

Cite this: *Chem. Sci.*, 2025, 16, 6975

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Diversifying fluoroalkanes: light-driven fluoroalkyl transfer *via* vinylboronate esters†

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We outline a new synthetic strategy to prepare tertiary difluoromethylene-containing molecules from fluoroalkane precursors and vinyl-pinacol boronic ester (vinyl-BPin) reagents. Under irradiation, fluoroalkyl(vinyl)pinacol boronate esters [vinyl-BPin-CF₂R][−] undergo a conjugate radical addition process to form new C–C bonds, which does not require air-free conditions and tolerates oxygen and nitrogen-containing heterocycles as well as many classical functional groups. We demonstrate the versatility of this method through a one-pot synthetic protocol using RCF₂H precursors and vinyl-BPin reagents in the presence of a Brønsted base. Widely available fluoroalkanes (HFC-23 and HFC-32) and difluoromethyl heteroarenes are used in this protocol, representing distinct strategies to generate tertiary –CF₂H, –CF₃ and –CF₂–heteroarene molecules. Experimental and theoretical mechanistic investigations reveal a reaction sequence involving radical initiation followed by an ionic 1,2-boronate rearrangement.

Received 6th March 2025
Accepted 16th March 2025

DOI: 10.1039/d5sc01776a

rsc.li/chemical-science

Introduction

Targeted fluorination of organic compounds can often favorably modulate their physical and chemical properties,^{1–3} and this strategy is prominently used in the development of medicinal chemistry, agrochemistry, and material sciences.^{4–6} Importantly, ~30% of marketed pharmaceuticals contain one or more fluorine atoms.^{4,6} While trifluoromethyl (–CF₃) architectures are the most widely occurring fluoroalkyl group in marketed drugs,^{7–9} other fluoroalkyl units, such as difluoromethylenes, are attractive candidates for pharmacophore development because they are bioisosteres of carbonyl and ether groups (Fig. 1a).^{10–12}

Fluorinated boronic esters (such as α -trifluoromethyl and α -difluoroalkyl boronic esters) represent an attractive entry point for the construction of more complex fluoroalkylated compounds because they can be diversified through cross-coupling and homologation chemistry.^{13–20} Current strategies to prepare α -trifluoromethyl boronic esters include the addition of either 2,2,2-trifluorodiazoethane or 2-trifluoromethyl oxirane derivatives to an organoboron precursor (Fig. 1b); however, these methods are limited to –CF₃ units^{21–23} and synthetic routes to prepare α -difluoroalkylated boronic esters are not known.

1,2-Boronate rearrangements are a class of reactions used for the construction of new C–CF₂R bonds and proceed with retention of the boronic ester.^{24–27} Although the addition of electrophiles to a boronate ester is the most common method to induce 1,2-boronate rearrangements,^{28–39} recent reports by Studer,^{40–42} Aggarwal,^{43,44} and Renaud⁴⁵ showed an alternative

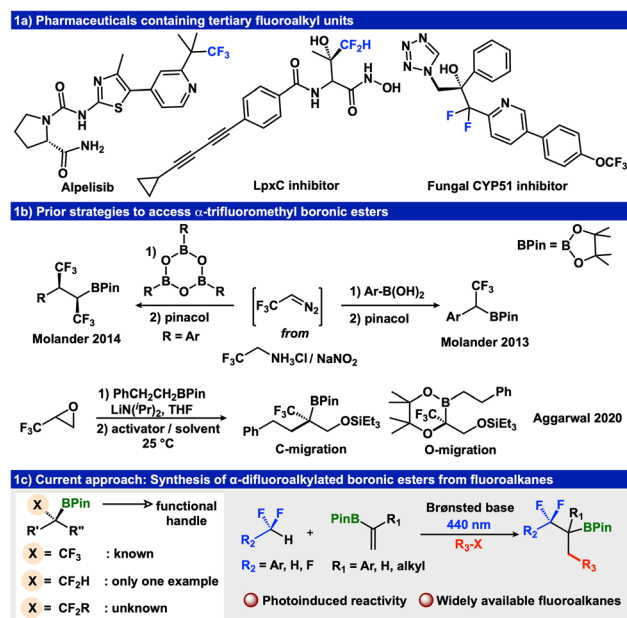


Fig. 1 (a) Pharmaceutically relevant compounds featuring tertiary fluoroalkyl groups (b) prior examples of α -trifluoromethyl boronic ester synthesis, and (c) current approach: synthesis of α -difluoroalkylated boronic esters.

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† Electronic supplementary information (ESI) available: Experimental and computational details. See DOI: <https://doi.org/10.1039/d5sc01776a>

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approach: radical addition.^{40,41,43–46} These reactions enable the construction of tertiary boronic esters through the addition of a C–X bond to a vinyl BPin. However, these prior examples are limited to non-fluorinated nucleophiles, likely due to challenges in forming the key RCF₂[−] vinyl boronate.⁴⁷

Our group previously established that fluoroalkyl vinyl-BPin can serve as an entry point to α,α -difluoroalkylated olefin products,⁴⁷ and can be prepared from the corresponding B₃N₃Me₆ adducts [RCF₂B₃N₃Me₆][−], ultimately derived from deprotonation of the difluoroalkane (*i.e.* RCF₂H). Key precedent using non-fluorinated alkyl groups has established that radical-induced conjugate addition triggers 1,2-boronate rearrangements,^{40–45,47} and in this manuscript, we develop this strategy to prepare tertiary carbon centers that are uniquely substituted with fluoroalkyl groups (RCF₂H; R = H, F, Ph, heteroarene) and -BPin units (Fig. 1c).

We previously found that the fluoroalkyl binding affinity of borane Lewis acids can be used to describe and predict the stability of fluoroalkyl borane adducts.^{48–50} The free energy of CF₃[−] binding (ΔG) to boron-based Lewis acids is a useful metric to correlate with the stability of a given Lewis acid–CF₃[−] adduct.⁴⁹ Large $-\Delta G$ values indicate irreversible binding of CF₃[−] to the Lewis acid while adducts with small $-\Delta G$ values are prone to decomposition. To determine the fluoroalkyl affinity of BPin Lewis acids, we calculated the ΔG values using DFT at the M06-2X-D3/6-311++G(d,p)/SMD(1,2-dimethoxyethane) level of theory (Fig. 2, ESI S28–S32[†]). Based on the DFT calculations, vinyl-BPin species have a higher affinity for fluoroalkyl anions than B₃N₃Me₆. Additionally, CF₃[−] has the lowest affinity for vinyl-BPin species while CF₂H[−] has the highest.

Results and discussion

To establish the feasibility of conjugate addition, we allowed [K(18-crown-6)(vinyl-BPin–CF₂Ph)] (1a) and 2-bromoacetophenone (2) to react in tetrahydrofuran-dimethyl sulfoxide (2 : 1) for 18 h at 28 °C under 440 nm irradiation (Kessil lamp). In the presence of 1 mol% Ru(bpy)₃Cl₂·6H₂O as a photocatalyst, the reaction afforded the conjugate addition product 3a with 38% conversion, as assessed by ¹⁹F NMR spectroscopy (Table 1, entry 1). We found that even in the absence of Ru(bpy)₃Cl₂·6H₂O, the

Table 1 Optimization of radical-initiated 1,2-boronate rearrangement^a

Entry	Photocatalyst/activator	Solvent	Yield 3a
1	Ru(bpy) ₃ Cl ₂ ·6H ₂ O (1 mol%)	THF : DMSO (2 : 1)	38%
2	—	THF : DMSO (2 : 1)	35%
3	Ru(bpy) ₃ Cl ₂ ·6H ₂ O (1 mol%)	THF : DMSO (2 : 1)	0% ^b
4	NaI (50 mol%)	THF : DMSO (2 : 1)	53%
5	NaI (150 mol%)	THF : DMSO (2 : 1)	36%
6	NaI (50 mol%)	THF : DME (2 : 1)	63%
7	NaI (50 mol%)	THF : DME (2 : 1)	70% ^c
8	—	THF : DME (2 : 1)	62% ^d
9	[^t Bu ₄ N]I (50 mol%)	THF : DME (2 : 1)	68%

^a 1a (0.023 mmol), PhCOCH₂Br (0.035 mmol), THF/DMSO or DME (1.0 mL), 18 h, 28 °C, 440 nm blue light. ¹⁹F NMR yields are reported (PhOCF₃ used as internal standard). ^b Performed in the absence of blue light. ^c 50 mol% 15-C-5 was used. ^d PhCOCH₂I used instead of PhCOCH₂Br.

product formed in 35% yield, suggesting that no photocatalyst is required (Table 1, entry 2). No reaction occurred in the absence of blue light, even when heated to 80 °C (Table 1, entry 3, ESI S11[†]), consistent with a photo- rather than a thermal-induced reaction. We evaluated a series of solvents and activators and found that a combination of 50 mol% NaI/15-C-5 in tetrahydrofuran-dimethoxyethane (2 : 1) furnished the final product with up to 70% conversion, as assessed by ¹⁹F NMR spectroscopy (Table 1, entries 4–7, ESI S11–S13[†]). In the absence of 15-C-5, we observed <10% NaF by ¹⁹F NMR spectroscopy (−121.3 ppm), which we attribute to Na-promoted fluoride elimination.⁵¹ To clarify the role of NaI as a reaction additive, we performed two control experiments: (i) a reaction using PhCOCH₂I, which afforded 3a in a similar yield (62%) (Table 1, entry 8), and (ii) using tetrabutyl ammonium iodide ([^tBu₄N]I) as an alternative iodide source, which yielded 3a in 68%. (Table 1, entry 9). These results are consistent with an iodide (I[−]) promoted Finkelstein reaction that generates a weaker C–I (*vs.* C–Br) bond, thus facilitating homolysis.^{43,52,53}

After achieving 70% conversion of 3a, we assessed the reaction scope by varying the vinyl-BPin derivatives (Fig. 3, entries 3a–3d). Aliphatic vinyl-BPin reagents responded moderately, with 28–65% isolated yields (Fig. 3, entries 3b–3d). We explored the scope of radical coupling partners by investigating *p*-substituted 2-bromoacetophenone derivatives (Fig. 3) and found both electron-rich and deficient substrates afforded similar yields (3e (53%), 3f (62%) and 3g (60%)). Pyridine and benzofuran units are common structural motifs in pharmaceutical and medicinal chemistry,^{54–58} and substrates with these motifs afforded 3i (59%) and 3j (55%) in good isolated yields. We examined the viability of a series of radical precursors with this methodology (Fig. 3). 2-Iodoacetone nitrile afforded the difluoromethyl-containing conjugate addition product 3k in

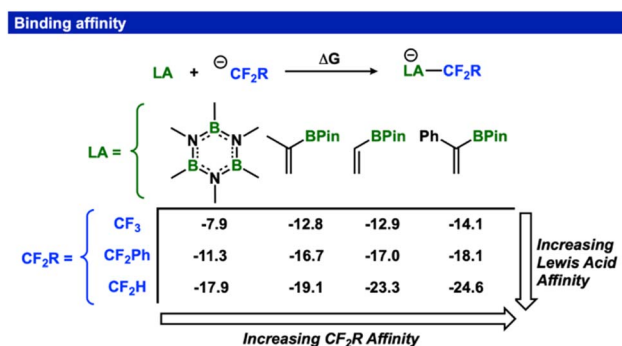


Fig. 2 Calculated ΔG (kcal mol^{−1}) values for fluoroalkyl binding. M06-2X-D3/6-311++G(d,p)/SMD(1,2-dimethoxyethane), *T* = 25 °C.



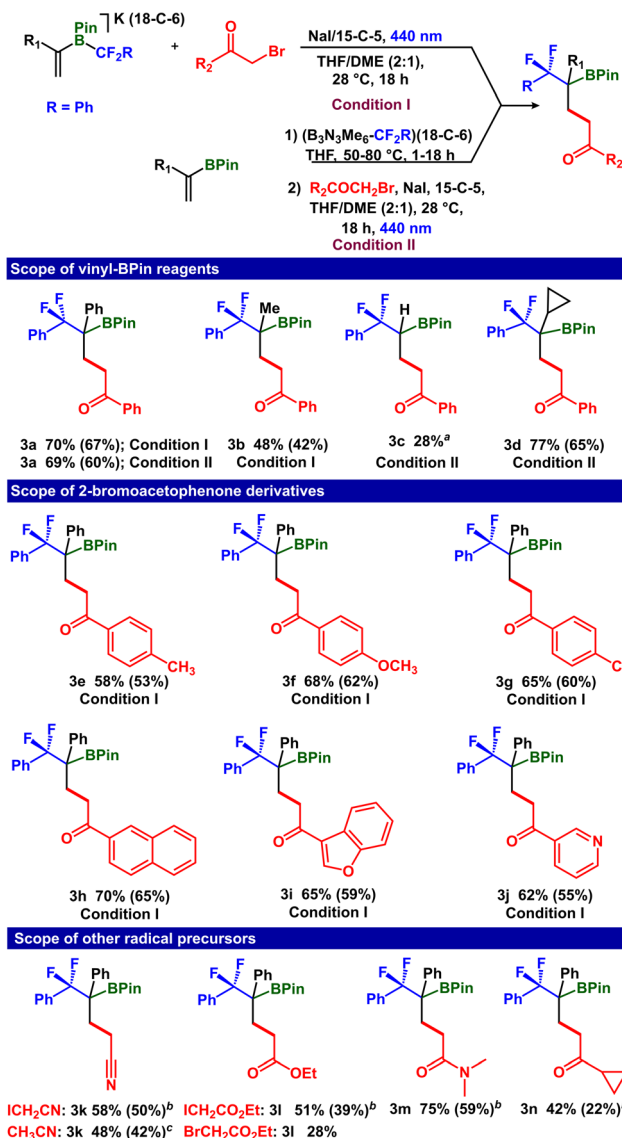
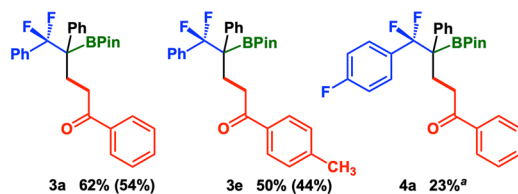
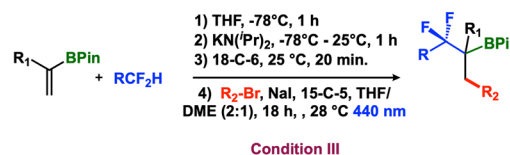


Fig. 3 Scope of vinyl-BPin, 2-bromo acetophenone derivatives and other radical precursors. Fluoroalkyl vinyl-BPin (0.1 mmol), R₂-COCH₂Br (0.15 mmol), NaI (0.05 mmol), 15-C-5 (0.05 mmol), THF/DME (2.4 mL), 18 h, 28 °C, 440 nm light [Me₆B₃N₃CF₂R](K(18-C-6)) (0.15 mmol), vinyl-BPin (0.15 mmol), ArCOCH₂Br (0.23 mmol), NaI (0.075 mmol), 15-C-5 (0.075 mmol), THF/DME (3.0 mL), 18 h, 28 °C, 440 nm light. ¹⁹F NMR yields (PhOCF₃ used as internal standard). Isolated yields are in parentheses. ^a¹⁹F NMR yield only (unstable to column chromatography). ^b Iodide radical precursor was used instead of bromide (No NaI or 15-C-5 added). ^c 2.0 equiv. redox-active ester (1,3-dioxoisindolin-2-yl adamantane-1-carboxylate) was used.

58% yield. Alternatively, **3k** was formed from acetonitrile in 48% yield when 2 equivalents of redox-active ester (1,3-dioxoisindolin-2-yl adamantane-1-carboxylate) was used as a radical initiator. Ethyl haloacetates furnished **3l** in 51% and 28% yield for X = I and X = Br, respectively. 2-Iodo-*N,N*-dimethylacetamide afforded **3m** in 75% yield. Finally, 2-bromo-1-cyclopropylethan-1-one furnished **3n** in 42% yield. These results demonstrate compatibility of the method with radical precursors across a wide range of electronic environments.

One-pot photochemical reactivity



Scope of fluoroalkanes

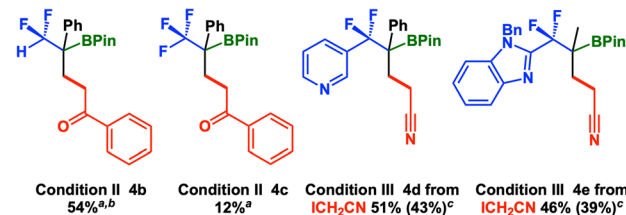


Fig. 4 Scope of one-pot reactions (top) and scope in fluoroalkanes (bottom). Vinyl-BPin (0.15 mmol), fluoroalkane (RCF₂H) (0.15 mmol), R₂-Br (0.23 mmol), NaI (0.075 mmol), 15-C-5 (0.075 mmol), THF/DME (3.0 mL), 18 h, 28 °C, 440 nm light. ¹⁹F NMR yields (PhOCF₃ used as internal standard). Isolated yields in parentheses. ^a¹⁹F NMR yield. ^b Unstable to column chromatography. ^c No NaI or 15-C-5 was added as iodide radical precursor was used instead of bromide.

To improve the broad accessibility of the protocol, we evaluated the requirement of B₃N₃Me₆ by examining the direct deprotonation of ArCF₂H by 1.5 equiv. KN(iPr)₂ in the presence of vinyl-BPin (condition III).⁴⁷ We found that deprotonation and subsequent conjugate radical addition were achievable in a one-pot sequence where both the fluoroalkyl and 2-bromoacetophenone were modified (Fig. 4). 2-Bromoacetophenones with *p*-H and *p*-CH₃ afforded moderate isolated yields (**3a** (62%) and **3e** (50%)) comparable to the borazine protocol (*cf.* Fig. 3), and 1-(difluoromethyl)-4-fluorobenzene furnished **4a** with 23% yield.

We also investigated the scope of the fluoroalkyl units derived from hydrofluorocarbons (HFCs) and difluoromethyl heteroarenes. Our group previously established a strategy to repurpose refrigerants or HFCs as chemical synthons for -CF₃ and -CF₂H sources.^{48,49,59} We evaluated the feasibility of a one-pot difluoromethylation and trifluoromethylation reaction using [K(18-C-6)(B₃N₃Me₆-CF₂H)] and [K(18-C-6)(B₃N₃Me₆-CF₃)] with a vinyl-BPin derivative (Fig. 4) and obtained **4b** and **4c** with 54% and 12% conversion, respectively. We found that 3-(difluoromethyl) pyridine and *N*-benzyl-2-difluoromethylbenzimidazole both were also viable fluoroalkyl precursors and afforded **4d** (51%) and **4e** (46%) when using iodoacetone as the radical source (see details in ESI†).

To elucidate the operative mechanistic pathway, we performed a series of experiments. Without irradiation, no product formed, which suggests that photochemical activation is necessary (Table 1, entry 3). To examine whether radical



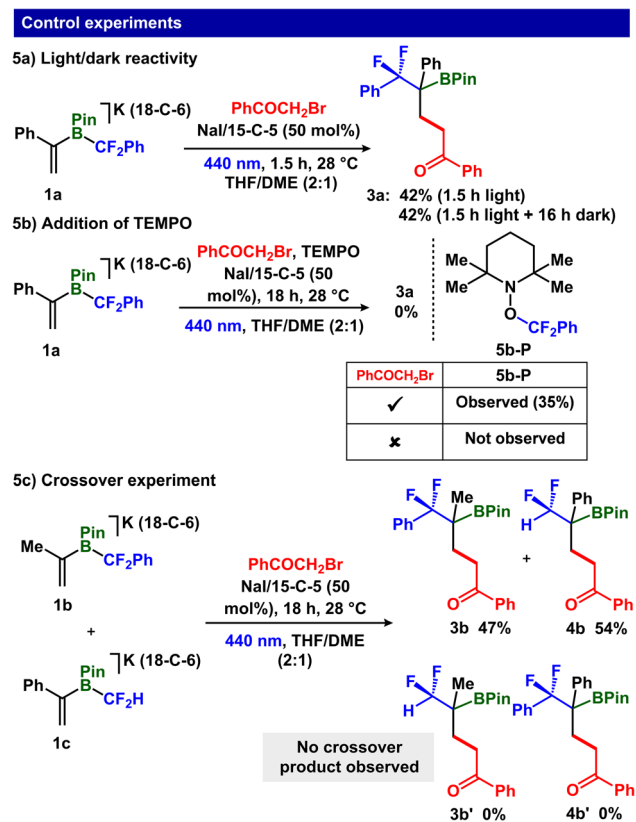


Fig. 5 (a) Light/dark reactivity. (b) TEMPO as a radical trap. (c) Crossover experiment.

propagation is operative in this system, we found that, although 42% conversion of **3a** occurred within 1.5 h of constant irradiation, no additional product formed after stirring in the absence of light for another 16.5 h (Fig. 5a).⁶⁰ Additionally, during quantum yield measurements, we found that $\Phi = 0.21$ for the formation of **3k** (details in ESI†). Unfortunately, neither of these results (no reactivity post-irradiation and $\Phi < 1$) can confirm or refute a radical propagation mechanism.⁶⁰ To investigate the presence of radical intermediates, we introduced the radical quencher, TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl), which completely shut down the reaction (*i.e.* 0% conversion of product **3a**), with the formation of the TEMPO-CF₂Ph adduct (**5b-P**; Fig. 5b). These results implicate the intermediacy of fluoroalkyl radicals that may undergo intra- or intermolecular coupling. To examine the feasibility of the latter pathway, we performed a crossover experiment using vinylboronate esters containing a CF₂Ph group (**1b**) and a CF₂H group (**1c**). When subjected to a conjugate addition reaction in the presence of PhCOCH₂Br (Fig. 5c), we only observed **3b** and **4b**, with no crossover products (**3b'** and **4b'**). These results suggest that intermolecular fluoroalkyl transfer does not occur, and the intramolecular pathway was further investigated by DFT calculations.

DFT analysis of the reaction mechanism was performed using M06-2X-D3/6-311++G(d,p) + LANL2DZ(I)/SMD(1,2-dimethoxyethane) and modeled using iodoacetonitrile. Initiation of the reaction occurs *via* homolysis of the C-I bond in

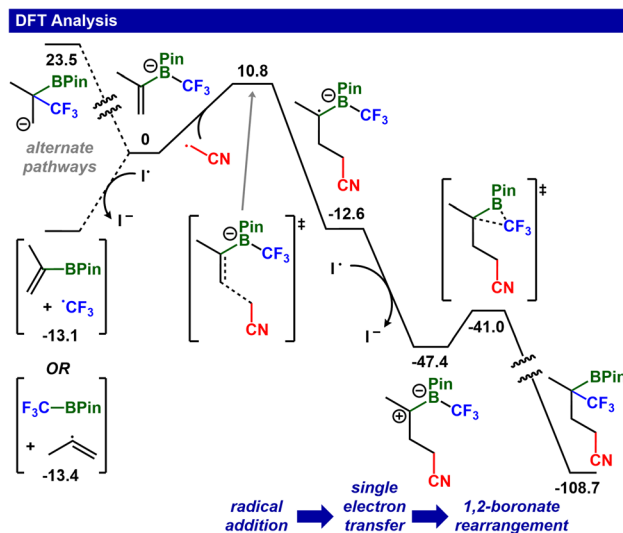
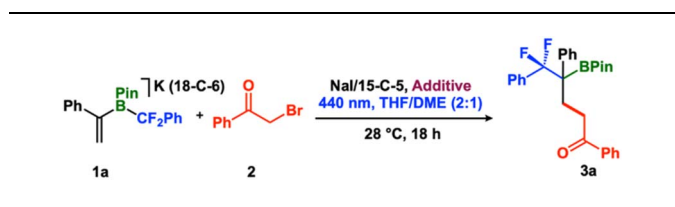


Fig. 6 Calculated Gibbs free energies (in kcal mol⁻¹) of the proposed mechanism. M06-2X-D3/6-311++G(d,p) + LANL2DZ(I)/SMD(1,2-dimethoxyethane), $T = 25$ °C. The analysis starts with $\cdot\text{CH}_2\text{CN}$, which is formed from homolysis of ICH₂CN with light.

iodoacetonitrile ($\Delta G = 42.3$ kcal mol⁻¹) (Fig. 6 and ESI S28–S30†). Addition of the $\cdot\text{CH}_2\text{CN}$ radical to the fluoroalkylated vinyl-Bpin ($\Delta G^\ddagger = 10.8$ kcal mol⁻¹) generates an anionic radical species that can undergo single electron transfer (SET) to I⁻ (termination) or iodoacetonitrile (propagation). Importantly, the termination step is thermodynamically favorable ($\Delta G = -34.8$ kcal mol⁻¹, $E = 1.51$ V) while the propagation step is not ($\Delta G = 7.5$ kcal mol⁻¹, $E = -0.33$ V) (ESI S28 and S29†), suggesting that radical propagation is not a significant contributor in the reaction mechanism. After SET, the boronate ester undergoes ionic rearrangement ($\Delta G^\ddagger = 6.4$ kcal mol⁻¹) to afford the final product, and these calculated results are consistent with mechanistic proposals on related non-fluoroalkylated vinyl boronate esters.⁴⁵ Alternate mechanisms were also investigated using DFT analysis (Fig. 6 (left), also see full computational details in ESI†). A non-radical mechanism can proceed *via* a 1,2-boronate rearrangement as the initial step to produce a carbanion intermediate; however, the barrier ($\Delta G^\ddagger > 23.5$ kcal mol⁻¹) is significantly higher than that when radical addition is the first step. A third pathway beginning with single-electron transfer leads to radical release (trifluoromethyl or 2-propenyl); however, this pathway is inconsistent with the absence of radical crossover products.

The developed reaction sequence provides a unique protocol for accessing α -difluoromethylene-containing molecules featuring both BPin and carbonyl units. To evaluate the tolerance of the developed method to common functional groups, we assessed how the yield of a representative reaction (forming **3a**) responds to a variety of exogenous additives.⁶¹ We found that the reaction was highly robust, with minimal changes to the yield in the presence of aldehydes, ketones, amides, acyl chlorides, amines, alcohols, water, and air (Table 2). These results implicate a high probability of reaction compatibility



Table 2 Tolerance to additives^a

Additive	Yield (%)
—	70
PhCHO	68
PhCOPh	69
PhCOCl	68
PhCONMe ₂	74
PhCO ₂ Et	67
PhOH	58
PhCH ₂ NH ₂	56
Et ₃ N	77
<i>i</i> -Pr ₂ NEt	78
H ₂ O	73
PhCH ₂ I	70
Undistilled DME	68

^a **1a** (0.015 mmol), PhCOCH₂Br (0.023 mmol), additive (0.023 mmol) THF/DME (1.2 mL), 18 h, 28 °C, 440 nm blue light. ¹⁹F NMR yields reported (PhOCF₃ used as internal standard).

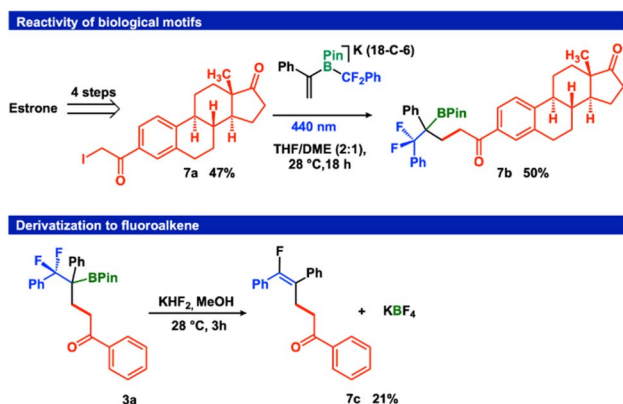


Fig. 7 Reactivity of estrone derivative (top) and derivatization reaction to form a monofluoroalkene (bottom).

with many functional groups used in pharmaceutical development.

To examine compatibility with more complex substrates, we evaluated the viability of the methodology with an estrone derivative **7a** (47%), which furnished **7b** in 50% isolated yield. Importantly, this substrate highlights high selectivity and reaction compatibility, properties that are needed when pursuing late-stage fluorination of biologically-relevant steroid cores (Fig. 7 and ESI S19[†]). Finally, we found that the Bpin unit in **3a** can be induced to undergo an elimination reaction when treated with KHF₂, forming monofluoroalkene **7c** in 21% yield (Fig. 7). We propose the monofluoroalkene forms by defluorination of an intermediate $-\text{BF}_3\text{K}$ intermediate (BF_4^- noted in the ¹⁹F NMR spectrum). Importantly, such monofluoroalkenes

are a sought-after class of molecules that are bioisosteres of amides, exhibiting enhanced stability and bioactivity,^{10,62} highlighting another potential application of the developed methodology.

Conclusion

In conclusion, we developed a metal-free strategy to generate quaternary carbon centers containing both a fluoroalkyl and a BPin unit by coupling a conjugate radical addition to vinyl-pinacol boronate esters with 1,2-boronate rearrangements. This synthetic strategy provides a unique application of directly using fluoroalkyl nucleophiles derived from fluoroalkanes for the synthesis of complex fluorinated molecules. We demonstrated the versatility of this method through one-pot syntheses of tertiary difluoromethylene-containing molecules directly from RCF₂H precursors with vinyl-BPin reagents in the presence of a Brønsted base. This reaction sequence can enable the use of widely available CH₂F₂ (HFC-32) and HCF₃ (HFC-23) as chemical synthons, which are currently underutilized precursors. The method is versatile and compatible with undistilled solvents, competitive functional groups, and biologically active scaffolds, providing access to unique fluoroalkylated compounds that may be subjected to additional derivatization reactions to generate medicinally relevant fluoroalkylated compounds.

Data availability

All relevant experimental data and characterization details are provided in the ESI.[†]

Author contributions

The manuscript was written through the contributions of all authors. The project was designed by K. Chakrabarti and N. K. Szymczak with input during execution from all authors. All optimizations, syntheses and characterizations were performed by K. Chakrabarti and C. Sunil. The theoretical calculations and actinometry were performed by B. M. Farris. S. Berritt, K. Cas-saidy and J. Lee provided insights related to the project development.

Conflicts of interest

NKS holds a patent relating to difluoroalkyl transfer reagents.

Acknowledgements

This work was supported by the NSF (CHE 1955284) and by the Advanced Research Computing at the University of Michigan for computational resources. We thank Dr Russell Bornschein for Mass Spectrometry assistance.



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