Advancing Dearomative Difluoromethylation of *N*-heterocycles and Pharmaceuticals

Sandeep Kumawat, Tarun Bhatt, and Kishore Natte*

Department of Chemistry, Indian Institute of Technology Hyderabad, Kandi, Sangareddy 502 285, Telangana, India. *Email: kishore.natte@chy.iith.ac.in

Abstract: Given the significant prevalence of *N*-heterocycles in small-molecule pharmaceuticals, the selective incorporation of a difluoromethyl (−CF_2H) motif and the creation of a new functional group within the same molecular framework are of paramount importance in drug discovery and development. However, such integrated approaches remain underexplored, presumably due to the lack of efficient synthetic methods. In the present research, we introduce a new platform and broadly applicable technique for the difluoromethylation of various *N*-heterocyclic substrates using low-cost and commercially available bromo(difluoro)acetic acid in the presence of K_2CO_3 at room temperature to produce >70 desired complex Het−*N*CF_2H products featuring either imine and/or ketone functional group, which were hitherto impossible to produce. Depending on the type of *N*-heterocycle, this advance also permits the inclusion of two CF_2H units. Crucial to success is the more nucleophilicity and less steric hindrance on the nitrogen atom of the heteroarene ring that enables *N*-difluoromethylative dearomatization of *N*-heterocycles. Overall, this unique transformation was transition metal-free, practical, scalable (>50 grams), tolerant to diverse reactive functional groups with excellent chemoselectivity, adaptable to diversities of challenging *N*-heteroaromatic ring systems, and could be used for the late-stage diversification of 18 commercial drug molecules. Mechanistic investigation revealed the formation of *N*-difluoromethylquinolinium salt as a key intermediate, which occurs *via* nucleophilic substitution followed by decarboxylation with bromo(difluoro)acetic acid. Ultimately, we have also unveiled a prominent synthetic application for rapid hydrodefluorinative reduction in a single step to access complex *N*-methylated Fsp^3-enriched motif. This cost-effective strategy encompasses a full package of medicinally important functionalities (heterocycle, −*N*CF_2H, and imine/keto), making them highly valuable in the preparation of chemical libraries and effective drugs.

1. Introduction

Nitrogen heterocycles (*N*-heterocycles) are present in more than 85% of marketed and investigational drugs.[1, 2] Statistically, over the past few years, there has been an ever-increasing amount of *N*-heterocycles per prescribed medicine.[1] Notably, both five- and six-membered *N*-heterocycles are especially valued for their prevalence among the best-selling clinically approved drugs worldwide to date **(Figure 1A)**.[1, 3] These facts highlight the critical

role of *N*-heterocycles in pharmacological function.[1, 3] Simultaneously, the introduction of fluorine atoms into *N*-heterocyclic substrates represents a powerful tool in biological research to enhance the therapeutic efficacy of structurally complex pharmaceutical molecules.[4-8] Undoubtedly, the combination of these two (*N*-heterocycles + Fluoro substitution) distinctive different physicochemical properties is immensely occurring in new chemical entities (NCEs) with diverse biological functions, as exemplified by the expeditious construction of fluorinated motifs onto *N*-heterocyclic frameworks among the FDA-approved drug molecules.[9, 10]

Complex *N*-heterocycles bearing the difluoromethyl moiety (Het−*N*CF_2H) have always been attractive in the isostere-based drug design and development **(Figure 1C)**.[11-15] Also, the −*N*CF_2H unit markedly influences lipophilicity, cellular membrane permeability, and conformational preferences **(Figure 1D)**.[11, 16-18] While *N*-difluoromethylated products hold great promise as therapeutic targets, there is a scarcity of preparative methods. Consequently, designing robust protocols for both practical applications and fundamental research has become critically important. Historically, *N*-difluoromethylated compounds were produced by the insertion of a difluorocarbene into the N-H bond of *N*-heterocycles using various difluoromethylating agents.[11, 13] Generally, chlorodifluoromethane (Freon 22) is used as a key reagent to produce various −*N*CF_2H motifs.[13] Sometimes, bromo- and iododifluoromethane are also employed for the incorporation of CF_2 carbene on *N*-heterocycles.[13] However, such gaseous Freons are always avoided in the pharma industry, limiting the practical application of this reagent. Alternatively, other difluorocarbene precursors (e.g., $ClCF_2CO_2Na$, $BrCF_2CO_2Et$, $TMSCF_2Br$, $TMSCF_3$, etc.) have been developed. However, they are less pertinent in advancing *N*-difluoromethylation strategies.[13] Further, depending on the type of *N*-heteroarene, difluoromethylation reagent, and reaction conditions, this method could provide exclusively either −*N*CF_2H compounds and/or *N*-difluoromethyl-2-pyridones **(Figure 1E)**.[19-29] Nevertheless, these approaches are restricted to simple *N*-heterocycles and have a quite narrow scope, as well as not applicable to late-stage *N*-difluoromethylation with commercial drugs, despite the potential for broad application in modern drug discovery and medicinal chemistry. Late-stage functionalization (LSF) is a powerful tool and plays a vital role in advancing the drug optimization process.[30] In fact, LSF in organofluorine chemistry is considered the most versatile for rapid modification of existing bioactive compounds to produce a wide range of new congeners that were previously unanticipated with potential significance in the pharmaceutical process.[31] Considering this, the search for environmentally responsible, safer, and more reliable late-stage *N*-difluoromethylation of structurally complex molecules (e.g., commercial drugs) exhibiting advanced functionalities with low-cost fluorinating agents under metal-free and ambient conditions remains a challenging but rewarding task.

Moreover, quinolin-4(1*H*)-Imines are gaining prominence in clinical research and development **(Figure 1B)**.[32, 33] It is generally accepted that the introduction of the difluoromethylene group into organic molecules can lead to impressive increases in the pharmacodynamic activity of drug candidates.[16, 34] Consequently, every year, a large number

of diversified fluoro-pharmaceuticals often appear in the marketed drugs.[5] Given the vital importance of these advantages, the incorporation of the CF_2H motif into such *N*-heterocycles represents a highly attractive approach, as these site-specific fluorinated compounds serve as medicinally relevant scaffolds to quickly diversify molecular fragments. In addition, quinolone derivatives are highly attractive in core pharmaceuticals such as Ivacaftor, Nalidixic acid, Ciprofloxacin, and many more (these drugs contain N-H/R) **(Figure 1B)**;[35, 36] the replacement of the CF_2H group with an *N*-alkyl fragment or N-H bond in such drugs would play an essential role in drug repositioning.[37] However, efforts to prepare the aforementioned structurally complex variants of the pharmaceutically privileged Het–*N*CF_2H compounds featuring either imine or ketone functional groups remain an underdeveloped goal in organofluorine chemistry, presumably due to the lack of synthetic methodologies.

Based on our continuous interest in organofluorine methodologies[38, 39] and owing to the excellent nucleophilicity of the nitrogen atom in *N*-heterocycles, we hypothesized that difluoromethyl species could selectively difluoromethylate the nitrogen atom in the heterocycle **(Figure 1F)**. Once the activated heteroarenium salt is generated, it increases the acidity of the hydrogen atom in the external N-H bond of *N*-heterocycles. Next, deprotonation and π electron transfer from the external nitrogen atom of amine to the nitrogen atom of the heteroarene enables the unprecedented *N*-difluoromethylative dearomatized product **(Figure 1F)**. According to this concept, we sought to investigate the reactivity of bromo(difluoro)acetic acid (commercially available, a benchtop stable and inexpensive solid) and introduce a new platform for the preparation of previously unexplored *N*-difluoromethylated compounds with the concurrent formation of a new imine or ketone moiety **(Figure 1G)**, which is unusual compared to classical and/or already reported methods. Overall, this unique methodology was transition metal-free, safe, practical, scalable (>50 grams), tolerant to numerous reactive functional groups with excellent chemoselectivity, adaptable for important *N*-heterocyclic systems, and could be used for the late-stage diversification of 18 commercial drug molecules. Exceptionally, the synthesized products in this work encompass a comprehensive package of medicinally important functionalities (quinoline, –*N*CF_2H, and imine/keto), making it immediately applicable in the preparation of chemical libraries and innovative pharmaceuticals.

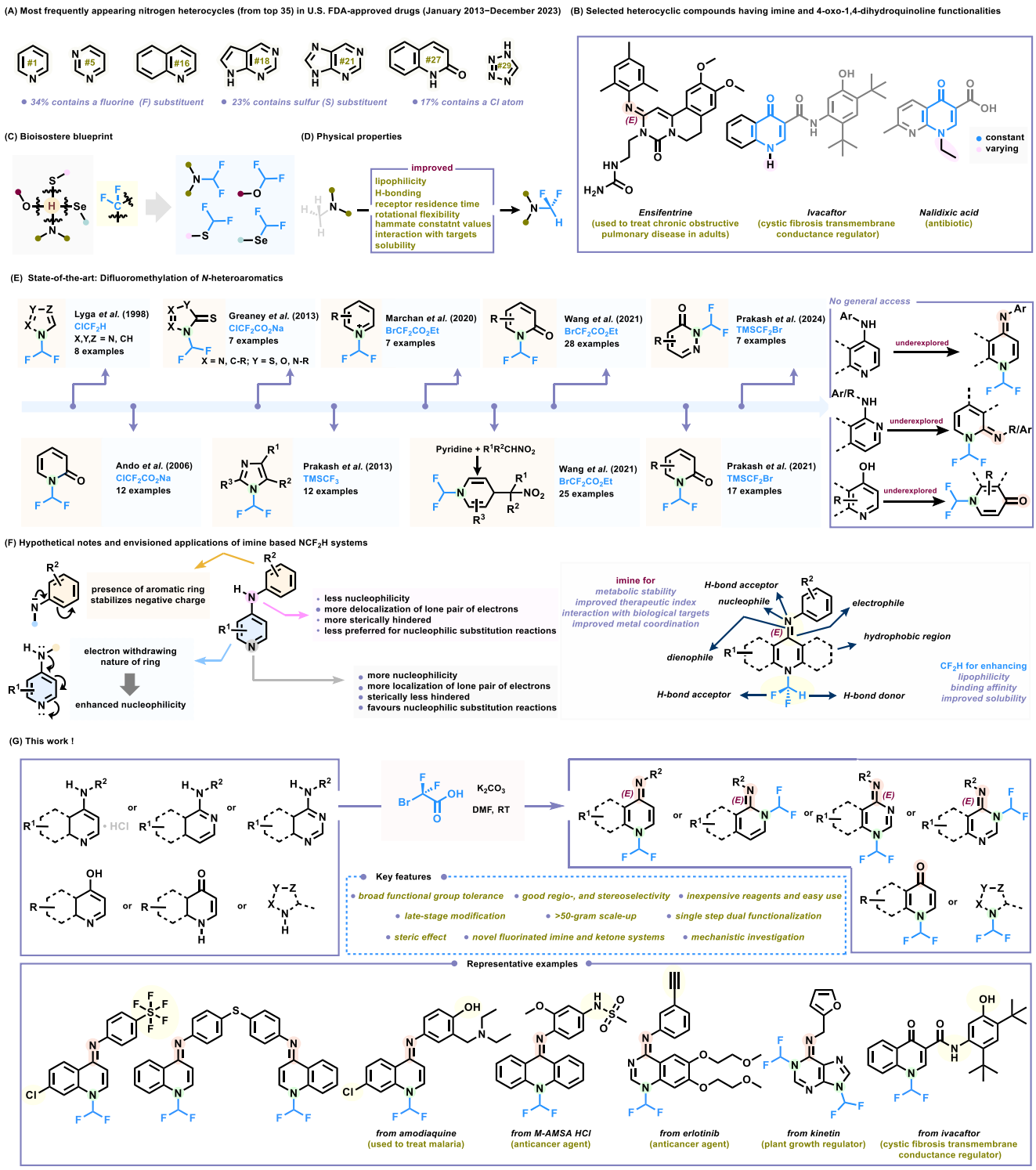


Figure 1. Difluoromethylation of *N*-heteroaromatics. (A) Most frequently appearing nitrogen heterocycles (from the top 35) in U.S. FDA-approved drugs. (B) Selected heterocyclic compounds having imine and 4-oxo-1,4-dihydroquinoline functionalities. (E) State-of-the-art: Difluoromethylation of *N*-heteroaromatics (selected references). (F) Concept note. (G) This work.

2. Results and Discussion

Since Het–*N*CF_2H motifs are prevalent in pharmaceutical settings and plant-based products,[11-14] our goal was to design the reaction with readily available and inexpensive reagents, possibly under ambient and metal-free conditions. As briefly exemplified in **Figure 2**, we evaluated various difluoromethylation reagents (**Figure 2A**) for the difluoromethylation of the hydrochloride salt form of *N*-(3-fluoro-4-morpholinophenyl)quinolin-4-amine (**1a**) as a model compound (validated the chemical structure of **1a** with Single crystal X-ray diffraction (ScXRD) (**CCDC: 2410081**). Among the employed difluoromethylation reagents, ethyl bromodifluoroacetate (**2a**) (1.2 equiv.) gave (*E*)-1-(difluoromethyl)-*N*-(3-fluoro-4-morpholinophenyl)quinolin-4(1H)-imine (**3a**) in 55% isolated yield using 2.5 equivalents of K_2CO_3 and DMF (2 ml) at room temperature for 18 h (**3a** is validated with ScXRD, **CCDC: 2413933**). Under the same conditions, only an appreciable yield of **3a** was achieved with chlorodifluoroacetic acid (**2b**) and diethyl (bromodifluoromethyl)phosphonate (**2c**). The reaction was unsuccessful with the TMS-CF_2Br reagent (**2d**). To our delight, the desired product **3a** was obtained in 92% isolated yield with bromo(difluoro)acetic acid (**2e**) as a CF_2H reagent. In general, the synthetic utility of difluoromethylation methods in pharmaceutical manufacturing relies on the cost and commercial accessibility of difluoromethylation reagents, including simplified experimental settings. Compared to the price of other CF_2H reagents (**see ESI, Table S1**), bromo(difluoro)acetic acid is inexpensive, available in large quantities, and easy to handle even on a large scale, thereby improving cost efficiencies. Although this reagent (**2e**) has been known for a while in constructing a few fluorinated molecules,[38-43] the ability to demonstrate *N*-difluoromethylation with complex *N*-heterocycles remains underexplored. Next, we screened the concentration of (**2e**) and observed that a minimum of 1.2 equiv. was required for an excellent yield of **3a** (**Figure 2B**). Encouraged by the above-mentioned results, we continued our investigation with 2.5 equiv. of various bases and discovered that K_2CO_3 (92% of **3a**) and Cs_2CO_3 (88% of **3a**) are best among other bases, such as Na_2CO_3, KOH, and NaOH (27-79% of **3a**) (**Figure 2C**). Considering the cost-effectiveness of the reaction, we proceeded the further optimization experiments with K_2CO_3 (B1). Further, we evaluated the concentration of K_2CO_3 and concluded that 2.5 equiv. is necessary for achieving a high yield of **3a** (**Figure 2D**). We also carried out the reaction by using solvents such as DMSO, H_2O, EtOH, THF, and DMF (**Figure 2E**). The best yield of **3a** (92%) was obtained in DMF as a solvent, and other solvents yielded inferior results (15-49% of **3a**). Upon screening the reaction time, we found that 18 h is optimal to achieve **3a** in high yield (**Figure 2F**). We also adapted the EcoScale tool and calculated the value for the conversion of **1a** to **3a**, and the results have shown that this protocol is safe and economically viable (**see the ESI, 7. EcoScale calculations**).

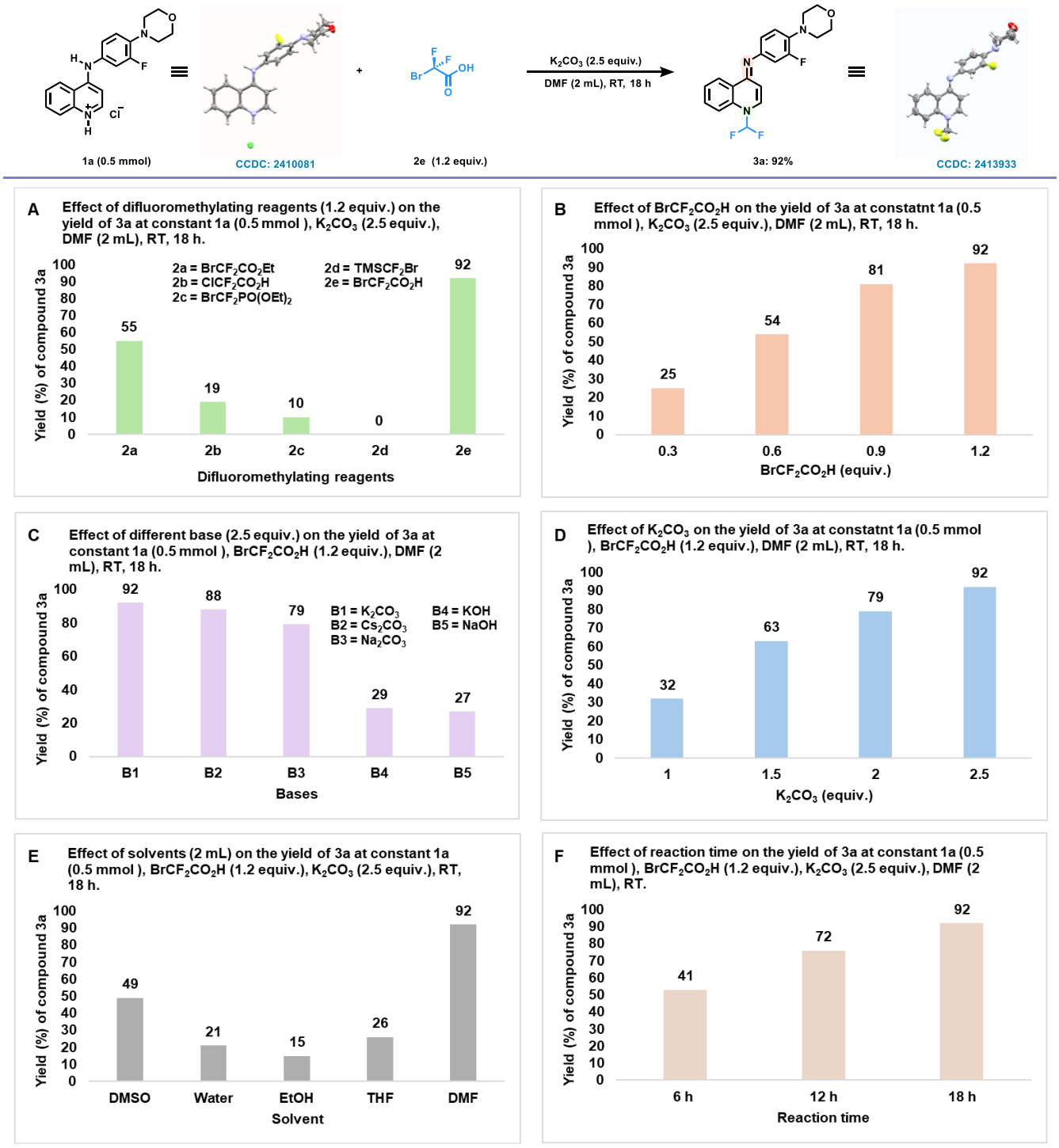


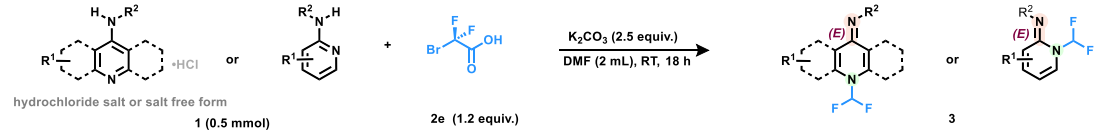
Figure 2. Optimization experiments for the conversion of **1a** to **3a.**

With viable reaction conditions in hand for the difluoromethylation of *N*-heterocycles, the study was advanced with a full exploration of structural scope compatibility, and results were summarized in **Figure 3**. Various *N*-Phenylquinolin-4-amine compounds derived from medicinally relevant structural moieties[44] were effectively difluoromethylated in high to

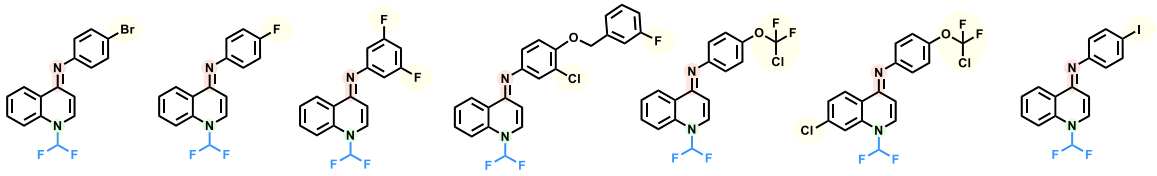
excellent yields. The high functional group tolerance of C-X bonds (X = halogen) of *N*-phenylquinolin-4-amine is a valuable asset in all areas of preparative chemistry, especially in the pharmaceutical industry. Pleasingly, the reaction worked well with a range of halide-substituted *N*-phenylquinolin-4-amine, giving the desired difluoromethylated products **3b–3h** in high yields. Interestingly, no dehalogenation of the C-X bond or byproduct took place. Next, sulfur-containing compounds can be found in a broad range of drugs owing to their different biological activities.[45] Specifically, -SCF_3 and -SF_5 are fascinating functional groups with significant potential in modern drug development. Bearing this in mind, a wide set of sulfur-based building blocks was demonstrated here with our optimized conditions.

For instance, *N*-phenylquinolin-4-amine comprising -SCF_3, -SF_5, -SCH_3, and diphenyl sulfide, including sulfonamide, were well accommodated in this protocol and delivered the respective *N*-difluoromethylated products in very good yields **(3i-3p)**, highlighting the remarkable sulfur resistance of this method. Unlike conventional strategies, our reaction conditions were amenable to double *N*-difluoromethylation featuring the imine unit, giving **3q** in 89% yield without eroding the diphenyl sulfide group. We also evaluated 2-methyl-*N*-phenylquinolin-4-amine, delivering the expected product **(3r)** in very good yield, and the chemical structure was unambiguously confirmed by single-crystal X-ray crystallography (**3r** is validated with ScXRD**, CCDC: 2410062)**. The reaction demonstrated good tolerance to the ether functionalities and afforded the desired products in excellent yields **(3s and 3t)**. The tolerance towards the alkene functional group **(3u)** is especially significant, as it provides opportunities for hydrofunctionalization and coupling reactions. Under optimal conditions, important crucial molecular skeletons, such as morpholine and piperazine-containing drug fragments, were also proved compatible, delivering the desired products efficiently in high yields **(3v-3aa)**. Azo compounds have been found to be promising candidates as drug carriers due to their versatile biological activities, but the survival of such a valuable functional group is very scarce. Interestingly, *N*-phenylquinolin-4-amine derivatives bearing azo moiety were successfully *N*-difluoromethylated in very good yields with this cost-effective approach **(3ab-3ac)**. Additionally, our protocol also accommodated biologically relevant heterocycles and was readily converted to *N*-difluoromethylated products in a very selective manner **(3ad-3ag)**. Additionally, it was noteworthy that *N*-pyridyl-substituted aniline could proceed well and provide the corresponding 1-(difluoromethyl)-*N*-phenylpyridin-2(1*H*)-imine in 87% yield **(3ah)**. *N*-(pyridin-2-yl)pivalamide and *tert*-butyl (3-methylpyridin-2-yl)carbamate are valuable pyridine-based molecular frameworks, undergo the selective *N*-difluoromethylation in 95% and 93% yield, respectively **(3ai and 3aj)**. The malaria treatment drug, amodiaquine,[46] was successfully *N*-difluoromethylated to access compound **3ak** in 79% isolated yield. Neratinib, a protein kinase inhibitor used to treat breast cancer,[47] was also *N*-difluoromethylated, albeit in 14% yield **(3al)** owing to less conversion. Further, amsacrine hydrochloride (m-AMSA hydrochloride, an anticancer agent)[48] can be directly difluoromethylated to give **3am** in 60% yield with this simple procedure. In addition, difluoromethylation of Piroxicam (CP-16171),[49] a pain relief drug, under standard conditions gave a mixture of corresponding *N*-

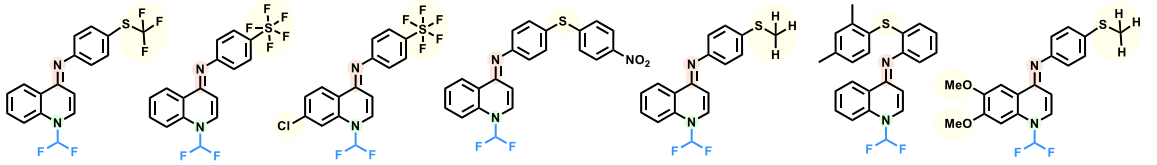
and *O*-difluoromethylated products **(3an + 3an′)** in a ratio of 1:0.6 (determined by ^{1}H NMR), which were found to be nonseparable with column chromatography. However, crystallization of the nonseparable mixture **(3an + 3an′)** gave yellow crystals of the major *N*-difluoromethylated isomer (validated the chemical structure of **3an** with ScXRD, **CCDC: 2410066**), and the minor isomer **3an′** did not result in any crystallization. Acalabrutinib, useful for the treatment of mantle cell lymphoma (MCL) in adults,[50] was successfully converted into the desired product **3ao** in a 41% isolated yield at 24 h of reaction time.



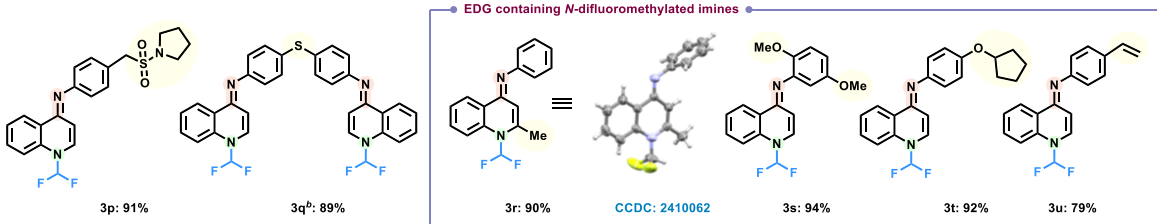
Halogen containing *N*-difluoromethylated imines



Sulfur based *N*-difluoromethylated imines

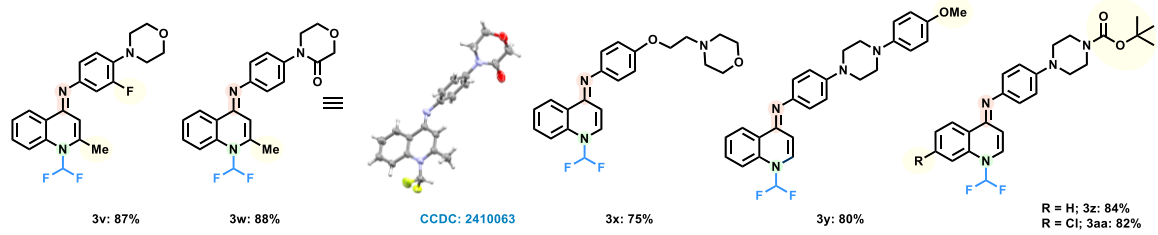


EDG containing *N*-difluoromethylated imines



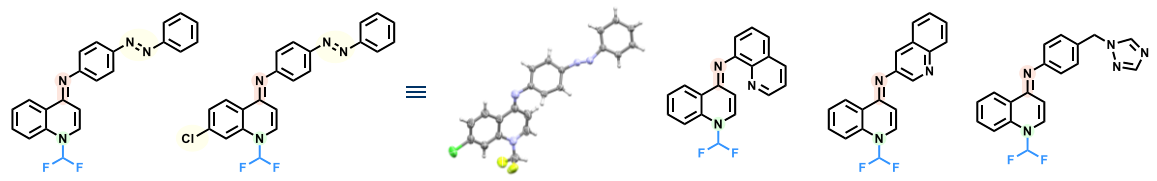
Morpholine based *N*-difluoromethylated imines

Piperazine based *N*-difluoromethylated imines



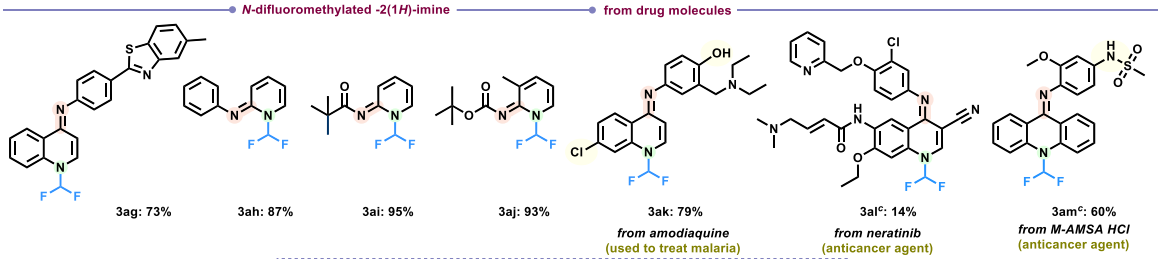
Azo based *N*-difluoromethylated imines

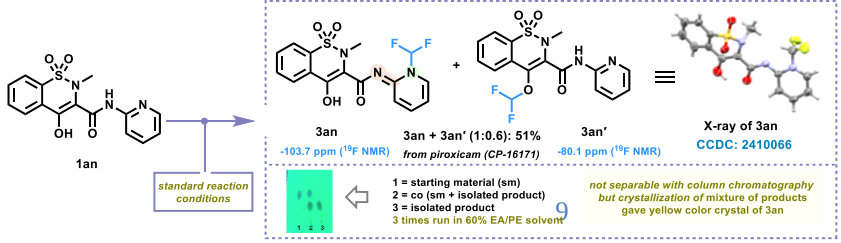
Heterocyclic ring containing *N*-difluoromethylated imines



N-difluoromethylated -2(1*H*)-imine

from drug molecules





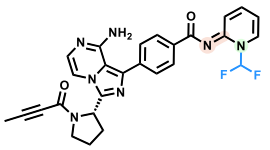


Figure 3. Substrate scope for *N*-difluoromethylation of quinolinamines[a]. [a]Reaction conditions: **1** (0.5 mmol), **2e** (0.6 mmol), K_2CO_3 (1.25 mmol), DMF (2mL), RT, 18 h. Isolated yield is provided. [b]**2e** (1.2 mmol), K_2CO_3 (2.5 mmol), DMF (3mL), RT, 18 h. [c]24 h.

Quinazolinamine derivatives are the common molecular frameworks in biologically active compounds.[3] Several top-selling commercial drugs, such as gefitinib, erlotinib, osimertinib, and many more, comprise quinazoline core and are considered as a "privileged structure" in drug design.[3] Since quinazolines have two nitrogen atoms, we sought to utilize one of them suitably for *N*-difluoromethylation in order to enhance their biological profiles. In this vein, commercially available drugs such as Erlotinib (used to treat non-small cell lung cancer and pancreatic cancer)[51] and FAAH-IN-2 (O-Desmorpholinopropyl Gefitinib),[52] a metabolite of Gefitinib underwent the current difluoromethylation process smoothly and afforded corresponding products in synthetically useful yields **(Figure 4, 5a-5b)**. The exceptional tolerance of alkyne and halide functionality in these drugs provides a useful route for further diversification of medicinally relevant molecules. Surprisingly, 2,5-dichloro-*N*-(2-(isopropylsulfonyl)phenyl)pyrimidin-4-amine, a synthetic intermediate of anaplastic lymphoma kinase (ALK) inhibitors,[53] gave somewhat unexpected product 5-chloro-1-(difluoromethyl)-4-((2-(isopropylsulfonyl)phenyl)amino)pyrimidin-2(1*H*)-one (**5c**) under routine conditions. To get some insight into this unusual behavior, a crystal structure of **5c (CCDC: 2413970)** was obtained, and it revealed the presence of a strong intramolecular hydrogen bonding between the H-atom of the free N-H bond and the O-atom of the SO_2 functional group. We believe this could be a possible reason for the decrease in the acidity of the H-atom of the N-H bond, which restricts deprotonation.[54] The nucleophilic addition of water on the *ortho* site of the pyrimidine ring (*Ipso* to the Cl atom), followed by the substitution of the chloride atom, leads to the formation of a stabilized *N*-difluoromethylated product **5c**. Most importantly, Kinetin, a plant hormone that regulates cell growth in plants,[55] could also provide double difluoromethylated product **(5d)** in 81% isolated yield (validated the chemical structure of **5d** with ScXRD, **CCDC: 2410069**). 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-*N*-(2-chloro-6-methylphenyl)thiazole-5-carboxamide, a key intermediate of dasatinib drug,[56] gave 61% isolated yield of a mixture of **5e** and **5e′** (ratio of **5e** and **5e′** is 1:0.9; determined by ^{19}F NMR). To the best of our knowledge, the preparation of such novel *N*-difluoromethylated products holding imine functional groups is completely unknown.

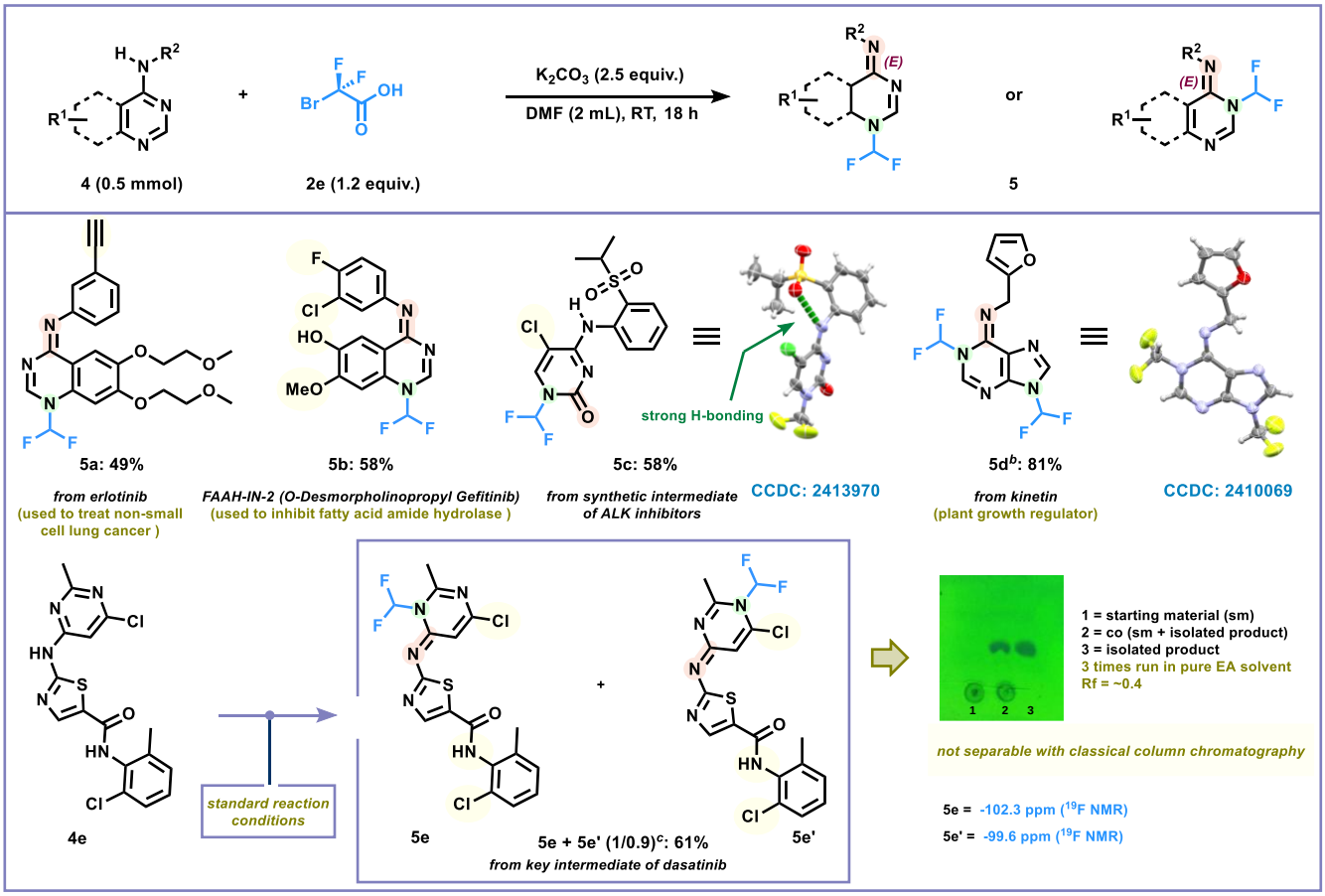


Figure 4. Substrate scope for *N*-difluoromethylation of various quinazolinamine[a]. [a]Reaction conditions: **4** (0.5 mmol), **2e** (0.6 mmol), K_2CO_3 (1.25 mmol), DMF (2mL), RT, 18 h. Isolated yield is provided. [b]**2e** (1.2 mmol), K_2CO_3 (2.5 mmol), DMF (3mL), RT, 18 h. [c]24 h.

Next, under the same conditions, we surveyed the scope of the reaction with pyridin-4-ol and quinolin-4-ol derivatives with bromo(difluoro)acetic acid **(Figure 5)**. Since functionalized pyridines are considered attractive scaffolds and found in many bioactive compounds,[1, 2] site-selective installation of the $-CF_2H$ group onto nitrogen atoms would create a valuable platform for the preparation of an array of *N*-difluoromethylated products. Unsubstituted 4-hydroxypyridine, 3-methylpyridin-4-ol, and halogen-substituted 4-hydroxypyridines underwent the selective *N*-difluoromethylation with simultaneous formation of ketone functional group in good to excellent yields **(7a-7e)**, underscores that chloride and iodo substituents are also tolerated by the reaction conditions. Gratifyingly, challenging pyridine derivatives such as (*E*)-3-(4-fluorostyryl)pyridin-4-ol and (*E*)-3-(4-(trifluoromethyl)styryl)pyridin-4-ol, also reacted smoothly to afford the corresponding difluoromethylated products **7f** and **7g**, with isolated yields of 76% and 78%, respectively.

Quinolones and their derivatives play a fundamental role as the pharmacophore for several drug molecules.[57] In this vein, we sought to apply our reaction conditions to enhance their clinical development. A variety of 4-hydroxyquinolines with halide-substituents and electron-donating groups worked well under optimal conditions, delivering the

corresponding *N*-difluoromethylated products in high yields **(7h-7n)**. Interestingly, difluoromethylation of two hydroxy groups containing 1,10-phenanthroline-4,7-diol selectively underwent both *N*- and *O*-difluoromethylation within the molecule and gave the respective product **7o** in 89% isolated yield, displaying the potential double difluoromethylation of the present method. The fused heterocyclic compound containing both triazole and pyrimidine rings, such as 5-Methyl-2-(methylthio)[1,2,4]triazolo[1,5-a]pyrimidin-7-ol found in biologically active compounds also reacted efficiently to give **7p** in high yield. Additionally, 4-quinolone of several therapeutic compounds proceeded smoothly to provide targeted difluoromethylated products **7q-7s** (74 -78% yield). When conducting experiments with quinolin-4-ol and quinolone derivatives, minor amounts of *O*-difluoromethylated products were also detected. For confirmation, we have isolated *O*-difluoromethylated products **(22% yield of 7n′)** of **6n** and analysed them with NMR and HRMS. Next, we assessed this protocol for the late-stage functionalization of the quinolone-based drug. For instance, Ivacaftor (listed 13th in the top-200-selling drugs in 2023),[3] which is used to treat cystic fibrosis, could be selectively *N*-difluoromethylated in 64% isolated yield **(7t)**, thus demonstrating the advantages of this simple operational approach. In addition, we also investigated the influence of the steric effect and subjected the unseen examples of **6u** and **6v** to difluoromethylation under standard conditions. As a result, difluoromethylation of **6u** (carboxylate moiety is neighbor to C=O) favored selective *N*-difluoromethylated product **(7u)** in 81% yield. Whereas difluoromethylation of **6v** (carboxylate moiety is neighbor to N-H) favored selective *O*-difluoromethylated product **(7v)** in 78% yield **(Figure 5)**. These results clearly suggest that steric hindrance governs the selective *O*- and *N*-difluoromethylation in these reactions.

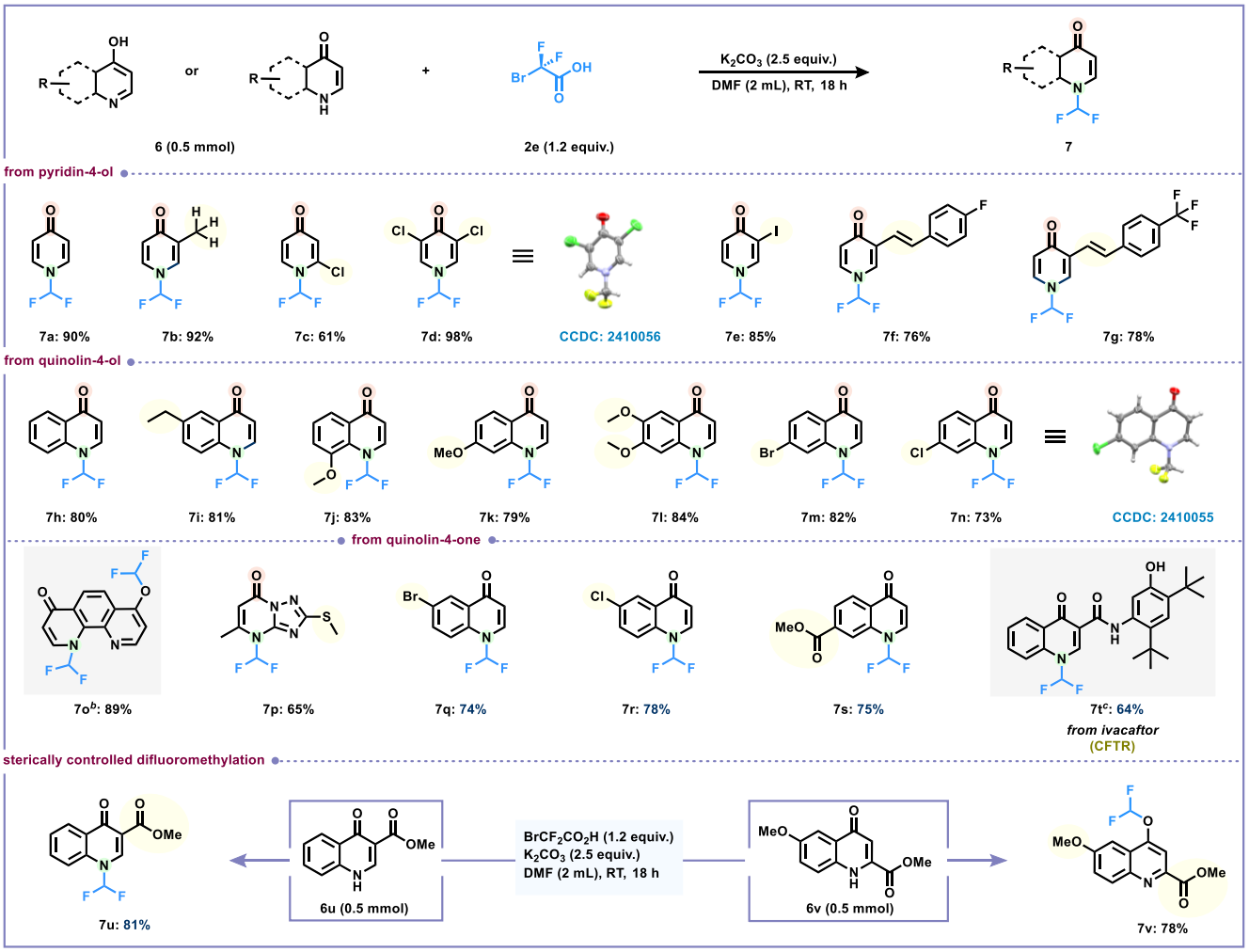


Figure 5. Substrate scope for *N*-difluoromethylation of pyridine-4-ol, quinoline-4-ol, and quinoline-4-one[a]. [a]Reaction conditions: **6** (0.5 mmol), **2e** (0.6 mmol), K_2CO_3 (1.25 mmol), DMF (2mL), RT, 18 h. Isolated yield is provided. [b]**2e** (1.2 mmol), K_2CO_3 (2.5 mmol), DMF (3mL), RT, 18 h. [c]24 h.

Encouraged by the above results, we became interested in late-stage *N*-difluoromethylation with bromo(difluoro)acetic acid in a straightforward manner **(Figure 6A)**. Notably, four APIs, Azathioprine, Aprovel, Lansoprazole, and Mercaptopurine, were selectively *N*-difluoromethylated under standard conditions to give products **9a-9d**, signifying tolerance of key functional groups in more complex settings. Azathioprine, which contains a purine ring and is used to treat rheumatoid arthritis,[58] gave the corresponding product **9a** (verified the chemical structure of **9a** with ScXRD, **CCDC: 2410064**) in 71% isolated yield. Another drug molecule, Aprovel, bearing tetrazole ring system, is used to treat high blood pressure,[59] also underwent *N*-difluoromethylation to afford the product **9b** (verified the chemical structure **9b** with ScXRD, **CCDC: 2410078**) in synthetically useful yield. Lansoprazole (used to treat stomach ulcers)[60] also delivered corresponding *N*-difluoromethylated product **9c** in 72% isolated yield. Furthermore, Mercaptopurine, a chemotherapy drug,[61] was also feasible for double *N*-difluoromethylation and afforded **9d**

even in a higher yield (78%). These results underscore the functional group tolerance and the generality of this *N*-difluoromethylation procedure.

Based on these results, we next assessed the scope of the difluoromethylation of biologically active lactams under optimal conditions at room temperature **(Figure 6B)**. First, the commercially available Sildenafil Lactam, used to treat erectile dysfunction,[62] was applied for difluoromethylation. However, surprisingly *O*-difluoromethylated product is obtained in 72% isolated yield **(11a)**. Similarly, Triacetyl-ganciclovir, an orally active antiviral agent,[63] also delivered an *O*-difluoromethylated product with a 61% yield **(11b)**. Also, the Brexpiprazole intermediate (an antipsychotic drug)[64] and a simple pyridinone system gave *O*-difluoromethylated products in 73% and 91% yield, respectively **(11c and 11d)**. It is well known that in the presence of a polar aprotic solvent, either at room temperature or higher temperature, the lactam form becomes a more stable form from its tautomeric lactim form owing to its extra stabilization through resonance.[65, 66] Gratifyingly, our reaction conditions (DMF as a polar aprotic solvent at room temperature) are completely in favor of lactam form, in which nucleophilicity and localization of lone pair of electrons on the *O*-atom are higher as compared to the *N*-atom. We believe this could be a probable reason for selective *O*-difluoromethylation instead of *N*-difluoromethylation with lactams. All these products **(11a-11d)** are isolated for the first time to furnish novel medicinally relevant *O*-CF_2H motifs. Overall, this approach provides a simple and straightforward route for drug discovery applications.

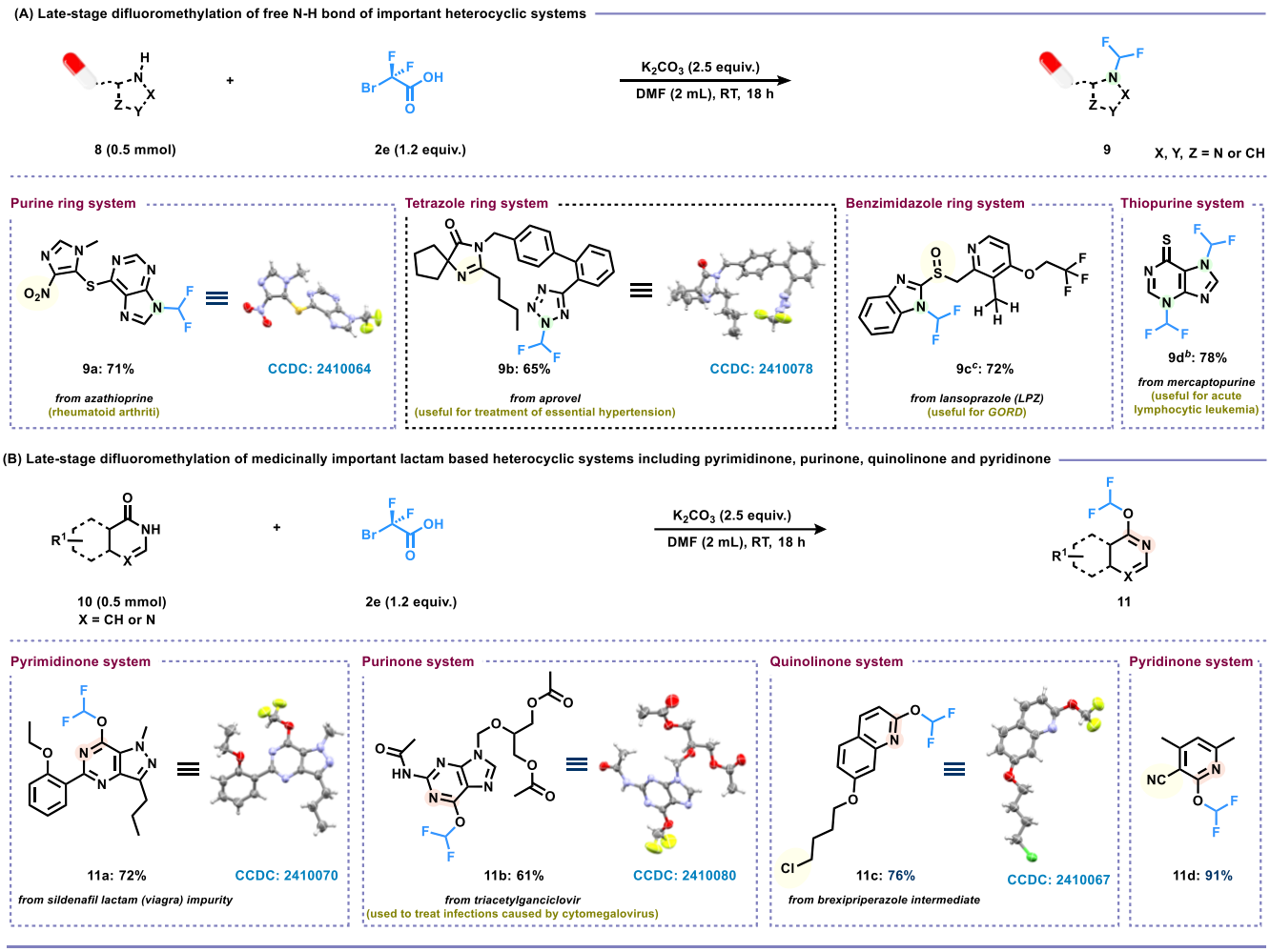


Figure 6. Substrate scope for *N*-difluoromethylation of drug candidates[a]. (A) late-stage difluoromethylation of free N-H bond of important heterocyclic systems. (B) late-stage difluoromethylation of medicinally important lactam-based heterocyclic systems, including pyrimidinone, purinone, quinolinone, and pyridinone. [a]Reaction conditions: **6** or **10** (0.5 mmol), **2e** (0.6 mmol), K_2CO_3 (1.25 mmol), DMF (2mL), RT, 18 h. Isolated yield is provided. [b]**2e** (1.2 mmol), K_2CO_3 (2.5 mmol), DMF (3mL), RT, 18 h. [c]24 h.

Scaling up the production of fluorinated compounds poses a significant challenge in medicinal chemistry because of the costs associated with fluorinating reagents, specialized equipment, safety standards, and maintaining precise reaction conditions. By keeping this in mind and to demonstrate the synthetic utility of our simplified protocol, we conducted the difluoromethylation with *N*-(3-fluoro-4-morpholinophenyl)quinolin-4-amine **(1a)** on the 142-mmol scale (>50 gram) and achieved the desired product (*E*)-1-(difluoromethyl)-*N*-(3-fluoro-4-morpholinophenyl)quinolin-4(1H)-imine **(3a)** in 89% isolated yield **(for experimental set-up and reaction procedure, see ESI, Figure S12)**, and the performance of this scale-up is virtually identical with 0.5 mmol-scale of the reaction, displaying the easiness of the method **(Figure 7A)**.

Hydrodefluorination is a process that converts a C-F bond to a C-H bond, which is significant in creating novel therapeutic agents.[67] By keeping this in mind, we sought to

showcase the synthetic potential of imine-based *N*-difluoromethylated products using the hydrodefluorination approach. In this vein, we mixed **3a**, $NaBH_4$, and Al_2O_3 (all are solid reagents) and grinded with hand in a Mortar-pestle by slowly adding 30 drops of methanol (3 drops per minute). These conditions led to a valuable 3D shape *N*-methylated motif **21** in 47% isolated yield **(Figure 7B)**, and this result underscores that our proposed synthetic strategy provides versatile access to high Fsp^3-enriched scaffolds, which holds the promise of drug discovery in medicinal chemistry purposes. It should be noted that rapid synthesis of compound **21** with high Fsp^3 is difficult to access using conventional strategies.

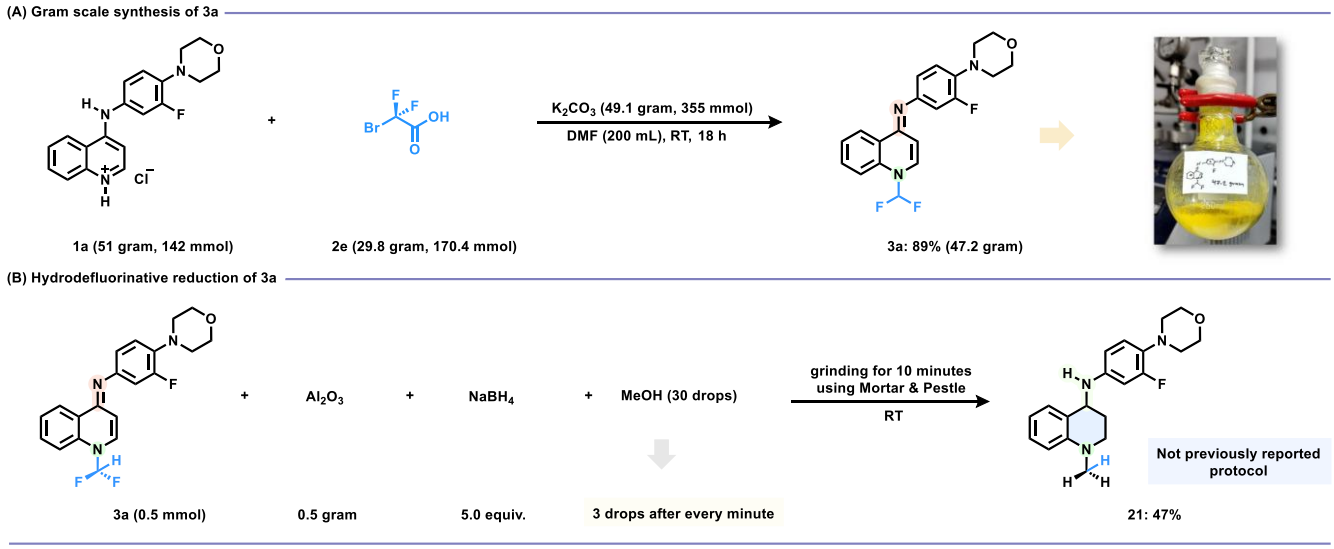


Figure 7. (A) Gram scale synthesis of **3a**. (B) Hydrodefluorinative reduction of **3a**.

To gain insight into how the *N*-difluoromethylation reaction works, we conducted a few control experiments. Initially, we executed a deuterium labelling experiment with **1a** using D_2O (10 equiv.) under standard conditions. This experiment resulted in an 86% isolated yield of the desired deuterated product **(*d*-3a)** with 74% deuterium incorporation **(Figure 8A)**. Next, we treated ***d*-3a** with H_2O (10 equiv.) under the same conditions in the absence of **2e**, and the result showed that there was no exchange of H-D; and ***d*-3a** was recovered with 79% isolated yield **(Figure 8B)**, showcasing the stability of ***d*-3a**. Further, to identify the source of the H atom in the CF_2-H unit of **3a**, we carried out the reaction of ***d*-1a** (34%-D incorporation; for the preparation of ***d*-1a**, **see ESI, Figure S8-S9**) with **2e** under standard conditions, but no deuterium incorporation was observed, and **3a** was isolated with 89% yield (0%-D incorporation) **(Figure 8C)**. This finding clearly validates that the hydrogen atom of the CF_2-H unit in **3a** is not a part of the N-H component of **1a**. This implies that $BrCF_2CO_2H$ could be a source of the H atom in the CF_2H unit of **3a**, which is corroborated by the literature.[28] To know the reaction intermediate, we first treated **1a** with **2e** under standard conditions without adding K_2CO_3. The analysis of the crude reaction mixture by HRMS revealed the formation of intermediate **3a′,** while the desired product **3a** was not detected. Later, the addition of K_2CO_3 (2.5 equiv.) in the same reaction mixture resulted in the formation of **3a**, evidencing the requirement of K_2CO_3 for transforming **3a′** to **3a**.

Based on the results obtained from our control experiments and literature precedents,[20, 28] we proposed a probable reaction mechanism **(Figure 8E)**. Although, **2e** is known to generate a CF_2 carbene precursor in a basic medium,[38] but surprisingly the formation of intermediate **3a′** without a base directed the first step of the reaction to be a simple nucleophilic substitution reaction between the starting material **(12)** and **2e**. The more nucleophilicity of the N-atom of *N*-heteroarene (**12)** and a rapid release of CO_2 gas *via* decarboxylation resulted formation of intermediate **13**. It is presumed that the formation of intermediate **13** renders the N-H bond dissociation energy *via* increasing the acidity of the H-atom attached to the N-H bond, which could be probably due to the electron-withdrawing nature of the *N*-heteroarene (intermediate **13**). Finally, K_2CO_3 abstracts the acidic proton from the N-H bond and generates another intermediate **14,** which further undergoes π electron transfer to deliver the highly stabilized *N*-difluoromethylated product featuring an imine **(15)** functional group **(Figure 8E).** Importantly, our methodology was found to be highly efficient and suitable for *N*-aromatic substituted heteroarene-4-amines. For instance, when *N*-methylpyridin-4-amine **(16a)** and chloroquine **(16b)** were applied to the difluoromethylation under standard conditions, only a trace amount of corresponding products **17a**, and **17b**, respectively, was detected (analysed by ^{19}F NMR). Whereas amodiaquine **(1ak)** was successfully transformed into imine-based *N*-difluoromethylated product **3ak**. This protocol has some limitations with 4-methyl pyridine systems **(18a)** which may be due to less acidity of the H-atom of C(sp^3)-H bond.

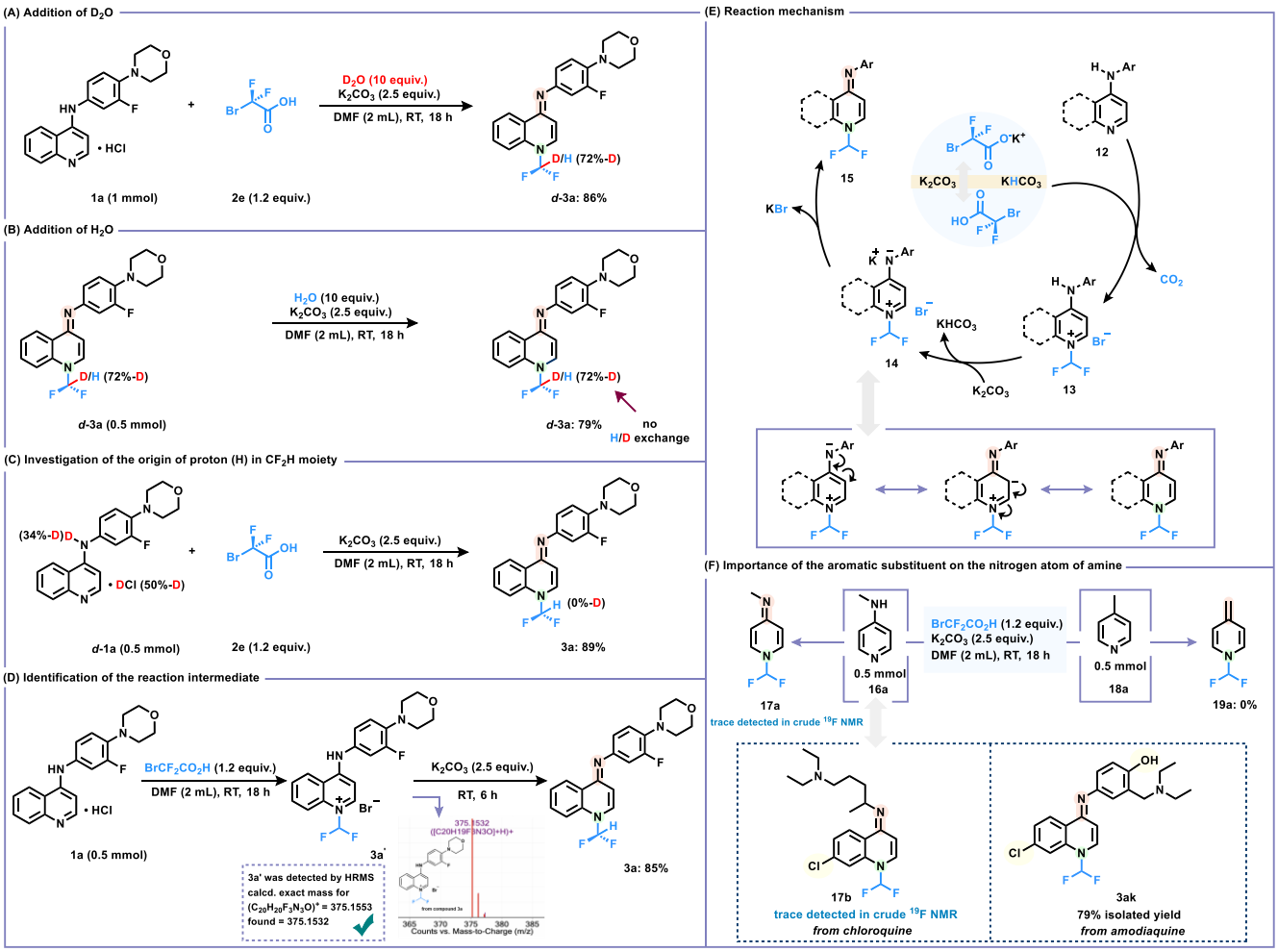


Figure 8. Mechanistic investigation. (A) Addition of D_2O. (B) Addition of H_2O. (C) Investigation of the origin of a proton (H) in CF_2H moiety. (D) Identification of the reaction intermediate. (E) Reaction mechanism. (F) Importance of the aromatic substituent on the *N*-atom of amines.

3. Conclusions

In summary, the first efficient access to Het–*N*CF_2H complex products featuring either imine and/or ketone moieties was unlocked herein. The methodology utilizes inexpensive, commercially available, and bench-stable bromo(difluoro)acetic acid as a difluoromethylating agent with K_2CO_3 as a base. Depending on the type of nitrogen heterocycle, this approach also permits the incorporation of two CF_2H units. The key to accomplishing the aforementioned products is the increased nucleophilicity and reduced steric hindrance on the nitrogen atom of the heteroarene ring. The ambient reaction conditions and high chemoselectivity have permitted the difluoromethylation of >70 privileged *N*-heterocyclic substrates (e.g., derivatives of quinolines, quinazolines, pyridines, lactams, etc.), including 18 commercial drugs. In addition, this streamlined approach can run up to a 142-mmol scale (>50 g) with exceptional inclusion of the CF_2H group in **1a** comprising the imine unit. Mechanistic investigations concluded that *N*-difluoromethylquinolinium salt serves as a key intermediate for the decarboxylative *N*-

difluoromethylation with bromo(difluoro)acetic acid. In the end, for the first time, we have successfully proven the rapid hydrodefluorinative reduction in a single step, utilizing it to construct a complex *N*-methylated Fsp^3-enriched scaffold. We anticipate this comprehensive cost-effective strategy significantly expands the drug-like chemical space accessible to small-molecule *N*-difluoromethylated compounds.

EXPERIMENTAL PROCEDURES

Details regarding the experimental procedures can be found in the supplemental experimental procedures.

RESOURCE AVAILABILITY

Lead contact Further information and requests for resources should be directed to, and will be fulfilled by, the lead contact, Kishore Natte (kishore.natte@chy.iith.ac.in) **ORCID:** 0000-0001-8557-1969

Materials availability All other data supporting the findings of this study are available within the article and the supplemental information or from the lead contact upon reasonable request.

Data and code availability

Experimental details and procedures, mechanistic experiments, EcoScale calculation, price comparison table, crystal structure data, and spectral data for all compounds (PDF).

Accession Codes

Deposition Number for **1a** (CCDC: 2410081), for **3a** (CCDC: 2413933), for **3r** (CCDC: 2410062), for **3w** (CCDC: 2410063), for **3ac** (CCDC: 2410065), for **3an** (CCDC: 2410066), for **5c** (CCDC: 2413970), for **5d** (CCDC: 2410069), for **7d** (CCDC: 2410056), for **7n** (CCDC: 2410055), for **9a** (CCDC: 2410064), **9b** (CCDC: 2410078), for **11a** (CCDC: 2410070), **11b** (CCDC: 2410080), for **11c** (CCDC: 2410067) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* the joint Cambridge Crystallographic DataCentre (CCDC) and Fachinformationszentrum Karlsruhe.

ACKNOWLEDGMENTS

K.N. acknowledges the Seed Grant (SG-128) from IIT Hyderabad and CRG/2023/005734 from the Science and Engineering Research Board for financial support. S.K. is thankful to the University Grants Commission (UGC) New Delhi for awarding junior research fellowships (JRF). T. B. is thankful to PMRF. We acknowledge P. S. Ramana Babu for helping with the crystal structure analysis. We acknowledge Md. Samiuddin, Ashok Yeligeti, and Dr. B. Surender for measuring NMR.

AUTHOR CONTRIBUTIONS

S.K. and K.N. conceived and designed the experiments. S.K. and T.B. performed the experiments and mechanism studies. S.K. analyzed the X-ray crystal structure of the isolated products. S.K. and K.N. analyzed the data. S.K. and K.N. co-wrote the manuscript. K.N. directed the project. All authors discussed the results and commented on the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES AND NOTES

(1) Marshall, C. M.; Federice, J. G.; Bell, C. N.; Cox, P. B.; Njardarson, J. T. An Update on the Nitrogen Heterocycle Compositions and Properties of U.S. FDA-Approved Pharmaceuticals (2013–2023). *J. Med. Chem.* **2024**, *67* (14), 11622-11655. DOI: 10.1021/acs.jmedchem.4c01122.

(2) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57* (24), 10257-10274. DOI: 10.1021/jm501100b.

(3)https://bpb-us-e2.wpmucdn.com/sites.arizona.edu/dist/9/130/files/2024/07/Top200BrandNameDrugBySales2023V3.pdf.

(4) Fier, P. S.; Hartwig, J. F. Selective C-H Fluorination of Pyridines and Diazines Inspired by a Classic Amination Reaction. *Science* **2013**, *342* (6161), 956-960. DOI: doi:10.1126/science.1243759.

(5) Jun-An Ma, D. C. Emerging Fluorinated Motifs: Synthesis, Properties, and Applications. *2020 Wiley - VCH Verlag GmbH & Co. KGaA*.

(6) Fernandes, A. J.; Giri, R.; Houk, K. N.; Katayev, D. Review and Theoretical Analysis of Fluorinated Radicals in Direct CAr−H Functionalization of (Hetero)arenes. *Angew. Chem. Int. Ed.* **2024**, *63* (16), e202318377. DOI: https://doi.org/10.1002/anie.202318377.

(7) Klose, I.; Patel, C.; Mondal, A.; Schwarz, A.; Pupo, G.; Gouverneur, V. Fluorspar to fluorochemicals upon low-temperature activation in water. *Nature* **2024**, *635* (8038), 359-364. DOI: 10.1038/s41586-024-08125-1.

(8) Xu, P.; Wang, Z.; Guo, S.-M.; Studer, A. Introduction of the difluoromethyl group at the meta- or para-position of pyridines through regioselectivity switch. *Nature Commun.* **2024**, *15* (1), 4121. DOI: 10.1038/s41467-024-48383-1.

(9) Sheikhi, N.; Bahraminejad, M.; Saeedi, M.; Mirfazli, S. S. A review: FDA-approved fluorine-containing small molecules from 2015 to 2022. *Euro. J. Med. Chem.* **2023**, *260*, 115758. DOI: https://doi.org/10.1016/j.ejmech.2023.115758.

(10) https://drughunter.com/articles/acs-spring-2024-first-time-disclosures.

(11) Sap, J. B. I.; Meyer, C. F.; Straathof, N. J. W.; Iwumene, N.; am Ende, C. W.; Trabanco, A. A.; Gouverneur, V. Late-stage difluoromethylation: concepts, developments and perspective. *Chem. Soc. Rev.* **2021**, *50* (14), 8214-8247, 10.1039/D1CS00360G. DOI: 10.1039/D1CS00360G.

(12) Hayashi, H.; Katsuyama, H.; Takano, H.; Harabuchi, Y.; Maeda, S.; Mita, T. In silico reaction screening with difluorocarbene for N-difluoroalkylative dearomatization of pyridines. *Nature Synth.* **2022**, *1* (10), 804-814. DOI: 10.1038/s44160-022-00128-y.

(13) Milcent, T.; Crousse, B. Construction of N-CFH, N-CF , and N-CHCF Motifs. In *Emerging Fluorinated Motifs*, 2020; pp 723-761.

(14) Luo, Q.; Ni, C.; Gu, Y.; Hu, J. The Difluoromethylation Protocols. In *PATAI'S Chemistry of Functional Groups*, pp 1-75.

(15) Liu, Q.; Wu, Y.; Chen, P.; Liu, G. One-Pot Synthesis of 1-(Trifluoromethyl)-4-fluoro-1,2-dihydroisoquinolines and 4,4-Difluoro-1,2,3,4-tetrahydroisoquinolines. *Org. Lett.* **2013**, *15* (24), 6210-6213. DOI: 10.1021/ol403059z.

(16) Müller, K.; Faeh, C.; Diederich, F. Fluorine in Pharmaceuticals: Looking Beyond Intuition. *Science* **2007**, *317* (5846), 1881-1886. DOI: doi:10.1126/science.1131943.

(17) Hu, C.; Jiang, L.; Guo, Z.; Mumtaz, Y.; Liu, J.; Qin, J.; Chen, Y.; Lin, Z.; Yi, W. Synthesis of N-Difluoromethyl Carbonyl Compounds from N-Difluoromethylcarbamoyl Fluorides. *Angew. Chem. Int. Ed.* **2024**, *63* (15), e202319758. DOI: https://doi.org/10.1002/anie.202319758.

(18) Zivkovic, F. G.; Wycich, G.; Liu, L.; Schoenebeck, F. Access to N-Difluoromethyl Amides, (Thio)Carbamates, Ureas, and Formamides. *J. Am. Chem. Soc.* **2024**, *146* (2), 1276-1281. DOI: 10.1021/jacs.3c13711.

(19) Lyga, J. W.; Patera, R. M. N-difluoromethylation of phenylazoles. *J. Fluor. Chem.* **1998**, *92* (2), 141-145. DOI: https://doi.org/10.1016/S0022-1139(98)00262-0.

(20) Gandioso, A.; El Fakiri, M.; Rovira, A.; Marchán, V. A simple method for the synthesis of N-difluoromethylated pyridines and 4-pyridones/quinolones by using BrCF2COOEt as the difluoromethylation reagent. *RSC Adv.* **2020**, *10* (50), 29829-29834, 10.1039/D0RA06322C. DOI: 10.1039/D0RA06322C.

(21) Prakash, G. K. S.; Krishnamoorthy, S.; Ganesh, S. K.; Kulkarni, A.; Haiges, R.; Olah, G. A. N-Difluoromethylation of Imidazoles and Benzimidazoles Using the Ruppert–Prakash Reagent under Neutral Conditions. *Org. Lett.* **2014**, *16* (1), 54-57. DOI: 10.1021/ol403007j.

(22) Zhu, Z.; Tang, J.; Kyriazakos, S.; Knieb, A.; Xu, Y.; Zhang, C.; Prakash, G. K. S. Mono- and Difluoromethylation of 3(2H)-Pyridazinones. *Org. Lett.* **2024**, *26* (38), 8106-8109. DOI: 10.1021/acs.orglett.4c03002.

(23) Ando, M.; Wada, T.; Sato, N. Facile One-Pot Synthesis of N-Difluoromethyl-2-pyridone Derivatives. *Org. Lett.* **2006**, *8* (17), 3805-3808. DOI: 10.1021/ol061481f.

(24) Zhou, S.; Sun, Z.-Y.; Zhu, K.; Zhao, W.; Tang, X.; Guo, M.; Wang, G. Metal-Free Difunctionalization of Pyridines: Selective Construction of N-CF2H and N-CHO Dihydropyridines. *Org. Lett.* **2021**, *23* (6), 2205-2211. DOI: 10.1021/acs.orglett.1c00352.

(25) Zhu, Z.; Krishnamurti, V.; Ispizua-Rodriguez, X.; Barrett, C.; Prakash, G. K. S. Chemoselective N- and O-Difluoromethylation of 2-Pyridones, Isoquinolinones, and Quinolinones with TMSCF2Br. *Org. Lett.* **2021**, *23* (16), 6494-6498. DOI: 10.1021/acs.orglett.1c02305.

(26) Zhou, S.; Hou, X.; Yang, K.; Guo, M.; Zhao, W.; Tang, X.; Wang, G. Direct Synthesis of N-Difluoromethyl-2-pyridones from Pyridines. *J. Org. Chem.* **2021**, *86* (9), 6879-6887. DOI: 10.1021/acs.joc.1c00228.

(27) Li, S.-W.; Wang, G.; Ye, Z.-S. Difluorocarbene enabled ester insertion/1,4-acyl rearrangement of 2-acetoxylpyridines: Modular access to gem-difluoromethylenated 2-pyridones. *Tetrahedron Lett.* **2023**, *119*, 154413. DOI: https://doi.org/10.1016/j.tetlet.2023.154413.

(28) Duan, J.; Choy, P. Y.; Gan, K. B.; Kwong, F. Y. N-Difluoromethylation of N-pyridyl-substituted anilines with ethyl bromodifluoroacetate. *Org. Biomol. Chem.* **2022**, *20* (9), 1883-1887, 10.1039/D2OB00119E. DOI: 10.1039/D2OB00119E.

(29) Thomoson, C. S.; Wang, L.; Dolbier, W. R. Use of fluoroform as a source of difluorocarbene in the synthesis of N-CF2H heterocycles and difluoromethoxypyridines. *J. Fluor. Chem.* **2014**, *168*, 34-39. DOI: https://doi.org/10.1016/j.jfluchem.2014.08.015.

(30) Guillemard, L.; Kaplaneris, N.; Ackermann, L.; Johansson, M. J. Late-stage C–H functionalization offers new opportunities in drug discovery. *Nature Rev. Chem.* **2021**, *5* (8), 522-545. DOI: 10.1038/s41570-021-00300-6.

(31) Britton, R.; Gouverneur, V.; Lin, J.-H.; Meanwell, M.; Ni, C.; Pupo, G.; Xiao, J.-C.; Hu, J. Contemporary synthetic strategies in organofluorine chemistry. *Nature Rev. Methods Primers* **2021**, *1* (1), 47. DOI: 10.1038/s43586-021-00042-1.

(32) Bachovchin, K. A.; Sharma, A.; Bag, S.; Klug, D. M.; Schneider, K. M.; Singh, B.; Jalani, H. B.; Buskes, M. J.; Mehta, N.; Tanghe, S.; et al. Improvement of Aqueous Solubility of Lapatinib-Derived Analogues: Identification of a Quinolinimine Lead for Human African Trypanosomiasis Drug Development. *J. Med. Chem.* **2019**, *62* (2), 665-687. DOI: 10.1021/acs.jmedchem.8b01365.

(33) Rodrigues, T.; da Cruz, F. P.; Lafuente-Monasterio, M. J.; Gonçalves, D.; Ressurreição, A. S.; Sitoe, A. R.; Bronze, M. R.; Gut, J.; Schneider, G.; Mota, M. M.; et al. Quinolin-4(1H)-imines are Potent Antiplasmodial Drugs Targeting the Liver Stage of Malaria. *J. Med. Chem.* **2013**, *56* (11), 4811-4815. DOI: 10.1021/jm400246e.

(34) Grygorenko, O. O.; Melnykov, K. P. Fluorinated building blocks in drug design: new pathways and targets. *Future Med. Chem.* **2024**, *16* (14), 1375-1378. DOI: 10.1080/17568919.2024.2379229.

(35) Hu, Y.-Q.; Zhang, S.; Xu, Z.; Lv, Z.-S.; Liu, M.-L.; Feng, L.-S. 4-Quinolone hybrids and their antibacterial activities. *Euro. J. Med. Chem.* **2017**, *141*, 335-345. DOI: https://doi.org/10.1016/j.ejmech.2017.09.050.

(36) Shen, C.; Wang, A.; Xu, J.; An, Z.; Loh, K. Y.; Zhang, P.; Liu, X. Recent Advances in the Catalytic Synthesis of 4-Quinolones. *Chem* **2019**, *5* (5), 1059-1107. DOI: 10.1016/j.chempr.2019.01.006 (acccessed 2024/12/21).

(37) Pushpakom, S.; Iorio, F.; Eyers, P. A.; Escott, K. J.; Hopper, S.; Wells, A.; Doig, A.; Guilliams, T.; Latimer, J.; McNamee, C.; et al. Drug repurposing: progress, challenges and recommendations. *Nature Rev. Drug Discov.* **2019**, *18* (1), 41-58. DOI: 10.1038/nrd.2018.168.

(38) Kumawat, S.; Natte, K. Accessing structurally diverse aryl difluoromethyl ethers with bromo(difluoro)acetic acid. *Chem. Commun.* **2024**, *60* (94), 13935-13938, 10.1039/D4CC04782F. DOI: 10.1039/D4CC04782F.

(39) Kumawat, S.; Natte, K. Iron(II) Triflate as a Photocatalyst for Trifluoromethylation of Functionalized Arenes under Blue LED Light: Access to Bioactive Compounds. *J. Catal.* **2024**, *434*, 115506–115506. https://doi.org/10.1016/j.jcat.2024.115506.

(40) Yang, J.; Jiang, M.; Jin, Y.; Yang, H.; Fu, H. Visible-Light Photoredox Difluoromethylation of Phenols and Thiophenols with Commercially Available Difluorobromoacetic Acid. *Org. Lett.* **2017**, *19* (10), 2758-2761. DOI: 10.1021/acs.orglett.7b01118.

(41) Zeng, X.; Yang, J.; Deng, W.; Feng, X.-T.; Zhao, H.-Y.; Wei, L.; Xue, X.-S.; Zhang, X. Copper Difluorocarbene Enables Catalytic Difluoromethylation. *J. Am. Chem. Soc.* **2024**, *146* (24), 16902-16911. DOI: 10.1021/jacs.4c04949.

(42) Gedde, O. R.; Bonde, A.; Golbækdal, P. I.; Skrydstrup, T. Pd-Catalyzed Difluoromethylations of Aryl Boronic Acids, Halides, and Pseudohalides with ICF2H Generated ex Situ. *Chem. Euro. J.* **2022**, *28* (34), e202200997. DOI: https://doi.org/10.1002/chem.202200997.

(43) Charlesworth, N. G.; Arunprasath, D.; Graham, M. A.; Argent, S. P.; Datsenko, O. P.; Mykhailiuk, P. K.; Denton, R. M. Modular synthesis of cyclic β-difluoroamines. *Chem. Commun.* **2024**, *60* (60), 7701-7704, 10.1039/D4CC00640B. DOI: 10.1039/D4CC00640B.

(44) Shiro, T.; Fukaya, T.; Tobe, M. The chemistry and biological activity of heterocycle-fused quinolinone derivatives: A review. *Euro. J. Med. Chem.* **2015**, *97*, 397-408. DOI: https://doi.org/10.1016/j.ejmech.2014.12.004.

(45) Criscieli Taynara Barce, F.; Beatriz Fuzinato dos, S.; Caren Daniele Galeano da, S.; George, B.; Beatriz Amaral Lopes da, S.; Nelson Luís de Campos, D. Review of the Syntheses and Activities of Some Sulfur-Containing Drugs. *Current Org. Synth.* **2020**, *17* (3), 192-210. DOI: http://dx.doi.org/10.2174/1570179417666200212113412.

(46) Olliaro, P. L.; Mussano, P. Amodiaquine for treating malaria. *Cochrane Database of Systematic Reviews* **2003**, (2). DOI: 10.1002/14651858.CD000016.

(47) Feldinger K, K. A. P. o. n. a. i. p. i. t. t. o. b. c. B. C. D. M. P.-.

(48) Nitiss, J. L. Targeting DNA topoisomerase II in cancer chemotherapy. *Nature Rev. Cancer* **2009**, *9* (5), 338-350. DOI: 10.1038/nrc2607.

(49) Mostafa, G. A. E.; Al-Dosseri, A. S.; Al-Badr, A. A. Chapter Seven - Piroxicam. In *Profiles of Drug Substances, Excipients and Related Methodology*, Brittain, H. G. Ed.; Vol. 45; Acad. Press, 2020; pp 199-474.

(50) Roeker, L. E.; DerSarkissian, M.; Ryan, K.; Chen, Y.; Duh, M. S.; Wahlstrom, S. K.; Hakre, S.; Yu, L.; Guo, H.; Mato, A. R. Real-world comparative effectiveness of acalabrutinib and ibrutinib in patients with chronic lymphocytic leukemia. *Blood Adv.* **2023**, *7* (16), 4291-4301. DOI: 10.1182/bloodadvances.2023009739 (acccessed 1/4/2025).

(51) Hata, A.; Katakami, N.; Kunimasa, K.; Yoshioka, H.; Fujita, S.; Kaji, R.; Tachikawa, R.; Tomii, K.; Imai, Y.; Iwasaku, M.; et al. Erlotinib for Pretreated Squamous Cell Carcinoma of the Lung in Japanese Patients. *Japanese J. Clinic. Onco.* **2011**, *41* (12), 1366-1372. DOI: 10.1093/jjco/hyr159 (acccessed 1/4/2025).

(52) Tripathy, M.; Bui, A.; Henderson, J.; Sun, J.; Woods, C. R.; Somani, S.; Doan, T.; Louis Sam Titus, A. S. C.; Mohan, C. FAAH inhibition ameliorates breast cancer in a murine model. *Oncotarget* **2023**, *14* (1), FAAH; breast cancer; cancer therapy; apoptosis.

(53) Marsilje, T. H.; Pei, W.; Chen, B.; Lu, W.; Uno, T.; Jin, Y.; Jiang, T.; Kim, S.; Li, N.; Warmuth, M.; et al. Synthesis, Structure–Activity Relationships, and in Vivo Efficacy of the Novel Potent and Selective Anaplastic Lymphoma Kinase (ALK) Inhibitor 5-Chloro-N2-(2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine (LDK378) Currently in Phase 1 and Phase 2 Clinical Trials. *J. Med. Chem.* **2013**, *56* (14), 5675-5690. DOI: 10.1021/jm400402q.

(54) Huque, F. T. T.; Platts, J. A. The effect of intramolecular interactions on hydrogen bond acidity. *Org. Biomol. Chem.* **2003**, *1* (8), 1419-1424, 10.1039/B300598D. DOI: 10.1039/B300598D.

(55) Kadlecová, A.; Maková, B.; Artal-Sanz, M.; Strnad, M.; Voller, J. The plant hormone kinetin in disease therapy and healthy aging. *Ageing Research Rev.* **2019**, *55*, 100958. DOI: https://doi.org/10.1016/j.arr.2019.100958.

(56) Lombardo, L. J.; Lee, F. Y.; Chen, P.; Norris, D.; Barrish, J. C.; Behnia, K.; Castaneda, S.; Cornelius, L. A. M.; Das, J.; Doweyko, A. M.; et al. Discovery of N-(2-Chloro-6-methyl- phenyl)-2-(6-(4-(2-hydroxyethyl)- piperazin-1-yl)-2-methylpyrimidin-4- ylamino)thiazole-5-carboxamide (BMS-354825), a Dual Src/Abl Kinase Inhibitor with Potent Antitumor Activity in Preclinical Assays. *J. Med. Chem.* **2004**, *47* (27), 6658-6661. DOI: 10.1021/jm049486a.

(57) Gao, F.; Zhang, X.; Wang, T.; Xiao, J. Quinolone hybrids and their anti-cancer activities: An overview. *Euro. J. Med. Chem.* **2019**, *165*, 59-79. DOI: https://doi.org/10.1016/j.ejmech.2019.01.017.

(58) Coulthard, S. A.; Berry, P.; McGarrity, S.; McLaughlin, S.; Ansari, A.; Redfern, C. P. F. Azathioprine with Allopurinol: Lower Deoxythioguanosine in DNA and Transcriptome Changes Indicate Mechanistic Differences to Azathioprine Alone. *Inflammatory Bowel Diseases* **2017**, *23* (6), 946-955. DOI: 10.1097/mib.0000000000001131 (acccessed 1/4/2025).

(59) Taguchi, I.; Toyoda, S.; Takano, K.; Arikawa, T.; Kikuchi, M.; Ogawa, M.; Abe, S.; Node, K.; Inoue, T. Irbesartan, an angiotensin receptor blocker, exhibits metabolic, anti-inflammatory and antioxidative effects in patients with high-risk hypertension. *Hypertension Research* **2013**, *36* (7), 608-613. DOI: 10.1038/hr.2013.3.

(60) Lai Kam, C.; Lam Shiu, K.; Chu Kent, M.; Wong Benjamin, C. Y.; Hui Wai, M.; Hu Wayne, H. C.; Lau George, K. K.; Wong Wai, M.; Yuen Man, F.; Chan Annie, O. O.; et al. Lansoprazole for the Prevention of Recurrences of Ulcer Complications from Long-Term Low-Dose Aspirin Use. *New England J. Med. 346* (26), 2033-2038. DOI: 10.1056/NEJMoa012877 (acccessed 2025/01/04).

(62) Lennard, L. The clinical pharmacology of 6-mercaptopurine. *Euro. J. Clinic. Pharmaco.* **1992**, *43* (4), 329-339. DOI: 10.1007/BF02220605.

(63) Ghofrani, H. A.; Osterloh, I. H.; Grimminger, F. Sildenafil: from angina to erectile dysfunction to pulmonary hypertension and beyond. *Nature Rev. Drug Discov.* **2006**, *5* (8), 689-702. DOI: 10.1038/nrd2030.

(64) Faulds, D.; Heel, R. C. Ganciclovir. *Drugs* **1990**, *39* (4), 597-638. DOI: 10.2165/00003495-199039040-00008.

(63) Chen, W.; Suo, J.; Liu, Y.; Xie, Y.; Wu, M.; Zhu, F.; Nian, Y.; Aisa, H. A.; Shen, J. Industry-Oriented Route Evaluation and Process Optimization for the Preparation of Brexpiprazole. *OPRD.* **2019**, *23* (5), 852-857. DOI: 10.1021/acs.oprd.8b00438.

(65) Frank, J.; Katritzky, A. R. Tautomeric pyridines. Part XV. Pyridone–hydroxypyridine equilibria in solvents of differing polarity. *J. Chem. Soc. Perkin Transac. 2* **1976**, (12), 1428-1431, 10.1039/P29760001428. DOI: 10.1039/P29760001428.

(66) Aue, D. H.; Betowski, L. D.; Davidson, W. R.; Bowers, M. T.; Beak, P.; Lee, J. Gas-phase basicities of amides and imidates. Estimation of protomeric equilibrium constants by the basicity method in the gas phase. *J. Am. Chem. Soc.* **1979**, *101* (6), 1361-1368. DOI: 10.1021/ja00500a001.

(67) Muta, K.; Okamoto, K.; Nakayama, H.; Wada, S.; Nagaki, A. Defluorinative functionalization approach led by difluoromethyl anion chemistry. *Nature Commun.* **2025**, *16* (1), 416. DOI: 10.1038/s41467-024-52842-0.