Defluorinative Functionalization Approach led by Difluoromethyl Anion Chemistry

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Abstract:

Organofluorine compounds have greatly benefited the pharmaceutical, agrochemical, and materials sectors. However, they are plagued by concerns associated with PFAS. 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.

Main Text:

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 bio-accumulative 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 exceptional 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, 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 (*34,35*). 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 (*36*). 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 exceptional 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 innovative 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.

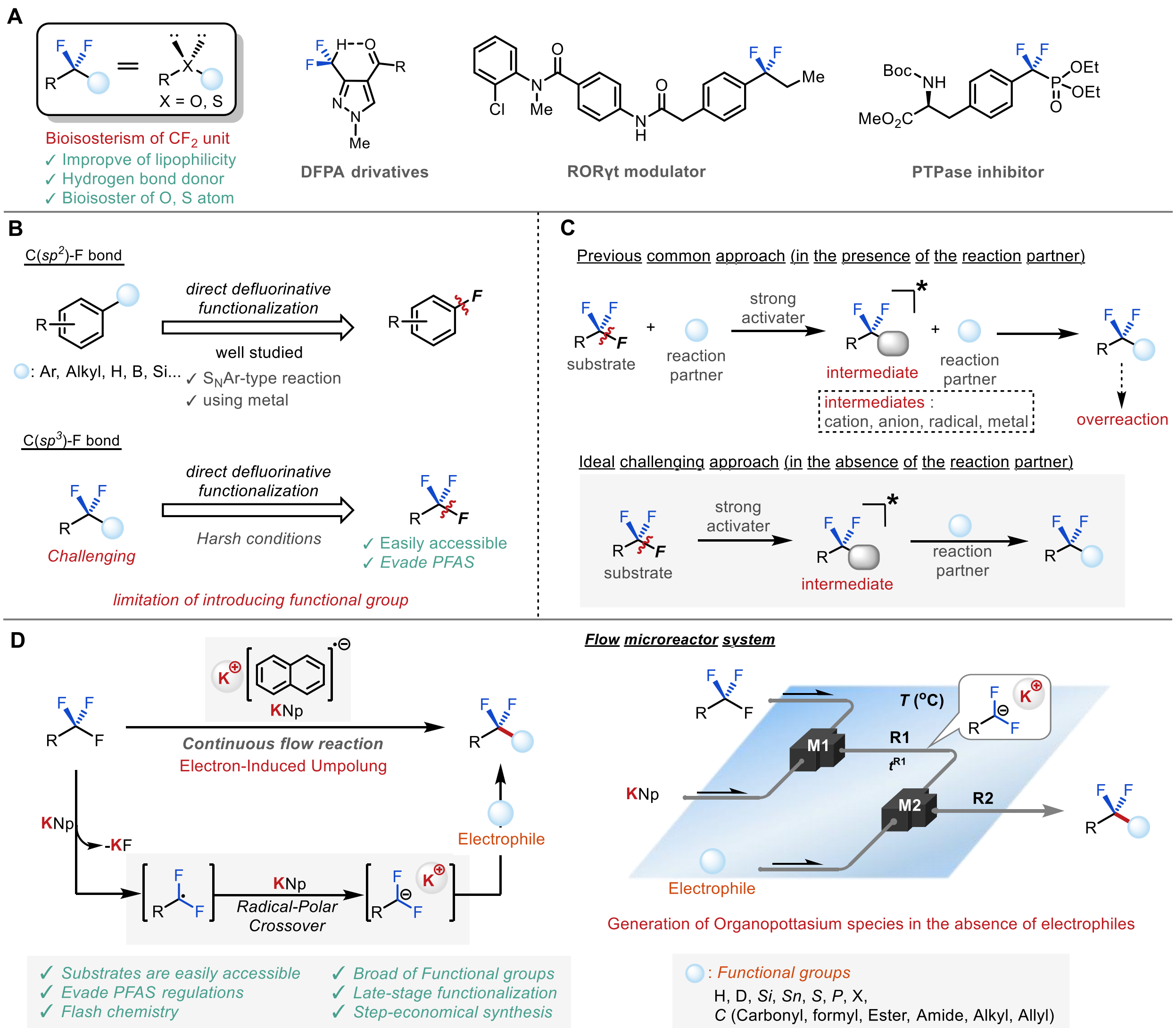
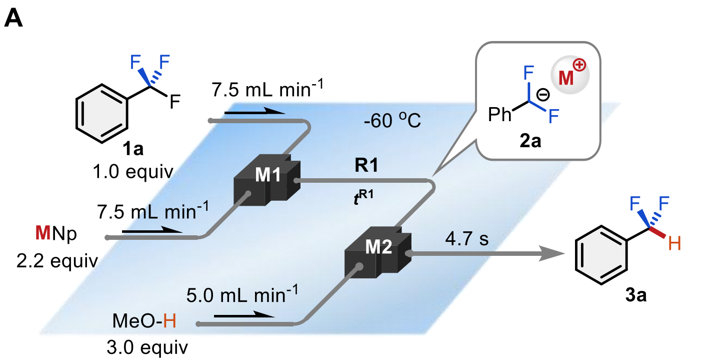


Fig. 1. Representative bioactive difluoromethyl compounds, and strategies for defluorinative functionalization. (**A**) Selected pharmaceutical difluoromethyl compounds. (**B**) Developments of C(sp^2)–F bond functionalization and the challenging goal of C(sp^3)–F bond functionalization. (**C**) Previous 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.

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 (*37*). 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; Table S1). 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.



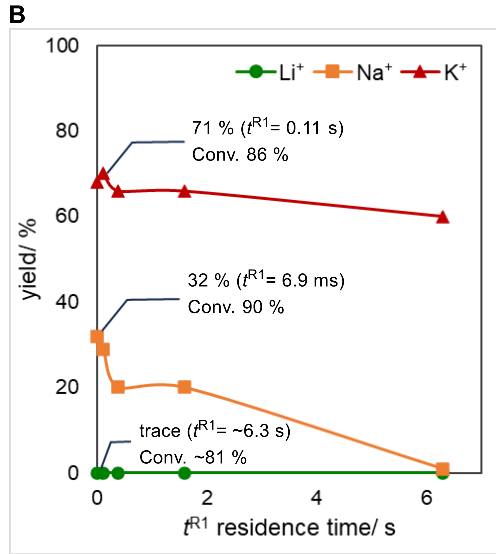


Fig. 2. Hydrodefluorination in the absence of methanol. (**A**) Flow microreactor system for the generation and reaction of the difluoromethyl anion in the absence of the electrophile. (**B**) Effect of alkali metal on defluorination at -60 °C (yields and conversions were determined by gas chromatography).

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 (Table S2). We have previously reported that unstable intermediates can be utilized for synthesis in the absence of electrophiles using a flow microreactor (*38*). These systems are particularly effective in controlling unstable reactive species in the absence of electrophiles (Fig. 2A). 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. 2B). 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 DFT calculations. There is a proportional relationship between the decomposition energy and hardness of alkali metal cations (*39*). To gain confidence in the generation of difluoromethyl anions, we attempted direct monitoring of reactive intermediate **2a** (Fig. S2 and S3). 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, such as our recently reported examples for observing unstable organolithium intermediates (*40*). A solution of **1a** and KNp was mixed in a micromixer and subsequently passed through the tube reactor for 0.31 sec 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 msec at -78 °C (Table 3S, 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 sec 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 (*41*), improved yields, though to a lesser extent than DME (*42*). The potassium cation, coordinated into naphthalene rings (*43*), 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 sec 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).

Afterwards, we explored the possibility of introducing electrophiles other than hydrogen using the same flow microreactor system (Fig. 3A). 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**). 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 (Scheme S2). 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 (**3i**–**3k**). 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 of heteroatomic functional groups such as phosphoryl, halo, silyl, stannyl, and sulfide groups in moderate yields (**3l**–**3r**), all of which are important functional groups in pharmaceutical research.

Next, we investigated the scope of hydrodefluorination for various benzotrifluoride derivatives to assess the generality of our flow system (Fig. 3B). 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 (*44*), 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.

To demonstrate the practical utility of this protocol, we applied it to late-stage functionalization (LSF) using the optimized flow conditions at hand (Fig. 4A). 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 (*45*). 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 approximately 6.3 sec, making this route highly efficient from a time-economic standpoint (Fig. 4B). The present method significantly reduced the number of synthetic steps and time involved while providing the corresponding synthetic intermediate with remarkable productivity of approximately 8.5 g h^{-1} without the need for toxic reagents.
The current protocol facilitates the exploration of previously uncharted C(*sp*^{3})–F bond LSF via mono-selective cleavage while achieving high productivity. Therefore, we propose this time- and cost-effective LSF approach as a new methodology that will expedite drug and agrochemical discovery.

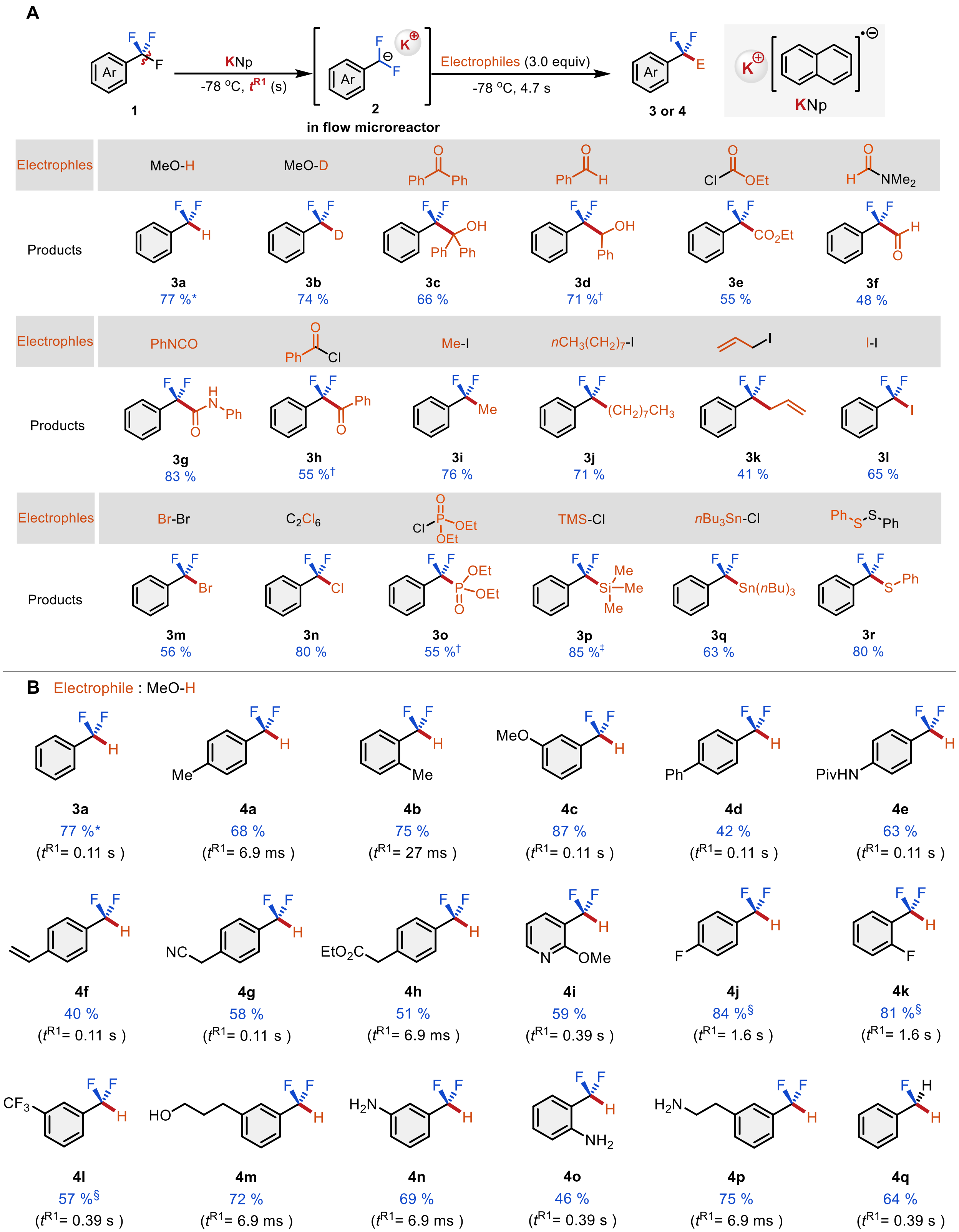


Fig. 3. Scope of defluorinative functionalization and hydrodefluorination of aryl bearing fluorine atoms using flow microreactor system. (**A**) Scope of electrophiles of defluorinative functionalization. (**B**) Scope of substrates of hydrodefluorination.

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),

t^{R1}= 0.11 sec. 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 4.0 equiv of trimethylsilyl chloride. §Using diglyme as cosolvent instead of 1,2-dimethoxyethane. See supplementary materials for further details.

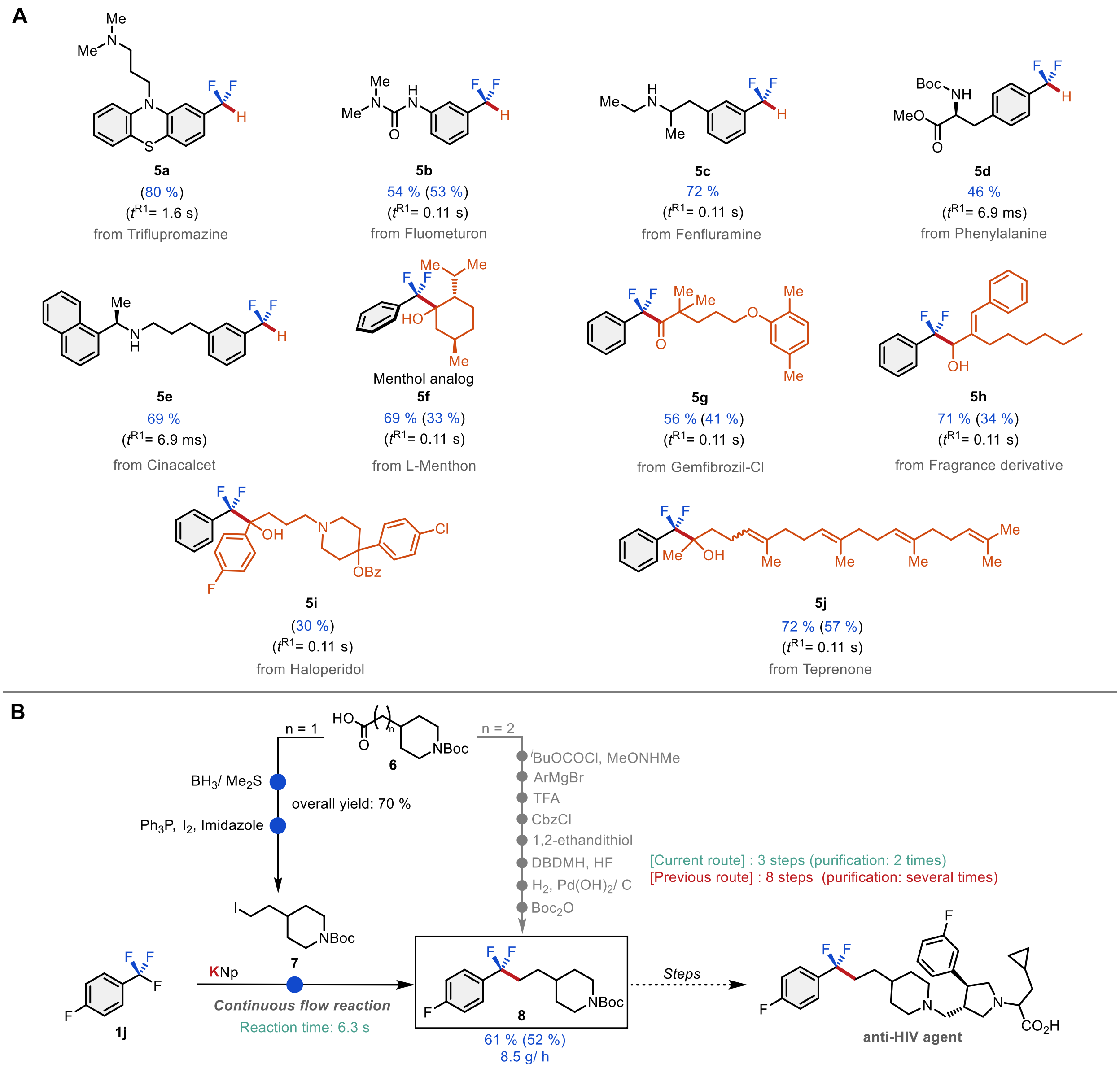


Fig. 4. Practical applications (**A**) Late-stage functionalization: Hydrodefluorination of benzotrifluoride derivatives. Defluorinative cross-coupling with bioactive molecules. (**B**) Step- and time-economical synthesis of pharmaceutical key intermediates.

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 materials for further details.

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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.

Data and materials availability: Dates are available in the supplementary materials.

Supplementary Materials

Supplementary Text

Figs. S1 to S4

Tables S1 to S12

Scheme S1 to S3

References (*46*–*73*)