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Comparative study of the ring opening of 1-CF_3-epoxy ethers mediated by Brönsted acids and hexafluoro-2-propanol

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Dedicated to Prof. Richard D. Chambers on the occasion of his 70th birthday.

Abstract

In order to evaluate more deeply the nature of the activation of oxirane ring opening reactions by HFIP, ring opening of both CF_3-epoxy ethers **1a** (R = Ph) and **1b** (R = CH_2CH_2Ph) with HFIP alone, and with hard (MeOH) or soft (PhSH) nucleophiles in HFIP, were investigated and compared to reactions performed with Brönsted acids. Nucleophilic ring opening reactions in HFIP were facilitated with PhSH and only α-substituted trifluoromethyl ketone **5** was isolated (nucleophilic ring opening), while with MeOH, both processes, nucleophile and electrophile-assisted ring opening were in competition. In the Brönsted acid-catalysed ring opening of 1-CF_3-epoxy ethers **1** in HFIP, only the acid-catalysed ring opening process occurred with an inversed regioselectivity.

Keywords: Fluorinated alcohols; Hexafluoro-2-propanol; Trifluoromethyl-epoxy ethers; Trifluoromethyl ketones; Oxirane ring-opening; Hydrogen bonds; Brönsted acid

1. Introduction

α-CF_3-epoxy ethers are valuable building blocks for the synthesis of various α-substituted trifluoromethyl ketones (TFMKs), which can be powerful inhibitors of a variety of hydrolytic enzymes [1]. α-Amino and α-thio TFMKs can be synthesised by nucleophilic ring opening reactions of 1-CF_3-epoxy ethers with amines [2] or metal amides [3], and with thiolates, respectively [4]. In all cases nucleophiles are introduced at the β-carbon atom of the oxirane ring (nucleophilic ring opening). Conversely, the regioselectivity of oxirane ring opening of 1-CF_3-epoxy ethers with Lewis acids (electrophile assisted ring opening) has been found to depend strongly on the structure of the oxirane ring and on the Lewis acid [5]. For instance, in the reaction of 2-phenyl-α-CF_3-epoxy ether (PhEE, **1a**) with $EtAlCl_2$, cleavage occurs through the C_β–O bond because of the stabilization of the positive charge on the benzylic position, while with the 2-phenylethyl derivative (REE, **1b**) cleavage occurs through the C_α–O bond since the alkoxy carbenium ion is the most stable despite of the electron-withdrawing effect of CF_3 group (Scheme 1) [5].

Fluoro alcohols such as hexafluoroisopropanol (HFIP) and trifluoroethanol (TFE) are solvents with peculiar properties [6] and consequently they are often used in studies of peptide and protein structure [7], solvolysis [8] and for their effect on reaction transformations [9], notably the activation of hydrogen peroxide for oxidation, epoxidation and the Baeyer-Villiger rearrangement [10].

Recently we found that HFIP can activate oxirane ring opening [11], and this has been applied to α-CF_3-epoxy ethers which could easily react with aromatic amines and even with carboxylic acids without any base catalysis [12,13]. Interestingly, in these reactions, despite the

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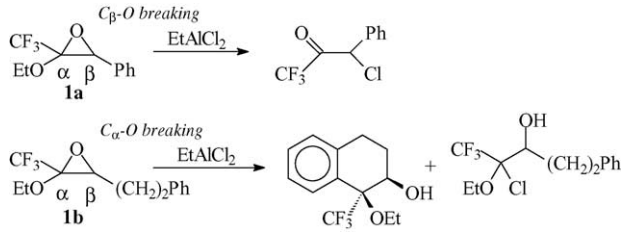
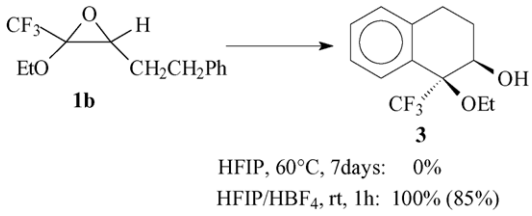


Scheme 1.



Scheme 3.

electrophile-type assistance by HFIP, regioselectivity was not dependent on the β-substituent and was the same as the nucleophilic processes (C_β–O bond cleavage).

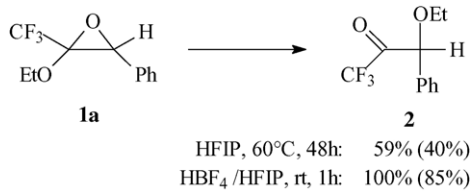
The purpose of this study was to evaluate more deeply the nature of the activation of oxirane ring opening reactions by HFIP, and our studies are reported in this paper. Therefore, we took both CF_3-epoxy ethers (**1a**, **1b**), and have investigated their reactions with hard (MeOH) and soft (PhSH) nucleophiles and compared the activating effect of HFIP to that of Brönsted acids.

2. Results

2.1. Acid catalysed rearrangement of epoxy ethers

We first investigated the activating effect of HFIP ($pK_a = 9.3$) on the possible acidic rearrangement of the epoxy ethers **1** in the absence of any other external nucleophile. After 2 days under reflux in HFIP, 59% of PhEE **1a** was consumed and α-ethoxy trifluoromethyl ketone **2** was isolated in 40% yield (Scheme 2). Conversely, REE **1b** was stable in HFIP and completely recovered even after 7 days of reflux. The acid-catalysed oxirane ring opening was then investigated with a Brönsted acid ($H^+BF_4^-$) in various solvents. In a non-polar solvent (CH_2Cl_2), oxirane **1** led to the formation of a complex reaction mixture and in isopropanol no reaction took place. In HFIP the quantitative conversion of **1a** into compound **2** occurred after 1 h at room temperature (Scheme 2). It is worth noting that only one drop of 50% ethereal solution of HBF_4 in 5 mL of HFIP was required for this complete acidic rearrangement. No incorporation of HFIP was observed, although HFIP has been reported to act as a nucleophile with styrene oxide [10g].

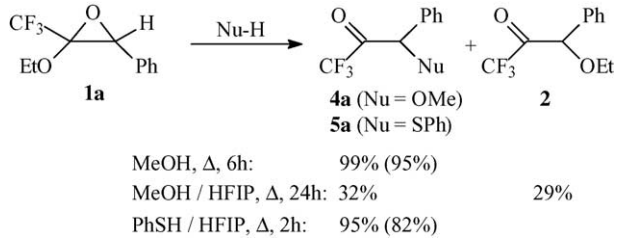
Under the same conditions REE **1b** was also completely converted to a sole product, which has been proved by NMR to be the tetralol **3** already obtained by the ring opening of **1b** in the presence of $TiCl_4$ (Scheme 3) [5].



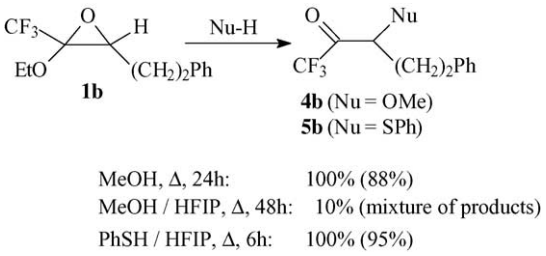
Scheme 2.

2.2. Nucleophilic oxirane ring opening in HFIP

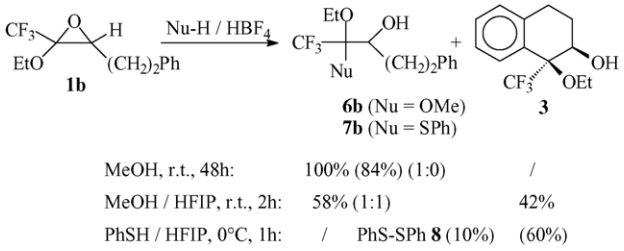
Next we evaluated the effect of HFIP on the ring opening of CF_3-epoxy ethers in the presence of external nucleophiles. It has been already observed that HFIP activates oxirane ring opening reactions with aromatic amines while more nucleophilic aliphatic amines were deactivated [11]. As HFIP is a strong hydrogen bond donor, this interaction could be the reason for deactivation of nucleophiles. Therefore we investigated the ring opening of **1** with methanol as a hard nucleophile and with PhSH as a soft one and a less strong hydrogen bond acceptor [14,15]. In a control experiment, the reaction of phenyl substituted CF_3-epoxy ether **1a** was conducted with MeOH as a solvent. Reflux was required for the reaction to occur, and after 6 h α-methoxy TFMK **4a** was quantitatively formed, resulting from the expected nucleophilic process of oxirane ring opening (Scheme 4). When the reaction was performed with 2 equiv. of MeOH in HFIP, 61% conversion occurred after 24 h at reflux and an approximately 1:1 mixture of **4a** and the rearranged product **2** was obtained. In HFIP, the electrophilic process of rearrangement competed with the nucleophilic ring opening process. Conversely, PhEE **1a** reacted with PhSH in HFIP only through nucleophilic ring opening pathway and after 2 h at reflux gave the ketone **5a** in 95% yield with no traces of formation of **2**. In a control experiment conducted in THF, thiophenol did not react with **1a** at reflux temperature. This process constitutes an excellent alternative to ring opening with thiolates [4b], useful for substrates and products sensitive to a basic medium. This would be of particular interest for reactions performed with the non-racemic epoxy ether **1** where products easily undergo racemisation under basic conditions [16].



Scheme 4.



Scheme 5.



Scheme 6.

The same investigation was performed with the β-alkyl substituted CF_3-epoxy ether **1b** (REE). Reaction of **1b** in MeOH was slower than for **1a** and 24 h at reflux were needed for a complete conversion to α-methoxy TFMK **4b** (Scheme 5). Reaction of REE with 2 equiv. of MeOH in HFIP was very slow with 10% conversion into a mixture of compounds after 48 h of reflux. Similarly to PhEE **1a**, when REE **1b** reacted with PhSH in HFIP the nucleophilic ring opening pathway was complete in 6 h of reflux, and provided quantitatively **5b** (95%) (Scheme 5). Here again, as expected, no product resulting from the rearrangement of **1b** into **3** was detected. Neither did cycloalkylation by the thiophenyl substituent of **5b** occur, while the corresponding β-phenylamino-trifluoromethyl ketones readily cyclized in HFIP [12].

2.3. Acid-catalysed nucleophilic oxirane ring opening in HFIP

Finally, we compared the activating effect of HFIP alone, and that of a Brönsted acid (HBF_4) in ring opening reactions. For this we chose **1b** as model substrate since only this epoxy ether can exhibit different regioselectivity depending on whether an electrophilic (Lewis acid) or nucleophilic process occurs.

HBF_4-catalyzed ring opening of **1b** was first investigated in MeOH (one drop of 50% ethereal solution of HBF_4 in 5 mL of MeOH). The complete conversion required 48 h at room temperature instead of 24 h of reflux as in MeOH alone. The sole product formed was **6b**, resulting from a C_α–O cleavage. It was isolated as a single diastereoisomer, whose configuration could not be determined (Scheme 6). When MeOH was used as the nucleophile (2 equiv.) in a HBF_4-catalyzed reaction in HFIP, the reaction was much faster (2 h at room temperature) and provided a mixture of **3** (42%) and **6b** (58%) but as a mixture of both diastereoisomers. When the same experiment was performed with PhSH as the nucleophile in HFIP in the presence of HBF_4, the reaction was complete after 1 h at 0 °C and tetralol **3** and disulphide **8** were isolated in 60% and 10% yield, respectively. Disulphide **8** was not formed from PhSH under the reaction conditions. Therefore the disulphide could be the result of a previous addition of PhSH at the C_α-atom of the epoxy ether, leading to **7b**, which could undergo a cycloalkylation leading to the tetralol **3**, since PhS^- is a good leaving group, especially under acid conditions.

The most striking result of these experiments is the complete inversion of regioselectivity when the oxirane ring opening, performed in HFIP, is catalyzed with one drop of Brönsted acid.

3. Discussion and conclusion

Hexafluoroisopropanol, when used as solvent, is able to promote oxirane ring opening of CF_3-substituted epoxy ethers, but in a different way to Lewis and Brönsted acids used as catalysts. Acidic rearrangement is not an easy process in HFIP and it occurs only with the more reactive phenyl-substituted epoxy ether **1a**, after a long reaction time at reflux. The consequence is that this process does not often compete with nucleophilic ring opening.

Oxirane ring opening with nucleophiles in HFIP showed two distinct patterns. With a hard nucleophile and good hydrogen bond acceptor (MeOH), the presence of HFIP disfavoured the ring opening by the nucleophile, compared to reactions performed in MeOH alone (Schemes 4 and 5), and compared to reactions performed in MeOH in the presence of the Brönsted acid, HBF_4 (Scheme 6). MeOH is deactivated by the strong hydrogen bond donation ability of HFIP and can react only with the more reactive epoxy ether **1a**, the acidic rearrangement into ketone **2** being a competitive process. With a soft nucleophile and weaker hydrogen bond acceptor (PhSH), HFIP activated the ring opening compared to reaction performed in THF. Remarkably, despite of this activation, regioselectivity is the same as in purely nucleophilic processes, with the exclusive formation of α-substituted trifluoromethyl ketones **5a** and **5b** resulting from the addition of the nucleophile to C–β. Conversely, oxirane ring opening of the epoxy ether **1b** in the presence of Lewis acid (Scheme 1), or in the presence of HBF_4 (Scheme 6) resulted only in a C–α bond cleavage by either external nucleophile or internal one (phenyl group). In summary, hard nucleophiles and good hydrogen bond acceptors (alcohols, aliphatic amines) are not suitable for oxirane ring opening in HFIP, while softer nucleophiles and weaker hydrogen bond acceptors (thiols, aromatic amines, carboxylic acids) are not deactivated, and nucleophilic ring opening of oxiranes are facilitated by HFIP keeping the regioselectivity at the less hindered C-atom. With thiols, this constitutes clean access to α-thio trifluoromethyl ketones

with the following advantages: no effluent, and neutral conditions compatible with substrates sensitive to basic conditions, and in particular racemisation of chiral compounds.

Besides this insight into the role of HFIP in the ring opening reactions of oxiranes, interesting results were obtained concerning the activation of Brönsted acid by HFIP. Its high ionising power and strong ability to solvate anionic species allows generation of a proton from HBF_4 in only a weakly solvated state [17]. The consequence is that one drop of 50% ethereal solution of HBF_4 in 5 mL of HFIP is sufficient to markedly increase the rates of epoxy ether ring opening reactions. Under these conditions, without a nucleophile, the acidic rearrangement of **1a** and **1b** occurred very smoothly in HFIP in 1h at room temperature and provided quantitatively the rearranged ketone **2** and the tetralol **3**, respectively (Schemes 2 and 3). HFIP is also able to strongly activate Brönsted acid catalysed ring opening with nucleophiles. Reaction of MeOH with REE **1b** in HFIP/H^+ was complete in 2 h, while the same reaction performed in MeOH/H^+ required 48 h to proceed quantitatively (Scheme 6). Furthermore, the addition of only one drop of HBF_4 in HFIP is sufficient to markedly modify the process of ring opening with a nucleophile: while in HFIP alone, the epoxy ether **1b** did not react with MeOH, it could react in the presence of H^+ through an electrophile-assisted pathway with a C_α–O cleavage leading to a 1:1 mixture of diastereoisomers, clearly indicating the formation of a carbenium ion (Scheme 6).

4. Experimental

^1H, ^{13}C and ^{19}F NMR spectra were recorded on a 200 MHz multinuclear spectrometer in $CDCl_3$ solutions with TMS (for ^1H and ^{13}C) and $CFCl_3$ (for ^{19}F) as external standards. GC analysis was performed on a capillary column (SE-30, 10 M). Silicagel 60A was used for column chromatography and silica 60 F254 plates for preparative TLC.

1-CF_3-epoxy ethers **1a** and **1b** were synthesised by known procedures [18]. Fifty percent solutions of HBF_4 in Et_2O, MeOH, PhSH and HFIP were obtained from commercial sources and used as received.

4.1. Acid catalyzed ring opening of *1a* in HFIP

To a solution of 1 mmol of **1a** (232 mg) in 5 mL of HFIP one drop of a 50% solution of HBF_4 in Et_2O was added and stirred at room temperature for 1 h. The solvent was poured into 20 mL of CH_2Cl_2 and the solution washed twice with a saturated solution of $NaHCO_3$ and dried over Na_2SO_4. After evaporation of the solvent, **2** was obtained as sole reaction product, isolated by column chromatography (SiO_2, CH_2Cl_2:Et_2O = 9:1) as a mixture of ketone and small amount of its hydrate form.

3-Ethoxy-1,1,1-trifluoro-3-phenyl-2-propanone (***2***) [19]: 197 mg (85%); *ketone form*: ^{19}F NMR δ −75.3 (s); ^1H NMR δ 1.2 (t, J = 7 Hz, 3H), 3.5 (q, J = 7 Hz, 2H), 5.2 (s, 1H), 7.4 (m, 5H); *hydrate form*: ^{19}F NMR δ −82.7 (s); ^1H NMR δ 1.2 (t, J = 7 Hz, 3 H), 3.5 (q, J = 7 Hz, 2H), 4.6 (s, 1H), 7.4 (m, 5H).

4.2. Acid catalysed ring opening of *1b* in HFIP

To a solution of 1 mmol of **1b** (260 mg) in 5 mL of HFIP one drop of a 50% solution of HBF_4 in Et_2O was added and stirred at room temperature for 1 h. The solvent was poured into 20 mL of CH_2Cl_2 and the solution washed twice with a saturated solution of $NaHCO_3$ and dried over Na_2SO_4. After evaporating the solvent, **3** was obtained as sole reaction product, and was purified by column chromatography (SiO_2, CH_2Cl_2:Et_2O = 9:1).

1-Ethoxy-1-(trifluoromethyl)-2-cis-tetralol (***3***) [5]: 221 mg (85%); oil, ^{19}F NMR δ −74.6 (s); ^1H NMR δ 1.25 (t, J = 7 Hz, 3H), 1.9 (m, 1H), 2.2 (m, 1H), 2.7 (m, 1H), 2.75 (br, s, OH), 2.95 (m, 1H), 3.5 (m, 1H), 3.7 (m, 1H), 4.4 (dd, J = 9, 3 Hz, 1H), 7.2 (m, 3H), 7.7 (m, 1H).

4.3. Nucleophilic ring opening of *1a* in MeOH

A solution of 1 mmol of **1a** (232 mg) in MeOH (5 mL) was stirred at reflux temperature for 6 h. The solvent was evaporated and α-methoxy TFMK **4a** obtained as the sole reaction product, isolated by column chromatography (SiO_2, CH_2Cl_2:Et_2O = 9:1) as a mixture of ketone and a small amount of its hydrate form.

1,1,1-Trifluoro-3-methoxy-3-phenyl-2-propanone (***4a***) [19]: 207 mg (95%); *ketone form*: ^{19}F NMR δ −75.6 (s); ^1H NMR δ 3.3 (s, 3H), 5.1 (s, 1H), 7.3 (m, 5H); *hydrate form*: ^{19}F NMR δ −82.7 (s); ^1H NMR δ 3.2 (s, 3H), 4.4 (s, 1H), 7.3 (m, 5H).

4.4. Nucleophilic ring opening of *1b* in MeOH

A solution of 1 mmol of **1b** (260 mg) in MeOH (5 mL) was stirred at reflux temperature for 24 h. The solvent was evaporated and α-methoxy TFMK **4b** obtained as the sole reaction product, purified by column chromatography (SiO_2, CH_2Cl_2:Et_2O = 9:1) and isolated as a mixture of ketone and hydrate forms. The pure hydrate form was obtained by crystallization (hexane) in a 15% yield.

1,1,1-Trifluoro-3-methoxy-5-phenyl-2-pentanone (***4b***): 215 mg (88%); *ketone form:* ^{19}F NMR δ −76.7 (s); ^1H NMR δ 2.3 (m, 2H), 3.0 (m, 2H), 3.8 (s, 3H), 4.3 (dd, J = 8, 5 Hz, 1 H), 7.4 (m, 5 H); ^{13}C NMR δ 30.9, 32.7, 60.4, 81.7, 122.9 (q, J = 289 Hz), 126.3, 128.3, 128.4, 128.5, 140.1 and 141.3, 181.8 (q, J = 33 Hz, C=O); IR (neat) 1766, 1147 cm^{-1}; *hydrate form:* ^{19}F NMR δ −83.2 (s); ^1H NMR δ 2.3 (m, 2H), 3.0 (m, 2 H), 3.65 (s, 3 H), 3.75 (dd, J = 9, 3.5 Hz, 1H), 7.4 (m, 5 H); ^{13}C NMR δ 30.9, 32.7, 58.5, 80.2, 94.0 (q, 31 Hz, CCF_3-H), 115.4 (q, J = 294 Hz), 126.3,

128.3, 128.4, 128.5, 140.1 and 141.3, IR (neat) 3450, 1147 cm^{-1}; Anal. Calcd for $C_{12}H_{13}F_3O_2 \times H_2O$: C, 54.6; H, 5.7. Found: C, 54.5; H, 5.8.

4.5. Acid catalyzed ring opening of **1b** in MeOH

To a solution of 1 mmol of **1b** (260 mg) in 5 mL of MeOH one drop of a 50% solution of HBF_4 in Et_2O was added and stirred at room temperature for 48 h. The solvent was poured into 20 mL of CH_2Cl_2 and the solution washed twice with a saturated solution of $NaHCO_3$ and dried over Na_2SO_4. After evaporating the solvent, **6b** was obtained as the sole reaction product, and purified by column chromatography (SiO_2, CH_2Cl_2:Et_2O = 9:1).

2-Ethoxy-1,1,1-trifluoro-2-methoxy-5-phenyl-3-pentanol (***6b***): 245 mg (84%); oil; ^{19}F NMR δ −73.5 (s); ^1H NMR δ 1.3 (t, J = 7 Hz, 3H), 2.0 (m, 2H), 2.75 (m, 1H), 3.05 (m, 1H), 3.5 (s, 3H), 3.65 (q, J = 7 Hz, 2H), 3.9 (d, J = 10 Hz, 1H), 7.3 (m, 5H); ^{13}C NMR δ 15.0, 32.4, 32.6, 50.7, 58.8, 71.7, 98.7 (q, J = 28 Hz), 123.0 (q, J = 293 Hz), 125.9, 128.3, 128.5, 141.6; IR (neat) 3575, 1175, 1144, 1069 cm^{-1}. Anal. Calcd for $C_{14}H_{19}F_3O_3$: C, 57.5; H, 6.6. Found: C, 57.4; H, 6.8.

4.6. Acid catalyzed ring opening of **1b** in MeOH/HFIP

To a solution of 1 mmol of **1b** (260 mg) and 20 mmol of MeOH (640 mg) in 5 mL of HFIP one drop of a 50% solution of HBF_4 in Et_2O was added and stirred at room temperature for 2 h. The solvent was poured into 20 mL of CH_2Cl_2 and the solution washed twice with a saturated solution of $NaHCO_3$ and dried over Na_2SO_4. After evaporating the solvent, products **3** and **6b** (1:1 mixture of diastereoisomers) were separated by column chromatography (SiO_2, CH_2Cl_2:Et_2O = 20:1).

1-Ethoxy-1-(trifluoromethyl)-2-cis-tetralol (***3***) [5]: 114 mg (39%); 2-ethoxy-1,1,1-trifluoro-2-methoxy-5-phenyl-3-pentanol (**6b**): 120 mg (45%); oil; ^{19}F NMR δ −73.5 (s) and −73.6 (s); ^1H NMR δ 1.3 (t, J = 7 Hz, 3H), 2.0 (m, 2H), 2.75 (m, 1H), 3.05 (m, 1H), 3.4 and 3.5 (s, 3H), 3.65 (m, 2H), 3.85 (m, 1H), 7.3 (m, 5H); ^{13}C NMR δ 15.0, 32.4, 32.6, 50.7 and 50.8, 58.8 and 58.9, 71.7 and 71.8, 98.7 (q, J = 28 Hz), 123.0 (q, J = 293 Hz), 125.9, 126.2, 128.3, 128.4, 128.5, 141.6.

4.7. Nucleophilic ring opening of **1a** with PhSH in HFIP

A solution of 232 mg of **1a** (1 mmol) and 165 mg of PhSH (1.5 mmol) in HFIP (5 mL) was stirred at reflux for 2 h. The reaction mixture was diluted with 20 mL of CH_2Cl_2 and washed twice with a saturated solution of $NaHCO_3$ and dried over Na_2SO_4. After evaporation of the solvent, **5a** was obtained as the sole reaction product, and was purified by column chromatography (SiO_2, CH_2Cl_2).

1,1,1-Trifluoro-3-phenyl-3-phenylthio-2-propanone (***5a***): 243 mg (82%); oil; ^{19}F NMR δ −75.9 (s); ^1H NMR δ 5.2 (s, 1H), 7.1–7.4 (m, 10H) [4b].

4.8. Nucleophilic ring opening of **1b** with PhSH in HFIP

A solution of 260 mg of **1b** (1 mmol) and 165 mg of PhSH (1.5 mmol) in HFIP (5 mL) was stirred at reflux for 6 h. The reaction mixture was diluted with 20 mL of CH_2Cl_2 and washed twice with a saturated solution of $NaHCO_3$ and dried over Na_2SO_4. After evaporating the solvent, **5b** was obtained as the sole reaction product, and was purified by column chromatography (SiO_2, CH_2Cl_2).

1,1,1-Trifluoro-5-phenyl-3-phenylthio-2-propanone (***5b***): 308 mg (95%); oil; ^{19}F NMR δ −74.9 (s); ^1H NMR δ 2.1 (m, 2H), 2.75 (t, J = 8 Hz, 2H), 3.85 (t, J = 7 Hz, 1H), 7.1–7.5 (m, 10H) [4b].

4.9. Acid catalysed ring opening of **1b** with PhSH in HFIP

A solution of 260 mg of **1b** (1 mmol) and 165 mg of PhSH (1.5 mmol) in HFIP (5 mL) was cooled to 0 °C, one drop of a 50% solution of HBF_4 in Et_2O was added and stirred at 0 °C for 1 h. The reaction mixture was diluted with 20 mL of CH_2Cl_2 and washed twice with a saturated solution of $NaHCO_3$ and dried over Na_2SO_4. After evaporating the solvent, the crude reaction mixture was separated by column chromatography (SiO_2, CH_2Cl_2).

1-Ethoxy-1-(trifluoromethyl)-2-cis-tetralol (***3***): 156 mg (60%); *diphenylsulphide* (***8***): 22 mg.

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