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Graphical Abstract

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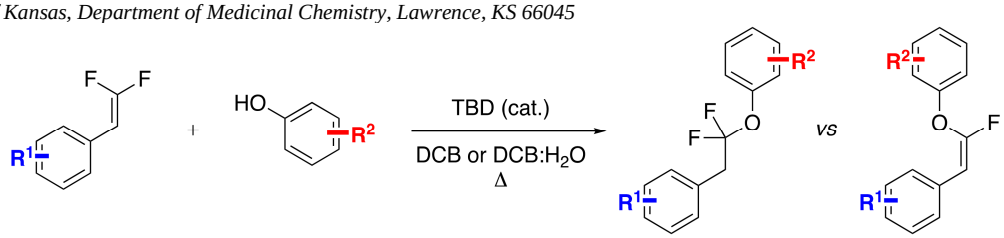

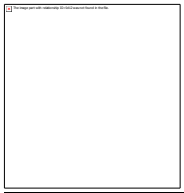

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Organocatalytic Strategy for Hydrophenolation of *Gem*-Difluoroalkenes

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To Steve, Congratulations on the 2018 Tetrahedon Award ☺

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ABSTRACT

Gem-difluoroalkenes are an easily accessed fluorinated functional group, and a useful intermediate for elaborating into more complex fluorinated compounds. Currently, most functionalization reactions of *gem*-difluoroalkenes, with or without a transition metal-based catalyst system, involve the addition or removal of a fluorine atom to generate trifluorinated or monofluorinated products, respectively. In contrast, we present a complementary "fluorine-retentive" reaction that exploits an organocatalytic strategy to add phenols across *gem*-difluoroalkenes to deliver β,β-difluorophenethyl arylethers. The products are produced in good to moderate yields and selectivities, thus providing a range of compounds that are underrepresented in the synthetic and medicinal chemistry literature.

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1. Introduction

Fluorine-induced perturbations of an organic molecule's physicochemical properties can enable new reactivities that contrast the reactivity of the respective non-fluorinated counterpart, as evidenced by the case of *gem*-difluoroalkenes.[1,2] For these substrates, the σ-withdrawing effects of the fluorine substituents activate the difluorinated position for regioselective attack by a variety of nucleophiles under both metal-catalyzed and non-catalyzed nucleophilic functionalization conditions (**Figure 1**).[1] However, many of these reactions undergo a net addition/elimination process that defluorinates the substrate. Specifically, these reactions proceed through either unstable β-fluoroanions (**Figure 1a**)[3-6] or β-fluoroorganometal intermediates (**Figure 1b**)[7-24] that both undergo β-fluoride elimination and deliver monofluorinated products.[1] This elimination process can be overridden using the nucleophile as a solvent,[25-32] which restricts use to liquid, inexpensive, and readily-available nucleophiles. In a special case, nucleophilic attack of the fluorinated position of a *gem*-difluoroalkene by a fluoride anion delivers trifluoromethyl-containing products, though these reactions benefit from an *in situ* equilibrium between the difluoroalkene and the α-trifluormethyl anion that avoids degradation of the organic moiety (**Figure 1c**).[33-38] A second rare exception involves the addition of 3-hydroxypyridine to *gem*-difluoroalkenes to selectively provide the hydrophenolated product,[39] though this strategy was not applied to other phenolic nucleophiles. In a more general method, the nucleophilic addition of aryl thiols to *gem*-difluoroalkenes generates β,β-difluorophenethyl arylthioethers using an organocatalytic strategy (1,1,3,3-tetramethylguanidine, TMG, **Figure 1e**) without β-fluoride elimination,[40] though additional examples of "fluorine-retentive" nucleophilic hydro-functionalization of *gem*-difluoroalkenes remain elusive (**Figure 1d**). To complement this reaction, we herein present a new organocatalytic system for the regioselective nucleophilic addition reactions of phenols to *gem*-difluoroalkenes that minimizes the loss of fluoride (**Figure 1f**).

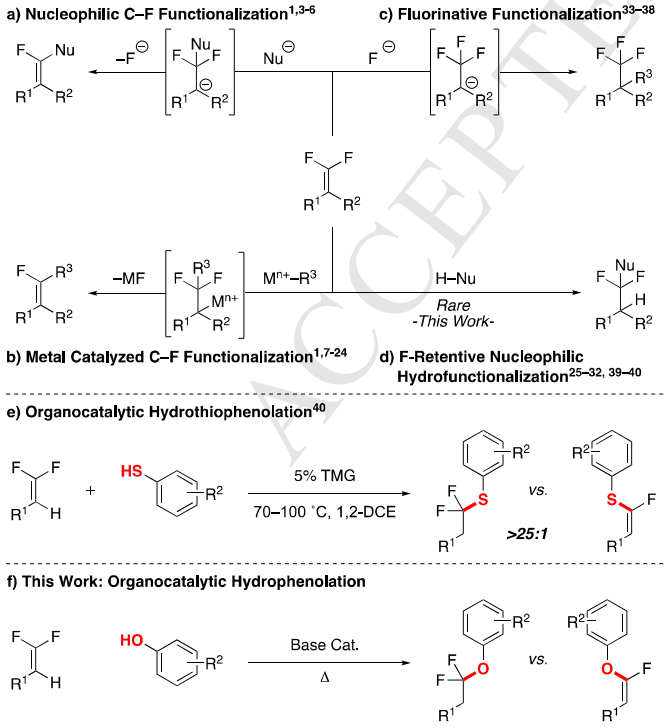
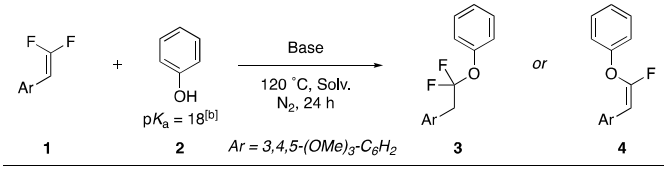


Figure 1: Representative Reactions of *Gem*-Difluoroalkenes.

2. Results/Discussion

Standard optimization delivered improved conditions for adding phenolic nucleophiles across *gem*-difluoroalkenes (**Table 1**). Initially, we explored similar conditions to those used for functionalization with aryl thiols [**entry 1**: 25% TMG, 1,2-dichloroethane (1,2-DCE), 80 °C]; however, using these conditions, phenolic nucleophiles reacted poorly, giving no yield of desired β,β-difluorophenethylarylether product **3** or α-monofluorovinylether side product **4**. Utilizing the same catalyst with a higher boiling solvent and higher temperatures provided low yield and moderate selectivity of **3** (**entry 2**). Considering the intrinsic differences in acidity and nucleophilicity between phenolic and thiophenolic nucleophiles, we explored the use of stronger bases, such as ^{t}BuOK (**entry 3**), 1,8-diazabicylco[5.4,0]undec-7ene (DBU, **entry 4**), and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD, **entry 5**). Use of the stronger nitrogenous bases improved the yields of product **3**, but did not greatly increase selectivity, while the inorganic ^{t}BuOK selectively delivered **4**. The use of stronger phosphorazine superbases reduced the selectivity versus α-monofluorovinylether side product **4** (**entry 6**), presumably due to degredation of desired product **3**. The use of aromatic solvents provided improved selectivity versus other solvents (**entries 3, 7–10**), while increased temperature and loading of TBD improved the yield of desired product (**entries 11–14**). When performed in the presence of air, the reaction generated a complex mixture of more highly oxidized products, and ongoing work aims to optimize conditions to selectively produce these side products. Finally, we settled on the use of 50% TBD in 1,2-dichlorobenzene (DCB) under N_2 at 140 °C for 24 h as the standard conditions (**entry 15**). In control reactions, subjection of pure **3** to the optimized conditions generated mixtures of **3**:**4**, indicating that the product is instable to the reaction conditions. Thus for any specific substrate, optimization of the time, temperature, and strength of base might improve the reaction outcome.



1 **2** **3** **4**

Entry	Base	pK_a[b]	Solv.	Conv.	3	4
1[c]	TMG	16	DCE	40	0	0
2	TMG	16	$(NO_2)C_6H_5$	40	22	9
3[d]	^{t}BuOK	N/D	$(NO_2)C_6H_5$	39	7	25
4[d]	DBU	17	$(NO_2)C_6H_5$	30	15	7
5	TBD	21	$(NO_2)C_6H_5$	83	46	14
6	P_2Et	25	$(NO_2)C_6H_5$	72	33	19
7	TMG	16	DMF	84	18	30
8	TMG	16	DMSO	98	6	64
9	TMG	16	Anisole	65	16	3
10	TMG	16	DCB	56	18	3
11	TBD	21	DCB	90	53	10
12[e]	TBD	21	DCB	89	61	11
13[d,e]	TBD	21	DCB	63	31	5
14[e,f]	TBD	21	DCB	>99	70	17
15[g]	TBD	21	DCB	>99	60	17

Table 1: Optimization of Reaction Conditions. [a] **1** (1.0 equiv., 0.10 mmol), **2** (5.0 equiv., 0.50 mmol), base (0.25 equiv., 0.025 mmol), solvent (1.0 M, 0.10 mL), 120 °C, for 4 h under an N_2 atmosphere. Conversion of **1** and yields of **3** and **4** were determined by ^{19}F NMR analysis using α,α,α-trifluorotoluene (TFT) as a standard (10 μL). [b] p*K*a in THF.[41,42] [c] 80 °C. [d] 100 °C. [e] 0.50 equiv. base. [f] 140 °C. [g] **1** (1.0 equiv., 0.50

mmol), **2** (5.0 equiv., 2.5 mmol), TBD (0.50 equiv., 0.25 mmol), DCB (1.0 M, 1.0 mL), 140 ˚C, for 24 h under an N_2 atmosphere.

Using these conditions, a range of phenols were successfully added across *gem*-difluoroalkenes. Reactions of various electron-deficient phenols (Table 2, **6a–f**) gave the desired β,β-difluorophenethyl arylethers (**6**) in good yields (>65%) and high selectivities (>7:1) versus the α-monofluorovinylether side products (**7**). Using the standard reaction conditions, electron-neutral and ortho-substituted phenols (**3**, **6g–j**) delivered the β,β-difluorophenethyl arylethers in moderate to low yields (30–50%) and selectivities (2:1–4:1). Reactions of electron-rich phenols delivered the anticipated products in low yields and selectivities (**6k–l**), though reoptimization of the base might improve the reactivity of these less acidic substrates. A range of useful functional groups for further functionalization were tolerated, like halides (**6c–f**) and nitrogen based functional groups (**6a–b**), though an aniline-drived phenol (**6l**) was a poor substrate.

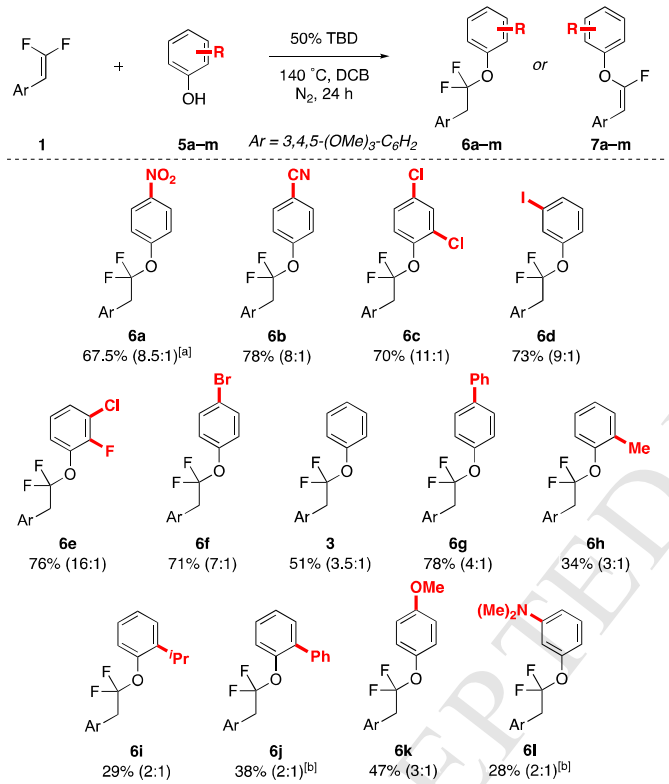


Table 2: Scope of Phenol Nucleophiles. Standard conditions: **1** (1.0 equiv., 0.50 mmol), **5a–o** (5.0 equiv., 2.5 mmol), TBD (0.50 equiv., 0.25 mmol), DCB (0.50 M, 1.0 mL), 140 ˚C, for 24 h under an N_2 atmosphere. The selectivity of **6:7** was determined by ^{19}F NMR analysis of the crude reaction mixture using TFT (50 µL) as a standard and is reported in parentheses. Yields are reported as the isolated yield of >95% pure material and represent the average of 2 runs. [a] 1.0 equiv. TBD. [b] Contains trifluoroethylbenzene side product.

Many synthetically and biomedically useful functional groups were tolerated on the *gem*-difluoroalkene substrate. Specifically, reactions tolerated thioethers and ethers (**9a–b**), morpholine (**9c**), nitrogen-containing functional groups (**9k–l**), halides (**9m–p**) amides (**9q**), and pseudohalides (**9r**). Reactions of electron-rich *gem*-difluoroalkenes generally afforded products in good yields and high selectivities (**9a–i**), although aniline-based and ^{t}Bu-based *gem*-difluoroalkenes reacted in lower yields (**9e–f**). Using electron-deficient substrates, the standard reaction conditions generally delivered products in low yield and <1:1 selectivity (**9j–r**), though substrates bearing 3-α,β-unsaturated carbonyl and 3-NO_2 groups afforded products in sufficient yield and selectivity (**9j, k**). To address this limitation, further optimization revealed that a biphasic reaction mixture (9:1 DCB:H_2O) improved both the selectivities and yields (**9l–r**). Presumably for these eletron-deficient substrates, the water in the biphasic system (1) provided additional protons to quench the reactive β-fluoroanion, and/or (2) minimized degradation of the product by sequestering some of the base in the aqueous phase. Ortho-substituted *gem*-difluoroalkenes reacted inconsistently, with a 2-(4-^{t}Bu)-Ph-substituted substrate giving high yield (**9d**), a 2-Me-substituted substrate reacting in low yield and low conversion (**9h**), and a 2,6–Me_2-substituted substrate not reacting at all (**9i**).

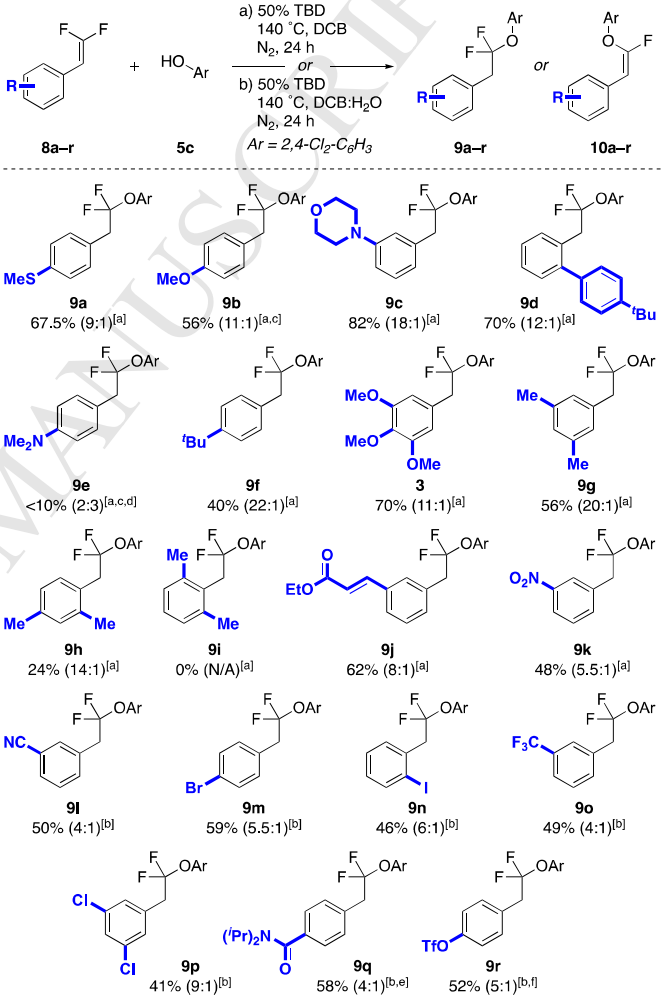


Table 3: Scope of *Gem*-difluoroalkene Electrophiles. [a] Standard conditions: **8a–r** (1.0 equiv., 0.50 mmol), **5c** (5.0 equiv., 2.5 mmol), TBD (0.50 equiv., 0.25 mmol), DCB (0.50 M, 1.0 mL), 140 ˚C, for 24 h under an N_2 atmosphere. The selectivity of **9:10** was determined by ^{19}F NMR analysis of the crude reaction mixture using TFT (50 µL) as a standard and is reported in parentheses. Yields are reported as the isolated yield of >95% pure material and represent the average of 2 runs. [b] Standard conditions: **8a–r** (1.0 equiv., 0.50 mmol), **5c** (3.0 equiv., 1.5 mmol), TBD (0.50 equiv., 0.25 mmol), DCB (0.45 M, 0.90 mL), H_2O (0.05 M, 0.10 mL), 140 ˚C, for 24 h under an N_2 atmosphere. The selectivity of **9:10** was determined by ^{19}F NMR analysis of the crude reaction mixture using TFT (50 µL) as a standard and is reported in parentheses. Yields are reported as the isolated yield of >95% pure material and represent the average of 2 runs. [c] 4-Bromophenol used as the nucleophile. [d] Yield is

reported from ^{19}F analysis of the crude reaction mixture. [e] Second run used 0.40 mmol of **8q.** [f] Second run used 0.30 mmol of **8r**.

Heteroaryl-substituted *gem*-difluoroalkenes reacted similarly to their aryl-derived counterparts. Electron-rich heteroaryl groups, such as indole and pyrazole, gave high selectivity (**12a, b**), though the yield of pyrazole **12b** was moderate. A 2-substituted dibenzothiophene reacted in moderate yield and selectivity (**12c**). When subjected to the biphasic conditions, a pyridyl substrate gave good yield and selectivity (**12d**). This series of reactions also highlighted the compatibility of sulfonamide (**12a**) and acetal (**12d**) protecting groups.

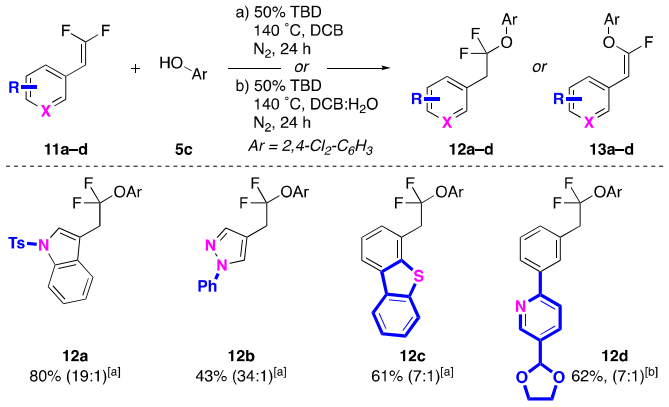


Table 4: Scope of Heteroaryl *Gem*-Difluoroalkene Electrophiles. [a] Standard conditions a: **11a–e** (1.0 equiv., 0.50 mmol), **5c** (5.0 equiv., 2.5 mmol), TBD (0.50 equiv., 0.25 mmol), DCB (0.50 M, 1.0 mL), 140 ˚C, for 24 h under an N_2 atmosphere. The selectivity of **12:13** was determined by ^{19}F NMR analysis of the crude reaction mixture using TFT (50 µL) as a standard and is reported in parentheses. Yields are reported as the isolated yield of >95% pure material and represent the average of 2 runs. [b] Standard conditions b: **11a–e** (1.0 equiv., 0.50 mmol), **5c** (3.0 equiv., 1.5 mmol), TBD (0.50 equiv., 0.25 mmol), DCB (0.45 M, 0.90 mL), H_2O (0.050 M, 0.10 mL), 140 ˚C, for 24 h under an N_2 atmosphere. The selectivity of **12:13** was determined by ^{19}F NMR analysis of the crude reaction mixture using TFT (50 µL) as a standard and is reported in parentheses. Yields are reported as the isolated yield of >95% pure material and represent the average of 2 runs.

3. Mechanistic Considerations

The present reaction presumably operates through an addition / protonation sequence, in which the base plays key roles as both a promoter and a quencher of the reaction. Initially, organic base (**B**) activates the phenol pronucleophile, and subsequently, the phenoxide nucleophile adds to the electrophilic difluorinated carbon of the *gem*-difluoroalkene. This addition generates an instable β-fluoro anionic intermediate (**A**) that can react *via* two pathways. First, intermediate (**A**) can either accept a proton from the phenol pronucleophile or from the protonated organic base (**B**) to provide the desired product **3**. Second, fluoride elimination from anionic intermediate (**A**) can provide the undesired monofluoroalkene **4**. Alternatively, **4** can form *via* base-mediated elimination of HF from **3**.

Based on this presumed mechanism, the pK_a of the base catalyst must fall within a narrow range to selectively provide **3** over **4**. The base catalyst must be sufficiently basic to deprotonate the phenol. In THF, a non-coordinating aprotic solvent, phenol's pK_a of 18 disfavors deprotonation by weaker bases, such as TMG (pK_a = 16), though stronger bases, such as TBD (pK_a = 21), efficiently deprotonate and activate the phenol. However, bases that are too strong will decompose product **3** to generate **4**. Specfically, the strong σ-electron withdrawing effect of the *gem*-difluoro group and ethereal oxygen activates **3** for elimination. Such deprotonation was observed in control experiments involving the base-mediated decomposition of **3**, particularly with strong "superbases," such as the phosphorazine base P_2Et (pK_a = 25). Therefore in the present studies, TBD provided appropriate reactivity, specifically balancing activation of the phenol with decomposition of product. However, we note that other currently unexplored bases might also work for this reaction. Further, for any specific substate combination with distinct pK_as of the phenol and product, an alternate base might prove optimal.

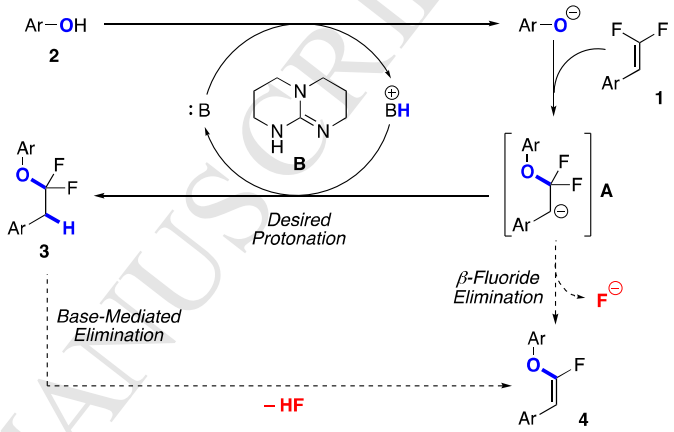


Figure 2: Plausible Reaction Mechanism.

4. Conclusion

In conclusion, we developed an organocatalytic method to convert *gem*-difluoroalkenes to β,β-difluorophenethyl arylethers. In contrast to classical syntheses of such products that require harsh conditions[43-45] and/or gaseous reagents[46] and that many times rely on functional group interconversions[47-56] for generating the fluorine-based substructure, our convergent method utilizes only catalytic quantities of a weak amine base to add phenol nucleophiles across *gem*-difluoroalkenes and deliver the desired products in moderate to good yields and selectivities. Notably, this reaction contrasts the many reactions of *gem*-difluoroalkenes that selectively generate monofluoroalkene products.[1] This method delivers a class of products that are underrepresented in synthetic and biomedical literature, and it tolerates many useful functional groups for further functionalization and for medicinal chemistry. Further efforts aim to enable the addition of other nucleophiles, such as alkyl alcohols, to *gem*-difluoroalkenes, and to expand the scope of such reactions to include aliphatic and secondary *gem*-difluoroalkenes.

5. Experimental Section

General Considerations: Unless otherwise noted, reactions were performed under an atmosphere of air using oven-dried glassware. Organocatalytic reactions of phenols and *gem*-difluoroalkenes were performed in one-dram borosilicate glass scintillation vials sealed with a screw-top cap containing a PTFE-lined septum. Unless otherwise noted all other reactions were performed in round-bottom flasks sealed with rubber septa. PTFE syringes equipped with stainless-steel needles were used to transfer air- and moisture-sensitive liquid reagents. Reactions were monitored by either ^{19}F NMR with an internal standard of α,α,α–trifluorotoluene or by thin-layer chromatography (TLC)

on UNIPLATE Silica Gel HLF plates, visualized by quenching of fluorescence. Normal phase column chromatography was conducted using a automated separations system utilizing gradient elution with VWR Common Silica Gel 60 Å, 40–60 µm. Reverse phase column chromatography was conducted using an automated flash chromatography system utilizing gradient elution with a Teledyne ISCO C18 Redisep Rf Gold 50 g column. Isolated yields reported in the manuscript represent an average of at least 2 independent runs of final compound deemed to be at least 95% pure by NMR. Yields reported in the supporting information refer to a single experiment. Unless otherwise noted, compounds were isolated in >98% purity as determined by ^{1}H and ^{19}F NMR.

Unless otherwise noted, reagents were purchased from commercial sources and used as received. 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD) was purchased form Sigma Aldrich. Solvents, including dimethylformamide (DMF), toluene (PhMe), dichloromethane (DCM), methanol (MeOH), acetonitrile (MeCN), and tetrahydrofuran (THF) were used directly from a solvent purification system, in which solvent was dried by passage through two columns of activated alumina under argon. Chemical abbreviations utilized in this document include: 1,2–Dichlorobenzene (DCB), *N*-methylpyrrolidine (NMP), α,α,α-trifluorotoluene (TFT), sodium sulfate (Na_2SO_4), magnesium sulfate ($MgSO_4$), ethyl acetate (EtOAc), diethyl ether (Et_2O), ammonium chloride (NH_4Cl), ^{n}butyl lithium (^{n}BuLi), sodium hydroxide (NaOH), ^{t}butyl carbonate anhydride (Boc_2O), potassium carbonate (K_2CO_3), and hydrochloric acid (HCl).

Proton nuclear magnetic resonance (^{1}H NMR) and fluorine nuclear magnetic resonance (^{19}F NMR) were taken on a Bruker DRX 500 spectrometer (500 and 376 MHz respectively). Fluorine nuclear magnetic resonance (^{19}F NMR) was taken on a Bruker AVIII 400 Avance spectrometer (376 MHz). Proton and carbon nuclear magnetic resonance (^{13}C NMR) were taken on a Bruker AVIII 500 Avance spectrometer with a CPDUL cryoprobe (500 and 126 MHz respectively). Chemical shifts (δ) for protons are reported in parts per million (ppm) downfield from tetramethylsilane, and are referenced to the proton resonance of residual solvent in the NMR solvent ($CHCl_3$: δ = 7.26 ppm; DMSO: δ = 2.50 ppm). Chemical shifts (δ) for carbon are reported in ppm downfield from tetramethylsilane, and are referenced to the carbon resonance of the solvent residual peak ($CDCl_3$: δ = 77.2 ppm; DMSO: δ = 39.52 ppm). Chemical shifts for fluorine are reported in ppm upfield from trichlorofluoromethane (0 ppm), and are referenced to added TFT as a standard (δ = –63.77 ppm) unless otherwise specified. NMR data are represented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet), coupling constant in Hertz (Hz), integration. High-resolution mass determinations were obtained either by electrospray ionization (ESI) on a Waters LCT Premier™ mass spectrometer or by atmospheric-pressure chemical ionization (APCI-hexanes/PhMe) on a Waters Q-Tof Premier™, for which sample plus near mass internal exact mass standard were dissolved in hexanes, and hexanes or PhMe/hexanes were used as ionization solvent. Infrared spectra were measured on a Perkin Elmer Spectrum Two Fourier Transform Infrared Spectrometer by drying samples on a diamond ATR Sample base plate. Uncorrected melting points were measured on a Thomas Hoover Capillary Melting Point apparatus.

General Procedure for the Preparation of *Gem*-Difluoroalkenes (A): An oven-dried 3-neck round-bottomed flask equipped with a magnetic stir bar was charged with aryl aldehyde (1.0 equiv.) and triphenylphosphine (1.2 or 1.5 equiv.). The system was sealed with three PFTE septa, and subsequently evacuated and backfilled with N_2 three times. Dry NMP was added *via* syringe transfer (PTFE syringe with oven-dried stainless-steel needle), and the system was immersed in a preheated 100 °C oil bath. Once no solid reagents remained (approximately 2 min of heating), potassium bromodifluoroacetate (1.5 or 1.8 equiv.) was added portionwise over 0.5 h, with the rate of addition controlling the evolution of CO_2 gas. Once all of the potassium bromodifluoroacetate was added, the solution was allowed to stir for 0.5–1 h. Upon completion, the reaction was cooled to room temperature and then quenched with H_2O. Subsequently, Et_2O was added to the reaction, and the mixture was washed with H_2O (five times), and the aqueous layer was back-extracted with Et_2O (two times). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude material was dry-packed onto silica gel and then eluted through a plug of silica gel with EtOAc:hexanes (1:1) to remove triphenylphosphine oxide. Subsequently, H_2O_2 (30% in H_2O) was added to the mother liquor and allowed to react for 30 min to oxidize the residual triphenylphosphine. The organic layer was washed with H_2O (three times), dried over Na_2SO_4, concentrated, and subjected to normal phase flash chromatography using EtOAc and hexanes.

General Procedure for the Organocatalyzed Addition of Phenols to *Gem*-Difluoroalkenes (B-1): An oven-dried one-dram vial equipped with a magnetic stir bar was charged with 1 equivalent of difluoroalkene and 5 equivalents of phenol. The system was brought into a glovebox, and 0.5 equivalents of TBD were added. Dry DCB (1 mL) was added *via* syringe transfer (PTFE syringe with oven-dried stainless-steel needle), and the vial was sealed with a screw-top cap containing a PTFE-lined septum. The system was removed from the glovebox, and placed within a heating mantle preheated to 140 ˚C and stirred for 24 h. The reaction was cooled to room temperature, and then standardized by adding 50 µL of TFT. The mixture was diluted with DCM, and then stirred for 5 min. The reaction was analyzed by ^{19}F NMR, and then washed 3X with 1 N NaOH (aq.). The combined aqueous layer was extracted 2X with DCM, and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was loaded onto celite and then purified by flash reverse phase chromatography with gradient elution from 98% H_2O in MeCN to 100% MeCN to provide the desired product in >95% purity.

General Procedure for the Organocatalyzed Addition of Phenols to *Gem*-Difluoroalkenes (B-2): An oven-dried one-dram vial equipped with a magnetic stir bar was charged with 1 equivalent of difluoroalkene and 3 equivalents of phenol. The system was brought into a glovebox, and 0.5 equivalents of TBD were added. Dry DCB (0.9 mL) was added *via* syringe transfer (PTFE syringe with oven-dried stainless-steel needle), and the vial was sealed with a screw-top cap containing a PTFE-lined septum. The system was removed from the glovebox, and distilled H_2O (0.1 mL, distilled under N_2 to remove dissolved O_2) was added *via* syringe transfer (PTFE syringe with oven-dried stainless-steel needle) under N_2. The reaction was placed within a heating mantle preheated to 140 ˚C and stirred for 24 h. The reaction was cooled to room temperature, and then standardized by adding 50 µL of TFT. The mixture was diluted with DCM, and then stirred for 5 min. The reaction was analyzed by ^{19}F NMR, and then washed 3X with 1 N NaOH (aq.). The combined aqueous layer was extracted 2X with DCM, and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was loaded onto celite and then purified by flash reverse phase chromatography with gradient elution from

98% H_2O in MeCN to 100% MeCN to provide the desired product in >95% purity.

Compounds in Table 1:

5-(2,2-difluoro-2-phenoxyethyl)-1,2,3-trimethoxybenzene (3): Following General Procedure B-1, 0.115 g (0.50 mmol) of compound **1** was reacted with 0.236 g (2.50 mmol) of phenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 ˚C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H_2O, furnishing 0.080 g (49% yield) of desired product **3** as a colorless solid (MP = 65–66 ˚C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (t, *J* = 7.9 Hz, 2 H), 7.19 (t, *J* = 7.5 Hz, 1 H), 7.14 (d, *J* = 8.0 Hz, 2 H), 6.60 (s, 2 H), 3.87 (s, 9 H), 3.39 (t, *J* = 11.0 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.2, 150.5, 137.6 (d, *J* = 1.4 Hz), 129.4, 127.7 (t, *J* = 3.3 Hz), 125.6, 123.8, 121.7 (t, *J* = 267.0 Hz), 107.6, 60.9, 56.2, 42.5 (t, *J* = 30.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –70.44 (t, *J* = 11.0 Hz, 2 F); IR (film) 2940, 2841, 2252, 1699, 1592, 1509, 1492, 1463, 1423, 1361, 1324, 1262, 1238, 1194, 1156, 1128, 1068, 1051, 1026, 1005, 942, 909, 828, 807, 764, 749, 692, 658, 649 cm^{-1}; HRMS (HAPCI+) calc. for $C_{17}H_{18}F_2O_4$ (M+) 324.1173, found 324.1171.

(*E*)-5-(2-fluoro-2-phenoxyvinyl)-1,2,3-trimethoxybenzene (4): Following General Procedure B-1, 0.115 g (0.50 mmol) of compound **1** was reacted with 0.236 g (2.50 mmol) of phenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 ˚C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H_2O, furnishing desired product 0.024 g (16% yield, 6:1 *E*:*Z*) **4** as an orange oil; Characterization represents major *E* isomer; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 8.7, 7.5 Hz, 2 H), 7.17–7.14 (m, 3 H), 6.66 (s, 2 H), 5.65 (d, *J* = 5.6 Hz, 1 H), 3.82 (s, 3 H), 3.76 (s, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.7, 154.0 (d, *J* = 3.5 Hz), 153.3, 130.1, 127.6 (d, *J* = 8.4 Hz), 124.5, 117.5, 116.3, 105.0 (d, *J* = 4.1 Hz), 92.7 (d, *J* = 38.6 Hz), 61.0, 56.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ –83.38 (d, *J* = 5.6 Hz, 1 F). Minor Z isomer characteristic peaks: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.24 (d, *J* = 28.2 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –83.80 (d, *J* = 28.1 Hz, 1 F).

Compounds in Table 2:

5-(2,2-difluoro-2-(4-nitrophenoxy)ethyl)-1,2,3-trimethoxybenzene (6a): Following General Procedure B-1, 0.115 g (0.50 mmol) of compound **1** was reacted with 0.348 g (2.50 mmol) of 4-nitrophenol in the presence of 0.066 g (0.5 mmol) of TBD at 140 ˚C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H_2O, furnishing 0.125 g (69% yield, 3% of ***E*-7a**) of desired product **6a** as a dark yellow solid (MP = 117–120 ˚C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, *J* = 9.2 Hz, 2 H), 7.28 (d, *J* = 8.9 Hz, 2 H), 6.57 (s, 2 H), 3.88 (s, 6 H), 3.86 (s, 3 H), 3.42 (t, *J* = 11.4 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.4, 153.3, 145.0, 138.0, 126.8 (t, *J* = 3.4 Hz), 125.4, 124.0 (t, *J* = 269.3 Hz), 121.4 (t, *J* = 1.9 Hz), 116.6, 107.7, 61.0, 56.3, 42.5 (t, *J* = 29.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ ; ^{19}F NMR (376 MHz, $CDCl_3$) δ –71.41 (t, *J* = 11.4 Hz, 2 F); IR (film) 2940, 2841, 1614, 1592, 1522, 1509, 1492, 1461, 1424, 1346, 1325, 1301, 1238, 1209, 1157, 1124, 1060, 1009, 943, 930, 911, 853, 801, 764, 750, 723, 692, 649 cm^{-1}; HRMS (HAPCI+) calc. for $C_{17}H_{18}F_2NO_6$ (M+H) 370.1102, found 370.1099. ***E*-7a** characteristic peaks: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 (d, *J* = 5.8 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –85.52 (d, *J* = 5.9 Hz, 1 F).

4-(1,1-difluoro-2-(3,4,5-trimethoxyphenyl)ethoxy)benzonitrile (6b): Following General Procedure B-1, 0.115 g (0.50 mmol) of compound **1** was reacted with 0.298 g (2.50 mmol) of 4-hydroxybenzonitrile in the presence of 0.033 g (0.25 mmol) of TBD at 140 ˚C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H_2O, furnishing 0.143 g (82% yield, 5% ***E*-7b**, 1% ***Z*-7b**) of desired product **6b** as a yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.8 Hz, 2 H), 7.23 (d, *J* = 8.4 Hz, 2 H), 6.56 (s, 2 H), 3.87 (s, 6 H), 3.85 (s, 3 H), 3.40 (t, *J* = 11.3 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.9, 153.3, 133.8, 126.9 (t, *J* = 3.4 Hz), 124.0 (t, *J* = 269.6 Hz), 121.8 (d, *J* = 1.8 Hz), 118.3, 117.0, 109.2, 107.7, 61.0, 56.3, 42.5 (t, *J* = 29.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –71.23 (t, *J* = 11.5 Hz, 2 F); IR (film) 2940, 2842, 2253, 2231, 1596, 1505, 1464, 1424, 1360, 1325, 1296, 1253, 1241, 1210, 1173, 1156, 1129, 1068, 1004, 908, 841, 802, 732, 649 cm^{-1}; HRMS (ESI+) calc. for $C_{18}H_{17}F_2NO_4Na$ (M+Na) 372.1023, found 372.1026. ***E*-7b** characteristic peaks: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76 (d, *J* = 5.7 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –85.31 (d, *J* = 5.5 Hz, 1 F); ***Z*-7b** characteristic peaks: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.43 (d, *J* = 27.8 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –85.81 (d, *J* = 32.89 Hz, 1 F).

5-(2-(2,4-dichlorophenoxy)-2,2-difluoroethyl)-1,2,3-trimethoxybenzene (6c): Following General Procedure B-1, 0.115 g (0.50 mmol) of compound **1** was reacted with 0.408 g (2.50 mmol) of 2,4-dichlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 ˚C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H_2O, furnishing 0.145 g (72% yield) of desired product **6c** as a clear oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 2.5 Hz, 1 H), 7.27–7.25 (m, 1 H), 7.19 (dd, *J* = 8.8, 2.5 Hz, 1 H), 6.60 (s, 2 H), 3.87 (s, 6 H), 3.85 (s, 3 H), 3.43 (t, *J* = 11.0 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.2, 145.3 (t, *J* = 1.7 Hz), 137.8, 131.3, 130.3, 128.2, 127.8, 127.0 (t, *J* = 3.5 Hz), 124.07 (t, *J* = 269.4 Hz), 123.93 (t, *J* = 2.0 Hz), 107.9, 61.0, 56.3, 42.4 (t, *J* = 29.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –70.83 (t, *J* = 11.0 Hz, 2 F); IR (film) 2940, 2839, 1592, 1508, 1476, 1463, 1423, 1360, 1324, 1258, 1238, 1128, 1061, 1008, 942, 867, 808, 764, 700, 666, 528 cm^{-1}; HRMS (HAPCI+) calc. for $C_{17}H_{16}Cl_2F_2O_4$ (M+) 392.0394, found 394.0424.

5-(2,2-difluoro-2-(3-iodophenoxy)ethyl)-1,2,3-trimethoxybenzene (6d): Following General Procedure B-1, 0.115 g (0.50 mmol) of compound **1** was reacted with 0.551 g (2.50 mmol) of 3-iodophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 ˚C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H_2O, furnishing 0.158 g (71% yield, **2% *E*-7d**) of desired product **6d** as a brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53–7.50 (m, 2 H), 7.12 (dd, *J* = 8.25, 2.15 Hz, 1 H), 7.03 (t, *J* = 8.01 Hz, 1 H), 6.56 (s, 2 H), 3.86 (s, 9 H), 3.36 (t, *J* = 11.08 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.1, 150.7 (d, *J* = 2.30 Hz), 137.7 (d, *J* = 1.69 Hz), 134.7, 130.9, 130.7, 127.3 (t, *J* = 3.39 Hz), 123.8 (t, *J* = 267.33 Hz), 121.2, 107.6, 93.5, 60.9, 56.2, 42.4 (t, *J* = 29.73 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –70.60 (t, *J* = 11.13 Hz, 2 F); IR (film) 2938, 2839, 1591, 1583, 1509, 1465, 1422, 1360, 1324, 1260, 1237, 1192, 1156, 1126, 1054, 1008, 945, 910, 865, 832, 765, 750, 735, 686, 665, 649 cm^{-1}; MS (EI+) calc. for $C_{17}H_{17}F_2IO_4$ (M+) 450.0, found 449.9. ***E*-7d** characteristic peaks: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.67 (d, *J* = 5.7 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –84.19 (d, *J* = 5.6 Hz, 1 F).

5-(2-(3-chloro-2-fluorophenoxy)-2,2-difluoroethyl)-1,2,3-trimethoxybenzene (6e): Following General Procedure B-1, 0.115 g (0.50 mmol) of compound **1** was reacted with 0.26 mL

(2.50 mmol) of 2-fluoro-3-chlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 ˚C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H_2O, furnishing 0.139 g (74% yield, 5% ***E*-7e**) of desired product **6e** as a clear solid (MP = 50–51 ˚C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (ddd, *J* = 8.1, 6.3, 1.6 Hz, 1 H), 7.19 (ddd, *J* = 8.3, 6.8, 1.4 Hz, 1 H), 7.01 (td, *J* = 8.3, 1.9 Hz, 1 H), 6.60 (s, 2 H), 3.87 (s, 6 H), 3.86 (s, 3 H), 3.43 (t, *J* = 11.1 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ ;153.2, 150.4, 137.7 (t, *J* = 1.5 Hz), 127.5, 127.0 (t, *J* = 3.5 Hz), 123.97, 123.96 (t *J* = 269.8 Hz), 123.93, 122.6, 122.3 (d, *J* = 15.8 Hz), 107.6, 61.0, 56.2, 42.2 (t, *J* = 29.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –71.19 (td, *J* = 11.3, 5.3 Hz, 2 F), –131.17 (p, *J* = 6.2 Hz, 1 F); IR (film) 2941, 2842, 2253, 1705, 1595, 1509, 1483, 1462, 1424, 1360, 1325, 1275, 1260, 1243, 1181, 1156, 1129, 1069, 1027, 1004, 956, 907, 838, 821, 764, 746, 650 cm^{-1}; HRMS (HAPCI+) calc. for $C_{17}H_{16}ClF_3O_4$ (M+) 376.0689, found 376.0682. ***E*-7e** characteristic peaks: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.64 (d, *J* = 6.1 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –85.26 (d, *J* = 6.1 Hz, 1 F).

5-(2-(4-bromophenoxy)-2,2-difluoroethyl)-1,2,3-trimethoxybenzene (6f): Following General Procedure B-1, 0.115 g (0.50 mmol) of compound **1** was reacted with 0.432 g (2.50 mmol) of 4-bromophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 ˚C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H_2O, furnishing 0.137 g (68% yield, 3% ***E*-7f**) of desired product **6f** (or 2) as a clear oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.8 Hz, 2 H), 7.01 (d, *J* = 8.6 Hz, 2 H), 6.57 (s, 2 H), 3.86 (s, 9 H), 3.37 (t, *J* = 11.1 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.2, 149.4, 137.7 (t, *J* = 1.6 Hz), 132.4, 127.4, 123.7 (t, *J* = 267.9 Hz), 123.6, 118.6, 107.6, 60.9, 56.2, 42.4 (t, *J* = 29.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –70.87 (t, *J* = 11.2 Hz, 2 F); IR (film) 2939, 2842, 2252, 1594, 1509, 1486, 1464, 1424, 1361, 1324, 1275, 1260, 1239, 1199, 1156, 1129, 1068, 1012, 908, 827, 797, 764, 744, 698, 649 cm^{-1}; HRMS (HAPCI+) calc. for $C_{17}H_{17}BrF_2O_4$ (M+) 402.0278, found 402.0267. ***E*-7f** characteristic peaks: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.66 (d, *J* = 5.7 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –84.44 (d, *J* = 5.7 Hz, 1 F).

4-(1,1-difluoro-2-(3,4,5-trimethoxyphenyl)ethoxy)-1,1'-biphenyl (6g): Following General Procedure B-1, 0.115 g (0.50 mmol) of compound **1** was reacted with 0.426 g (2.50 mmol) of 4-phenylphenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 ˚C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by flash normal phase chromatography using a gradient of hexanes to 5% PhMe and 15% EtOAc in hexanes, furnishing 0.107 g of pure compound **6g** as colorless solid (MP = 67–70 ˚C), and 0.053 g of 80% pure compound **6g**; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56–7.54 (m, 4 H), 7.44 (t, *J* = 7.6 Hz, 2 H), 7.35 (t, *J* = 7.4 Hz, 1 H), 7.22 (d, *J* = 8.2 Hz, 2 H), 6.62 (s, 2 H), 3.88 (s, 9 H), 3.42 (t, *J* = 11.0 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) d 153.2, 149.9 (t, *J* = 2.1 Hz), 140.4, 138.7, 137.7 (t, *J* = 1.3 Hz), 128.9, 128.2, 127.7 (t, *J* = 3.2 Hz), 127.5, 127.2, 123.9 (t, *J* = 266.4 Hz), 122.0, 107.7, 61.0, 56.3, 42.6 (t, *J* = 30.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –70.42 (t, *J* = 10.9 Hz, 2 F); IR (film) 2253, 1595, 1510, 1486, 1464, 1424, 1325, 1241, 1131, 1009, 905, 729, 650 cm^{-1}; HRMS (HAPCI+) calc. for $C_{23}H_{22}F_2O_4$ (M+) 400.1486, found 400.1478.

5-(2,2-difluoro-2-(*o*-tolyloxy)ethyl)-1,2,3-trimethoxybenzene (6h): Following General Procedure B-1, 0.115 g (0.50 mmol) of compound **1** was reacted with 0.26 mL (2.50 mmol) of o-cresol in the presence of 0.033 g (0.25 mmol) of TBD at 140 ˚C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by normal-phase flash chromatography using a gradient of 0–10% EtOAc in hexanes with 1% PhMe, followed by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H_2O, furnishing 0.068 g (40% yield) of desired product **6h** as a pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (dd, *J* = 8.4, 1.7 Hz, 1 H), 7.15 (t, *J* = 7.0 Hz, 2 H), 7.08 (dt, *J* = 7.5, 7.0, 1.4 Hz, 1 H), 6.60 (s, 2 H), 3.87 (s, 6 H), 3.86 (s, 3 H), 3.41 (t, *J* = 10.6 Hz, 2 H), 2.05 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.1, 148.9, 137.7 (d, *J* = 1.3 Hz), 131.22, 131.19, 127.8 (t, *J* = 3.7 Hz), 126.7, 125.5, 124.1 (t, *J* = 266.8 Hz), 121.9 (d, *J* = 1.7 Hz), 107.8, 61.0, 56.3, 42.7 (t, *J* = 30.7 Hz), 16.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ –69.81 (t, *J* = 10.6 Hz, 2 F); IR (film) 2939, 2840, 1591, 1508, 1494, 1460, 1423, 1360, 1324, 1262, 1238, 1177, 1156, 1126, 1091, 1042, 1009, 944, 892, 862, 832, 749, 704, 658, 618 cm^{-1}; HRMS (HAPCI+) calc. for $C_{18}H_{20}F_2O_4$ (M+) 338.1330, found 338.1320.

5-(2,2-difluoro-2-(2-isopropylphenoxy)ethyl)-1,2,3-trimethoxybenzene (6i): Following General Procedure B-1, 0.115 g (0.50 mmol) of compound **1** was reacted with 0.336 mL (2.50 mmol) of 2-isoporpylphenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 ˚C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H_2O, furnishing 0.061 g (34% yield) of desired product **6i** as a clear oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.26 (m, 2 H), 7.18 (dt, *J* = 6.2, 2.5 Hz, 2 H), 6.64 (s, 2 H), 3.90 (s, 9 H), 3.45 (t, *J* = 10.3 Hz, 2 H), 2.90 (p, *J* = 6.9 Hz, 1 H), 1.08 (d, *J* = 6.9 Hz, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.2, 147.6 (t, *J* = 1.8 Hz), 141.3, 127.9 (t, *J* = 3.8 Hz), 126.6, 126.5, 125.8, 124.0 (t, *J* = 266.4 Hz), 121.7 (t, *J* = 2.0 Hz), 107.8, 61.0, 56.2, 42.8 (t, *J* = 30.6 Hz), 26.5, 23.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ –69.54 (t, *J* = 10.4 Hz, 2 F); IR (film) 2963, 2840, 1592, 1508, 1489, 1459, 1423, 1362, 1323, 1260, 1238, 1179, 1156, 1127, 1086, 1045, 1009, 944, 892, 860, 829, 809, 752, 722, 705, 659, 603, 545, 529 ,472, 455 cm^{-1}; HRMS (HAPCI+) calc. for $C_{20}H_{24}F_2O_4$ (M+) 366.1643, found 366.1638.

2-(1,1-difluoro-2-(3,4,5-trimethoxyphenyl)ethoxy)-1,1'-biphenyl (6j): Following General Procedure B-1, 0.115 g (0.50 mmol) of compound **1** was reacted with 0.426 g (2.50 mmol) of 2-phenylphenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 ˚C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H_2O, furnishing 0.127 g (40 % yield, 23% ***E*-7j**, 3% ***Z*-7j**) of compound **6j** as a pale oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.38 (m, 1 H), 7.34–7.29 (m, 7 H), 7.25 (td, *J* = 7.4, 1.3 Hz, 1 H), 6.35 (s, 2 H), 3.84 (s, 3 H), 3.75 (s, 6 H), 3.19 (t, *J* = 10.8 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.0, 147.5, 138.1, 135.3, 131.3, 129.6, 129.4, 128.9, 128.4, 128.0, 127.7, 127.4 (d, *J* = 3.8 Hz), 127.2, 125.7, 123.9 (t, *J* = 269.2 Hz), 122.1 (d, *J* = 2.2 Hz), 107.6, 60.9, 56.1, 42.6 (t, *J* = 30.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –69.38 (t, *J* = 10.9 Hz, 2 F); IR (film) 2938, 2839, 1754, 1699, 1591, 1507, 1479, 1460, 1422, 1359, 1324, 1275, 1259, 1235, 1188, 1155, 1125, 1045, 1010, 946, 916, 830, 748, 701, 660, 613, 569, 528 cm^{-1}; HRMS (HAPCI+) calc. for $C_{23}H_{22}F_2O_4$ (M+) 400.1486, found 400.1486. ***E*-7j** characteristic peaks: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.61 (d, *J* = 6.2 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –84.18 (d, *J* = 6.2 Hz, 1 F); *Z*-7j characteristic peaks: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.06 (d, *J* = 28.7 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –84.21 (d, *J* = 28.7 Hz, 1 F).

5-(2,2-difluoro-2-(4-methoxyphenoxy)ethyl)-1,2,3-trimethoxybenzene (6k): Following General Procedure B-1, 0.115 g (0.50 mmol) of compound **1** was reacted with 0.310 g (2.50 mmol) of 4-methoxyphenol in the presence of 0.033 g (0.25

mmol) of TBD at 140 ˚C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H_2O, furnishing 0.089 g (51% yield, 5% ***E*-7k**) of desired product **6k** as a colorless solid (MP = 64–66 ˚C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.6 Hz, 2 H), 6.83 (d, *J* = 9.0 Hz, 2 H), 6.59 (s, 2 H), 3.86 (s, 9 H), 3.77 (s, 3 H), 3.36 (t, *J* = 10.9 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.3, 153.1, 143.7, 137.6 (d, *J* = 1.4 Hz), 127.8 (d, *J* = 3.2 Hz), 123.8 (t, *J* = 266.8 Hz), 123.2, 114.4, 107.6, 60.9, 56.2, 55.6, 42.4 (t, *J* = 30.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –70.65 (t, *J* = 11.0 Hz, 2 F); IR (film) 3003, 2939, 2839, 2252, 1702, 1592, 1506, 1463, 1423, 1362, 1324, 1298, 1267, 1241, 1192, 1156, 1128, 1040, 1009, 943, 910, 842, 807, 784, 763, 735, 698, 649 cm^{-1}; HRMS (HAPCI+) calc. for $C_{18}H_{20}F_2O_5$ (M+) 354.1279, found 354.1269. ***E*-7k** characteristic peaks: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.57 (d, *J* = 5.7 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –83.52 (d, *J* = 5.8 Hz, 1 F).

3-(1,1-difluoro-2-(3,4,5-trimethoxyphenyl)ethoxy)-*N*,*N*-dimethylaniline (6l): Following General Procedure B-1, 0.115 g (0.50 mmol) of compound **1** was reacted with 0.343 g (2.50 mmol) of 3-dimethylaminophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 ˚C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by normal-phase flash chromatography using a gradient of 0–30% EtOAc in hexanes to remove 3-dimethylaminophenol, followed by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H_2O, furnishing 0.051 g (28% yield, 3% ***E*-7l**) of compound **6l** as a yellow semisolid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (t, *J* = 8.2 Hz, 1 H), 6.59 (s, 2 H), 6.55 (dd, *J* = 8.4, 2.5 Hz, 1 H), 6.52 (d, *J* = 7.5 Hz, 1 H), 6.46 (t, *J* = 2.4 Hz, 1 H), 3.87 (s, 6 H), 3.86 (s, 3 H), 3.37 (t, *J* = 11.1 Hz, 2 H), 2.93 (s, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.1, 151.7, 151.6 (t, *J* = 2.3 Hz), 137.6, 129.6, 127.9 (t, *J* = 3.2 Hz), 123.9 (t, *J* = 266.1 Hz), 109.7, 109.5, 107.6, 105.9, 61.0, 56.2, 42.6 (t, *J* = 30.6 Hz), 40.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ –69.93 (t, *J* = 11.1 Hz, 2 F); IR (film) 2938, 2840, 1699, 1608, 1592, 1505, 1460, 1423, 1358, 1324, 1263, 1236, 1126, 1045, 1003, 941, 876, 838, 812, 765, 750, 687, 668, 612, 528 cm^{-1}; HRMS (ESI+) calc. for $C_{19}H_{24}F_2NO_4$ (M+H) 368.1673, found 368.1662. ***E*-7l** characteristic peaks: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.61 (d, *J* = 5.5 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –82.25 (d, *J* = 5.7 Hz, 1 F).

Compounds in Table 3:

(4-(2-(2,4-dichlorophenoxy)-2,2-difluoroethyl)phenyl)(methyl)sulfane (9a): Following General Procedure B-1, 0.093 g (0.50 mmol) of compound **8a** was reacted with 0.408 g (2.50 mmol) of 2,4-dichlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 ˚C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H_2O, furnishing 0.112 g (68% yield, 2% ***E*-10a**) of desired product **9a** as a tan solid (MP = 69–70 ˚C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 2.2 Hz, 1 H), 7.32 (d, *J* = 8.1 Hz, 2 H), 7.25 (d, *J* = 8.4 Hz, 2 H), 7.23 (d, *J* = 8.7 Hz, 1 H), 7.18 (ddd, *J* = 8.8, 2.5, 1.0 Hz, 1 H), 3.45 (t, *J* = 11.1 Hz, 2 H), 2.49 (d, *J* = 1.1 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.3, 138.3, 131.3, 131.2, 130.3, 128.4, 128.3 (t, *J* = 3.4 Hz), 127.7, 126.6, 124.1 (t, *J* = 2.0 Hz), 124.0 (t, *J* = 269.7 Hz), 41.7 (t, *J* = 29.4 Hz), 15.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ –71.10 (t, *J* = 11.1 Hz, 2 F); IR (film) 2924, 1476, 1433, 1408, 1352, 1324, 1283, 1260, 1217, 1174, 1119, 1095, 1061, 1019, 958, 907, 868, 843, 800, 762, 733, 696, 675, 650 cm^{-1}; HRMS (HAPCI+) calc. for $C_{15}H_{12}Cl_2F_2OS$ (M+) 347.9954, found 347.9944. ***E*-10a** characteristic peaks: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.69 (d, *J* = 6.0 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –85.56 (d, *J* = 6.1 Hz, 1 F).

1-bromo-4-(1,1-difluoro-2-(4-methoxyphenyl)ethoxy)benzene (9b): Following General Procedure B-1, 0.086 g (0.50 mmol) of compound **8b** was reacted with 0.433 g (2.50 mmol) of 4-bromophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 ˚C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H_2O, furnishing 0.097 g (56% yield) of desired product **9b** as a peach solid (MP = 51–52 ˚C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.9 Hz, 2 H), 7.29 (d, *J* = 8.3 Hz, 2 H), 7.01 (d, *J* = 8.5 Hz, 2 H), 6.91 (d, *J* = 8.8 Hz, 2 H), 3.82 (s, 3 H), 3.39 (t, *J* = 11.1 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.3, 149.6, 132.4, 131.6, 123.97 (t, *J* = 3.3 Hz), 123.91 (t, *J* = 267.2 Hz), 123.6 (d, *J* = 1.4 Hz), 118.6, 114.0, 55.3, 41.4 (t, *J* = 29.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –71.48 (t, *J* = 11.2 Hz, 2 F); IR (film) 3005, 2937, 2838, 1614, 1585, 1515, 1486, 1464, 1442, 1352, 1324, 1303, 1248, 1200, 1179, 1127, 1116, 1087, 1067, 1036, 1013, 908, 847, 821, 796, 785, 764, 736, 697, 677, 650 cm^{-1}; HRMS (HAPCI+) calc. for $C_{15}H_{13}BrF_2O_2$ (M+) 342.0067, found 342.0067.

4-(3-(2-(2,4-dichlorophenoxy)-2,2-difluoroethyl)phenyl)morpholine (9c): Following General Procedure B-1, 0.112 g (0.50 mmol) of compound **8c** was reacted with 0.408 g (2.50 mmol) of 2,4-dichlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 ˚C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H_2O, furnishing 0.148 g (78% yield, 6% ***E*-10c**, 1% ***Z*-10c**) of desired product **9c** as a yellow solid (MP = 61–64 ˚C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 2.5 Hz, 1 H), 7.32 (d, *J* = 7.9 Hz, 1 H), 7.30–7.28 (m, 1 H), 7.23 (dd, *J* = 8.8, 2.5 Hz, 1 H), 7.00 (t, *J* = 1.9 Hz, 1 H), 6.97 (d, *J* = 7.5 Hz, 1 H), 6.93 (dd, *J* = 8.3, 2.4 Hz, 1 H), 3.92–3.90 (m, 4 H), 3.51 (t, *J* = 11.2 Hz, 2 H), 3.24–3.22 (m, 4 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.4, 145.3, 132.4 (t, *J* = 3.4 Hz), 131.2, 130.3, 129.2, 128.3, 127.7, 124.1 (t, *J* = 269.2 Hz), 124.0 (t, *J* = 1.9 Hz), 122.4, 118.1, 115.1, 67.0, 49.4, 42.4 (t, *J* = 29.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –70.77 (t, *J* = 11.30 Hz, 2 F); IR (film) 2967, 2860, 2250, 1604, 1585, 1495, 1476, 1449, 1380, 1353, 1325, 1304, 1274, 1259, 1245, 1218, 1175, 1120, 1097, 1068, 998, 976, 908, 869, 837, 812, 763, 745, 697, 650, 618 cm^{-1}; HRMS (ESI+) calc. for $C_{18}H_{18}Cl_2F_2NO_2$ (M+H) 388.0683, found 388.0669. ***E*-10c** characteristic peaks: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73 (d, *J* = 6.3 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –85.25 (d, *J* = 6.7 Hz, 1 F); ***Z*-10c** characteristic peaks: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.26 (d, *J* = 28.7 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –84.99 (d, *J* = 28.6 Hz, 1 F).

4'-(*tert*-butyl)-2-(2-(2,4-dichlorophenoxy)-2,2-difluoroethyl)-1,1'-biphenyl (9d): Following General Procedure B-1, 0.136 g (0.50 mmol) of compound **8d** was reacted with 0.408 g (2.50 mmol) of 2,4-dichlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 ˚C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H_2O, furnishing 0.153 g (70% yield, 3% ***E*-10d**) of desired product **9d** as a colorless solid (MP = 76–78 ˚C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (s, 1 H), 7.64–7.62 (m, 3 H), 7.55 (d, *J* = 7.9 Hz, 2 H), 7.49 (t, *J* = 7.7 Hz, 1 H), 7.46 (d, *J* = 2.1 Hz, 1 H), 7.43 (d, *J* = 7.6 Hz, 1 H), 7.31 (dd, *J* = 8.9, 1.3 Hz, 1 H), 7.24 (dt, *J* = 8.9, 1.8 Hz, 1 H), 3.63 (t, *J* = 11.1 Hz, 2 H), 1.45 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.6, 145.3, 141.4, 138.1, 132.0 (t, *J* = 3.4 Hz), 131.3, 130.3, 129.6, 129.4, 128.9, 128.5, 127.7, 127.0, 126.6, 125.9, 124.20 (t, *J* = 2.1 Hz), 124.15 (t, *J* = 269.3 Hz), 42.3 (t, *J* = 29.3 Hz), 34.7, 31.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ –70.80 (t, *J* = 11.0 Hz, 2 F); IR (film) 2964, 2250, 1476, 1352,

1324, 1256, 1218, 1174, 1116, 1097, 1062, 1043, 1016, 907, 868, 837, 813, 794, 763, 734, 704, 650, 617 cm^{-1}; HRMS (HAPCI+) calc. for $C_{24}H_{22}Cl_2F_2O$ (M+) 434.1016, found 434.0999. ***E*-10d** characteristic peaks: ^1H NMR (500 MHz, $CDCl_3$) δ 5.83 (d, *J* = 6.2 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –85.04 (d, *J* = 6.1 Hz, 1 F).

1-(2-(4-(*tert*-butyl)phenyl)-1,1-difluoroethoxy)-2,4-dichlorobenzene (9f): Following General Procedure B-1, 0.098 g (0.50 mmol) of compound **8f** was reacted with 0.408 g (2.50 mmol) of 2,4-dichlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 ˚C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H_2O, furnishing 0.074 g (41% yield) of desired product **9f** as a clear oil; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43–7.40 (m, 3 H), 7.35 (d, *J* = 8.1 Hz, 2 H), 7.28–7.26 (m, 1 H), 7.20 (ddd, *J* = 8.8, 2.5, 0.8 Hz, 1 H), 3.50 (t, *J* = 11.3 Hz, 2 H), 1.36 (9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.8, 145.4, 131.3, 130.4, 130.3, 128.6, 128.4, 127.7, 125.5, 124.2 (t, *J* = 269.8 Hz), 124.1 (t, *J* = 2.1 Hz), 41.7 (t, *J* = 29.2 Hz), 34.7, 31.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ –71.02 (t, *J* = 11.4 Hz, 2 F); IR (film) 2965, 2869, 1477, 1352, 1325, 1274, 1260, 1218, 1175, 1159, 1124, 1097, 1062, 1026, 907, 869, 838, 805, 764, 745, 697, 651 cm^{-1}; HRMS (HAPCI+) calc. for $C_{18}H_{18}Cl_2F_2O$ (M+) 358.0703, found 358.0701.

1-(2,2-difluorovinyl)-3,5-dimethylbenzene (8g): Following General Procedure A, 3,5-dimethylbenzaldehyde (2.10 mL, 15.0 mmol) was reacted with PPh_3 (6.23 g, 22.5 mmol) and $BrCF_2CO_2K$ (6.05 g, 27.0 mmol). Following workup, the product was purified by flash chromatography using a gradient of 0–10% EtOAc in hexanes, furnishing 1.163 g (44% yield) of desired product **8g** as a clear oil; ^1H NMR (400 MHz, $CDCl_3$) δ 6.97 (bs, 2 H), 6.90 (bs, 1 H), 5.21 (dd, *J* = 26.4, 4.0 Hz, 1H), 2.32 (s, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.3 (dd, *J* = 298.2, 287.4 Hz), 138.3, 130.3 (t, *J* = 6.7 Hz), 128.9 (t, *J* = 2.2 Hz), 125.6 (dd, *J* = 6.6, 3.7 Hz), 82.3 (dd, *J* = 28.9, 13.6 Hz), 21.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ –82.39 (dd, *J* = 32.5, 26.5 Hz, 1 F), –84.62 (dd, *J* = 32.5, 4.0 Hz, 1F); IR (film) 3019, 2921, 2868, 1726, 1605, 1448, 1379, 1350, 1297, 1198, 1160, 1038, 965, 892, 851, 814, 765, 750, 715, 690, 583, 539, 515 cm^{-1}; HRMS (TAPCI) calc. for $C_{10}H_{10}F_2$ (M) 168.0751, found 168.0744.

2,4-dichloro-1-(2-(3,5-dimethylphenyl)-1,1-difluoroethoxy)benzene (9g): Following General Procedure B-1, 0.085 g (0.50 mmol) of compound **8i** was reacted with 0.408 g (2.50 mmol) of 2,4-dichlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 ˚C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H_2O, furnishing 0.092 g (55% yield) of desired product **9i** as a pale yellow oil; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 2.5 Hz, 1 H), 7.25 (d, *J* = 8.6 Hz, 1 H), 7.18 (dd, *J* = 8.8, 2.5 Hz, 1 H), 7.02 (s, 2 H), 6.97 (s, 1 H), 3.42 (t, *J* = 11.4 Hz, 2 H), 2.33 (s, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.5, 138.0, 131.3 (t, *J* = 3.2 Hz), 131.2, 130.3, 129.5, 128.6, 128.4, 127.7, 124.2 (t, *J* = 269.5 Hz), 124.1 (d, *J* = 2.2 Hz), 42.1 (t, *J* = 29.3 Hz), 21.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ –70.95 (t, *J* = 11.4 Hz, 2 F); IR (film) 3010, 2920, 1608, 1584, 1476, 1433, 1382, 1353, 1298, 1276, 1251, 1218, 1168, 1096, 1061, 962, 866, 847, 809, 764, 751, 715, 695, 661 cm^{-1}; HRMS (HAPCI+) calc. for $C_{16}H_{14}Cl_2F_2O$ (M+) 330.0390, found 330.0391.

1-(2,2-difluorovinyl)-2,4-dimethylbenzene (8h): Following General Procedure A, 2,4-dimethylbenzaldehyde (3.20 mL, 22.0 mmol) was reacted with PPh_3 (8.84 g, 33.0 mmol) and $BrCF_2CO_2K$ (8.76 g, 40.0 mmol). Following workup, the product was purified by flash chromatography using a gradient of 0–10% EtOAc in hexanes, furnishing 1.57 g (41% yield) of desired product **8h** as a clear oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 8.4, 2.0 Hz, 1 H), 7.02 (dd, *J* = 4.2, 2.3 Hz, 2 H), 5.34 (dd, *J* = 25.6, 3.9 Hz, 1 H), 2.32 (s, 3 H), 2.27 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.2 (dd, *J* = 295.2, 288.1 Hz), 137.2, 135.8 (dd, *J* = 4.8, 1.7 Hz), 131.1, 128.1 (dd, *J* = 7.9, 2.0 Hz), 127.0, 126.0 (dd, *J* = 6.9, 4.9 Hz), 79.3 (dd, *J* = 28.7, 14.9 Hz), 21.2, 20.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ –84.76 (dd, *J* = 33.1, 4.1 Hz, 1 F), –85.53 (ddd, *J* = 33.1, 25.5, 1.8 Hz, 1F); IR (film) 2923, 1726, 1616, 1569, 1505, 1453, 1379, 1345, 1281, 1250, 1235, 1180, 1111, 1074, 1037, 948, 917, 876, 836, 818, 765, 750, 721, 615, 581, 549, 534 cm^{-1}; HRMS (HAPCI+) calc. for $C_{10}H_{10}F_2$ (M+) 168.0751, found 168.0745.

2,4-dichloro-1-(2-(2,4-dimethylphenyl)-1,1-difluoroethoxy)benzene (9h): Following General Procedure B-1, 0.084 g (0.50 mmol) of compound **8h** was reacted with 0.408 g (2.50 mmol) of 2,4-dichlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 ˚C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H_2O, furnishing 0.050 g (27% yield, 8% ***E*-10h**) as a pale yellow semisolid; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 2.5 Hz, 1 H), 7.25–7.22 (m, 2 H), 7.17 (dd, *J* = 8.8, 2.4 Hz, 1 H), 7.04 (s, 1 H), 7.01 (d, *J* = 7.9 Hz, 1 H), 3.50 (t, *J* = 11.3 Hz, 2 H), 2.40 (s, 3 H), 2.31 (s, 3 H); ^{13}C (126 MHz, $CDCl_3$) δ 145.4 (t, *J* = 1.6 Hz), 137.74, 137.68, 131.7, 131.4, 131.3, 130.3, 128.5, 127.7, 127.0 (t, *J* = 3.1 Hz), 126.8, 124.6 (t, *J* = 271.0 Hz), 124.2 (t, *J* = 2.0 Hz), 38.6 (t, *J* = 29.2 Hz), 21.2, 20.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ –70.43 (t, *J* = 11.4 Hz, 2 F); IR (film) 2923, 1702, 1618, 1583, 1508, 1476, 1382, 1347, 1311, 1258, 1217, 1126, 1095, 1060, 963, 942, 866, 810, 792, 762, 694, 673, 626, 566, 465, 455 cm^{-1}; MS (EI+) calc. for $C_{16}H_{14}Cl_2F_2O$ (M+) 330.0, found 330.0. ***E*-10h** characteristic peaks: ^1H NMR (500 MHz, $CDCl_3$) δ 5.83 (d, *J* = 6.4 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –85.72 (d, *J* = 6.4 Hz, 1 F).

ethyl (*E*)-3-(3-(2-(2,4-dichlorophenoxy)-2,2-difluoroethyl)phenyl)acrylate (9j): Following General Procedure B-1, 0.119 g (0.50 mmol) of compound **8j** was reacted with 0.408 g (2.50 mmol) of 2,4-dichlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 ˚C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H_2O, furnishing 0.127 g (64% yield) of desired product **9j** as a colorless solid (MP = 70–72 ˚C); ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 16.0 Hz, 1 H), 7.56 (s, 1 H), 7.49 (d, *J* = 7.5 Hz, 1 H), 7.42–7.36 (m, 3 H), 7.23 (d, *J* = 8.8 Hz, 1 H), 7.17 (dd, *J* = 8.8, 2.5 Hz, 1 H), 6.47 (d, *J* = 16.0 Hz, 1 H), 4.27 (q, *J* = 7.1 Hz, 2 H), 3.51 (t, *J* = 10.9 Hz, 2 H), 1.34 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.0, 145.1, 144.2, 134.8, 132.5, 132.3 (t, *J* = 3.4 Hz), 131.4, 130.4, 130.3, 129.1, 128.4, 127.7, 127.5, 124.1 (d, *J* = 1.8 Hz), 123.9 (t, *J* = 269.7 Hz), 118.9, 60.6, 42.0 (t, *J* = 29.4 Hz), 14.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ –70.81 (t, *J* = 10.9 Hz, 2 F); IR (film) 2983, 2253, 1709, 1640, 1608, 1585, 1476, 1438, 1385, 1367, 1354, 1322, 1274, 1260, 1228, 1179, 1163, 1119, 1097, 1061, 983, 909, 865, 840, 812, 763, 750, 694 cm^{-1}; HRMS (HAPCI+) calc. for $C_{19}H_{16}Cl_2F_2O_3$ (M+) 400.0445, found 400.0435.

2,4-dichloro-1-(1,1-difluoro-2-(3-nitrophenyl)ethoxy)benzene (9k): Following General Procedure B-1, 0.093 g (0.50 mmol) of compound **8k** was reacted with 0.408 g (2.50 mmol) of 2,4-dichlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 ˚C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H_2O,

furnishing 0.083 g (47% yield, 3% ***E*-10k**, 1% **Z-10k**) of desired product **9k** as a clear solid (MP = 96–97 ˚C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, *J* = 2.1 Hz, 1 H), 8.22 (dd, *J* = 8.3, 2.5 Hz, 1 H), 7.75 (d, *J* = 7.7 Hz, 1 H), 7.55 (t, *J* = 7.9 Hz, 1 H), 7.39 (d, *J* = 2.5 Hz, 1 H), 7.24 (d, *J* = 9.0 Hz, 1 H), 7.20 (dd, *J* = 8.8, 2.3 Hz, 1 H), 3.61 (t, *J* = 10.5 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.9 (d, *J* = 1.9 Hz), 136.9, 133.5, 131.7, 130.4, 129.5, 128.4, 127.9, 125.8, 124.1 (t, *J* = 2.0 Hz), 123.5 (t, *J* = 269.6 Hz), 123.1, 41.9 (t, *J* = 30.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –70.75 (t, *J* = 10.6 Hz, 2 F); IR (film) 2956, 2923, 2870, 1702, 1532, 1475, 1352, 1324, 1300, 1258, 1216, 1173, 1158, 1125, 1097, 1068, 1061, 1027, 970, 908, 866, 802, 765, 34, 697, 677, 657 cm^{-1}; HRMS (HAPCI+) calc. for $C_{14}H_9Cl_2F_2NO_3$ (M+) 346.9928, found 346.9925. ***E*-10k** characteristic peaks: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73 (d, *J* = 6.0 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –81.93 (d, *J* = 5.5 Hz, 1 F); ***Z*-10k** characteristic peaks: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.21 (d, *J* = 28.0 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –82.18 (d, *J* = 27.9 Hz, 1 F).

3-(2-(2,4-dichlorophenoxy)-2,2-difluoroethyl)benzonitrile (9l): Following General Procedure B-2, 0.083 g (0.50 mmol) of compound **8l** was reacted with 0.245 g (1.50 mmol) of 2,4-dichlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 ˚C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H_2O, furnishing 0.080 g (49% yield) of desired compound **9l** as a colorless solid (MP = 81–83 ˚C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 2.3 Hz, 1 H), 7.65–7.63 (m, 2 H), 7.48 (dt, *J* = 8.5, 4.3 Hz, 1 H), 7.39 (t, *J* = 2.0 Hz, 1 H), 7.24–7.18 (m, 2 H), 3.53 (t, *J* = 10.6 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.0, 135.2, 134.3, 133.1, 131.72, 131.66, 130.4, 129.4, 128.4, 127.8, 124.1. 123.5 (t, *J* = 269.9 Hz), 118.6, 112.9, 41.8 (t, *J* = 29.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –70.80 (t, *J* = 10.6 Hz, 2 F); IR (film) 3082, 2955, 2230, 1704, 1587, 1476, 1434, 1382, 1352, 1303, 1278, 1261, 1242, 1232, 1219, 1179, 1102, 1071, 1056, 1003, 976, 942, 918, 904, 873, 866, 823, 811, 800, 758, 738, 694, 644, 618, 577, 463 cm^{-1}; HRMS (HAPCI+) calc. for $C_{15}H_9Cl_2F_2NO$ (M+) 327.0029, found 327.0031.

2-(2,2-difluorovinyl)-1,3-dimethylbenzene (8l): Following General Procedure A, 2,6-dimethylbenzaldehyde (2.2 mL, 15.0 mmol) was reacted with PPh_3 (5.91 g, 22.5 mmol) and $BrCF_2CO_2K$ (6.17 g, 27.0 mmol). Following workup, the product was purified by flash chromatography using a gradient of 0–10% EtOAc in hexanes, furnishing 0.763 g (28% yield) of desired product **8l** as a clear oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (dd, *J* = 8.6, 6.4 Hz, 1 H), 7.07 (d, *J* = 7.5 Hz, 2 H), 5.23 (dd, *J* = 27.5, 2.3 Hz, 1 H), 2.29 (s, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) 155.0 (q, *J* = 291.7, 288.4 Hz), 137.5 (dd, *J* = 2.6, 1.4 Hz), 127.8, 127.6, 78.1 (dd, *J* = 27.3, 20.6 Hz), 20.5 (d, *J* = 2.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –83.38 (dd, *J* = 32.5, 27.0 Hz, 1 F), –87.16 (dd, *J* = 33.1, 2.4 Hz, 1 F); IR (film) 3024, 2956, 2923, 2330, 1736, 1586, 1468, 1445, 1380, 1329, 1276, 1254, 1222, 1166, 1096, 1032, 932, 850, 802, 768, 746, 698, 599, 537 cm^{-1}; HRMS (TAPCI) calc. for $C_{10}H_{10}F_2$ (M) 168.0751, found 168.0741.

1-(2-(4-bromophenyl)-1,1-difluoroethoxy)-2,4-dichlorobenzene (9m): Following General Procedure B-2, 0.110 g (0.50 mmol) of compound **8m** was reacted with 0.245 g (1.50 mmol) of 2,4-dichlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 ˚C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H_2O, furnishing 0.113 g (59% yield) of desired compound **9m** as a colorless solid (MP = 52–53 ˚C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 8.3, 1.7 Hz, 2 H), 7.40 (d, *J* = 2.3 Hz, 1 H), 7.28 (d, *J* = 8.7 Hz, 2 H), 7.22 (dd, *J* = 8.8, 1.5 Hz, 1 H), 7.19 (dd, *J* = 8.8, 2.3 Hz, 1 H), 3.45 (t, *J* = 10.9 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.2, 132.4, 131.7, 131.5, 130.6 (t, *J* = 3.2 Hz), 130.4, 128.5, 127.8, 124.2, 123.8 (t, *J* = 269.9 Hz), 122.2, 41.7 (t, *J* = 29.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –71.02 (t, *J* = 10.8 Hz, 2 F); IR (film) 2925, 1701, 1583, 1476, 1433, 1408, 1384, 1350, 1260, 1217, 1099, 1073, 1061, 1014, 897, 868, 843, 799, 762, 672, 623, 565, 489 cm^{-1}; HRMS (HAPCI+) calc. For $C_{14}H_9BrCl_2F_2O$ (M+) 379.9182, found 379.9169.

2,4-dichloro-1-(1,1-difluoro-2-(2-iodophenyl)ethoxy)benzene (9n): Following General Procedure B-2, 0.133 g (0.50 mmol) of compound **8n** was reacted with 0.245 g (1.50 mmol) of 2,4-dichlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 ˚C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H_2O, furnishing 0.105 g (49% yield) of desired compound **9n** as a colorless solid (MP = 54–55 ˚C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 7.9, 1.3 Hz, 1 H), 7.52 (dd, *J* = 7.8, 1.6 Hz, 1 H), 7.40 (d, *J* = 2.5 Hz, 1 H), 7.35 (td, *J* = 7.6, 1.3 Hz, 1 H), 7.27–7.25 (m, 1 H), 7.19 (dd, *J* = 8.8, 2.5 Hz, 1 H), 7.01 (td, *J* = 7.7, 1.7 Hz, 1 H), 3.77 (t, *J* = 10.9 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.3, 140.0, 135.2 (t, *J* = 2.8 Hz), 131.8, 131.5, 130.4, 129.6, 128.7, 128.4, 127.8, 124.4, 124.1 (t, *J* = 270.1 Hz), 102.2, 46.1 (t, *J* = 29.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –69.75 (t, *J* = 10.8 Hz, 2 F); IR (film) 2924, 1698, 1584, 1565, 1475, 1436, 1384, 1349, 1276, 1258, 1216, 1124, 1096, 1061, 1046, 1014, 868, 811, 765, 748, 694, 671, 652, 626, 613, 566, 488, 473, 459 cm^{-1}; HRMS (HAPCI+) calc. for $C_{14}H_9Cl_2F_2IO$ (M+) 427.9043, found 427.9029.

2,4-dichloro-1-(1,1-difluoro-2-(3-(trifluoromethyl)phenyl)ethoxy)benzene (9o): Following General Procedure B-2, 0.104 g (0.50 mmol) of compound **8o** was reacted with 0.245 g (1.50 mmol) of 2,4-dichlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 ˚C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H_2O, furnishing 0.094 g (51% yield) of desired compound **9o** as a clear oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (s, 1 H), 7.60 (t, *J* = 7.7 Hz, 2 H), 7.49 (t, *J* = 7.8 Hz, 1 H), 7.40 (t, *J* = 2.0 Hz, 1 H), 7.24 (dd, *J* = 8.8, 1.4 Hz, 1 H), 7.19 (dd, *J* = 8.8, 2.4 Hz, 1 H), 3.56 (t, *J* = 10.7 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.2, 134.2, 132.6 (t, *J* = 3.3 Hz), 131.6, 130.4, 129.0, 128.5, 127.8, 127.6 (q, *J* = 4.0 Hz), 125.3, 124.9 (q, *J* = 3.9 Hz), 124.1, 123.8 (t, *J* = 269.7 Hz), 123.1, 42.1 (t, *J* = 29.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$, β,β,β-trifluoroethanol as standard with ppm = –79.40) δ –64.86 (s, 3 F), –72.02 (t, *J* = 11.0 Hz, 2 F); IR (film) 2949, 1584, 1477, 1454, 1435, 1354, 1329, 1257, 1202, 1166, 1126, 1100, 1076, 1062, 870, 800, 764, 751, 703, 664, 617, 564 cm^{-1}; HRMS (HAPCI+) calc. for $C_{15}H_9Cl_2F_5O$ (M+) 369.9951, found 369.9934.

2,4-dichloro-1-(2-(3,5-dichlorophenyl)-1,1-difluoroethoxy)benzene (9p): Following General Procedure B-2, 0.105 g (0.50 mmol) of compound **8p** was reacted with 0.245 g (1.50 mmol) of 2,4-dichlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 ˚C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H_2O, furnishing 0.078 g (42% yield, 1% ***E*-10p**, 1% trifluoroethylbenzene side product) of desired compound **9p** as a pinkish colorless solid (MP = 46–47 ˚C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 2.4 Hz, 1 H), 7.35 (t, *J* = 1.9 Hz, 1 H), 7.31 (d, *J* = 2.0 Hz, 2 H), 7.24 (d, *J* = 8.7 Hz, 1 H), 7.20 (dd, *J* = 8.8,

2.4 Hz, 1 H), 3.45 (t, *J* = 10.6 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.1, 135.1, 134.7, 131.7, 130.5, 129.3, 128.5, 128.3, 127.8, 124.1, 123.5 (t, *J* = 269.8 Hz), 41.7 (t, *J* = 30.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –70.61 (t, *J* = 10.6 Hz, 2 F); IR (film) 1592, 1570, 1476, 1436, 1385, 1351, 1258, 1062, 867, 800, 763, 702, 643, 565 cm^{-1}; HRMS (HAPCI+) calc. for $C_{14}H_8Cl_4F_2O$ (M+) 369.9297, found 369.9300. ***E*-10p** characteristic peaks: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.75 (d, *J* = 5.8 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –81.75 (d, *J* = 5.8 Hz, 1 F).

4-(2,2-difluorovinyl)-*N*,*N*-diisopropylbenzamide (8q): Following General Procedure A, compound **8q–1** (0.823, 3.60 mmol) was reacted with PPh_3 (1.50 g, 5.30 mmol) and $BrCF_2CO_2K$ (1.42 g, 6.50 mmol) in NMP (2.0 mL, 2 M). Following workup, the product was purified by flash chromatography using a gradient of 0–30% EtOAc in hexanes, furnishing 0.655 g (69% yield) of desired product **8q** as a colorless solid (MP = 43–44 ˚C); ^{1}H NMR (500 MHz, DMSO-D_6, 25 °C) δ 7.41 (d, *J* = 8.1 Hz, 2 H), 7.29 (d, *J* = 8.2 Hz, 2 H), 5.85 (dd, *J* = 28.1, 4.1 Hz, 1 H), 3.61 (bs, 2 H), 1.38–1.15 (m, 12 H); ^{1}H NMR (500 MHz, DMSO-D_6, 60 °C) δ 7.41 (d, *J* = 7.9 Hz, 2 H), 7.28 (d, *J* = 7.9 Hz, 2 H), 5.79 (dd, *J* = 27.8, 4.0 Hz, 1 H), 3.64 (hept, *J* = 6.4 Hz, 2 H), 1.28 (bs, 12 H); ^{13}C NMR (126 MHz, DMSO-D_6, 60 °C) δ 169.8, 156.1 (dd, *J* = 297.8, 286.2 Hz), 138.2 (t, *J* = 2.3 Hz), 130.5 (dd, *J* = 7.8, 5.8 Hz), 128.1 (dd, *J* = 6.6, 3.8 Hz), 126.3, 82.3 (dd, *J* = 29.5, 11.8 Hz), 20.9; ^{19}F NMR (376 MHz, DMSO-D_6, 25 °C) δ –82.16 (dd, *J* = 32.1, 28.1 Hz, 1 F), –84.02 (dd, *J* = 32.2, 4.1 Hz, 1 F); IR (film) 3434, 2252, 2126, 1729, 1660, 1345, 1276, 1052, 1024, 1005, 822, 760, 623 cm^{-1}; HRMS (ESI+) calc. for $C_{15}H_{20}F_2NO$ (M+H) 268.1513, found 268.1500.

4-(2-(2,4-dichlorophenoxy)-2,2-difluoroethyl)-*N*,*N*-diisopropylbenzamide (9q): Following General Procedure B-2, 0.134 g (0.50 mmol) of compound **8q** was reacted with 0.245 g (1.50 mmol) of 2,4-dichlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 ˚C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H_2O, furnishing 0.126 g (59% yield, 3% ***E*-10q**, 1% ***Z*-10q**) of desired compound **9q** as a orange solid (MP = 81–83 ˚C); ^{1}H NMR (500 MHz, $CDCl_3$, 25 ˚C) δ 7.40 (d, *J* = 7.9 Hz, 2 H), 7.37 (d, *J* = 2.5 Hz, 1 H), 7.29 (d, *J* = 7.9 Hz, 2 H), 7.23 (d, *J* = 8.9 Hz, 1 H), 7.18 (dd, *J* = 8.8, 2.5 Hz, 1 H), 3.74 (bs, 1 H), 3.49 (t, *J* = 11.0 Hz, 2 H), 1.46 (bs, 6 H), 1.21 (bs, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 145.2, 138.6, 132.1 (t, *J* = 3.2 Hz), 131.5, 130.9, 130.3, 128.5, 127.8, 126.2, 125.8, 124.2, 124.0 (t, *J* = 271.0 Hz), 41.99 (t, *J* = 29.3 Hz), 20.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ –70.73 (t, *J* = 11.3 Hz, 2 F); IR (film) 2993, 2969, 2933, 1628, 1474, 1440, 1375, 1360, 1339, 1261, 1241, 1226, 1214, 1204, 1112, 1094, 1058, 1028, 902, 876, 856, 842, 811, 800, 771, 753, 676, 578 cm^{-1}; HRMS (ESI+) calc. for $C_{21}H_{23}Cl_2F_2NO_2Na$ (M+Na) 452.0972, found 452.0966. ***E*-10q** characteristic peaks: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.70 (d, *J* = 6.1 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –84.19 (d, *J* = 5.9 Hz, 1 F); ***Z*-10q** characteristic peaks: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.24 (d, *J* = 28.6 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –84.28 (d, *J* = 29.0 Hz, 1 F).

4-(2-(2,4-dichlorophenoxy)-2,2-difluoroethyl)phenyl trifluoromethanesulfonate (9r): Following General Procedure B-2, 0.144 g (0.50 mmol) of compound **8r** was reacted with 0.245 g (1.50 mmol) of 2,4-dichlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 ˚C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H_2O, furnishing 0.110 g (49% yield) of desired compound **9r** as a light brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.6 Hz, 2 H), 7.39 (d, *J* = 2.4 Hz, 1 H), 7.30–7.27 (m, 2 H) 7.23 (d, *J* = 8.8 Hz, 1 H), 7.20 (dd, *J* = 8.8, 2.4 Hz, 1 H), 3.53 (t, *J* = 10.6 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.4, 145.0 (t, *J* = 1.7 Hz), 132.7, 132.2 (t, *J* = 3.5 Hz), 131.7, 130.4, 129.7, 127.8, 124.2 (t, *J* = 2.1 Hz), 123.6 (t, *J* = 269.3 Hz), 121.5, 118.9 (q, *J* = 320.7 Hz), 41.6 (t, *J* = 29.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$, delay time = 5 s) δ –70.80 (t, *J* = 10.6 Hz, 2 F), –73.85 (s, 3 F); IR (film) 1704, 1601, 1584, 1504, 1476, 1421, 1353, 1251, 1212, 1183, 1140, 1113, 1100, 1061, 1020, 946, 890, 807, 764, 729, 694, 674, 640, 609, 579, 523, 492 cm^{-1}; HRMS (HAPCI+) calc. for $C_{15}H_9Cl_2F_5O_4S$ (M+) 449.9519, found 449.9516.

Compounds in Table 4:

3-(2-(2,4-dichlorophenoxy)-2,2-difluoroethyl)-1-tosyl-1*H*-indole (12a): Following General Procedure B-1, 0.167 g (0.50 mmol) of compound **11a** was reacted with 0.408 g (2.50 mmol) of 2,4-dichlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 ˚C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H_2O, furnishing 0.209 g (84% yield, 3% ***E*-13a**, 1% ***Z*-13a**) of desired product **12a** as an orange solid (MP = 90–93 ˚C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.3 Hz, 1 H), 7.78 (d, *J* = 8.2 Hz, 2 H), 7.68 (s, 1 H), 7.60 (d, *J* = 7.9 Hz, 1 H), 7.38 (d, *J* = 2.3 Hz, 1 H), 7.35 (t, *J* = 7.8 Hz, 1 H), 7.27 (t, *J* = 7.3 Hz, 1 H), 7.22–7.16 (m, 5 H), 3.61 (t, *J* = 10.8 Hz, 2 H), 2.32 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.1, 135.3, 135.0, 131.5, 130.8, 130.3, 130.0, 129.2, 128.5, 128.3, 127.7, 126.9, 126.3, 125.4, 125.0, 124.3 (t, *J* = 1.9 Hz), 123.9 (t, *J* = 269.4 Hz), 123.4, 119.8, 113.7, 112.8 (t, *J* = 3.7 Hz), 32.1 (t, *J* = 31.5 Hz), 21.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ –70.61 (t, *J* = 10.9 Hz, 2 F); IR (film) 2258, 1598, 1476, 1448, 1369, 1324, 1275, 1259, 1217, 1188, 1175, 1122, 1090, 1061, 1020, 977, 908, 869, 811, 784, 765, 747, 703, 672, 750 cm^{-1}; HRMS (ESI+) calc. for $C_{23}H_{18}Cl_2F_2NO_3S$ (M+H) 496.0353, found 496.0371. ***E*-13a** characteristic peaks: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 (d, *J* = 3.5 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –86.14 (d, *J* = 3.0 Hz, 1 F); ***Z*-13a** characteristic peaks: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.42 (d, *J* = 29.0 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –80.20 (d, *J* = 29.1 Hz, 1 F).

4-(2-(2,4-dichlorophenoxy)-2,2-difluoroethyl)-1-phenyl-1*H*-pyrazole (12b): Following General Procedure B-1, 0.104 g (0.50 mmol) of compound **11b** was reacted with 0.408 g (2.50 mmol) of 2,4-dichlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 ˚C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H_2O, furnishing 0.081 g (44% yield) of desired product **12b** as a yellow solid (MP = 44–46 ˚C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (s, 1 H), 7.74 (s, 1 H), 7.70–7.68 (m, 2 H), 7.45 (dd, *J* = 8.6, 7.3 Hz, 2 H), 7.42 (d, *J* = 2.5 Hz, 1 H), 7.30–7.26 (m, 2 H), 7.20 (dd, *J* = 8.9, 2.5 Hz, 1 H), 3.47 (t, *J* = 11.0 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.2, 142.1, 140.1, 131.5, 130.4, 129.6, 128.4, 127.8, 127.3, 126.7, 124.2 (t, *J* = 1.9 Hz), 123.9 (t, *J* = 268.7 Hz), 119.2, 113.0 (t, *J* = 3.9 Hz), 31.9 (t, *J* = 31.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –71.98 (t, *J* = 11.0 Hz, 2 F); IR (film) 3053, 2927, 1601, 1576, 1505, 1476, 1431, 1403, 1385, 1343, 1258, 1215, 1187, 1120, 1097, 1062, 1042, 1017, 955, 905, 867, 838, 808, 756, 711, 691, 674, 656 cm^{-1}; HRMS (ESI+) calc. for $C_{17}H_{13}Cl_2F_2N_2O$ (M+H) 369.0373, found 369.0347.

4-(2-(2,4-dichlorophenoxy)-2,2-difluoroethyl)dibenzo[*b*,*d*]thiophene (12c): Following General Procedure B-1, 0.123 g (0.50 mmol) of compound **11c** was reacted with 0.408 g (2.50 mmol) of 2,4-dichlorophenol in the

presence of 0.033 g (0.25 mmol) of TBD at 140 ˚C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H_2O, furnishing 0.119 g (58% yield, 1% ***E*-13c**, 6% unknown side product) of desired product **12c** as a colorless solid (MP = 119–121 ˚C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.0 Hz, 2 H), 7.90–7.88 (m, 1 H), 7.57 (d, *J* = 7.4 Hz, 1 H), 7.52–7.47 (m, 3 H), 7.40 (s, 1), 7.25 (d, *J* = 8.8 Hz, 1 H), 7.18 (d, *J* = 7.9 Hz, 1 H), 3.82 (t, *J* = 10.9 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.2 (d, *J* = 1.7 Hz), 141.3, 139.1, 136.2, 136.0, 131.5, 130.3, 129.3, 128.7, 127.7, 127.0, 126.3 (t, *J* = 24.6 Hz), 124.8, 124.6, 124.4 (t, *J* = 1.9 Hz), 124.3 (t, *J* = 270.6 Hz), 122.9, 121.9, 121.3, 41.3 (t, *J* = 30.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –69.59 (t, *J* = 11.0 Hz, 2 F); IR (film) 1476, 1444, 1405, 1385, 1352, 1325, 1265, 1170, 1122, 1099, 1062, 1022, 907, 842, 817, 797, 733, 706, 650, 618 cm^{-1}; HRMS (HAPCI+) calc. for $C_{20}H_{12}Cl_2F_2OS$ (M+) 407.9954, found 407.9940. ***E*-13c** characteristic peaks: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.97 (d, *J* = 5.7 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –82.77 (d, *J* = 5.8 Hz, 1 F).

2-(3-(2-(2,4-dichlorophenoxy)-2,2-difluoroethyl)phenyl)-5-(1,3-dioxolan-2-yl)pyridine (12d): Following General Procedure B-2, 0.1446 g (0.50 mmol) of compound **11d** was reacted with 0.245 g (1.50 mmol) of 2,4-dichlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 ˚C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H_2O, furnishing 0.137 g (61% yield, 4% ***E*-13d**, 1% ***Z*-13d**) of desired compound **12d** as a yellow solid (MP = 84–86 ˚C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (d, *J* = 2.2 Hz, 1 H), 8.05 (s, 1 H), 7.96 (q, *J* = 2.7, 1.9 Hz, 1 H), 7.86 (dd, *J* = 8.1, 2.3 Hz, 1 H), 7.76 (d, *J* = 8.2 Hz, 1 H), 7.47 (d, *J* = 4.7 Hz, 2 H), 7.38 (d, *J* = 2.6 Hz, 1 H), 7.24 (d, *J* = 8.8 Hz, 1 H), 7.17 (dd, *J* = 8.9, 2.6 Hz, 1 H), 5.91 (s, 1 H), 4.16–4.11 (m, 2 H), 4.10–4.05 (m, 2 H), 3.59 (t, *J* = 11.1 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.0, 148.4, 145.4, 139.4, 135.1, 132.24, 132.17 (t, *J* = 2.9 Hz), 131.5, 131.4, 130.3, 129.5, 129.0, 128.5, 127.7, 126.6, 124.18, 124.12 (t, *J* = 269.6 Hz), 120.3, 102.1, 65.6, 42.3 (t, *J* = 29.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –70.75 (t, *J* = 11.0 Hz, 2 F); IR (film) 2887, 1703, 1601, 1569, 1475, 1354, 1256, 1095, 1062, 1025, 982, 942, 864, 839, 799, 757, 698, 564 cm^{-1}; HRMS (ESI+) calc. for $C_{22}H_{18}Cl_2F_2NO_3$ (M+H) 452.063, found 452.0627. ***E*-13d** characteristic peaks: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (d, *J* = 6.0 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –84.69 (d, *J* = 5.9 Hz, 1 F); ***Z*-13d** characteristic peaks: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.34 (d, *J* = 28.7 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –84.63 (d, *J* = 28.4 Hz, 1 F).

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References and notes

1. Zhang, X.; Cao, S. *Tetrahedron Letters* **2017,** *58*, 375-392.
2. Orsi, D. L.; Altman, R. A. *Chem Commun (Camb)* **2017,** *53*, 7168-7181.
3. Suda, M. *Tetrahedron Letters* **1980,** *21*, 2555-2556.
4. Amii, H.; Uneyama, K. *Chem Rev* **2009,** *109*, 2119-83.
5. Wang, M.; Liang, F.; Xiong, Y.; Cao, S. *RSC Advances* **2015,** *5*, 11996-11999.
6. Hung, M.-H.; Rozen, S.; Smart, B. E. *The Journal of Organic Chemistry* **1994,** *59*, 4332-4335.
7. Yokota, M.; Fujita, D.; Ichikawa, J. *Org Lett* **2007,** *9*, 4639-42.
8. Yu, L.; Tang, M. L.; Si, C. M.; Meng, Z.; Liang, Y.; Han, J.; Sun, X. *Org Lett* **2018,** *20*, 4579-4583.
9. Yang, L.; Ji, W. W.; Lin, E.; Li, J. L.; Fan, W. X.; Li, Q.; Wang, H. *Org Lett* **2018,** *20*, 1924-1927.
10. Tan, D. H.; Lin, E.; Ji, W. W.; Zeng, Y. F.; Fan, W. X.; Li, Q. J.; Gao, H.; Wang, H. G. *Advanced Synthesis & Catalysis* **2018,** *360*, 1032-1037.
11. Zhang, J.; Dai, W.; Liu, Q.; Cao, S. *Org Lett* **2017,** *19*, 3283-3286.
12. Zell, D.; Dhawa, U.; Muller, V.; Bursch, M.; Grimme, S.; Ackermann, L. *Acs Catalysis* **2017,** *7*, 4209-4213.
13. Sakaguchi, H.; Uetake, Y.; Ohashi, M.; Niwa, T.; Ogoshi, S.; Hosoya, T. *J Am Chem Soc* **2017,** *139*, 12855-12862.
14. Lu, X.; Wang, Y.; Zhang, B.; Pi, J. J.; Wang, X. X.; Gong, T. J.; Xiao, B.; Fu, Y. *J Am Chem Soc* **2017,** *139*, 12632-12637.
15. Li, J.; Lefebvre, Q.; Yang, H.; Zhao, Y.; Fu, H. *Chem Commun (Camb)* **2017,** *53*, 10299-10302.
16. Kong, L.; Liu, B.; Zhou, X.; Wang, F.; Li, X. *Chem Commun (Camb)* **2017,** *53*, 10326-10329.
17. Watabe, Y.; Kanazawa, K.; Fujita, T.; Ichikawa, J. *Synthesis-Stuttgart* **2017,** *49*, 3569-3575.
18. Cai, S. H.; Ye, L.; Wang, D. X.; Wang, Y. Q.; Lai, L. J.; Zhu, C.; Feng, C.; Loh, T. P. *Chem Commun (Camb)* **2017,** *53*, 8731-8734.
19. Xie, J.; Yu, J.; Rudolph, M.; Rominger, F.; Hashmi, A. S. *Angew Chem Int Ed Engl* **2016,** *55*, 9416-21.
20. Thornbury, R. T.; Toste, F. D. *Angew Chem Int Ed Engl* **2016,** *55*, 11629-32.
21. Kong, L.; Zhou, X.; Li, X. *Org Lett* **2016,** *18*, 6320-6323.
22. Dai, W.; Shi, H.; Zhao, X.; Cao, S. *Org Lett* **2016,** *18*, 4284-7.
23. Xiong, Y.; Huang, T.; Ji, X.; Wu, J.; Cao, S. *Org Biomol Chem* **2015,** *13*, 7389-92.
24. Tian, P.; Feng, C.; Loh, T. P. *Nat Commun* **2015,** *6*, 7472.
25. Bobek, M.; Kavai, I.; De Clercq, E. *J Med Chem* **1987,** *30*, 1494-7.
26. Mitchell, W. L.; Ravenscroft, P.; Hill, M. L.; Knutsen, L. J.; Judkins, B. D.; Newton, R. F.; Scopes, D. I. *J Med Chem* **1986,** *29*, 809-16.
27. Koch, H. F.; Kielbania, A. J. *Journal of the American Chemical Society* **1970,** *92*, 729-730.
28. Paleta, O.; Svoboda, J.; Dědek, V. *Journal of Fluorine Chemistry* **1983,** *23*, 171-191.
29. Matsukawa, Y.; Mizukado, J.; Quan, H. D.; Tamura, M.; Sekiya, A. *Angew Chem Int Ed Engl* **2005,** *44*, 1128-30.
30. Il'in, A. A.; Bakhmutov, Y. L.; Ivanova, L. M.; Furin, G. G.; Tolstikova, T. G.; Sukhinin, V. S. *Russian Journal of Applied Chemistry* **2004,** *77*, 98-101.
31. Nguyen, T.; Wakselman, C. *Journal of Fluorine Chemistry* **1995,** *74*, 273-277.
32. Middleton, W. J.; Bingham, E. M. *Journal of Fluorine Chemistry* **1983,** *22*, 561-574.
33. Qiao, Y.; Si, T.; Yang, M. H.; Altman, R. A. *J Org Chem* **2014,** *79*, 7122-31.
34. Gao, B.; Zhao, Y.; Hu, J. *Angew Chem Int Ed Engl* **2015,** *54*, 638-42.
35. Gao, B.; Zhao, Y.; Ni, C.; Hu, J. *Org Lett* **2014,** *16*, 102-5.
36. Zhang, B.; Zhang, X.; Hao, J.; Yang, C. *European Journal of Organic Chemistry* **2018,** *2018*, 5007-5015.
37. Tang, H. J.; Lin, L. Z.; Feng, C.; Loh, T. P. *Angew Chem Int Ed Engl* **2017,** *56*, 9872-9876.

38. Tian, P.; Wang, C. Q.; Cai, S. H.; Song, S.; Ye, L.; Feng, C.; Loh, T. P. *J Am Chem Soc* **2016,** *138*, 15869-15872.
39. Fuss, A.; Koch, V. *Synthesis-Stuttgart* **1990,** *1990*, 604-608.
40. Orsi, D. L.; Easley, B. J.; Lick, A. M.; Altman, R. A. *Org Lett* **2017,** *19*, 1570-1573.
41. Kolomeitsev, A. A.; Koppel, I. A.; Rodima, T.; Barten, J.; Lork, E.; Roschenthaler, G. V.; Kaljurand, I.; Kutt, A.; Koppel, I.; Maemets, V.; Leito, I. *J Am Chem Soc* **2005,** *127*, 17656-66.
42. Kaljurand, I.; Rodima, T.; Pihl, A.; Maemets, V.; Leito, I.; Koppel, I. A.; Mishima, M. *J Org Chem* **2003,** *68*, 9988-93.
43. Jelier, B. J.; Howell, J. L.; Montgomery, C. D.; Leznoff, D. B.; Friesen, C. M. *Angew Chem Int Ed Engl* **2015,** *54*, 2945-9.
44. Lepri, S.; Buonerba, F.; Maccaroni, P.; Goracci, L.; Ruzziconi, R. *Journal of Fluorine Chemistry* **2015,** *171*, 82-91.
45. Feiring, A. E.; Rozen, S.; Wonchoba, E. R. *Journal of Fluorine Chemistry* **1998,** *89*, 31-34.
46. Zhang, Z.; Tang, X.; Dolbier, W. R., Jr. *Org Lett* **2015,** *17*, 4401-3.
47. Pohmakotr, M.; Boonkitpattarakul, K.; Ieawsuwan, W.; Jarussophon, S.; Duangdee, N.; Tuchinda, P.; Reutrakul, V. *Tetrahedron* **2006,** *62*, 5973-5985.
48. Li, Y.; Hu, J. *Journal of Fluorine Chemistry* **2008,** *129*, 382-385.
49. Kosobokov, M. D.; Dilman, A. D.; Struchkova, M. I.; Belyakov, P. A.; Hu, J. *J Org Chem* **2012,** *77*, 2080-6.
50. Li, Y.; Hu, J. *Angew Chem Int Ed Engl* **2007,** *46*, 2489-92.
51. Betterley, N. M.; Surawatanawong, P.; Prabpai, S.; Kongsaeree, P.; Kuhakarn, C.; Pohmakotr, M.; Reutrakul, V. *Org Lett* **2013,** *15*, 5666-9.
52. Yang, X. Y.; Fang, X.; Yang, X. J.; Zhao, M.; Han, Y. Z.; Shen, Y. J.; Wu, F. H. *Tetrahedron* **2008,** *64*, 2259-2269.
53. Choi, Y.; Yu, C.; Kim, J. S.; Cho, E. J. *Org Lett* **2016,** *18*, 3246-9.
54. Brigaud, T.; Laurent, E. *Tetrahedron Letters* **1990,** *31*, 2287-2290.
55. Furuta, S.; Kuroboshi, M.; Hiyama, T. *Tetrahedron Letters* **1995,** *36*, 8243-8246.
56. Gouault, S.; Guérin, C.; Lemoucheux, L.; Lequeux, T.; Pommelet, J.-C. *Tetrahedron Letters* **2003,** *44*, 5061-5064.

Supplementary Material

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