besides the fluorohydrin **2** two fractions of other compounds have been separated by column chromatography from higher oligomers. The first of these was identified to be a 2:1 mixture of two diastereomeric *trans*-2-(2′-fluorocyclohexyloxy)cyclohexanols (**3**) (only one isomer is shown) while the second fraction was identified to be a mixture of two diastereomeric 'trimers' **4** (only one of the possible isomers is shown) which were formed according to the following mechanism (Scheme 1).

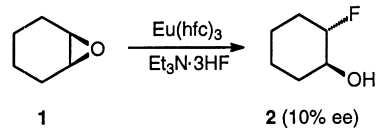
Under acidic conditions the fluorohydrin **2** formed in the first step attacks the protonated epoxide **1** to form **3** which can attack another molecule of **1** to form the diastereomers of **4**. This type of cascade we previously observed in reactions of aryl glycidethers with Olah's reagent [19].

Thus, to accomplish enantioselective ring opening of epoxides a chiral non-racemic catalyst must compete with the proton. Consequently a less acidic but more nucleophilic fluorinating reagent should be used. On the other hand, we found that $BF_3{\cdot}OEt_2$ catalyzed the ring opening of epoxides with $Et_3N{\cdot}3HF$ [27] while in other cases reactions of specific epoxides with $BF_3{\cdot}OEt_2$ led directly to fluorohydrins [12,29]. In order to open the epoxide asymmetrically an optically active analogue of BF_3 could be successful. Brown and Singaram succeeded in the application of chloro-, bromo-, or iodo diisopinocampheyl boranes for the stoichiometric S_N2-like asymmetric ring opening of cyclohexene oxide (**1**) to produce the corresponding halohydrins with good chemical yield and with 22, 84, or 91% ee, respectively, by direct halide transfer from the haloborane to the substrate [30]. Thus, we treated (−)-diisopinocampheylchloroborane in dichloromethane with antimony trifluoride and reacted the formed (−)-diisopinocampheyl-fluoroborane with cyclohexene oxide (**1**) at −78°C according to the protocol [30]. However, apart from some remaining **1**, cyclohexanone was the main product. The fluorohydrin **2** was not formed under these conditions. On the other hand, reactions of **1** with $Et_3N{\cdot}3HF$ in the presence of 20 or 120 mol% of (−)-diisopinocampheyl-chloroborane at room temperature gave mixtures of the racemic fluorohydrin **2** and the corresponding racemic chlorohydrin **8** as the main products.

From NMR spectroscopy it is known that chiral lanthanide shift reagents give diastereomeric complexes with *meso*-epoxides [31,32]. With **1** and 15 mol% $Eu(hfc)_3$ in $CDCl_3$ we found 0.105 ppm (32 Hz) shift difference of the methine protons in the ^1H NMR spectrum. Thus, we next treated **1** with $Et_3N{\cdot}3HF$ in the presence of 5–10 mol% of this chiral complex in CH_2Cl_2 at 0°C or room temperature. After 90 h besides cyclohexanone 12–25% of (*S,S*)-(+)-2-fluorocyclohexanol (**2**) was formed with 4–10% ee (Scheme 2).

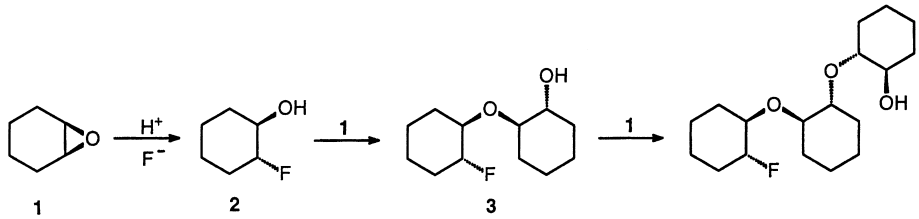
As mentioned earlier ring opening with Olah's reagent occurred very fast at −78°C. Thus, we treated **1** in dichloromethane with this reagent in the presence of $Eu(hfc)_3$ at this temperature. After 1 h the epoxide **1** was completely consumed and the fluorohydrin **2** was formed as the main product while compounds **3** and **4** have been identified as minor components of the mixture. All fluorohydrins were racemic suggesting that this enantiopure europium complex as well as $Eu(facam)_3$ and $Pr(hfc)_3$ did not participate in the reaction.

Zinc tartrate was used to enantioselectively catalyze the ring opening of **1** with butyl mercaptan or azide, to give the hydroxy thioether (85% ee) or hydroxy azide (42% ee),



1 2 (10% ee)

Scheme 2.



Scheme 1.

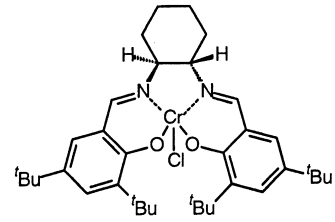
respectively [33,34]. The reaction of **1** with $Et_3N{\cdot}3HF$ in the presence of 10 or 50 mol% of this polymeric catalyst [35] without solvent at 55°C gave 66% (GC) of racemic fluorohydrin **2**. In contrast the ring opening of **1** with Olah's reagent in dichloromethane in the presence of 10 mol% of the catalyst at −40 or −20°C, respectively, after 15 min gave 63–78% (GC) of (*S,S*)-(+)-2-fluorocyclohexanol (**2**) with 4–10% ee. Bigger amounts of Zn tartrate did not increase the enantiomeric excess. Racemic product **2** was formed at −78°C or above −10°C.

In 1964 Cohen et al. described KHF_2 as a reagent which can be used for ring opening of sugar epoxides [36]. For these reactions, however, complexing solvents like ethylene glycol or its ethers and high temperatures are necessary while the yield was usually quite low. Later (for references reviewed until 1990 see [12]) this reagent has also been applied (particularly in such cases when acidic amine/HF complexes were not useful) for ring opening other sugar epoxides [37,38] steroid epoxides [39], a prostaglandin precursor [40,41] or glycidol [42]. In order to improve the solubility of KHF_2 for the ring opening of an epoxide derived from myo-inositol, 18-crown-6 was used in DMF as the solvent [43]. We used the same system for regioselective ring opening of terminal epoxides to form 1-fluoro-2-hydroxy compounds regioselectively [26].

By this method ring opening of enantiopure (2*R*,3*S*)-1,2-epoxy-3-methylpentane (**5**) with KHF_2/18-crown-6 in triethylene glycol (TEG) at 100°C after 12 h gave a low yield of a 25:75 mixture of the corresponding optically active fluorohydrins **6** and **7** besides products of ring opening of **5** with the solvent. No traces of rearranged or diastereoisomeric fluorinated products have been detected in the crude product mixture by ^{19}F NMR spectroscopy showing that this ring opening is an S_N2-process [44] (Scheme 3).

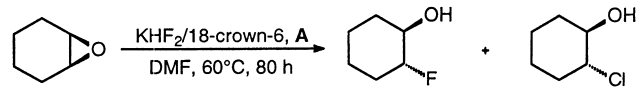
All the earlier mentioned results suggest that in order to achieve high enantioselectivity in the ring opening of epoxides a S_N2-like mechanism is desirable [10]. Consequently, Lewis acid activation and nucleophilic attack of the fluoride equivalent should be concerted or, alternatively, direct delivery of a nucleophile from a metal center may occur [45]. Jacobsen's (salen) complexes [46] such as the (*S,S*)-(+)-(salen)chromium chloride complex **A** have been shown to be useful catalysts for enantioselective epoxide ring opening with azide (Scheme 4) [45,47,48].

Thus, we reacted cyclohexene oxide (**1**) with KHF_2/18-crown-6 and 100 mol% of **A** in DMF at 60°C. After 80 h 92% of the epoxide **1** was consumed and two products



A

Scheme 4.



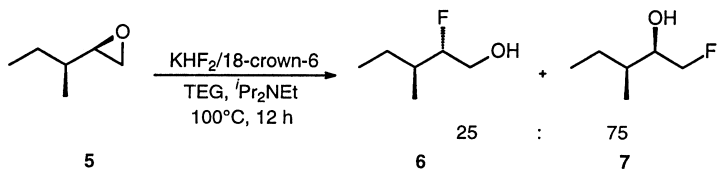
1 92% cv **2** (55% ee) 89 : 11 **8** (20% ee)

Scheme 5.

(89:11) were found in the crude product mixture, namely (*R,R*)-(−)-2-fluorocyclohexanol (**2**) (55% ee) and (*R,R*)-(−)-2-chlorocyclohexanol (**8**) (20% ee). The enantiomeric excess of the fluorohydrin **2** and of the chlorohydrin **8** was determined gas chromatographically using a chiral β-cyclodextrin phase. The absolute stereochemistry followed from comparison of the retention time in chiral gas chromatography and optical rotation with those of authentic samples (Scheme 5) [49,10].

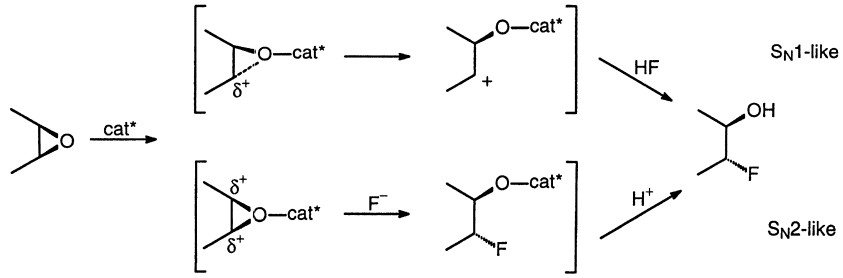
With a lower amount of the Lewis acid a higher temperature was necessary while the enantiomeric excess dropped dramatically. With 10 mol% of catalyst **A** after 80 h at 100°C 65% conversion of the epoxide **1** was detected. Products **2** and **8** were formed in 94:6 ratio but **2** showed only 11% ee.

Asymmetric ring opening of epoxides in the presence of Lewis acids in general can proceed via different mechanisms. According to an S_N1-like reaction, complexation of the enantiopure Lewis acid at the epoxide leads to a nonsymmetric charge distribution in the transition state providing an intermediate carbenium ion which is still complexed by the Lewis acid during nucleophilic attack of the fluoride equivalent. Due to the long distance to the electrophilic center, the influence of the chiral Lewis acid is low and a high enantiomeric excess cannot be expected. On the other hand, in cases when activation by the Lewis acid and nucleophilic attack are concerted (S_N2-like), there is generally a good chance for efficient asymmetric induction since the coordinated enantiopure metal complex can steer the fluoride to the preferred position (Scheme 6).

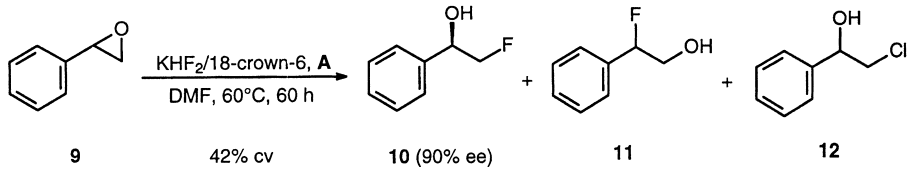


5 **6** **7**

Scheme 3.



Scheme 6.



Scheme 7.

The alternative formation of a (salen)chromium fluoride complex from **A** by chloride/fluoride exchange and subsequent direct delivery of the fluoride from the metal center to the epoxide, as it has been postulated in reactions with other nucleophiles [45], appears unlikely in the fluoride case since the liberated chloride is more nucleophilic than fluoride and hence the chlorohydrin **8** should be formed in bigger amount, particularly when complex **A** was employed in equimolar amount.

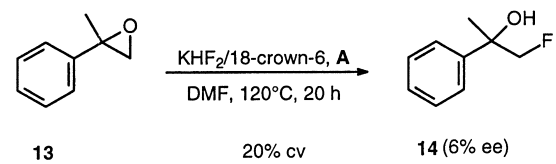
Several racemic epoxides were also opened using the mentioned system of reagents with racemate cleavage. Styrene oxide (**9**) was treated with KHF_2/18-crown-6 and 50 mol% of the (*S*,*S*)-(+)-(salen)CrCl complex **A** in DMF at 60°C. After 60 h 42% conversion of **9** was found and 86% of a 92:8 mixture of (*R*)-(−)-2-fluoro-1-phenylethanol (**10**) (90% ee) and 2-fluoro-2-phenylethanol (**11**) and 14% of 2-chloro-1-phenylethanol (**12**) was formed. The main product **10** was separated from its regioisomer **11** and from **12** by column chromatography and isolated in pure form in 70% yield (based on converted **1**). In this reaction the bulky Lewis acid also changed the regioselectivity of ring opening. Earlier we had found that refluxing **9** with KHF_2/18-crown-6 in DMF for 36 h gave a 75:25 mixture of racemic **10** and **11** (Scheme 7) [26].

With 10 mol% of catalyst **A** 55% of **9** was converted after 110 h at 90°C. Besides **12** (18%) a mixture of **10** and **11** was formed (82%). In this reaction the enantiomeric excess of the main product **10** dropped to 50%.

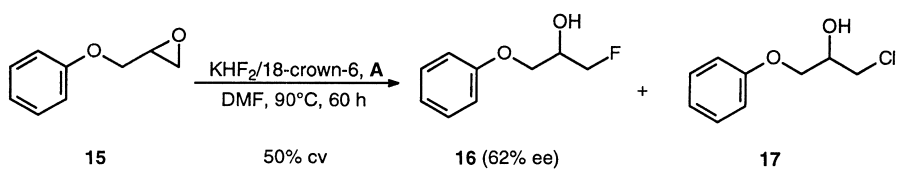
The reaction of 2-methylstyrene oxide (**13**) with KHF_2/18-crown-6 in the presence of 10 mol% of catalyst **A** in DMF was much less selective and gave 20% of 1-fluoro-2-phenylpropanol (**14**) after 20 h at 120°C with only 6% ee (Scheme 8).

Phenyl glycidether (**15**) was treated with KHF_2/18-crown-6 in the presence of 50 mol% of **A** in DMF. After 60 h at 90°C 50% of **15** has been converted and a 60:40 mixture of 1-fluoro-3-phenoxypropan-2-ol (**16**) and 1-chloro-3-phenoxypropan-2-ol (**17**) was formed. Regioisomeric fluorohydrin or oligomeric products as in the case of ring opening of **15** with Olah's reagent [19] were not found in the product mixture. Pure **16** (62% ee) was isolated by column chromatography in 57% yield (based on converted **15**). The absolute configuration of the product has not yet been determined (Scheme 9).

In contrast, in the presence of 10% of the catalyst **A** only 34% of **16** showing only 5% ee was formed after a reaction time of 100 h at 100°C.



Scheme 8.



Scheme 9.

3. Conclusion

The first enantioselective fluorination of *meso*- or racemic organic molecules by introduction of the fluoride ion has been accomplished. Asymmetric ring opening of epoxides occurred with KHF_2/18-crown-6 as the fluoride source and a molar amount of Jacobsen's Lewis acidic (*S*,*S*)-(+)-(salen)-chromium chloride complex **A** as enantiopure mediator. The reaction of cyclohexene oxide (**1**) was found to be *trans*-diastereoselective and proceeded with 55% ee to form (*R*,*R*)-(−)-2-fluorocyclohexanol (**2**). From racemic epoxides such as styrene oxide (**9**) or phenyl glycidether (**15**), mainly or exclusively the products with fluorine in the primary position were formed with 90 or 62% ee, respectively. A S_N2-like ring opening by activation of the epoxides with the enantiopure Lewis acidic complex **A** followed by nucleophilic attack of the fluoride equivalent seems to be operating. With catalytic amounts of **A**, Eu(hfc)$_3$ or zinc tartrate with much lower enantioselectivity was detected. In all reactions in the presence of the (salen)chromium chloride complex **A**, minor amounts of corresponding chlorohydrins were formed with less than 20% ee. This seems to be due to partial transfer of chloride directly from the complex to the epoxide (S_N2 reaction) with chirality transfer and by partial decomposition of the complex and attack of the chloride at the complexed epoxide (S_N2-like reaction).

4. Experimental

IR spectra were recorded with a Nicolet 5DXC-FT-IR spectrometer (KBr), ν [cm^{-1}]. ^{1}H NMR (300.13 MHz), ^{13}C NMR (75.5 MHz), and ^{19}F NMR (282.4 MHz) were recorded in $CDCl_3$ on a Bruker WM 300 apparatus with TMS for ^{1}H NMR, $CDCl_3$ for ^{13}C NMR, and $CFCl_3$ for ^{19}F NMR as internal standards. Mass spectra (70 eV) were obtained by GLC/MS using a Varian GC 3400 (quartz capillary column HP1 (0.33 μm) dimensions: 25 m, ∅ 0.2 mm). GC was performed on a Hewlett-Packard 5890 II gas chromatograph with HP1 (0.52 μm), dimensions: 25 m, ∅ 0.33 mm. The enantiomeric excess was determined by chiral GC (β-cyclodextrin column, Supelco, Beta-Dex® 120 (0.25 μm), dimensions: 30 m, ∅ 0.25 mm). (Salen)chromium chloride (**A**) has been prepared according to [50]. Olah's reagent and $Et_3N{\cdot}3HF$ was kindly supplied by Bayer AG, Leverkusen. All other starting materials and reagents were obtained from Acros (Janssen) or Fluka. The used solvents were purified by distillation.

4.1. Ring opening of cyclohexene oxide (*1*) with Olahs reagent

In a dried, argon flushed Teflon® vessel with a rubber septum and stirring bar Olah's reagent (0.3 ml, 1 mmol) in methylene chloride (5 ml) was cooled to −78°C. Using a syringe cyclohexene oxide (**1**) (98 mg, 1 mmol) dissolved in methylene chloride (1 ml) was injected drop by drop and stirred for 15 min. The reaction mixture was poured into ice-water (25 ml) and adjusted to pH 7–8 using aqueous ammonia. The organic layer was separated and the aqueous extracted with methylene chloride (3×10 ml). The combined organic layer was washed with water (2×10 ml) and dried over magnesium sulfate. The solvent was evaporated and the crude product mixture was analyzed by ^{19}F NMR spectroscopy. Five singlets representing compounds **2**, **3**, and **4** (cf. text) were found. Subsequently the mixture was separated by column chromatography (silica gel 70–260 mesh, cyclohexane/ethyl acetate 5:1) into three fractions.

4.1.1. Trans-2-fluorocyclohexanol (*2*)

Mp 22°C ([28]: Mp 22°C). IR (neat) ν: 3402 (br, ν-OH), 2936 and 2862 (ss, ν-CH and ν-CH_2), 1450 (s, δ-CH_2), 1376 (m), 1236 (m), 1040 (s), 924 (m), 855 (m). ^{1}H NMR δ: 1.21–1.48 (m, 4H, CH_2), 1.66–1.76 (m, 2H, CH_2), 1.97–2.10 (m, 2H, CH_2), 2.80 (br s, 1H, OH), 4.26 (dddd, 1H, $^2J_{H,F}$=51.6 Hz, $^3J_{H2a,H3a}$=10.7 Hz, $^3J_{H2a,H1a}$=8.4 Hz, $^3J_{H2a,H3e}$=4.8 Hz, CHF). ^{13}C NMR δ: 23.3 (d, $^3J_{C,F}$ =5.1 Hz, C-4), 23.5 (s, C-5), 30.2 (d, $^2J_{C,F}$=15.3 Hz, C-3), 31.7 (d, $^3J_{C,F}$=7.6 Hz, C-6), 73.1 (d, $^2J_{C,F}$=17.8 Hz, C-1), 96.6 (d, $^1J_{C,F}$=172.9 Hz, C-2). ^{19}F NMR δ: −182.3 (m, $^2J_{H,F}$=51.6 Hz). ^{1}H and ^{19}F NMR data agree with published ones [28]. GC/MS *m/z* (%): 118 (9) [M^+], 100 (4) [M^+-H_2O], 98 (4) [M^+−HF], 57 (100) [$C_3H_5O^+$].

4.1.2. Trans-2-(2′-fluorocyclohexyloxy)cyclohexanol (*3*)

One isomer was separated chromatographically with >90% purity. IR (neat) ν: 3418 (br, ν-OH), 2924 and 2852 (ss, ν-CH and ν-CH_2), 1450 (s, δ-CH_2), 1374 (m), 1238 (m), 1082 (s), 1040 (s) 924 (m), 855 (m). ^{1}H NMR δ: 1.02–1.48 (m, 8H, CH_2), 1.50–1.75 (m, 4H, CH_2), 1.78–2.12 (m, 4H, CH_2), 2.60–2.76 (br s 1H, OH), 3.03–3.19 (m, 1H, CHOH), 3.25–3.51 (m, 2H, CHOCH), 4.33 (dddd, 1H, $^2J_{H,F}$=50.0 Hz, $^3J_{H2a',H3a'}$=11.0 Hz, $^3J_{H2a',H1a'}$=8.3 Hz, $^3J_{H2a',H3e'}$=5.0 Hz). ^{13}C NMR δ: 22.2 (s), 22.8 (s), 23.0 (d, $^3J_{C,F}$=12.9 Hz, C-4′), 23.6 (s), 29.9 (d, $^2J_{C,F}$=17.8 Hz, C-3′), 30.9 (s, C-6), 31.1 (s, C-3), 31.2 (d, $^2J_{C,F}$=10.2 Hz, C-6′), 74.6 (s, C-1), 81.8 (d, $^2J_{C,F}$=17.8 Hz, C-1′), 85.2 (s, C-2), 95.6 (d, $^1J_{C,F}$=175.3 Hz, C-2′). ^{19}F NMR δ: −179.9 (m, $^2J_{H,F}$=50.0 Hz). GC/MS *m/z* (%): 216 (1) [M^+], 196 (5) [M^+−H], 170 (4), 157 (14), 118 (28) [$C_6H_{11}OF^+$], 100 (5) [$M^+-C_6H_{12}O_2$], 99 (38) [$C_6H_{11}O^+$], 98 (100) [$C_6H_{10}O^+$].

4.1.3. 2-(2′-Fluorocyclohexyloxy)-1-(2″-hydroxycyclohexyloxy)cyclohexane (*4*)

Mixture of two diastereomers (ratio 5:4). ^{1}H NMR δ: 1.02–1.30 (m), 1.49–1.70 (m), 1.77–2.12 (m), 2.93–3.18 (m), 3.20–3.54 (m), 4.30 (dddd, 1H, $^2J_{F,H}$=50.0 Hz, $^3J_{H2a',H3a'}$=11.0 Hz, $^3J_{H2a',H1a'}$=8.3 Hz, $^3J_{H2a',H3e'}$=5.0 Hz, CHF), 4.71 and 4.75 (br s, 1H, OH). ^{13}C NMR δ: several signals between 22.5 and 25 ppm and 29.5 and 33 ppm which were not assigned, 75.4 (s, C-1″), 75.7 (s, C-1″) 77.8 (d, $^2J_{C,F}$=15.2 Hz, C-2′), 78.7 (d, $^2J_{C,F}$=17.8 Hz, C-2′), 93.6 (d, $^1J_{C,F}$=183.5 Hz, C-1′), 95.2 (d, $^1J_{C,F}$=178.9 Hz,

C-1′). ^{19}F NMR δ: −179.4 (d,$^2J_{H,F}$=50.0 Hz), −179.7 ($^2J_{H,F}$=51.0 Hz). GC/MS *m/z* (%): 296 (1) [M^+-H_2O], 294 (0.5) [M^+−HF], 199 (19) [$M^+-C_6H_{12}OF$], 198 (17) [$M^+-C_6H_{11}OF$], 170 (4), 157 (78) [$C_6H_{11}O^+$], 98 (50) [$C_6H_{10}O^+$], 81 (100) [$C_6H_9^+$].

4.2. Ring opening of (2R,3S)-1,2-epoxy-3-methylpentane (**5**) with KHF_2/18-crown-6 [44]

Under an argon atmosphere a solution of 18-crown-6 (116 mg, 0.44 mmol), (*i*-Pr)$_2$EtN (284 mg, 2.2 mmol) and KHF_2 (1.56 g, 20 mmol) in dried triethylene glycol (TEG, 30 ml) was heated at 130°C until a homogeneous solution was formed. At 100°C the epoxide **5** prepared according to [51] (440 mg, 4.4 mmol) in TEG (2 ml) was added and stirred for 6 h. After cooling to room temperature the mixture was poured into water (50 ml) and extracted with methylene chloride (5×10 ml). The combined organic layer was washed with water (2×10 ml) and dried over magnesium sulfate. The solvent was evaporated and the residue analyzed by GC and ^{19}F NMR spectroscopy. With 45% of non-reacted **5**, 15% of 3-methyl-1-(triethyleneglycoxy)-pentan-2-ol, 6% of 3-methylpentan-1,2-diol and 24% of several unidentified volatile compounds 10% of the two fluorinated products **6** and **7** (75:25) were found. No other fluorinated compounds were detected by ^{19}F NMR spectroscopy. ^{19}F NMR of **6** δ: −192.4 (m, $^2J_{F,H}$=48.2 Hz, integration 25%). ^{19}F NMR of **7** δ: −229.4 (dt, $^2J_{F,H}$=47.7 Hz, $^3J_{F,H}$=19.1 Hz, integration 75%). GC/MS *m/z* (%): 120 (<1) [M^+], 100 (4) [M^+−HF], 87 (17) [M^+-CH_2F], 83 (100) [$C_6H_{11}^+$].

4.3. Ring opening of cyclohexene oxide (**1**) with $Et_3N{\cdot}3HF$ in the presence of Eu(hfc)$_3$

In a dried, argon flushed glass vessel with a rubber septum and stirring bar, $Et_3N{\cdot}3HF$ (0.3 ml, 1.5 mmol) and cyclohexene oxide (**1**) (98 mg, 1 mmol) in methylene chloride (1 ml) was treated with Eu(hfc)$_3$ (119 mg , 0.1 mmol) and stirred at 25°C for 90 h. Subsequently the mixture was poured into highly diluted aqueous ammonia (pH 7–8, 10 ml) and extracted with methylene chloride (3×5 ml). The combined organic layer was washed with water (5 ml) and dried over magnesium sulfate. After evaporation of the solvent the residue was filtered through a short column with 3 cm silica gel (cyclohexane:ethyl acetate 5:1) and analyzed by chiral GC (column temperature 92°C). In the best case 10% ee was detected.

4.4. Ring opening of cyclohexene oxide (**1**) with Olahs reagent in the presence of zinc tartrate

In a dried, argon flushed Teflon® vessel with a rubber septum and stirring bar Olah's reagent (0.3 ml, 1 mmol) and zinc tartrate prepared according to [34] (21 mg, 0.1 mmol) were mixed with methylene chloride (5 ml) at−78°C. After warming to−40 or −20°C, respectively, cyclohexene oxide (**1**) (98 mg, 1 mmol) dissolved in methylene chloride (1 ml) was injected drop by drop using a syringe and stirred for 15 min. Then the reaction mixture was worked up as described before (Section 4.1). The solvent was partially evaporated and the crude product mixture was filtered through a short column with 2 cm of silica gel. The solvent was removed and the residue analyzed by gas chromatography to show 78% of **2** and 22% of isomers of compounds **3** and **4**. After separation by column chromatography (silica gel 70–260 mesh, cyclohexane:ethyl acetate 5:1) the enantiomeric excess of (*S,S*)-(+)-**2** was determined as mentioned earlier to range between 7 and 10% ee in several experiments.

4.5. Ring opening of epoxides with KHF_2/18-crown-6 in the presence of (salen)chromium complex **A**: general procedure

Under an argon atmosphere a mixture of the epoxide (1 mmol) and complex **A** (632 mg, 1 mmol, 316 mg, 0.5 mmol, or 63 mg, 0.1 mmol, respectively) in dry DMF (5 ml) was stirred for 15 min at room temperature, treated with 18-crown-6 (422 mg, 1.6 mmol) and KHF_2 (310 mg, 4 mmol) and heated with stirring at the temperature and for the time given ahead. After cooling to room temperature the mixture was poured into water (25 ml) and extracted with methylene chloride (5×10 ml). The combined organic layer was washed with water (2×10 ml) and dried over magnesium sulfate. The solvent was evaporated and the crude product was filtered (column with 3 cm of silica gel, cyclohexane:ethyl acetate 5:1) in order to remove traces of **A** and oligomeric material. After removing the solvent the residue was analyzed by GC (HP 1, 40–280°C, heating rate 10°C/min) and chiral GC (Beta-Dex® 120, temperature given ahead). Pure fluorohydrins were separated by column chromatography (silica gel 70–260 mesh, cyclohexane:ethyl acetate 5:1).

4.5.1. (R,R)-(−)-2-Fluorocyclohexanol (**2**)

According to the general procedure cyclohexene oxide (**1**) (30 mg, 0.3 mmol) was reacted in the presence of **A** (190 mg, 0.3 mmol) at 60°C for 80 h to form, after 92% conversion of **1**, a 89:11 mixture (GC) of (*R,R*)-(−)-2-fluorocyclohexanol (**2**) and (*R,R*)-(−)-2-chloro-cyclohexanol (**8**). Compound **2** was separated by column chromatography. Yield: 18.5 mg (64% based on consumed epoxide **1**). Spectroscopic data of **2** agree with those given earlier. Compound **8** was not isolated. The structure was determined by comparison with an authentic sample [10]. The enantiomeric excess was determined by chiral GC (column temperature 92°C) to be 55% for **2** and 20% for **8**.

4.5.2. (R)-(−)-2-Fluoro-1-phenylethanol (**10**)

According to the general procedure, styrene oxide (**9**) (72 mg, 0.6 mmol) was reacted in the presence of **A**

(190 mg, 0.3 mmol) at 60°C for 60 h to form, after 42% conversion of **9**, a 79:7:14 mixture (GC) of (*R*)-(−)-2-fluoro-1-phenylethanol (**10**), 2-fluoro-2-phenylethanol (**11**) and 2-chloro-2-phenylethanol (**12**). Compound **10** was separated by column chromatography. Yield: 23.4 mg (70% based on consumed epoxide **9**). $[\alpha]_D^{22}$ −13.3° (*c*=3, CH_2Cl_2) [52]: $[\alpha]_D$ −51.7° (*c*=1.6 $CHCl_3$). ^{1}H NMR δ: 2.03 (br s, 1H, OH), 4.40 (ddd, $^3J_{H,H}$=8.1 Hz, $^2J_{HH}$=9.5 Hz, $^2J_{H,F}$=48.4 Hz, 1H, H-2), 4.50 (ddd, $^3J_{H,H}$=3.6 Hz, $^2J_{H,H}$= 9.5 Hz, $^2J_{HF}$=46.6 Hz, 1H, H-1), 5.01 (ddd, $^3J_{H,H}$=3.3 Hz, $^3J_{HH}$=8.1 Hz, $^3J_{H,H}$=11.5 Hz, 1H, H-1), 7.36 (m, 5H, H_{arom}). These data agree with published ones [52]. ^{13}C NMR δ: 73.0 (d, $^2J_{C,F}$=20.4, C-1), 87.2 (t, $^1J_{C,F}$=175.1 Hz, 175.1 Hz, C-2), 126.3 (d, C-4, C-8), 128.4 (d, C-6), 128.6 (d, C-5, C-7), 138.2 (s, C-3). ^{19}F NMR δ: −220.5 (dt, $^3J_{H,F}$=45.8 Hz). GC/MS *m/z* (%): 140 (8) [M^+], 122 (2) [M^+-H_2O], 121 (2) [M^+−F], 107 (100) [M^+-CH_2F], 79 (59), 77 (43) [$C_6H_5^+$], 61 (4) [$C_2H_2OF^+$], 51 (14) [$C_4H_3^+$], 39 (6) [$C_3H_3^+$]. Compounds **11** and **12** were not isolated. Their structure was determined by comparison (GC) with authentic samples [53,10]. Moreover, typical signals of **11** were found in the ^{1}H and ^{19}F NMR spectra of samples enriched in this compound. The enantiomeric excess of **10** was determined after acetylation (Ac_2O/pyridine) to the corresponding acetate by chiral GC to be 90% (column temperature 120°C).

*4.5.3. 1-Fluoro-2-phenylpropan-2-ol (**14**)*

According to the general procedure, methylstyrene oxide (**13**) (80 mg, 0.6 mmol) was reacted in the presence of **A** (190 mg, 0.3 mmol) at 120°C for 20 h to form, after 20% conversion of **13**, 1-fluoro-2-phenylpropan-2-ol (**14**) which was separated by column chromatography. Yield: 9 mg (48% based on consumed **13**). ^{1}H NMR δ: 1.49 (s, 3H, H-3), 4.40 (dd, $^2J_{H,H}$=9.3 Hz, $^2J_{H,F}$=47.7 Hz, 1H, H-2), 4.46 (dd, $^2J_{H,H}$=8.8 Hz, $^2J_{H,F}$=47.7 Hz, 1H, H-2), 7.25–7.39 (m, 3H, H_{arom}), 7.44–7.49 (m, 2H, H_{arom}). ^{19}F NMR δ: −223.7 (dd, $^2J_{H,F}$=45.8 Hz). ^{1}H and ^{19}F NMR data agree with published ones [54]. GC/MS *m/z* (%): 154 (4) [M^+], 139 (5) [M^+-CH_3], 122 (9) [139−OH], 121 (100) [M^+-CH_2F], 105 (5), 91 (8) [$C_7H_7^+$], 77 (11) [$C_6H_5^+$], 65 (2) [$C_5H_5^+$], 61 (10) [$C_2H_2OF^+$], 43 (59) [$C_2H_3O^+$]. The enantiomeric excess was determined by chiral GC to be 6% (column temperature 120°C).

*4.5.4. 1-Fluoro-3-phenoxypropan-2-ol (**16**)*

According to the general procedure, phenyl glycidether (**15**) (90 mg, 0.6 mmol) was reacted in the presence of **A** (190 mg, 0.3 mmol) at 90°C for 60 h to form, after 50% conversion of **15**, a 60:40 mixture of 1-fluoro-3-phenoxypropan-2-ol (**16**) and 1-chloro-3-phenoxypropan-2-ol (**17**). Compound **16** was separated by column chromatography. Yield: 17.4 mg (57% based on consumed epoxide **15**). ^{1}H NMR δ: 3.0 (bs, 1H, OH), 4.04–4.10 (m, 2H, H-3), 4.16–4.31 (dm, $^2J_{HF}$=18.0 Hz, 1H, H-2), 4.55 (ddd, $^2J_{H,H}$= 9.5 Hz, $^3J_{H,H}$=13.4 Hz, $^2J_{H,F}$=47.2 Hz, 1H, H-1), 4.57 (ddd, $^2J_{H,H}$=9.5 Hz, $^3J_{H,H}$=13.4 Hz, $^2J_{H,F}$=47.2 Hz, 1H, H-1), 6.93 (m, 3H, H_{arom}), 7.30 (m, 2H, H_{arom}). ^{19}F NMR δ: −223.4 (dt, $^2J_{HF}$=45.7 Hz, $^3J_{HF}$=19.1 Hz). GC/MS *m/z* (%): 171 (8) [M^++1], 170 (75) [M^+], 137 (6) [M^+-CH_2F], 126 (15), 119 (8), 108 (6), 107 (38) [$M^+-C_2H_4FO$], 95 (30), 94 (100) [$C_6H_6O^+$], 79 (18), 77 (72) [$C_6H_5^+$], 66 (16) [$C_6H_6O^+-CO$], 65 (16) [$C_5H_5^+$], 51 (15) [$C_4H_3^+$], 43 (3) [$C_2H_3O^+$], 39 (17) [$C_3H_3^+$]. The ^{1}H and ^{19}F NMR data agree with published ones [55]. The enantiomeric excess was determined by chiral GC to be 62% (column temperature 120°C). Compound **17** was not isolated. The structure was determined by comparison (GC, HP 1) with an authentic sample [56].

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