Chemistry–A European Journal
Research Article
doi.org/10.1002/chem.202203578
Chemistry Europe
European Chemical Societies Publishing
www.chemeurj.org

Preparation and Functionalization of Mono- and Polyfluoroepoxides via Fluoroalkylation of Carbonyl Electrophiles

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Abstract: We outline a new synthetic method to prepare mono- and polyfluoroepoxides from a diverse pool of electrophiles (ketones, acyl chlorides, esters) and fluoroalkyl anion equivalents. The initially formed α-fluoro alkoxides undergo subsequent intramolecular ring closure when heated. We demonstrated the versatility of the method through the isolation of 16 mono- and polyfluoroepoxide products. These compounds provide unique entry points for further diversification via either fluoride migration coupled with ring opening, or defluorinative functionalization reactions, the latter of which can be used as a late-stage method to install select bioactive moieties. The reaction sequences described herein provide a pathway to functionalize the commonly observed products formed from 1,2-addition into carbonyl electrophiles

Introduction

The incorporation of –C–F instead of –C–H bonds into bioactive organic compounds is a widely used strategy to improve activity.[1–5] These modifications can increase metabolic stability and lipophilicity, and because of these desirable properties, the number of FDA approved drugs containing fluorine have almost doubled within the past 20 years.[6,7] Fluorination has similarly impacted the agrochemical and materials science industry.[8] Driven by these societal benefits, the development of synthetic approaches to both install and further diversify organofluorinated compounds is routinely targeted by many contemporary synthetic methods.[9–12] Methods that provide multiple branch points from a single fluorinated intermediate are particularly desirable.

α-Fluoroepoxides represent attractive synthetic targets for drug development because, in addition to modulation of physiochemical properties for drug discovery/development, they can provide synthetic access to functionally diverse organofluorinated compounds.[13,14] Of particular note is that, in addition to epoxide ring-expansion reactions,[15] fluoroepoxides can also undergo fluorine migration reactions upon ring opening.[16,17] Epoxide ring-expansion/migration reactions are useful reaction sequences used in drug discovery to build molecular complexity from relatively simple precursors.[18,19]

α-Fluoroepoxides are currently prepared by: 1) oxygenation of vinyl fluorides,[20] 2) fluoride substitution of halogenated epoxides,[21] and 3) addition-cyclization reactions from carbonyl electrophiles (Figure 1ai).[22–25] The latter route is an attractive pathway that requires neither strongly oxidizing conditions nor pre-synthesis of the reactive epoxide. Representative addition-cyclization reactions involve the reaction of carbonyl electrophiles with either $Br_2CFCOOEt$,[22] α-fluorosulfoximines,[23] diarylfluoromethylsulfonium salts,[24] or in situ generated LiCHIF,[25] providing access to α-H, α-COOEt, and α-alkyl substituted α-fluoroepoxides. In contrast, α-aryl variants are not reported through addition-cyclization sequences, despite their potential conversion to either organofluorides with one or more stereogenic centers[26] or α-fluorinated ketones.[16] More broadly, Darzens-type reactions are used to form epoxides from deprotonated α-halo carbonyls, where the leaving group is either chloride or bromide.[27] A key step in several of the above examples, and epoxide synthesis in general, is base-promoted ring closure of a halohydrin containing a good leaving group (e.g. Br^- or I^-).[22,25]

Deconstruction of already prepared C–F bonds is an alternative strategy that has gained prominence as an attractive tool to form fluorinated motifs.[28–37] Most sp^3 C–F bonds have strong bonds (BDEs ranging from 97 to 131 kcal/mol),[8,38] rendering them resistant to unassisted C–F cleavage/addition reactions. Thus, compared to C–Br and C–I bonds, the participation of C–F bonds in S_N2 pathways is far less common. However, select examples have demonstrated that intramolecular systems can enable this pathway, where the incoming nucleophile originates from a deprotonated alcohol.[39–41] In addition to the intramolecular formation of 5 or 6-membered rings,[40] 3-membered rings (epoxides) can also form (Figure 1a, ii).[25,42,43] For example, ethylene oxide was reported to form

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/chem.202203578

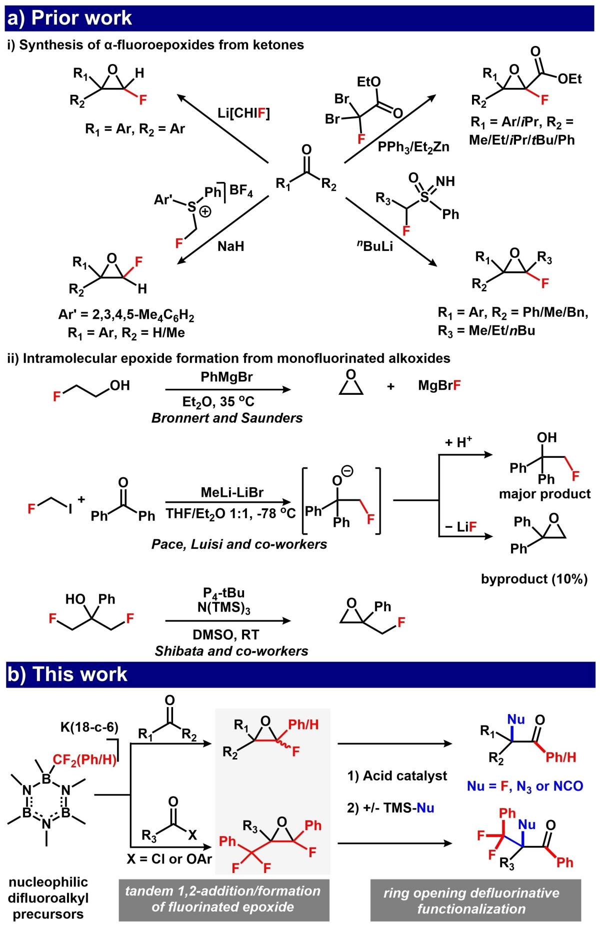


Figure 1. A. a) Prior work on i) synthesis of α-fluoroepoxides via addition-cyclization reactions and ii) epoxide formation from intramolecular ring-closure of fluoroalkyl alkoxides. b) This work: synthesis of fluoroepoxides by fluoroalkylation of carbonyl electrophiles and their ring opening defluorinative functionalization.

from 2-fluoroethanol under basic conditions,[42] and a defluorinated epoxide was reported as a side product in 10% yield from the reaction of benzophenone with a $LiCH_2F$.[41] To the best of our knowledge, there are no reports of similar reactions from polyfluorinated alcohols. These precedents provide support that an alternative route to α-fluoroepoxides can be developed by using α-fluoroalkyl alcohols, readily accessible precursors prepared via 1,2-addition reactions to a ketone substrate with nucleophilic fluoroalkyl reagents.

Results and Discussion

We previously showed that a Lewis acid/base pair approach can enable access to fluoroalkyl anion equivalents from the corresponding fluoroalkanes.[44–47] 1,2-addition reactions of a fluoroalkyl $B_3N_3Me_6$ adduct (**1-CF_2Ph**) with ketones afforded α-fluoroalkyl alcohols in moderate to high yields.[46] Although the 1,2-addition products of ketones are stable at room temperature indefinitely, we recently discovered that reactions to form these compounds undergo a subsequent reaction when heated to 90 °C in toluene (Figure 2a) to produce the ring-closed α-fluoroepoxide (**2a**). In this manuscript, we show the development of this observation into a synthetic method to prepare a variety of α-fluoroepoxides as well as subsequent transformations of these products.

To evaluate whether the formation of **2a** proceeds through the 1,2-addition product, H-**2a**′, as the intermediate, we monitored reactions between an authentic sample of H-**2a**′ and 1 equiv. ^{t}BuOK at 90 °C in toluene solvent (Figure 2b). Under these conditions, **2a** formed in low yield (6%), which contrasts with high yields observed for reactions between **1-CF_2Ph** and benzophenone above. We propose the yield discrepancy is due to the low solubility of K-**2a**′ (potassium alkoxide of H-**2a**′). When 18-crown-6 (a component of **1-CF_2Ph**) was introduced as an additive to increase the solubility of K-**2a**′, **2a** formed in 99% yield, as established by ^{19}F NMR spectroscopy. These results indicate an addition-cyclization sequence with ketone electrophiles initiated by **1-CF_2Ph**. To clarify the reaction pathway, we monitored the reaction progress using in situ ^{19}F NMR spectroscopy (Figure 2c). We observed that K-**2a**′ formed quantitatively within 6 minutes at 60 °C in THF. K-**2a**′ underwent clean first order decay ($k = 0.0189\ min^{-1}$) concomitant with first order growth of **2a** ($k = 0.0185\ min^{-1}$), *without* the formation of additional intermediates. The rate profiles are consistent with K-**2a**′ serving as the direct precursor to **2a**.

We evaluated the ketone scope for the formation of the α-fluoroepoxides. A variety of symmetric and asymmetric ketones smoothly underwent an addition-cyclization sequence with **1-**

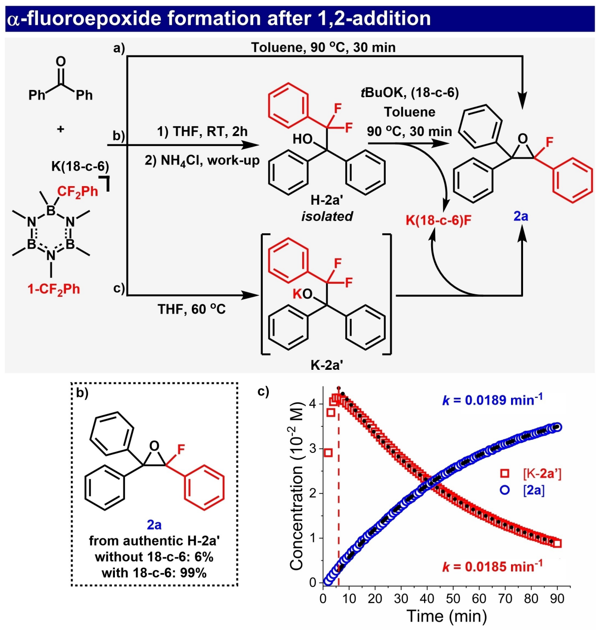


Figure 2. Reactions to probe the pathway to form α-fluoroepoxide **2a**. a) Standard conditions: 0.08 M in toluene, 90 °C, 30 min. b) Synthesis of **2a** from authentic H-**2a**′ and ^{t}BuOK. Yield of **2a** determined by ^{19}F NMR spectroscopy. c) Kinetic study of reaction progress to form **2a** at 60 °C in THF using in situ ^{19}F NMR spectroscopy. Raw data plotted with red squares (**K-2a**′) and blue circles (**2a**) with fits shown as black dashes and dots.

CF_2Ph to access the α-fluoroepoxides without additional reagents (Figure 3a). The corresponding α-fluoroepoxides were produced in >80% chemical yields (assessed by ^{19}F NMR) when

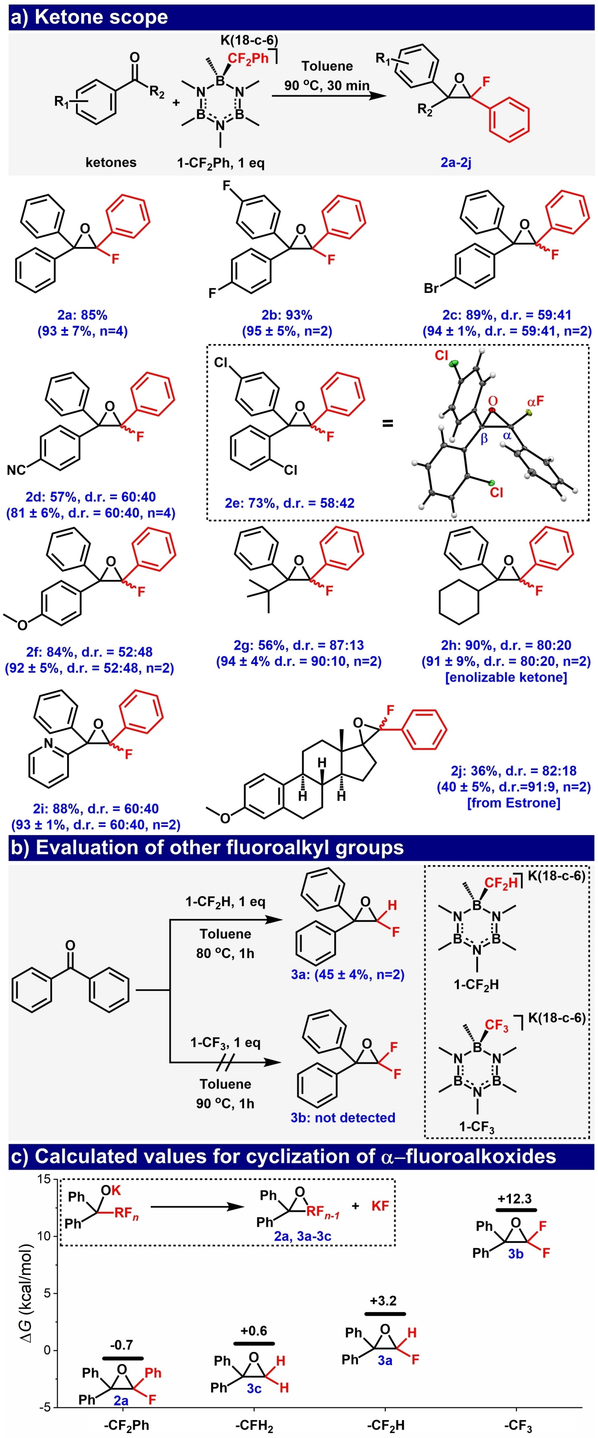


Figure 3. a) Synthesis of α-fluoroepoxides from ketones and **1-CF_2Ph** with ORTEP of **2e** (50% probability ellipsoids). b) evaluation using **1-CF_2H** and **1-CF_3**. Isolated yields (0.4 mmol scale, top row) and ^{19}F NMR yields (bottom row, shown as average with standard deviations from *n* individual experiments) of afforded fluoroepoxides. d.r. was determined by ^{19}F NMR spectroscopy (except **2e**, ^1H NMR spectroscopy). Purity of isolated compounds reported in Table S19. c) Calculated values for cyclization (M062X/6-311++g(d,p)).

R_2 = arenes (**2a**–**2f**) or bulky alkyls (**2g** and **2h**). A single crystal X-ray diffraction study (Figure 3a) confirmed the identity of **2e**: $\angle_{COC}$ = 62.1°, C_α-F_α = 1.369 Å, C_α-O = 1.386 Å C_β-O = 1.480 Å, C_α-C_β = 1.481 Å. The triangular ring of **2e** shares similar metrical parameters with a reported α-fluoroepoxide.[25] The method tolerates sterically-congested enolizable ketones, as shown by the formation of **2h** (90% isolated). However, we found that less sterically encumbered enolizable ketones such as acetophenone, propiophenone and isobutyrophenone proceeded in lower yields (5%, 19%, 39%, respectively, with formation of $PhCF_2H$ and the 1,2-addition byproducts. See Figures S83-86 and Table S2 for details). Electronic effects at the *para*-site of R_2 did not affect yields significantly. We found that *para*-substituted arenes with both electron-withdrawing groups (**2b**, **2c**, and **2d**) and electron-donating groups (**2f**) all afforded >80% chemical yields with a moderate d.r. (≈60:40). A heterocycle, pyridine, was also tolerated (**2i**). Finally, this method was applied to the epoxidation of a steroid derivative (estrone), giving **2j** in 36% isolated yield.[48]

The viability of the addition-cyclization sequence with ketones and other fluoroalkyl-$B_3N_3Me_6$ adducts (**1-CF_2H** and **1-CF_3**) was assessed to evaluate the generality of the method to prepare other α-fluoroepoxides (Figure 3b). With conditions analogous to that used to prepare **2a**, α-fluoroepoxide **3a** formed from benzophenone when using **1-CF_2H** (See Figures S107–112, Tables S5-9 for optimization and discussion). In contrast, only the 1,2-addition product formed and *not* the α-fluoroepoxide **3b** when using **1-CF_3**.[49] For all of the fluoroalkyl reagents examined, the 1,2-addition reactions with benzophenone were fast and high yielding. Thus, we propose that the more challenging step is ring-closure from the α-fluoroalkyl alkoxides. Density functional theory (DFT) studies were used to clarify the thermodynamic differences when forming the epoxides [M062X/6-311++g(d,p)].[50] We found that the formation of α-fluoroepoxides from the corresponding α-fluoroalkyl potassium alkoxides (addition products) follows the trend: (from most to least favored): α-CF_2Ph ≈ α-CFH_2 > α-CF_2H ≫ α-CF_3. Within this span, the ΔG for ring-closure between the α-CF_2Ph-alkoxide (**K-2a′**) and α-CFH_2-alkoxide or α-CF_2H-alkoxide are within 2 kcal/mol and 4 kcal/mol, respectively. In contrast, epoxide formation from α-CF_3-alkoxide is 13 kcal/mol higher in ΔG than from the analogous **K-2a′**. The latter result contrasts with Darzens-type reactions that are commonly used for the formation of epoxides from α-halo (Br or Cl) carbonyl compounds: these require electron withdrawing groups adjacent to the halide leaving group. These computational results provide support for the experimental result that **K-2a′**, α-CFH_2-alkoxide[24] and α-CF_2H-alkoxide undergo ring-closure, while α-CF_3-alkoxide does not. Overall, the experimental and theoretical results suggest the viability of the addition-cyclization epoxidation from α-fluoroalkyl alcohols with less than three fluorine atoms, and are consistent with an electronic, rather than steric effect.

The compatibility of the addition-cyclization reaction sequence with electron-deficient ketones suggested that α-fluoroalkyl ketones could be used to construct polyfluoroepoxides. We evaluated both aroyl chlorides and esters as electrophiles that could be used in a three-step reaction with 2 equivalents **1-CF$_2$Ph**. In this sequence of reactions, the initially formed α-fluoroalkyl ketones undergo subsequent addition-cyclization to form polyfluoroepoxides. Although such molecules are versatile building blocks for the synthesis of potentially bioactive molecules, the development of a straightforward and general synthesis toward polyfluoroepoxides with benzylic fluorides remains a challenge.

As a direct route to polyfluoroepoxides with benzylic fluorides, we evaluated reactions between benzoyl chloride/phenyl benzoate and **1-CF$_2$Ph**. After introducing 1 equiv. of **1-CF$_2$Ph** to benzoyl chloride or phenyl benzoate, the α,α-difluorinated ketone (**4a'**) formed in 95% and 85% yield, respectively. When 2 equiv. of **1-CF$_2$Ph** was added to benzoyl chloride or phenyl benzoate, the polyfluoroalkoxide (**4a''**) formed in 95% and 81% yield, respectively. After heating the **4a''** toluene solution (from phenyl benzoate) at 90°C for 12 h, polyfluoroepoxide **4a** was afforded in 93% yield, and scale up enabled isolation (d.r. = 88:12; see Figure S117 for discussion of absolute configurations). Each of the diastereomers exhibited distinct sets of resonances in the ^{19}F NMR spectra, and a single crystal X-ray diffraction study (Figure 4b) confirmed the identity of **4a**: $\angle_{COC} = 61.9°$, C_α-F_α = 1.369 Å, C_α-O = 1.402 Å C_β-O = 1.463 Å, C_α-C_β = 1.475 Å.

The reaction tolerated a variety of substitution patterns on the aryl rings. Interestingly, benzoyl chlorides containing either electron-rich substrates (**4c**: 62% and **4d**: 90%), or electron-deficient substrates (**4b**: 59% and **4e**: 71%) provided higher yields than from an electron-neutral precursor (**4a**: 53%). These results potentially implicate competing electronic effects needed to facilitate both the nucleophilic addition reaction and the subsequent ring closure. Finally, among all the tested benzoyl chlorides, the sterically hindered mesityl group provided the corresponding epoxide (**4c**) with the highest diastereoselectivity (d.r. = 94:6).

As an alternative entry point to benzoyl chlorides, aryl esters are versatile precursors that can be prepared from widely available benzoic acids. We found that aryl esters provided the same products (**4a**) with similar d.r. (≈88:12) but significantly higher yields (Figure 4b Table). For these substrates, conversions using electronically-distinct OAr groups (Ar=Ph, *p*-F–Ph, *p*-OMe–Ph), afforded **4a** in 84%, 84%, and 62% chemical yields, respectively. The polyfluoroepoxides exhibit high stability, and compounds **4a**–**4e** are stable as solids/oils for >12 months when stored in the air. Overall, this synthetic strategy represents a potentially convergent route to polyfluoroepoxides, structurally unique compounds that potentially can be ring opened and converted to fluorinated analogues of bioactive compounds, for example, protein tyrosine phosphatase 1B (PTP-1B) inhibitors.[51]

Next, we evaluated whether the mono- and polyfluoroepoxides could be further diversified via ring opening reactions (Figure 5). Prior work established that mono-fluorinated epoxides undergo Brønsted acid-catalyzed 1,2-fluorine migration[16] using *p*-toluene-sulfonic acid (*p*-TsOH). We found that, when treated with 2–5% *p*-TsOH, both symmetric and asymmetric α-fluoroepoxides (**2a** and **2c**) afforded the α-fluoroketones (**5a** and **5b**) after 3 h at room temperature in dichloromethane (DCM) or 1,2- dichloroethane (DCE). This reaction sequence tolerates *p*-Br aryl moieties (**5b**), demonstrating the potential for further diversification in cross-coupling reactions. 1,2-F migration of unstable fluoroepoxides **2f** and **3a** (derived from a different fluoroalkyl precursor, **1-CF$_2$H**) are promoted by silica and water, producing **5c** (82% isolated, from **2f**) and an α-fluoroaldehyde **5d** (42%, from **3a**) over 2 steps, respectively. Notably, the synthesis of **5d** was previously reported through acid-catalyzed ring opening of α-fluoroaziridine, which involved 3 steps[52] or fluorination of silyl enol ethers using extremely reactive F_2.[53] In contrast to Meinwald-type rearrangement of mono-fluoroepoxides, the polyfluoroepoxide **4a** was very stable

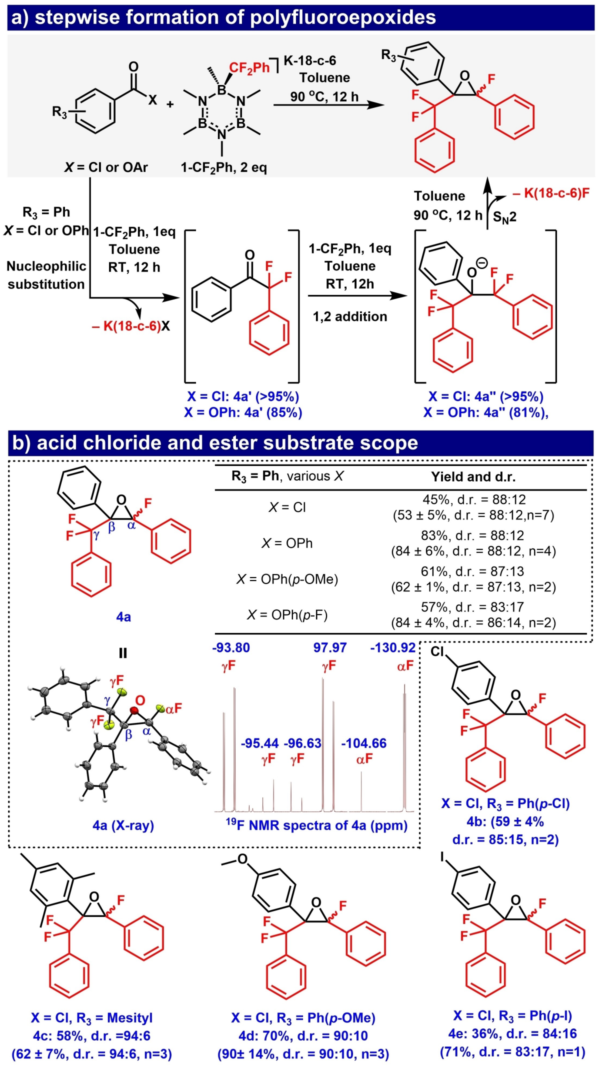
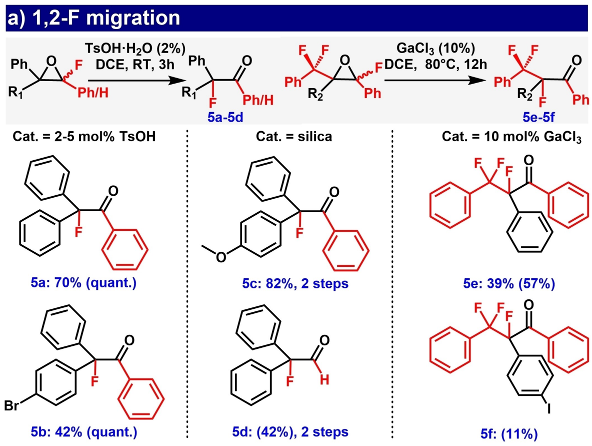


Figure 4. Synthesis of polyfluoroepoxides from **1-CF$_2$Ph** and acyl chlorides or esters. a) Reactions identifying the 2 key intermediates (**4a'** and **4a''**). b) Scope for the synthesis of polyfluoroepoxides from **1-CF$_2$Ph** and acyl chlorides or esters. ORTEP of **4a** shown with 50% probability. Isolated yields (0.4 mmol scale, top row) and ^{19}F NMR yields (bottom row, shown as average ± standard deviation from *n* individual experiments) of the products. d.r. determined by ^{19}F NMR spectroscopy. Purity of isolated compounds reported in Table S19. **4a**–**4d** prepared and isolated at 0.4 mmol scale and **4e** at 0.1 mmol scale.



Epoxide	Acid Catalyst (mol%)	Product	Yield (%)
2a	$TsOH\cdot H_2O$ (2%)	5a	99
4a	$TsOH\cdot H_2O$ (2%)	5e	0
4a	$FeCl_3$ (20%)	5e	37
4a	$GaCl_3$ (10%)	5e	57

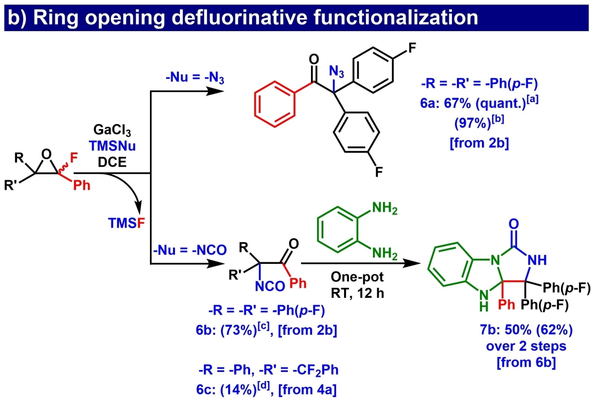


Figure 5. Conversion of selected synthesized fluoroepoxides (0.4 mmol scale for **5 c** and 0.1 mmol scale for all others) a) 1, 2-F migration, b) Nucleophilic substitution of fluoroepoxides and subsequent construction of heterocycles. [a]: RT, 5 mol% $GaCl_3$, 12 h, DCE.[b]: RT, 10 mol% $FeCl_3$, 12 h.[c]: 80 °C, 5 mol% $GaCl_3$, 12 h.[d]: 80 °C, 10 mol% $GaCl_3$, 12 h. Purity of isolated compounds reported in Table S19.

and did not react with *p*-TsOH (2-10 mol%) in DCE (0.01 M) even at 80 °C for 3 days (Table in Figure 5). Various Lewis acids were screened for ring-opening reactions (see Figure S169 and Table S14). We found that 10 mol% $GaCl_3$ was an effective catalyst for this transformation to access **5 e** (from **4 b**) and **5 f** (from **4 e**) in 57% (39% isolated) and 11% yield, respectively. **5 f** has an Ar–I moiety, providing a potential avenue to further elaboration via subsequent cross-coupling reactions.[54]

We next investigated whether the acid-catalyzed ring-opening could be coupled with a defluorinative functionalization reaction with trimethylsilyl (TMS) reagents (Figure 5b). Because azide[55–57] and isocyanate[58] groups are widely used in pharmaceutical development and evaluation of metabolic pathways, we targeted reactions using TMS-N_3 and TMS-NCO. These reactions required different conditions than the 1,2-F migrations noted above. For example, using 5 mol% *p*-TsOH in the presence of 1.5 equiv. TMS-N_3 mainly afforded the intramolecular 1,2-F migration products (**5 a**) from **2 a**, instead of the –N_3 substituted products. However, we found that 5 mol% $GaCl_3$ enabled tandem ring opening defluorinative functionalization reactions from a representative fluoroepoxide **2 b** (see Figures S197-202 and Tables S15–17 for screening and optimizations). The –N_3 and –NCO substituted products **6 a** and **6 b**, were formed in quantitative (67% isolated) and 73% yield, respectively. We note that similar yields were afforded using $FeCl_3$ (97% yield of **6 a**), albeit with higher loadings (10 mol%).

To highlight the utility of late-stage defluorinative functionalization with -NCO and -N_3 nucleophiles, we targeted the formation of medicinally-relevant heterocycles from the products. In addition to the well-known click reactions of organic azides to form triazoles, organic isocyanates also can be converted to benzimidazoles by reactions with 1,2-diaminobenzenes.[59] We evaluated the latter reaction by subjecting **6 b**, without purification, to *o*-phenylenediamine. Instead of forming a benzimidazoles, we identified the major product was the benzimidazole-fused heterocycle **7 b**. The structure was determined by LC-MS, IR, ^{19}F NMR, ^{13}C NMR, ^{1}H NMR, and 2D NMR spectroscopy (see spectra, analysis, and discussion in Figures S217–S225). The ring opening defluorinative functionalization reaction was less effective when using the polyfluoroepoxide as the substrate (see screening results in Figure S203 and Table S18), which afforded **6 c** in 14% yield and the major byproduct was identified to be the 1,2-F migration product **5 e** (39%). Overall, these transformations demonstrate the wide applications of fluoroepoxides in organic synthesis and their great potential in pharmaceutical discovery by providing access to unique chemical scaffolds.

Conclusion

We developed a synthetic approach to prepare α-fluoroepoxides that are largely inaccessible using prior methods. The α-fluoroepoxides were synthesized from $B_3N_3Me_6$ stabilized fluoroalkyl transfer agents and carbonyl electrophiles (ketones, acyl chlorides or esters), and their formation proceeds through an addition-cyclization pathway. The afforded α-fluoroepoxides were used for subsequent conversion into α-fluoroketones, α-fluoroaldehyde, and medicinally-relevant molecules, highlighting the potential value of fluoroepoxides as intermediates in organic synthesis. This work enables access to a variety of α-fluoroepoxides with F at benzylic sites, many of which may be amenable to structure/activity/relationship studies and/or drug discovery.[2,18]

Acknowledgements

This work was supported by the NSF (CHE 1955284), and the NSF (CHE-0840456) for X-ray instrumentation. We thank Dr. Fengrui Qu for assistance with X-ray crystallography. This research was supported in part through computational resources and services provided by Advanced Research Computing at the University of Michigan, Ann Arbor. Dr. John Kiernicki and Dr.

Michael Wade Wolfe are thanked for insightful discussions. Dr. James Shanahan is acknowledged for preliminary computational work

Conflict of Interest

The corresponding author holds a patent relating to compound 1.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: boron · epoxide · defluorinative functionalization · fluoroalkylation · main group

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[48] Other substrates including cyclopentanone, benzaldehyde, chalcone, N-methyl-isatin, and N-phenyl-isatin were also examined for epoxidation with our approach (see Figures S83–99 and Table S2–3 for details). However, the major products from these reactions were the 1,2-addition products. Low yield (6%) of the fluoroepoxide was identified from benzaldehyde.
[49] Fluoride abstracting agents were examined, although we did not find suitable conditions to form **3b**. See Figure S106 and Table S4 for details.
[50] Note that the lattice enthalpy of KF was not considered in these calculations. Although inclusion of the extended structure of KF would afford more accurate ΔG values, these calculations were performed to examine thermodynamic differences between the series of compounds. See Figure S3 and Table S1 for Details.
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[60] Deposition Numbers 2204633 (for **2e**), 2195232 (for **4a**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

Manuscript received: November 17, 2022
Accepted manuscript online: December 7, 2022
Version of record online: December 29, 2022