JOC The Journal of Organic Chemistry Cite This: J. Org. Chem. XXXX, XXX, XXX−XXX

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pubs.acs.org/joc

Palladium-Catalyzed Difluoromethylation of Aryl Chlorides and Bromides with $TMSCF_2H$

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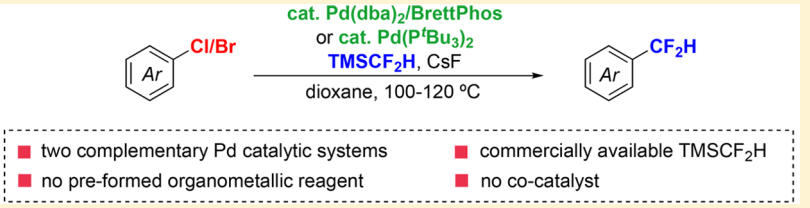
Supporting Information



ABSTRACT: A palladium-catalyzed cross-coupling of aryl chlorides/bromides with $TMSCF_2H$ is described. Two different catalysts, $Pd(dba)_2$/BrettPhos and $Pd(P^tBu_3)_2$, are demonstrated and provide a variety of difluoromethylated arenes in good yields.

The introduction of fluoroalkyl substituents onto aromatic rings can favorably impact the lipophilicity, binding selectivity, and metabolic stability of bioactive molecules.[1] As such, the development of mild and selective methods for the fluoroalkylation of arenes has been the subject of intense research.[2] A variety of transition-metal-mediated and -catalyzed methods have been developed to address the synthetic challenges associated with late-stage fluoroalkylation.[2,3] However, despite significant progress in this area, these investigations have overwhelmingly focused on trifluoromethylation reactions.[4] Analogous methods for (hetero)arene difluoromethylation have lagged behind, though not for lack of pharmaceutical/agrochemical relevance.[5] The difluoromethyl (CF_2H) substituent has attracted significant attention based on its unique ability to act as a lipophilic hydrogen bond donor.[6] CF_2H has thus been employed as a bioisostere for phenols, carbinols, thiols, and hydroxamic acids.[7]

The reaction of aryl halide electrophiles with difluoromethyl nucleophiles would serve as an enabling approach for the late-stage installation of CF_2H groups.[8−12] Several recent reports have demonstrated Cu-mediated and Cu-catalyzed methods for the coupling of aryl iodides with (difluoromethyl)-trimethylsilane ($TMSCF_2H$), (difluoromethyl)trialkylstannanes, and difluoromethylzinc reagents.[9] However, these copper systems currently remain limited to aryl iodide electrophiles. The Ni-catalyzed difluoromethylation of aryl halides and pseudohalides has been achieved using (dppf)Ni(COD) as the catalyst and $(DMPU)_2Zn(CF_2H)_2$ as the difluoromethyl source.[3c] Nickel-catalyzed difluoromethylations of aryl chlorides[8c] and aryl bromides[8d] utilizing a radical mechanism has also been reported using the gases chlorodifluoromethane and bromodifluoromethane as difluoromethyl sources. In 2014, Shen reported the first Pd-catalyzed difluoromethylation of aryl bromides and iodides with $TMSCF_2H$ using dppf as the supporting ligand (Figure 1a).[10]

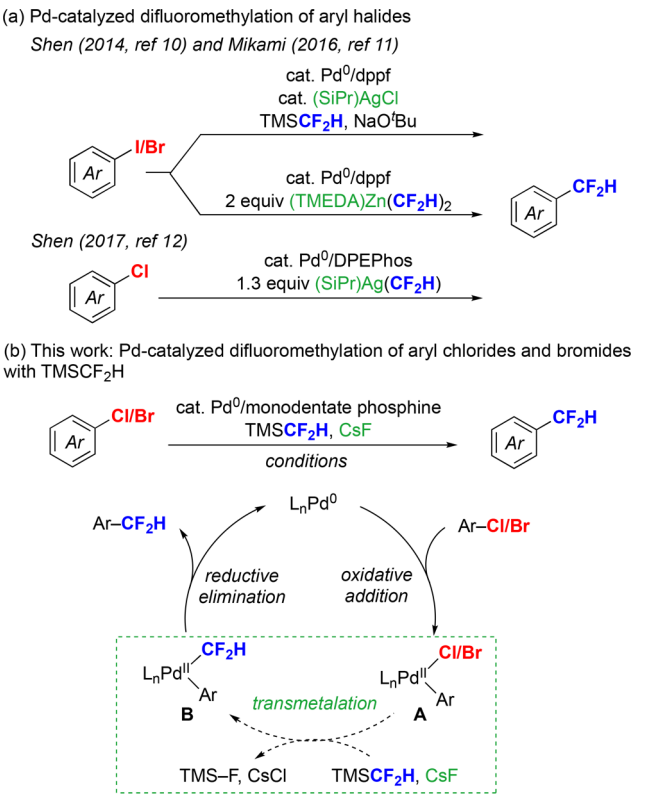


Figure 1. Pd-catalyzed difluoromethylation of aryl halides.

A major challenge identified in this report was inefficient transmetalation between $TMSCF_2H$ and the Pd catalyst under

Received: January 31, 2019

DOI: 10.1021/acs.joc.9b00324
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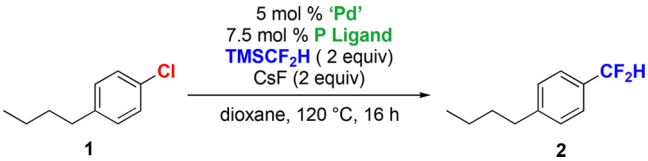
the reaction conditions. Shen resolved this issue by using an *N*-heterocyclic carbene-ligated silver complex as a cocatalyst to facilitate transmetalation. Subsequent work by Mikami demonstrated the Pd^0/dppf-catalyzed difluoromethylation of aryl iodides and bromides using the more reactive organozinc transmetalating reagent $(TMEDA)Zn(CF_2H)_2$ (Figure 1a).[11a] Most recently, Shen and co-workers reported that Pd^0/DPEPhos catalyzes the reaction of aryl chlorides with (NHC)-$Ag(CF_2H)$ (Figure 1a).[12,13]

We targeted a new difluoromethylation method that both obviates the need for stoichiometric organozinc/silver reagents and enables the use of readily available aryl chlorides and bromides as substrates. A recent report from our group on Cu-catalyzed difluoromethylation showed that the combination of commercially available $TMSCF_2H$ and CsF in dioxane at 120 °C offers a good balance between transmetalation reactivity and stability of the $TMSCF_2H$ reagent.[9f] In contrast, other activator/solvent combinations resulted in rapid decomposition of $TMSCF_2H$ or the prohibitively slow transfer of CF_2H to the Cu center.[9f] We reasoned that similar conditions might prove effective for the critical transmetalation step of a Pd-catalyzed difluoromethylation (Figure 1b). Additionally, we hypothesized that the use of electron-rich and sterically large monodentate ligands such as P^tBu_3 and/or dialkylbiaryl phosphines could facilitate the activation and subsequent difluoromethylation of aryl chloride/bromide substrates.[14] We report herein that this approach has enabled the identification of two new Pd catalyst systems for the difluoromethylation of aryl chlorides and bromides with $TMSCF_2H$ and CsF.

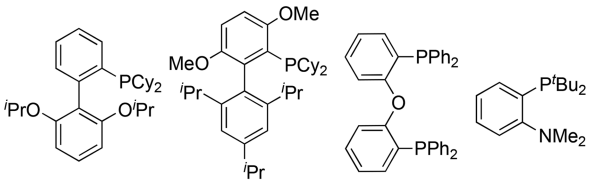
We first evaluated a series of phosphine ligands for the Pd-catalyzed reaction of aryl chloride **1** with $TMSCF_2H$/CsF to form **2** (Table 1). Consistent with our hypotheses, bulky electron-rich monophosphines such as BrettPhos and P^tBu_3 afforded moderate to good yields at 120 °C in dioxane (Table 1, entries 1−4). In contrast, bidentate ligands such as dppf and DPEPhos afforded low yields under analogous conditions (entries 6−7). Further optimization of the reaction temperature and Pd^0 source for these reactions uncovered two different catalyst systems with similar efficacy. The first (Method A) involves the use of 3 mol % of $Pd(dba)_2$ and 4.5 mol % of BrettPhos at 100 °C, which affords the difluoromethylated product **2** in 88% yield (entry 3). Comparable results were obtained with 5 mol % of $Pd(P^tBu_3)_2$ at 120 °C (Method B), which affords **2** in 78% yield (entry 8).

We next evaluated the scope of this transformation using Methods A and B (Scheme 1). Aryl chlorides and bromides bearing ether and amine substituents underwent difluoromethylation in good yields using both methods (see products **4**, **13**, **14**, and **17**). Mono-*ortho*-substituted aryl chlorides gave excellent yields under both sets of conditions (products **7** and **11**). However, di-*ortho*-substituted substrates performed significantly better under Method B (products **6** and **8**). Various heterocycle-containing substrates, including benzodioxole (**10**), dibenzofuran (**11** and **15**), benzodioxane (**18**), carbazole (**16**), and morpholine (**19** and **20**) derivatives, were compatible with both methods. The tricyclic aryl chloride containing drugs chlorprothixene and clomipramine were converted to difluoromethylated analogues **13** and **14** in moderate isolated yields. Finally, the difluoromethylation of a benzylic chloride proceeded under both Methods A and B to afford **12** in approximately 50% yield. The additional substrate scope including functionalities that are currently challenging under

Table 1. Optimization of Pd-Catalyzed Difluoromethylation of 1[a]



entry	Pd	ligand	yield of **2** (%)
1	$Pd(dba)_2$	RuPhos	35
2	$Pd(dba)_2$	BrettPhos	73
3[b]	**$Pd(dba)_2$**	**BrettPhos**	**88 (100 °C)**
4	$Pd(dba)_2$	P^tBu_3	36
5	$Pd(dba)_2$	**L1**[c]	56
6	$Pd(dba)_2$	DPEPhos[c]	trace
7	$Pd(dba)_2$	dppf[c]	3
8	**$Pd(P^tBu_3)_2$**	**-**	**78**
9	$Pd(P^tBu_3)_2$	-	41 (100 °C)



RuPhos BrettPhos DPEPhos **L1**

[a]General conditions: aryl chloride **1** (0.1 mmol, 1 equiv), Pd catalyst (0.05 equiv), ligand (0.075 equiv), $TMSCF_2H$ (2 equiv), CsF (2 equiv) in dioxane (0.3 mL) at 120 °C, 16 h. Yields are determined by ^{19}F NMR spectroscopy using (trifluoromethoxy)benzene as internal standard. [b]Catalyst loading of 3 mol % $Pd(dba)_2$ and 4.5 mol % BrettPhos were used. [c]0.010 equiv of ligand was used.

the optimized conditions is tabulated in the Supporting Information.

A final set of experiments was conducted to probe the mass balance in these transformations. 4-Chloroanisole **21** was treated with $TMSCF_2H$/CsF under Pd catalysis, and the crude reaction mixture was assayed by ^{19}F NMR spectroscopy and gas chromatography (Scheme 2). Under Method B, the difluoromethylated product **22** was formed in 81% yield along with three side products derived from methylation (**23**), protodechlorination (**24**), and homocoupling (**25**) of the aryl chloride. Conducting the reaction using Method A resulted in 79% yield of **22** along with just two byproducts: methylated compound **23** and protodechlorinated **24**. Notably, using Method A, but at higher temperature (120 °C), resulted in a significant decrease in the yield of **22** (to 68%) along with increased yields of both byproducts **23** and **24**.

The methylated product of this reaction (**22**) could be formed via the palladium-catalyzed reaction of the aryl chloride substrate with either $TMSCF_2H$ or TMSF (the product generated after transmetalation).[15] To distinguish these possibilities, we conducted the reaction of **21** with TMSF (formed *in situ* from a prestirred solution of TMSCl/CsF, 1:2, 2 equiv)[15] with each catalyst system. Product **22** was not detected with either catalyst. This result suggests that **22** derives from competing transfer of CH_3 versus CF_2H from the difluoromethylating reagent $TMSCF_2H$.[16]

DOI: 10.1021/acs.joc.9b00324
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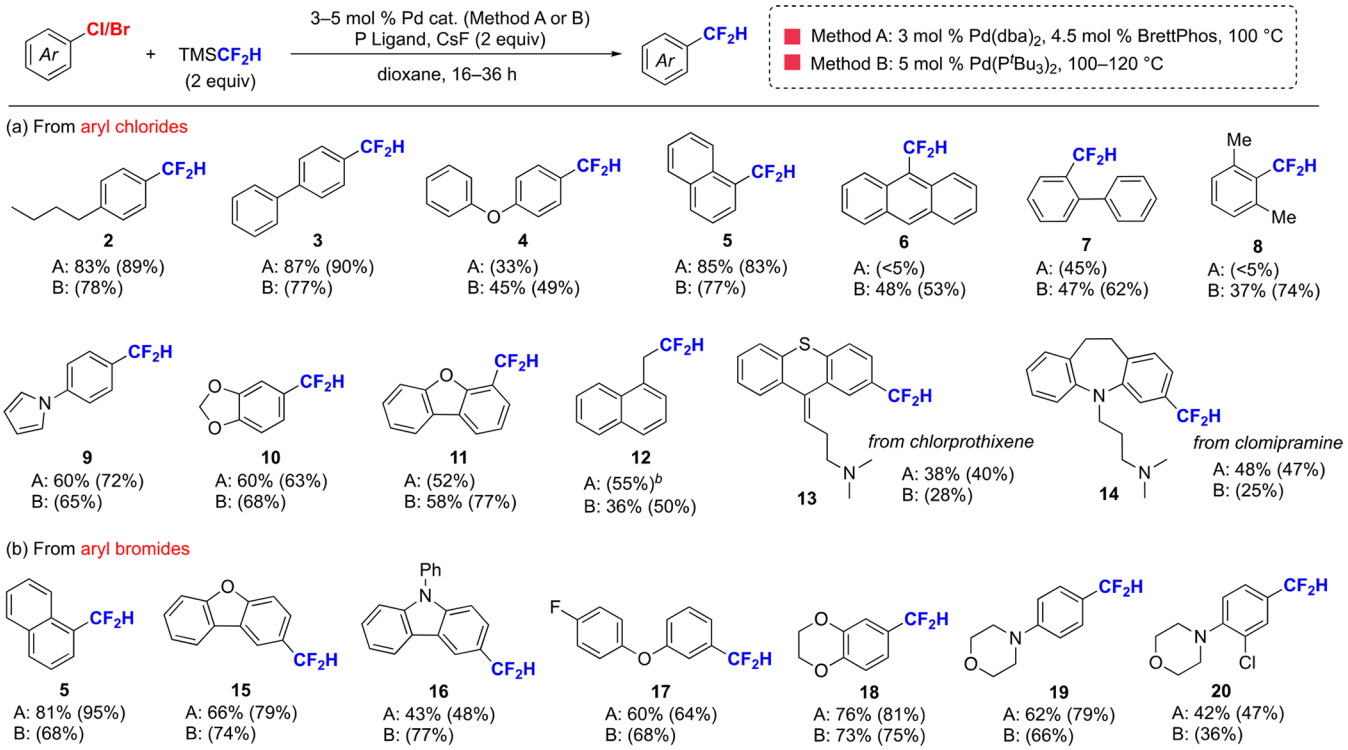
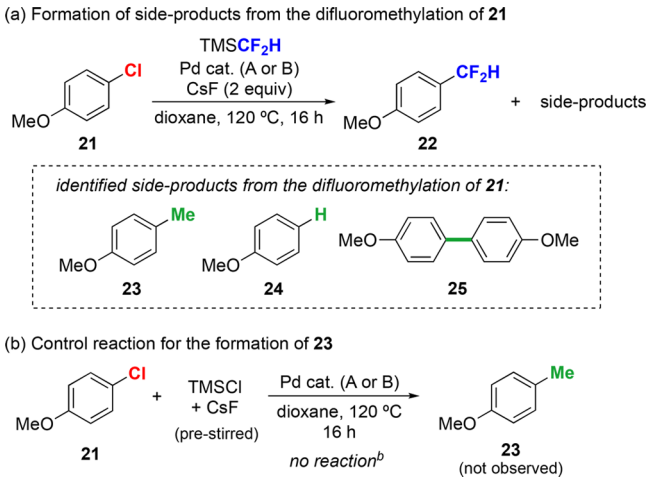
Scheme 1. Scope of Pd-Catalyzed Difluoromethylation of Aryl Chlorides and Bromides[a]



[a]General conditions: aryl chloride or bromide (0.5 mmol, 1 equiv), Pd catalyst (0.03−0.05 equiv), BrettPhos (for Method A, 0.075 equiv), $TMSCF_2H$ (2 equiv), CsF (2 equiv) in dioxane (1.5 mL) at 100−120 °C, 16−36 h (see the Experimental Section for details). Isolated yields. Yields in parentheses are based on ^{19}F NMR analysis from a 0.1 mmol scale reaction. [b]Catalyst loading of 5 mol % $Pd(dba)_2$ and 7.5 mol % BrettPhos at 120 °C.

Scheme 2. Analysis of Side-Product Formation from the Difluoromethylation of Aryl Chloride 21[a]



[a]General conditions: aryl chloride **21** (0.1 mmol, 1 equiv), Pd catalyst, $TMSCF_2H$ (2 equiv), CsF (2 equiv) in dioxane (0.3 mL), 120 °C, 16 h. Method A: $Pd(dba)_2$ (3 mol %), BrettPhos (4.5 mol %). Method B: $Pd(P^tBu_3)_2$ (5 mol %). Yields are determined by ^{19}F NMR spectroscopy and GC analysis using trifluoromethoxybenzene and neopentyl benzene as internal standards, respectively. [b]The unreacted aryl chloride **21** was observed together with 5% of protodechlorinated side-product **24**.

In conclusion, this Note demonstrates two new methods for the Pd-catalyzed difluoromethylation of aryl chlorides and bromides. The methods use electron-rich monophosphine ligands (BrettPhos and P^tBu_3) in combination with commercial $TMSCF_2H$ as the difluoromethyl source. They are compatible with aryl chloride and bromide substrates bearing both electron-donating and electron-withdrawing substituents, as well as with several heterocycles. We anticipate that this observation will aid in the future development of other reactions utilizing this reagent.

EXPERIMENTAL SECTION

General Information. All commercial reagents were used as received, unless stated otherwise. $Pd(P^tBu_3)_2$ was synthesized according to a literature procedure.[17] ^1H and ^{13}C NMR chemical shifts are reported in parts per million (ppm) with the residual solvent peak ($CHCl_3$, 7.26 ppm for ^1H NMR and 77.23 for ^{13}C NMR) as an internal reference. ^{19}F chemical shifts are reported in ppm and are referenced to the solvent lock. Multiplicities are reported as follows: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). ^{19}F NMR yields for catalytic difluoromethylation reactions were obtained using (trifluoromethoxy)benzene (−58.3 ppm) as the internal standard with a relaxation delay of 5 s. Difluoromethylated products **2**−**5**, **7**−**12**, **14**−**16**, **18**, and **19** have been previously reported and matched spectral data with the literature.

General Procedure A for the Difluoromethylation of Aryl Chlorides/Bromides. In a glovebox, the aryl halide (0.5 mmol, 1 equiv), $Pd(dba)_2$ (8.6 mg, 0.015 mmol), BrettPhos (12 mg, 0.0225 mmol), CsF (152 mg, 1.0 mmol, 2 equiv), dioxane (1.5 mL, 0.33 M), and $TMSCF_2H$ (136 μL, 1.0 mmol, 2 equiv) were combined in a 4 mL vial. The vial was sealed with a Teflon-lined screw cap and brought out of the glovebox. The reaction was allowed to stir vigorously at 100 °C for 16 h (aryl bromides were allowed to react for 2 days). The reaction mixture was allowed to cool to room temperature, filtered through a plug of Celite that was then washed with Et_2O or DCM, and concentrated under vacuum. The crude residue was purified via silica

DOI: 10.1021/acs.joc.9b00324
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gel chromatography. *A 1.0 mmol scale reaction was performed with this procedure for the synthesis of compound* **5**.

General Procedure B for the Difluoromethylation of Aryl Chlorides/Bromides. In a glovebox, the aryl halide substrate (0.500 mmol, 1 equiv), $Pd(P^tBu_3)_2$ (12.8 mg, 0.025 mmol, 0.05 equiv), CsF (152 mg, 1.0 mmol, 2 equiv), dioxane (1.5 mL, 0.33 M), and $TMSCF_2H$ (136 μL, 1.0 mmol, 2 equiv) were combined in a 4 mL vial. The vial was sealed with a Teflon-lined screw cap and brought out of the glovebox. The reaction was allowed to stir vigorously at 120 °C (100 °C for aryl bromides) for 16 h (24 h for aryl bromides). The reaction mixture was allowed to cool to room temperature, filtered through a plug of Celite that was then washed with Et_2O or DCM, and concentrated under vacuum. The crude residue was purified via silica gel chromatography. *In a separate reaction, ^{19}F NMR yields were obtained using 0.1 mmol scale of aryl chloride/bromide under analogous conditions. Trifluoromethoxybenzene (1 equiv, 0.5 M in THF) was used as internal standard.*

1-Butyl-4-(difluoromethyl)benzene (2).[9a] Synthesized using Method A and 1-butyl-4-chlorobenzene (84 mg, 0.5 mmol). The crude mixture was purified by flash chromatography on silica gel (hexanes/Et_2O, 99:1). This procedure afforded **2** as a colorless oil (76 mg, 83% yield); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.41 (d, J = 7.7 Hz, 2H), 7.26 (d, J = 7.7 Hz, 2H), 6.61 (t, J = 56.7 Hz, 1H), 2.65 (t, J = 7.8 Hz, 2H), 1.60 (tt, J = 7.8, 6.8, 2H), 1.35 (tq, J = 7.3, 6.8 Hz, 2H), 0.94 (t, J = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 146.1 (t, J = 1.9 Hz), 132.0 (t, J = 22.5 Hz), 128.9, 125.7 (t, J = 5.9 Hz), 115.7 (t, J = 237.9 Hz), 35.7, 33.7, 22.5, 14.1; ^{19}F NMR ($CDCl_3$, 376 MHz) −109.7 (d, J = 56.7 Hz, 2F); HRMS (EI/magnetic sector) calcd for $C_{11}H_{14}F_2$ $[M]^+$ m/z 184.1064, found 184.1070.

4-(Difluoromethyl)biphenyl (3).[9a] Synthesized using Method A and 4-chlorobiphenyl (94 mg, 0.5 mmol). The crude mixture was purified by flash chromatography on silica gel (hexanes). This procedure afforded **3** as a white solid (89 mg, 87% yield); mp 79−80 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.69 (d, J = 8.0 Hz, 2H), 7.64−7.57 (multiple peaks, 4H), 7.49−7.47 (multiple peaks, 2H), 7.40 (m, 1H), 6.71 (t, J = 56.5 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 143.9 (t, J = 2.1 Hz), 140.4, 133.4 (t, J = 22.5 Hz), 129.1, 128.1, 127.6, 127.5, 126.3 (t, J = 6.0 Hz), 115.0 (t, J = 238.5 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −110.4 (d, J = 56.5 Hz, 2F); HRMS (EI/magnetic sector) calcd for $C_{13}H_{10}F_2$ $[M]^+$ m/z 204.0751, found 204.0759.

4-(Difluoromethyl)diphenyl Ether (4).[12b] Synthesized using Method B and 4-chlorodiphenyl ether (102 mg, 0.5 mmol). The crude residue was purified by flash chromatography on silica gel (pentane). This procedure afforded **4** as a colorless oil (54 mg, 45% yield); ^1H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, J = 8.2 Hz, 2H), 7.40−7.36 (multiple peaks, 2H), 7.19−7.15 (m, 1H), 7.06−7.04 (multiple peaks, 4H), 6.63 (t, J = 57.1 Hz, 1H); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$) δ 159.8 (t, J = 2.0 Hz), 156.4, 130.2, 129.1 (t, J = 23 Hz), 127.5 (t, J = 6.0 Hz), 124.3, 119.8, 118.5, 114.8 (t, J = 238 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −109.1 (d, J = 57.1 Hz, 2F); HRMS (EI/magnetic sector) calcd for $C_{13}H_{10}F_2O$ $[M]^+$ m/z 220.0694, found 220.0697.

1-(Difluoromethyl)naphthalene (5).[8c] Synthesized using Method A and 1-chloronaphthalene (81 mg, 0.5 mmol). The crude mixture was purified by flash chromatography on silica gel (pentane). This procedure afforded **5** as a colorless oil (75.5 mg, 85% yield). *Using Method A and 1-chloronaphthalene (162 mg, 1.0 mmol), **5** was obtained as a colorless oil (156 mg, 88% yield);* ^1H NMR ($CDCl_3$, 400 MHz) δ 8.18 (d, J = 8.1 Hz, 1H), 7.96 (d, J = 8.1 Hz, 1H), 7.91 (m, 1H), 7.69 (dd, J = 7.1, 1.4 Hz, 1H), 7.62−7.48 (multiple peaks, 2H), 7.50 (dd, J = 7.7, 1.4 Hz, 1H), 7.14 (t, J = 55.2 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 134.0, 131.7 (t, J = 1.8 Hz), 129.9 (t, J = 3.0 Hz), 129.8 (t, J = 20.8 Hz), 129.0, 127.4, 126.6, 125.0 (t, J = 8.7 Hz), 124.9, 123.8 (t, J = 1.2 Hz), 115.6 (t, J = 238.4 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −110.9 (d, J = 55.2 Hz, 2F); HRMS (EI/magnetic sector) calcd for $C_{11}H_8F_2$ $[M]^+$ m/z 178.0594, found 178.0598.

9-(Difluoromethyl)anthracene (6). Synthesized using Method B and 4-chloroanthracene (106 mg, 0.5 mmol). The crude mixture was purified via two sequential silica gel columns as follows. In the first column, the product was eluted with a gradient of pentane to 2.5% Et_2O/97.5% pentane. In the second column, the product was eluted with DCM/pentane (5:95). Compound **6** was obtained as a yellow solid (55 mg, 48% yield); mp 59−60 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.47 (d, J = 9.0 Hz, 2H), 8.05 (d, J = 8.5 Hz, 2H), 8.01 (t, J = 54.0 Hz, 1H), 7.62−7.59 (multiple peaks, 2H), 7.53−7.50 (multiple peaks, 2H); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$) δ 131.7 (t, J = 2.0 Hz), 131.4, 129.8 (t, J = 3.6 Hz), 129.4, 127.6, 125.5, 123.5−123.3 (two overlapping peaks), 114.3 (t, J = 236 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −106.7 (d, J = 54.0 Hz, 2F); HRMS (EI/magnetic sector) calcd for $C_{15}H_{10}F_2$ $[M]^+$ m/z 228.0745, found 228.0756.

2-(Difluoromethyl)biphenyl (7).[18] Synthesized using Method B and 2-chlorobiphenyl (94.3 mg, 0.500 mmol). The crude residue was purified by flash chromatography on silica gel (pentane). This procedure afforded **7** as a colorless oil (48 mg, 47% yield); ^1H NMR (500 MHz, $CDCl_3$) δ 7.81−7.79 (multiplet, 1H), 7.54−7.41 (multiple peaks, 5H), 7.38−7.35 (multiple peaks, 3H), 6.55 (t, J = 55.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$) δ 141.6 (t, J = 6.7 Hz), 138.8, 131.9 (t, J = 22 Hz), 130.7 (t, J = 1.9 Hz), 130.4, 129.7, 128.6, 128.1, 128.1, 125.8 (t, J = 5.2 Hz), 113.3 (t, J = 236). ^{19}F NMR (470 MHz, $CDCl_3$) δ −107.4 (d, J = 55.0 Hz, 2F). HRMS (EI/magnetic sector) calcd for $C_{13}H_{10}F_2$ $[M]^+$ m/z 204.0745, found 204.0742.

2-Difluoromethyl-1,3-dimethylbenzene (8).[9a] Synthesized using Method B and 2-chloro-1,3-dimethylbenzene (70 mg, 0.5 mmol). The crude residue was purified by flash chromatography on silica gel (pentane). This procedure afforded **8** as a colorless oil (29 mg, 37% yield); ^1H NMR (500 MHz, $CDCl_3$) δ 7.21 (t, J = 7.7 Hz, 1H), 7.05 (d, J = 7.7 Hz, 2H), 6.98 (t, J = 54.0 Hz, 1H), 2.48 (s, 6H); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$) δ 137.3 (t, J = 3.9 Hz), 130.5 (t, J = 1.8 Hz), 130.2 (t, J = 20 Hz), 129.4, 114.7 (t, J = 236 Hz), 19.7 (t, J = 1.8 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −112.0 (d, J = 54.0 Hz, 2F).

1-(4-(Difluoromethyl)phenyl)-1*H*-pyrrole (9).[10] Synthesized using Method A and 1-(4-chlorophenyl)-1*H*-pyrrole (89 mg, 0.5 mmol). The crude mixture was purified by flash chromatography on silica gel (gradient of hexanes/Et_2O from 98:2 to 90:10). This procedure afforded **9** as a white solid (58 mg, 60% yield); mp 85−87 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.58 (d, J = 8.2 Hz, 2H), 7.48 (d, J = 8.2 Hz, 2H), 7.14 (t, J = 2.2 Hz, 2H), 6.68 (t, J = 56.4 Hz, 1H), 6.41 (t, J = 2.2 Hz, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 176 MHz) δ 142.6, 131.6 (t, J = 22.8 Hz), 127.3 (t, J = 6.0 Hz), 120.4, 119.3, 114.6 (t, J = 238.5 Hz), 111.4; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −110.3 (d, J = 56.3 Hz, 2F); HRMS (EI/magnetic sector) calcd for $C_{11}H_9F_2N$ $[M]^+$ m/z 193.0703, found 193.0706.

5-(Difluoromethyl)benzo[*d*][1,3]dioxole (10).[18] Synthesized using Method A and 5-chlorobenzo-[*d*][1,3]dioxole (78 mg, 0.5 mmol). The crude mixture was purified by flash chromatography on silica gel (hexanes/Et_2O, 98:2). This procedure afforded **10** as a colorless oil (52 mg, 60% yield); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.99−6.97 (multiple peaks, 2H), 6.85 (d, J = 7.8 Hz, 1H), 6.54 (t, J = 56.6 Hz, 1H), 6.01 (s, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 149.5 (t, J = 1.4 Hz), 148.0, 128.3 (t, J = 22.6 Hz), 120.1 (t, J = 7.1 Hz), 114.6 (t, J = 238.1 Hz), 108.2, 105.8 (t, J = 5.4 Hz), 101.5; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −108.0 (d, J = 56.6 Hz, 2F); HRMS (EI/magnetic sector) calcd for $C_8H_6F_2O_2$ $[M]^+$ m/z 172.0336, found 172.0339.

4-(Difluoromethyl)dibenzofuran (11).[18] Synthesized using Method B and 4-chlorodibenzofuran (101.3 mg, 0.500 mmol). The crude residue was purified by flash chromatography on silica gel (gradient of pentane to pentane/Et_2O 95:5). This procedure afforded **11** as a colorless oil (63 mg, 58% yield); ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 (dd, J = 7.7, 1.4 Hz, 1H), 7.97 (d, J = 7.7 Hz, 1H), 7.67 (d, J = 7.6 Hz, 1H), 7.63 (d, J = 8.3 Hz, 1H), 7.53−7.49 (m, 1H), 7.43 (t, J = 7.8 Hz, 1H), 7.39 (t, J = 7.5 Hz, 1H), 7.23 (t, J = 55.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$) δ 156.6, 153.3 (t, J = 5.1 Hz), 128.1, 125.4, 124.0 (t, J = 5.7 Hz), 123.6, 123.5, 123.3 (t, J = 1.8 Hz), 123.0, 121.0, 118.7 (t, J = 24 Hz), 112.2, 112.1 (t, J = 237 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.1 (d, J = 55.6 Hz, 2F); HRMS (EI/magnetic sector) calcd for $C_{13}H_8F_2O$ $[M]^+$ m/z 218.0538, found 218.0532.

1-(Difluoromethyl)methylnaphthalene (12).[19] Synthesized using Method B and 1-(chloromethyl)-naphthalene (88 mg, 0.5 mmol). The crude residue was purified by silica gel column chromatography (pentane). This procedure afforded compound **12** as a colorless oil (35 mg, 36% yield); ^1H NMR (500 MHz, $CDCl_3$) δ

DOI: 10.1021/acs.joc.9b00324
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8.01 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 8.1 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.59−7.56 (m, 1H), 7.54−7.51 (m, 1H), 7.48−7.43 (multiple peaks, 2H), 6.10 (tt, J = 57.0, 4.7 Hz, 1H), 3.63 (td, J = 17, 4.7 Hz, 2H); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$) δ 134.1, 132.4, 129.2, 128.9 (t, J = 5.9 Hz), 128.7, 128.6, 126.7, 126.1, 125.7, 123.5, 116.7 (t, J = 242 Hz), 38.1 (t, J = 22 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.4 (dt, J = 57.0, 16.8 Hz, 2F); HRMS (EI/magnetic sector) calcd for $C_{12}H_{10}F_2$ $[M]^+$ m/z 192.0745, found 192.0748.

(*Z*)-3-(2-(Difluoromethyl)-9*H*-thioxanthen-9-ylidene)-*N*,*N*-dimethylpropan-1-amine (13). Synthesized using Method A and chlorprothixene (158 mg, 0.5 mmol). The crude mixture was purified by flash chromatography on silica gel (conc. $NH_4OH/CH_3OH/CHCl_3$, 1:10:150). This procedure afforded **13** as a colorless oil (63 mg, 38% yield); ^1H NMR ($CDCl_3$, 700 MHz) δ 7.56 (s, 1H), 7.52 (d, J = 8.1 Hz, 1H), 7.48 (d, J = 7.7 Hz, 1H), 7.36 (d, J = 7.8 Hz, 2H), 7.28 (t, J = 7.6 Hz, 1H), 7.25−7.18 (m, 1H), 6.66 (t, J = 56.5 Hz, 1H), 5.97 (t, J = 7.3 Hz, 1H), 2.61 (q, J = 7.3 Hz, 2H), 2.50 (t, J = 7.4 Hz, 2H), 2.26 (s, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 138.2, 137.3, 136.1, 134.3, 132.3 (t, J = 22.7 Hz), 131.2, 131.0, 127.5, 127.2, 127.2, 126.0, 126.1, 125.8 (t, J = 6.2 Hz), 124.4 (t, J = 6.0 Hz), 114.7 (t, J = 238.9 Hz), 59.7, 45.5, 28.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −108.0 (d, J = 56.5 Hz, 2F); HRMS (ESI/TOF) calcd for $C_{19}H_{20}F_2NS$ $[M + H]^+$ m/z 332.1285, found 332.1291.

3-(3-(Difluoromethyl)-10,11-dihydro-5*H*-dibenzo[*b*,*f*]-azepin-5-yl)-*N*,*N*-dimethylpropan-1-amine (14).[8c] Synthesized using Method A and clomipramine (158 mg, 0.5 mmol). The crude mixture was purified by flash chromatography on silica gel (conc. $NH_4OH/CH_3OH/CHCl_3$, 1:10:175) and afforded **14** as a colorless oil (79 mg, 48% yield); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.21 (s, 1H), 7.17−7.07 (multiple peaks, 4H), 7.06−6.84 (multiple peaks, 2H), 6.57 (t, J = 56.7 Hz, 1H), 3.79 (t, J = 7.1 Hz, 2H), 3.16 (s, 4H), 2.32 (t, J = 7.2 Hz, 2H), 2.16 (s, 6H), 1.73 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 148.5, 147.9, 136.2 (t, J = 2.1 Hz), 134.7, 132.5 (t, J = 22.7 Hz), 130.4, 129.5, 126.5, 123.0, 120.4, 119.1 (t, J = 6.1 Hz), 116.8 (t, J = 5.7 Hz), 114.8 (t, J = 239.4 Hz), 57.5, 48.9, 45.5, 32.5, 31.6, 26.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ −108.6 (d, J = 56.7 Hz, 2F); HRMS (ESI/TOF) calcd for $C_{20}H_{25}F_2N_2$ $[M + H]^+$ m/z 331.1986, found 331.1990.

2-(Difluoromethyl)dibenzo[*b*,*d*]furan (15).[12a] Synthesized using Method A and 2-bromodibenzo[*b*,*d*]furan (124 mg, 0.5 mmol). The crude mixture was purified by flash chromatography on silica gel (hexanes). This procedure afforded **15** as a white solid (72 mg, 66% yield); mp: 86−87 °C; ^1H NMR ($CDCl_3$, 700 MHz) δ 8.13 (s, 1H), 7.98 (d, J = 7.7 Hz, 1H), 7.64 (d, J = 8.0 Hz, 2H), 7.61 (d, J = 4.0 Hz, 1H), 7.51 (t, J = 7.7 Hz, 1H), 7.39 (t, J = 7.5 Hz, 1H), 6.82 (t, J = 56.7 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 176 MHz) δ 156.7, 127.9, 124.6 (t, J = 5.9 Hz), 124.6, 123.6, 123.2, 123.2, 121.1, 120.9, 118.4 (t, J = 6.3 Hz), 115.0 (t, J = 238.6 Hz), 112.0, 111.9; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −108.6 (d, J = 56.9 Hz, 2F); HRMS (EI/magnetic sector) calcd for $C_{13}H_8F_2O$ $[M]^+$ m/z 218.0543, found 218.0544.

3-(Difluoromethyl)-9-phenyl-9*H*-carbazole (16).[12a] Synthesized using Method A and 3-bromo-9-phenyl-9*H*-carbazole (161 mg, 0.5 mmol). The crude mixture was purified by flash chromatography on silica gel (gradient of hexanes/EtOAc from 99:1 to 90:10). This procedure afforded **16** as a pale yellow oil (72 mg, 66% yield); ^1H NMR ($CDCl_3$, 700 MHz) δ 8.31 (d, J = 1.8 Hz, 1H), 8.18 (d, J = 7.8 Hz, 1H), 7.63 (dd, J = 8.2, 7.4 Hz, 2H), 7.56 (dt, J = 8.3, 1.6 Hz, 3H), 7.52 (d, J = 7.5 Hz, 1H), 7.49−7.40 (multiple peaks, 3H), 7.36−7.31 (m, 1H), 6.87 (t, J = 56.9 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 176 MHz) δ 142.2, 141.7, 137.4, 130.2, 128.1, 127.4, 126.8, 126.3 (t, J = 22.4 Hz), 123.5 (t, J = 5.6 Hz), 123.4, 123.2, 120.7, 120.7, 118.3 (t, J = 6.5 Hz), 116.0 (t, J = 237.5 Hz), 110.3, 110.2; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −106.5 (d, J = 56.7 Hz, 2F); HRMS (EI/magnetic sector) calcd for $C_{19}H_{13}F_2N$ $[M]^+$ m/z 293.1016, found 293.1014.

1-(Difluoromethyl)-3-(4-fluorophenoxy)benzene (17). Synthesized using Method A and 1-bromo-3-(4-fluorophenoxy)benzene (134 mg, 0.5 mmol). The crude mixture was purified by flash chromatography on silica gel (pentane). This procedure afforded **17** as a colorless oil (72 mg, 60% yield); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.41 (t, J = 7.9 Hz, 1H), 7.24−7.21 (m, 1H), 7.13−6.98 (multiple peaks, 6H), 6.60 (t, J = 56.4 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 176 MHz) δ 159.4 (d, J = 242.1 Hz), 158.4, 152.3 (d, J = 2.5 Hz), 136.4 (t, J = 22.4 Hz), 130.5, 121.2 (d, J = 8.6 Hz), 120.3 (d, J = 2.1 Hz), 120.2 (t, J = 6.2 Hz), 116.8 (d, J = 23.4 Hz), 115.2 (t, J = 6.1 Hz), 114.4 (t, J = 239.3 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −111.0 (d, J = 56.5 Hz, 2F), −119.1 (m, 1F); HRMS (EI/magnetic sector) calcd for $C_{13}H_9F_3O$ $[M]^+$ m/z 238.0605, found 238.0607.

6-(Difluoromethyl)-2,3-dihydrobenzo[*b*][1,4]dioxine (18).[20] Synthesized using Method A and 6-bromo-2,3-dihydrobenzo[*b*][1,4]-dioxine (108 mg, 0.5 mmol). The crude mixture was purified by flash chromatography on silica gel (gradient of hexane/EtOAc from 99:1 to 90:10). This procedure afforded **18** as a colorless oil (67 mg, 76% yield). Using Method B, compound **18** was isolated in 75% yield; ^1H NMR ($CDCl_3$, 700 MHz) δ 7.03 (d, J = 2.0 Hz, 1H), 6.98 (dd, J = 8.4, 1.7 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 6.54 (t, J = 56.7 Hz, 1H), 4.35−4.26 (multiple peaks, 4H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 176 MHz) δ 145.7, 143.8, 127.9 (t, J = 22.8 Hz), 119.0 (t, J = 6.3 Hz), 117.8, 115.1 (t, J = 6.1 Hz), 114.7 (t, J = 237.9 Hz), 64.6, 64.5; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −112.1 (d, J = 56.3 Hz, 2F); HRMS (EI/magnetic sector) calcd for $C_9H_8F_2O_2$ $[M]^+$ m/z 186.0492, found 186.0490.

4-(4-(Difluoromethyl)phenyl)morpholine (19).[18] Synthesized using Method A and 4-(4-bromo-phenyl)morpholine (121 mg, 0.5 mmol). The crude mixture was purified by flash chromatography on silica gel (gradient of hexane/EtOAc from 90:10 to 50:50). This procedure afforded **19** as a colorless oil (66 mg, 62% yield); ^1H NMR ($CDCl_3$, 700 MHz) δ 7.41 (d, J = 8.3 Hz, 2H), 6.93 (d, J = 8.5 Hz, 2H), 6.58 (t, J = 56.9 Hz, 1H), 3.91−3.82 (m, 4H), 3.28−3.14 (m, 4H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 176 MHz) δ 153.1, 126.9 (t, J = 5.9 Hz), 125.5 (t, J = 22.7 Hz), 115.3 (t, J = 236.9 Hz), 115.0, 66.9, 48.7; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −108.5 (d, J = 56.9 Hz, 2F); HRMS (ESI/TOF) calcd for $C_{11}H_{14}F_2NO$ $[M + H]^+$ m/z 214.1043, found 214.1042.

4-(2-Chloro-4-(difluoromethyl)phenyl)morpholine (20). Synthesized using Method A and 4-(4-bromo-2-chlorophenyl)morpholine (138 mg, 0.5 mmol). The crude mixture was purified by flash chromatography on silica gel (gradient of hexane/EtOAc from 90:10 to 75:25). This procedure afforded **20** as a thick yellow oil (52 mg, 42% yield); ^1H NMR ($CDCl_3$, 700 MHz) δ 7.52 (s, 1H), 7.37 (dd, J = 8.3, 1.9 Hz, 1H), 7.08 (d, J = 8.3 Hz, 1H), 6.57 (t, J = 56.5 Hz, 1H), 4.02−3.71 (m, 4H), 3.09 (m, 4H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 176 MHz) δ 151.3 (t, J = 1.8 Hz), 130.0 (t, J = 23.1 Hz), 129.0, 128.4 (t, J = 6.0 Hz), 125.3 (t, J = 6.0 Hz), 120.4, 114.1 (t, J = 238.8 Hz), 67.2, 51.6; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −110.0 (d, J = 56.5 Hz, 2F); HRMS (ESI/TOF) calcd for $C_{11}H_{13}ClF_2NO$ $[M + H]^+$ m/z 248.0654, found 248.0650.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b00324.

Additional substrate scope and copies of NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the NSF (CHE-1664961 and a graduate fellowship to J.R.B.).

DOI: 10.1021/acs.joc.9b00324
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DOI: 10.1021/acs.joc.9b00324
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