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A metal-free strategy to construct fluoroalkyl–olefin linkages using fluoroalkanes†

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We present a metal-free strategy to access fluoroalkyl–olefin linkages from fluoroalkane precursors and vinyl-pinacol boronic ester (BPin) reagents. This reaction sequence is templated by the boron reagent, which induces C–C bond formation upon oxidation. We developed this strategy into a one-pot synthetic protocol using RCF₂H precursors directly with vinyl-BPin reagents in the presence of a Brønsted base, which tolerated oxygen- and nitrogen-containing heterocycles, and aryl halogens. We also found that HCF₃ (HCF-23; a byproduct of the Teflon industry) and CH₂F₂ (HCF-32; a low-cost refrigerant) are amenable to this protocol, representing distinct strategies to generate RCF₂H and RCF₃ molecules. Finally, we demonstrate that the vinyl difluoromethylene products can be readily derivatized, representing an avenue for late-stage modification after installing the fluoroalkyl unit.

Introduction

Fluorine-containing functional groups are often incorporated within medicinally-relevant compounds to modulate molecular properties, including metabolic stability, lipophilicity, stereo-electronics, and affinity to biological targets.^{1,2} In addition to these general features, difluoromethylene units (–CF₂–) are considered as bioisosteres of oxygen atoms in ether, carbonyl, and sulfonyl groups.³ For example, within a series of ledipasvir (GS-5885) variants that feature an Ar–X–Ar linkage, highest activity was found when X = CF₂, compared to –O– or –CH₂– analogues.⁴ Despite their potential advantages, molecules containing Ar–CF₂–R and Ar–CF₂–Ar linkages are not common in commercial pharmaceuticals, likely due to limited synthetic pathways for direct –CF₂–R incorporation.

Metal-free routes to prepare Ar–CF₂–alkyl and Ar–CF₂–Ar linkages include radical difluorination of C–H bonds using fluorine atom transfer reagents (*e.g.* Selectfluor),^{5,6} or fluorodeoxygenation of ketones using trifluorosulfuranes (*e.g.* DAST; Et₂NSF₃)^{7,8} and defluorinative functionalization.^{9–13} Many of these strategies require reagents that are toxic, explosive,¹⁴ and of limited scope, which lessen their synthetic utility.¹⁵ Metal-catalyzed routes include reactions of aryl/alkyl boronic acids with ArCF₂X; (X = halide, amides),^{16–19} and recently,

reactions of ArCF₂SiMe₃ with aryl halides.²⁰ However, limitations of these approaches include: (a) low availability of ArCF₂X electrophiles and pronucleophiles, and (b) low compatibility of procedures needed to prepare the requisite reagents.^{9,21–24}

Difluoromethanes (RCF₂H; R = H, R = Ar) are widely available pronucleophiles²⁵ that can be unmasked by deprotonation,²⁶ and represent an attractive entry point to access R–CF₂–R' molecules. A key challenge to broad use of RCF₂H compounds as synthons is that upon deprotonation, RCF₂[–] anions decompose to fluorocarbenes *via* fluoride elimination, even at ambient temperatures.²⁷ To overcome this deleterious pathway, our group developed a strategy to use Lewis acids (*e.g.* hexamethylborazine; B₃N₃Me₆) to stabilize RCF₂[–] anions against defluorination.^{28–33}

One class of fluorinated compounds that is underdeveloped is aryl/alkyl difluoromethylene containing internal olefins.³⁴ These moieties are an attractive functionality in medicinal chemistry, and are present within marketed drugs such as tafluprost and glecaprevir (Fig. 1a).^{35,36} Such motifs are particularly desirable not only because fluorine atoms may improve metabolic stability and/or binding affinity with the target of interest,³⁷ but also because they are amenable to late-stage functionalization.^{38,39} This latter feature exploits an olefin as a functional handle to build molecular complexity and/or as a branch point for structure–activity relationship studies in drug discovery. Unfortunately, there are limited synthetic strategies to access vinyl difluoromethylene linkages and most proceed by coupling RCF₂Br (R = aryl, alkyl, ester) electrophiles with either alkane, alkyne, or aryl nucleophiles (Fig. 1b).^{40–49} Alternatively, RCF₂-internal olefins have been prepared photochemically *via* either Ru or Ni based catalytic systems.^{50,51} Although promising, all these strategies require electrophilic

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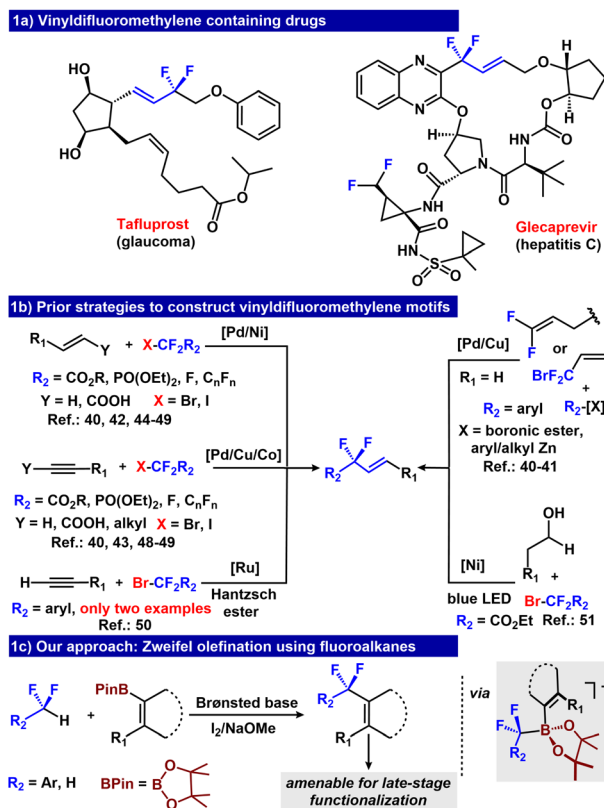


Fig. 1 (a) Vinyl difluoromethylene containing drugs. (b) Prior strategies to construct vinyl difluoromethylene motifs. (c) Our approach: Zweifel olefination using fluoroalkanes.

RCF_2Br as RCF_2^- sources, whose preparation by radical bromination is incompatible with many substrate classes.^{21,22} Defluoroalkylation of trifluoromethyl alkenes is an alternative approach to access vinyl difluoromethylene linkages.⁵²⁻⁵⁶

Zweifel olefination represents an attractive metal-free route to construct a vinylic C–C bond.⁵⁷⁻⁵⁹ This reaction sequence proceeds through an anionic vinyl borate intermediate. Oxidation induces 1,2-rearrangement, and addition of an alkoxide base leads to a product containing a new C–C bond. We hypothesized that if the key anionic vinyl borate intermediate could be accessed by deprotonating RCF_2H molecules, subsequent oxidation would provide α,α -difluoroalkylated vinyl compounds. Our group previously established that fluoroalkyl $B_3N_3Me_6$ adducts $[RCF_2B_3N_3Me_6]^-$ can transfer the RCF_2^- group to stronger Lewis acids such as $B(OMe)_3$.^{26,29,30,33} Given the similar Lewis acidity of $R-BPin$ to $B(OMe)_3$,^{60,61} we hypothesized that $[(R)(ArCF_2)BPin]^-$ could be formed analogously,⁶² and if $R = vinyl$, the borate intermediate would be uniquely situated for a net Zweifel olefination reaction to form α,α -difluoroalkylated olefin products (Fig. 1c).

Results and discussion

To establish feasibility of fluoroalkyl transfer to $R-BPin$, we allowed an equimolar mixture of $[K(18-crown-6)(B_3N_3Me_6-CF_2Ph)]$ (**1**) and $Ph-BPin$ (**2a**) to react in tetrahydrofuran solvent

for 1.5 h at 50 °C. The reaction furnished $[K(18-c-6)(Ph-BPin-CF_2Ph)]$ (**2b**) quantitatively (Fig. 2) as assessed by 1H , ^{13}C , ^{19}F , ^{11}B NMR and ESI-MS analyses (^{11}B : 3.95 ppm and ^{19}F : –104.21 ppm). The clean transfer of $PhCF_2^-$ from $B_3N_3Me_6$ to $Ph-BPin$ demonstrates feasibility of the approach. To evaluate the Zweifel olefination sequence, we introduced **1** to vinyl-BPin **2c**. The reaction afforded adduct **2d** with 98% conversion, as assessed by ^{19}F and ^{11}B NMR spectroscopy (^{11}B : 3.67 ppm and ^{19}F : –105.66 ppm), and was isolated as a white powder in 88% yield.

After achieving clean conversion to **2d** above, we evaluated a one-pot Zweifel olefination sequence to form α,α -difluoroalkylated olefin (**2e**). Initial conditions using 1 equiv. I_2 and NaOMe at room temperature afforded **2e** in 26% yield (ESI, Table S1,† entry 1). The identity of **2e** was established by 1H and ^{19}F NMR spectroscopy (1H NMR: vinyl hydrogen at 5.79–5.82 ppm (m) and ^{19}F NMR: –95.41 ppm). The yield was increased to 40% by lowering the temperature to –78 °C prior to adding I_2 and NaOMe (ESI, Table S1,† entry 2). Importantly, increasing the stoichiometry of I_2 and NaOMe to 2 equiv. further improved the conversion to 94% (Fig. 2).

We assessed the reaction scope by varying the vinyl-BPin derivatives (Fig. 3, entries **3a–3i**). Aliphatic vinyl-BPin reagents generally responded well, with good yields (73–81%; Fig. 3, entries **3a–3c**). Dihydronaphthalene and *2H*-chromene derivatives furnished 89 and 84% isolated yields for **3e** and **3g**, respectively. The latter substrate is of particular interest because chromene derivatives are an important class of heterocycles used in cosmetic agents, food additives, and biodegradable agrochemicals.^{63,64} Acyclic vinyl-BPin reagents were also tolerated, affording **3d** (77%), **3f** (89%) and **3i** (94%) in good yields.

Although the reaction sequence provides high yields of $PhCF_2$ -olefin products, one limitation to broad scope adoption is the requirement of $B_3N_3Me_6$. To overcome this requirement, we evaluated whether the use of $B_3N_3Me_6$ could be eliminated in the Zweifel olefination sequence. Importantly, because **2c** is more Lewis acidic than $B_3N_3Me_6$, we hypothesized that it could effect the direct capture/olefination of $PhCF_2^-$ following

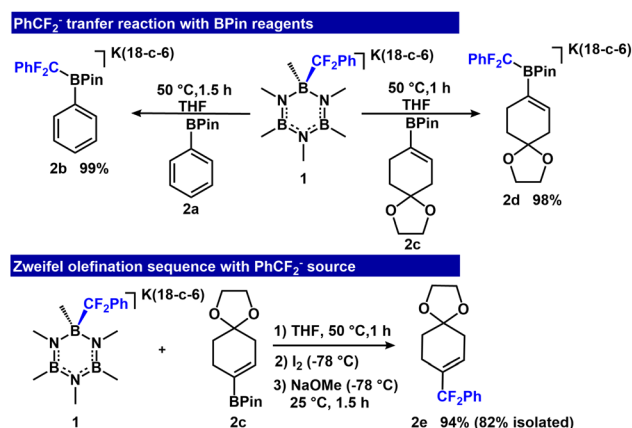


Fig. 2 $PhCF_2^-$ transfer reactions to aryl and vinyl-BPin (top) and Zweifel olefination (bottom).

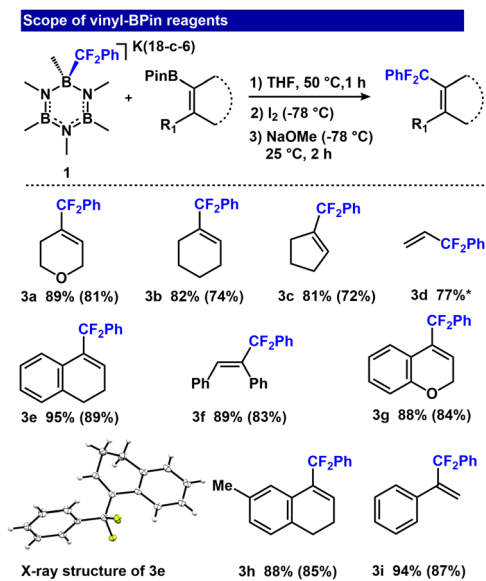


Fig. 3 Zweifel olefination scope by varying the vinyl-BPin reagents. R-BPin (0.1 mmol), [K(18-c-6)(B₃N₃Me₆-CF₂Ph)] (0.1 mmol), I₂ (0.2 mmol), NaOMe (0.2 mmol), THF (1.8 mL). ¹⁹F NMR yields (isolated yields in parentheses). *Only ¹⁹F NMR yield acquired due to product volatility.

deprotonation of PhCF₂H. To examine the feasibility of the one-pot Zweifel olefination strategy, we evaluated a series of bases to deprotonate ArCF₂H in the presence of **2c**. We optimized the formation of **2d** in a single step starting from **2c**, PhCF₂H and base. In the absence of 18-crown-6, deprotonation of PhCF₂H with 1.5 equiv. KN(^{*i*}Pr)₂ gave 95% conversion to **2d**, but for the tandem Zweifel reaction, only 27% yield of **2e** (Fig. 4, ESI Table S2†). However, adding 18-crown-6 after deprotonation enabled subsequent conversion to **2e** in 64% yield over two steps.

After demonstrating feasibility of the one-pot methodology, we assessed scope in both the vinyl-BPin, and fluoroalkyl component (Fig. 5). Although most of the previous scope in vinyl-BPin (Fig. 3) translated to the one-pot method, two substrates were incompatible (**3f** and **3a**), which we attribute to deleterious reactivity with KN(^{*i*}Pr)₂. Dihydronaphthalene and the 2*H*-chromene derivative responded well, providing isolated yields of 71% (**3e**) and 51% (**3g**). Vinyl-BPin reagents containing aliphatic functionality afforded moderate isolated yields (**2e** (56%) and **3b** (40%)). Styrenyl-BPin similarly afforded **3i** in 72% isolated yield.

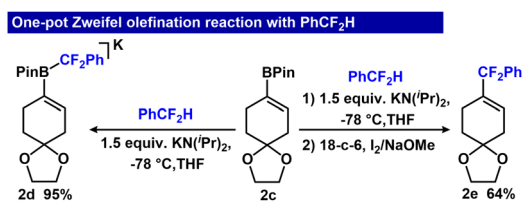


Fig. 4 Strategy for the one-pot Zweifel olefination reaction by *in situ* deprotonation of PhCF₂H with KN(^{*i*}Pr)₂. **2c** (0.06 mmol), KN(^{*i*}Pr)₂ (0.09 mmol), 18-c-6 (0.06 mmol), I₂ (0.12 mmol), NaOMe (0.12 mmol), THF (1 mL). ¹⁹F NMR yields (PhOCF₃ used as internal standard).

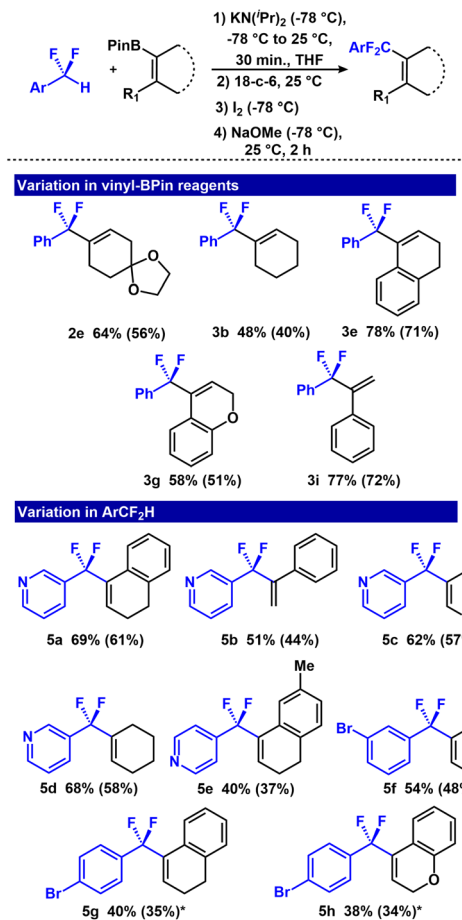


Fig. 5 Scope of one-pot Zweifel olefination reaction. BPin derivatives (0.26 mmol), KN(^{*i*}Pr)₂ (0.39 mmol), 18-c-6 (0.26 mmol), I₂ (0.52 mmol), NaOMe (0.52 mmol), THF (3 mL). ¹⁹F NMR yields (PhOCF₃ used as internal standard). Isolated yields are in parentheses. *5–8% hydrodechlorination also observed.

Next, we explored the scope in pronucleophile by investigating difluoromethyl pyridine and difluoromethyl aryl bromide substrates. Pyridine units are an important structural motif in pharmaceutical and medicinal chemistry.^{65,66} We evaluated the reactivity of 3-(difluoromethyl)pyridine and 4-(difluoromethyl)pyridine with four representative vinyl-BPin substrates: dihydronaphthalene, 2*H*-chromene, cyclohexenyl and styrenyl (Fig. 5). They all furnished the Py-CF₂-olefin products in 44–61% isolated yields (**5a–5e**). Finally, although aryl bromides generally have low compatibility with electrochemical and photoredox fluorination reactions,^{67,68} they were compatible with the one-pot Zweifel protocol. For example, 1-bromo-4-(difluoromethyl)benzene and 1-bromo-3-(difluoromethyl)benzene substrates provided their respective products in 34–48% (**5f–5h**) isolated yield.

Our group previously demonstrated that hydrofluorocarbons (HFCs) can be used as low cost -CF₃, and -CF₂H sources,^{28–30} representing a strategy to repurpose refrigerants or fluorinated waste products that are produced on a >15 kt scale.^{69,70} Importantly, the use of CH₂F₂ (HCF-32) as a fluoroalkyl precursor affords products that are also pro-nucleophiles, primed for subsequent



functionalization. We evaluated the feasibility of a one-pot difluoromethylation reaction using $[K(18-c-6)(B_3N_3Me_6-CF_2H)]$ (**6a**) and vinyl-BPin derivatives. Although higher temperature (80 °C) was required for $-CF_2H$ transfer, the previously optimized conditions for Zweifel olefination afforded **6b** in 76% yield (Fig. 6, ESI Table S3†). We also evaluated the protocol using dihydronaphthalene and styrenyl BPin derivatives, which provided conversions of 72% and 68% for **6c** and **6d**, respectively (Fig. 6). We directly compared this approach to Me_3Si-CF_2H , a common $-CF_2H$ pronucleophile that requires activation by F^- or OH^- .^{71–73} Addition of vinyl-BPin (**2c**) to a solution of Me_3Si-CF_2H activated with either $[Me_4N][OH]$ or $[^tBu_4N][F]$ did not afford ^{19}F NMR resonances consistent with the $-CF_2H$ analogue of **2d** (see ESI, S75†), under similar conditions used with **6a** (see ESI, Fig. S114 and S115†). These results highlight the challenge of selective nucleophilic fluoroalkyl transfer from $R-SiMe_3$ reagents that contain more than one nucleophilic sites, and demonstrate a clear advantage for using $-CF_2R$ transfer reagents that do not need an activator.

Next, we examined the feasibility of the Zweifel olefination using other fluoroalkanes (HCF_3 , CH_3CF_2H , CF_3CFH_2 and CF_3CH_3). We found that the HCF_3 -derived reagent, $[(B_3N_3Me_6-CF_3)(K(18-c-6))]$, was readily adapted, affording the trifluoromethyl containing product, **6e**, in 65% isolated yield (Fig. 6c). When translating these conditions to fluoroethanes, we found that

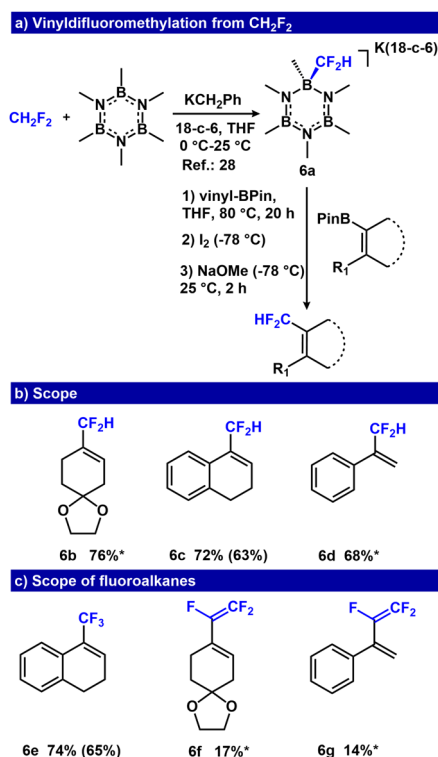


Fig. 6 (a) Zweifel olefination for the synthesis of vinyldifluoromethane molecules from CH_2F_2 . (b) Scope of vinyldifluoromethanes, conditions: $R-BPin$ (0.2 mmol), $[K(18-c-6)(B_3N_3Me_6-CF_2H)]$ (0.2 mmol), I_2 (0.4 mmol), $NaOMe$ (0.4 mmol), THF (4.0 mL). (c) Scope in fluoroalkanes. *Only ^{19}F NMR yield acquired due to product volatility. ^{19}F NMR yields (isolated yields are in parentheses).

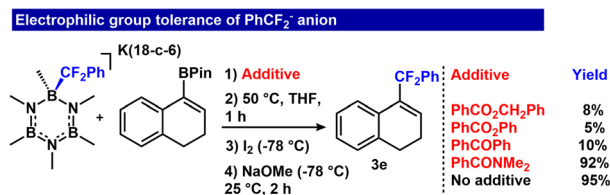


Fig. 7 Tolerance to ester, ketone and amide additives.

although CH_3CF_2H and CF_3CH_3 did not afford the olefination products, CF_3CFH_2 furnished **6f** and **6g** with 17% and 14% yield as assessed by ^{19}F NMR spectroscopy. In these cases, β -fluoride elimination occurred at the first step (generating $[(B_3N_3Me_6-CF=CF_2)(K(18-c-6))]$), a species competent for the net Zweifel olefination (Fig. 6c, ESI S78–S80†). Finally, we attempted the direct capture/olefination of HCF_2^- following deprotonation of CF_2H_2 . Deprotonation of CF_2H_2 with 5 equiv. $KN(^iPr)_2$ gave 32% conversion to the vinyl boronate intermediate, that when subjected to $NaOMe/I_2$, afforded 9% yield of **6d** over two steps (ESI S77†).

Given previous data showing rapid transfer of the RCF_2^- unit to carbonyl electrophiles,²⁶ we examined whether transfer to vinyl BPin may occur in the presence of another, competitive electrophile. We performed a series of competition experiments to examine reaction tolerance to carbonyl electrophiles as additives. The addition of esters and a ketone (benzyl benzoate, phenyl benzoate and benzophenone) provided low conversion to the final product (Fig. 7, 8%, 5% and 10%, respectively). However, the reaction tolerated an amide electrophile, N,N -dimethylbenzamide, and we observed only 3% reduction in product formation (92% yield of **3e**) (Fig. 7, ESI S78†). These results demonstrate the feasibility of the reaction sequence with select competitive electrophiles.

We next investigated the feasibility of late-stage modifications of three representative $Ar-CF_2$ -olefins formed from the

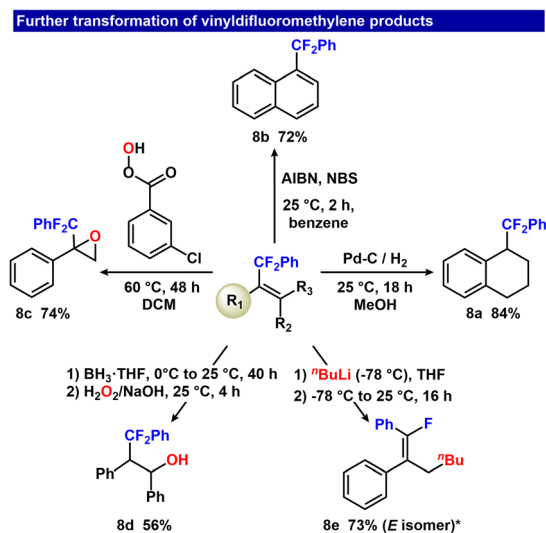


Fig. 8 Further transformation of vinyldifluoromethylene products spanning oxidative, reductive and substitution chemistry. *10% Z isomer also formed.

Zweifel olefination sequence (Fig. 8). Hydrogenation of **3e** using Pd/C at 25 psi H₂ furnished **8a** in 84% isolated yield. A net dehydrogenation reaction was effected by treating **3e** with AIBN/NBS at room temperature, affording **8b** in 72% isolated yield. An epoxidation reaction of **3i** with m-CPBA in CH₂Cl₂ at 60 °C provided **8c** in 74% isolated yield. Reduction of **3f** via BH₃ hydroboration followed by oxidation furnished **8d** in 56% isolated yield. Finally, a defluorinative S_N2' reaction with ⁿBuLi yielded the *E* isomer **8e** with 73% isolated yield (9 : 1 selectivity of *E/Z* alkenes).

Conclusion

In summary, we have developed a metal-free strategy to access vinyldifluoromethylene molecules from fluoroalkane precursors and vinyl-BPin reagents. Lewis acidic boranes stabilize and template α,α -difluoroalkyl- and vinylic-moieties, ultimately enabling C–C bond formation. This strategy was extended to a straightforward one-pot synthesis using RCF₂H precursors and vinyl-BPin reagents. We showed that this reaction sequence can be used to generate RCF₂H precursors directly from inexpensive CH₂F₂ (HCF-32), which represents a new strategy to repurpose this underutilized synthon. Importantly, we demonstrated that this CF₂H[−] reactivity is a unique application of the deprotonation approach, and not possible using the most common –CF₂H transfer reagent: Me₃Si–CF₂H. Finally, we established that the vinyldifluoromethylene products can be readily derivatized, representing an avenue for late-stage modification of fluoroalkylated compounds.

Data availability

All relevant experimental data and characterization details are provided in the ESI†. Crystallographic data for compound **3e** has been deposited at the Cambridge Crystallographic Data Centre (CCDC) under access number 2299679.

Author contributions

The manuscript was written through contributions of all authors. The project was designed by K. Chakrabarti, M. M. Wade Wolfe, S. Guo, and N. K. Szymczak. All optimizations, syntheses and characterizations were performed by K. Chakrabarti. J. W. Tucker and J. Lee provided insights related to project development. All authors have given approval to the final version of the manuscript.

Conflicts of interest

NKS holds a patent relating to fluoroalkyl transfer reagents.

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Notes and references

- 1 K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881–1886.
- 2 M. Inoue, Y. Sumii and N. Shibata, *ACS Omega*, 2020, **5**, 10633–10640.
- 3 Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa and H. Liu, *Chem. Rev.*, 2016, **116**, 422–518.
- 4 J. O. Link, J. G. Taylor, L. Xu, M. Mitchell, H. Guo, H. Liu, D. Kato, T. Kirschberg, J. Sun, N. Squires, J. Parrish, T. Keller, Z.-Y. Yang, C. Yang, M. Matles, Y. Wang, K. Wang, G. Cheng, Y. Tian, E. Mogalian, E. Mondou, M. Cornpropst, J. Perry and M. C. Desai, *J. Med. Chem.*, 2014, **57**, 2033–2046.
- 5 S. P. Vincent, M. D. Burkart, C.-Y. Tsai, Z. Zhang and C.-H. Wong, *J. Org. Chem.*, 1999, **64**, 5264–5279.
- 6 P. T. Nyffeler, S. G. Durón, M. D. Burkart, S. P. Vincent and C.-H. Wong, *Angew. Chem., Int. Ed.*, 2005, **44**, 192–212.
- 7 L. N. Markovskij, V. E. Pashinnik and A. V. Kirsanov, *Synthesis*, 1973, **1973**, 787–789.
- 8 J. Hu, W. Zhang and F. Wang, *Chem. Commun.*, 2009, 7465–7478.
- 9 K. Aikawa, K. Maruyama, J. Nitta, R. Hashimoto and K. Mikami, *Org. Lett.*, 2016, **18**, 3354–3357.
- 10 V. V. Levin, A. A. Zemtsov, M. I. Struchkova and A. D. Dilman, *Org. Lett.*, 2013, **15**, 917–919.
- 11 R. Gupta, A. K. Jaiswal, D. Mandal and R. D. Young, *Synlett*, 2020, **31**, 933–937.
- 12 D. Mandal, R. Gupta, A. K. Jaiswal and R. D. Young, *J. Am. Chem. Soc.*, 2020, **142**, 2572–2578.
- 13 D. Mandal, R. Gupta and R. D. Young, *J. Am. Chem. Soc.*, 2018, **140**, 10682–10686.
- 14 H. A. Tennekes, *Toxicology*, 2010, **276**, 1–4.
- 15 F. S. Fawcett, C. W. Tullock and D. D. Coffman, *J. Am. Chem. Soc.*, 1962, **84**, 4275–4285.
- 16 Z. Feng, Q.-Q. Min, Y.-L. Xiao, B. Zhang and X. Zhang, *Angew. Chem., Int. Ed.*, 2014, **53**, 1669–1673.
- 17 J.-W. Gu, W.-H. Guo and X. Zhang, *Org. Chem. Front.*, 2015, **2**, 38–41.
- 18 Y.-C. Luo, F.-F. Tong, Y. Zhang, C.-Y. He and X. Zhang, *J. Am. Chem. Soc.*, 2021, **143**, 13971–13979.
- 19 A. Bunnell, N. Laloo, C. Brigham and M. S. Sanford, *Org. Lett.*, 2023, **25**, 7584–7588.
- 20 K. Choi, M. G. Mormino, E. D. Kalkman, J. Park and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2022, **61**, e202208204.
- 21 J. He and C. U. Fittman, *Synth. Commun.*, 1999, **29**, 855–862.
- 22 Y. Masato, S. Daiki and I. Masahiko, *Chem. Lett.*, 1994, **23**, 2357–2360.
- 23 L. Santos, A. Panossian, M. Donnard, J.-P. Vors, S. Pazenok, D. Bernier and F. R. Leroux, *Org. Lett.*, 2020, **22**, 8741–8745.
- 24 P. Clavel, M. P. Léger-Lambert, C. Biran, F. Serein-Spirau, M. Bordeaux, N. Roques and H. Marzouk, *Synthesis*, 1999, **1999**, 829–834.



- 25 D. E. Yerien, S. Barata-Vallejo and A. Postigo, *Chem.–Eur. J.*, 2017, **23**, 14676–14701.
- 26 J. B. Geri, M. M. Wade Wolfe and N. K. Szymczak, *J. Am. Chem. Soc.*, 2018, **140**, 9404–9408.
- 27 A. Streitwieser Jr and F. Mares, *J. Am. Chem. Soc.*, 1968, **90**, 2444–2445.
- 28 J. B. Geri, E. Y. Aguilera and N. K. Szymczak, *Chem. Commun.*, 2019, **55**, 5119–5122.
- 29 J. B. Geri, M. M. Wade Wolfe and N. K. Szymczak, *Angew. Chem., Int. Ed.*, 2018, **57**, 1381–1385.
- 30 J. B. Geri and N. K. Szymczak, *J. Am. Chem. Soc.*, 2017, **139**, 9811–9814.
- 31 S. Guo, W. Sun, J. W. Tucker, K. D. Hesp and N. K. Szymczak, *Chem.–Eur. J.*, 2023, **29**, e202203578.
- 32 M. M. Wade Wolfe, S. Guo, L. S. Yu, T. R. Vogel, J. W. Tucker and N. K. Szymczak, *Chem. Commun.*, 2022, **58**, 11705–11708.
- 33 M. M. Wade Wolfe, J. P. Shanahan, J. W. Kampf and N. K. Szymczak, *J. Am. Chem. Soc.*, 2020, **142**, 18698–18705.
- 34 D. O'Hagan, Y. Wang, M. Skibinski and A. M. Z. Slawin, *Pure Appl. Chem.*, 2012, **84**, 1587–1595.
- 35 J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432–2506.
- 36 Y. N. Lamb, *Drugs*, 2017, **77**, 1797–1804.
- 37 Y. Matsumura, in *Fluorine in Medicinal Chemistry and Chemical Biology*, 2009, pp. 47–66.
- 38 S. Woo and R. A. Shenvi, *Acc. Chem. Res.*, 2021, **54**, 1157–1167.
- 39 M. D. Levin, T. Q. Chen, M. E. Neubig, C. M. Hong, C. A. Theulier, I. J. Kobylanski, M. Janabi, J. P. O'Neil and F. D. Toste, *Science*, 2017, **356**, 1272–1276.
- 40 Z. Feng, Y.-L. Xiao and X. Zhang, *Acc. Chem. Res.*, 2018, **51**, 2264–2278.
- 41 Q.-Q. Min, Z. Yin, Z. Feng, W.-H. Guo and X. Zhang, *J. Am. Chem. Soc.*, 2014, **136**, 1230–1233.
- 42 X.-T. Feng, J.-X. Ren, X. Gao, Q.-Q. Min and X. Zhang, *Angew. Chem., Int. Ed.*, 2022, **61**, e202210103.
- 43 L. Liao, R. An, H. Li, Y. Xu, J.-J. Wu and X. Zhao, *Angew. Chem., Int. Ed.*, 2020, **59**, 11010–11019.
- 44 G. Li, T. Wang, F. Fei, Y.-M. Su, Y. Li, Q. Lan and X.-S. Wang, *Angew. Chem., Int. Ed.*, 2016, **55**, 3491–3495.
- 45 Z. Feng, Q.-Q. Min, H.-Y. Zhao, J.-W. Gu and X. Zhang, *Angew. Chem., Int. Ed.*, 2015, **54**, 1270–1274.
- 46 F. Ke, C. Yu, X. Li, H. Sheng and Q. Song, *Org. Lett.*, 2023, **25**, 2733–2738.
- 47 G. Wu and A. Jacobi von Wangelin, *Chem. Sci.*, 2018, **9**, 1795–1802.
- 48 E. Zhu, X.-X. Liu, A.-J. Wang, T. Mao, L. Zhao, X. Zhang and C.-Y. He, *Chem. Commun.*, 2019, **55**, 12259–12262.
- 49 M. Ke, Q. Feng, K. Yang and Q. Song, *Org. Chem. Front.*, 2016, **3**, 150–155.
- 50 S. Sumino, M. Uno, T. Fukuyama, I. Ryu, M. Matsuura, A. Yamamoto and Y. Kishikawa, *J. Org. Chem.*, 2017, **82**, 5469–5474.
- 51 Y. Bai, L. Cao, S. Li, G. a. Zhang, Y. Liu, F. Zhao and J. Wu, *Org. Lett.*, 2023, **25**, 6511–6516.
- 52 N. A. Phillips, G. J. Coates, A. J. P. White and M. R. Crimmin, *Chem.–Eur. J.*, 2020, **26**, 5365–5368.
- 53 C. Zhu, M.-M. Sun, K. Chen, H. Liu and C. Feng, *Angew. Chem., Int. Ed.*, 2021, **60**, 20237–20242.
- 54 L. Tang, Z.-Y. Liu, W. She and C. Feng, *Chem. Sci.*, 2019, **10**, 8701–8705.
- 55 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.
- 56 F. Ye, Y. Ge, A. Spannenberg, H. Neumann, L.-W. Xu and M. Beller, *Nat. Commun.*, 2021, **12**, 3257.
- 57 G. Zweifel, H. Arzoumanian and C. C. Whitney, *J. Am. Chem. Soc.*, 1967, **89**, 3652–3653.
- 58 D. S. Matteson, *Chem. Rev.*, 1989, **89**, 1535–1551.
- 59 R. J. Armstrong and V. K. Aggarwal, *Synthesis*, 2017, **49**, 3323–3336.
- 60 M. A. Beckett, G. C. Strickland, J. R. Holland and K. Sukumar Varma, *Polymer*, 1996, **37**, 4629–4631.
- 61 I. B. Sivaev and V. I. Bregadze, *Coord. Chem. Rev.*, 2014, **270–271**, 75–88.
- 62 A. Yokawa and S. Ito, *Chem.–Asian J.*, 2020, **15**, 3432–3436.
- 63 N. Kaur, in *Metal and Nonmetal Assisted Synthesis of Six-Membered Heterocycles*, ed. N. Kaur, Elsevier, 2020, pp. 351–412.
- 64 A. Chaudhary, K. Singh, N. Verma, S. Kumar, D. Kumar and P. P. Sharma, *Mini-Rev. Med. Chem.*, 2022, **22**, 2736–2751.
- 65 E. Khan, *ChemistrySelect*, 2021, **6**, 3041–3064.
- 66 S. De, A. Kumar S K, S. K. Shah, S. Kazi, N. Sarkar, S. Banerjee and S. Dey, *RSC Adv.*, 2022, **12**, 15385–15406.
- 67 J.-B. Xia, C. Zhu and C. Chen, *J. Am. Chem. Soc.*, 2013, **135**, 17494–17500.
- 68 K. Chen, N. Berg, R. Gschwind and B. König, *J. Am. Chem. Soc.*, 2017, **139**, 18444–18447.
- 69 *Difluoromethane (HFC-32) CAS No. 75-10-5*, European Centre for Ecotoxicology and Toxicology of Chemicals, Brussels, 2nd edn, 2008.
- 70 D. J. Sheldon and M. R. Crimmin, *Chem. Soc. Rev.*, 2022, **51**, 4977–4995.
- 71 M. Miele and V. Pace, *Aust. J. Chem.*, 2021, **74**, 623–625.
- 72 X. Ispizua-Rodriguez, C. Barrett, V. Krishamurti and G. K. Surya Prakash, in *The Curious World of Fluorinated Molecules*, ed. K. Seppelt, Elsevier, 2021, vol. 6, pp. 117–218.
- 73 R. Britton, V. Gouverneur, J. H. Lin, M. Meanwell, C. Ni, G. Pupo, J. C. Xiao and J. Hu, *Nat. Rev. Methods Primers*, 2021, **1**, 48.

