Ring-Opening of 1-CF_3-Substituted Epoxy Ethers with Carboxylic, Thiocarboxylic, and Phosphinic Acids in Basic Medium and in Hexafluoro-2-propanol

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Dedicated to L. M. Yagupolskii on the occasion of his 80th birthday

Keywords: Epoxy ethers / Fluorine / Hydrogen bonds / Trifluoromethyl ketones / Ring opening

Ring-opening of 1-CF_3-substituted epoxy ethers with carboxylic acids was achieved in Et_3N as solvent, and α-CF_3-substituted acyloins and corresponding esters were obtained in good yields. In hexafluoro-2-propanol (HFIP) as solvent, the carboxylic acids acted as nucleophiles, and α-carbonyloxy trifluoromethyl ketones were isolated in good yields. After reduction, CF_3-substituted glycols were obtained as monoesters on one or the other hydroxy group. This reaction also allowed the preparation of α-carbonylsulfanyl- and α-phosphoryloxy trifluoromethyl ketones and corresponding alcohols.

Introduction

Trifluoromethyl ketones (TFMKs) are a biologically interesting class of compounds, as they are potent inhibitors of variety of hydrolytic enzymes.[1] This activity is associated with their tendency to form hydrates that mimic the tetrahedral intermediates formed during hydrolysis of esters and amides.[2] The α-substituted TFMKs most widely studied as enzyme inhibitors are α-peptidyl derivatives[2,3] and, to a lesser extent, α-alkylthio trifluoromethyl ketones.[4]

While α-hydroxy ketones (or acyloins) are useful building blocks, the corresponding trifluoromethyl ketones have been less commonly reported, probably due to their instability.[5,6] It was recently shown that the parent compounds, α-trifluoromethyl acyloins (α-acyl trifluoromethyl alcohols), induce apoptosis of human cancer cells,[7] which makes them a potent bioactive class of compounds.

Some years ago we reported a synthesis of 1-CF_3-substituted epoxy ethers by Wittig olefination of ethyl trifluoroacetate and subsequent epoxidation by MCPBA.[8] Nucleophilic oxirane ring opening of these epoxy ethers offers a general method for the synthesis of various α-functionalized CF_3-substituted ketones, and alcohols by further reduction. In this way, β-CF_3-substituted β-hydroxy amines and sulfides could readily be synthesized.[9] Previously, oxirane ring opening of 1-CF_3-substituted epoxy ethers with carboxylic acids had not been studied, although it could provide a good route to α-hydroxy TFMKs in protected form, thus solving the problem of their stability.

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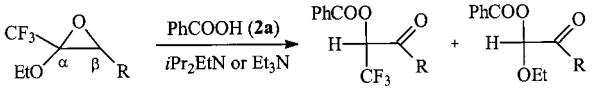
Results and Discussion

Ring-Opening with RCOOH

a) In Et_3N: The nucleophilicity of carboxylic acids can be enhanced by converting them into carboxylates. Enantioselective ring opening of oxiranes with benzoic acid and salen catalyst could be improved, as reported by Jacobsen, by performing the reactions in iPr_2NEt as solvent.[10]

Treatment of 1-CF_3-substituted 2-phenylepoxy ether **1** (PhEE) with 1.2 equivalent of benzoic acid (**2a**) and iPr_2NEt as solvent at 50 °C was stopped after 7 hours, at which point there was no more conversion of starting material. Compound **1** had largely been converted (89%), but no formation of the expected trifluoromethyl ketone was observed. Instead, 80% of the α-trifluoromethyl acyloin ester **3a** and 20% of product **4a** (Scheme 1) was formed. The

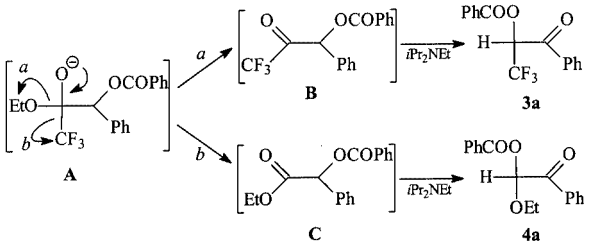


1 (R = Ph)	**3a** 80% (56%)	**4a** 20%
6 (R = Hex)	**7a** 67% (45%)	**8a** 33%
9 (R = CH_2CH_2Ph)	**10a** 80% (65%)	**11a** 20%

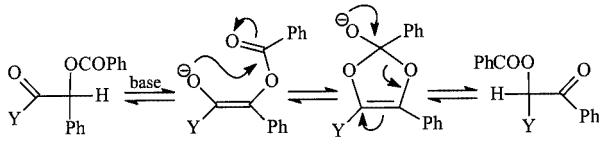
Scheme 1

same results were obtained in Et_3N. Similarly, 1-CF_3-substituted 2-hexylepoxy ether **6** (HexEE) and 1-CF_3-substituted 2-(2-phenylethyl)epoxy ether **9** (PhenEE), when treated with acid **2a**, produced mixtures of α-CF_3-substituted acyloin ester **7a/10a** and α-benzoyloxy-α-ethoxy ketone **8a/11a**, respectively.

Both compounds **3a** and **4a** could be formed from the same intermediate **A**, the result of nucleophile ring opening with C_β−O cleavage. Intermediate **A** could provide either **B** or **C** (Scheme 2), which could in turn further rearrange into **3a** and **4a**, respectively, through their enol forms (Scheme 3).



Scheme 2



Scheme 3

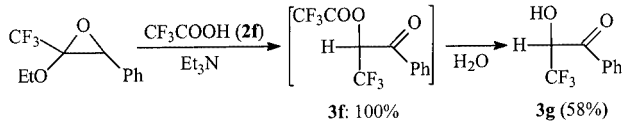
In order to verify this hypothesis, the reaction was performed at lower temperature (4 °C) and monitored by GC (Figure 1). Under these conditions, **3a** was accompanied by another product, which was further determined to be **B** and named **5a** (vide infra). Once isolated, **5a** was placed in *i*Pr_2NEt and was rapidly and quantitatively converted at room temperature into **3a**. The intermediate **C** could not be detected.

The reaction was then extended to other acids (Table 1). PhEE **1** was able to react with various aromatic and aliphatic acids **2a**−**f** in Et_3N as solvent, providing acyloin esters **3** as major products that could be isolated in 51−74% yields. When PhEE was treated with trifluoroacetic acid, α-CF_3-substituted acyloin trifluoroacetate **3f** was formed as the only product. Hydrolysis occurred during the workup procedure, however, and only α-trifluoromethyl acyloin **3g** was isolated (Scheme 4). The high selectivity of the reaction with TFA could be explained by its stronger acidity, which could promote the departure of the ethoxy group, while the haloform-type elimination of the CF_3 group should be disfavored with the weaker conjugate base.

Table 1. Ring-opening of PhEE **1** with carboxylic acids in Et_3N

Epoxy ether	R′ (R′-COOH)	Time[a] [h]	**3**[b] [%]
PhEE (**1**)	Ph (**2a**)	6	56
	3,4-di$MeOC_6H_3$(**2b**)	8	57
	4-NO_2-C_6H_4 (**2c**)	5	67
	CH_3 (**2d**)	7	51
	C_7H_{15} (**2e**)	13	74
	CF_3 (**2f**)	16	58[c]

[a] Stirring in Et_3N at 50 °C. [b] Isolated yield after column chromatography. [c] α-CF_3-substituted acyloin **3g** was isolated in 58% yield.



Scheme 4

In conclusion, the ring opening of 1-CF_3-substituted epoxy ethers with different carboxylic acids under basic conditions occurred at the β-carbon atom, through a nucleophilic pathway, whatever the substituent on the β-carbon atom. The rearrangement, promoted by the presence of base, provided new α-trifluoromethyl acyloins.

b) In Hexafluoropropan-2-ol (HFIP): In order to avoid the base-promoted rearrangement of the ketone **5a**, the ring opening reaction of 1-CF_3-substituted epoxy ethers with carboxylic acids in the absence of amine was investigated. There were evident questions: are carboxylic acids nucleophilic enough to allow the nucleophile ring opening (Scheme 5, path a) or/and would their acidity (p*K*a PhCOOH = 4.2) favor the formation of the α-CF_3-substituted alkoxy carbocation (path b) as already observed with Lewis acids?[11]

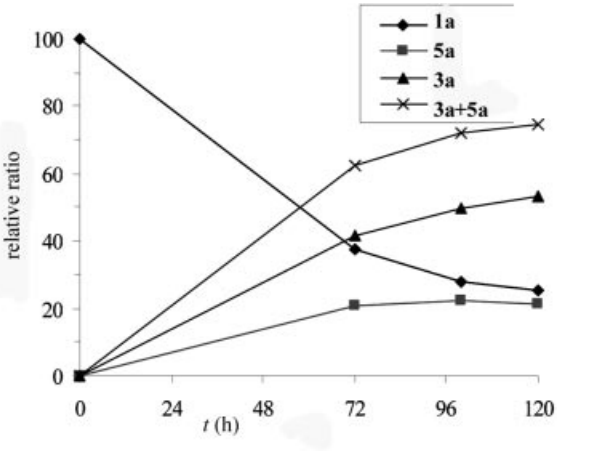
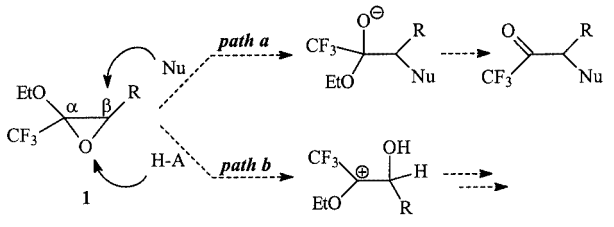


Figure 1. Reaction of PhEE **1a** in PhCOOH/*i*Pr_2NEt at 4° C

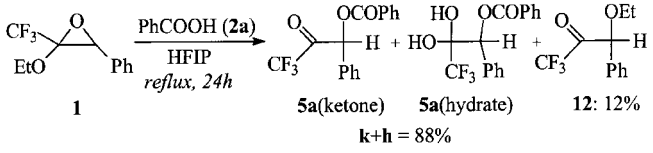


Scheme 5

Actually, PhEE **1** reacted slowly with PhCOOH in CH_3CN or nitromethane, giving only 20% conversion after 24 hours at reflux, with the formation of a complex mixture of compounds.

We have recently found that hexafluoro-2-propanol (HFIP) can activate oxirane ring opening with neutral nucleophiles, with no need to generate the corresponding anionic species.[12] The use of HFIP as solvent had further been applied to 1-CF_3-substituted epoxy ethers, which reacted with aromatic amines to afford α-amino trifluoromethyl ketones as primary products.[13] We thus investigated the ring opening of 1-CF_3-substituted epoxy ethers with carboxylic acids in HFIP.

PhEE **1** was allowed to react with 1.2 equiv. of PhCOOH in HFIP at reflux. The reaction was stopped after 24 hours, and 88% of α-benzoyloxy TFMK **5a** was obtained as a mixture of ketone and hydrate forms in a variable ratio (see Exp. Section), together with a small amount of the acyloin ether **12** (12%) (Scheme 6).



Scheme 6

Similar reactivity was observed on treatment of PhEE **1** with various carboxylic acids (Table 2). The CF_3-substituted acyloin ester **5c** of the less nucleophilic 4-nitrobenzoic acid was isolated in good yield. Besides aromatic carboxylic acids, aliphatic acids (acetic and heptanoic acids) could also be used as nucleophiles.

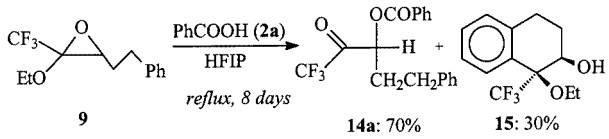
Table 2. Ring-opening of 1-CF_3-substituted epoxy ethers (**1**, **6**, **9**) with carboxylic acids in HFIP

Epoxy ether	R′ (R′-COOH)	Time[a]	Conv.[b] [%]	**5**[b]	**12**[b]	**15**[b]
PhEE (**1**)	Ph (**2a**)	24 h	92	88 (62)	12	
	3,4-diMeOC_6H_3 (**2b**)	25 h	88	78 (65)	22	
	4-NO_2-C_6H_4 (**2c**)	24 h	100	81 (77)	19	
	CH_3 (**2d**)	31 h	93	67 (53)	33	
	C_7H_{15} (**2e**)	31 h	95	75 (68)	25	
HexEE (**6**)	Ph (**2a**)	8 d	77	100 (50) **13a**		
PhenEE (**9**)	Ph (**2a**)	8 d	66	70 (32) **14a**		30

[a] Stirring in HFIP at 60 °C. [b] Conversion and relative ratios were calculated from ^1H and ^{19}F NMR spectra from the disappearance of starting compound; isolated yield in parenthesis.

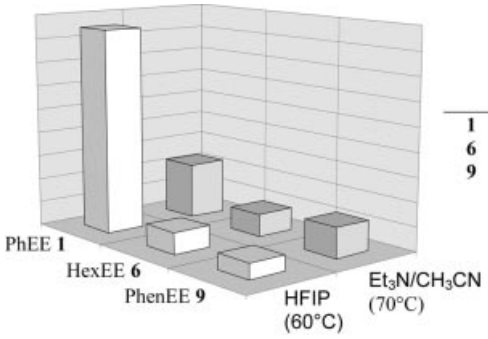
The reactions between carboxylic acids and 1-CF_3-substituted epoxy ethers in HFIP without addition of base were slower than those with carboxylates. However, HFIP has a strong activating effect relative to other solvents. All products arose from $C_\beta-O$ cleavage. Compounds **12** result from the acid-catalyzed rearrangement of **1**, with migration of the ethoxy group. In HFIP, TFMKs **5** could be isolated without further rearrangement into α-CF_3-substituted acyloin esters **3**.

Alkyl-substituted 1-CF_3-substituted epoxy ethers **6** and **9** were much less reactive, and conversions were limited. The reaction with **6** provided the acyloin ester **13a**, which was isolated in a 50% yield (Table 2). In the case of substrate **9**, the acyloin ester **14a** was also a major reaction product; however, it was accompanied by the *cis*-tetralol **15** (Scheme 7). This latter product results from Cα−O ring opening of 1-CF_3-substituted epoxy ether by internal nucleophile (phenyl group) and had previously been obtained from treatment of PhenEE with Lewis acids.[11]



Scheme 7

From all these results we can conclude that HFIP activates the oxirane ring in comparison to CH_3CN. Furthermore, under both sets of conditions (basic with Et_3N, and in HFIP), the main process is the cleavage of $C_\beta-O$, whatever the nature of the substituent at C-β (except for the formation of tetralol **15**). Nevertheless, the substituent on C-β has a great influence on the rate of reaction. In order to quantify this effect, we measured the rate constants of the reaction in Et_3N/CH_3CN and in HFIP (Figure 2): under basic conditions the phenyl derivative **1** was the most reactive, the hexyl analogue **6** and the 2-phenylethyl **9** being 2.4 times and 1.8 times less reactive, respectively. The difference in the reactivities of the epoxy ethers was more pronounced in HFIP: alkyl 1-CF_3-substituted epoxy ethers were 9 times (**6**) and 13 times (**9**) less reactive than the phenyl-substituted one (**1**).

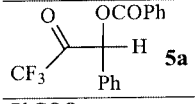
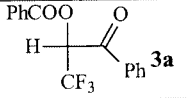
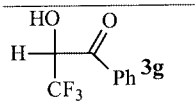


	k_1 (10^{-5} s^{-1}) Et_3N	HFIP
1	4.6	1.7
6	1.9	0.2
9	2.5	0.1

Figure 2. The effect of the structure of 1-CF_3-substituted epoxy ethers on their rate of reaction with PhCOOH in HFIP and in Et_3N/CH_3CN

This marked phenyl substituent effect on the rate of reaction in HFIP suggests a strong development of positive charge on carbon atoms. This activation is not due to the acidity of HFIP, since its p*K*a (9.3) is higher than that of PhCOOH (p*K*a = 4.2), but more probably due to the polarization of the oxirane ring by its strong hydrogen bond-donor ability (α = 2.96 for HFIP, 0.19 for CH_3CN, and 1.12 for AcOH)[14] and its strong ionizing power (Y = 3.82).[15] Surprisingly, unlike in reactions with Lewis acids, the nucle-

Table 3. Reduction of CF_3-substituted acyloin derivatives with $NaBH_4$

Substrate	Reaction Cond.[a]	Conv.[b]	**16** *anti/ syn*	**17** *anti/ syn*	**18** *anti/ syn*
 **5a**	EtOH, –78°C, 1h	100%	40/33		20/7
	HFIP, 0°C,1h	100%	45/55		
 **3a**	EtOH, –78°C, 1h	100%		71/29	
	HFIP, 0°C,1h	100%		45/55	
 **3g**	EtOH, –78°C, 1h	100%			77/23
	HFIP, 0°C,1h	100%			100/0

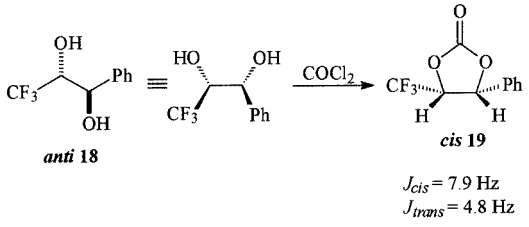
[a] Reducing agent was slowly added to the solution of ketone at low temperature and, if necessary, the temperature was allowed slowly to rise to that indicated. [b] conversion and relative ratios were determined from ^1H and ^{19}F NMR spectra.

ophile preferentially attacks at the C_β atom, even with alkyl-substituted epoxy ethers **6**, **9**.

Reduction of Acyloin Esters

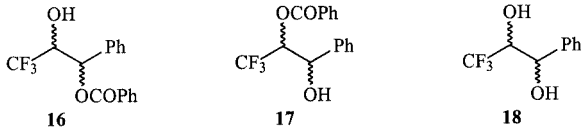
With α-CF_3-substituted acyloin **3g**, its benzoyl ester **3a**, and its trifluoromethyl acyloin ester **5a** to hand, reduction offered the potential to provide CF_3-substituted glycols monoprotected on either hydroxy group. Since we had used HFIP for the ring opening reaction of 1-CF_3-substituted epoxy ethers, reduction in HFIP as solvent was also investigated and compared to reductions in ethanol. The results are presented in Table 3.

α-Benzoyloxy TFMK **5a** was reduced with $NaBH_4$ in EtOH at −78 °C and the reaction was complete within one hour. Besides the β-benzoyloxy CF_3-substituted alcohol **16** (*anti*/*syn* = 60:40, as determined by NMR spectroscopic data for the corresponding cyclic carbonate, Scheme 8), 27% of glycol **18** was formed. Conversely, reduction in HFIP at 0 °C selectively gave the glycol monoester **16** (*anti*/*syn* = 45:55). The lack of stereoselectivity might have been due to the presence of two competitive repulsive substituents (OCOPh and Ph) but could also have been because of the presence of the ketone in the hydrate form, which has previously been reported to modify the stereoselectivity of TFMK reduction.[16]



Scheme 8

Reduction of the α-trifluoromethyl acyloin derivative **3a** gave α-benzoyloxy-α-CF_3-substituted alcohol **17** in an *anti*/*syn* ratio of 71:29 in EtOH and of 45:55 in HFIP. After prolonged reaction times, **17** was converted into **16** by benzoyl transfer, and so the reaction time had to be carefully controlled. This rearrangement is facilitated by basic reaction conditions, as has been established in a separate experiment in Et_3N.



The α-CF_3 acyloin **3g** was also quantitatively reduced in EtOH in one hour at −78 °C to CF_3-substituted glycol **18** in a 77:23 *anti*/*syn* ratio. The reaction in HFIP was very selective, only the *anti* isomer of **18** being formed. Selectivity in favor of the *anti* product could be explained either by the fact that CF_3 is much bigger than OH or by a possible hydrogen bond between hydroxyl and carbonyl group. However, the complete selectivity in HFIP could not be explained.

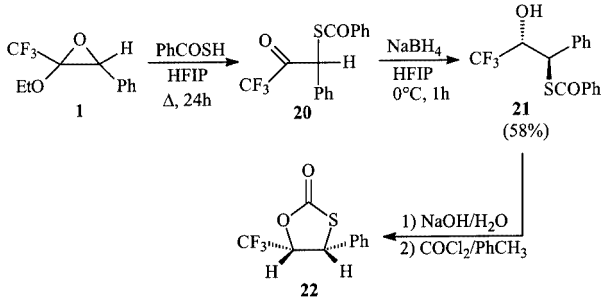
The use of HFIP as a solvent for reduction with $NaBH_4$ offers two main advantages: milder reaction conditions could be employed and the ester function was not hydrolyzed.

Extension to Other Acids

The ring opening reactions of 1-CF_3-substituted epoxy ethers were extended to thiobenzoic and phosphinic acids. There are only a few reported examples of trifluoromethyl ketones and alcohols substituted with thioester and phosphate functions, and no general synthetic route to these compounds is available.[17,18]

In a first experiment, for purposes of comparison, PhEE **1** and thiobenzoic acid were mixed in Et_3N. After 1 hour of stirring at room temperature, an intractable mixture was obtained. The reaction was then performed in HFIP and without addition of amine. It was complete after 24 hours at reflux, α-benzoylsulfanyl CF_3-substituted ketone **20** being formed as the sole product, as determined by NMR and IR spectroscopy (Scheme 9). TFMK derivative **20** was further reduced with $NaBH_4$ in HFIP at 0 °C and, within one hour, the corresponding alcohol **21** was formed and isolated in 58% overall yield. Surprisingly, the reduction was

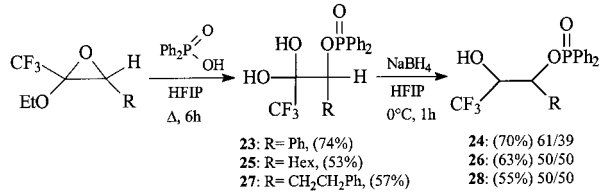
diastereoselective and the *anti* diastereoisomer **21** was obtained. Its structure was determined after hydrolysis and cyclization by phosgene to the 1,3-oxathiolan-2-one **22**, and HOEMSY NMR experiments showed a correlation between the CF_3 group and the phenyl protons, indicating their *cis* orientation. In an NMR experiment with the minor product, a correlation of CF_3 and H_β was observed (*trans* structure).



Scheme 9

The two β-alkyl-α-CF_3-substituted epoxy ethers **6** and **9** exhibited lower reactivities and their reactions produced mixtures of unstable compounds, accompanied in the case of **9** by tetralol **15**.

Diphenylphosphinic acid also acted as nucleophile, and PhEE **1** was converted in 6 hours at reflux in HFIP (Scheme 10). α-Diphenylphosphoryloxy CF_3-substituted ketone **23** was obtained as the only product, and was isolated in its hydrate form in 75% yield. HexEE **6** and PhenEE **9** reacted similarly, CF_3-substituted ketone derivatives **25** and **27** (hydrate forms) being isolated in 53% and 57% yields, respectively. Here the reduction of these hydrates again gave alcohols **24**, **26**, and **28** without stereoselectivity.



Scheme 10

Conclusion

In conclusion, 1-CF_3-substituted epoxy ethers were able to react with carboxylic acids if Et_3N was used to generate carboxylates; the reaction did not stop at first stage, however, but the ring opening products underwent rearrangements to afford α-CF_3-substituted acyloin esters. If HFIP was used as solvent for oxirane ring opening reactions, carboxylic acids could be used directly as nucleophiles and α-substituted CF_3-substituted ketones could be isolated in good yields. No base was required for this reaction, and the activating effect of HFIP did not affect the regioselectivity of nucleophile ring opening. Valuable new synthons – namely, α-carbonyloxy CF_3-substituted ketones and the corresponding glycols as monoesters on one or the other hydroxy group – are now available. Oxirane ring opening with thiobenzoic acid and phosphinic acid offers a route to new classes of α-substituted trifluoromethyl ketones and corresponding alcohols. The use of β-carbonylsulfanyl alcohols as precursors of trifluoromethyl-substituted thiols and episulfides is under investigation.

Experimental Section

General Remarks: ^1H, ^{13}C, ^{19}F, and ^{31}P NMR spectra were recorded on 200 and 400 MHz multinuclear spectrometers in $CDCl_3$ solutions with TMS (for ^1H and ^{13}C), $CFCl_3$ (for ^{19}F), and H_3PO_4 (for ^{31}P) as external standards. GC analysis were performed on a capillary column (SE-30, 10 M). Silica gel (60A) was used for column chromatography and silica 60 F254 plates for preparative TLC.

1-CF_3-substituted epoxy ethers **1**, **6** and **9** were synthesized by known procedures.[8] Et_3N, *i*Pr_2NEt, TFA, $NaBH_4$, carboxylic acids, thiobenzoic acid, diphenylphosphinic acid, and HFIP were obtained from commercial sources and were used as received.

Ring-opening of 1-CF_3-substituted Epoxy Ethers with RCOOH and Et_3N. Typical Procedure: Compound **1** (0.5 mmol) was added to a mixture of **2a** (0.6 mmol) and Et_3N (0.6 mmol), and the mixture was stirred at 50 °C. The reaction was monitored by GC analysis. After 6 hours, the reaction mixture was dissolved in CH_2Cl_2 (20 mL) and washed with HCl (0.5 M) and then twice with a saturated solution of $NaHCO_3$. It was dried over $MgSO_4$ and solvent was evaporated under reduced pressure. The crude reaction mixture was analyzed by ^1H and ^{19}F NMR spectroscopy and the product was purified by column chromatography (SiO_2, CH_2Cl_2/petroleum ether, 1:1)

1-Benzoyl-2,2,2-trifluoroethyl Benzoate (3a): 86 mg, 56%; white crystals, m.p. 92–93 °C (m.p.[6c] 87–88 °C). ^1H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 6.55 (q, $^3J_{H,F}$ = 7 Hz, 1 H), 7.4–7.6 (m, 2 H), 7.6–7.7 (m, 1 H), 8.0–8.2 (m, 2 H) ppm. ^{13}C NMR: δ = 71.4 (q, $^2J_{C,F}$ = 32 Hz, CCF_3), 122.0 (q, $^1J_{C,F}$ = 282 Hz, CF_3), 128.7, 129.0, 130.3, 134.3, 134.6, 134.7, 164.7, 188.4 ppm. ^{19}F NMR: δ = −71.5 (d, $^3J_{F,H}$ = 7 Hz) ppm. IR (neat): $\tilde{\nu}$ = 1743, 1695 cm^{-1}. $C_{16}H_{11}F_3O_3$: calcd. C 62.34, H 3.60; found C 62.23, H 3.58.

1-Ethoxy-2-oxo-2-phenylethyl Benzoate (4a): 17 mg, 12%; oil. ^1H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 1.2 (t, $^3J_{H,H}$ = 7 Hz, 3 H), 4.25 (q, $^3J_{H,H}$ = 7 Hz, 2 H), 6.5 (s, 1 H), 7.4–7.6 (m, 6 H), 8.0–8.2 (m, 4 H) ppm. ^{13}C NMR: δ = 14.0, 62.5, 75.0, 128.6, 128.8, 129.3, 130.2, 133.8, 134.2, 165.2, 189.8 ppm. IR (neat): $\tilde{\nu}$ = 1726, 1694, 1233, 1108 cm^{-1}.

1-Benzoyl-2,2,2-trifluoroethyl 3,4-Dimethoxybenzoate (3b): 105 mg, 57%; white crystals, m.p. 119 °C. ^1H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 3.9 (2s, 6 H), 6.5 (q, $^3J_{H,F}$ = 7 Hz, 1 H), 6.88 (d, *J* = 9.0 Hz, 1 H), 7.4–7.65 (m, 4 H), 7.75 (dd, *J* = 9 and 2 Hz, 1 H), 8.0 (d, *J* = 7.0 Hz, 2 H) ppm. ^{13}C NMR: δ = 55.9, 56.0, 71.1 (q, $^2J_{C,F}$ = 32 Hz, CCF_3), 110.4, 112.3, 119.9, 122.0 (q, $^1J_{C,F}$ = 282 Hz, CF_3), 124.7, 128.8, 134.4, 134.6, 148.8, 154.1, 164.3, 188.5 ppm. ^{19}F NMR: δ = −71.6 (d, $^3J_{F,H}$ = 7 Hz) ppm. IR (neat): $\tilde{\nu}$ = 1729, 1701 cm^{-1}. $C_{18}H_{15}F_3O_5$ (368.3): calcd. C 58.70, H 4.11; found C 58.50, H 4.01.

(1-Benzoyl-2,2,2-trifluoroethyl 4-Nitrobenzoate (3c): 118 mg, 67%; white crystals, m.p. 93−94 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 6.55 (q, $^3J_{H,F}$ = 7 Hz, 1 H), 7.45−7.7 (m, 3 H), 8.0 (d, *J* = 7.0 Hz, 2 H), 8.3 (m, 4 H) ppm. ^{13}C NMR: δ = 71.8 (q, $^2J_{C,F}$ = 32 Hz, CCF_3), 121.5 (q, $^1J_{C,F}$ = 281 Hz, CF_3), 123.7, 128.8, 129.0, 131.3, 133.0, 134.3, 134.7, 151.1, 162.8, 187.5 ppm. ^{19}F NMR: δ = −71.3 (d, $^3J_{F,H}$ = 7 Hz) ppm. IR (neat): $\tilde{\nu}$ = 1741, 1697 cm^{-1}. $C_{16}H_{10}F_3O_5N$ (353.2507): calcd. C 54.40, H 2.85, N 3.97; found C 54.20, H 2.76, N 3.85.

1-Benzoyl-2,2,2-trifluoroethyl Acetate (3d): 63 mg, 51%; oil. ^{1}H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 2.2 (s, 3 H), 6.3 (q, $^3J_{H,F}$ = 7 Hz, 1 H), 7.4−7.7 (m, 3 H), 7.95 (d, *J* = 7.0 Hz, 2 H) ppm. ^{13}C NMR: δ = 20.0, 71.0 (q, $^2J_{C,F}$ = 32 Hz, CCF_3), 121.7 (q, $^1J_{C,F}$ = 282 Hz, CF_3), 128.8, 134.5, 135.0, 168.9, 188.4 ppm. ^{19}F NMR: δ = −71.75 (d, $^3J_{F,H}$ = 7 Hz) ppm. IR (neat): $\tilde{\nu}$ = 1759, 1703 cm^{-1}. $C_{11}H_9F_3O_3$ (246.1831): calcd. C 53.67, H 3.68; found C 53.53, H 3.76.

1-Benzoyl-2,2,2-trifluoroethyl Octanoate (3e): 122 mg, 74%; oil. ^{1}H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 0.90 (m, 3 H), 1.1−1.4 (m, 10 H), 2.5 (t, $^3J_{H,H}$ = 7 Hz, 2 H), 6.3 (q, $^3J_{H,F}$ = 7 Hz, 1 H), 7.4−7.7 (m, 3 H), 7.95 (d, *J* = 7.0 Hz, 2 H) ppm. ^{13}C NMR: δ = 14.0, 22.6, 24.6, 28.8, 31.6, 33.4, 41.4, 70.8 (q, $^2J_{C,F}$ = 32 Hz, CCF_3), 121.8 (q, $^1J_{C,F}$ = 282 Hz, CF_3), 128.9, 134.4, 134.7, 171.8, 188.5 ppm. ^{19}F NMR: δ = −71.75 (d, $^3J_{F,H}$ = 7 Hz) ppm. IR (neat): $\tilde{\nu}$ = 1755, 1704 cm^{-1}. $C_{17}H_{21}F_3O_3$ (330.3439): calcd. C 61.81, H 6.41; found C 61.91, H 6.54.

3,3,3-Trifluoro-2-hydroxy-1-phenylpropan-1-one (3g): 59 mg, 58%; m.p. 83−85 °C (m.p.[6c] 80−81 °C). ^{1}H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 4.35 (d, $^3J_{H,H}$ = 8 Hz, OH), 5.45 (qd, $^3J_{H,F}$ = 7 and $^3J_{H,H}$ = 8 Hz, 1 H), 7.4−7.75 (m, 3 H), 8.0 (d, *J* = 8.0 Hz, 2 H) ppm. ^{13}C NMR: δ = 71.0 (q, $^2J_{C,F}$ = 32 Hz, CCF_3), 122.3 (q, $^1J_{C,F}$ = 284 Hz, CF_3), 129.0, 129.4, 133.4, 135.2, 193.2 ppm. ^{19}F NMR: δ = −74.2 (d, $^3J_{F,H}$ = 7 Hz) ppm. IR (neat): $\tilde{\nu}$ = 3370, 1682 cm^{-1}. $C_9H_7F_3O_2$ (204.1463): calcd. C 52.95, H 3.42; found C 53.41, H 3.22.

2-Oxo-1-(trifluoromethyl)octyl Benzoate (7): 71 mg, 45%; oil. ^{1}H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 0.9 (m, 3 H), 1.3 (m, 6 H), 1.6 (m, 2 H), 2.65 (m, 2 H), 5.7 (q, $^3J_{H,F}$ = 7 Hz, 1 H), 7.4−7.7 (m, 3 H), 8.1 (d, *J* = 8.0 Hz, 2 H) ppm. ^{13}C NMR: δ = 13.9, 22.4, 22.8, 28.5, 31.5, 40.0, 74.7 (q, $^2J_{C,F}$ = 32 Hz, CCF_3), 121.8 (q, $^1J_{C,F}$ = 281 Hz, CF_3), 127.8, 128.7, 128.8, 130.2, 134.3, 164.6, 198.7 ppm. ^{19}F NMR: δ = −72.1 (d, $^3J_{F,H}$ = 7 Hz) ppm. IR (neat): $\tilde{\nu}$ = 1733 cm^{-1}. $C_{16}H_{19}F_3O_3$ (316.3171): calcd. C 60.75, H 6.05; found C 60.61, H 6.12.

2-Oxo-4-phenyl-1-(trifluoromethyl)butyl Benzoate (10): 109 mg, 65%; m.p. 66−67 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 3.0 (m, 4 H), 5.7 (q, $^3J_{H,F}$ = 7 Hz, 1 H), 7.1−7.4 (m, 5 H), 7.4−7.7 (m, 3 H), 8.1 (d, *J* = 7.0 Hz, 2 H) ppm. ^{13}C NMR: δ = 28.9, 41.7, 74.7 (q, $^2J_{C,F}$ = 32 Hz, CCF_3), 121.7 (q, $^1J_{C,F}$ = 282 Hz, CF_3), 126.4, 127.7, 128.3, 128.6, 128.8, 130.3, 134.4, 140.0, 164.6, 197.8 ppm. ^{19}F NMR: δ = −72.0 (d, $^3J_{F,H}$ = 7 Hz) ppm. IR (neat): $\tilde{\nu}$ = 1732, 1728 cm^{-1}. $C_{18}H_{15}F_3O_3$ (336.3075): calcd. C 64.29, H 4.50; found C 64.38, H 4.59.

Ring-opening of 1-CF_3-substituted Epoxy Ethers with RCOOH in HFIP. Typical Procedure: Compounds **1** (0.5 mmol) and **2a** (0.6 mmol) were dissolved in HFIP (5 mL) and the mixture was stirred under reflux for 24 hours. Solvent was evaporated (or distilled). CH_2Cl_2 (20 mL) was added, and the solution was washed twice with a saturated solution of $NaHCO_3$. After evaporation of solvent, the crude reaction product was analyzed by NMR. Products were isolated by column chromatography (SiO_2, CH_2Cl_2 :ethyl acetate = 9 :1) and **5** was obtained as a mixture of ketone and hydrate forms. The ketone form could be isolated as a pure compound by distillation, but quickly reverts to equilibrium with its hydrate form. The hydrate could be isolated by crystallization. The structures of **5**, **13**, and **14** were confirmed by their rearrangement into **3**, **7**, and **10** in the presence of Et_3N. (room temp., 2 h).

(3,3,3-Trifluoro-2-oxo-1-phenylpropyl Benzoate (5a): 108 mg, 62%; **Ketone Form:** ^{1}H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 6.6 (s, 1 H), 7.3−7.7 (m, 8 H), 8.1 (d, *J* = 7.0 Hz, 2 H) ppm. ^{13}C NMR: δ = 76.8, 115.5 (q, $^1J_{C,F}$ = 293 Hz, CF_3), 128.4, 128.6, 128.8, 129.4, 130.0, 134.0, 165.8, 185.7 (q, $^2J_{C,F}$ = 34 Hz, C=O) ppm. ^{19}F NMR: δ = −75.2 (s) ppm. IR (neat): $\tilde{\nu}$ = 1773, 1721 cm^{-1}. **Hydrate Form:** ^{1}H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 3.3 (OH), 3.5 (OH), 6.3 (s, 1 H), 7.3−7.7 (m, 8 H), 8.1 (d, *J* = 7.0 Hz, 2 H) ppm. ^{13}C NMR: δ = 75.0, 93.4 (q, $^2J_{C,F}$ = 31 Hz, CCF_3), 122.0 (q, $^1J_{C,F}$ = 282 Hz, CF_3), 165.2 ppm. ^{19}F NMR: δ = −82.25 (s) ppm. IR (neat): $\tilde{\nu}$ = 3512, 1701 cm^{-1}. $C_{16}H_{11}F_3O_3{\cdot}H_2O$ (326.2687): calcd. C 58.90, H 4.02; found C 58.75, H 3.99.

3-Ethoxy-1,1,1-trifluoro-3-phenylacetone (12):[19] 9 mg, 8%. ^{1}H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 1.2 (t, $^3J_{H,H}$ = 7 Hz, 3 H), 3.5 (q, $^3J_{H,H}$ = 7 Hz, 2 H), 5.2, (s, 1 H), 7.4 (m, 5 H) ppm. ^{19}F NMR: δ = −75.3 (s) ppm. IR: $\tilde{\nu}$ = 1768, 1151 cm^{-1}.

3,3,3-Trifluoro-2-oxo-1-phenylpropyl 3,4-Dimethoxybenzoate (5b): 121 mg, 65%. ^{1}H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 3.9 (2s, 6 H), 6.25 (s, 1 H), 6.5 (s, 1 H), 6.9 (d, *J* = 9.0 Hz, 1 H), 7.3−7.6 (m, 6 H), 7.7 (dd, *J* = 9 and 2 Hz, 1 H) ppm. ^{13}C NMR: δ = 56.0, 76.5, 110.5, 112.4, 115.4 (q, $^1J_{C,F}$ = 293 Hz, CF_3), 120.7, 124.4, 128.7, 129.4, 130.3, 148.9, 154.0, 165.4, 186.0 (q, $^2J_{C,F}$ = 35 Hz, C=O) ppm. ^{19}F NMR: δ = −75.3 (s), −82.15 (s) ppm. IR (neat): $\tilde{\nu}$ = 1773, 1715 cm^{-1}. $C_{18}H_{17}F_3O_6{\cdot}H_2O$ (404.3351): calcd. C 55.96, H 4.44; found C 56.66, H 4.21.

3,3,3-Trifluoro-2-oxo-1-phenylpropyl 4-Nitrobenzoate (5c): 139 mg, 77%. ^{1}H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 6.25 (s, 1 H), 6.60 (s, 1 H), 7.3−7.6 (m, 5 H), 8.3 (m, 4 H), ^{13}C NMR: δ = 77.7, 118.3 (q, $^1J_{C,F}$ = 293 Hz, CF_3), 123.7, 128.6, 128.9, 129.4, 129.6, 129.7, 131.1, 132.7, 133.7, 151.1, 163.2, 185.4 (q, $^2J_{C,F}$ = 35 Hz, C=O) ppm. ^{19}F NMR: δ = −75.1 (s), −82.2 (s) ppm. IR (neat): $\tilde{\nu}$ = 1774, 1733 cm^{-1}. $C_{16}H_{10}F_3O_5N$ (353.2507): calcd. C 54.40, H 2.85, N 3.97; found C 53.99, H 2.84, N 3.73.

3,3,3-Trifluoro-2-oxo-1-phenylpropyl Acetate (5d): 68 mg, 53%. ^{1}H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 2.2 (s, 3 H), 6.1 (s, 1 H), 6.3 (s, 1 H), 7.4−7.7 (m, 5 H) ppm. ^{13}C NMR: δ = 42.0, 76.3, 115.3 (q, $^1J_{C,F}$ = 293 Hz, CF_3), 128.5, 128.7, 129.3, 130.4, 171.0, (C=O non observed) ppm. ^{19}F NMR: δ = −75.35 (s), −82.64 (s) ppm. IR (neat): $\tilde{\nu}$ = 1755, 1703 cm^{-1}. $C_{11}H_9F_3O_3{\cdot}1/3H_2O$: calcd. C 52.49, H 3.86; found C 52.39, H 3.83.

3,3,3-Trifluoro-2-oxo-1-phenylpropyl Octanoate (5e): 115 mg, 68%. ^{1}H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 0.9 (t, $^3J_{H,H}$ = 7 Hz, 3 H), 1.3 (m, 6 H), 1.65 (m, 2 H), 2.45 (m, 2 H), 6.1 (s, 1 H), 6.3 (s, 1 H), 7.4 (m, 5 H) ppm. ^{13}C NMR: δ = 14.0, 22.5, 24.7, 28.9, 31.6, 33.6, 115.3 (q, $^1J_{C,F}$ = 293 Hz, CCF_3), 128.8, 129.2, 130.0, 130.3, 170.0, 185.9 (q, $^2J_{C,F}$ = 35 Hz, C=O) ppm. ^{19}F NMR: δ = −75.4 (s), −82.5 (s) ppm. IR (neat): $\tilde{\nu}$ = 1755, 1704 cm^{-1}. $C_{17}H_{21}F_3O_3$ (330.3439): calcd. C 61.81, H 6.41; found C 61.60, H 6.46.

1-(2,2,2-Trifluoroacetyl)heptyl Benzoate (13): 81 mg, 50%. ^{1}H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 0.9 (m, 3 H), 1.1−1.6 (m, 8 H), 2.0 (m, 2 H), 5.35 (dd, $^3J_{H,H}$ = 9 and 4 Hz, 1 H), 5.6 (dd, *J* = 6 and 5 Hz, 1 H), 7.3−7.6 (m, 3 H), 8.05 (d, *J* = 7.0 Hz, 2 H) ppm.

^{13}C NMR: δ = 14.0, 22.5, 25.1, 28.7, 30.0, 31.4, 74.4, 115.4 (q, $^{1}J_{C,F}$ = 292 Hz, CF_3), 128.6, 129.9, 133.8, 165.7, 187.7 (q, $^{2}J_{C,F}$ = 34 Hz, C=O) ppm. ^{19}F NMR: δ = −76.2 (s), −81.95 (s) ppm. IR (neat): $\tilde{\nu}$ = 1773, 1726 cm^{-1}. $C_{16}H_{19}F_3O_3$: calcd. C 60.75, H 6.05; found C 60.60, H 6.10.

3,3,3-Trifluoro-2-oxo-1-(2-phenylethyl)propyl Benzoate (14): 55 mg, 32%. ^1H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 2.35 (m, 2 H), 2.90 (m, 2 H), 5.40 (dd, $^{3}J_{H,H}$ = 9 and 3 Hz, 1 H), 5.55 (t, $^{3}J_{H,H}$ = 6 Hz, 1 H), 7.1−7.4 (m, 5 H), 7.4−7.6 (m, 3 H), 8.0 (d, *J* = 7.0 Hz, 2 H) ppm. ^{13}C NMR: δ = 31.4, 31.6, 73.8, 115.4 (q, $^{1}J_{C,F}$ = 293 Hz, CF_3), 126.4, 128.4, 128.7, 128.8, 130.0, 133.9, 139.5, 165.6, 188.0 (q, $^{2}J_{C,F}$ = 34 Hz, CCF_3) ppm. ^{19}F NMR: δ = −76.05 (s), −81.85 (s) ppm. IR (neat): $\tilde{\nu}$ = 1773, 1724 cm^{-1}. $C_{18}H_{15}F_3O_3$: calcd. C 64.29, H 4.50; found C 64.15, H 4.52.

1-Ethoxy-1-(trifluoromethyl)-2-*cis*-tetralol (15):[11] ^{19}F NMR: δ = −74.4 (s) ppm.

Reduction of CF_3-Substituted Acyloin Derivatives with $NaBH_4$. Typical Procedure: $NaBH_4$ (1.0 mmol) was slowly added to a cooled mixture of CF_3-substituted acyloin (**3a**, **3g**, **5a**, 0.5 mmol) in alcohol (EtOH or HFIP, 5 mL) and the mixture was stirred. The reaction was monitored by GC analysis. Excess reducing agent was decomposed by addition of 1.0 M HCl solution, and the mixture was extracted twice with methylene chloride (10 mL). The organic fractions were combined, washed with a saturated solution of $NaHCO_3$ and with water, and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The crude reaction mixture was analyzed by ^1H and ^{19}F NMR spectroscopy. The structures of the products were determined after separation by preparative TLC (CH_2Cl_2), while their configurations were determined first by hydrolysis of pure diastereoisomer to glycol **18**, followed by cyclization with $COCl_2$ to afford the 1,3-dioxolan-2-one **19**.

Reduction of **5a** in HFIP afforded after workup and separation:

3,3,3-Trifluoro-2-hydroxy-1-phenylpropyl Benzoate (16). *anti*-16: 57 mg, 37%; oil. ^1H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 2.9 (d, $^{3}J_{H,H}$ = 7 Hz, OH), 4.45 [m, 1 H, 2-H), 6.2 (d, $^{3}J_{H,H}$ = 6 Hz, 1 H, 3-H), 7.3−7.7 (m, 8 H), 8.05 (d, *J* = 7.0 Hz, 2 H) ppm. ^{13}C NMR: δ = 72.3 (q, $^{2}J_{C,F}$ = 30 Hz, CCF_3), 73.9, 126.9, 127.7, 128.5, 128.8, 129.2, 129.4, 129.8, 133.5, 135.3, 166.2 ppm. ^{19}F NMR: δ = −75.5 (d, $^{3}J_{F,H}$ = 7 Hz) ppm. IR (neat): $\tilde{\nu}$ = 3446, 1708 cm^{-1}.

***syn*-16:** 67 mg, 43%; white crystals, m.p. 98−99 °C. ^1H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 2.82 (d, $^{3}J_{H,H}$ = 9 Hz, OH), 4.33 [m, 1 H, 2-H), 6.35 (d, $^{3}J_{H,H}$ = 3 Hz, 1 H, 3-H), 7.3−7.7 (m, 8 H), 8.1 (d, *J* = 7.0 Hz, 2 H) ppm. ^{13}C NMR: δ = 72.7, 73.3 (q, $^{2}J_{C,F}$ = 30 Hz, CCF_3), 123.4 (q, $^{1}J_{C,F}$ = 283 Hz, CF_3), 126.9, 128.6, 128.8, 129.0, 129.3, 129.9, 133.6, 135.9, 165.2 ppm. ^{19}F NMR: δ = −76.4 (d, $^{3}J_{F,H}$ = 5.9 Hz) ppm. IR (neat): $\tilde{\nu}$ = 3425, 1690 cm^{-1}. $C_{16}H_{13}F_3O_3$: calcd. C 61.94, H 4.22; found C 61.90, H 4.29.

Reduction of **3a** in EtOH afforded, after workup and separation:

2,2,2-Trifluoro-1-[hydroxy(phenyl)methyl]ethyl Benzoate (17). *anti*-17: 98 mg, 63%; oil. ^1H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 2.8 (s, OH), 5.2 (d, $^{3}J_{H,H}$ = 7 Hz, 1 H, 3-H), 5.8 (qd, $^{3}J_{H,F}$ = 6.9 and $^{3}J_{H,H}$ = 7 Hz, 1 H, 2-H), 7.2−7.5 (m, 8 H), 7.9 (d, *J* = 7.0 Hz, 2 H) ppm. ^{13}C NMR: δ = 71.9, 72.2 (q, $^{2}J_{C,F}$ = 30 Hz, CCF_3), 123.5 (q, $^{1}J_{C,F}$ = 283 Hz, CF_3), 127.1, 128.3, 128.5, 128.9, 129.9, 133.8, 138.3, 164.5 ppm. ^{19}F NMR: δ = −72.85 (d, $^{3}J_{F,H}$ = 6.9 Hz) ppm. IR (neat): $\tilde{\nu}$ = 3478, 1724 cm^{-1}. $C_{16}H_{13}F_3O_3$: calcd. C 61.94, H 4.22; found C 61.76, H 4.23.

***syn*-17:** 30 mg, 19%; oil. ^1H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 2.4 (d, $^{3}J_{H,H}$ = 4 Hz, OH), 5.2 (dd, $^{3}J_{H,H}$ = 4 and 5 Hz, 1 H, 3-H), 5.8 (qd, $^{3}J_{H,F}$ = 7 and $^{3}J_{H,H}$ = 5 Hz, 1 H, 2-H), 7.2−7.7 (m, 8 H), 8.1 (d, *J* = 7.0 Hz, 2 H) ppm. ^{13}C NMR: δ = 71.4, 72.2 (q, $^{2}J_{C,F}$ = 30 Hz, CCF_3), 123.1, (q, $^{1}J_{C,F}$ = 282 Hz, CF_3), 126.5, 128.5, 128.7, 128.8, 130.0, 133.9, 138.2, 164.7 ppm. ^{19}F NMR: δ = −73.0 (d, $^{3}J_{F,H}$ = 7.0 Hz) ppm.

Reduction of **3g** in EtOH afforded after, workup and separation by prep. TLC (CH_2Cl_2/EtOAc, 4:1):

3,3,3-Trifluoro-1-phenylpropane-1,2-diol (18). *anti*-18: 60 mg, 58%, oil. ^1H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 4.1 (dq, $^{3}J_{H,H}$ = 6.3 and $^{3}J_{H,F}$ = 7 Hz, 1 H, 2-H), 4.85 (d, $^{3}J_{H,H}$ = 6.3 Hz, 1 H), 7.3 (m, 5 H) ppm. ^{13}C NMR: δ = 72.7, 73.3 (q, $^{2}J_{C,F}$ = 29 Hz, CCF_3), 124.5 (q, $^{1}J_{C,F}$ = 281 Hz, CF_3), 127.1, 128.7, 128.9, 138.4 ppm. ^{19}F NMR: δ = −75.05 (d, $^{3}J_{F,H}$ = 7 Hz) ppm. IR (neat): $\tilde{\nu}$ = 3391, 3265 cm^{-1}. $C_9H_9F_3O_2$: calcd. C 52.43, H 4.40; found C 52.60, H 4.50.

***syn*-18:** 15 mg, 15%; oil. ^1H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 4.0 (dq, $^{3}J_{H,H}$ = 3 and $^{3}J_{H,F}$ = 7 Hz, 1 H, 2-H), 4.95 (d, $^{3}J_{H,H}$ = 3.0 Hz, 1 H, 3-H), 7.3 (m, 5 H) ppm. ^{13}C NMR: δ = 70.7, 73.6 (q, $^{2}J_{C,F}$ = 29 Hz, CCF_3), 124.3 (q, $^{1}J_{C,F}$ = 281 Hz, CF_3), 126.4, 128.6, 128.7, 138.1 ppm. ^{19}F NMR: δ = −77.05 (d, $^{3}J_{F,H}$ = 7 Hz) ppm.

Hydrolysis of Glycol Monoesters 16, 17: A diastereoisomer of glycol monoester **16** or **17** (0.5 mmol) was added to a solution of NaOH (40 mg) in water (0.15 mL) and the mixture was stirred at 90 °C for 5 min. The solution was diluted with water, neutralized with 1 M HCl, and extracted twice with CH_2Cl_2 (10 mL). The combined organic fractions were dried over $MgSO_4$, solvent was evaporated, and a clean diastereoisomer of glycol **18** was obtained.

Cyclization of Glycol 18: Compound **18** (0.5 mmol) and Et_3N (126 mg) were dissolved in toluene (4 mL). The solution was cooled to 0 °C, 20% $COCl_2$ (1.5 mL) in toluene was added, and the mixture was stirred for an additional 30 min. The reaction was stopped by addition of MeOH (2 mL) and CH_2Cl_2 (20mL), and the solution was washed twice with a saturated solution of $NaHCO_3$ and with water. After removal of solvent, clean cyclized product was obtained.

4-Phenyl-5-(trifluoromethyl)-1,3-dioxolan-2-one (19). *cis*-19: ^1H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 5.0 (qd, $^{3}J_{H,F}$ = 6.3 and $^{3}J_{H,H}$ = 7.9 Hz, 1 H, 5-H), 5.9 (d, $^{3}J_{H,H}$ = 7.9 Hz, 1 H, 4-H), 7.0−7.4 (m, 5 H) ppm. ^{13}C NMR: δ = 75.8 (q, $^{2}J_{C,F}$ = 32 Hz, CCF_3), 78.2, 121.7 (q, $^{1}J_{C,F}$ = 283 Hz, CF_3), 126.5, 129.0, 129.1, 130.3, 134.8, 162.6 ppm. ^{19}F NMR: δ = −73.4 (d, $^{3}J_{F,H}$ = 6.3 Hz) ppm. IR (neat): $\tilde{\nu}$ = 1799 cm^{-1}. ***trans*-19:** ^1H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 4.75 (qd, $^{3}J_{H,F}$ = 5.6 and $^{3}J_{H,H}$ = 4.8 Hz, 1 H, 5-H), 5.65 (d, $^{3}J_{H,H}$ = 4.8 Hz, 1 H, 4-H), 7.3−7.6 (m, 5 H) ppm. ^{19}F NMR: δ = −79.3 (d, $^{3}J_{F,H}$ = 5.6 Hz) ppm.

Ring-opening of PhEE 1 with Thiobenzoic Acid in HFIP: Compound **1** (0.5 mmol) and PhCOSH (0.6 mmol) were dissolved in HFIP (5 mL) and the solution was stirred under reflux for 24 hours. Solvent was evaporated, CH_2Cl_2 (20 mL) was added, and the solution was washed twice with a saturated solution of $NaHCO_3$. After evaporation of solvent, the crude reaction product was analyzed by NMR spectroscopy.

(3,3,3-Trifluoro-2-oxo-1-phenylpropyl) Benzenecarbothioate (20): ^1H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 6.0 (s), 7.3−7.8 (m, 8 H), 8.0 (d, *J* = 7.0 Hz, 2 H) ppm. ^{13}C NMR: δ = 52.5, 115.9 (q, $^{1}J_{C,F}$ = 294 Hz, CF_3), 127.5, 128.8, 129.2, 129.5, 134.2, 135.2, 186.7 (q, $^{3}J_{C,F}$ = 35 Hz, C=O), 190.2 ppm. ^{19}F NMR: δ = −75.4 (s) ppm. IR (neat): $\tilde{\nu}$ = 1765, 1661 cm^{-1}.

TFMK **20** was reduced in HFIP as described above, and alcohol **21** was obtained.

***anti*-(3,3,3-Trifluoro-2-hydroxy-1-phenylpropyl) Benzenecarbothioate (21):** 95 mg, 58%; white crystals, m.p. 80−81 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 4.6 (m, 1 H, 2-H), 5.2 (d, $^3J_{H,H}$ = 3.3 Hz, 1 H), 7.3−7.7 (m, 8 H), 8.0 (d, *J* = 7.0 Hz, 2 H) ppm. ^{13}C NMR: δ = 47.4, 73.2 (q, $^2J_{C,F}$ = 30 Hz, CCF_3), 123.9 (q, $^1J_{C,F}$ = 284 Hz, CF_3), 127.3, 128.4, 128.5, 128.6, 129.4, 133.9, 135.0, 136.1, 190.1 ppm. ^{19}F NMR: δ = −75.35 (d, $^3J_{F,H}$ = 6.9 Hz) ppm. IR (neat): $\tilde{\nu}$ = 3468, 1661, 905 cm^{-1}. $C_{16}H_{13}F_3O_2S$: calcd. C 58.89, H 4.02; found C 59.02 H 4.03.

Alcohol **21** was first hydrolyzed, and then cyclized under the same reaction conditions as used for the benzoyloxy derivatives **16** and **17**. The structure of the 1,3-oxathiolan-2-one was determined by HOEMSY NMR experiments.

4-Phenyl-5-(trifluoromethyl)-1,3-oxathiolan-2-one (22). *cis*-22: ^{1}H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 5.1 (qd, $^3J_{H,F}$ = 6.0 and $^3J_{H,H}$ = 6.6 Hz, 1 H, 5-H), 5.2 (d, $^3J_{H,H}$ = 6.6 Hz, 1 H, 4-H), 7.4−7.6 (m, 5 H) ppm. ^{13}C NMR: δ = 51.6, 78.6 (q, $^2J_{C,F}$ = 33 Hz, CCF_3), 121.4 (q, $^1J_{C,F}$ = 281 Hz, CF_3), 127.3, 128.7, 128.8, 129.6, 132.4, 169.4 ppm. ^{19}F NMR: δ = −71.5 (d, $^3J_{F,H}$ = 6.0 Hz) ppm. IR (neat): $\tilde{\nu}$ = 1728 cm^{-1}.

***trans*-22:** ^{1}H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 4.9 (qd, $^3J_{H,F}$ = 5.7 and $^3J_{H,H}$ = 5.4 Hz, 1 H, 5-H), 5.15 (d, $^3J_{H,H}$ = 5.4 Hz, 1 H, 4-H), 7.4−7.6 (m, 5 H) ppm. ^{19}F NMR: δ = −77.6 (d, $^3J_{F,H}$ = 5.7 Hz) ppm.

Ring Opening of 1-CF_3-Substituted Epoxy Ethers with Diphenylphosphinic Acid in HFIP: Compound **1** (or **6** or **9**, 0.5 mmol) and Ph_2POOH (0.6 mmol) was dissolved in HFIP (5 mL), and the mixture was stirred under reflux for 6 hours. Solvent was evaporated, CH_2Cl_2 (20 mL) was added, and the solution was washed twice with a saturated solution of $NaHCO_3$. After evaporation of solvent, the crude reaction product was analyzed by NMR spectroscopy and, after column chromatography (SiO_2, CH_2Cl_2/EtOAc, 9:1), the pure hydrate form was obtained (Scheme 10). After reduction by $NaBH_4$ (2 equiv.) in HFIP at 0 °C for 1 hour, the alcohol was obtained and isolated by column chromatography (SiO_2, CH_2Cl_2/EtOAc, 9:1) (Scheme 10).

3,3,3-Trifluoro-2-oxo-1-phenylpropyl Diphenylphosphinate (23): 156 mg, 74%. ^{1}H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 5.3 (d, $^3J_{H,P}$ = 11 Hz, 1 H), 7.2−7.6 (m, 13 H), 7.8 (m, 2 H) ppm. ^{13}C NMR: δ = 79.9 (d, $^2J_{C,P}$ = 7 Hz), 93.5 (q, $^2J_{C,F}$ = 32 Hz), 122.5 (q, $^1J_{C,F}$ = 289 Hz), 127.9, 128.2, 128.5, 128.7, 129.0, 131.1, 131.3, 132.1, 132.3, 132.8, 133.0, 134.1 ppm. ^{19}F NMR: δ = −80.8 (s) ppm. ^{31}P NMR: δ = 92.0 (d, $^3J_{P,H}$ = 12 Hz) ppm. IR (neat): $\tilde{\nu}$ = 1186, 1132, 1022, 986 cm^{-1}.

3,3,3-Trifluoro-2-hydroxy-1-phenylpropyl Diphenylphosphinate (24): 102 mg, 70%; white crystals, m.p. 107−110 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 4.3 (m, 1 H, 2-H), 5.25 (dd, $^3J_{H,P}$ = 10 and $^3J_{H,H}$ = 7 Hz, 1 H, 3-H), 5.45 (dd, $^3J_{H,P}$ = 10 and $^3J_{H,H}$ = 2 Hz, 1 H, 3-H), 5.75 (br. s, OH), 5.95 (d, $^3J_{H,H}$ = 10 Hz, OH), 7.1−7.9 (m, 15 H) ppm. ^{13}C NMR: δ = 73.7 (q, $^2J_{C,F}$ = 29 Hz), 78.0 (d, $^2J_{C,P}$ = 5.5 Hz), 78.3 (d, $^2J_{C,P}$ = 6 Hz), 123.6 (q, $^1J_{C,F}$ = 284 Hz), 124.1 (q, $^1J_{C,F}$ = 284 Hz), 126.4, 127.5, 128.3, 128.4, 128.7, 129.1, 131.1, 131.3, 131.9, 132.1, 132.6, 132.7, 135.3 ppm. ^{19}F NMR: δ = −72.7 (d, $^3J_{F,H}$ = 6.6 Hz), −74.4 (d, $^3J_{F,H}$ = 6.9 Hz) ppm. ^{31}P NMR: δ = 88.5 (m) ppm. IR (neat): $\tilde{\nu}$ = 3236, 1203, 1169, 1129, 1111, 991, 907 cm^{-1}. $C_{21}H_{18}F_3O_3P$: calcd. C 62.07, H 4.46; found C 61.53, H 4.47.

1-(Trifluoroacetyl)heptyl Diphenylphosphinate (25): 114 mg, 53%. ^{1}H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 0.8 (m, 3 H), 0.9−1.4 (m, 8 H), 1.9 (m, 2 H), 4.4 (m, 1 H), 7.3−7.7 (m, 6 H), 7.7−8.0 (m, 4 H) ppm. ^{13}C NMR: δ = 13.9, 22.2, 22.5, 25.9, 28.4, 31.4, 80.2 (d, $^2J_{C,P}$ = 7 Hz), 92.9 (q, $^2J_{C,F}$ = 31 Hz), 123.0 (q, $^1J_{C,F}$ = 288 Hz), 127.8, 128.3, 128.6, 130.4, 130.9, 131.4, 131.6, 132.2, 132.4, 132.6, 132.8 ppm. ^{19}F NMR: δ = −80.6 (s) ppm. ^{31}P NMR: δ = 90.3 (d, $^3J_{P,H}$ = 8.1 Hz) ppm. IR (neat): $\tilde{\nu}$ = 1439, 1180, 1132, 976, 906 cm^{-1}.

1-(2,2,2-Trifluoro-1-hydroxyethyl)heptyl Diphenylphosphinate (26): 69 mg, 63%; oil. ^{1}H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 0.8, (m, 3 H), 1.0−1.4 (m, 8 H), 1.8 (m, 2 H), 4.1 (m, 1 H), 4.4 (m, 1 H), 4.5 (m, 1 H), 5.8 (br. s, OH), 6.2 (d, $^3J_{H,H}$ = 6.5 Hz, OH), 7.4−7.7 (m, 6 H), 7.7−7.9 (m, 4 H) ppm. ^{13}C NMR: δ = 13.8, 22.3, 25.6, 28.5, 31.4, 71.6 (q, $^2J_{C,F}$ = 29 Hz, CCF_3), 77.3 (d, $^2J_{C,P}$ = 6 Hz), 78.3 (d, $^2J_{C,P}$ = 7 Hz), 124.4 (q, $^1J_{C,F}$ = 284 Hz, CF_3), 128.4, 128.6, 131.3, 131.5, 131.7, 131.9, 132.5 ppm. ^{19}F NMR: δ = −73.1 (d, $^3J_{F,H}$ = 6.6 Hz), −75.0 (d, $^3J_{F,H}$ = 6.9 Hz) ppm. ^{31}P NMR: δ = 86.0 (d, $^3J_{P,H}$ = 10 Hz), 87.3 (m) ppm. IR (neat): $\tilde{\nu}$ = 3256, 1168, 1130, 1110, 1013, 981, 941 cm^{-1}. $C_{21}H_{26}F_3O_3P$: calcd. C 60.87, H 6.32; found C 60.67, H 6.51.

3,3,3-Trifluoro-2-oxo-1-(2-phenylethyl)propyl Diphenylphosphinate (27): 128 mg, 57%. ^{1}H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 2.0−2.3 (m, 4 H), 4.4 (m, 1 H), 7.0−7.3 (m, 5 H), 7.4−7.7 (m, 6 H), 7.7−8.0 (m, 4 H) ppm. ^{13}C NMR: δ = 32.1, 79.8 (d, $^2J_{C,P}$ = 7 Hz), 93.0 (q, $^2J_{C,F}$ = 31 Hz), 123.1 (q, $^1J_{C,F}$ = 288 Hz), 125.9, 127.8, 128.0, 128.3, 128.5, 128.7, 128.8, 131.0, 131.6, 131.8, 132.2, 132.5, 132.8, 133.1, 140.6 ppm. ^{19}F NMR: δ = −80.7 (s) ppm. ^{31}P NMR: δ = 90.5 (d, $^3J_{P,H}$ = 9 Hz) ppm. IR (neat): $\tilde{\nu}$ = 1439, 1180, 1132, 969, 906 cm^{-1}.

3,3,3-Trifluoro-2-hydroxy-1-(2-phenylethyl)propyl Diphenylphosphinate (28): 68 mg, 55%. ^{1}H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 2.2 (m, 2 H), 2.6 (m, 2 H), 4.05 (m, 1 H), 4.1 (m, 1 H), 4.4 (m, 1 H), 4.5 (m, 1 H), 5.7 (br. s, OH), 6.1 (d, $^3J_{H,H}$ = 10 Hz, OH), 6.85 (m, 2 H), 7.05−7.25 (m, 3 H), 7.3−7.65 (m, 6 H), 7.7−7.85 (m, 4 H) ppm. ^{13}C NMR: δ = 31.3, 33.0, 71.5 (q, $^2J_{C,F}$ = 30 Hz), 71.6 (q, $^2J_{C,F}$ = 30 Hz), 76.9 (d, $^2J_{C,P}$ = 7 Hz), 77.9 (d, $^2J_{C,P}$ = 7 Hz), 124.4 (q, $^1J_{C,F}$ = 284 Hz, CF_3); 126.1, 128.0, 128.4, 128.7, 130.4, 131.3, 131.6, 131.7, 131.9, 132.6, 140.3 ppm. ^{19}F NMR: δ = −72.9 (d, $^3J_{F,H}$ = 6.9 Hz), −74.9 (d, $^3J_{F,H}$ = 6.6 Hz) ppm. ^{31}P NMR: δ = 86.4 (m), 87.8 (m) ppm. IR (neat): $\tilde{\nu}$ = 3240, 1168, 1131, 1111, 1020, 981, 907. $C_{23}H_{22}F_3O_3P$: calcd. C 63.60, H 5.10; found C 63.69, H 5.13.

Kinetic Experiments. In HFIP: Acid **2a** (0.6 mmol) and dodecane (20 mg, internal standard) were dissolved in HFIP (5 mL) and the mixture was heated on an oil bath at 60 °C. The reaction was started by addition of CF_3-substituted epoxy ether (0.5 mmol) and reaction progress was monitored by removal of aliquots (50 μL) that were quenched with a saturated solution of $NaHCO_3$, extracted with CH_2Cl_2, and analyzed by GC (SE-30, 75 °C, 5 min, 20 °C/min). First-order rate constants for consumption of starting compound were calculated by the least squares method from the equation $\ln c = \ln c_0 + k_1 t$.

In Et_3N: Acid **2a** (0.6 mmol), Et_3N (0.6 mmol), and dodecane (20 mg) were dissolved in CH_3CN (5mL) and the mixture was stirred for 20 min at 70 °C. After that, the 1-CF_3-substituted epoxy ether (0.5 mmol) was added and the mixture was stirred at 70 °C. Reaction progress was monitored by removal of aliquots (50 μL) that were quenched by a saturated solution of $NaHCO_3$, extracted with CH_2Cl_2, and analyzed by GC as above.

Good correlations were observed in all kinetic experiments, and errors of measurement were less than 10%.

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