JOC The Journal of Organic Chemistry

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Difluoromethylation of Alkyl Bromides and Iodides with $TMSCF_2H$

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Cite This: J. Org. Chem. 2021, 86, 2854–2865 Read Online

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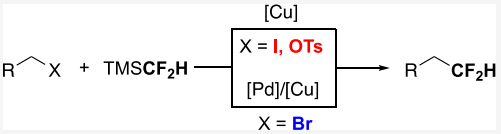
ABSTRACT: We describe, for the first time, two protocols for direct difluoromethylation of unactivated alkyl bromides and iodides. Reactions of alkyl iodides with $TMSCF_2H$ were mediated by a copper catalyst using CsF as the activator, while reactions of less reactive alkyl bromides required a combination of palladium and a stoichiometric amount of CuI as the catalysts. Preliminary mechanistic studies of the synergistic Pd/Cu-catalyzed difluoromethylation of alkyl bromides suggest that it proceeds likely via a Pd(I)/Pd(III) catalytic cycle.



INTRODUCTION

Organofluorine compounds are continuously gaining momentum, particularly in the field of pharmaceutical and agrochemical industries, as an emerging tool to leverage the compounds' chemical and biological properties including the metabolic stability and cell permeability that are important for the pharmacokinetics and pharmacodynamics of the drug candidates.[1] Consequently, development of efficient methods for the installation of a fluorine or a fluoroalkyl group such as trifluoromethyl, difluoromethyl, and trifluoromethoxy has become an active research topic in synthetic community.[2] Among many fluoroalkyl groups, the difluoromethyl group ($-CF_2H$) has attracted great attention, mainly owing to its different property from other fluoroalkyl groups. Largely because of the strong electronegativity of fluorine, it has been estimated that the kinetic acidity of the proton in $PhCF_2H$ in dimethyl sulfoxide (DMSO) is roughly 10^4 times higher than that in PhMe.[3] The weakly acidic proton in the difluoromethyl group is therefore able to act as a hydrogen bonding donor to interact with the heteroatom in the host protein, and the difluoromethyl group is now generally considered by the medicinal chemists as an isosteric and isopolar functional group to hydroxyl ($-OH$) and thiol ($-SH$) units in drug design.[4]

To date, most efforts for the incorporation of the difluoromethyl group have been focused on the construction of the $C(sp^2)-CF_2H$ bond,[5] while synthetic routes to install a difluoromethyl group onto a sp^3-hybridized carbon are far less developed. One of the well-known methods for the formation of the $C(sp^3)-CF_2H$ bond is the reaction of a nucleophilic difluoromethylation reagent $TMSCF_2H$ with activated electrophiles such as aldehydes, ketones, or imines using CsF[6] or KO^{t}Bu[7] as the promoter. Notably, Xiao and co-workers reported a Ph_3P/ICH_2CH_2I system which could effectively activate the hydroxyl group for nucleophilic difluoromethylation.[8] Likewise, $PhSO_2CF_2H$[9] and $PhSO_2CF_2TMS$[10] can also be used as the nucleophilic "difluoromethyl" surrogates under basic conditions to react with the activated electrophiles via nucleophilic phenylsulfonyldifluoromethylation and subsequent desulfonylation processes. An alternative route for the generation of the $C(sp^3)-CF_2H$ bond is the reaction of an enolate with a difluorocarbene precursor under basic conditions. In this aspect, several difluoromethyl precursors such as difluoromethyl-(4-nitrophenyl)-bis(carbomethoxy)-methylide sulfonium ylide,[11] *S*-difluoromethyl-*S*-phenyl-*S*-(2,3,4,5-tetramethylphenyl) sulfonium salt,[12] *S*-(bromodifluoromethyl)diarylsulfonium salts,[13] or $TMSCF_2Br$[14] have been reported. However, the substrates for such a reaction were mainly limited to activated soft carbon nucleophiles such as malonates, β-ketoesters, 2,2-diaryl acetates, or acetamides. A third route toward the $C(sp^3)-CF_2H$ bond formation relied on photoredox catalysis-promoted difluoromethyl radical addition to an unsaturated double bond, followed by proton abstraction.[15] Several stable reagents such as HCF_2SO_2Cl,[16] HCF_2CO_2H,[17] $Ph_3P^+CF_2CO_2^-$,[18] $[Ph_3PCF_2Br]^+Br^-$,[19] $[Ph_3PCF_2H]^+Br^-$,[20] *N*-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine,[21] and 2-((difluoromethyl)sulfonyl) benzo[*d*]thiazole[22] have been identified as the suitable difluoromethyl radical precursors for this transformation. More recently, Liu and co-workers reported two copper-catalyzed difluoromethylation approaches for the reactions of aliphatic acids or alkyl-substituted pyridinium salts with $[(DMPU)_2Zn(CF_2H)_2]$ under mild conditions.[23] Despite these achievements, methods that are able to construct the $C(sp^3)-CF_2H$ bond under mild conditions are still highly demanded (Figure 1).

An attractive approach for the formation of $C(sp^3)-CF_2H$ bond would be a transition-metal-mediated or -catalyzed difluoromethylation of alkyl halides using $TMSCF_2H$ as the

Received: November 20, 2020
Published: January 19, 2021

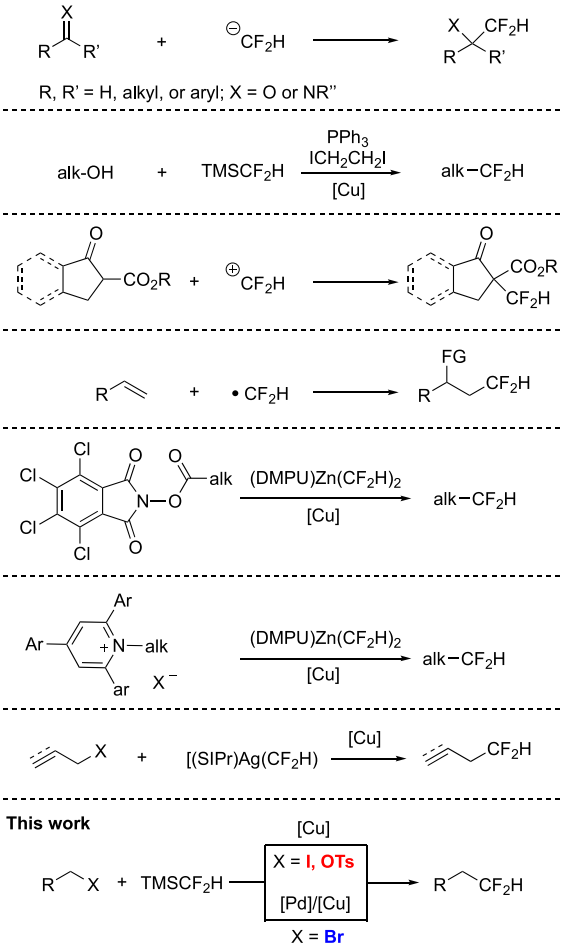


Figure 1. Approaches for the formation of C(sp^3)−CF_2H bond.

difluoromethyl source since both starting materials are easily available, and the transition-metal catalytic reactions are conducted under mild conditions which could tolerate various functional groups and are amenable to late-stage functionalization of the multi-functionalized drug molecules. Previously, we have established a copper-catalyzed direct difluoromethylation of activated alkyl halides such as allylic and propargylic bromides and iodides.[24] However, efforts to extend this methodology to unactivated alkyl halides failed to give the desired difluoromethylated products. Herein, we have now discovered two different approaches for the direct difluoromethylation of primary alkyl iodides and bromides with $TMSCF_2H$. We found that reactions of primary alkyl iodides with $TMSCF_2H$ occurred smoothly at 40 °C in the presence of 1 equiv of CuI using CsF as the activator. However, under the same reaction conditions, reaction of primary alkyl bromides with $TMSCF_2H$ did not occur. The addition of 10 mol % of the palladium catalyst derived from $Pd(dba)_2$ and 1,1′-ferrocenediyl-bis(diphenylphosphine) (DPPF) promoted the reaction to full conversion and gave the desired difluoromethylated alkanes in high yields. Initial mechanistic studies suggest that the Pd-catalyzed difluoromethylation of alkyl bromides might proceed via a Pd(I)−Pd(III) catalytic cycle.

RESULTS AND DISCUSSION

Optimization of Conditions for Difluoromethylation of Primary Alkyl Electrophiles with $TMSCF_2H$. 3-Phenyl propyl iodide and $TMSCF_2H$ were chosen as the substrates for the development of reaction conditions. Extensive screening of the copper salts, the activators, and the solvents disclosed that a reaction using CuI as the promoter and CsF as the activator occurred in polar solvent dimethylformamide (DMF) and gave the desired product **1a** in 87% yield after 6 h at 40 °C (standard condition A in Scheme 1). Control experiments showed that the reaction in the absence of CuI occurred in less than 5% yield (Scheme 1, entry 2). Likewise, the direct reaction of 3-phenyl propyl iodide and $TMSCF_2H$ in the presence of a combination of CsF and 18-crown-6 as the promoter also gave the desired product in less than 5% yield (Scheme 1, entry 3). Replacing CuI with CuBr, CuCl, or reducing the amount of CuI to 0.5 equiv led to dramatically decreasing the product yield (Scheme 1, entries 4−6). The use of CsF as the activator is important since reactions using other activators such as KO^{t}Bu or NaO^{t}Bu of TBAF gave much lower yields (Scheme 1, entries 7−9). Likewise, the use of DMF as a solvent is crucial because reactions in NMP or DMAc offered low yields of 35−49%, while reactions in other solvents such as DMSO or tetrahydrofuran did not take place at all (Scheme 1, entries 10−13). Notably, under the standard reaction conditions, reactions of analogous alkyl electrophiles, tosylate and mesylate, gave difluoromethylated alkanes in 53 and 49% yields, respectively, while reactions of alkyl triflate and nosylate did not afford the desired products (Scheme 1, entries 14−17). Most striking, reaction of alkyl bromide with $TMSCF_2H$ did not occur to give the corresponding difluoromethylated alkanes under the standard conditions (Scheme 1, entry 19).

To address the challenge in the reaction of alkyl bromide with $TMSCF_2H$, we decided to reexamine the reaction conditions by addition of different additives. A broadband screening of the additives led us to find that the reaction in the presence of $Pd(dba)_2$ (10 mol %) and DPPF (10 mol %) as the catalyst occurred in full conversion after 6 h at 50 °C to give the coupled product in 92% yield (standard condition B in Scheme 1). Control experiments showed that the reaction in the absence of either palladium catalyst or CuI did not occur, thus illustrating that the synergistic bimetallic catalytic system might operate under these conditions. Previously, we found that direct transmetalation of the difluoromethyl group from $TMSCF_2H$ to [LPd(Ar)(X)] in the presence of various activators was a rather difficult process. Often, the formation of CF_2H_2, CF_2HCF_2H, or difluoroethylene was observed.[25] Likewise, the same phenomena was observed for the stoichiometric reaction of the alkyl-substituted Pd(II) complex [LPd(Me)(X)] with $TMSCF_2H$. Instead, we found that it is much easier for the difluoromethyl group to transfer from $TMSCF_2H$ to CuI to form a stable [$CuCF_2H$] species which then can readily transmetalate the difluoromethyl group to the putative palladium complex. Thus, in this reaction, the [$CuCF_2H$] complex could act as a transmetalation shuttle for the cooperative bimetallic catalytic system. Efforts to further optimize the reaction conditions in terms of the different palladium precursors, ligands, solvents, and copper(I) salts led to inferior results (Scheme 1, entries 20−32). Finally, we also tried to reduce the amount of the palladium catalyst and CuI. However, reaction using 5 mol % palladium catalyst or 0.5 equiv of CuI gave the coupled product in significantly reduced 58 and 45% yields, respectively (Scheme 1, entries 33−34).

Scope for Difluoromethylation of Primary Alkyl Electrophiles with $TMSCF_2H$. Under the standard conditions A and B, we studied the generality and scope of the

https://dx.doi.org/10.1021/acs.joc.0c02783
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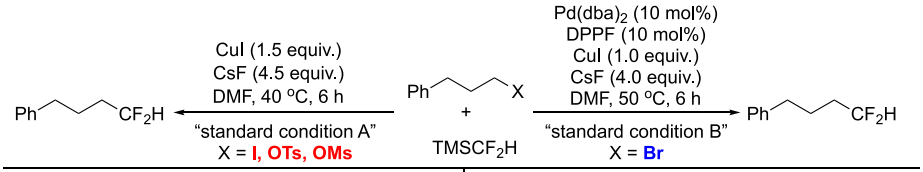
Scheme 1. Optimization of Reaction for Copper-Mediated Difluoromethylation of Primary Alkyl Electrophiles with $TMSCF_2H$[a,b]



entry	X	variation from condition A	yield (%)	entry	X	variation from condition B	yield (%)
1	I	none	87	18	Br	none	92
2	I	No CuI	<5	19	Br	no $Pd(dba)_2$/DPPF	-
3	I	No CuI, 18-crown-6 (1.0 equiv)	<5	20	Br	no CuI	-
4	I	CuBr instead of CuI	-	21	Br	no ligand	-
5	I	CuCl instead of CuI	39	22	Br	$Pd(OAc)_2$ instead of $Pd(dba)_2$	50
6	I	0.5 equivalent of CuI	37	23	Br	$PdCl_2$ instead of $Pd(dba)_2$	72
7	I	^{t}BuOK instead of CsF	-	24	Br	PPh_3 instead of DPPF	40
8	I	^{t}BuONa instead of CsF	5	25	Br	XPhos instead of DPPF	81
9	I	TBAF instead of CsF	27	26	Br	XantPhos instead of DPPF	70
10	I	NMP instead of DMF	35	27	Br	DPEPhos instead of DPPF	57
11	i	DMAc instead of DMF	49	28	Br	NMP instead of DMF	59
12	I	DMSO instead of DMF	-	29	Br	DMAc instead of DMF	66
13	I	THF instead of DMF	-	30	Br	CuBr	56
14	OTf	none	-	31	Br	CuCl	69
15	OTs	none	53	32	Br	IPrCuCl	-
16	OMs	none	49	33	Br	$Pd(dba)_2$/DPPF (5.0 mol%)	58
17	ONs	none	-	34	Br	0.5 equivalent of CuI	45

[a]Reaction condition A: alkyl electrophiles (0.10 mmol), $TMSCF_2H$ (0.45 mol), CuI (0.15 mmol), and CsF (0.45 mmol) in DMF (1.0 mL) at 40 °C for 6 h; condition B: alkyl bromide (0.10 mmol), $TMSCF_2H$ (0.40 mmol), $Pd(dba)_2$ (0.010 mmol), DPPF (0.010 mmol), CuI (0.10 mmol), and CsF (0.40 mmol) in DMF (1.0 mL) at 50 °C for 6 h. [b]Yields were determined by ^{19}F NMR spectroscopy using trifluorotoluene as an internal standard.

substrates of alkyl electrophiles for the difluoromethylation reaction. As summarize in Scheme 2, a wide range of unhindered alkyl iodides and bromides reacted with $TMSCF_2H$ under conditions A or B to give the difluoromethylated alkanes in good yields. In general, reactions of alkyl bromides under condition B gave the desired difluoroalkanes in higher yields than that of alkyl iodides under condition A. For example, the reaction of (3-bromopropoxy)benzene with $TMSCF_2H$ under condition B occurred to give compound **2e** in 92% yield, while the reaction of (3-iodopropoxy)benzene under condition A generated compound **2e** in 80% yield. Under both conditions, a variety of common functional groups including aryl fluoride (**2c**), ester (**2d**, **2h**−**q**), nitro (**2f**), protected aldehyde (**2g**), cyano (**2k**), amide (**2t**), and alkene (**2u**, **2w**) were compatible. It is noteworthy that a substrate with aryl chloride, which is the common coupling partner in the traditional cross-coupling reaction, reacted under both conditions in high yields (**2l**). The reaction of alkyl bromide with an aryl bromide group, however, reacted under condition B in low 28% yield because of the competition aryl difluoromethylation (Scheme 2, **2j**). Nevertheless, the aryl bromide group is compatible with the condition A. For example, the reaction of 3-iodopropyl 4-bromobenzoate with $TMSCF_2H$ under condition A generated product **2j** in 58% yield. Additionally, alkyl halides with heteroarene such as thiophene (**2o**), pyrazole (**2p**), indole (**2r**), and carbazole (**2s**) can be difluoromethylated in good to excellent yields.

Furthermore, reactions of alkyl tosylates with $TMFCF_2H$ under condition A occurred smoothly to give the corresponding difluoromethylated products in good yields (**2a**, **2w**−**x**). However, our system gave low yields for those substrates that are easy to undergo elimination to give stable alkenes. For examples, reactions of β-benzoxyl-ethyl bromide and iodides under both conditions gave the difluoromethylated product **2y** in low 27 and 20% yields, respectively. The main side products in these reactions were vinyl benzyl ether. In addition, our system is rather sensitive to the steric hindrance of the alkyl bromides and iodides. Accordingly, the reaction of alkyl iodide with a quaternary carbon center at γ-position gave the product in a low yield of 33%, while secondary alkyl halides and substrates with β-substituents are unreactive. Specifically, reactions of secondary benzylic bromides did not give the coupled product.

Mechanistic Studies of Palladium-Mediated Difluoromethylation of Primary Alkyl Bromides. Since palladium-catalyzed cross-coupling reactions usually undergo a Pd(0)/Pd(II) catalytic cycle, we did a study to check whether the synergistic Pd/Cu-catalyzed difluoromethylation of alkyl bromide with $TMFCF_2H$ proceeds via a typical Pd(0)/Pd(II). We synthesized [(DPPF)Pd(CH_3)(I)] and then used it in stoichiometric amounts in the reaction with $TMSCF_2H$ under the mock catalytic conditions. We assume that transmetalating the difluoromethyl group from $TMSCF_2H$ to [(DPPF)Pd(CH_3)(I)] would generate [(DPPF)Pd(CH_3)(CF_2H)], which would then undergo reductive elimination to give CH_3CF_2H. However, under these conditions, the formation of CH_3CF_2H was not observed, as determined by ^{19}F NMR spectroscopy (Figure 2, eq 1), which indicates that the Pd(0)/Pd(II) catalytic cycle is not in operation. An often proposed alternative catalytic cycle for Pd-catalyzed cross coupling of alkyl halides is that the reaction goes through a Pd(I)/Pd(III) catalytic cycle. To gain evidence of the possible Pd(I)/Pd(III) catalytic cycle, we synthesized Pd(I) complex

https://dx.doi.org/10.1021/acs.joc.0c02783
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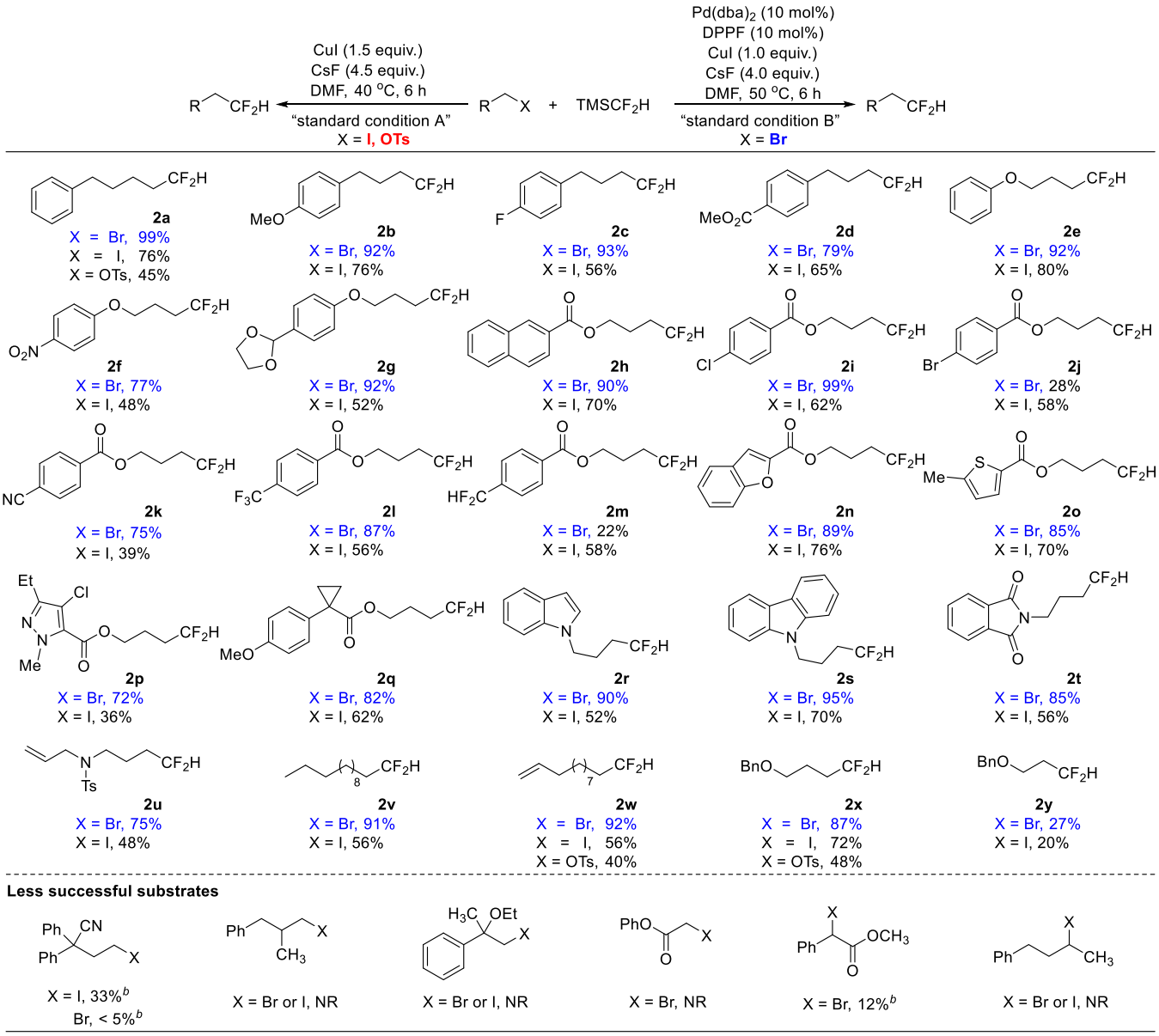
Scheme 2. Scope for Difluoromethylation of Primary Alkyl Electrophiles with $TMSCF_2H$[a,b]



[a]Reaction condition A: alkyl iodide or tosylate (0.3 mmol), $TMSCF_2H$ (1.35 mmol), CuI (0.45 mmol), and CsF (1.35 mmol) in DMF (3.0 mL) at 40 °C for 6 h; condition B: alkyl bromide (0.3 mmol), $TMSCF_2H$ (1.35 mmol), $Pd(dba)_2$ (0.030 mmol), DPPF (0.031 mmol), CuI (0.30 mmol), and CsF (1.19 mmol) in DMF (3.0 mL) at 50 °C for 6 h. [b]Yields were determined by ^{19}F NMR spectroscopy using trifluorotoluene as an internal standard.

$[Pd_2(CH_3CN)_6]_2BF_4$ and then used it as a catalyst for the coupling of 11-bromoundec-1-ene with $TMFCF_2H$ under otherwise identical conditions with condition B. Under these conditions, the reaction went smoothly to generate 12,12-difluorododec-1-ene in the quantitative yield (Figure 2, eq 2), thus providing evidence that a Pd(I)/Pd(III) catalytic cycle might be operating for the current difluoromethylation protocol. Furthermore, if the reaction does proceed via a Pd(I)/Pd(III) cycle, the oxidative addition of an alkyl halide to a Pd(I) intermediate to generate a key Pd(III) intermediate for product-forming reductive elimination might involve a single-electron-transfer (SET) process and an alkyl radical. To probe whether this is the case, we studied two different set of experiments. In the first experiment, we add 4.0 equiv of TEMPO to the Pd-catalyzed difluoromethylation of 3-phenyl propyl bromide with $TMFCF_2H$ (Figure 2, eq 3). It was found that the reaction was completely shut down. In the second experiment, we conducted a standard radical clock experiment by choosing bromomethylcyclopropane as the substrate. Under condition B, we found that the reaction occurred smoothly to give (2,2-difluoroethyl)cyclopropane in 60% yield and 4,4-difluorobut-1-ene in 16% yield (Figure 2, eq 4). Both the radical inhibition and the radical clock experiments are consistent with a pathway that involves an alkyl free radical in the coupling reaction, thus supporting the Pd(I)/Pd(III) cycle, even though we could not rule out other possible pathways such as a Pd(0)/Pd(II) catalytic cycle via a SET oxidative addition of alkyl bromide to an ionic Pd(0) complex. On the other hand, the mechanism for the copper-mediated difluoromethylation of alkyl iodides is complicated, just like

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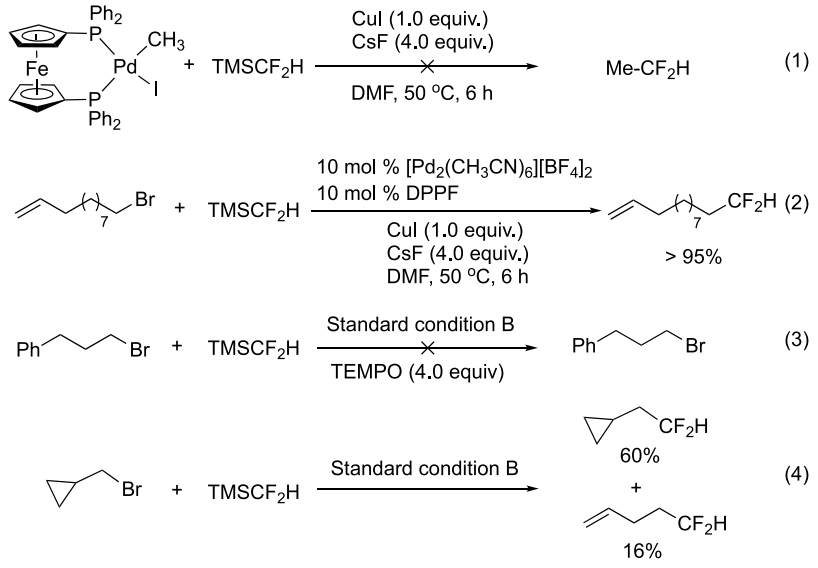

Figure 2. Mechanistic studies of palladium-mediated difluoromethylation of primary alkyl bromides.

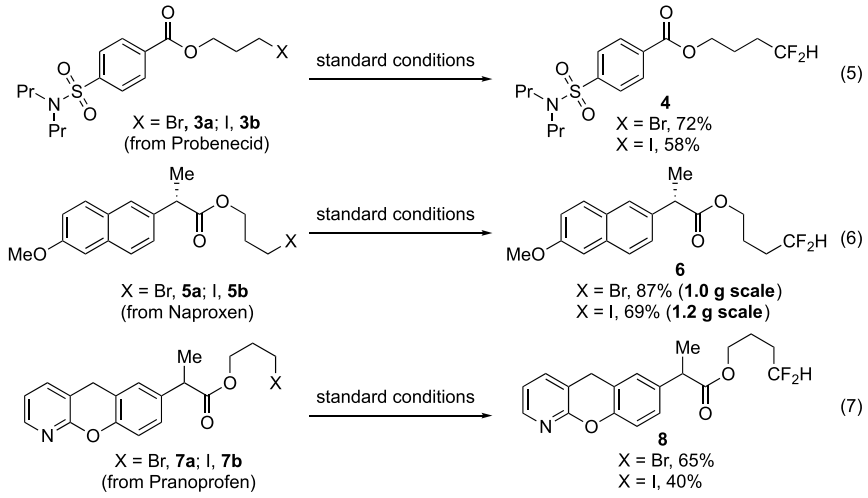

Figure 3. Application of the difluoromethylating protocols in the preparation of difluoromethylated derivatives of drug molecules.

other copper-catalyzed cross-coupling reactions, that will be investigated in our future studies.

Application. To demonstrate the applicability of the protocols, we tried to utilize both reactions for the preparation of difluoromethylated drug molecules. As summarized in Figure 3, 3-iodo- or 3-bromo-propyl esters of probenecid, a uric acid reducer, were successfully difluoromethylated under conditions A or B to give difluoromethylated product **4** in 58 and 72%, respectively (Figure 3, eq 5). Similarly, alkyl halides **5a** and **5b** derived from naproxen, a nonsteroidal anti-inflammatory drug, reacted with $TMSCF_2H$ under conditions A or B to generate difluoromethylated derivative **6** in 70 and 87% yield, respectively (Figure 3, eq 6). Remarkably, both reactions of 3-bromo- or 3-iodo-propyl ester of naproxen **5b** could be conducted in the gram scale without erosion of the yield under conditions A or B, thus demonstrating the robustness and scalability of the protocol for its potential applications. Likewise, alkyl halides **7a**–**b** derived from another nonsteroidal anti-inflammatory drug pranoprofen reacted with $TMSCF_2H$ under conditions A or B to generate difluoromethylated derivative **8** in 65 and 40% yield, respectively.

CONCLUSIONS

For the first time, we demonstrated that unactivated alkyl bromides and iodides were able to couple with $TMSCF_2H$ to give the corresponding difluoromethylated derivatives. It was found that reactions of alkyl iodides with $TMSCF_2H$ could be mediated by a copper catalyst using CsF as the activator, while less reactive alkyl bromides required the combination of palladium and a stoichiometric amount of CuI to promote the reaction. A variety of common functional groups were compatible with both conditions. However, these conditions were highly sensitive to the steric hindrance of the substrates. Secondary alkyl halides and β-branched primary alkyl bromides did not react at all, and alkyl halides with a quaternary carbon center at γ-position were not suitable as well. Mechanistic studies of the synergistic Pd/Cu-catalyzed difluoromethylation of alkyl bromides suggest that the reaction proceeds via a Pd(I)/Pd(III) catalytic cycle. Applications of the methods in the preparation of three difluoromethylated drug molecule derivatives were conducted to demonstrate the protocols' potential application in the late-stage modification of lead compounds. Currently, expanding the protocols to sterically

https://dx.doi.org/10.1021/acs.joc.0c02783
J. Org. Chem. 2021, 86, 2854−2865

hindered β-branched primary alkyl halides and secondary halides is undergoing in our laboratory and will be reported in due course.

EXPERIMENTAL SECTION

General Information. All solvents were purified by the standard method. ^{1}H, ^{19}F, and ^{13}C NMR spectra were acquired on 400; 376; 101, 126, and 151 MHz spectrometer (400 MHz for ^{1}H; 376 MHz for ^{19}F; and 101, 126, and 151 MHz for ^{13}C). ^{1}H NMR and ^{13}C NMR chemical shifts were determined relative to an internal standard TMS at δ 0.0 ppm, and ^{19}F NMR chemical shifts were determined relative to $CFCl_3$ as an internal standard. Chemical shifts (δ) are reported in parts per million, and coupling constants (J) are reported in hertz (Hz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, and m = multiplet. All reactions were monitored by thin-layer chromatography or ^{19}F NMR. Flash column chromatography was carried out using 300−400 mesh silica gel at medium pressure.

Materials. All reagents were received from commercial sources. Solvents were freshly dried and degassed according to the purification handbook Purification of Laboratory Chemicals[26] before using.

Preparation of Alkyl Electrophiles. Alkyl electrophiles were prepared by the known methods according to the reported procedure.[27]

2-(4-(3-Bromopropoxy)phenyl)-1,3-dioxolane. 4-(3-Bromopropoxy)benzaldehyde[28] (1.0 g, 4.1 mmol), ethylene glycol (1.0 g, 16 mmol), *p*-toluenesulfonic acid (17 mg, 0.10 mmol), and toluene (30.0 mL) were added to a round-bottomed flask equipped with a Dean−Stark trap with a condenser. The solution was heated to 150 °C in an oil bath for 10 h. The solution was washed with NaOH (0.1 M) and extracted with EtOAc (50.0 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography on silica gel. Colorless oil (915 mg, 80%). Eluent: ethyl acetate/petroleum ether (1/8), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, J = 8.6 Hz, 2H), 6.91 (d, J = 8.5 Hz, 2H), 5.75 (s, 1H), 4.17−3.95 (m, 6H), 3.59 (t, J = 6.4 Hz, 2H), 2.31 (p, J = 6.1 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 159.4, 130.3, 127.9, 114.3, 103.6, 65.4, 65.2, 32.3, 30.0 ppm. MS (EI): 286 (100). HRMS (FI-TOF) m/z: $[M]^+$ calcd for $C_{12}H_{15}BrO_3$, 286.0199; found, 286.0206. IR (KBr): ν_{max} 2940, 1693, 1600, 1509, 1251, 1161, 1025, 833, 616 cm^{-1}.

2-(4-(3-Iodopropoxy)phenyl)-1,3-dioxolane. To a solution of 2-(4-(3-bromopropoxy)phenyl)-1,3-dioxolane (572 mg, 2.00 mmol) in acetone (10.0 mL), KI (1.0 g, 6.0 mmol) was added gradually. Then, the reaction mixture was stirred at 50 °C in an oil bath overnight. Solvent was removed and then diluted with water. The mixture was extracted with ethyl acetate for three times. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give the product. Colorless oil (648 mg, 97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 5.74 (s, 1H), 4.15−3.95 (m, 6H), 3.34 (t, J = 6.7 Hz, 2H), 2.25 (p, J = 6.2 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 159.4, 130.3, 127.9, 114.4, 103.6, 67.3, 65.2, 32.9, 2.5 ppm. MS (EI): 333 (100). HRMS (FI-TOF) m/z: $[M]^+$ calcd for $C_{12}H_{15}IO_3$, 334.0060; found, 334.0067. IR (KBr): ν_{max} 2952, 1693, 1601, 1493, 1281, 1177, 1026, 823, 706 cm^{-1}.

General Procedure for Preparation of Alkyl Bromides and Iodides. To a solution of alkyl acid (1.2 equiv), 4-dimethylaminepyridine (0.2 equiv), and dicyclohexylcarbodiimide (1.2 equiv) in dry CH_2Cl_2 (10.0 mL) at room temperature was added 3-bromopropan-1-ol or 3-iodopropan-1-ol (1.0 equiv) in dry CH_2Cl_2 (3.0 mL). The reaction was stirred at room temperature for overnight before being diluted with CH_2Cl_2 (10.0 mL) and quenched with H_2O (200 mL). The aqueous layer was separated and extracted two times with CH_2Cl_2 (10.0 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography on silica gel.

3-Bromopropyl 4-Bromobenzoate. Colorless oil (457 mg, 71%). Eluent: ethyl acetate/petroleum ether (1/40), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, J = 8.3 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H), 4.44 (t, J = 6.0 Hz, 2H), 3.51 (t, J = 6.5 Hz, 2H), 2.29 (p, J = 6.2 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 165.6, 131.7, 131.1, 128.8, 128.2, 62.9, 31.7, 29.3 ppm. MS (DART): 320.9 $[M + H]^+$; HRMS (DART-Positive) m/z: $[M + H]^+$ calcd for $C_{10}H_{11}Br_2O_2$, 320.9120; found, 320.9119. IR (KBr): ν_{max} 2930, 1721, 1590, 1398, 1271, 1116, 1012, 756 cm^{-1}.

3-Iodopropyl 4-Bromobenzoate. Yellow oil (574 mg, 78%). Eluent: ethyl acetate/petroleum ether (1/40), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H), 4.38 (t, J = 6.0 Hz, 2H), 3.27 (t, J = 6.8 Hz, 2H), 2.26 (p, J = 6.4 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 165.6, 131.7, 131.1, 128.8, 128.2, 62.8, 32.4, 1.2 ppm. HRMS (FI-TOF) m/z: $[M]^+$ calcd for $C_{10}H_{10}BrIO_2$, 367.8910; found, 367.8903. IR (KBr): ν_{max} 2957, 1721, 1590, 1398, 1270, 1115, 1102, 849, 755 cm^{-1}.

3-Bromopropyl 4-Cyanobenzoate. Colorless oil (347 mg, 65%). Eluent: ethyl acetate/petroleum ether (1/8), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13−8.06 (m, 2H), 8.13−8.06 (m, 2H), 4.47 (t, J = 6.1 Hz, 2H), 3.51 (t, J = 6.5 Hz, 2H), 2.30 (p, J = 6.3 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$): δ 164.8, 133.8, 132.3, 130.1, 117.9, 116.5, 63.5, 31.6, 29.2 ppm. MS (EI): 130 (100), 167 (3.59). HRMS (FI-TOF) m/z: $[M]^+$ calcd for $C_{11}H_{10}NBrO_2$, 266.9889; found, 266.9888. IR (KBr): ν_{max} 2965, 2231, 1727, 1404, 1277, 1108, 1019, 861, 767 cm^{-1}.

3-Iodopropyl 4-Cyanobenzoate. Yellow oil (460 mg, 73%). Eluent: ethyl acetate/petroleum ether (1/8), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14−8.08 (m, 2H), 7.74−7.70 (m, 2H), 4.42 (t, J = 6.1 Hz, 2H), 3.27 (t, J = 6.8 Hz, 2H), 2.28 (p, J = 6.4 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 164.8, 133.8, 132.3, 130.1, 118.0, 116.6, 65.4, 32.2, 1.0 ppm. MS (EI): 130 (100), 315 (5.22). HRMS (FI-TOF) m/z: $[M]^+$ calcd for $C_{11}H_{10}NIO_2$, 314.9755; found, 314.9751. IR (KBr): ν_{max} 2956, 1709, 1461, 1282, 1259, 1095, 913, 748 cm^{-1}.

3-Bromopropyl 4-Iodobenzoate. Yellow oil (574 mg, 78%). Eluent: ethyl acetate/petroleum ether (1/30), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 8.0 Hz, 2H), 7.70 (d, J = 8.0 Hz, 2H), 4.43 (t, J = 6.0 Hz, 2H), 3.51 (t, J = 6.5 Hz, 2H), 2.29 (p, J = 6.1 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 165.8, 137.7, 131.0, 129.4, 100.9, 62.9, 31.7, 29.3 ppm. MS (DART): 368.9 $[M + H]^+$; HRMS (DART-Positive) m/z: $[M + H]^+$ calcd for $C_{10}H_{11}IBrO_2$, 368.8982; found, 368.8979. IR (KBr): ν_{max} 2962, 1722, 1586, 1420, 1268, 1116, 1008, 752 cm^{-1}.

3-Iodopropyl 4-Iodobenzoate. White solid (384 mg, 61%). mp 49.8 °C. Eluent: ethyl acetate/petroleum ether (1/30), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, J = 8.0 Hz, 2H), 7.71 (d, J = 8.0 Hz, 2H), 4.37 (t, J = 6.0 Hz, 2H), 3.27 (t, J = 6.8 Hz, 2H), 2.26 (p, J = 6.4 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 165.8, 137.8, 131.0, 129.4, 100.9, 64.8, 32.4, 1.2 ppm. MS (EI): 231 (100), 416 (3.24). HRMS (FI-TOF) m/z: $[M]^+$ calcd for $C_{10}H_{10}I_2O_2$, 415.8765; found, 415.8771. IR (KBr): ν_{max} 2956, 1720, 1586, 1393, 1268, 1115, 1007, 752 cm^{-1}.

3-Bromopropyl 5-Methylthiophene-2-carboxylate. Colorless oil (408 mg, 78%). Eluent: ethyl acetate/petroleum ether (1/30), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, J = 3.6 Hz, 1H), 6.74 (d, J = 3.5 Hz, 1H), 4.38 (t, J = 6.0 Hz, 2H), 3.50 (t, J = 6.5 Hz, 2H), 2.49 (s, 3H), 2.25 (p, J = 6.2 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 161.9, 148.2, 140.0, 130.7, 126.4, 62.5, 31.8, 29.4, 15.7 ppm. MS (EI): 125 (100), 262 (13.46). HRMS (EI-TOF) m/z: $[M]^+$ calcd for $C_9H_{11}BrSO_2$, 261.9663; found, 261.9653. IR (KBr): ν_{max} 3400, 2926, 2854, 2117, 1711, 1541, 1462, 1383, 1284, 1165 cm^{-1}.

3-Iodopropyl 5-Methylthiophene-2-carboxylate. Colorless oil (483 mg, 78%). Eluent: ethyl acetate/petroleum ether (1/30), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, J = 3.6 Hz, 1H), 6.74 (d, J = 3.5 Hz, 1H), 4.31 (t, J = 6.0 Hz, 2H), 3.25 (t, J = 6.7 Hz, 2H), 2.49 (s, 3H), 2.22 (p, J = 6.4 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 161.9, 148.2, 134.0, 130.7, 126.4, 64.4, 32.5, 1.4 ppm. MS (EI): 125 (100), 310 (7.55). HRMS (EI-TOF) m/z: $[M]^+$ calcd for $C_9H_{11}ISO_2$, 309.9525; found, 309.9518. IR (KBr): ν_{max} 3095, 2932, 2877, 1618, 1580, 1427, 1351, 1180, 1027, 737 cm^{-1}.

https://dx.doi.org/10.1021/acs.joc.0c02783
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3-Bromopropyl 4-Chloro-5-ethyl-2-methyl-pyrazole-3-carboxylate. Colorless oil (419 mg, 68%). Eluent: ethyl acetate/petroleum ether (1/30), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.41 (t, J = 5.8 Hz, 2H), 4.03 (s, 3H), 3.54 (t, J = 6.4 Hz, 2H), 2.57 (q, J = 7.5 Hz, 2H), 2.24 (p, J = 6.1 Hz, 2H), 1.17 (t, J = 7.6 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 158.9, 150.3, 128.5, 113.0, 62.7, 40.5, 31.4, 29.4, 19.2, 12.7 ppm. MS (EI): 173 (100), 307 (81.42). HRMS (EI-TOF) m/z: [M]$^+$ calcd for $C_{10}H_{14}O_2N_2ClBr$, 307.9922; found, 307.9926. IR (KBr): ν_{max} 2972, 1721, 1474, 1273, 1123, 1031, 985, 770 cm^{-1}.

3-Iodopropyl 4-Chloro-5-ethyl-2-methyl-pyrazole-3-carboxylate. White solid (528 mg, 77%). mp 29 °C. Eluent: ethyl acetate/petroleum ether (1/30), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.38 (t, J = 5.8 Hz, 2H), 4.06 (s, 3H), 3.33 (t, J = 6.7 Hz, 2H), 2.61 (q, J = 6.3 Hz, 2H), 2.23 (p, J = 6.3 Hz, 2H), 1.20 (t, J = 7.6 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 158.9, 150.4, 128.6, 113.1, 64.6, 40.5, 32.0, 19.2, 12.7, 1.6 ppm. MS (EI): 171 (100), 356 (27.85). HRMS (EI-TOF) m/z: [M]$^+$ calcd for $C_{10}H_{14}N_2IClO_2$, 355.9789; found, 355.9798. IR (KBr): ν_{max} 2971, 1718, 1449, 1273, 1121, 1031, 983, 772 cm^{-1}.

3-Bromopropyl 1-(4-Methoxyphenyl)-cyclopropanecarboxylate. Colorless oil (555 mg, 89%). Eluent: ethyl acetate/petroleum ether (1/30), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 4.14 (t, J = 6.0 Hz, 2H), 3.79 (s, 3H), 3.27 (t, J = 6.5 Hz, 2H), 2.05 (p, J = 6.2 Hz, 2H), 1.56 (q, J = 3.8 Hz, 2H), 1.16 (q, J = 3.8 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 174.6, 158.6, 131.4, 131.4, 113.5, 62.5, 55.2, 31.6, 29.4, 28.3, 16.8 ppm. MS (EI): 191 (100), 312 (20.87). HRMS (EI-TOF) m/z: [M]$^+$ calcd for $C_{14}H_{17}BrO_3$, 312.0361; found, 312.0365. IR (KBr): ν_{max} 3006, 2957, 2836, 2117, 1679, 1581, 1464, 1384, 1293, 1166 cm^{-1}.

3-Iodopropyl 1-(4-Methoxyphenyl)-cyclopropanecarboxylate. Yellow oil (560 mg, 78%). Eluent: ethyl acetate/petroleum ether (1/30), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 4.06 (t, J = 5.9 Hz, 2H), 3.78 (s, 3H), 3.02 (t, J = 6.8 Hz, 2H), 2.00 (p, J = 6.5 Hz, 2H), 1.56 (q, J = 3.6 Hz, 2H), 1.15 (q, J = 3.6 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 174.6, 158.6, 131.5, 131.5, 113.5, 64.4, 55.3, 32.1, 28.3, 16.8, 1.6 ppm. MS (EI): 191 (100), 360 (81.39). HRMS (EI-TOF) m/z: [M]$^+$ calcd for $C_{14}H_{17}IO_3$, 360.0222; found, 360.0216. IR (KBr): ν_{max} 3419, 3005, 2956, 2834, 1720, 1612, 1516, 1464, 1336, 1246 cm^{-1}.

3-Bromopropyl 4-(Dipropylsulfamoyl)benzoate. Colorless oil (567 mg, 70%). Eluent: ethyl acetate/petroleum ether (1/4), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, J = 8.5 Hz, 2H), 7.84 (d, J = 8.5 Hz, 2H), 4.46 (t, J = 6.0 Hz, 2H), 3.51 (t, J = 6.5 Hz, 2H), 3.06 (t, J = 7.6 Hz, 4H), 2.30 (p, J = 6.2 Hz, 2H), 1.50 (h, J = 7.4 Hz, 4H), 0.82 (t, J = 7.4 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 160.2, 139.6, 128.5, 125.4, 122.2, 58.5, 45.1, 26.8, 24.5, 17.1, 6.2 ppm. MS (EI): 405.8 (100). HRMS (EI-TOF) m/z: [M]$^+$ calcd for $C_{16}H_{25}BrNSO_4$, 406.0682; found, 406.0679. IR (KBr): ν_{max} 2966, 2935, 2875, 1467, 1217, 1088, 994, 869, 778, 603 cm^{-1}.

3-Iodopropyl 4-(Dipropylsulfamoyl)benzoate. Colorless oil (661 mg, 73%). Eluent: ethyl acetate/petroleum ether (1/4), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, J = 8.3 Hz, 2H), 7.85 (d, J = 8.3 Hz, 2H), 4.42 (t, J = 6.1 Hz, 2H), 3.28 (t, J = 6.8 Hz, 2H), 3.07 (dd, J = 8.5, 6.8 Hz, 4H), 2.28 (p, J = 6.2 Hz, 2H), 1.52 (h, J = 7.4 Hz, 4H), 0.84 (t, J = 7.4 Hz, 6H); ^{13}C{^{1}H}NMR (101 MHz, $CDCl_3$): δ 165.0, 144.4, 133.2, 130.2, 127.0, 65.2, 49.9, 32.3, 21.9, 11.2, 1.0 ppm. MS (EI): 424 (100), 454 (1.57). HRMS (EI-TOF) m/z: [M]$^+$ calcd for $C_{16}H_{24}INSO_4$, 453.0471; found, 453.0481. IR (KBr): ν_{max} 3426, 2965, 2874, 1723, 1599, 1574, 1466, 1399, 1272, 1105 cm^{-1}.

3-Bromopropyl (2*S*)-2-(6-Methoxy-2-naphthyl)propanoate. Colorless oil (504 mg, 72%). Eluent: ethyl acetate/petroleum ether (1/20), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74−7.63 (m, 3H), 7.39 (dd, J = 8.5, 1.8 Hz, 1H), 7.17−7.09 (m, 2H), 4.27−4.15 (m, 2H), 3.90 (s, 3H), 3.86 (q, J = 7.2 Hz, 1H), 3.28 (td, J = 6.6, 1.9 Hz, 2H), 2.08 (p, J = 6.3 Hz, 2H), 1.58 (d, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 174.5, 157.7, 135.6, 133.7, 129.3, 128.9, 127.2, 126.1, 125.9, 119.1, 105.6, 62.4, 55.3, 45.4, 31.6, 29.4, 18.5 ppm. MS (EI): 185 (100), 350 (12.22). HRMS (EI-TOF) m/z: [M]$^+$ calcd for $C_{17}H_{19}BrO_3$, 350.0518; found, 350.0515. IR (KBr): ν_{max} 3429, 3000, 2971, 1720, 1604, 1502, 1483, 1247, 1160, 858 cm^{-1}.

3-Iodopropyl (2*S*)-2-(6-Methoxy-2-naphthyl)propanoate. White solid (485 mg, 61%). mp 56 °C. Eluent: ethyl acetate/petroleum ether (1/20), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, J = 8.6 Hz, 2H), 7.64 (s, 1H), 7.37 (d, J = 8.5 Hz, 1H), 7.15−7.08 (m, 2H), 4.13 (dq, J = 11.0, 5.4 Hz, 2H), 3.90 (s, 3H), 3.84 (q, J = 7.1 Hz, 1H), 3.03 (td, J = 6.8, 2.1 Hz, 2H), 2.04 (p, J = 6.5 Hz, 2H), 1.57 (d, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 174.5, 157.7, 135.6, 133.7, 129.3, 128.9, 127.2, 126.1, 125.9, 119.0, 105.6, 64.3, 55.3, 45. 4, 32. 2, 18.4, 1.4 ppm. MS (EI): 185 (100), 398 (36.67). HRMS (EI-TOF) m/z: [M]$^+$ calcd for $C_{17}H_{19}IO_3$, 398.0379; found, 398.0380. IR (KBr): ν_{max} 3436, 2978, 1731, 1631, 1459, 1417, 1324, 1271, 1121, 1029 cm^{-1}.

3-Bromopropyl 2-(5*H*-Chromeno[2,3-*b*]pyridin-7-yl)-propanoate. Yellow oil (360 mg, 48%). Eluent: ethyl acetate/petroleum ether (1/3), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, J = 3.7 Hz, 1H), 7.48 (d, J = 7.3 Hz, 1H), 7.13−7.02 (m, 3H), 6.97 (dd, J = 7.3, 4.8 Hz, 1H), 4.21−4.10 (m, 2H), 4.04 (s, 2H), 3.64 (q, J = 7.2 Hz, 1H), 3.27 (tq, J = 6.4, 3.6 Hz, 2H), 2.06 (p, J = 6.2 Hz, 2H), 1.44 (d, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 174.3, 158.4, 150.8, 146.6, 138.4, 135.8, 127.4, 127.2, 119.8, 119.7, 117.3, 115.3, 62.4, 44.8, 31.5, 29.3, 28.1, 18.5 ppm. MS (DART): 376.1 [M + H]$^+$; HRMS (DART-Positive) m/z: [M + H]$^+$ calcd for $C_{18}H_{19}NBrO_3$, 376.0543; found, 376.0538. IR (KBr): ν_{max} 2968, 1733, 1666, 1512, 1340, 1106, 979, 727 cm^{-1}.

General Procedure for Copper-Mediated Difluoromethylation of Alkyl Iodides or Tosylates. In an argon-filled glovebox, an oven-dried 25 mL Schlenk tube with the Teflon-coated stirrer bar was charged with copper iodide (86 mg, 0.45 mmol), cesium fluoride (205 mg, 1.35 mmol), and difluoromethyltrimethylsilane (169 mg, 1.35 mmol) in DMF (3.0 mL). The suspension was stirred at room temperature for 6 h before the alkyl iodide (0.3 mmol) or alkyl tosylate (0.3 mmol) was added. The mixture was then stirred at 40 °C in an oil bath for 6 h. The solution was diluted with Et_2O (20.0 mL), filtered through a short plug of silica gel, and washed with Et_2O (20.0 mL). The resulting organic solution was washed with saturated aqueous NH_4Cl solution (20.0 mL), water (20.0 mL), and brine (20.0 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel.

General Procedure for a Pd/Cu Co-catalyzed Difluoromethylation of Alkyl Bromides. In an argon-filled glovebox, an oven-dried 25 mL Schlenk tube with the Teflon-coated stirrer bar was charged with alkyl bromide (0.3 mmol), Pd(dba)$_2$ (17 mg, 0.030 mmol), DPPF (17 mg, 0.031 mmol), copper iodide (57 mg, 0.30 mmol), cesium fluoride (182 mg, 1.19 mmol), and difluoromethyltrimethylsilane (150 mg, 1.20 mmol) in DMF (3.0 mL). The mixture was stirred at 50 °C in an oil bath for 6 h. The solution was diluted with Et_2O (20.0 mL), filtered through a short plug of silica gel, and washed with Et_2O (20.0 mL). The resulting organic solution was washed with saturated aqueous NH_4Cl solution (20.0 mL), water (20.0 mL), and brine (20.0 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel.

(5,5-Difluoropentyl)benzene (2a). Colorless oil (X = I, 42 mg, 76%; X = Br, 55 mg, quant.; X = OTs, 25 mg, 45%). Eluent: petroleum ether, R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33−7.13 (m, 5H), 5.78 (tt, J = 56.9, 4.5 Hz, 1H), 2.63 (t, J = 7.6 Hz, 2H), 1.85 (ttd, J = 17.6, 8.0, 4.6 Hz, 2H), 1.68 (dt, J = 15.5, 7.6 Hz, 2H), 1.50 (dd, J = 16.7, 9.2 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −115.76 (dt, J = 56.9, 17.6 Hz); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 142.0, 128.4, 125.9, 117.4 (t, ^1J(C, F) = 239.3 Hz), 35.7, 34.0 (t, ^2J(C, F) = 20.4 Hz), 30.9, 21.8 (t, ^3J(C, F) = 5.3 Hz) ppm. The physical and spectral data were consistent with those previously reported.[29]

1-(4,4-Difluorobutyl)-4-methoxybenzene (2b). Colorless oil (X = I, 46 mg, 76%; X = Br, 55 mg, 92%). Eluent: ethyl acetate/petroleum ether (1/50), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (d, J = 8.5 Hz, 2H), 6.85 (d, J = 8.5 Hz, 2H), 5.80 (tt, J = 56.8, 4.2 Hz, 1H), 3.80 (s, 2H), 2.63 (t, J = 7.2 Hz, 2H), 1.92−1.67 (m,

https://dx.doi.org/10.1021/acs.joc.0c02783
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4H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −115.75 (dt, J = 56.8, 17.1 Hz); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 158.1, 133.4, 129.4, 117.4 (t, ^1J(C, F) = 239.4 Hz), 114.0, 55.4, 34.3, 33.6 (t, ^2J(C, F) = 20.8 Hz), 24.1 (t, ^3J(C, F) = 5.0 Hz) ppm. The physical and spectral data were consistent with those previously reported.[30]

1-(4,4-Difluorobutyl)-4-fluorobenzene (2c). Colorless oil (X = I, 31 mg, 56%; X = Br, 52 mg, 93%). Eluent: petroleum ether, R_f = 0.6. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (dd, J = 8.7, 5.4 Hz, 2H), 6.98 (t, J = 8.8 Hz, 2H), 5.81 (tt, J = 56.8, 4.1 Hz, 1H), 2.65 (t, J = 7.3 Hz, 2H), 1.91−1.70 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −115.9 (dt, J = 56.8, 17.1 Hz, 2 F), −117.4 (ddd, J = 14.1, 8.8, 5.4 Hz, 1 F); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 161.4 (d, ^1J(C, F) = 244.1 Hz), 137.0 (d, ^4J(C, F) = 2.7 Hz), 129.7 (d, ^3J(C, F) = 8.0 Hz), 117.2 (t, ^1J(C, F) = 239.3 Hz), 115.2 (d, ^2J(C, F) = 21.1 Hz), 34.3, 33.4 (t, ^2J(C, F) = 21.1 Hz), 23.8 (t, ^3J(C, F) = 4.5 Hz) ppm. MS (EI): 109 (100), 188 (30.79). HRMS (EI-TOF) m/z: [M]$^+$ calcd for $C_{10}H_{11}F_3$, 188.0807; found, 188.0811. IR (KBr): ν_{max} 2957, 2865, 2837, 1613, 1584, 1442, 1301, 1178, 1004, 832 cm^{-1}.

Methyl 4-(4,4-Difluorobutyl)benzoate (2d). Yellow oil (X = I, 44 mg, 65%; X = Br, 54 mg, 79%). Eluent: ethyl acetate/petroleum ether (1/30), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, J = 8.3 Hz, 2H), 7.24 (d, J = 8.3 Hz, 2H), 5.80 (tt, J = 56.6, 3.8 Hz, 1H), 3.89 (s, 3H), 2.72 (t, J = 7.2 Hz, 2H), 1.91−1.73 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −115.96 (dt, J = 56.6, 17.0 Hz); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 167.1, 146.8, 129.9, 128.5, 128.3, 117.2 (t, ^1J(C, F) = 239.0 Hz), 52.1, 35.2, 33.5 (t, ^2J(C, F) = 21.0 Hz), 23.4 (t, ^3J(C, F) = 5.4 Hz) ppm. MS (EI): 91 (100), 228 (16.64). HRMS (EI-TOF) m/z: [M]$^+$ calcd for $C_{12}H_{14}O_2F_2$, 228.0962; found, 228.0966. IR (KBr): ν_{max} 2954, 1720, 1610, 1436, 1282, 1180, 1112, 1004, 975, 764 cm^{-1}.

(4,4-Difluorobutoxy)benzene (2e). Colorless oil (X = I, 45 mg, 80%; X = Br, 51 mg, 92%). Eluent: ethyl acetate/petroleum ether (1/50), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (dd, J = 7.4, 2.0 Hz, 2H), 6.99−6.83 (m, 3H), 5.92 (tt, J = 56.8, 4.3 Hz, 1H), 4.00 (t, J = 5.9 Hz, 2H), 2.13−1.90 (m, 4H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −116.16 (dt, J = 56.8, 17.4 Hz); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 158.7, 129.5, 120.9, 117.1 (t, ^1J(C, F) = 238.8 Hz), 114.5, 66.7, 31.1 (t, ^2J(C, F) = 21.3 Hz), 22.1 (t, ^3J(C, F) = 5.5 Hz) ppm. The physical and spectral data were consistent with those previously reported.[17]

1-(4,4-Difluorobutoxy)-4-nitrobenzene (2f). Brown oil (X = I, 33 mg, 48%; X = Br, 53 mg, 77%). Eluent: ethyl acetate/petroleum ether (1/6), R_f = 0.3. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, J = 9.2 Hz, 2H), 6.95 (d, J = 9.2 Hz, 2H), 5.98 (tt, J = 56.9, 4.0 Hz 1H), 4.12 (t, J = 5.7 Hz, 2H), 2.16−1.96 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −115.66 (dt, J = 56.9, 17.7 Hz); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 163.7, 141.6, 126.0, 114.4 (t, ^1J(C, F) = 239.3 Hz), 114.4, 67.7, 30.8 (t, ^2J(C, F) = 21.9 Hz), 21.8 (t, ^3J(C, F) = 5.3 Hz) ppm. MS (DART): 249.1 [M + NH$_4$]$^+$; HRMS (DART-Positive) m/z: [M + H]$^+$ calcd for $C_{10}H_{12}O_3NF_2$, 232.0780; found, 232.0779. IR (KBr): ν_{max} 2970, 1608, 1343, 1263, 1111, 989, 845, 753 cm^{-1}.

2-(4-(4,4-Difluorobutoxy)phenyl)-1,3-dioxolane (2g). Yellow oil (X = I, 40 mg, 52%; X = Br, 71 mg, 92%). Eluent: ethyl acetate/petroleum ether (1/8), R_f = 0.3. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (dd, J = 6.8, 1.8 Hz, 2H), 6.87 (dd, J = 6.8, 1.8 Hz, 2H), 5.94 (tt, J = 56.7, 4.0 Hz, 1H), 5.74 (s, 1H), 4.16−3.95 (m, 6H), 2.10−1.88 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −116.19 (dt, J = 56.7, 17.4 Hz); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 159.5, 130.2, 128.0, 117.1 (t, ^1J(C, F) = 239.4 Hz), 114.3, 103.7, 66.8, 65.3, 31.0 (t, ^2J(C, F) = 21.4 Hz), 22.0 (t, ^3J(C, F) = 5.7 Hz) ppm. MS (DART): 259.1 [M + H]$^+$; HRMS (DART-Positive) m/z: [M + H]$^+$ calcd for $C_{13}H_{17}O_3F_2$, 259.1140; found, 259.1139. IR (KBr): ν_{max} 2362, 1685, 1603, 1509, 1257, 1162, 1028, 820 cm^{-1}.

4,4-Difluorobutyl 2-Naphthoate (2h). Yellow oil (X = I, 55 mg, 70%; X = Br, 71 mg, 90%). Eluent: ethyl acetate/petroleum ether (1/20), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (s, 1H), 8.04 (dd, J = 8.6, 1.5 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 8.8 Hz, 2H), 7.61−7.51 (m, 2H), 5.95 (tt, J = 56.7, 4.0 Hz, 1H), 4.43 (t, J = 6.0 Hz, 2H), 2.13−1.91 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −116.26 (dt, J = 56.8, 17.2 Hz); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 166.6, 135.6, 132.5, 131.1, 129.4, 128.3, 127.8, 127.3, 126.7, 125.1, 116.8 (t, ^1J(C, F) = 239.3 Hz), 64.0, 31.0(t, ^2J(C, F) = 21.9 Hz), 21.7 (t, ^3J(C, F) = 5.3 Hz) ppm. MS (DART): 282.1 [M + NH$_4$]$^+$; HRMS (DART-Positive) m/z: [M + H]$^+$ calcd for $C_{15}H_{15}O_2F_2$, 265.1035; found, 265.1033. IR (KBr): ν_{max} 2970, 1716, 1468, 1286, 1228, 1197, 1058, 983, 779 cm^{-1}.

4,4-Difluorobutyl 4-Chlorobenzoate (2i). Yellow oil (X = I, 57 mg, 62%; X = Br, 74 mg, quant.). Eluent: ethyl acetate/petroleum ether (1/30), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, J = 8.7 Hz, 2H), 7.40 (d, J = 8.7 Hz, 2H), 5.91 (tt, J = 56.7, 4.1 Hz, 1H), 4.35 (t, J = 6.0 Hz, 2H), 2.06−1.88 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −116.35 (dt, J = 56.7, 17.2 Hz); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 165.6, 139.6, 131.0, 128.8, 128.5, 116.7 (t, ^1J(C, F) = 239.3 Hz), 64.13, 30.9 (t, ^2J(C, F) = 21.9 Hz), 21.5 (t, ^3J(C, F) = 6.0 Hz) ppm. MS (DART): 266.1 [M + NH$_4$]$^+$; HRMS (DART-Positive) m/z: [M + NH$_4$]$^+$ calcd for $C_{11}H_{15}F_2NClO_2$, 266.0754; found, 266.0753. IR (KBr): ν_{max} 2971, 1723, 1595, 1403, 1274, 1120, 1016, 851, 760 cm^{-1}.

4,4-Difluorobutyl 4-Bromobenzoate (2j). Yellow oil (X = I, 51 mg, 58%; X = Br, 24 mg, 28%). Eluent: ethyl acetate/petroleum ether (1/30), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, J = 8.6 Hz, 2H), 7.57 (d, J = 8.6 Hz, 2H), 5.91 (tt, J = 56.7, 4.1 Hz, 1H), 4.35 (t, J = 6.0 Hz, 2H), 2.07−1.88 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −116.35 (dt, J = 56.7, 17.2 Hz); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 165.7, 131.8, 131.0, 128.9, 128.2, 116.7 (t, ^1J(C, F) = 240.1 Hz), 64.16, 30.0 (t, ^2J(C, F) = 21.1 Hz), 21.5 (t, ^3J(C, F) = 6.0 Hz) ppm. MS (DART): 312.0 [M + NH$_4$]$^+$; HRMS (DART-Positive) m/z: [M + H]$^+$ calcd for $C_{11}H_{12}F_2BrO_2$, 292.9983; found, 292.9982. IR (KBr): ν_{max} 2970, 1722, 1591, 1398, 1273, 1119, 849, 757 cm^{-1}.

4,4-Difluorobutyl 4-Cyanobenzoate (2k). Yellow oil (X = I, 28 mg, 39%; X = Br, 54 mg, 75%). Eluent: ethyl acetate/petroleum ether (1/7), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, J = 8.6 Hz, 2H), 7.74 (d, J = 8.6 Hz, 2H), 5.89 (tt, J = 56.0, 3.6 Hz, 1H), 4.39 (t, J = 6.0 Hz, 2H), 2.08−1.91 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −116.41 (dt, J = 56.5, 17.2 Hz); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 164.8, 133.8, 132.3, 130.1, 118.2, 117.9, 116.6 (t, ^1J(C, F) = 239.3 Hz), 64.7, 30.8 (t, ^2J(C, F) = 21.9 Hz), 21.4 (t, ^3J(C, F) = 5.3 Hz) ppm. MS (DART): 257.1 [M + NH$_4$]$^+$; HRMS (DART-Positive) m/z: [M + H]$^+$ calcd for $C_{12}H_{12}F_2NO_2$, 240.0831; found, 240.0830. IR (KBr): ν_{max} 2971, 2232, 1725, 1277, 1178, 1057, 768, 692 cm^{-1}.

4,4-Difluorobutyl 4-(Trifluoromethyl)benzoate (2l). Yellow oil (X = I, 47 mg, 56%; X = Br, 73 mg, 87%). Eluent: ethyl acetate/petroleum ether (1/30), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, J = 8.2 Hz, 2H), 7.70 (d, J = 8.2 Hz, 2H), 5.89 (tt, J = 56.4, 3.8 Hz, 1H), 4.39 (t, J = 6.0 Hz, 2H), 2.09−1.85 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −63.20 (s, 3 F), −116.41 (dt, J = 56.4, 17.1 Hz, 2 F); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 165.2, 134.5 (q, ^2J(C, F) = 49.1 Hz), 133.3, 130.0, 125.5, 123.6 (q, ^1J(C, F) = 272.8 Hz), 116.6 (t, ^1J(C, F) = 239.3 Hz), 64.4, 30.9 (t, ^2J(C, F) = 21.9 Hz), 21.5 (t, ^3J(C, F) = 6.0 Hz) ppm. MS (DART): 300.1 [M + NH$_4$]$^+$; HRMS (DART-Positive) m/z: [M + NH$_4$]$^+$ calcd for $C_{12}H_{15}F_5NO_2$, 300.1017; found, 300.1016. IR (KBr): ν_{max} 2970, 1727, 1413, 1327, 1277, 1128, 1018, 863, 776 cm^{-1}.

4,4-Difluorobutyl 4-(Difluoromethyl)benzoate (2m). Colorless oil (X = I, 46 mg, 58%; X = Br, 17 mg, 22%). Eluent: ethyl acetate/petroleum ether (1/30), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, J = 8.1 Hz, 2H), 7.58 (d, J = 8.1 Hz, 2H), 6.68 (t, J = 56.1 Hz, 1H), 5.92 (tt, J = 56.6, 4.0 Hz, 1H), 4.38 (t, J = 6.0 Hz, 2H), 2.10−1.90 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −112.33 (d, J = 56.1 Hz, 2 F), −116.37 (dt, J = 56.6, 17.2 Hz, 2 F); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 165.6, 138.6 (t, ^2J(C, F) = 22.5 Hz), 132.2, 130.0, 125.7 (t, ^3J(C, F) = 6.0 Hz), 116.7 (t, ^1J(C, F) = 239.3 Hz), 114.0 (t, ^1J(C, F) = 239.3 Hz), 64.3, 30.9 (t, ^2J(C, F) = 21.9 Hz), 21.5 (t, ^3J(C, F) = 5.3 Hz) ppm. MS (DART): 282.1 [M + NH$_4$]$^+$; HRMS (DART-Positive) m/z: [M + H]$^+$ calcd for $C_{12}H_{13}F_4O_2$, 265.0846; found, 265.0845. IR (KBr): ν_{max} 2960, 1724, 1375, 1277, 1218, 1122, 766, 709 cm^{-1}.

4,4-Difluorobutyl Benzofuran-2-carboxylate (2n). Yellow oil (X = I, 58 mg, 76%; X = Br, 67 mg, 89%). Eluent: ethyl acetate/petroleum ether (1/30), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ

https://dx.doi.org/10.1021/acs.joc.0c02783
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7.72 (d, J = 7.9 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.57 (s, 1H), 7.53−7.49 (m, 1H), 7.34 (t, J = 7.5 Hz, 1H), 5.97 (tt, J = 56.6, 4.1 Hz, 1H), 4.46 (t, J = 6.1 Hz, 2H), 2.09−1.90 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −116.36 (dt, J = 56.6, 17.2 Hz); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 159.4, 155.8, 145.3, 127.8, 126.9, 123.9, 122.9, 116.7 (t, ^1J(C, F) = 239.3 Hz), 114.1, 112.4, 64.3, 30.9 (t, ^2J(C, F) = 21.9 Hz), 21.6 (t, ^3J(C, F) = 5.3 Hz) ppm. MS (EI): 162 (100), 254 (74.52). HRMS (EI-TOF) m/z: $[M]^+$ calcd for $C_{13}H_{12}F_2O_3$, 254.0755; found, 254.0759. IR (KBr): ν_{max} 2973, 1758, 1599, 1456, 1408, 1369, 1090, 978, 893, 762 cm^{-1}.

4,4-Difluorobutyl 5-Methylthiophene-2-carboxylate (2o). Yellow oil (X = I, 49 mg, 70%; X = Br, 59 mg, 85%). Eluent: ethyl acetate/petroleum ether (1/40), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, J = 3.7 Hz, 1H), 6.75 (dd, J = 3.7, 1.0 Hz, 1H), 5.87 (tt, J = 56.6, 4.1 Hz, 1H), 4.29 (t, J = 6.0 Hz, 2H), 2.50 (s, 3H), 2.05−1.82 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −116.29 (dt, J = 56.6, 17.2 Hz); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 162.1, 148.2, 134.0, 130.8, 126.4, 116.8 (t, ^1J(C, F) = 238.6 Hz), 63.8, 31.0 (t, ^2J(C, F) = 21.1 Hz), 21.6 (t, ^3J(C, F) = 5.3 Hz), 15.7 ppm. MS (EI): 125 (100), 234 (24.6). HRMS (EI-TOF) m/z: $[M]^+$ calcd for $C_{10}H_{12}F_2O_2S$, 234.0526; found, 234.0529. IR (KBr): ν_{max} 2970, 1708, 1461, 1407, 1340, 1217, 1018, 980, 815, 749 cm^{-1}.

4,4-Difluorobutyl 4-Chloro-3-ethyl-1-methyl-1*H*-pyrazole-5-carboxylate (2p). Yellow oil (X = I, 30 mg, 36%; X = Br, 61 mg, 72%). Eluent: ethyl acetate/petroleum ether (1/10), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.88 (tt, J = 56.4, 3.7 Hz, 1H), 4.36 (t, J = 6.0 Hz, 2H), 4.07 (s, 3H), 2.62 (q, J = 7.6 Hz, 2H), 2.29−1.77 (m, 4H), 1.21 (t, J = 7.6 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −116.52 (dt, J = 56.4, 17.3 Hz); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 159.09, 150.45, 128.67, 116.64 (t, ^1J(C, F) = 239.1 Hz), 113.11, 64.13, 40.52, 30.87 (t, ^2J(C, F) = 21.5 Hz), 21.31 (t, ^3J(C, F) = 5.6 Hz), 19.20, 12.71 ppm. MS (EI): 173 (100), 280 (85.58). HRMS (EI-TOF) m/z: $[M]^+$ calcd for $C_{11}H_{15}F_2O_2N_2Cl$, 280.0790; found, 280.0785. IR (KBr): ν_{max} 3417, 2974, 1720, 1475, 1450, 1276, 1123, 1092, 980, 955 cm^{-1}.

4,4-Difluorobutyl 1-(4-Methoxyphenyl)cyclopropane-1-carboxylate (2q). Yellow oil (X = I, 53 mg, 62%; X = Br, 70 mg, 82%). Eluent: ethyl acetate/petroleum ether (1/20), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 5.69 (tt, J = 56.7, 4.1 Hz, 1H), 4.06 (d, J = 5.6 Hz, 2H), 3.79 (s, 3H), 1.82−1.64 (m, 4H), 1.56 (d, J = 2.9 Hz, 2H), 1.16 (d, J = 2.9 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −116.27 (dt, J = 56.7, 16.8 Hz, 2 F); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 174.8, 158.7, 131.6, 131.5, 116.8 (t, ^1J(C, F) = 238.9 Hz), 113.6, 63.9, 55.3, 30.9 (t, ^2J(C, F) = 21.5 Hz), 28.3, 21.4 (t, ^3J(C, F) = 5.7 Hz), 16.8 ppm. MS (EI): 147 (100), 284 (66.12). HRMS (EI-TOF) m/z: $[M]^+$ calcd for $C_{15}H_{18}F_2O_3$, 284.1224; found, 284.1218. IR (KBr): ν_{max} 2962, 2838, 1720, 1613, 1517, 1293, 1247, 1169, 1092, 987 cm^{-1}.

1-(4,4-Difluorobutyl)-1*H*-indole (2r). Yellow oil (X = I, 33 mg, 52%; X = Br, 56 mg, 90%). Eluent: ethyl acetate/petroleum ether (1/15), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J = 7.8 Hz, 1H), 7.39 (d, J = 8.2 Hz, 1H), 7.26 (t, J = 7.5 Hz, 1H), 7.14 (t, J = 7.2 Hz, 1H), 7.11 (d, J = 3.0 Hz, 1H), 6.55 (t, J = 2.6 Hz, 1H), 5.79 (tt, J = 56.5, 4.1 Hz, 1H), 4.21 (t, J = 6.9 Hz, 2H), 2.04 (dt, J = 14.9, 7.1 Hz, 2H), 1.91−1.74 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −116.12 (dt, J = 56.5, 17.7 Hz); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 135.9, 128.8, 127.7, 121.8, 121.2, 119.6, 116.8 (t, ^1J(C, F) = 239.4 Hz), 109.3, 101.6, 45.6, 31.4 (t, ^2J(C, F) = 21.4 Hz), 22.9 (t, ^3J(C, F) = 5.0 Hz) ppm. MS (EI): 130 (100), 209 (74.19). HRMS (EI-TOF) m/z: $[M]^+$ calcd for $C_{12}H_{13}F_2N$, 209.1011; found, 209.1014. IR (KBr): ν_{max} 2968, 1512, 1484, 1464, 1403, 1317, 1122, 743 cm^{-1}.

9-(5,5-Difluoropentyl)-9*H*-carbazole (2s). White solid (X = I, 57 mg, 70%; X = Br, 78 mg, 95%). mp 71.6 °C. Eluent: ethyl acetate/petroleum ether (1/10), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, J = 7.8 Hz, 2H), 7.56−7.42 (m, 2H), 7.41−7.36 (m, 2H), 7.28−7.21 (m, 2H), 5.74 (tt, J = 56.7, 4.4 Hz, 1H), 4.32 (t, J = 7.1 Hz, 2H), 1.98−1.75 (m, 2H), 1.82 (tdt, J = 17.5, 8.2, 3.8 Hz, 2H), 1.59−1.49 (p, J = 7.8 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −116.04 (dt, J = 56.7, 17.5 Hz); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 140.3, 125.7, 122.9, 120.4, 118.9, 116.9 (t, ^1J(C, F) = 239.3 Hz), 108.5, 42.6, 33.8 (t, ^2J(C, F) = 21.1 Hz), 28.5, 20.0 (t, ^3J(C, F) = 5.3 Hz) ppm. MS (EI): 180 (100), 273 (39.14). HRMS (EI-TOF) m/z: $[M]^+$ calcd for $C_{17}H_{17}F_2N$, 273.1329; found, 273.1333. IR (KBr): ν_{max} 3051, 2962, 2865, 1594, 1350, 1215, 1185, 1071, 993, 888 cm^{-1}.

2-(4,4-Difluorobutyl)isoindoline-1,3-dione (2t). Yellow oil (X = I, 40 mg, 56%; X = Br, 61 mg, 85%). Eluent: ethyl acetate/petroleum ether (1/6), R_f = 0.3. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (dd, J = 5.4, 3.0 Hz, 2H), 7.71 (dd, J = 5.4, 3.0 Hz, 2H), 5.84 (tt, J = 56.4, 3.7 Hz, 1H), 3.73 (t, J = 6.6 Hz, 2H), 1.96−1.78 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −116.24 (dt, J = 56.4, 16.9 Hz); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 168.3, 134.1, 132.0, 123.3, 116.6 (t, ^1J(C, F) = 239.3 Hz), 37.1, 31.6 (t, ^2J(C, F) = 21.1 Hz), 21.4 (t, ^3J(C, F) = 5.3 Hz) ppm. The physical and spectral data were consistent with those previously reported.[31]

***N*-Allyl-*N*-(4,4-difluorobutyl)-4-methylbenzenesulfonamide (2u).** Yellow oil (X = I, 43 mg, 48%; X = Br, 68 mg, 75%). Eluent: ethyl acetate/petroleum ether (1/4), R_f = 0.3. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, J = 8.3 Hz, 2H), 7.28 (d, J = 8.3 Hz, 2H), 5.81 (tt, J = 56.7, 4.2 Hz, 1H), 5.59 (ddt, J = 16.7, 10.0, 6.5 Hz, 1H), 5.19−5.09 (m, 2H), 3.75 (d, J = 6.5 Hz, 2H), 3.13 (t, J = 7.1 Hz, 2H), 2.40 (s, 3H), 1.91−1.75 (m, 2H), 1.73−1.62 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −116.22 (dt, J = 56.7, 17.7 Hz); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 143.5, 136.6, 133.0, 129.8, 127.1, 119.2, 115.9 (t, ^1J(C, F) = 239.4 Hz), 50.9, 46.6, 31.1 (t, ^2J(C, F) = 21.4 Hz), 21.5, 20.9 (t, ^3J(C, F) = 5.7 Hz) ppm. MS (DART): 304.1 $[M + H]^+$; HRMS (DART-Positive) m/z: $[M + H]^+$ calcd for $C_{14}H_{20}O_2SNF_2$, 304.1177; found, 304.1175. IR (KBr): ν_{max} 2930, 2878, 1598, 1494, 1305, 1287, 1033, 935, 816, 706 cm^{-1}.

1,1-Difluorotridecane (2v). Colorless oil (X = I, 41 mg, 56%; X = Br, 61 mg, 91%). Eluent: petroleum ether, R_f = 0.9. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.79 (tt, J = 57.0, 4.5 Hz, 1H), 1.92−1.72 (m, 2H), 1.44 (dt, J = 14.9, 6.8 Hz, 2H), 1.26 (s, 13H), 0.88 (t, J = 6.6 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −120.98 (dt, J = 57.0, 17.6 Hz); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 116.1 (t, ^1J(C, F) = 239.9 Hz), 32.7 (t, ^2J(C, F) = 20.7 Hz), 30.6, 28.28, 28.22, 28.07, 27.99, 27.69, 21.32, 20.75 (t, ^3J(C, F) = 5.6 Hz), 12.7 ppm. The physical and spectral data were consistent with those previously reported.[32]

12,12-Difluorododec-1-ene (2w). Colorless oil (X = I, 34 mg, 56%; X = Br, 56 mg, 92%; X = OTs, 24 mg, 40%). Eluent: petroleum ether, R_f = 0.9. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.93−5.61 (m, 2H), 5.02−4.87 (m, 2H), 2.06−1.97 (q, J = 6.9 Hz, 1H), 1.88−1.71 (m, 1H), 1.46−1.23 (m, 14H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −115.78 (d, J = 57.1, 17.5 Hz); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 139.2, 117.5 (t, ^1J(C, F) = 238.7 Hz), 114.1, 34.1 (t, ^2J(C, F) = 20.6 Hz), 33.8, 29.41, 29.37, 29.35, 29.1, 29.0, 28.9, 22.1 (t, ^3J(C, F) = 5.5 Hz) ppm. The physical and spectral data were consistent with those previously reported.[8]

((4,4-Difluorobutoxy)methyl)benzene (2x). Colorless oil (X = I, 43 mg, 72%; X = Br, 52 mg, 87%; X = OTs, 29 mg, 48%). Eluent: ethyl acetate/petroleum ether (1/100), R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$): δ ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38−7.26 (m, 5H), 5.85 (tt, J = 56.9, 4.5 Hz, 1H), 4.50 (s, 2H), 3.51 (t, J = 6.1 Hz, 2H), 2.02−1.86 (m, 2H), 1.81−1.71 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −116.01 (dt, J = 56.9, 17.7 Hz); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 138. 3, 128.5, 127.7, 127.6, 117.3 (t, ^1J(C, F) = 239.4 Hz), 73.0, 69.2, 31.2 (t, ^2J(C, F) = 21.4 Hz), 22.5 (t, ^3J(C, F) = 5.6 Hz) ppm. MS (DART): 218.1 $[M + NH_4]^+$; HRMS (DART-Positive) m/z: $[M + H]^+$ calcd for $C_{11}H_{15}OF_2$, 201.1085; found, 201.1085. IR (KBr): ν_{max} 3064, 2969, 2879, 1716, 1600, 1587, 1473, 1207, 1034, 989 cm^{-1}.

((4,4-Difluoropropoxy)methyl)benzene (2y). Colorless oil (X = I, 11 mg, 20%; X = Br, 15 mg, 27%). Eluent: ethyl acetate/petroleum ether (1/100), R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$): δ ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41−7.27 (m, 5H), 6.01 (tt, J = 56.9, 4.8 Hz, 1H), 4.52 (s, 2H), 3.63 (t, J = 6.1 Hz, 2H), 2.14 (tq, J = 16.7, 6.0 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −117.87 (dt, J = 56.8, 16.5 Hz); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 137.8, 128.4, 127.8, 127.6, 115.9 (t, ^1J(C, F) = 239.4 Hz), 73.2, 64.0 (t, ^3J(C, F) = 7.1 Hz), 34.8 (t, ^2J(C, F) = 21.7 Hz) ppm. The physical and spectral data were consistent with those previously reported.[33]

https://dx.doi.org/10.1021/acs.joc.0c02783
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4,4-Difluorobutyl 4-(*N*,*N*-Dipropylsulfamoyl)benzoate (4). Yellow oil (X = I, 65 mg, 58%; X = Br, 81 mg, 72%). Eluent: ethyl acetate/petroleum ether (1/3), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, J = 8.3 Hz, 2H), 7.89−7.80 (d, J = 8.3 Hz, 2H), 5.91 (tt, J = 57.0, 4.0 Hz, 1H), 4.38 (t, J = 5.8 Hz, 2H), 3.07 (t, J = 7.6 Hz, 4H), 2.07−1.90 (m, 4H), 1.52 (h, J = 7.4 Hz, 4H), 0.84 (t, J = 7.4 Hz, 6H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −116.46 (dt, J = 56.5, 17.1 Hz); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 164.7, 143.9, 132.8, 129.8, 126.6, 116.2 (t, ^1J(C, F) = 239.4 Hz), 64.1, 49.5, 30.4 (t, ^2J(C, F) = 21.4 Hz), 21.5, 21.0 (t, ^3J(C, F) = 5.0 Hz), 10.7 ppm. MS (DART): 378 $[M + H]^+$; HRMS (Dart-Positive) m/z: $[M + H]^+$ calcd for $C_{17}H_{26}F_2O_4NS$, 378.1545; found, 378.1543. IR (KBr): ν_{max} 2968, 2936, 2877, 1724, 1468, 1400, 1343, 1159, 1054, 765 cm^{-1}.

4,4-Difluorobutyl (*S*)-2-(6-Methoxynaphthalen-2-yl)-propanoate (6). Yellow oil (X = I, 667 mg, 69%; X = Br, 840 mg, 87%). Eluent: ethyl acetate/petroleum ether (1/15), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, J = 8.8 Hz, 2H), 7.65 (s, 1H), 7.38 (dd, J = 8.5, 1.6 Hz, 1H), 7.16−7.08 (m, 2H), 5.71 (tt, J = 56.8, 3.9 Hz, 1H), 4.10 (t, J = 5.8 Hz, 2H), 3.90 (s, 3H), 3.84 (q, J = 7.1 Hz, 1H), 1.85−1.68 (m, 4H), 1.57 (d, J = 7.2 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −116.39 (dt, J = 56.8, 17.2 Hz, 2F); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 174.6, 157.7, 135.6, 133.8, 129.3, 128.9, 127.2, 126.1, 125.9, 119.1, 116.7 (t, ^1J(C, F) = 239.3 Hz), 105.6, 63.6, 55.3, 45.5, 30.7 (t, ^2J(C, F) = 21.9 Hz), 21.4 (t, ^3J(C, F) = 5.3 Hz), 18.4 ppm. MS (EI): 185 (100), 322 (34.12). HRMS (EI-TOF) m/z: $[M]^+$ calcd for $C_{18}H_{20}F_2O_3$, 322.1381; found, 322.1385. IR (KBr): ν_{max} 2973, 2938, 1633, 1606, 1485, 1392, 1231, 1178, 1061, 981 cm^{-1}.

4,4-Difluorobutyl 2-(5*H*-Chromeno[2,3-*b*]pyridin-7-yl)-propanoate (8). Yellow oil (X = I, 41 mg, 40%; X = Br, 67 mg, 65%). Eluent: ethyl acetate/petroleum ether (1/2), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, J = 3.7 Hz, 1H), 7.51 (d, J = 7.1 Hz, 1H), 7.17−7.04 (m, 3H), 7.01 (t, J = 7.1 Hz, 1H), 5.78 (tt, J = 56.4, 4.0 Hz, 1H), 4.15−4.02 (m, 4H), 3.66 (q, J = 7.1 Hz, 1H), 1.88−1.67 (m, 4H), 1.47 (d, J = 7.1 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ −118.93 (dt, J = 56.4, 16.9 Hz); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 174.4, 158.4, 150.8, 146.7, 138.4, 135.8, 127.4, 127.2, 119.8, 119.7, 117.4, 116.6 (t, ^1J(C, F) = 239.3 Hz), 115.3, 63.7, 44.8, 30.8 (t, ^2J(C, F) = 21.1 Hz), 28.1, 21.4 (t, ^3J(C, F) = 6.0 Hz), 18.4 ppm. MS (DART): 348.1 $[M + H]^+$; HRMS (DART-Positive) m/z: $[M + H]^+$ calcd for $C_{19}H_{20}F_2NO_3$, 348.1406; found, 348.1403. IR (KBr): ν_{max} 2970, 1733, 1666, 1473, 1418, 1328, 1127, 781 cm^{-1}.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02783.

^{1}H, ^{19}F, and ^{13}C NMR spectra of compounds, **2a−y** and **3−8**, and high-resolution mass spectrometry data of alkyl halides and compounds **2c−d**, **2f−s**, **2u**, **2x**, **4**, **6**, and **8** (PDF)

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors gratefully acknowledge financial support from the National Natural Science Foundation of China (21625206, 21632009, 21572258, and 21421002) and the Strategic Priority Research Program of the Chinese Academy of Sciences (XDB20000000).

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https://dx.doi.org/10.1021/acs.joc.0c02783
J. Org. Chem. 2021, 86, 2854−2865