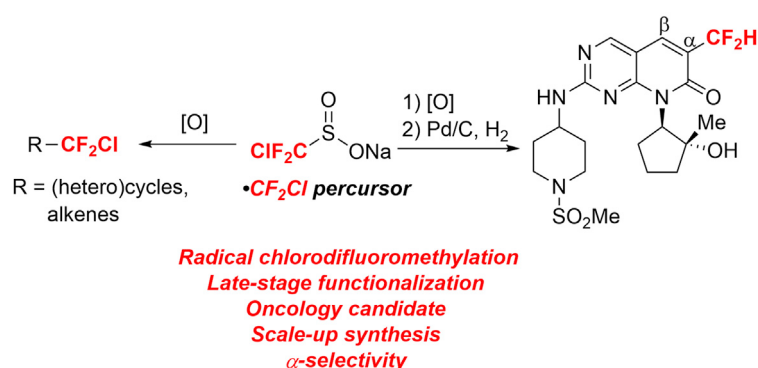


Article

A radical chlorodifluoromethylation protocol for late-stage difluoromethylation and its application to an oncology candidate



Depei Meng, Lingchun Li, Adam Brown, ..., Jared L. Piper, Min Zhou, Daniel W. Widlicka

shengquan.duan@pfizer.com (S.D.)
jinbohu@sioc.ac.cn (J.H.)

Highlights

A new radical chlorodifluoromethylation reagent ($ClCF_2SO_2Na$) is disclosed

The CF_2Cl radical is a suitable surrogate for accessing the CF_2H group

The reaction is chemo- and regioselective for (hetero)arenes and electron-rich alkenes

The preparation of the sodium chlorodifluoromethanesulfinate is developed

Meng et al. develop a radical chlorodifluoromethylation protocol using $ClCF_2SO_2Na$ as a chlorodifluoromethyl radical precursor. The CF_2Cl radical is an electrophilic surrogate for the nucleophilic CF_2H radical. This method is chemoselective and regioselective for the chlorodifluoromethylation of (hetero)arenes and electron-rich alkenes and is applied in the difluoromethylation of an oncology candidate.

Meng et al., Cell Reports Physical Science 2, 100394

April 21, 2021 © 2021 The Authors.

<https://doi.org/10.1016/j.xcrp.2021.100394>



Article

A radical chlorodifluoromethylation protocol for late-stage difluoromethylation and its application to an oncology candidate

Depei Meng,¹ Lingchun Li,¹ Adam Brown,² Jean-Nicolas Desrosiers,² Shengquan Duan,^{2,*} Cheryl M. Hayward,² Zhengbiao He,¹ Jinbo Hu,^{1,3,*} Teresa Makowski,² Mark Maloney,² Sébastien Monfette,² Hahdi Perfect,² Jared L. Piper,² Min Zhou,¹ and Daniel W. Widlicka²

SUMMARY

Radical fluoroalkylation is a powerful synthetic tool for the late-stage incorporation of fluorinated moieties into organic molecules, which is widely used in the development of pharmaceuticals and agrochemicals. Here, we report an efficient radical chlorodifluoromethylation protocol with sodium chlorodifluoromethanesulfinate, which is complementary to the existing late-stage difluoromethylation strategies. CF₂Cl radical is a suitable surrogate for accessing the CF₂H group while possessing completely different electronic properties compared to the CF₂H radical. This method is chemoselective and regioselective for the chlorodifluoromethylation of (hetero)arenes and electron-rich alkenes and shows good functionality, tolerance, and generality on scope. The preparation of the sodium chlorodifluoromethanesulfinate is thoroughly investigated and can be scaled up to hundreds of kilograms. The method is successfully implemented on the synthesis of an oncology candidate compound 1.

INTRODUCTION

Cyclin-dependent kinases (CDKs) are important cellular enzymes that regulate eukaryotic cell division and proliferation.^{1–3} Highly specific CDK4/6 inhibitors have shown excellent clinical benefit on cancer therapy, especially on breast cancer, as evidenced by the approval of the US Food and Drug Administration (FDA) of palbociclib (PD-0332991),⁴ ribociclib (LEE011),⁵ and abemaciclib (LY2835219).⁶ However, acquired resistance to the combination of CDK4/6 inhibitor and anti-hormonal therapies have been observed in patients following a period of largely stable disease. It is found that the overexpression of CDK2 is usually associated with abnormal regulation of the cell cycle.⁷ The development of an inhibitor that selectively inhibits CDK2, -4, and -6 is predicted to drive an efficacious response in patients who have relapsed on the CDK4/6-targeted therapies. Compound 1 is being nominated by Pfizer as a selective CDK2/4/6 inhibitor that is being studied in combination with other cancer therapeutics (Figure 1).⁸

During our development of a commercial route toward compound 1, it was realized that the lability of the difluoromethyl group would require it to be installed via a late-stage functionalization. Although many difluoromethylation methods have been developed,⁹ very few are suitable for late-stage functionalization on an industrial scale.¹⁰ Direct radical C-H functionalization^{11–16} was found to be a favorable method for the difluoromethylation to access compound 1 because of the mild nature of the reaction conditions, the convenience of the radical precursor, and the fact that no pre-functionalization

¹Key Laboratory of Organofluorine Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Ling-Ling Road, Shanghai 200032, China

²Pfizer Worldwide Research and Development, Eastern Point Rd., Groton, CT 06340, USA

³Lead contact

*Correspondence: shengquan.duan@pfizer.com (S.D.), jinbohu@sioc.ac.cn (J.H.)
<https://doi.org/10.1016/j.xcrp.2021.100394>



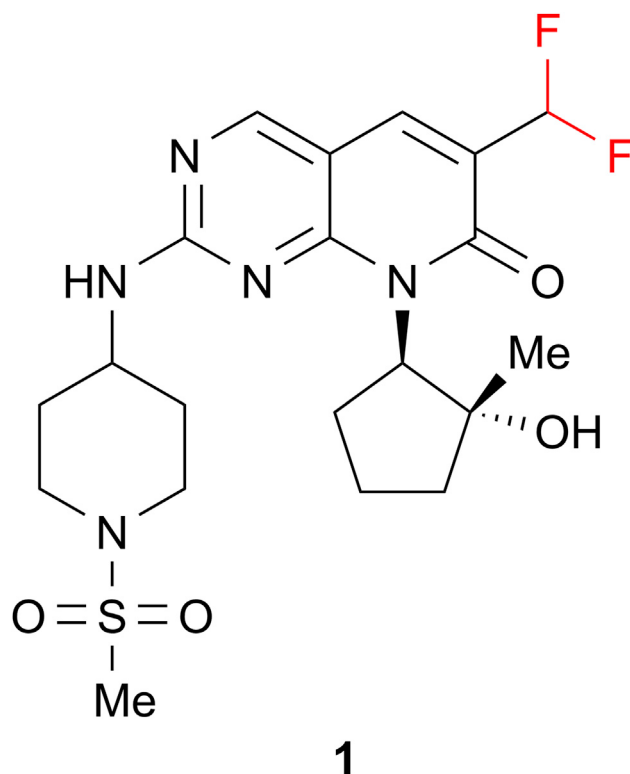


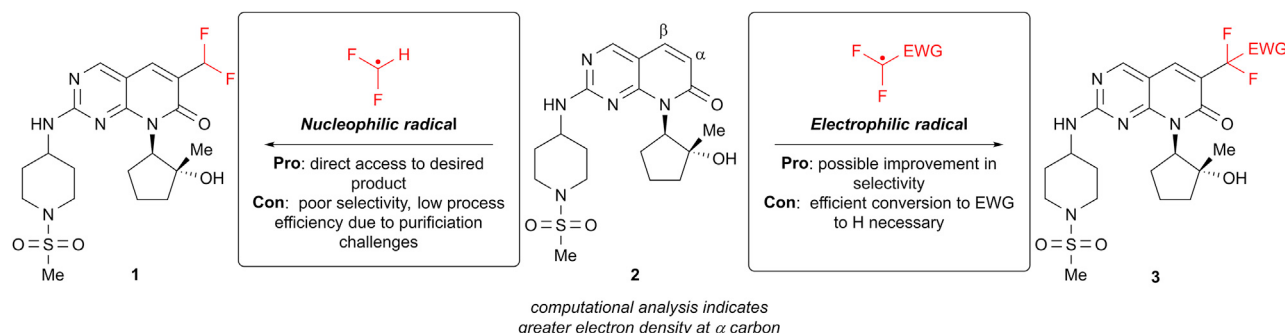
Figure 1. CDK 2/4/6 inhibitor 1

Compound 1 is nominated by Pfizer as a selective CDK2/4/6 inhibitor.

of the substrate was required before the key difluoromethylation. Such a strategy was used with $\text{HCF}_2\text{SO}_2\text{Na}$ as the difluoromethyl radical source^{17–20} to provide early clinical supply of compound 1 (Scheme 1, nucleophilic radical).

The poor yield observed for the radical difluoromethylation of **2** was due to indiscriminate reactivity of the difluoromethyl radical. While the desired product was favored, the impurity profile indicated the addition of the CF_2H moiety more than once, to the β position, and to different sites of the pyrimidine ring. This poor selectivity led to a complex reaction mixture with numerous low-level impurities, requiring multiple stages of purification (including column chromatography) and culminating in a process with overall poor efficiency.

Considering the electrophilicity of CF_3 radical $\text{CF}_3\text{SO}_2\text{Na}$ (Langlois' reagent)^{21,22} and recently reported radical chlorodifluoromethylation with chlorodifluoroacetic anhydride (McAttee et al.²³ and Kawamura et al.²⁴) or radical phenylsulfonyldifluoromethylation with $\text{PhSO}_2\text{CF}_2\text{I}$ (Su et al.¹⁶), we hypothesize that modification of the electronic property of our radical species would improve the selectivity of the desired C–H functionalization reaction. While the difluoromethyl radical is known to react in a nucleophilic manner, the replacement of the hydrogen of the difluoromethyl with an electron-withdrawing group reverses the character of the radical to that of an electrophile.^{23–25} Based on this premise, we explore the reactivity of **2** with electrophilic radical species that could be manipulated following the C–H functionalization reaction to provide our desired difluoromethyl species (Scheme 1, electrophilic radical). Furthermore, we establish a system capable of generating the desired electrophilic radical under conditions that are compatible with a highly



Scheme 1. Varying electronic property of CF_2X radical to improve direct functionalization

Because of different electronic property, the CF_2X ($\text{X} = \text{H}$ or EWG) radical shows reverse advantages and disadvantages in radical difluoroalkylation with compound 2.

functionalized molecule such as 2 and that can be carried out on an industrial scale.

RESULTS

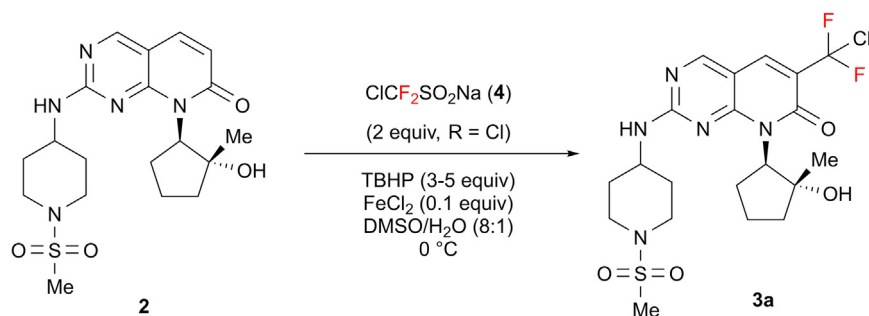
Chlorodifluoromethylation of compound 2

Our hypothesis was tested by studying the reactivity of 2 with radicals generated from $\text{ClCF}_2\text{SO}_2\text{Na}$ (4) and $\text{PhSO}_2\text{CF}_2\text{SO}_2\text{Na}$ (5), both of which should have significantly different electronic character and reactivity than the difluoromethyl radical. A variety of reaction conditions were studied to understand the radical difluoromethylation reaction (Table 1).

Initially, a variety of oxidants was explored in combination with $\text{ClCF}_2\text{SO}_2\text{Na}$ (4). *m*-CPBA (*meta*-Chloroperoxybenzoic acid), BPO (benzoyl peroxide), and DTBP (di-*tert*-butyl peroxide) were not effective for this reaction. However, cumenehydroperoxide (CHP), (diacetoxyiodo)benzene (PIDA), sodium persulfate, *t*-butyl hydroperoxide (TBHP), and oxone worked well (entries 1–5). TBHP (entry 1) was selected for its low cost, general compatibility with functional groups, and ease of isolation from reaction mixtures.²⁶ Notably, CHP (entry 2) was also used for larger-scale applications due to the higher temperature onset of this reagent, and therefore higher stability, under the exothermic radical-induced chlorodifluoromethylation process.^{27,28} After selecting the optimal oxidant, several reaction parameters were optimized.

The impact of the catalyst was then studied (entries 6–12), and it was found that iron salts were optimal. Very similar results were obtained with different types of iron catalysts, such as FeCl_2 , FeCl_3 , $\text{Fe}(\text{OTf})_2$, $\text{Fe}(\text{acac})_2$, and $(\text{NH}_4)_2\text{Fe}(\text{SO}_4)_2$. Other metal catalysts (e.g., Cu, Ni) were not as active, with the reaction yield decreasing considerably, and a more complicated reaction profile after an extended reaction time. FeCl_2 catalyst is selected due to its advantage in cost, handling, and commercial availability.^{29,30} The stoichiometry of the FeCl_2 does seem to have an impact on the reaction, with a detrimental effect at higher loading (entry 14). Although the chlorodifluoromethyl intermediate is prone to hydrolysis, it is relatively stable in the reaction media, which is typically a mixed aqueous system. Running the reaction at a higher temperature with more water will accelerate the hydrolysis and lower the yield (entries 13 and 14). Polar aprotic solvents (DMSO, sulfolane, and dimethyl formamide [DMF]) are preferred solvents for this reaction. The reaction also works in the acetone or methyl ethyl ketone (MEK), albeit with a lower yield (entries 16–18).

Table 1. Optimization of reaction conditions



Entry ^a	Modifications from standard conditions	Yield (%) ^b
1 ^c	none (standard conditions)	82–91
2	CHP (3 equiv) as the oxidant	93
3	$\text{PhI}(\text{OAc})_2$ as the oxidant in $t\text{-BuOH}/\text{MeCN}$ (9:1)	76
4	$\text{Na}_2\text{S}_2\text{O}_8$ as the oxidant in $\text{MeCN}/\text{H}_2\text{O}$ (9:1)	55
5	oxone as the oxidant	83
6 ^d	$\text{Cu}(\text{OTf})_2$ (0.3 equiv) as the catalyst	7
7 ^e	CuCl (0.3 equiv) as the catalyst	13
8 ^f	NiCl_2 (0.3 equiv) as the catalyst	12
9	FeCl_3 (0.1 equiv) as the catalyst	93
10	$\text{Fe}(\text{OTf})_2$ (0.1 equiv) as the catalyst	94
11	$\text{Fe}(\text{acac})_2$ (0.1 equiv) as the catalyst	85
12	$\text{NH}_4\text{Fe}(\text{SO}_4)_2$ (0.1 equiv) as the catalyst	91
13 ^g	DMSO/ H_2O (8:1) as the solvent mixture	54
14 ^h	DMSO/ H_2O (8:1) as the solvent mixture	77
15	DMSO/ H_2O (9:1) as the solvent mixture	84
16 ⁱ	sulfolane/ H_2O (8:1) as the solvent mixture	92–99
17	acetone/ H_2O (9:1) as the solvent mixture	77
18	$\text{MEK}/\text{H}_2\text{O}$ (9:1) as the solvent mixture	74
19	$\text{R}=\text{SO}_2\text{Ph}$ instead of Cl	86
20	$\text{R}=\text{H}$ instead of Cl	38

^aConditions: **2** (0.5 mmol, 1.0 equiv), **3** (2.5 equiv), CHP (5.0 equiv), cat., solvent/ H_2O (8:1, 3.0 mL), FeCl_2 (0.1 equiv.), T , 15 min.

^bYields were determined by ^{19}F NMR spectroscopy using PhCF_3 as an internal standard.

^cTBHP (2.5 equiv), DMSO/ H_2O (8:1, 2.7 mL), 1.5 h, repeated multiple times.

^d1.5 h.

^eCHP (3.0 equiv), 10 h.

^fCHP (3.0 equiv), 12 h.

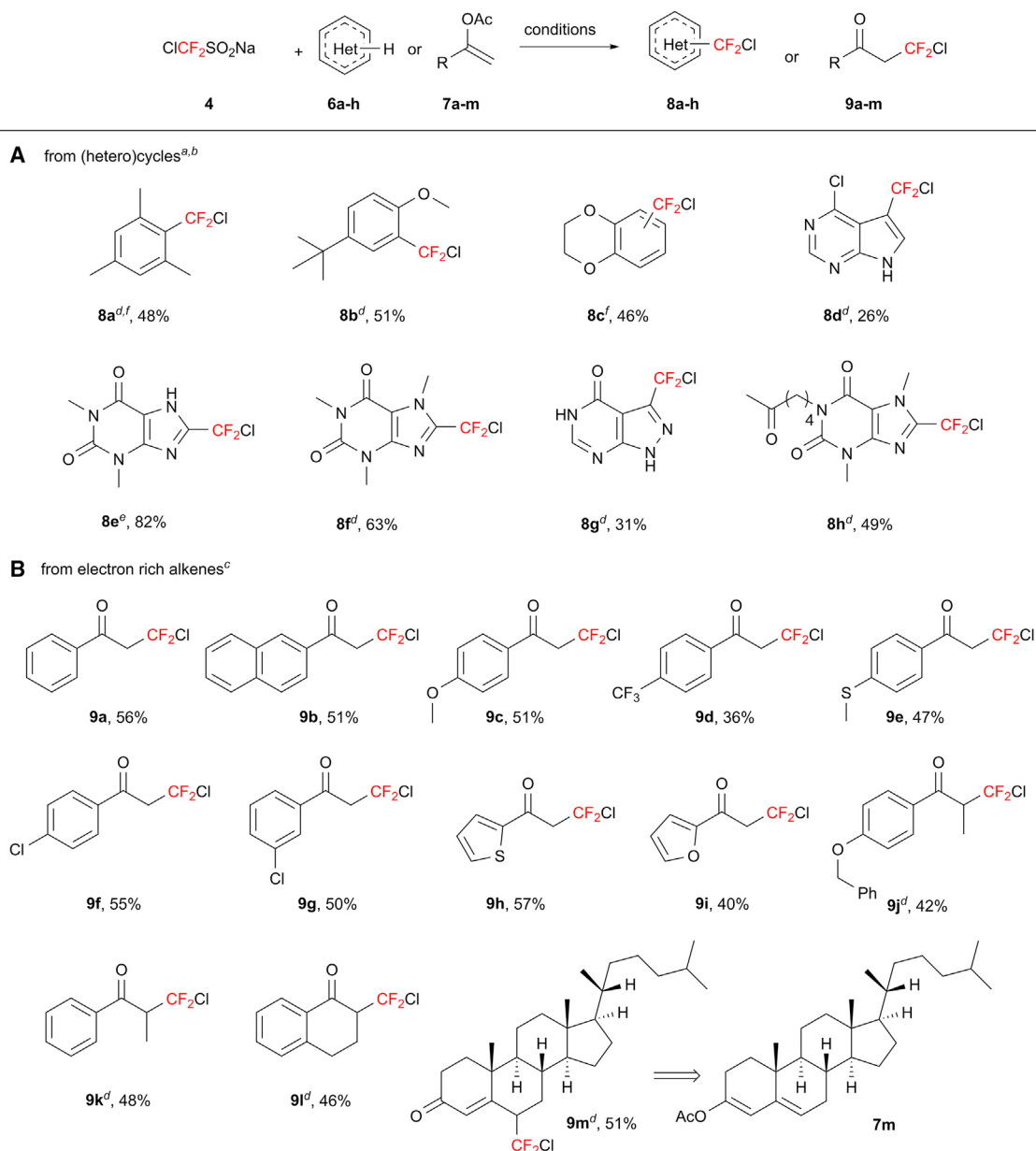
^gTBHP (5.0 equiv), FeCl_2 (0.5 equiv), 5°C – 25°C .

^hTBHP (5.0 equiv), FeCl_2 (0.5 equiv), 0°C – 5°C .

ⁱTBHP (2.5 equiv), 1.5 h, repeated multiple times.

Substitution of the chlorine with a benzenesulfonyl group was explored (entry 19) and a similar yield was obtained (86%). Gratifyingly, the desired radical functionalization proceeded with much higher efficiency and selectivity with these electrophilic radical species compared to a nucleophilic radical generated from $\text{HCF}_2\text{SO}_2\text{Na}$ (entry 20).

After demonstrating the generation and selective reaction of a masked difluoromethyl radicals with **2** under conditions that are operationally simple, we sought to explore our method in a variety of diverse substrates, and further develop the method for application toward the large-scale synthesis of compound **1**.



Scheme 2. Substrate scope of chlorodifluoromethylation with corresponding (hetero)cycles and alkenes

Unless otherwise noted, reactions were performed on 0.5 mmol scale and yields of isolated products are given.

^aArenes **6a–6c** (1.0 equiv), **4** (2.0 equiv), TBHP (3.0 equiv), FeCl_2 (1.0 equiv), and $\text{DMSO}/\text{H}_2\text{O}$ (5:1), 0°C, 4 h.

^bHeterocycles **6d–6h** (1.0 equiv), **4** (2.0 equiv), TBHP (3.0 equiv), FeCl_2 (0.08 equiv), and $\text{DCM}/\text{H}_2\text{O}$ (5:1), 0°C to room temperature (rt), 3 h.

^cAlkenes **7a–7m** (1.0 equiv), **4** (2.0 equiv), TBHP (3.0 equiv), and DMF, 0°C, 3 h.

^dExtra **4** and TBHP were added after 1 or 2 h.

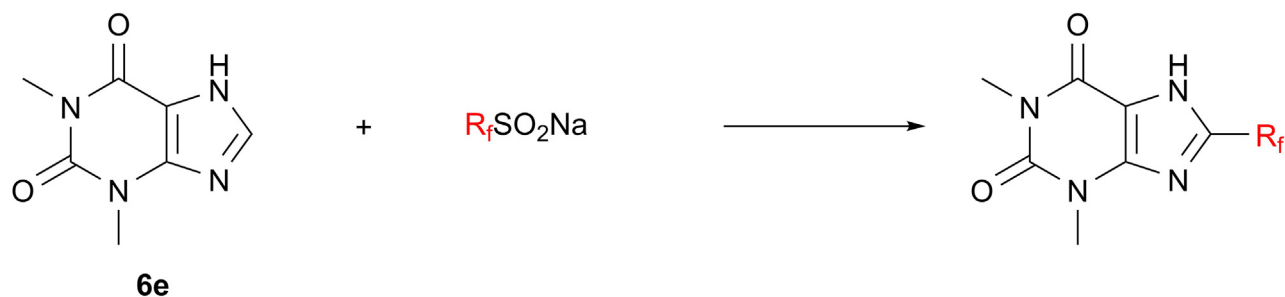
^eReactions were performed on a 10-mmol scale.

^fThe yields were determined by ^{19}F NMR spectroscopy using PhOCF_3 as an internal standard.

Scope of method with sulfonates **4** and **5**

We found that the chlorodifluoromethylation methodology can be applied to various substrates, such as (hetero)cycles or electron-rich alkenes (enol acetates) (Scheme 2; for more details, see Supplemental experimental procedures). When the amount of FeCl_2 was increased to 1.0 equiv, because of its ability to accelerate

Table 2. Fluoroalkylation of theophylline with different sulfonates



Entry ^a	R _f	Yield (%) ^b
1	CF ₃	75
2	CF ₂ Cl	81
3	CF ₂ H	17
4	CFH ₂	9

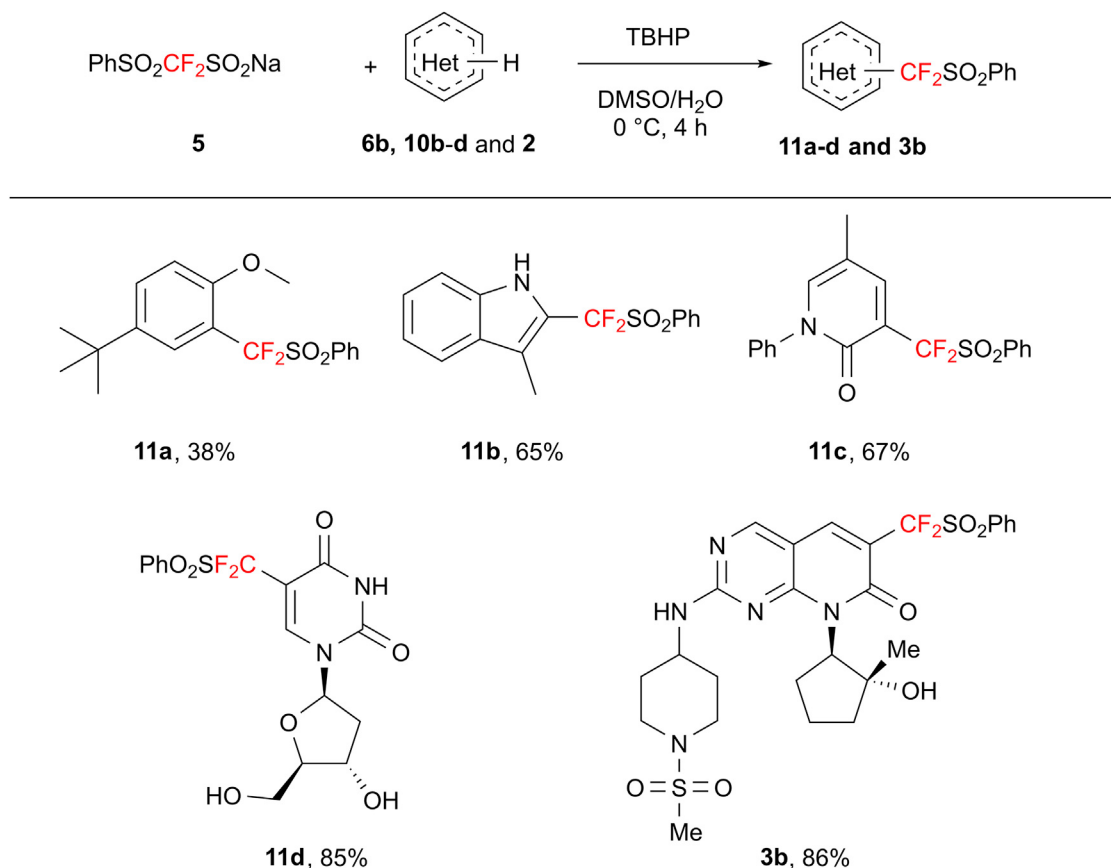
^aConditions: **6e** (0.1 mmol, 1.0 equiv), R_fSO₂Na (2.0 equiv), TBHP (3.0 equiv), FeCl₂ (0.08 equiv), and DCM/H₂O (0.5 mL/0.1 mL), 0°C, 3 h.

^bThe yield was determined by ¹⁹F NMR spectroscopy using PhOCF₃ as an internal standard.

the generation of ClCF₂ radical and promote the conversion of the reaction intermediate, mesitylene, anisole or 1,4-benzodioxane gave a corresponding single product (**6a** and **6b**) or a mixture of regioisomers (**6c**) in moderate yields (see Table S1). Deazapurine (**6d**), xanthines (**6e**, **6f**, and **6h**), and pyrazolino-pyrimidine (**6g**) can be directly chlorodifluoromethylated when the solvent was changed from DMSO to dichloromethane (DCM) (see Table S2). A gram-scale reaction was successfully performed with theophylline (**6e**). Besides reacting with (hetero)cycles, the ClCF₂ radical could also react with electron-rich alkenes to form α-chlorodifluoromethylketone in DMF without the FeCl₂ catalyst (see Table S3). Phenylvinyl acetate (**7a**), naphthyl acetate (**7b**), and arylvinyl acetates (**7c–7g**) with electron-donating groups or electron-withdrawing groups worked well under the optimal conditions and gave medium yields analogously. The trifluoromethyl substituted substrate (**7d**) was more reluctant to react than others because of the strong electron-withdrawing capacity of the trifluoromethyl group. Both thienyl and furyl could be used instead of aryl to provide the addition products (**7h** and **7i**), and non-terminal olefins were also compatible under similar conditions (**7j–7l**). Enol acetate from 4-cholesten-3-one, a precursor to a range of steroid hormone drugs, can also be used as a substrate, and the γ-chlorodifluoromethylated product was obtained in a 51% yield (**7m**). The moderate yields may be attributed to the stability of the products or to the activity of substrates. An extra portion of sulfinate and oxidant was needed for parts of substrates due to the incomplete conversion of substrates. Because of the electrophilicity of the CF₂Cl radical, the reaction typically occurred at the electron-rich site and no regio-isomers were observed except **6c**.

The fluoroalkylation of theophylline was carried out to further substantiate the hypothesis that the CF₂Cl radical was more likely to react in an electrophilic manner compared to the CF₂H radical. As shown in Table 2, higher reactivity of the CF₃ and CF₂Cl radicals was observed at the electron-rich site of the theophylline, which was not the case for the nucleophilic CF₂H and CH₂F radicals. It is evident that the CF₂Cl radical is very similar to the electrophilic CF₃ radical, but far different from CF₂H and CH₂F radicals.

Several radical phenylsulfonyldifluoromethylation with (hetero)cycles, including compound **2** (Scheme 3), were explored. All of the substrates showed good



Scheme 3. Reaction of (hetero)cycles with $\text{PhSO}_2\text{CF}_2\text{SO}_2\text{Na}$ (5)^{a,b,c}

^aConditions: (hetero)cycles (0.25 or 0.5 mmol, 1.0 equiv), 5 (2.0 equiv), TBHP (2.0 equiv), and DMSO/H₂O (2.5:1).

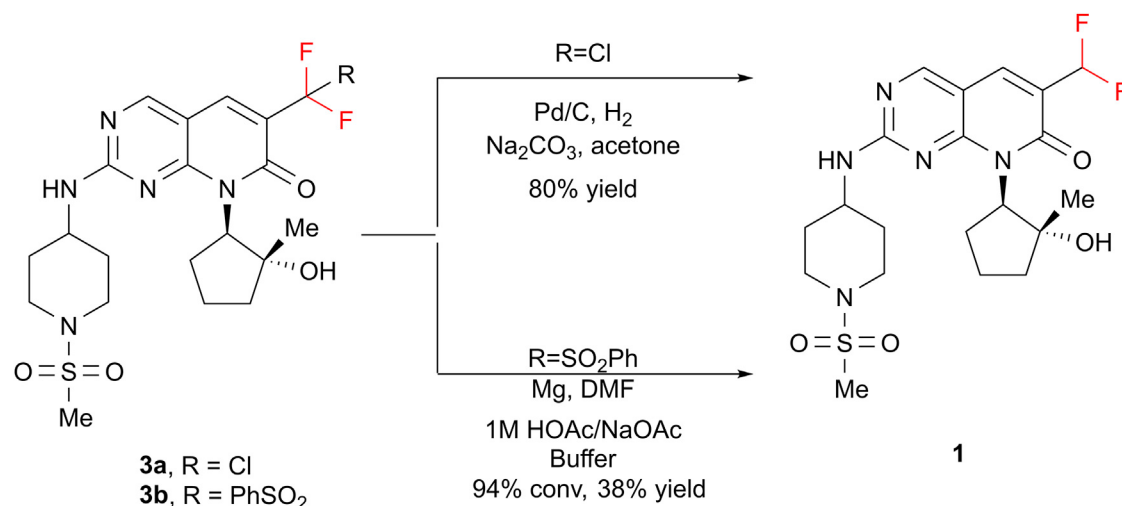
^b2 (0.25 mmol, 1.0 equiv), 5 (2.0 equiv), TBHP (2.0 equiv), FeCl₂ (0.1 equiv), and DMSO/H₂O (10:1).

^cIsolated yields.

reactivity under the standard reaction conditions. The electron-rich arene (6b), which was difficult to react with the HCF_2 radical,²³ could provide the addition product (10a) in a 38% yield. The nitrogen-containing heterocycles, such as skatole (10b), pirfenidone (10c), 2'-deoxyuridine (10d), and compound 2, performed better to afford corresponding difluoroalkylation products in good yields (65%–86%).

Application toward compound 1 and considerations for large-scale synthesis

With two high-yielding difluoroalkylation processes of 2 in hand with either benzenesulfonyl or chloro electron-withdrawing substituents on the difluoromethyl radical, we evaluated the downstream chemistry required to unmask the precursor to compound 1 (Scheme 4). Unexpectedly, the desulfonylation of 3b was not straightforward.³¹ Although high conversion was observed, only a 38% yield of 1 was obtained due to defluorination and, likely, reduction of the methanesulfonyl (SO_2Me) group. In contrast, hydrodechlorination of 3a is efficient, proceeding in the presence of either homogeneous or heterogeneous Pd catalyst to provide 1 in a good yield (see Table S4).²³ Chlorodifluoromethylation was therefore selected for application in our synthesis, and further development of both the reaction conditions and reagent synthesis were carried out.



Scheme 4. Method toward compound 1

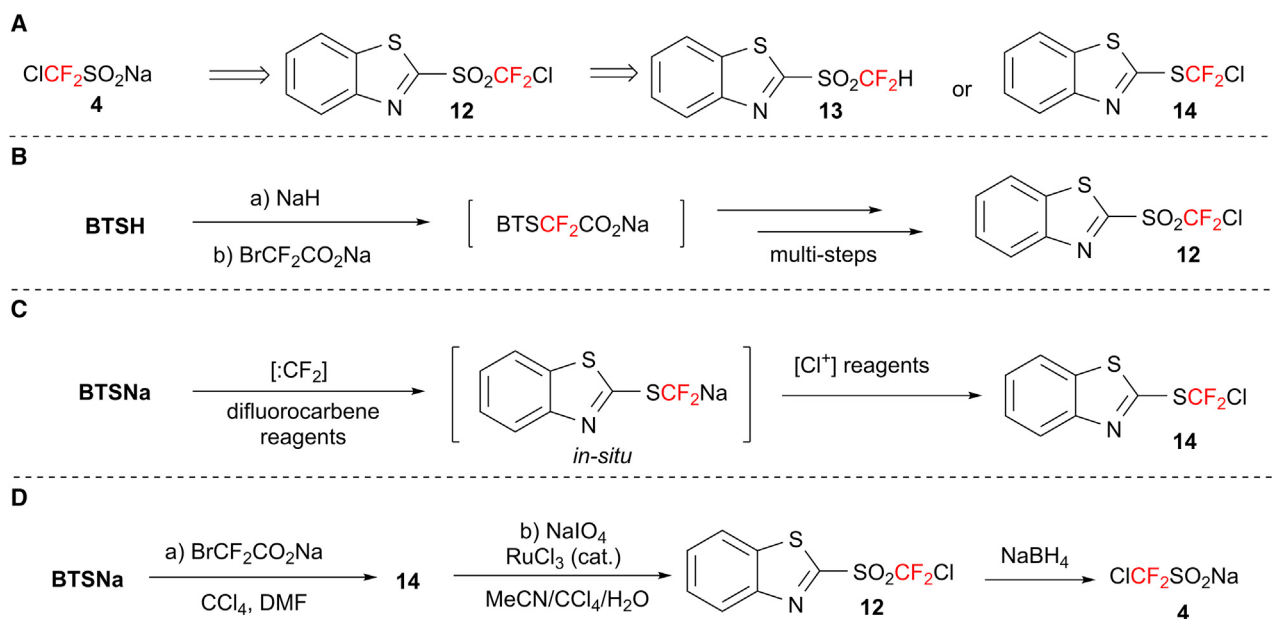
Hydrodechlorination of **3a** with Pd/C and desulfonation of **3b** with Mg.

Preparation of ClCF₂SO₂Na (**4**)

Multiple methods were developed for the preparation of the sodium sulfinate reagent, considering that a large quantity will be needed for this reagent.

As shown in [Scheme 5A](#) the key for the synthesis of **4** is to obtain either of the intermediates BTSCF₂Cl (**12**) or BTSCF₂Cl (**14**) (BT [2-benzothiazolyl]), as the oxidation reaction from sulfide to sulfone has been well established.³² In the first attempt, we decided to prepare BTSCF₂Cl (**12**) by decarboxylative chlorination of BTSCF₂CO₂Na (**15**). Based on the reported method of preparation of aryloxydifluoroacetic acids from the sodium salts of phenols,³³ the reaction conditions were further optimized to provide BTSCF₂CO₂Na from BTSH in a 94% ¹⁹F NMR yield ([Scheme 5B](#); [Table S5](#)).³⁴ The desired product **12** was obtained in a 77% ¹⁹F NMR yield when BTSCF₂CO₂Na was treated with CCl₄ in DMF at room temperature (see [Table S6](#)). During the optimization of this reaction, we found it infeasible that the above-mentioned procedure involved multiple reaction steps and several unstable intermediates, so we continued to develop another method to prepare **14** ([Scheme 5C](#)). Thus, we designed a new procedure for the preparation of the sodium sulfinate, as shown in [Scheme 5D](#) (for more details, see [Supplemental experimental procedures](#)). BTSNa was reacted with difluorocarbene to generate BTSCF₂[−]. Then, a suitable Cl⁺ reagent (i.e., CCl₄ or C₂Cl₆) was used to quench the *in situ*-generated BTSCF₂[−] species to yield **14**, which could be directly oxidized to **12** in a 56% yield over 2 steps. In the final step, ClCF₂SO₂Na (**4**) was obtained in a 79% yield via the reduction of **12** by NaBH₄.¹⁷

Although the above method provided quick access to the sulfinate reagent, the use of CCl₄ has been largely prohibited in the industry due to its high toxicity.³⁵ The effort to replace CCl₄ with other chlorination reagents was not successful and that forced us to develop a new stepwise method for the chlorination reaction ([Scheme 6](#)). To this end, the benzothiazole thiol was alkylated by a difluorocarbene (BrCF₂CO₂Na is shown in the scheme; ClCF₂H can also be used) to give compound **17** in a 85% yield. The sulfide was oxidized to sulfone using aqueous H₂O₂ with ammonium heptamolybdate as a catalyst. The chlorination was achieved by deprotonation with lithium hexamethyldisilazide (LiHMDS) and treatment with



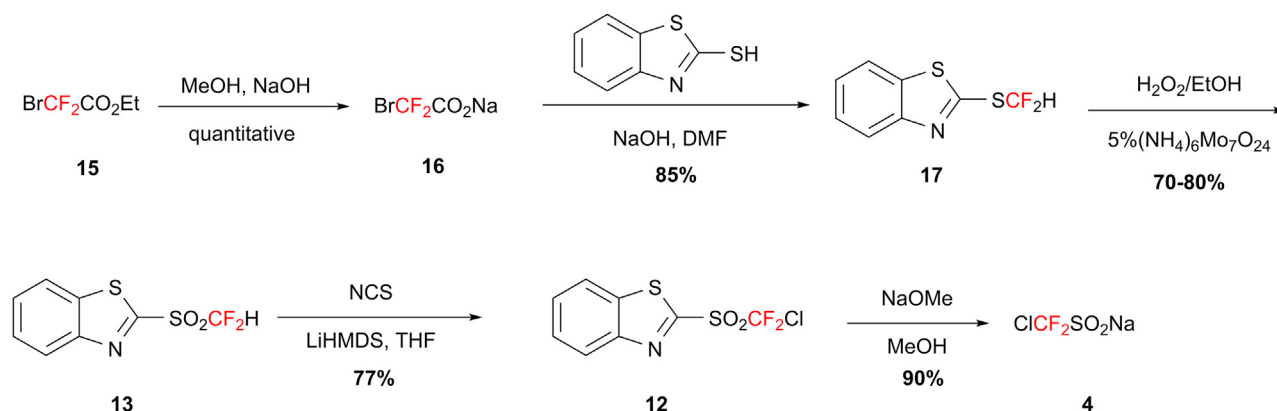
Scheme 5. Laboratory method

- (A) Retrosynthetic analysis for preparing $\text{ClCF}_2\text{SO}_2\text{Na}$ (**4**).
 (B) Preparation of BTSCF_2Cl (**12**) by decarboxylative chlorination (BT, 2-benzothiazolyl).
 (C) Preparation of BTSCF_2Cl (**14**) by difluorocarbene insertion.
 (D) Preparation of $\text{ClCF}_2\text{SO}_2\text{Na}$ (**4**) in laboratory.

N -chlorosuccinimide (NCS) (trichloroisocyanuric acid could also be used instead of NCS). This chlorination was more challenging than the carbon tetrachloride condition, but with careful control of the reaction temperature and the stoichiometry of LiHMDS and NCS, the impurity formation can be minimized and a 77% yield can be obtained. The most significant improvement of the process was achieved when we used NaOMe for the final C-S cleavage instead of NaBH_4 , as the isolation of the final product became much easier without the need to deal with the boron side products.

Preparation of compound 1

The newly developed radical chlorodifluoromethylation methodology allows quick access to compound **1** in a large quantity. Based on this key strategy, a short synthetic route (shown in Scheme 7) was developed and used for the clinical supply manufacturing of **1**. This route has the potential to be used for commercial manufacture due to the scalability of the two-step late-stage difluoromethylation. The synthesis starts from commercially available 5-bromo-2,4-dichloropyrimidine (**18**) and the chiral amino alcohol building block **19** (synthesis of **19** will be reported independently). The first $\text{S}_{\text{N}}\text{Ar}$ reaction is straightforward and the regioselectivity is typically $\sim 95:5$, favoring the desired product. The second $\text{S}_{\text{N}}\text{Ar}$ reaction between **20** and the aminopiperidine is slower and requires the use of polar aprotic solvents and elevated temperatures. Both steps give products in excellent yield and purity. The subsequent Heck coupling and cyclization sequence provides compound **2**, the substrate used for the chlorodifluoromethylation.³⁶ The Heck coupling usually gives a mixture of E/Z isomer at 95:5 ratio and only the E-isomer is obtained if an isolation is carried out. The isomerization/cyclization can be achieved using KOt-Bu as base. Finally, the chlorodifluoromethylation/hydrodechlorination affords the active pharmaceutical ingredient (API) in high



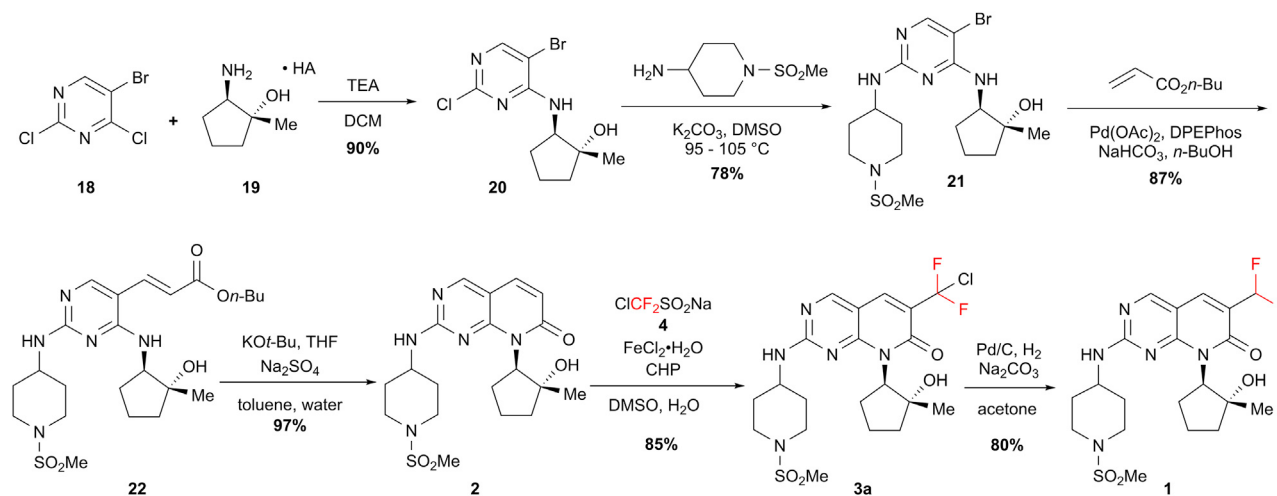
Scheme 6. Method for large-scale preparation

Preparation of $\text{ClCF}_2\text{SO}_2\text{Na}$ (4) from $\text{BrCF}_2\text{CO}_2\text{Et}$ (15) on industrial scale (for more details, see [supplemental experimental procedures](#)).

yield. The chlorodifluoromethylation can be carried out under batch or flow conditions. The hydrodechlorination works under both homogeneous and heterogeneous catalysis conditions.³⁷ For this specific substrate, the ketone type of solvents is preferred. An overall 40%–45% yield is obtained over the 6-step sequence.

DISCUSSION

In summary, we have successfully developed a radical chlorodifluoromethylation method, which is complementary to the existing late-stage difluoromethylation strategies reported in the literature. The CF_2Cl radical is a suitable surrogate for accessing the CF_2H group, while possessing completely different electronic properties compared to the CF_2H radical. This novel method is highly chemoselective and regioselective for the chlorodifluoromethylation of (hetero)arenes and electron-rich alkenes and shows good functionality tolerance and generality on scope. The preparation of the sodium chlorodifluoromethanesulfinate is thoroughly investigated and can be scaled up to hundreds of kilograms. The newly developed



Scheme 7. Synthetic application of 4

$\text{ClCF}_2\text{SO}_2\text{Na}$ (4) was used as a building block in the synthesis of oncology candidate 1.

method has been successfully implemented on the synthesis of an oncology candidate compound 1.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Jinbo Hu (jinbohu@sioc.ac.cn).

Materials availability

The reagents generated in this study are available from the lead contact upon reasonable request.

Data and code availability

The authors declare that data supporting the findings of this study are available within the article and the [Supplemental information](#).

Synthetic details and characterization

For further experimental descriptions, see the [Supplemental experimental procedures](#). In addition, see [Figures S1–S92](#) for all ^1H , ^{13}C , and ^{19}F NMR spectra. [Tables S1–S3](#) show the optimization of chlorodifluoromethylation with (hetero)cycles and alkenes. [Table S4](#) shows the optimization of the hydrodechlorination reaction. [Tables S5](#) and [S6](#) show the optimization for preparing BTSCF_2Cl from $\text{BTSCF}_2\text{CO}_2\text{Na}$.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at <https://doi.org/10.1016/j.xcrp.2021.100394>.

ACKNOWLEDGMENTS

This work was supported by the National Key Research and Development Program of China (2016YFB0101200), the National Natural Science Foundation of China (21632009), the Key Programs of the Chinese Academy of Sciences (KGZD-EW-T08), the Key Research Program of Frontier Sciences of CAS (QYZDJ-SSW-SLH049), and the Shanghai Science and Technology Program (18JC1410601). The authors would like to thank David Foley, Chris Morris, and Bao Nguyen for the compound characterization and Naila Mugheubi for the pXRD analysis. Thanks also go to Michaela Caporello, Jocelyn Baer, Jamie Buske, Michelle Buetti-Weekly, and Lindsay Dougherty for helping with the experimentation.

AUTHOR CONTRIBUTIONS

J.H. and S.D. conceived and led the project (J.H. for the synthetic methodology and S.D. for the application to the oncology candidate). D.M., L.L., Z.H., and M.Z. performed the synthetic and mechanistic experiments for the synthetic methodology and the preliminary application to the oncology candidate. A.B., J.-N.D., C.M.H., T.M., M.M., S.M., H.P., J.L.P., and D.W.W. were involved in the detailed experiments related to the oncology candidate. D.M., J.H., S.D., and A.B. co-wrote the manuscript. All of the authors discussed the results and commented on the manuscript. J.H. finalized the whole manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

Received: January 25, 2021

Revised: March 8, 2021

Accepted: March 17, 2021

Published: April 7, 2021

REFERENCES

- Nurse, P. (2000). A long twentieth century of the cell cycle and beyond. *Cell* 100, 71–78.
- Malumbres, M., Harlow, E., Hunt, T., Hunter, T., Lahti, J.M., Manning, G., Morgan, D.O., Tsai, L.H., and Wolgemuth, D.J. (2009). Cyclin-dependent kinases: a family portrait. *Nat. Cell Biol.* 11, 1275–1276.
- Diaz-Moralli, S., Tarrado-Castellarnau, M., Miranda, A., and Cascante, M. (2013). Targeting cell cycle regulation in cancer therapy. *Pharmacol. Ther.* 138, 255–271.
- Toogood, P.L., Harvey, P.J., Repine, J.T., Sheehan, D.J., VanderWel, S.N., Zhou, H., Keller, P.R., McNamara, D.J., Sherry, D., Zhu, T., et al. (2005). Discovery of a potent and selective inhibitor of cyclin-dependent kinase 4/6. *J. Med. Chem.* 48, 2388–2406.
- Rader, J., Russell, M.R., Hart, L.S., Nakazawa, M.S., Belcastro, L.T., Martinez, D., Li, Y., Carpenter, E.L., Attiyeh, E.F., Diskin, S.J., et al. (2013). Dual CDK4/CDK6 inhibition induces cell-cycle arrest and senescence in neuroblastoma. *Clin. Cancer Res.* 19, 6173–6182.
- Gelbert, L.M., Cai, S., Lin, X., Sanchez-Martinez, C., Del Prado, M., Lallena, M.J., Torres, R., Ajamie, R.T., Wishart, G.N., Flack, R.S., et al. (2014). Preclinical characterization of the CDK4/6 inhibitor LY2835219: in-vivo cell cycle-dependent/independent anti-tumor activities alone/in combination with gemcitabine. *Invest. New Drugs* 32, 825–837.
- Herrera-Abreu, M.T., Palafox, M., Asghar, U., Rivas, M.A., Cutts, R.J., Garcia-Murillas, I., Pearson, A., Guzman, M., Rodriguez, O., Grueso, J., et al. (2016). Early Adaptation and Acquired Resistance to CDK4/6 Inhibition in Estrogen Receptor-Positive Breast Cancer. *Cancer Res.* 76, 2301–2313.
- Freeman-Cook, K.D., Hoffman, R.L., Nagata, A., and Ninkovic, S. (2019). CDK 2/4/6 inhibitors (US patent), 10233188B2, filed July 31, 2017, and published March 19, 2019.
- Rong, J., Ni, C., and Hu, J. (2017). Metal-Catalyzed Direct Difluoromethylation Reactions. *Asian J. Org. Chem.* 6, 139–152.
- Caron, S. (2020). Where Does the Fluorine Come From? A Review on the Challenges Associated with the Synthesis of Organofluorine Compounds. *Org. Process Res. Dev.* 24, 470–480.
- Fujiwara, Y., Dixon, J.A., Rodriguez, R.A., Baxter, R.D., Dixon, D.D., Collins, M.R., Blackmond, D.G., and Baran, P.S. (2012). A new reagent for direct difluoromethylation. *J. Am. Chem. Soc.* 134, 1494–1497.
- Fujiwara, Y., Dixon, J.A., Ó'Hara, F., Funder, E.D., Dixon, D.D., Rodriguez, R.A., Baxter, R.D., Herlé, B., Sach, N., Collins, M.R., et al. (2012). Practical and innate carbon-hydrogen functionalization of heterocycles. *Nature* 492, 95–99.
- Tang, X.-J., Thomason, C.S., and Dolbier, W.R., Jr. (2014). Photoredox-catalyzed tandem radical cyclization of N-arylacrylamides: general methods to construct fluorinated 3,3-disubstituted 2-oxindoles using fluoroalkylsulfonyl chlorides. *Org. Lett.* 16, 4594–4597.
- Tang, X.-J., Zhang, Z., and Dolbier, W.R., Jr. (2015). Direct Photoredox-Catalyzed Reductive Difluoromethylation of Electron-Deficient Alkenes. *Chemistry* 21, 18961–18965.
- O'Brien, A.G., Maruyama, A., Inokuma, Y., Fujita, M., Baran, P.S., and Blackmond, D.G. (2014). Radical C-H functionalization of heteroarenes under electrochemical control. *Angew. Chem. Int. Ed. Engl.* 53, 11868–11871.
- Su, Y.-M., Hou, Y., Yin, F., Xu, Y.M., Li, Y., Zheng, X., and Wang, X.S. (2014). Visible light-mediated C-H difluoromethylation of electron-rich heteroarenes. *Org. Lett.* 16, 2958–2961.
- He, Z., Tan, P., Ni, C., and Hu, J. (2015). Fluoroalkylative aryl migration of conjugated N-arylsulfonylated amides using easily accessible sodium di- and monofluoroalkanesulfonates. *Org. Lett.* 17, 1838–1841.
- Chen, Q.-Y., and Long, Z.-Y. (1999). Preparation method for perfluoroalkane sulfinate (Chinese Patent), CN1221735A, filed November 20, 1998, and published July 7, 1999.
- Prakash, G.K.S., Ni, C., Wang, F., Hu, J., and Olah, G.A. (2011). From difluoromethyl 2-pyridyl sulfone to difluorinated sulfonates: a protocol for nucleophilic difluoro(sulfonato) methylation. *Angew. Chem. Int. Ed. Engl.* 50, 2559–2563.
- Zhang, Y.F., Kirchmeier, R.L., and Shreeve, J.M.S. (1992). Perhaloalkanesulfinyl Chlorides, RfS(O)Cl, and Perhaloalkanesulfinate Esters, RfS(O)ORf. *Inorg. Chem.* 31, 492–494.
- Langlois, B.R., Laurent, E., and Roidot, N. (1991). Trifluoromethylation of aromatic compounds with sodium trifluoromethanesulfinate under oxidative conditions. *Tetrahedron Lett.* 32, 7525–7528.
- Zhang, C. (2014). Application of Langlois' reagent in trifluoromethylation reactions. *Adv. Synth. Catal.* 356, 2895–2906.
- McAtee, R.C., Beatty, J.W., McAtee, C.C., and Stephenson, C.R.J. (2018). Radical Chlorodifluoromethylation: Providing a Motif for (Hetero)arene Diversification. *Org. Lett.* 20, 3491–3495.
- Kawamura, S., Henderson, C.J., Aoki, Y., Sekine, D., Kobayashi, S., and Sodeoka, M. (2018). Reactivity and properties of bis(chlorodifluoroacetyl) peroxide generated in situ from chlorodifluoroacetic anhydride for chlorodifluoromethylation reactions. *Chem. Commun. (Camb.)* 54, 11276–11279.
- Sakamoto, R., Kashiwagi, H., and Maruoka, K. (2017). The Direct C-H Difluoromethylation of Heteroarenes Based on the Photolysis of Hypervalent Iodine(III) Reagents That Contain Difluoroacetoxy Ligands. *Org. Lett.* 19, 5126–5129.
- Li, Y.F. (2007). tert-Butyl Hydroperoxide (TBHP): A Versatile Oxidizing Agent in Organic Synthesis. *Synlett* 18, 2922–2923.
- Cotton, H., Elebring, T., Larsson, M., Li, L., Sörensen, H., and Unge, S. (2000). Asymmetric synthesis of esomeprazole. *Tetrahedron Asymmetry* 11, 3819–3825.
- Sanchez, J., and Myers, T.N. (1991). Peroxides and compounds (organic). *Kirk-Othmer Encyclopedia of Chemical Technology* Vol. 18, 4th ed. (John Wiley & Sons), pp. 230–310, <https://onlinelibrary.wiley.com/doi/10.1002/0471238961.1518070119011403.a01>.
- Fürstner, A. (2016). Iron Catalysis in Organic Synthesis: A Critical Assessment of What It Takes To Make This Base Metal a Multitasking Champion. *ACS Cent. Sci.* 2, 778–789.
- Bolm, C., Legros, J., Le Pailh, J., and Zani, L. (2004). Iron-catalyzed reactions in organic synthesis. *Chem. Rev.* 104, 6217–6254.
- Ni, C., and Hu, J. (2005). Nucleophilic difluoromethylation of carbonyl compounds using TMSCF₂SO₂Ph and MgO-mediated desulfonylation. *Tetrahedron Lett.* 46, 8273–8277.
- Zhao, Y., Huang, W., Zhu, L., and Hu, J. (2010). Difluoromethyl 2-pyridyl sulfone: a new gem-difluoroolefination reagent for aldehydes and ketones. *Org. Lett.* 12, 1444–1447.
- Zhou, M., Ni, C., He, Z., and Hu, J. (2016). O-Trifluoromethylation of Phenols: Access to Aryl Trifluoromethyl Ethers by O-Carboxydifluoromethylation and

Decarboxylative Fluorination. *Org. Lett.* **18**, 3754–3757.

Tetrachloride (Final Report) (US Environmental Protection Agency), EPA/635/R-08/005F.

biblio?CC=WO&NR=2020065494&KC=&FT=E&locale=en_EP.

34. Chen, J., Lin, J., and Xiao, J. (2018). Decarboxylative nucleophilic difluoromethylation of aldehydes and imines. *Tetrahedron* **74**, 4295–4297.
35. US Environmental Protection Agency (2010). IRIS Toxicological Review of Carbon
36. Brown, A., Desrosiers, J.-N., Shengquan, D., Hawkins, J.M., Hayward, C.M., Maloney, M.T., Monfette, S., Perfect, H.H., and Widlicka, D.W. (2020). Synthesis of pyrido[2,3-D]pyrimidin-7(8H)-ones WO 2020/065494 A1, <https://worldwide.espacenet.com/publicationDetails/>
37. Pfizer Inc. (2019). New Method for Synthesis of 6-(difluoromethyl)-8-[(1R, 2R)-2-hydroxy-2-methylcyclopentyl]-2-[[1-(methylsulfonyl)piperidin-4-yl]amino]pyrido[2,3-d]pyrimidin-7(8H)-one (PF-068732600). IP.com PAD IPCOM000258916D.