Chemical Science

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

View Article Online
View Journal

Open Access Article. Published on 17 March 2026. Downloaded on 4/30/2026 7:36:22 AM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

Check for updates

Cite this: DOI: 10.1039/d6sc01042c

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 5th February 2026
Accepted 14th March 2026

DOI: 10.1039/d6sc01042c

rsc.li/chemical-science

A Brønsted acid–base approach for the net monoselective C–F substitution of (trifluoromethyl)alkanes

Nicholas J. Coradi and Jeffrey S. Bandar *

We disclose a method for the net coupling of nucleophiles with a single fluorine of unactivated (trifluoromethyl)alkanes. The process occurs *via* an initial base-promoted dehydrofluorination/defluorinative nucleophilic addition cascade to generate vinylfluoride intermediates that undergo a rapid hydrofluorination second step to yield *gem*-difluorinated products. Thus, the aliphatic-CF_3 group of commercial building blocks and complex medicinal compounds can now be transformed into numerous classes of valuable α,α-difluoro(thio)ether substructures in an efficient and modular manner.

Introduction

Selective C–F functionalization of multifluorinated compounds is a powerful synthetic strategy for the preparation of precisely fluorinated products.[1] An especially useful application of this concept is the substitution of a single fluorine of trifluoromethyl ($-CF_3$) groups to access *gem*-difluorinated motifs (Fig. 1).[2,3] Such transformations not only require initial activation of a strong C–F bond but also must not functionalize the relatively weaker C–F bonds of the *gem*-difluorinated products.[4]

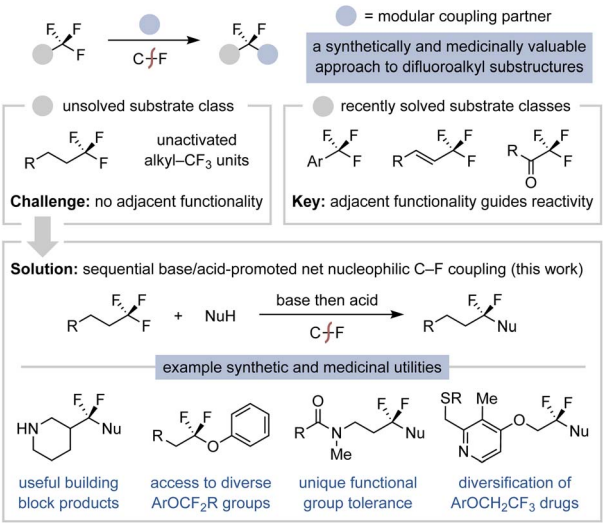

Fig. 1 Motivation for a C–F substitution method of (trifluoromethyl) alkanes. NuH = pronucleophile.

These challenges typically preclude monoselective $-CF_3$ functionalization *via* C–F insertion or fluoride abstraction mechanistic strategies.[5–7] Nonetheless, substantial recent effort has led to general solutions for monoselective functionalization of π-system-adjacent $-CF_3$ groups, where the appended functionality can be reduced or substituted (*e.g.*, S_N2') to initiate selective C–F removal (Fig. 1).[2,8–10] The Young group has also established a frustrated Lewis pair approach to selectively activate aryl- and heteroatom-adjacent trifluoromethyl groups.[11] However, there remains no method for the monoselective C–F coupling of simple (trifluoromethyl)alkanes, which is likely a consequence of the increased C–F bond strengths combined with the absence of adjacent functionality.[12] We herein describe a simple protocol for the net C–F substitution of (trifluoromethyl)alkanes that extends the synthetic advantages of defluorofunctionalization methodology to this important substrate class.

A method to substitute a single fluorine on an alkyl–CF_3 group would introduce a variety of useful synthetic capabilities. First, numerous building-block (trifluoromethyl)alkanes are commercially available and could be used as attractive precursors to difluorinated compounds.[13,14] This would offer a more modular and streamlined approach to *gem*-difluorinated substructures over existing multistep sequences that typically rely on difficult deoxyfluorination procedures.[3,15] Second, because $-CF_3$ groups are inert to most chemical reagents, they could be carried through multistep syntheses and later transformed into *gem*-difluorinated derivatives.[16] Third, (trifluoromethyl)alkyl substructures are frequently featured in complex compounds used in medicinal, materials, and agrochemical research due to the beneficial properties of multifluorinated alkyl groups.[17] Diversification of the $-CF_3$ group in these contexts would enable the rapid study of *gem*-difluoroalkyl analogs for potentially improved function. Thus, we were

Department of Chemistry, Colorado State University, Fort Collins, Colorado, 80523, USA. E-mail: jeff.bandar@colostate.edu

Open Access Article. Published on 17 March 2026. Downloaded on 4/30/2026 7:36:22 AM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

motivated to develop a C–F functionalization protocol to realize these myriad opportunities.

We reasoned the electron-withdrawing nature of a $-CF_3$ group could be leveraged for the reactivity of an adjacent α-C–H bond such that C–F substitution could be achieved *via* a base-promoted dehydrofluorination/nucleophilic hydro-functionalization cascade (Fig. 2a).[12] The initial elimination step is inspired by two reports of unactivated (trifluoromethyl)alkane dehydrofluorination, as initially documented in 2004 *via* a KO-*t*-Bu-promoted elimination of 6,6,6-trifluorohexanoic acid to the corresponding *gem*-difluoroalkene.[18] Next, the electrophilicity of unactivated *gem*-difluoroalkenes (*e.g.*, not Michael acceptor or styrene derivatives) is evidenced by prior studies on intermolecular alkyllithium and intramolecular alkoxide addition–elimination reactions that generate vinyl fluoride products.[19,20] These literature precedents, while limited, suggested an opportunity for C–F substitution directly from unactivated (trifluoromethyl) alkanes.[12,21] This reactivity could thus enable the use of alkyl–CF_3 groups as synthons and would also complement radical-based thiol and phenol addition methods of independently prepared *gem*-difluoroalkenes.[20a,22]

Our initial efforts to promote tandem dehydrofluorination and fluorine-retentive nucleophilic addition (using alcohols, thiols, and amines) led to over-reactivity, yielding α-substituted vinyl fluorides exclusively (Fig. 2a).[23,24] Nonetheless, we were encouraged by the fact that dehydrofluorination and intermolecular addition of common nucleophiles to an unactivated (trifluoromethyl)alkane occurs readily. We then realized that development of a regioselective hydrofluorination protocol for α-substituted fluoroalkenes could afford the desired α,α-difluorosubstituted target.[25] We thus revised our approach toward C–F substitution to a simple two-step substitution/hydrofluorination sequence.

We selected alcohols as coupling partners to develop this C–F substitution method due to the value of α,α-difluoroethers and the current limitations associated with their preparation (Fig. 2b).[26] These substructures are prominently featured in molecules used for medicinal, veterinary, agrochemical, battery, and electronic materials applications.[27] For example, the strong stereoelectronic conformational effects of α,α-difluoroethers regulate optical and physical properties that are critical for liquid crystal display (LCD) technology.[28] Difluoromethylene units are also commonly incorporated in bioactive compounds to increase lipophilicity and oxidative/metabolic stability, as well as to electronically modulate the properties of nearby functional groups.[17,29] The most practiced route to α,α-difluoroethers is a three-step acid coupling/thionation/fluorination sequence, a process that is difficult to scale and can be incompatible with medicinally relevant functional groups.[30] Alternative recent approaches, such as the use of AgF for the fluorination of thionoesters or the hydro-functionalization of *gem*-difluoroalkenes, can display a broader functional group tolerance.[15b,22] Selective alcohol coupling with (trifluoromethyl)alkanes could address important remaining limitations and unlock the unique capabilities of $-CF_3$ defluorofunctionalization methodology. Furthermore, successful implementation of this strategy could be the foundation for a generalized alkyl–CF_3 C–F substitution platform.

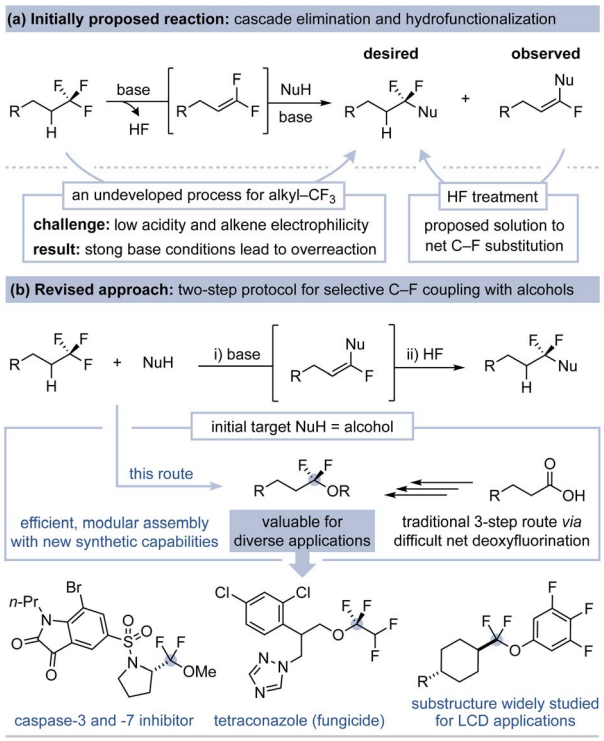

Fig. 2 (a) Initially proposed and (b) revised method design for a net C–F coupling reaction of (trifluoromethyl)alkanes and alcohols.

Results and discussion

We began this method development by studying the base-promoted cascade reaction between (trifluoromethyl)alkane **1** and 2-ethylhexan-1-ol (**2**) to form fluorovinyl ether **3** (Fig. 3a). First, we found that use of 3 eq. of KO-*t*-Bu or bis(trimethylsilyl) amide (K/NaHMDS) bases in DMF promote high-yielding product formation at room temperature (rt).[31] Weaker bases (*e.g.*, KOMe) and those with lithium countercations (*e.g.*, LiHMDS) do not promote the initial dehydrofluorination step. With KHMDS as a representative base, the yield of fluorovinyl ether **3** decreases in less polar solvents or when less base or alcohol is used. While the initial experiments were conducted with solid KHMDS base, the use of inexpensive and convenient KHMDS solution (in THF) also promotes the reaction in high yield, including when conducted under ambient atmosphere.

The potential for regioselective hydrofluorination of fluorovinyl ether **3** was assessed using crude material obtained from the reaction shown in Fig. 3a. Of the common commercial HF sources, Olah's reagent (Pyr·HF) and DMPU·HF promote hydrofluorination to form α,α-difluoroether **4** (75% and 95% yield, respectively), while less reactive HF reagents (*e.g.*, NEt_3·3HF and HBF_4) are ineffective (Fig. 3b).[32] Despite their good yields, we were concerned about the practicality of this protocol given that Olah's reagent and DMPU·HF readily etch glass and evolve HF fumes.[33] We therefore sought to find conditions that employ NEt_3·3HF, which is more easily handled and measured

 © 2026 The Author(s). Published by the Royal Society of Chemistry

Open Access Article. Published on 17 March 2026. Downloaded on 4/30/2026 7:36:22 AM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

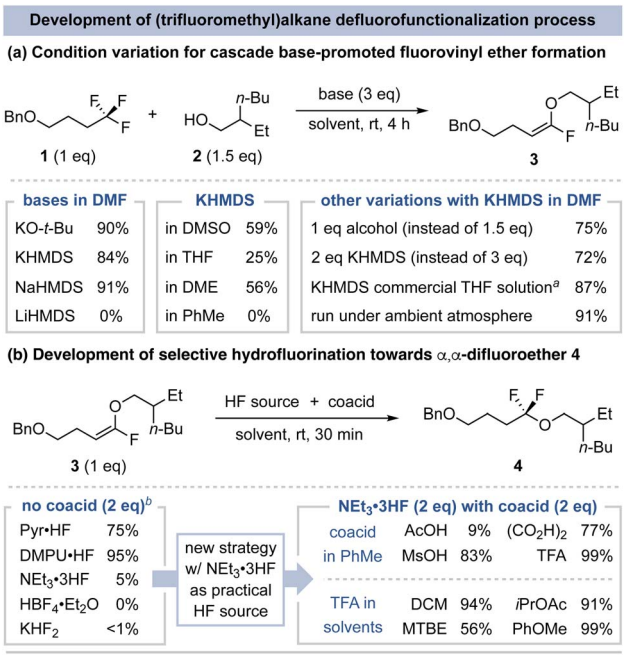

Fig. 3 Investigations of the two key steps to achieve net C–F substitution. Yields determined by ^{19}F NMR spectroscopy. [a]Other entries use solid base reagents. [b]PhMe as solvent.

as it does not etch glass or generate substantial HF vapors at rt.[34] We reasoned the poor hydrofluorination reactivity of $NEt_3 \cdot 3HF$ is due to its lower acidity and the corresponding difficulty of vinyl ether protonation. Paquin addressed a similar challenge for terminal alkene hydrofluorination *via* use of methanesulfonic acid (MsOH) as a coacid in conjunction with $NEt_3 \cdot 3HF$.[35] In the case of fluorovinyl ether **3**, use of MsOH (pK_a = 1.6 in DMSO)[36] with $NEt_3 \cdot 3HF$ increases the hydrofluorination yield to 83%, but with substantial side-product formation. We speculated that a less acidic coacid could prevent undesired reactivity and found that trifluoroacetic acid (TFA, pK_a = 3.5 in DMSO)[36] with $NEt_3 \cdot 3HF$ affords 99% yield of **4** in PhMe. Beyond practical advantages, the dual acid approach is useful as it allows the coacid strength to be adjusted to improve hydrofluorination when other pronucleophile classes are used (*vide infra*).

We next implemented the conditions identified in Fig. 3 for a simplified C–F substitution protocol with a substrate scope shown in Chart 1. During the optimization studies, we observed that addition of base to (trifluoromethyl)alkanes and alcohols in DMF is exothermic.[37] To address this, preparative scale reactions were cooled to 0 °C prior to base addition and then warmed and monitored (by TLC) until full conversion was reached. This protocol employs a solvent switch between the two steps, although we note that the entire procedure is often complete in 6 h and can be conducted in a one-pot manner.[38] Although KO-*t*-Bu and KHMDS bases can both promote the initial step (Fig. 3a), we found that KHMDS generally promotes full conversion of primary (trifluoromethyl)alkanes (Condition A) while KO-*t*-Bu is more effective for secondary substrates (Condition B).[39] We found the α,α-difluoroether products to be readily isolable and stable during storage, although we note previous studies have described variants that are prone towards hydrolysis.[15b]

Chart 1a shows example alcohols that undergo C–F coupling with model (trifluoromethyl)alkane **1**. Primary and secondary alcohols (**5–10**) provide α,α-difluoroethers in good yield, including those with oxetane (**6**) and azetidine (**14**) heterocycles that are prone to ring-opening under acidic conditions.[40] Perphenazine (**16**) and other hydroxyl-bearing drug fragments (**12**, **15**) also couple in moderate to good yield. In addition to tertiary-amine-bearing alcohols (**14**, **15**), unprotected primary amines (**13**) are tolerated with exclusive O-coupling selectivity. Chemoselectivity for $-CF_3$ defluorofunctionalization is observed in the presence of a secondary alkyl fluoride (**12**). Under the standard conditions, tertiary alcohols can form vinyl ether intermediates although the hydrofluorination step is low yielding.

Chart 1b demonstrates this protocol on commercially available (trifluoromethyl)alkane building blocks and their derivatives using 2-ethylhexan-1-ol (**2**) as the nucleophile. Substrates bearing diversifiable functionality such as aryl halides (**19**, **23**), secondary amines (**23**), ketals (**20**), or alkenes (**27**) are well tolerated. The ability to activate secondary $-CF_3$ groups allows for the functionalization of medicinally-relevant trifluoromethylated cyclohexanes (**20**, **21**) and piperidines (**22**). This protocol also tolerates amide groups (**24**, **25**) that would react under traditional deoxyfluorination sequences.[15] (Trifluoromethyl)alkyl-appended drugs, such as fluoxetine (**26**) and quinine (**27**) derivatives, provide moderate C–F substitution yields. Moreover, fluoxetine derivative **26** demonstrates this protocol's chemoselectivity for alkyl–CF_3 functionalization in contrast to many recently developed methods for Ar–CF_3 activation.[8]

Chart 1a and b collectively demonstrate that this method tolerates diverse functionality despite the use of relatively strong bases and acids. This led us to further investigate the compatibility of groups that are known to be acid-sensitive, as shown in Chart 1c. The acidic hydrofluorination step is chemoselective for the fluorovinyl ether intermediate over other olefins (**27**, **29**). Despite the use of excess TFA, ketals (**20**, **30**) and Boc-protected amines (**31**, **32**) remain intact.[41] We also note that an S_NAr-prone 2-substituted quinoline (**28**) gives good C–F coupling yield with only a minor amount of S_NAr observed during fluorovinyl ether formation, indicating tolerance for certain base-sensitive groups.[42]

We next sought to engage phenols in this coupling reaction given that the α,α-difluoroalkyl aryl ether linkage is valued in LCD technology and represents an alkylated derivative of medicinally-relevant Ar–OCF_3/CF_2H substituents.[26] The addition of 18-crown-6 to Condition A enables high-yielding aryl fluorovinyl ether formation, while the use of the stronger acid MsOH over TFA is needed to promote subsequent hydrofluorination.[43] Fig. 4a shows examples of C–F substitution on a carbazole-based (trifluoromethyl)alkane with electron-rich phenols (**33**, **34**), the vitamin E compound α-tocopherol (**35**), and the secondary-amide-bearing drug paracetamol (**36**). This procedure is also applicable to β-aryl (**37**) and free amine-

Open Access Article. Published on 17 March 2026. Downloaded on 4/30/2026 7:36:22 AM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

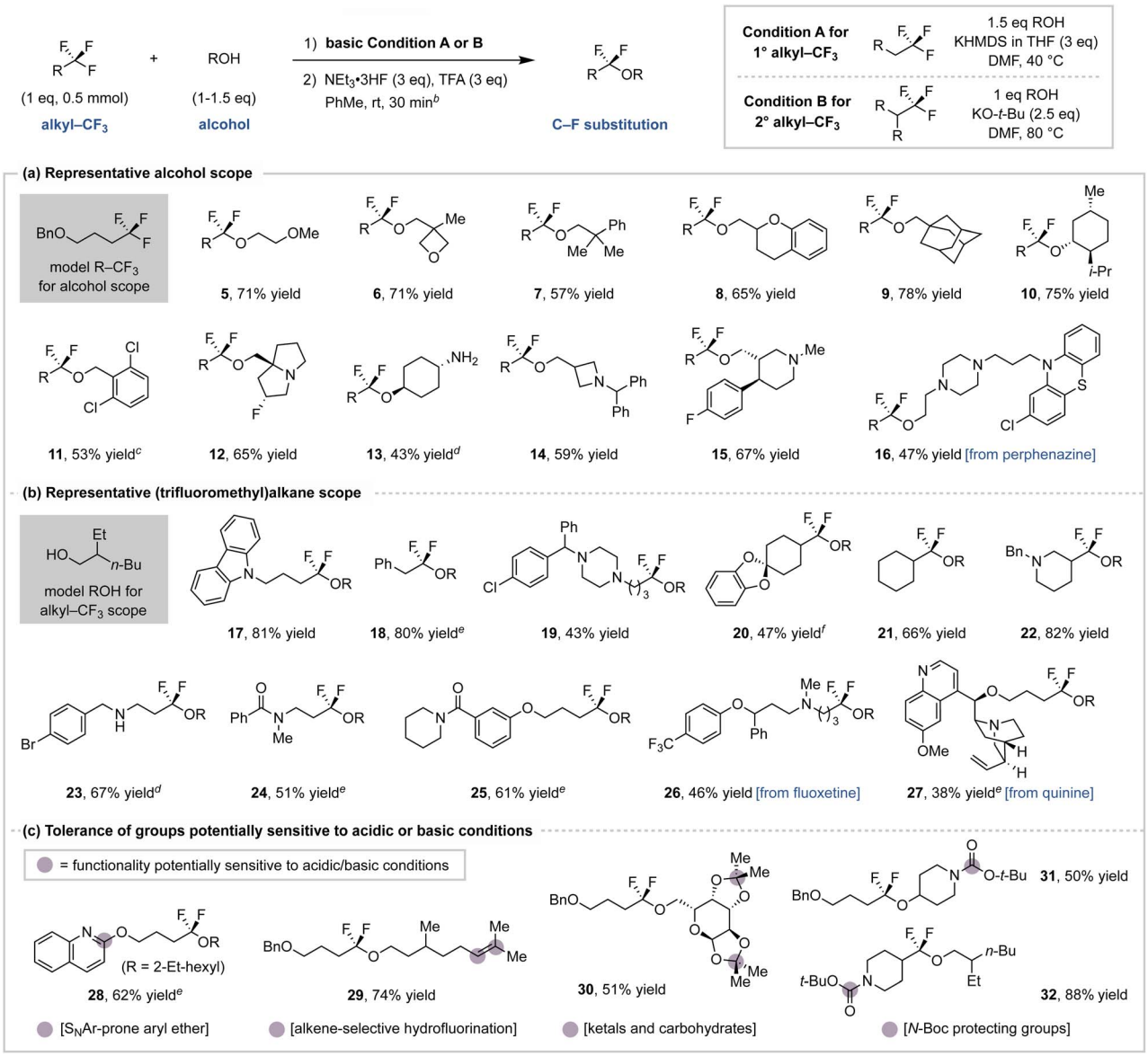

Chart 1 Substrate scope for (trifluoromethyl)alkane C–F substitution with alcohols.[a] [a]Isolated yields of 0.5 mmol scale reactions; the reaction progress for step 1 was monitored by TLC with times varying from 1–24 h. The use of racemic alcohol **2** results in a 1 : 1 dr for products that have multiple stereocenters (*e.g.*, **19**, **22**, **26** and **27**). [b]An additional 2 eq. of each acid used if an amine is present in the compound. [c]1 eq. of alcohol and 2.5 eq. of base used. [d]KO-*t*-Bu used as base with DMA as solvent. [e]NaHMDS used as base. [f]4 eq. of base used at 50 °C.

containing (**38**) (trifluoromethyl)alkanes. The generality of this C–F substitution protocol was further evaluated with thiol coupling partners. The use of the phenol coupling basic conditions enables formation of fluorovinyl alkylthioethers in good yields. However, due to the lower basicity of vinyl thioethers over vinyl ethers, we found that hydrofluorination requires the use of pyr·HF with CuCl as a Lewis acid additive.[44] Fig. 4b illustrates alkylthiol C–F coupling products that form in moderate to good yields (**39–41**). Collectively, the pronucleophile expansion in Fig. 4 provides an alkyl–CF_3 coupling route that complements radical-based hydrothiolation and -phenolation reactions of *gem*-difluoroalkenes.[45] The reactions shown in Fig. 4 are low yielding for electron-deficient phenols and thiophenols. We also note that arylamines and diarylphosphines undergo the first step of this method but do not undergo successful hydrofluorination under the optimized conditions; this information is described in the SI.

This C–F coupling method could be particularly useful when applied to the derivatization of aryl trifluoroethoxy substituents ($ArOCH_2CF_3$) that are commonly incorporated in medicinal compounds (Fig. 5).[46] Access to difluorinated derivatives ($ArOCH_2CF_2$–R) can be prohibitively difficult as this often requires the independent synthesis of each difluoroalkyl coupling partner (*e.g.*, $HOCH_2CF_2$–R) and its successful attachment to the arene.[47] In this regard, direct $ArOCH_2CF_3$ C–F diversification could substantially streamline difluoroalkyl analog study. Such a C–F substitution method must overcome several potential competing side reactions that are unique

 © 2026 The Author(s). Published by the Royal Society of Chemistry

Open Access Article. Published on 17 March 2026. Downloaded on 4/30/2026 7:36:22 AM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

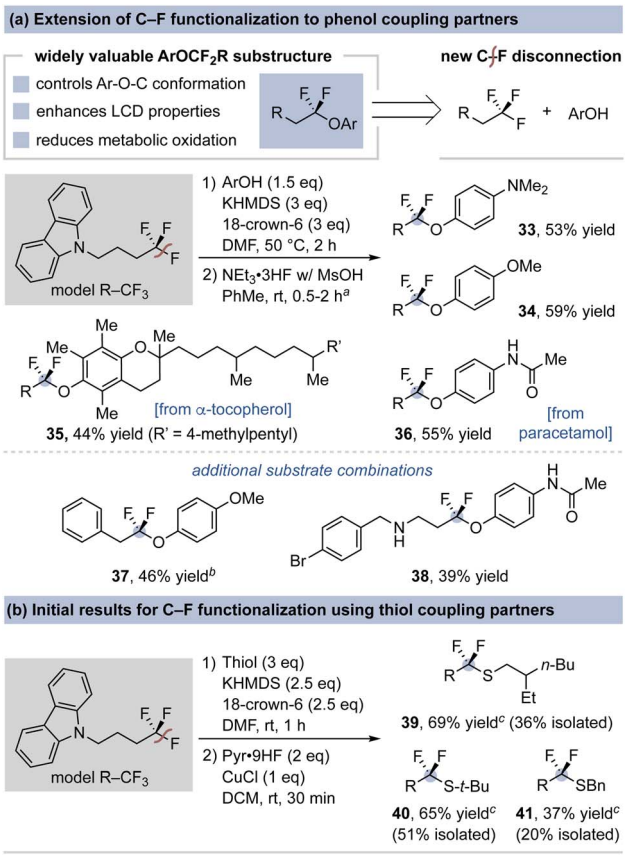

Fig. 4 Value and demonstration of the use of phenols and thiols for (trifluoromethyl)alkane C–F coupling. Isolated yields reported. [a]Excess (~8 eq.) acid used. [b]Used hydrofluorination conditions shown in Fig. 4b. [c]Yield determined in crude reaction material by ^{19}F NMR spectroscopy.

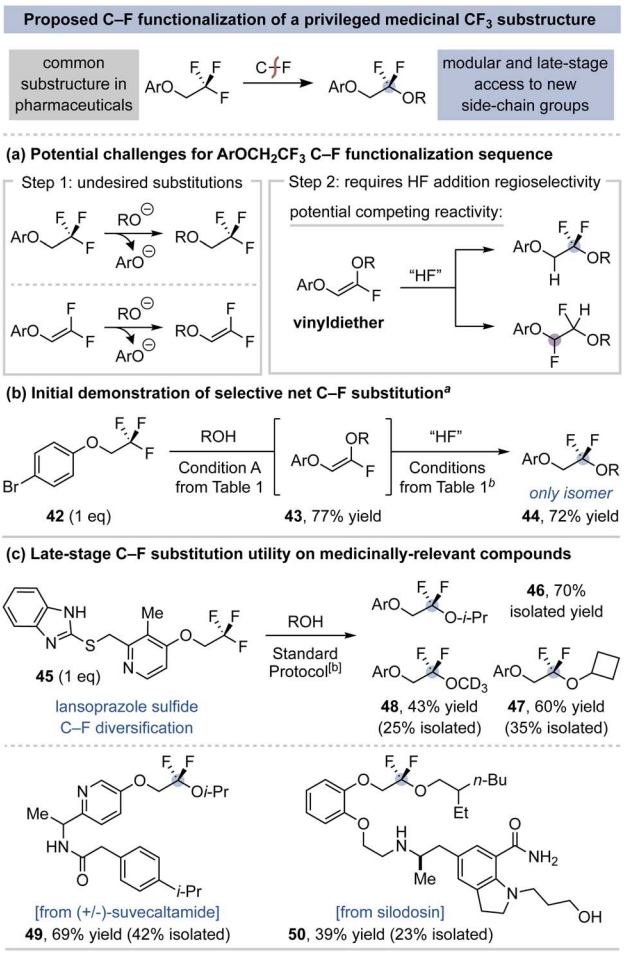

Fig. 5 Utility, challenges, and demonstrations of C–F coupling of (2,2,2-trifluoroethoxy)aryl substructures. [a]ROH = 2-ethylhexan-1-ol; yields determined by ^{19}F NMR spectroscopy. [b]MsOH used instead of TFA in step 2.

compared to the (trifluoromethyl)alkanes in Chart 1. This includes the potential for nucleophilic substitution of the aryloxy group over fluoride elimination, as well as the requirement of regioselective hydrofluorination of the 1,2-vinyldiether intermediate (Fig. 5a).[48]

Despite these potential challenges, we found that subjection of 1-bromo-4-(2,2,2-trifluoroethoxy)benzene (**42**) to Condition A affords the desired vinyldiether **43** in 77% yield (Fig. 5b). Hydrofluorination of **43** with TFA as the co-acid gives poor yield of **44** (25%), while use of MsOH provides **44** in 72% yield as a single regioisomer. The regioselective hydrofluorination of the 1,2-vinyldiether intermediate **43** is likely due to the initial protonation being guided by the greater donating ability of the alkylether substituent. This protocol was then implemented on complex pharmaceuticals and drug-like compounds (Fig. 5c).[49] A small library of lansoprazole sulfide difluoroalkyl analogs is shown through the coupling of *i*-PrOH (**46**), cyclobutanol (**47**), and methanol-d_3 (**48**). C–F substitution of (±)-suvecaltamide with *i*-PrOH (**49**) is notable as such products would be inaccessible through late stage deoxyfluorination given the incompatibility of the amide group.[15] Likewise, silodosin, which contains unprotected alcohol, amine, and amide groups, undergoes selective C–F coupling (**50**) to illustrate this method's broad potential for late-stage diversification.

Conclusions

In summary, (trifluoromethyl)alkanes are sufficiently reactive under basic conditions to generate functionalized fluorovinyl (thio)ether intermediates that undergo hydrofluorination to achieve net C–F substitution. This allows common (trifluoromethyl)alkane building blocks to serve as ideal retrons to functionalized *gem*-difluorinated units and provides new –CF_3 diversification opportunities for complex molecules. More broadly, we anticipate the versatility of the fluoroalkene intermediates will provide additional opportunities for selective C–F functionalization sequences of (trifluoromethyl) alkanes.

Author contributions

Both authors contributed to the conceptualization, analysis and writing of this project. N. J. C. was responsible for the methodology and J. S. B. was responsible for project administration and supervision.

Open Access Article. Published on 17 March 2026. Downloaded on 4/30/2026 7:36:22 AM. This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: all experimental procedures and characterization data (*e.g.*, NMR spectra, IR data, mass spectrometry data, and melting point analysis) for new compounds. See DOI: https://doi.org/10.1039/d6sc01042c.

Acknowledgements

This material is based upon work supported by the National Science Foundation under Grant No. CHE-1944478. We also thank Colorado State University (CSU) for funding and the Analytical Resources Core (RRID: SCR_021758) at CSU for instrument access, training and assistance with sample analysis.

Notes and references

1 For general reviews on C–F bond functionalization, see: (*a*) L. V. Hooker and J. S. Bandar, *Angew. Chem., Int. Ed.*, 2023, **62**, e202308880; (*b*) H. Amii and K. Uneyama, *Chem. Rev.*, 2009, **109**, 2119–2183; (*c*) T. Ahrens, J. Kohlmann, M. Ahrens and T. Braun, *Chem. Rev.*, 2015, **115**, 931–972; (*d*) Q. Shen, Y.-G. Huang, C. Liu, J.-C. Xiao, Q.-Y. Chen and Y. Guo, *J. Fluorine Chem.*, 2015, **179**, 14–22; (*e*) J.-D. Hamel and J.-F. Paquin, *Chem. Commun.*, 2018, **54**, 10224–10239; (*f*) S. Li and W. Shu, *Chem. Commun.*, 2022, **58**, 1066–1077; (*g*) T. Fujita, K. Fuchibe and J. Ichikawa, *Angew. Chem., Int. Ed.*, 2019, **58**, 390–402.

2 For reviews on selective trifluoromethyl defluorofunctionalization, see: (*a*) F. Jaroschik, *Chem.–Eur. J.*, 2018, **24**, 14572–14582; (*b*) F. Zhao, W. Zhou and Z. Zuo, *Adv. Synth. Catal.*, 2022, **364**, 234–267; (*c*) G. Yan, K. Qiu and M. Guo, *Org. Chem. Front.*, 2021, **8**, 3915–3942.

3 For reviews on synthetic routes to *gem*-difluorinated substructures, see: (*a*) D. R. Carvalho and A. H. Christian, *Org. Biomol. Chem.*, 2021, **19**, 947–964; (*b*) M.-C. Belhomme, T. Besset, T. Poisson and X. Pannecoucke, *Chem.–Eur. J.*, 2015, **21**, 12836–12865; (*c*) A. Lemos, C. Lemaire and A. Luxen, *Adv. Synth. Catal.*, 2019, **361**, 1500–1537; (*d*) D.-Q. Dong, H. Yang, J.-L. Shi, W.-J. Si, Z.-L. Wang and X.-M. Xu, *Org. Chem. Front.*, 2020, **7**, 2538–2575; (*e*) Z.-Y. Wang, Z. Zhang, W. Chen, Y. Liu, A. Sun and R. Xia, *Org. Biomol. Chem.*, 2025, **23**, 7383–7400; (*f*) Z. Feng, Y.-L. Xiao and X. Zhang, *Acc. Chem. Res.*, 2018, **51**, 2264–2278.

4 For discussions of C–F bond strengths, see: (*a*) D. O'Hagan, *Chem. Soc. Rev.*, 2008, **37**, 308–319; (*b*) D. M. Lemal, *J. Org. Chem.*, 2004, **69**, 1–11; (*c*) K. B. Wiberg and P. R. Rablen, *J. Am. Chem. Soc.*, 1993, **115**, 614–625.

5 For discussions of the challenge of direct C–F bond activation processes, see ref. 1c and: (*a*) J. L. Kiplinger, T. G. Richmond and C. E. Osterberg, *Chem. Rev.*, 1994, **94**, 373–431; (*b*) O. Eisenstein, J. Milani and R. N. Perutz, *Chem. Rev.*, 2017, **117**, 8710–8753.

6 For reviews of acid-promoted C–F activation and examples of over functionalization, see: (*a*) T. Stahl, H. F. T. Klare and M. Oestreich, *ACS Catal.*, 2013, **3**, 1578–1587; (*b*) J. Zhu, M. Pérez, C. B. Caputo and D. W. Stephan, *Angew. Chem., Int. Ed.*, 2016, **55**, 1417–1421; (*c*) W. Gu, M. R. Haneline, C. Douvris and O. V. Ozerov, *J. Am. Chem. Soc.*, 2009, **131**, 11203–11212.

7 A recent method for $ArCF_3$ C–F coupling operates *via* a rare example of fluorine atom abstraction; see: J. Koo, W. Kim, B. H. Jhun, S. Park, D. Song, Y. You and H. G. Lee, *J. Am. Chem. Soc.*, 2024, **146**, 22874–22880.

8 For selected examples of $ArCF_3$ C–F coupling reactions, see: (*a*) D. B. Vogt, C. P. Seath, H. Wang and N. T. Jui, *J. Am. Chem. Soc.*, 2019, **141**, 13203–13211; (*b*) S. E. Wright and J. S. Bandar, *J. Am. Chem. Soc.*, 2022, **144**, 13032–13038; (*c*) Y.-C. Luo, F.-F. Tong, Y. Zhang, C.-Y. He and X. Zhang, *J. Am. Chem. Soc.*, 2021, **143**, 13971–13979; (*d*) J. Xu, J.-W. Liu, R. Wang, J. Yang, K.-K. Zhao and H.-J. Xu, *ACS Catal.*, 2023, **13**, 7339–7346.

9 For examples of vinyl–CF_3 functionalization, see: (*a*) F. Liu, Q. Wu, X. Wang, Q. Dong and K. Sun, *Org. Chem. Front.*, 2025, **12**, 3725–3737; (*b*) Q. Tian, B. Pei, C. Wang, C. Zhang and Y. Li, *J. Org. Chem.*, 2022, **87**, 10908–10916; (*c*) F. Ye, Y. Ge, A. Spannenberg, H. Neumann, L.-W. Xu and M. Beller, *Nat. Commun.*, 2021, **12**, 3257; (*d*) S.-S. Yan, D.-S. Wu, J.-H. Ye, L. Gong, X. Zeng, C.-K. Ran, Y.-Y. Gui, J. Li and D.-G. Yu, *ACS Catal.*, 2019, **9**, 6987–6992.

10 For examples of α-carbonyl CF_3 C–F functionalization, see: (*a*) Y.-J. Yu, F.-L. Zhang, T.-Y. Peng, C.-L. Wang, J. Cheng, C. Chen, K. N. Houk and Y.-F. Wang, *Science*, 2021, **371**, 1232–1240; (*b*) M. W. Campbell, V. C. Polites, S. Patel, J. E. Lipson, J. Majhi and G. A. Molander, *J. Am. Chem. Soc.*, 2021, **143**, 19648–19654; (*c*) R. Doi, M. Ohashi and S. Ogoshi, *Angew. Chem., Int. Ed.*, 2016, **55**, 341–344; (*d*) H. Amii, T. Kobayashi, Y. Hatamoto and K. Uneyama, *Chem. Commun.*, 1999, 1323–1324.

11 (*a*) D. Mandal, R. Gupta, A. K. Jaiswal and R. D. Young, *J. Am. Chem. Soc.*, 2020, **142**, 2572–2578; (*b*) S. Yoshida, K. Shimomori, Y. Kim and T. Hosoya, *Angew. Chem., Int. Ed.*, 2016, **55**, 10406–10409; (*c*) R. Idogawa, Y. Kim, K. Shimomori, T. Hosoya and S. Yoshida, *Org. Lett.*, 2020, **22**, 9292–9297; (*d*) K. Lye and R. D. Young, *Chem. Sci.*, 2024, **15**, 2712–2724.

12 Net C–F functionalization reactions have been reported for polyhalogenated alkyl–CF_3 substructures (*e.g.*, hexafluoroisopropoxy derivatives) or through multistep sequences of specific substructures, see: (*a*) D. Chaudhary and M. R. Kuram, *J. Org. Chem.*, 2024, **89**, 7347–7351; (*b*) X.-J. Tang and Q.-Y. Chen, *Synlett*, 2020, **31**, 2046–2048; (*c*) K. Wu and Q.-Y. Chen, *Tetrahedron*, 2002, **58**, 4077–4084; (*d*) J.-L. Xu, C. Yang, D.-T. Dai, W.-S. Hou and Y.-H. Xu, *Adv. Synth. Catal.*, 2022, **364**, 1228–1232; (*e*) B. W. Metcalf,

 © 2026 The Author(s). Published by the Royal Society of Chemistry

Open Access Article. Published on 17 March 2026. Downloaded on 4/30/2026 7:36:22 AM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

E. T. Jarvi and J. P. Burkhart, *Tetrahedron Lett.*, 1985, **26**, 2861–2864.

13 For reviews on synthetic routes to (trifluoromethyl)alkanes, see: (*a*) C. Alonso, E. Martínez de Marigorta, G. Rubiales and F. Palacios, *Chem. Rev.*, 2015, **115**, 1847–1935; (*b*) X. Liu, C. Xu, M. Wang and Q. Liu, *Chem. Rev.*, 2015, **115**, 683–730; (*c*) D. Mandal, S. Maji, T. Pal, S. K. Sinha and D. Maiti, *Chem. Commun.*, 2022, **58**, 10442–10468; (*d*) W. Domowki and R. A. Koliński, *J. Fluorine Chem.*, 1972, **2**, 210–213; (*e*) S. Barata-Vallejo, B. Lantaño and A. Postigo, *Chem.–Eur. J.*, 2014, **20**, 16806–16829; (*f*) S. Kumawat, T. Bhatt, V. Goyal, H. Neumann, R. Zbořil, R. V. Jagadeesh, M. Beller and K. Natte, *Coord. Chem. Rev.*, 2025, **542**, 216885; (*g*) H. Xiao, Z. Zhang, Y. Fang, L. Zhu and C. Li, *Chem. Soc. Rev.*, 2021, **50**, 6308–6319.

14 Many (trifluoromethyl)alkyl-containing building blocks are available according to https://www.emolecules.com, such as those with halogen, alcohol, amine, and carbonyl groups for further synthetic diversification.

15 (*a*) C. Ni, M. Hu and J. Hu, *Chem. Rev.*, 2015, **115**, 765–825; (*b*) J. Newton, D. Driedger, M. B. Nodwell, P. Schaffer, R. E. Martin, R. Britton and C. M. Friesen, *Chem.–Eur. J.*, 2019, **25**, 15993–15997.

16 For the utility of late-stage C–F functionalization, see ref. 1a and: (*a*) N. J. Castellino, A. P. Montgomery, J. J. Danon and M. Kassiou, *Chem. Rev.*, 2023, **123**, 8127–8153; (*b*) M. Wang, J. Ruskin, J. Marques, N. Garrison and T. Lectka, *Chem. Rev.*, 2025, **125**, 9382–9428.

17 For reviews that show the utility of alkyl–CF_3 groups in medicinal, agricultural, and other commercial applications, see: (*a*) S. Jeanmart, A. J. F. Edmunds, C. Lamberth and M. Pouliot, *Bioorg. Med. Chem.*, 2016, **24**, 317–341; (*b*) Y. Ogawa, E. Tokunaga, O. Kobayashi, K. Hirai and N. Shibata, *iScience*, 2020, **23**, 101467; (*c*) P. Jeschke, *ChemBioChem*, 2004, **5**, 570–589; (*d*) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly and N. A. Meanwell, *J. Med. Chem.*, 2015, **58**, 8315–8359; (*e*) N. A. Meanwell, *J. Med. Chem.*, 2018, **61**, 5822–5880; (*f*) M. Kotthoff, J. Müller, H. Jürling, M. Schlummer and D. Fiedler, *Environ. Sci. Pollut. Res.*, 2015, **22**, 14546–14559; (*g*) H. Mei, J. Han, R. Takeda, T. Sakamoto, T. Miwa, Y. Minamitsuji, H. Moriwaki, H. Abe and V. A. Soloshonok, *ACS Omega*, 2019, **4**, 11844–11851.

18 (*a*) T. Pitterna, M. Böger and P. Maienfisch, *Chimia*, 2004, **58**, 108–116; (*b*) M. Jouffroy, P. Pye, S. Jerhaoui, W. Chen and M. Surkyn, *J. Org. Chem.*, 2022, **87**, 2136–2141.

19 (*a*) J. Ichikawa, Y. Wada, M. Fujiwara and K. Sakoda, *Synthesis*, 2002, 1917–1936; (*b*) S. Hayashi, T. Nakai and N. Ishikawa, *Chem. Lett.*, 1980, **9**, 935–938.

20 For reviews on fluorine-retentive reactions of *gem*-difluoroalkenes, see: (*a*) J. P. Sorrentino and R. A. Altman, *Synthesis*, 2021, **53**, 3935–3950; (*b*) S. Koley and R. A. Altman, *Isr. J. Chem.*, 2020, **60**, 313–339.

21 For examples of defluorinative elimination/addition sequences on activated alkyl–CF_3 substructures, such as those with acidifying β-aryl and -carbonyl groups, see: (*a*) M. Shigeno, Y. Shishido, A. Soga, K. Nozawa-Kumada and Y. Kondo, *J. Org. Chem.*, 2023, **88**, 1796–1802; (*b*) M. Bilska-Markowska, M. Kaźmierczak, W. Jankowski and M. Hoffmann, *Beilstein J. Org. Chem.*, 2024, **20**, 2946–2953; (*c*) M. Lecea, A. Grassin, L. Ferreiro-Mederos, S. Choppin, A. Urbano, M. C. Carreño and F. Colobert, *Eur. J. Org Chem.*, 2013, **2013**, 4486–4489; (*d*) A. T. Adam, F. R. Fronczek and D. A. Colby, *Org. Lett.*, 2020, **22**, 2630–2633.

22 For examples of radical-based heteroatom additions to unactivated *gem*-difluoroalkenes, see: (*a*) A. J. Intelli, R. T. Lee and R. A. Altman, *J. Org. Chem.*, 2023, **88**, 14012–14021; (*b*) R. M. Herrick, M. K. A. El-Gaber, G. Coy and R. A. Altman, *Chem. Commun.*, 2023, **59**, 5623–5626; (*c*) J. P. Sorrentino, R. M. Herrick, M. K. Abd El-Gaber, A. Z. Abdelazem, A. Kumar and R. A. Altman, *J. Org. Chem.*, 2022, **87**, 16676–16690; (*d*) Y.-Z. Liao, B.-Q. Ruan, H.-Y. Hu, H. Cheng, B.-Q. Wang and F. Pan, *Org. Lett.*, 2025, **27**, 9293–9298; (*e*) Y.-Y. Zhang, Y. Zhang, X.-S. Xue and F.-L. Qing, *Angew. Chem., Int. Ed.*, 2024, **63**, e202406324.

23 We studied the potential for fluorine-retentive addition to (4,4-difluorobut-3-en-1-yl)benzene and 2-ethylhexan-1-ol (**2**); use of strong organic (*e.g.*, guanidines and phosphazenes) and inorganic bases (*e.g.*, KO-*t*-Bu, KHMDS) under various conditions do not yield fluorine retentive addition and results in either no reaction or formation of vinyl ether products. These results indicate that β-fluoride elimination after nucleophilic addition is very facile and, in a similar vein, all attempts to achieve fluorine-retentive addition as part of a dehydrofluorination sequence from (trifluoromethyl)alkanes (*e.g.*, **1**) did not lead to α,α-difluoroether products.

24 We note that similar elimination-type products are known to form for polyhalogenated (trifluoromethyl)alkanes under basic conditions; for examples, see: (*a*) Y. Karuo, A. Tarui, K. Sato, K. Kawai and M. Omote, *Beilstein J. Org. Chem.*, 2022, **18**, 1567–1574; (*b*) T. Kubota, K. Yamamoto and T. Tanaka, *Chem. Lett.*, 1983, **12**, 167–168.

25 For reviews on hydrofluorination reactions, see: (*a*) X. Bertrand, L. Chabaud and J.-F. Paquin, *Chem.–Asian J.*, 2021, **16**, 563–574; (*b*) R. Gauthier and J.-F. Paquin, *Chem.–Eur. J.*, 2023, **29**, e202301896.

26 For reviews on the value of α-fluoro(thio)ethers, see: (*a*) F. Leroux, P. Jeschke and M. Schlosser, *Chem. Rev.*, 2005, **105**, 827–856; (*b*) B. Manteau, S. Pazenok, J.-P. Vors and F. R. Leroux, *J. Fluorine Chem.*, 2010, **131**, 140–158; (*c*) P. Jeschke, E. Baston and F. R. Leroux, *Mini-Rev. Med. Chem.*, 2007, **7**, 1027–1034; (*d*) H.-Y. Xiong, X. Pannecoucke and T. Besset, *Chem.–Eur. J.*, 2016, **22**, 16734–16749.

27 For discussions of specific α,α-difluoroether molecules studied in these applications, see: (*a*) A. K. Podichetty, S. Wagner, A. Faust, M. Schäfers, O. Schober, K. Kopka and G. Haufe, *Future Med. Chem.*, 2009, **1**, 969–989; (*b*) D. Bianchi, P. Cesti, S. Spezia, C. Garavaglia and L. Mirenna, *J. Agric. Food Chem.*, 1991, **39**, 197–201; (*c*) P. Kirsch, M. Bremer, A. Taugerbeck and T. Wallmichrath, *Angew. Chem., Int. Ed.*, 2001, **40**, 1480–1484; (*d*) P. T. Meinke, *J. Med. Chem.*, 2001, **44**, 641–659; (*e*)

Open Access Article. Published on 17 March 2026. Downloaded on 4/30/2026 7:36:22 AM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

C. V. Amanchukwu, Z. Yu, X. Kong, J. Qin, Y. Cui and Z. Bao, *J. Am. Chem. Soc.*, 2020, **142**, 7393–7403; (*f*) A. Casimiro-Garcia, J. I. Trujillo, F. Vajdos, B. Juba, M. E. Banker, A. Aulabaugh, P. Balbo, J. Bauman, J. Chrencik, J. W. Coe, R. Czerwinski, M. Dowty, J. D. Knafels, S. Kwon, L. Leung, S. Liang, R. P. Robinson, J.-B. Telliez, R. Unwalla, X. Yang and A. Thorarensen, *J. Med. Chem.*, 2018, **61**, 10665–10699.

28 (*a*) P. Kirsch and M. Bremer, *ChemPhysChem*, 2010, **11**, 357–360; (*b*) M. Hird, *Chem. Soc. Rev.*, 2007, **36**, 2070–2095.

29 For examples and discussions of difluoromethylene and α,α-difluoro(thio)ethers in medicinal chemistry, see ref. 26 and 27, and: B. M. Johnson, Y.-Z. Shu and N. A. Meanwell, *J. Med. Chem.*, 2020, **63**, 6315–6386.

30 For discussions and examples of traditional routes to α,α-difluoroethers, see ref. 15 and: (*a*) W. H. Bunnelle, B. R. McKinnis and B. A. Narayanan, *J. Org. Chem.*, 1990, **55**, 768–770; (*b*) M. Kuroboshi and T. Hiyama, *Synlett*, 1994, 251–252.

31 For reviews on HMDS bases, see: (*a*) R. E. Mulvey and S. D. Robertson, *Angew. Chem., Int. Ed.*, 2013, **52**, 11470–11487; (*b*) B. T. Watson, H. Lebel, H. C. Malinakova and J. C. Hershberger, Potassium Hexamethyldisilazide, in *Encyclopedia of Reagents for Organic Synthesis*, John Wiley & Sons, Ltd, 2007; (*c*) B. T. Watson and H. Lebel, Sodium Hexamethyldisilazide, in *Encyclopedia of Reagents for Organic Synthesis*, John Wiley & Sons, Ltd, 2005.

32 For discussions of common HF reagents, see: (*a*) S. Caron, *Org. Process Res. Dev.*, 2020, **24**, 470–480; (*b*) S. G. Sweeting and A. J. J. Lennox, *J. Am. Chem. Soc.*, 2025, **147**, 19329–19341; (*c*) G. Haufe, *Chem. Rec.*, 2023, **23**, e202300140; (*d*) S. Liang, G. B. Hammond and B. Xu, *Chem.–Eur. J.*, 2017, **23**, 17850–17861.

33 For discussions of Olah's reagent and DMPU·HF, as well as their safety considerations, see ref. 31 and: (*a*) G. A. Olah, J. T. Welch, Y. D. Vankar, M. Nojima, I. Kerekes and J. A. Olah, *J. Org. Chem.*, 1979, **44**, 3872–3881; (*b*) S. P. Kotun, G. K. S. Prakash and J. Hu, Pyridinium Poly(Hydrogen Fluoride), in *Encyclopedia of Reagents for Organic Synthesis*, John Wiley & Sons, Ltd, 2007; (*c*) O. E. Okoromoba, J. Han, G. B. Hammond and B. Xu, *J. Am. Chem. Soc.*, 2014, **136**, 14381–14384; (*d*) P. A. Champagne, J. Desroches, J.-D. Hamel, M. Vandamme and J.-F. Paquin, *Chem. Rev.*, 2015, **115**, 9073–9174.

34 For discussions and safety considerations of $Et_3N\cdot 3HF$, ref. 32 and: (*a*) S. Hara, Triethylamine Trihydrofluoride, in *Encyclopedia of Reagents for Organic Synthesis*, John Wiley & Sons, Ltd, 2005; (*b*) R. Franz, *J. Fluorine Chem.*, 1980, **15**, 423–434.

35 X. Bertrand and J.-F. Paquin, *Org. Lett.*, 2019, **21**, 9759–9762.

36 F. G. Bordwell, *Acc. Chem. Res.*, 1988, **21**, 456–463.

37 For a safety discussion on the use of strong bases in DMF, see: Q. Yang, M. Sheng and Y. Huang, *Org. Process Res. Dev.*, 2020, **24**, 1586–1601.

38 $Et_3N\cdot 3HF$ does not etch glass and can be transferred using typical glass syringes. However, we conducted step 2 in PTFE vessels to avoid any potential glass etching caused by the dual acid system. We note that the entire procedure (steps 1 and 2) can be conducted in a one-pot manner using a PTFE round bottom flask; this was done for substrate **5** and is described in the SI.

39 For example, the use of KO-*t*-Bu for the substrates in Chart 1a typically leads to 15–20% remaining (trifluoromethyl) alkane **1** that is difficult to separate from the α,α-difluoroether product. In contrast, KHMDS generally led to full consumption of **1**. For similar reasons, step 1 was monitored by TLC and the reaction time for each substrate (generally 4 h or 16 h) is described in the SI.

40 (*a*) J. A. Bull, R. A. Croft, O. A. Davis, R. Doran and K. F. Morgan, *Chem. Rev.*, 2016, **116**, 12150–12233; (*b*) H. Mughal and M. Szostak, *Org. Biomol. Chem.*, 2021, **19**, 3274–3286.

41 In these cases, we do not observe competing deprotection of the acid-sensitive groups. For examples of related acidic deprotections, see: (*a*) S. E. López and J. Salazar, *J. Fluorine Chem.*, 2013, **156**, 73–100; (*b*) I. W. Ashworth, B. G. Cox and B. Meyrick, *J. Org. Chem.*, 2010, **75**, 8117–8125; (*c*) W. Li, J. Li, Y. Wu, N. Fuller and M. A. Markus, *J. Org. Chem.*, 2010, **75**, 1077–1086; (*d*) J. Tian and L. Zhou, *Chem. Sci.*, 2023, **14**, 6045–6051.

42 Highly base-sensitive groups (*e.g.*, alkyl halides) are not tolerated in this protocol. For a discussion of nucleophilic substitution reactions of electron-deficient aryl ethers, see: M. Shigeno, K. Hayashi, K. Nozawa-Kumada and Y. Kondo, *Org. Lett.*, 2019, **21**, 5505–5508.

43 18-Crown-6 is likely needed to enhance the nucleophilicity of the phenoxide nucleophile for addition to the *gem*-difluoroalkene intermediate, while use of the stronger acid MsOH is likely need for protonation of the less basic fluorovinyl aryl ether intermediate.

44 We did not observe hydrofluorination of vinyl thioethers using Brønsted acid systems alone. We hypothesize that CuCl either disrupts H-bonding in Olah's reagent (see ref. 32) or may act as an acid to activate the vinylthioether towards fluoride addition; see: Y. Yamamoto, *J. Org. Chem.*, 2007, **72**, 7817–7831.

45 For radical-based routes for phenol/thiol addition to *gem*-difluoroalkenes, see ref. 22. For a nucleophilic phenol addition process to 2,2-difluorostyrenes, see: D. L. Orsi, M. R. Yadav and R. A. Altman, *Tetrahedron*, 2019, **75**, 4325–4336.

46 (*a*) J. Irurre, J. Casas and A. Messeguer, *Bioorg. Med. Chem. Lett.*, 1993, **3**, 179–182; (*b*) R. Szpera, P. G. Isenegger, M. Ghosez, N. J. W. Straathof, R. Cookson, D. C. Blakemore, P. Richardson and V. Gouverneur, *Org. Lett.*, 2020, **22**, 6573–6577.

47 For the synthesis of $ArOCH_2CF_3$ compounds, see: B. Pethő and Z. Novák, *Asian J. Org. Chem.*, 2019, **8**, 568–575.

48 We note that addition reactions to structurally related trifluorovinyl aryl ethers have been reported. (*a*) S. T. Iacono, N. J. Weeks and D. W. Smith Jr, *J. Fluorine Chem.*, 2023, **271**, 110187; (*b*) J. D. Moody, D. VanDerveer, D. W. Smith Jr and S. T. Iacono, *Org. Biomol. Chem.*, 2011, **9**, 4842–4849.

 © 2026 The Author(s). Published by the Royal Society of Chemistry

Open Access Article. Published on 17 March 2026. Downloaded on 4/30/2026 7:36:22 AM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

49 For references to the drug substructures used in Fig. 5c, see: (*a*) J. Rybniker, A. Vocat, C. Sala, P. Busso, F. Pojer, A. Benjak and S. T. Cole, *Nat. Commun.*, 2015, **6**, 7659; (*b*) T. S. Reger, Z.-Q. Yang, K.-A. S. Schlegel, Y. Shu, C. Mattern, R. Cube, K. E. Rittle, G. B. McGaughey, G. D. Hartman, C. Tang, J. Ballard, Y. Kuo, T. Prueksaritanont, C. E. Nuss, S. M. Doran, S. V. Fox, S. L. Garson, Y. Li, R. L. Kraus, V. N. Uebele, J. J. Renger and J. C. Barrow, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 1692–1696; (*c*) K. Shibata, R. Foglar, K. Horie, K. Obika, A. Sakamoto, S. Ogawa and G. Tsujimoto, *Mol. Pharmacol.*, 1995, **48**, 250–258.