nature communications

Article

https://doi.org/10.1038/s41467-024-52842-0

Defluorinative functionalization approach led by difluoromethyl anion chemistry

Received: 17 May 2024

Accepted: 24 September 2024

Published online: 07 January 2025

Check for updates

Kensuke Muta[1,2], Kazuhiro Okamoto[1], Hiroki Nakayama[1], Shuto Wada[1] & Aiichiro Nagaki[1]

Organofluorine compounds have greatly benefited the pharmaceutical, agrochemical, and materials sectors. However, they are plagued by concerns associated with Per- and Polyfluoroalkyl Substances. Additionally, the widespread use of the trifluoromethyl group is facing imminent regulatory scrutiny. Defluorinative functionalization, which converts the trifluoromethyl to the difluoromethyl motifs, represents the most efficient synthetic strategy. However, general methods for robust C(sp^3)–F bond transformations remain elusive due to challenges in selectivity and functional group tolerance. Here, we present a method for C(sp^3)–F bond defluorinative functionalization of the trifluoromethyl group via difluoromethyl anion in flow. This new approach tames the reactive difluoromethyl anion, enabling diverse functional group transformations. Our methodology offers a versatile platform for drug and agrochemical discovery, overcoming the limitations associated with fluorinated motifs.

Organofluorine compounds have played a pivotal role in diverse domains such as pharmaceuticals, agrochemicals, and materials due to the distinctive properties imparted by the incorporation of fluorine atoms[1–3]. However, the recent emergence of the Per- and Polyfluoroalkyl Substances (PFAS) issue has raised significant environmental and human health concerns[4]. Although trifluoromethyl group, previously pivotal in fluorine chemistry, is not necessarily bioaccumulative or toxic in itself, the European Union (EU) released new guidelines that encompass trifluoromethyl group within the scope of PFAS regulations in 2023[5]. Consequently, such regulations against these compounds are likely to become even more stringent in the future, underscoring the urgency for the development of alternative functional groups. In this context, the difluoromethyl motif emerges as a promising substituent that offers properties of improved potency-modulated lipophilicity akin to the trifluoromethyl group while simultaneously serving as a hydrogen bond donor and bioisostere of ethers and thiols[6–8]. This attribute endows bioactive compounds with unique characteristics that hold promise for advancements in the pharmaceutical and agrochemical domains (Fig. 1a).

The most efficient synthetic approach to access difluoromethyl compounds is through direct cleavage of the C(sp^3)–F bond in readily available trifluoromethyl compounds that are prevalent in numerous bioactive compounds[9]. Furthermore, transformation of the potentially regulated trifluoromethyl groups into useful functional groups represents a significant strategy to address the emerging societal challenges associated with the presence of these motifs. Despite the strength and remarkable inertness of C–F bonds, transformation reactions of the C(sp^2)–F bond for defluorinative functionalization have already been achieved via well-established S_NAr-type reactions[10]. Metal-catalyzed transformation reactions involving defluorinated functional groups such as aryl, silyl, and boryl moieties have also emerged as effective methods to cleave C(sp^2)–F bonds (Fig. 1b, top)[11,12]. In contrast, the direct functional-group transformation of the formidable C(sp^3)–F bonds remains an underexplored area (Fig. 1b, bottom). This limitation arises from the necessity of employing highly reactive reagents and harsh conditions to cleave the robust C(sp^3)–F bond, along with the significant challenge of maintaining functional group tolerance[9,10].

Approaches to the direct functionalization of C(sp^3)–F bonds involve three main types of intermediates: radical[13–23], carbocation[24–27], and carbanion species[28–32]. However, a common challenge arises from the inherent instability of the fluorine-containing intermediate produced. If the reaction intermediate involves an unstable active species,

[1]Department of Chemistry, Graduate School of Science, Hokkaido University, Sapporo, Japan. [2]Central Glass Co. Ltd., New-STEP Research Center, Kawagoe City, Saitama, Japan. e-mail: nagaki@sci.hokudai.ac.jp

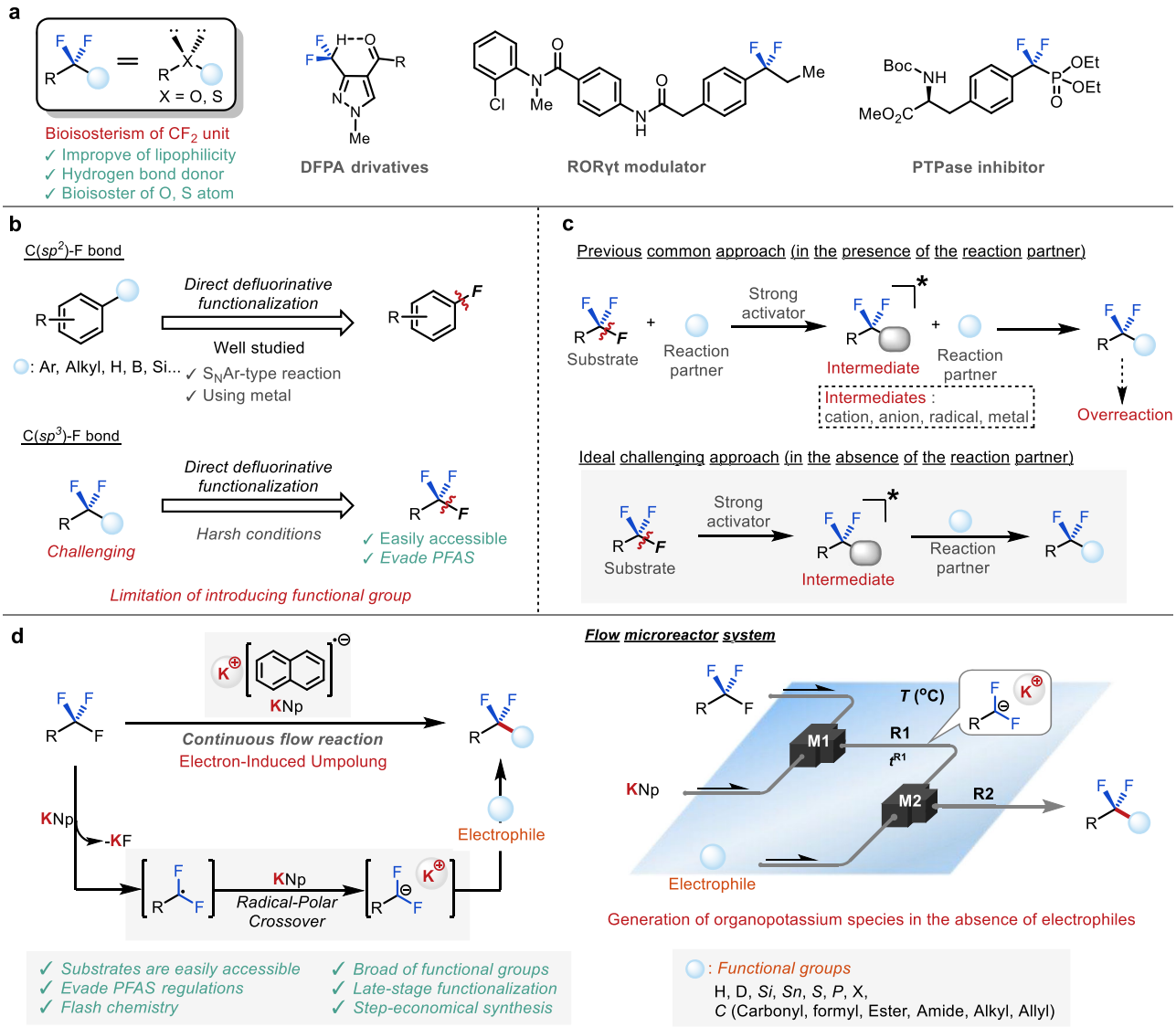

Fig. 1 | Representative bioactive difluoromethyl compounds, and strategies for defluorinative functionalization. a Selected pharmaceutical difluoromethyl compounds. **b** Developments of C(sp^2)–F bond functionalization and the challenging goal of C(sp^3)–F bond functionalization. **c** Previous common approaches and an ideal challenging approach for defluorinated functionalization of C(sp^3)–F bond. **d** This work: New strategy for C(sp^3)–F bond functionalization via electron-induced umpolung in the absence of electrophiles.

the reaction must be carried out while quenching in the presence of the reaction partner. Consequently, the applicability of these methods as general functionalization strategies is compromised due to their reliance on functional groups resistant to strong activation conditions (Fig. 1c, top). In particular, generating fluorine-containing carbanion species necessitates umpolung, which entails heightened activation barriers. Furthermore, the intact fluorine atoms on the activated carbon render this active species extremely destabilized. Additionally, achieving mono-selective defluorination is challenging because the remaining C(sp^3)–F bonds in the product weaken progressively as defluorination proceeds[33]. The ideal solution to this problem is the instantaneous generation of active species in the absence of the reaction partner. However, direct defluorination remains highly challenging due to the extreme instability of fluorine-containing intermediates (Fig. 1c, bottom). Recently, Ogoshi et al. reported utilizing transition metals to achieve stable fluorine-containing intermediates, albeit with limited functional groups that can be introduced, restricted to hydrogen[34–37]. Young et al. successfully addressed these challenges by employing a stepwise approach to stable cationic intermediates using a Frustrated Lewis pair. However, this method is accompanied by excessively long reaction times, along with concerns about functional group tolerance on the substrate due to the requirement of a strong Lewis acid[38]. Therefore, a direct and efficient method to introduce various functional groups remains an elusive goal for C(sp^3)–F bond functionalization and necessitates new strategies.

Flow microreactors have shown remarkable proficiency in controlling unstable reactive species even without a reaction partner, providing chemoselective control. Here, we describe the instantaneous electron-induced umpolung of trifluoromethyl compounds by organopotassium-reducing agents under flow conditions in the absence of electrophiles (Fig. 1d). This approach allows rapid and efficient access to various difluoromethyl compounds. This reaction design, which tames difluoromethyl anions, offers ultimate solutions to several challenges, including functional group tolerance, selectivity, late-stage functionalization, and synthesis that saves steps and time. We propose and demonstrate a new methodology for drug and agrochemical discovery, offering rapid access and high productivity for targeting drugs and their candidate compounds.

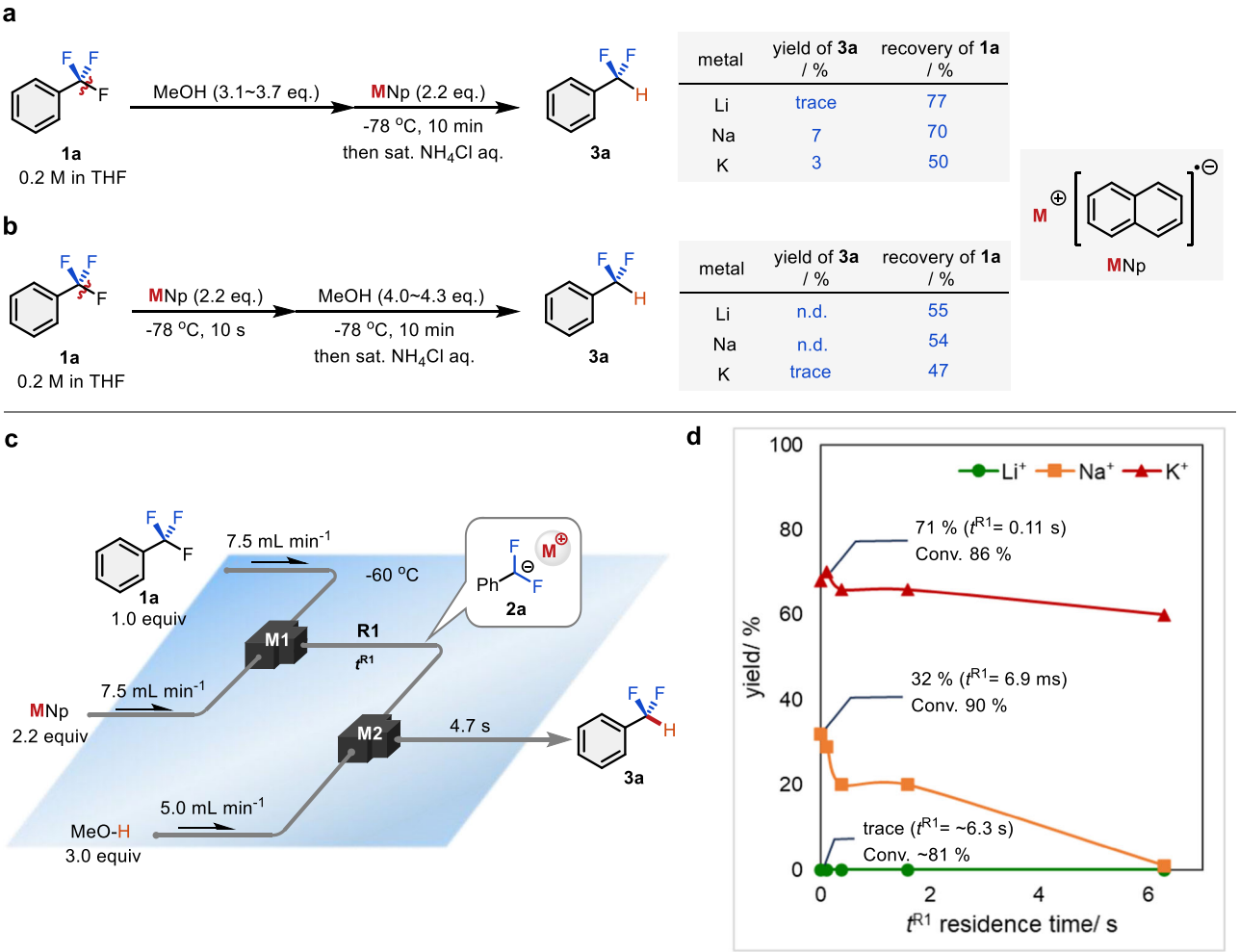

Fig. 2 | Hydrodefluorination under batch and flow conditions. a Using batch reactor in the presence of the methanol. **b** Using batch reactor in the absence of the methanol. **c** Flow microreactor system for the generation and reaction of the difluoromethyl anion in the absence of the electrophile. **d** Effect of alkali metal on defluorination at −60 °C.

Results

For a proof-of-concept and optimizations

For a proof-of-concept study, we initially assessed whether alkali metal naphthalenides (MNp) could effectively cleave the C(sp^3)–F bond and promote umpolung instantly in a conventional batch reaction. The significance of generating radical anion species in defluorination has been demonstrated through photoredox catalysis[13–18]. MNp was chosen not only for its strong organic radical-reducing properties but also for its affordability and ease of preparation in readily available solutions. The reduction potential of naphthalenide anion ($C_{10}H_8^-$) is −3.10 V[39]. Although the reduction potential of naphthalenide anion including counter cations would be reduced ($E > -3.10$ V), the reduction potential of trifluoromethyl arenes is approximately −2.50 V[14]. Thus, we speculated that the trifluoromethyl compound undergoes a two-electron reduction. As a model reaction, we performed the hydrodefluorination of benzotrifluoride **1a** at −78 °C in the presence of methanol as an electrophile, yielding the corresponding product **3a**. The best conversion was achieved using the potassium analog (KNp; Fig. 2a). While these results demonstrate the proof-of-concept for C(sp^3)–F bond functionalization, limitations arise due to the conditions requiring the presence of an electrophile.

Subsequently, we investigated the selective hydrodefluorination of **1a** in the absence of the electrophile. However, the ex-situ generation of highly unstable intermediates, such as difluoromethyl anions, proved challenging in a batch reactor system (Fig. 2b). We have previously reported that unstable intermediates can be utilized for synthesis in the absence of electrophiles using a flow microreactor[40]. These systems are particularly effective in controlling unstable reactive species in the absence of electrophiles (Fig. 2c). The impact of the countercation in these experiments was notably pronounced when using lithium as the alkali metal cation. The conversion of **1a** experienced a considerable decrease, resulting in only a trace of the desired compound. Conversely, with softer alkali metal cations such as sodium and potassium, there was a marked improvement in the yield of difluoromethylbenzene. Particularly, the use of the softest organopotassium reductant exhibited commendable conversion and facilitated the most successful selective hydrodefluorination reaction (Fig. 2d). This phenomenon can be attributed to the improved stability of the difluoromethyl anion intermediate **2a** induced by the potassium countercation. The effect of alkali metal cations on fluoromethyl anion derivatives is consistent with the stability of difluoromethyl metal species estimated by density functional theory (DFT) calculations. There is a proportional relationship between the decomposition energy and hardness of alkali metal cations[41]. To gain confidence in the generation of difluoromethyl anions, we attempted direct monitoring of reactive intermediate **2a** (Figs. S5 and S6). No direct observation of such highly unstable intermediates has been reported to date. Flow reaction systems allow for the in-line monitoring of products and have been used for a variety of analyses,

https://doi.org/10.1038/s41467-024-52842-0

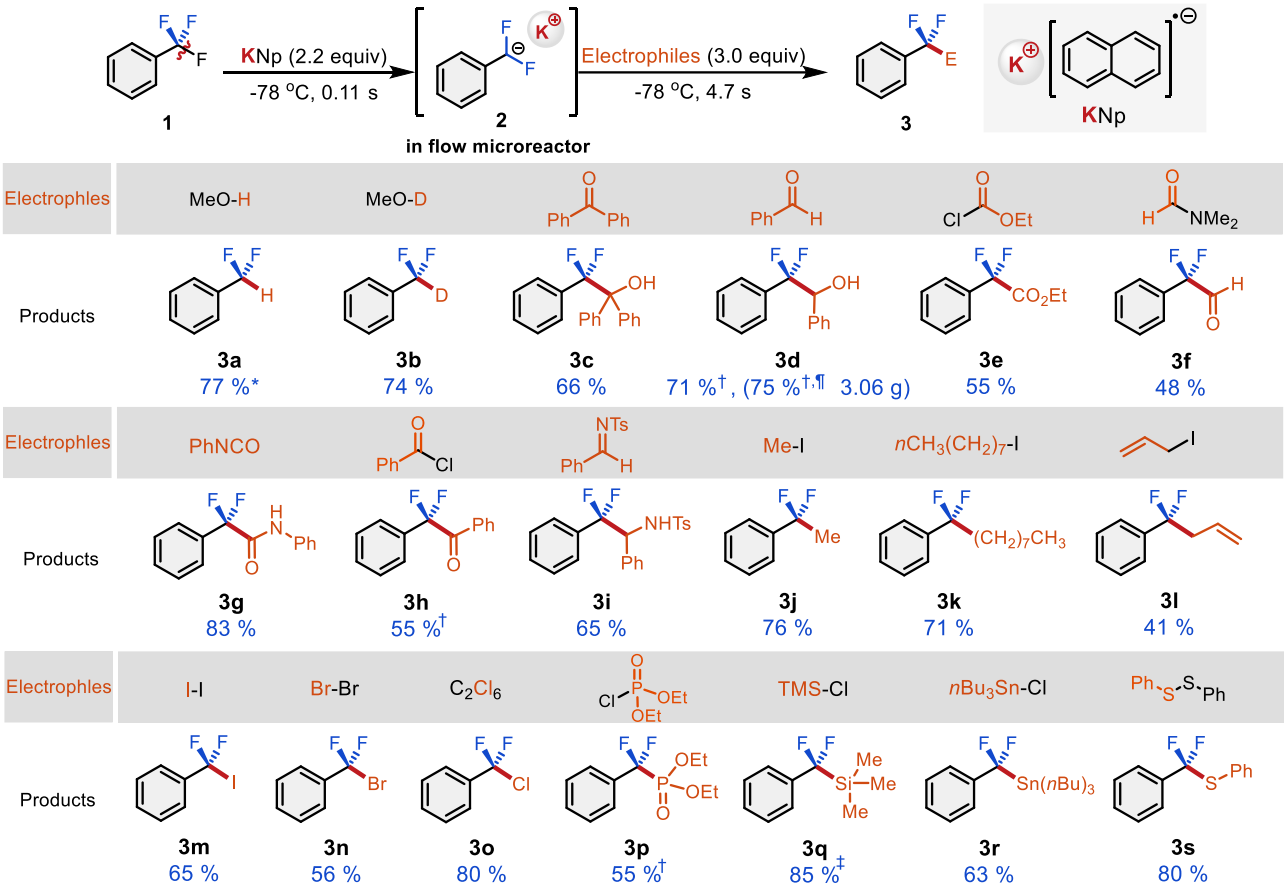

Fig. 3 | Scope of defluorinative functionalization of aryl bearing fluorine atoms using flow microreactor system. Scope of electrophiles of defluorinative functionalization. The defluorinative functionalization conditions were as follows: 1 (0.1 M in THF/1,2-dimethoxyethane, 7.5 mL/min), KNp (0.22 M in THF, 7.5 mL/min), electrophiles (0.45 M in THF/1,2-dimethoxyethane, 5.0 mL/min). The yields were determined using ^{19}F NMR spectroscopy. *The yields were determined using gas chromatography. †Isolated yields. ‡Using 4.0 equiv of trimethylsilyl chloride. ¶Continuous flow synthesis for 23 min. See Supplementary Information for further details.

such as our recently reported examples for observing unstable organolithium intermediates[42]. A solution of **1a** and KNp was mixed in a micromixer and subsequently passed through the tube reactor for 0.31 s at −78 °C, followed by passing through the in-line IR device. The obtained IR spectra indicate both a significant decrease in a peak attributed to **1a** (1325 cm^{-1}) and the appearance of two peaks attributed to **2a** (1510 and 1598 cm^{-1}). DFT calculations suggest that two characteristic peaks are expected in this region (1524 and 1640 cm^{-1}), indicating the formation of the difluoromethyl anion intermediate.

Optimizing with organopotassium reagents improved conversions and yields for t^{R1} = 6.9 ms at −78 °C (Table S3, entry 17). We further attempted to enhance reactivity by using 1,2-dimethoxyethane (DME) as a coordinating cosolvent alongside THF. Carrying out the reaction for t^{R1} = 0.11 s at −78 °C improved both conversion (96%) and yield (77%), reducing the over-reacted byproduct to trace levels (Table 3S, entry 36). Crown ether and other coordinating solvents, also known to stabilize fluorine-containing carbenoids, improved yields, though to a lesser extent than DME[43]. The potassium cation, coordinated into naphthalene rings[44], might be drawn away by the additional DME to facilitate faster electron transfer and the generation of difluoromethyl anion **2a**. The product **3a** was ultimately obtained in excellent yields at −78 °C and proven to be stable for over 6 s in this flow system. The significant decrease in yield for longer residence times or at higher temperatures indicates the critical importance of instantaneous electron reduction by KNp (Table S3, entries 34–41 and entries 58–80).

Scope of electrophiles and substrates

Afterwards, we explored the possibility of introducing electrophiles other than hydrogen using the same flow microreactor system (Fig. 3). Methanol-d_1 was converted into the desired product in good yield (**3b**). This result suggests that the introduced proton is derived from the methanolic proton, not from solvents or other proton sources. Electrophiles bearing carbonyl groups yielded the corresponding target products in good yields (**3c**–**3h**). Notably, gram-scale synthesis on the **3d** was also easily achieved by continuous operation for 23 min, obtaining the corresponding compound in 3.06 g. As well as imine was suitable for electrophile (**3i**) To demonstrate the efficacy of this approach, the reaction was carried out in the presence of benzoyl chloride and trifluoromethyl substrate **1a**. The quantitative recovery of substrate **1a** indicates that the undesired reduction of benzoyl chloride by strongly reducing KNp occurred faster than the desired defluorinative reaction with the substrate (Fig. S7) In other words, the generation and control of difluoromethyl anions without the presence of electrophiles are crucial. The R-CF_2-alkyl unit, known to act as a bioisostere for ether moieties, was successfully obtained in good yields by treatment with primary alkyl iodides (**3j**–**3l**). Typically, introducing a long-chain alkyl group is challenging when using organolithium species due to competing E2 elimination involving dehydroiodination. However, the successful reaction with various alkyl iodides observed in the present system suggests that employing organopotassium species plays a key role in improving selectivity. Our methodology also enabled the installation

https://doi.org/10.1038/s41467-024-52842-0

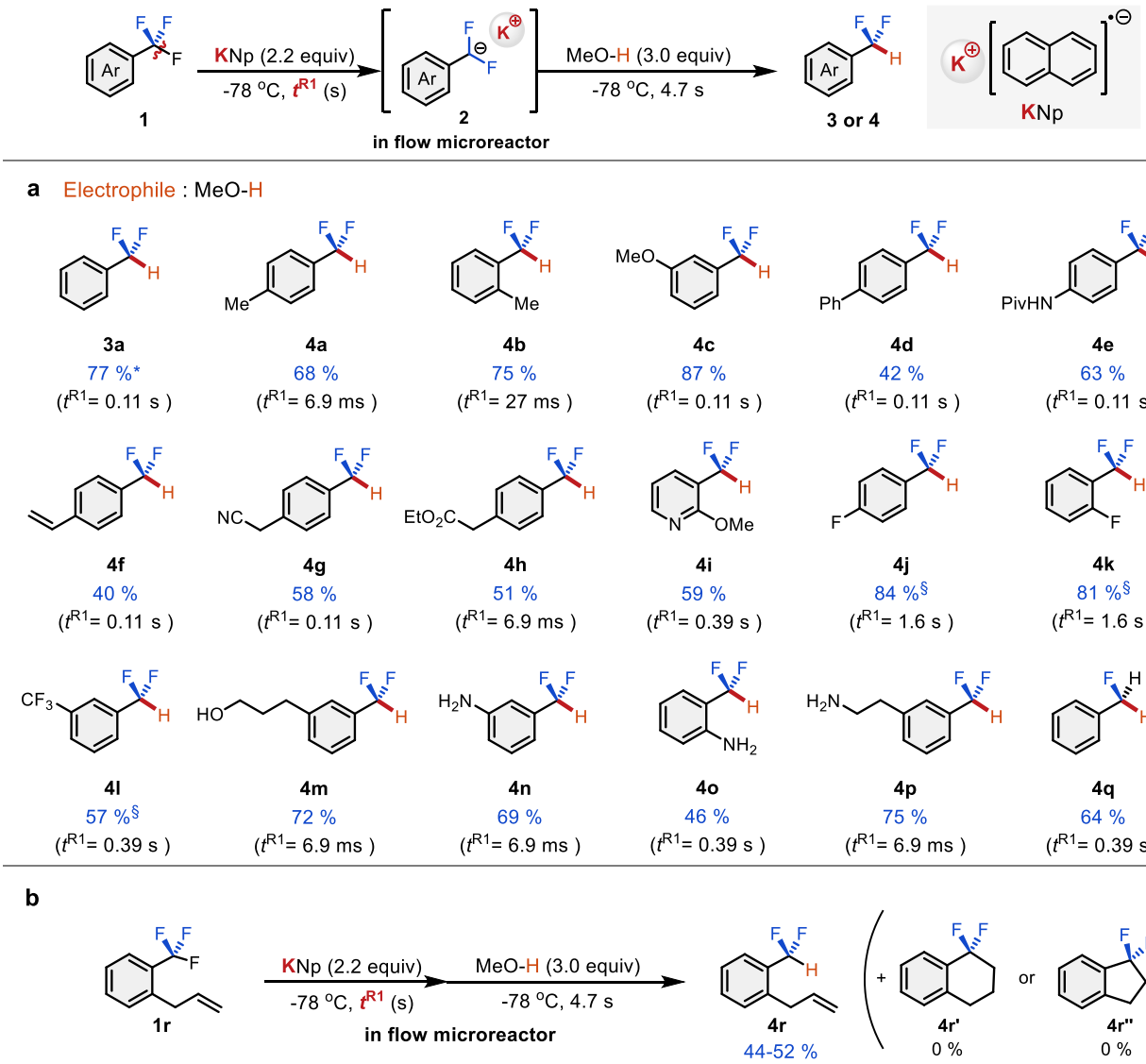

Fig. 4 | Scope of defluorinative functionalization and hydrodefluorination of aryl bearing fluorine atoms using flow microreactor system. a Scope of substrates of hydrodefluorination. **b** Investigation of radical clock experiment. The hydrodefluorination conditions were as follows: **1** (0.1 M in THF/1,2-dimethoxyethane, 7.5 mL/min), KNp (0.22 M in THF, 7.5 mL/min), methanol (0.45 M in THF/1,2-dimethoxyethane, 5.0 mL/min). The yields were determined using ^{19}F NMR spectroscopy. *The yields were determined using gas chromatography. †Isolated yields. §Using diglyme as cosolvent instead of 1,2-dimethoxyethane. See Supplementary Information for further details.

of heteroatomic functional groups such as phosphoryl, halo, silyl, stannyl, and sulfide groups in moderate yields (**3m**–**3s**), all of which are important functional groups in pharmaceutical research. On the other hand, boron derivatives (2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and triisopropyl borate) as electrophile were not appropriate for this reaction. The corresponding product with fluorine atoms and a boryl group at the benzyl position probably was unstable and decomposed[45].

Next, we investigated the scope of hydrodefluorination for various benzotrifluoride derivatives to assess the generality of our flow system (Fig. 4a). Several common functional groups, including methyl, methoxy, and phenyl, were well-tolerated, yielding the corresponding difluoromethyl arenes without issues (**4a**–**4d**). Even substrates bearing protic or electrophilic functional groups, and pyridine derivatives, were converted into the desired products in moderate to good yields (**4f**–**4i**). Notably, although styrene derivatives are known to oligomerize by reductive metalation agents even under flow conditions[46], our flow methodology enabled the selective cleavage of the C(sp^3)–F bond. Substrates bearing a C(sp^2)–F bond or another C(sp^3)–F bond also reacted to give hydrodefluorination products with high chemoselectivity in good yields (**4j**–**4l**). Moreover, the free hydroxy- and amino-substituted substrates cleaved the C(sp^3)–F bond, producing the corresponding products in good yield (**4m**–**4p**). Remarkably, difluoromethylbenzene, with a higher reduction potential than benzotrifluoride derivatives, also underwent hydrodefluorination to yield fluoromethylbenzene (**4q**). This result suggests that the sequential cleavage of multiple C(sp^3)–F bonds will enable further flexible molecular transformations. Furthermore, we carried out a radical clock experiment to investigate the reaction rate of radical-polar crossover by the second single-electron transfer (Fig. 4b). Using 2-Allyl(trifluoromethyl)benzene as substrate in our condition did not afford an intramolecularly cyclized product (**4r' or 4r''**), and hydrodefluorination product obtained (**4r**). Therefore, the second single-electron transfer is considered very fast.

Practical application

To demonstrate the practical utility of this protocol, we applied it to late-stage functionalization (LSF) using the optimized flow

https://doi.org/10.1038/s41467-024-52842-0

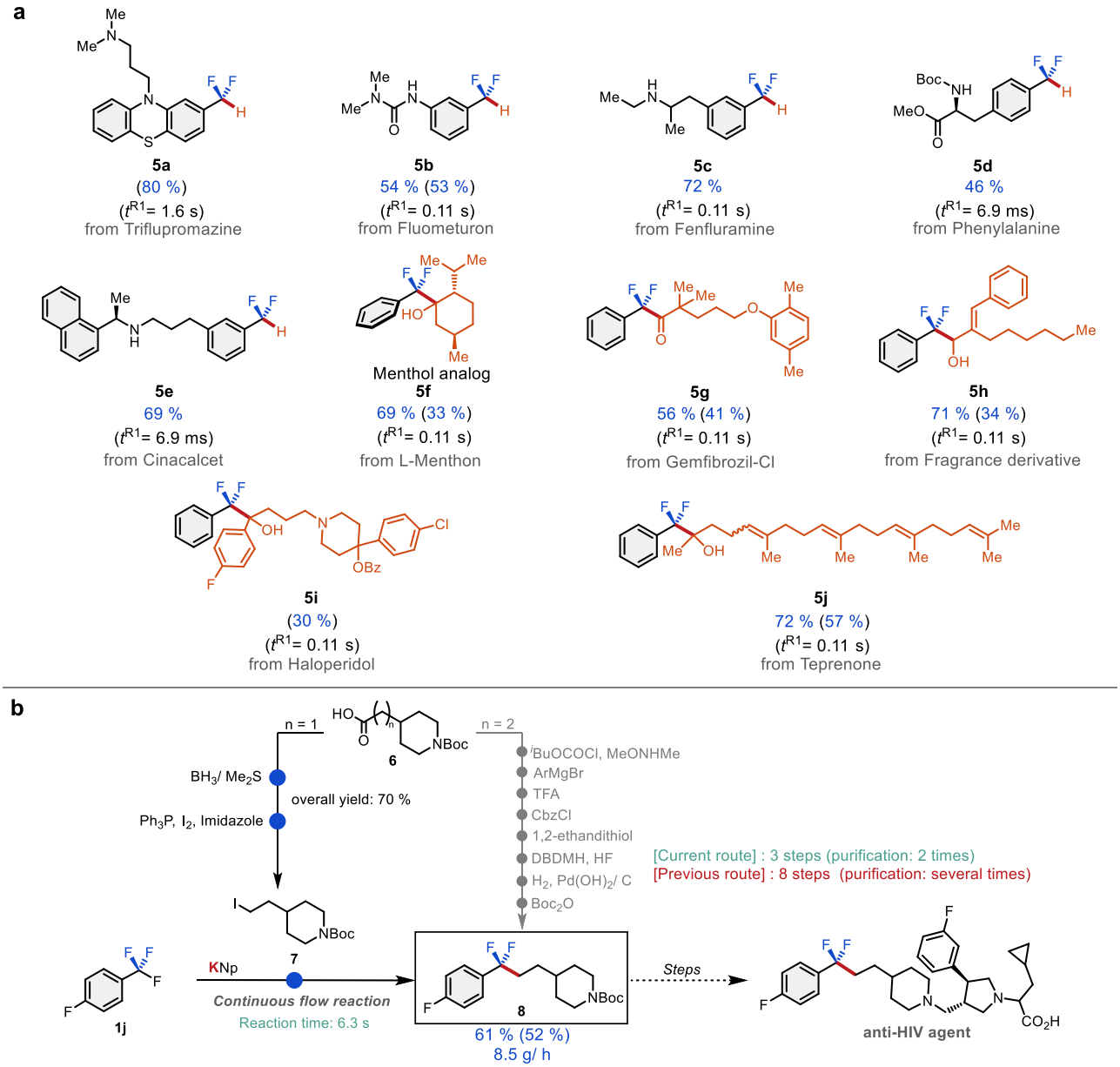

Fig. 5 | Practical applications. a Late-stage functionalization: Hydrodefluorination of benzotrifluoride derivatives. Defluorinative cross-coupling with bioactive molecules. **b** Step- and time-economical synthesis of pharmaceutical key intermediates. Reaction conditions: Substrate (0.1 M in THF/1,2-dimethoxyethane, 7.5 mL/min), KNp (0.22 M in THF, 7.5 mL/min), electrophiles (0.45 M in THF/1,2-dimethoxyethane, 5.0 mL/min). The yields were determined using ^{19}F NMR spectroscopy. Isolated yields are shown in parentheses. See Supplementary Information for further details.

conditions at hand (Fig. 5a). While the LSF strategy offers advantages for drug discovery by enabling direct functional group transformation of complex molecules, C(sp^3)–F bond LSF remains largely unexplored due to challenges in achieving broad functional group generality. In contrast, our approach shows that the C(sp^3)–F bond in bioactive molecules can be readily cleaved and transformed into various difluoromethyl products. The phenothiazine skeleton is one of the most significant frameworks in pharmaceuticals and is recognized for its antipsychotic properties, as seen in drugs like trifluoperazine and perphenazine. Triflupromazine was subjected to our protocol, yielding the corresponding difluoromethyl compound in excellent yield (**5a**). This method was also tolerant of substituted amino groups, such as those present in the herbicide fluometuron and the serotonin agonist fenfluramine (**5b, 5c**). l-Phenylalanine, an amino acid, and cinacalcet, a calcium receptor agonist, also underwent hydrodefluorination (**5d, 5e**). Moreover, our strategy utilizing difluoromethyl anion as key intermediates enabled the defluorinative cross-coupling of benzotrifluoride with bioactive substrates bearing electrophilic functional groups. l-Menthone was reacted to yield a fluorinated menthol analog in good yield (**5f**). Electrophiles containing more complex functional groups were also amenable substrates, such as the fibrate drug Gemfibrozil, fragrances, Haloperidol, and Teprenone (**5g**–**5j**).

Finally, as depicted the impact of our direct C(sp^3)–F bond functionalization strategy was demonstrated through efforts toward step- and time-economic synthesis of pharmaceutical intermediates. Difluoroalkyl compound **8** serves as a key synthetic intermediate in the total synthesis of the anti-HIV agent. Merck previously proposed an eight-step sequence for its synthesis[47]. Additionally, previous synthetic routes required the purification of intermediates multiple times. As an alternative, our approach utilized a pyrrolidine derivative **7**, synthesized in just two steps from readily available carboxylic acid **6**.

Compound **8** was directly accessible in ~6.3 s, making this route highly efficient from a time-economic standpoint (Fig. 5b). The present method significantly reduced the number of synthetic steps and time involved while providing the corresponding synthetic intermediate with remarkable productivity of ~8.5 g h^{-1} without the need for toxic reagents.

Discussion

In summary, we have developed the C(sp^3)–F bond functionalization via difluoromethyl anion in a flow system. Our strategy can most efficiently access a variety of difluoromethyl compounds through instantaneously electron-induced umpolung of trifluoromethyl compounds by potassium naphthalenide and strict control of residence time using a flow microreactor. The current protocol explores challenging C(sp^3) –F bond LSF. Therefore, we propose a step- and time-economical LSF approach for drug and agrochemical discovery, offering rapid access and high productivity for targeting drugs and their candidate compounds.

Methods

A flow microreactor system consisting of two T-shaped micromixers (**M1** and **M2** (inner diameter ϕ = 250 μm)), two microtube reactors (**R1** and **R2**), and three tube precooling units (P1, P2, and P3 (inner diameter ϕ = 1000 μm, length L = 100 cm)) was used. The flow microreactor system was cooled at −78 °C by a cooling bath. A solution of benzotrifluoride derivatives (0.10 M in THF/1,2-dimethoxyethane (DME) = 10/1) (flow rate: 7.5 mL/ min) and a solution of potassium naphtalenide (KNp) (0.22 M in THF) (flow rate: 7.5 mL/min) were introduced to **M1** by syringe pumps. The resulting solution was passed through **R1** (inner diameter ϕ = 1000 μm, length L = 3.5 cm) and was mixed with a solution of electrophile (0.45 M in THF/1,2-dimethoxyethane (DME) = 10/1) (flow rate: 5.0 mL/min) in **M2**. The resulting solution was passed through **R2** (inner diameter ϕ = 1000 μm, length L = 200 cm). After a steady state was reached, the outcoming solution was collected for 20 s in a vessel containing 4 mL of sat. aq. NH_4Cl. The yields of corresponding difluoromethyl arenes were determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The reaction mixture was extracted with EtOAc (3 × 5 mL) and was washed with brine. The combined organic layers were dried over Na_2SO_4, and filtered, concentrated under vacuum. Then, the crude product was purified by flash column chromatography on silica gel or/ and GPC to give a product. See Supplementary Information for further details.

Data availability

The authors declare that the data to support the findings of this study are available within the paper and its Supplementary Information. All data are available from the corresponding author upon request.

References

1. Zhou, Y. et al. Next generation of fluorine-containing pharmaceuticals, compounds currently in phase II–III clinical trials of major pharmaceutical companies: new structural trends and therapeutic areas. *Chem. Rev.* **116**, 422–518 (2016).
2. Ogawa, Y., Tokunaga, E., Kobayashi, O., Hirai, K. & Shibata, N. Current contributions of organofluorine compounds to the agrochemical industry. *iScience* **23**, 101467 (2020).
3. Berger, R., Resnati, G., Metrangolo, P., Weber, E. & Hulliger, J. Organic fluorine compounds: a great opportunity for enhanced materials properties. *Chem. Soc. Rev.* **40**, 3496–3508 (2011).
4. Henderson, W. M. et al. Per- and polyfluoroalkyl substances in the environment. *Science* **375**, eabg9065 (2022).
5. https://echa.europa.eu/documents/10162/f605d4b5-7c17-7414-8823-b49b9fd43aea.
6. Zafrani, Y., Saphier, S. & Gershonov, E. Utilizing the CF_2H moiety as a H-bond-donating group in drug discovery. *Future Med. Chem.* **12**, 361–365 (2020).
7. Hagmann, W. K. The many roles for fluorine in medicinal chemistry. *J. Med. Chem.* **51**, 4359–4369 (2008).
8. Boeckler, F. M. et al. Principles and applications of CF_2X moieties as unconventional halogen bond donors in medicinal chemistry, chemical biology, and drug discovery. *J. Med. Chem.* **66**, 10202–10225 (2023).
9. Zhao, F., Zhou, W. & Zuo, Z. Recent advances in the synthesis of difluorinated architectures from trifluoromethyl groups. *Adv. Synth. Catal.* **364**, 234–267 (2022).
10. Hooker, L. V. & Bandar, J. S. Synthetic advantages of defluorinative C–F bond functionalization. *Angew. Chem. Int. Ed.* **62**, e202308880 (2023).
11. Ahrens, T., Kohlmann, J., Ahrens, M. & Braun, T. Functionalization of fluorinated molecules by transition-metal-mediated C–F bond activation to access fluorinated building blocks. *Chem. Rev.* **115**, 931–972 (2015).
12. Fujita, T., Fuchibe, K. & Ichikawa, J. Transition-metal-mediatedand-catalyzed C–F bond activation by fluorine elimination. *Angew. Chem. Int. Ed.* **58**, 390–402 (2019).
13. Wang, H. & Jui, N. T. Catalytic defluoroalkylation of trifluoromethylaromatics with unactivated alkenes. *J. Am. Chem. Soc.* **140**, 163–166 (2018).
14. Gouverneur, V. et al. Organophotoredox hydrodefluorination of trifluoromethylareneswith translational applicability to drug discovery. *J. Am. Chem. Soc.* **142**, 9181–9187 (2020).
15. Wang, J. et al. Late-stage modification of drugs via alkene formal insertion into benzylic C–F bond. *Angew. Chem. Int. Ed.* **62**, e202215062 (2023).
16. Chen, K., Berg, N., Gschwind, R. & König, B. Selective single C(sp^3)–F bond cleavage in trifluoromethylarenes: merging visible-light catalysis with lewis acid activation. *J. Am. Chem. Soc.* **139**, 18444–18447 (2017).
17. Liu, C., Li, K. & Shang, R. Arenethiolate as a dual function catalyst for photocatalytic defluoroalkylation and hydrodefluorination of trifluoromethyls. *ACS Catal.* **12**, 4103–4109 (2022).
18. Sugihara, N., Suzuki, K., Nishimoto, Y. & Yasuda, M. Photoredox-catalyzed C–F bond allylation of perfluoroalkylarenes at the benzylic position. *J. Am. Chem. Soc.* **143**, 9308–9313 (2021).
19. Luo, C. & Bandar, J. S. Selective defluoroallylation of trifluoromethylarenes. *J. Am. Chem. Soc.* **141**, 14120–14125 (2019).
20. Wright, S. E. & Bandar, J. S. A base-promoted reductive coupling platform for the divergent defluorofunctionalization of trifluoromethylarenes. *J. Am. Chem. Soc.* **144**, 13032–13038 (2022).
21. Yue, W. & Martin, R. α-difluoroalkylationof benzyl amines with trifluoromethylarenes. *Angew. Chem. Int. Ed.* **62**, e202310304 (2023).
22. Yu, Y. et al. Sequential C–F bond functionalizations of trifluoroacetamides and acetates via spin-center shifts. *Science* **371**, 1232–1240 (2021).
23. Campbell, M. W. et al. Photochemical C–F activation enables defluorinative alkylation of trifluoroacetates and -acetamides. *J. Am. Chem. Soc.* **143**, 19648–19654 (2021).
24. Douvris, C. & Ozerov, O. V. Hydrodefluorination of perfluoroalkyl groups using silylium-carborane catalysts. *Science* **321**, 1188–1190 (2008).
25. Scott, V. J., Celenligil-Cetin, R. & Ozerov, O. V. Room-temperature catalytic hydrodefluorination of C(sp^3)–F bonds. *J. Am. Chem. Soc.* **127**, 2852–2853 (2005).
26. Gu, W., Haneline, M. R., Douvris, C. & Ozerov, O. V. Carbon-carbon coupling of C(sp^3)–F bonds using alumenium catalysis. *J. Am. Chem. Soc.* **131**, 11203–11212 (2009).

27. Yoshida, S., Shimomori, K., Kim, Y. & Hosoya, T. Single C–F bond cleavage of trifluoromethylarenes with an ortho-silyl group. *Angew. Chem. Int. Ed.* **55**, 10406–10409 (2016).
28. Amii, H., Hatamoto, Y., Seo, M. & Uneyama, K. A new C–F bond-cleavage route for the synthesis of octafluoro[2.2]paracyclophane. *J. Org. Chem.* **66**, 7216–7218 (2001).
29. Prakash, G. K. S. et al. Selective late-stage hydrodefluorination of trifluoromethylarenes: a facile access to difluoromethylarenes. *Eur. J. Org. Chem.* **16**, 2322–2326 (2017).
30. Box, J. R., Avanthay, M. E., Poole, D. L. & Lennox, A. J. J. Electronically ambivalent hydrodefluorination of aryl–CF_3 groups enabled by electrochemical deep-reduction on a Ni cathode. *Angew. Chem. Int. Ed.* **62**, e202218195 (2023).
31. Mena, S., Bernad, J. & Guirado, G. Electrochemical incorporation of carbon dioxide into fluorotoluene derivatives under mild conditions. *Catalysts* **11**, 880 (2021).
32. Avanthay, M. E., Goodrich, O. H., George, M. & Lennox, A. J. J. Bromide-mediated silane oxidation: a convenient and practical counter-elecrode process for undivided electrochemical reductions. Preprint at https://doi.org/10.26434/chemrxiv-2023-w3l2v (2023).
33. O'Hagan, D. Understanding organofluorine chemistry. An introduction to the C–F bond. *Chem. Soc. Rev.* **37**, 308–319 (2008).
34. Iwamoto, H., Imiya, H., Ohashi, M. & Ogoshi, S. Cleavage of C(sp^3)–F bonds in trifluoromethylarenes using a bis(NHC)nickel(0) complex. *J. Am. Chem. Soc.* **142**, 19360–19367 (2020).
35. Stahl, T., Klare, H. F. T. & Oestreich, M. C(sp3)–F Bond Activation of CF3 Substituted Anilines with Catalytically Generated Silicon Cations: Spectroscopic Evidence for a Hydride-Bridged Ru–S Dimer in the Catalytic Cycle. (*J. Am. Chem. Soc.* **135**, 1248–1251 (2013).
36. Driver, T. G. Niobium-Catalyzed Activation of Aryl Trifluoromethyl Groups and Functionalization of C–H Bonds: An Efficient and Convergent Approach to the Synthesis of N-Heterocycles. Angew. *Chem. Int. Ed.* **48**, 7974–7976 (2020).
37. Dang, H., Whittaker, A. M. & Lalic, G. Catalytic activation of a single C–F bond in trifluoromethyl arenes. *Chem. Sci.* **7**, 505–509 (2016).
38. Mandal, D., Gupta, R., Jaiswal, A. K. & Young, R. D. Frustrated Lewis-pair-meditated selective single fluoride substitution in trifluoromethyl groups. *J. Am. Chem. Soc.* **142**, 2572–2578 (2020).
39. Connelly, N. G. & Geiger, W. E. Chemical redox agents for organometallic chemistry. *Chem. Rev.* **96**, 877–910 (1996).
40. Colella, M. et al. Fluoro-substituted methyllithium chemistry: external quenching method using flow microreactors. *Angew. Chem. Int. Ed.* **59**, 10924–10928 (2020).
41. Luo, G., Luo, Y. & Qu, J. Direct nucleophilic trifluoromethylation using fluoroform: a theoretical mechanistic investigation and insight into the effect of alkali metal cations. *N. J. Chem.* **37**, 3274–3280 (2013).
42. Ashikari, Y. et al. Flowmicro in-line analysis-driven design of reactionsmediated by unstable intermediates: flash monitoring approach. *Chem. Eur. J.* **30**, e202303774 (2024).
43. Saito, T., Wang, J., Tokunaga, E., Tsuzuki, S. & Shibata, N. Direct nucleophilic trifluoromethylation of carbonyl compounds by potent greenhouse gas, fluoroform: Improving the reactivity of anionoid trifluoromethyl species in glymes. *Sci. Rep.* **8**, 11501 (2018).
44. Scott, T. A. et al. After 118 years, the isolation of two common radical anion reductants as simple, stable solids. *Chem. Commun.* **1**, 65–67 (2009).
45. Zhou, J., Jiang, B., Guo, M., Sumii, Y. & Shibata, N. Aryl *gem*-difluorovinyl pinacolboronates: synthesis and utility for Suzuki-Miyaura coupling reaction. *Chem. Lett.* **49**, 1439–1442 (2020).
46. Jiang, Y., Kurogi, T. & Yorimitsu, H. Reductive stereo- and regiocontrolled boryllithiation and borylsodiation of arylacetylenes using flow microreactors. *Nat. Synth.* **3**, 192–201 (2024).
47. Lynch, C. L. et al. 1,3,4-trisubstituted pyrrolidine CCR5 receptor antagonists: modifications of the arylpropylpiperidine side chains. *Bioorg. Med. Chem. Lett.* **13**, 119–123 (2003).

Acknowledgements

We thank Y. Ashikari (The University of Hokkaido) for supporting in-line IR analysis and helpful scientific discussion; M. Ishiya (The University of Hokkaido) for nuclear magnetic resonance (NMR) measurements; Instrumental Analysis Service at Hokkaido University for mass spectroscopy supports; H. V. Miyagishi (The University of Hokkaido), H. Soutome (AGC Inc.), D. E. Yoo (The University of Hokkaido), A. Ishii (Central Glass Co., Ltd), S. Narizuka (Central Glass Co., Ltd), R. Nadano (Central Glass Co., Ltd.) for helpful scientific discussion. This work was supported by the Japan Society for the Promotion (JSPS) through KAKENHI Grant Numbers, JP23K04744 (Grant-in-Aid for Scientific Research (C) (K.O. and A.N.)), JP20KK0121 (Fostering Joint International Research (B) (A.N.)), JP21H01936 (Grant-in-Aid for Scientific Research (B) (A.N.)), JP21H01706 (Grant-in-Aid for Scientific Research (B) (A.N.)), and JP21H05080 (Grant-in-Aid for Transformative Research Areas (B) (A.N.)). This work was also partially supported by AMED (JP21ak0101156 (A.N.)), the Core Research for Evolutional Science and Technology (CREST, JPMJCR18R1 (A.N.)), New Energy and Industrial Technology Development Organization (NEDO, PJ22031410 and PJ22220030 (A.N.)), the Japan Keirin Autorace Foundation (A.N.), the Ogasawara Foundation for the Promotion of Science & Engineering (A.N.), and Takahashi Industrial and Economic Foundation (K.O. and A.N.).

Author contributions

K.M. conceived the original concept; A.N. directed the project; K.M., K.O., and A.N. designed the experiments; K.M., H.N., and S.W. performed and analyzed with experiments; K.O. performed the DFT calculated; K.M. drafted the manuscript with feedback from all authors with some assistance from AI-technologies (Grammarly, DeepL, ChatGPT3.5, Claude) for improving clarity and language flow; Finally, K.M., K.O., and A.N. reviewed and edited the manuscript.

Competing interests

K.M. K.O., and A.N. are inventors of patent applications submitted by Hokkaido University and Central Glass Co., Ltd regarding the production method for compounds bearing fluorocarbon groups and microreactors. The authors declare no other competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41467-024-52842-0.

Correspondence and requests for materials should be addressed to Aiichiro Nagaki.

Peer review information *Nature Communications* thanks the anonymous reviewer(s) for their contribution to the peer review of this work. A peer review file is available.