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Controlling the Cleavage of Carbon–Carbon Bonds to Generate α,α-Difluorobenzyl Carbanions for the Construction of Difluoromethylbenzenes

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ABSTRACT: Controlling the cleavage of carbon–carbon bonds during a chemical reaction is a substantial challenge; however, synthetic methods that accomplish this objective produce valuable and often unexplored reactivity. We have designed a mild process to generate α,α-difluorobenzyl carbanions in the presence of potassium carbonate by exploiting the cleavage of C–C bonds during the release of trifluoroacetate. The initiating reagent is potassium carbonate, which represents an improvement over existing protocols that require strong base. Fragmentation studies across substituted arenes and heteroarenes were conducted along with computational analyses to elucidate reactivity trends. Furthermore, the mildly generated α,α-difluorobenzyl carbanions from electron-deficient aromatics and heteroaromatic rings can react with aldehydes to create derivatives of difluoromethylbenzenes, which are valuable synthetic targets.

INTRODUCTION

The cleavage of carbon–carbon bonds is quite challenging and rather unexplored, but if these bonds can be broken with high selectivity, organic molecules can be remodeled into higher value fine chemicals.[1,2] Although cutting-edge innovations in breaking C–C bonds have appeared, primarily through C–C bond activation, strategies to cleave these bonds are rare due to the high stability of the C–C bond.[3−5] The potential for this process in synthetic chemistry is substantial, and historically, its utility has originated from C–C bond rearrangements.[6]

Fluorinated organic molecules are valuable targets in the pharmaceutical and agrochemical industries, because the presence of fluorine usually imparts beneficial characteristics during development.[7,8] Synthetic methods to create fluorinated compounds are quite prevalent in the cases of fluorination and trifluoromethylation, but less developed for difluoromethyl groups (i.e., CF_2 group).[9] In medicinal chemistry, aryldifluoromethyl derivatives ($ArCF_2R$) constitute a discrete class of fluorinated compounds, and some of the representative examples that contain aryldifluoromethyl groups include a nitric oxide synthase inhibitor,[10] a CCR5 receptor antagonist,[11] a urea transporter B inhibitor,[12] and an analogue of fenofibrate that serves as a PPARα activator (Figure 1).[13] Some methods are available for the synthesis of difluoromethylbenzenes;[13−15] however, in the context of fundamental nucleophile reactivity, only two reactions are available to produce α,α-difluorobenzyl carbanions (Figure 1B).[16,17] The first is confined to a trimethylsilyldifluoromethylbenzene as a starting material.[16] Moreover, few trimethylsilyldifluoromethylbenzenes have been reported in the literature to participate as nucleophilic precursors, because this type of starting material is challenging to synthesize.[16−19] The second is a stabilized transfer reagent produced with the strong base, potassium diisopropylamide, and reported by Szymczak in 2018.[20] Currently, methods to generate these fluorinated carbanions are still needed along with additional studies of the reactivity and stability of these nucleophiles.

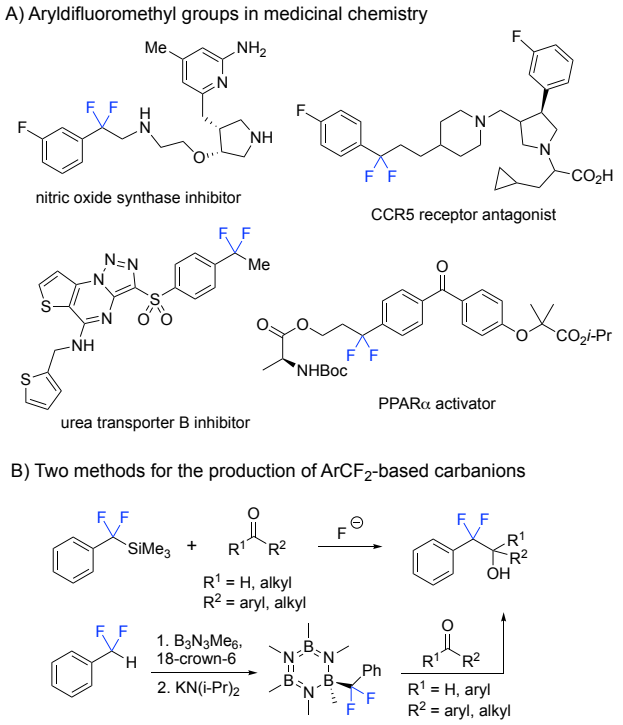


Figure 1. (a) Medicinal agents displaying an aryldifluoromethyl group. (b) Scope of nucleophilic additions with aryldifluoromethyl-based carbanions.

We have previously designed a mild process to generate α,α-difluorocarbanions by exploiting the cleavage of C–C bonds during the fragmentation of pentafluoro-*gem*-diols (Figure 2).[9] Specifically, our laboratory has shown the pentafluoro-*gem*-diols adjacent to a carbonyl group can be used to generate difluoroenolates from the release of trifluoroacetate.[9,21,22] This method for the production of fluoroenolates has enabled substantial advancement in the study of the reactivity due to its exceedingly mild conditions (for the fragmentation of a carbon–carbon bond).[23–29] Prior to these studies, the Guerrero group demonstrated that pentafluoro-*gem*-diols adjacent to secondary alcohols produce difluoroacetic acids following the release of fluoroform.[30,31] Herein, we have applied this approach to produce α,α-difluorobenzyl carbanions and construct difluoromethylbenzenes upon electron-deficient aromatics and heteroaromatic rings. This process can be controlled by the nature of the substrate as well as the reagents depending upon if trifluoroacetate or fluoroform is released.

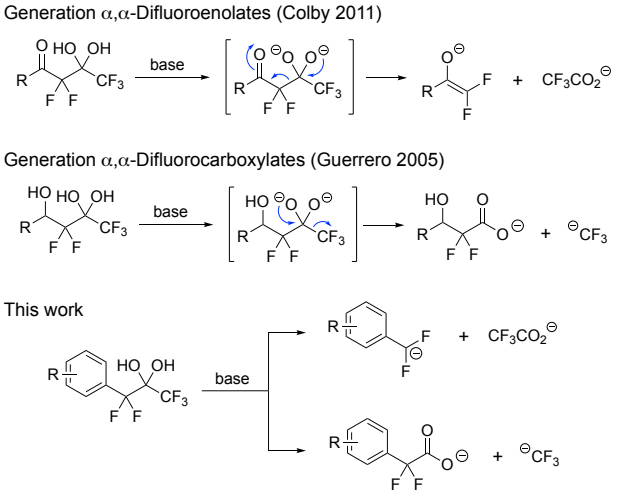
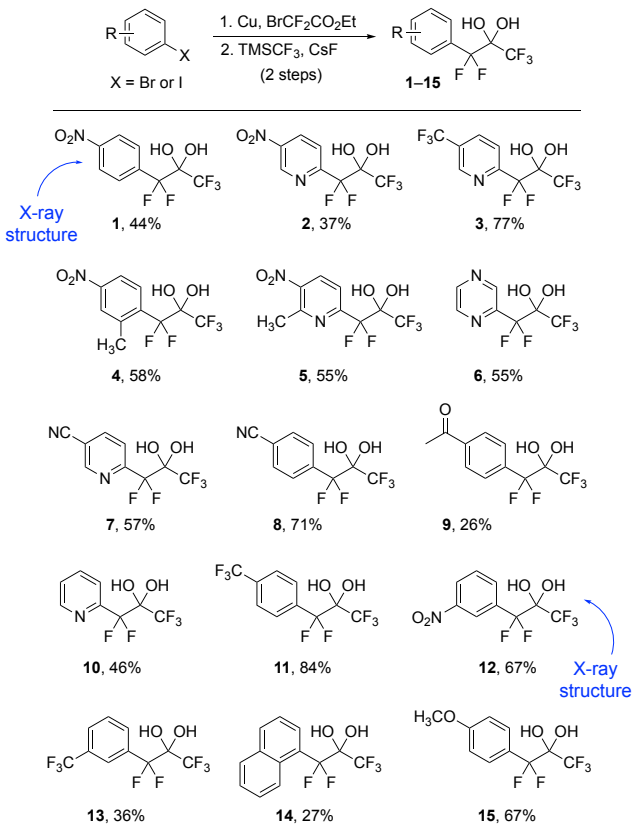


Figure 2. Fragmentations of α-Fluorinated-*gem*-diols.

RESULTS

We commenced our study with the synthesis of aryl pentafluoro-*gem*-diols as substrates for the fragmentation studies. Our two previous reports of synthetic strategies for the pentafluoro-*gem*-diols adjacent to ketones[9,32] do not translate to the aromatic or heteroaromatic class of compounds; therefore, we devised a new preparation, starting from readily available aryl bromides or iodides (Table 1). Accordingly, the aryl halide couples to bromodifluoroethyl acetate in the presence of copper[33] and then intermediate ester is treated with the Ruppert-Prakash reagent and cesium fluoride.[34] The aryl pentafluoro-*gem*-diols **1**–**15** are produced in two-steps with isolated yields of 27–84%. Substituted benzene, pyridine, naphthalene, and pyrazine participate in the process. Nitro, cyano, acetyl, and trifluoromethyl substituents are compatible with the transformations. X-ray structures of compounds **1** and **12** were obtained to define the structures of these novel molecules. To our knowledge, these X-ray data are the first crystal structures of aryl pentafluoro-*gem*-diols. All of these products will serve to define the role of electron-withdrawing versus election-donating substituents on the aromatic rings during the fragmentation studies.

Table 1. Synthesis of Aryl Pentafluoro-*gem*-diols **1**–**15**[a]



[a] Isolated yields.

The *para*-nitrobenzene **1** was selected for the initial base-promoted fragmentations. Potassium carbonate and cesium carbonate initiated the cleavage of the α-fluorinated-*gem*-diol **1** whereas the usual conditions of a mixture of lithium bromide and triethylamine only returned unreacted starting material.[9,22] The fragmentation of **1** in the presence of K_2CO_3 was analyzed by ^{19}F NMR, and the 1-difluoromethyl-4-nitrobenzene and the 2,2-difluoro-2-(4-nitrophenyl)acetic acid were observed along with trifluoroacetate and fluoroform (Figure 3). The unique peaks for each of the fluorinated compounds had excellent dispersion across –60 to –120 ppm in the ^{19}F NMR. Also, the fragmentation of **1** was complete in ten minutes at 60 °C in the presence of cesium carbonate with many common organic solvents (Table 2). Highly polar solvents such as DMPU, DMSO, and DMF primarily favored the release of trifluoroacetate and the formation of 1-difluoromethyl-4-nitrobenzene. On the other hand, less polar organic solvents, such as dioxane, THF, and trifluorotoluene, caused the production of 2,2-difluoro-2-(4-nitrophenyl)acetic acid from the release of fluoroform.

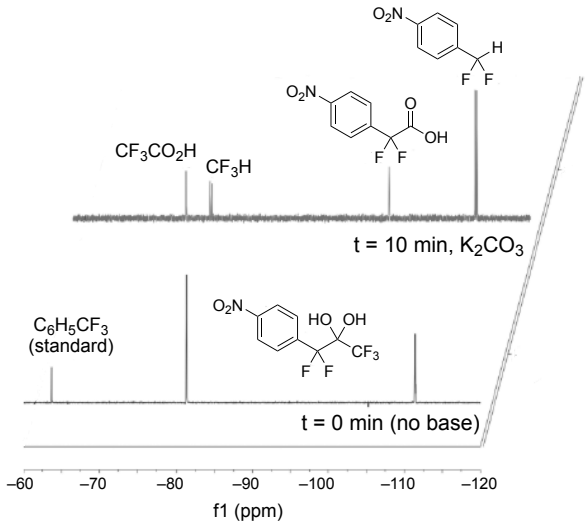
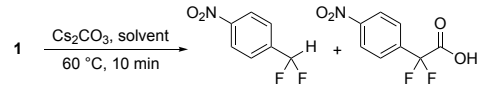


Figure 3. Comparison of ^{19}F NMR data of α-fluorinated-*gem*-diol **1** in DMSO at t = 0 min and t = 10 min after treatment with K_2CO_3.

Table 2. Fragmentation of Pentafluoro-*gem*-diol **1** in Cs_2CO_3

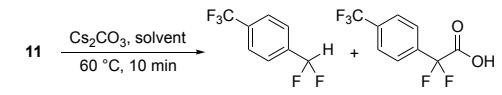


entry	solvent	release of trifluoroacetate[a]	release of fluoroform[a]
1	DMPU	95	5
2	NMP	91	9
3	DMF	88	12
4	acetone	83	17
5	DMSO	79	21
6	EtOAc	49	51
7	CH_3CN	45	55
8	dioxane	44	56
9	toluene	42	58
10	THF	34	66
11	DCE	34	66
12	trifluorotoluene	18	82

[a] ^{19}F NMR yields.

Next, the *para*-trifluoromethylbenzene **11** was subjected to a similar series of fragmentation experiments using cesium carbonate (Table 3). The results from these experiments show that the primary fragmentation pathway is the release of fluoroform which creates the difluoroacetic acid. The difluoromethylarene was a minor product in the most polar solvents and not observed in the less polar organic solvents. The choice of solvent plays an important role in directing the fragmentation of these α-fluorinated-*gem*-diols; however, the results of the reaction are dependent upon the nature of the starting material.

Table 3. Fragmentation of Pentafluoro-*gem*-diol **11** in Cs_2CO_3

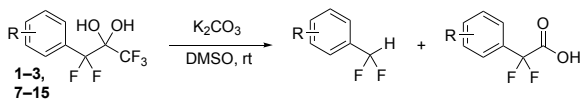


entry	solvent	release of trifluoroacetate[a]	release of fluoroform[a]
1	DMSO	17	83
2	DMPU	14	86
3	NMP	9	91
4	DMF	6	94
5	THF	2	98
6	CH_3CN	2	98
7	DCE	0	100
8	toluene	0	100
9	trifluorotoluene	0	100

[a] ^{19}F NMR yields.

In order to define the role of substrate in the two competing fragmentation processes, the α-fluorinated-*gem*-diols **1**–**3** and **7**–**15** were cleaved in potassium carbonate in DMSO at room temperature (Table 4). Potassium carbonate in DMSO was chosen because these conditions are the best potential for integration into a synthetic reaction. The pentafluoro-*gem*-diol **1** provides quantitative conversion to the difluoromethylarene **16** in K_2CO_3 and DMSO compared to 79% in Cs_2CO_3 in DMSO. Other electron-deficient substrates, such as 5-nitropyridine **2** and 5-trifluoromethylpyridine **3**, also provided exclusively the respective difluoromethylarenes from the release of trifluoroacetate. The *gem*-diols **7**–**11** formed a mixture of difluoromethylarene and difluoroacetic acid. Substrates **29**–**32** formed only the difluoroacetic acids products **30**–**32**, respectively, from the release of fluoroform. Although *gem*-diols **13**–**15** are considered electron-rich, the *meta*-nitrobenzene **12** displays similar reactivity to each of them. These results provide a unique perspective on the cleavage of carbon–carbon bonds across a series of similar α-fluorinated *gem*-diols.

Table 4. Fragmentation of compds **1**–**3** and **7**–**15** in K_2CO_3



entry	starting material	release of trifluoroacetate[a]	release of fluoroform[a]
1	**1** (*para*-nitrophenyl)	100	0
2	**2** (5-nitro-2-pyridyl)	100	0
3	**3** (5-CF_3-2-pyridyl)	100	0
4	**7** (5-cyano-2-pyridyl)	94	6
5	**8** (*para*-cyanophenyl)	54	46
6	**9** (*para*-acetylphenyl)	27	73
7	**10** (2-pyridyl)	14	86
8	**11** (*para*-CF_3-phenyl)	4	96
9	**12** (*meta*-nitrophenyl)	0	100
10	**13** (*meta*-CF_3-phenyl)	0	100
11	**14** (naphthyl)	0	100
12	**15** (*para*-CH_3O-phenyl)	0	100

[a] ^{19}F NMR yields.

Computational investigations using density functional theory[35] (B3LYP functional[36,37] and 6-31+G* basis[38]) and IEF-PCM model[39] yielded rather low (1.5 to 7 kcal/mol) barriers for either the release of trifluoroacetate or fluoroform. The product selectivity is thus determined mainly by the reaction energies as shown in Table 5 for *gem*-diols **1**–**3** and **7**–**15**. The fragmentation of *para*-nitrophenyl *gem*-diol **1** and 5-nitro-2-pyridyl *gem*-diol **2** was predicted to be exergonic with reaction energies of –39.9 and –44.4 kcal/mol, respectively. Products from the release of trifluoroacetate were energetically more favorable than those produced from the release of fluoroform, which were less exergonic (–32.4 and –32.0 kcal/mol). These data support the experimental observation of only products from the release of trifluoroacetate from the nitroaryl pentafluoro *gem*-diols **1** and **2**. However, the computational data contrasted the experimental results for **3** in which the release of trifluoroacetate was exclusively observed by ^{19}F NMR. The computational trend for compounds **7**–**15** agreed the experimental data as the production of fluoroform increases.

Table 5. Computed reaction energies and free energies (in kcal/mol) at 298.15 K for the fragmentation of each (doubly deprotonated) *gem*-diol **1**–**3** and **7**–**15** into anionic products[a]

compd	release of trifluoroacetate		release of fluoroform		difference	
	ΔU	ΔG	ΔU	ΔG	ΔΔU	ΔΔG
1	–25.6	–39.9	–15.9	–32.4	–9.7	–7.5
2	–30.9	–44.4	–16.0	–32.0	–14.9	–12.4
3	–13.9	–27.8	–16.9	–33.8	3.0	6.0
7	–18.2	–32.9	–16.5	–32.4	–1.7	–0.5
8	–12.0	–27.2	–16.5	–33.2	4.5	5.0

9	–12.2	–27.3	–17.2	–32.6	5.0	5.3
10	–10.0	–25.5	–18.3	–35.0	8.3	9.5
11	–10.1	–25.5	–17.0	–34.8	6.9	9.3
12	–8.9	–24.3	–15.7	–32.4	6.8	8.1
13	–8.6	–23.8	–16.9	–33.3	8.3	9.5
14	–10.3	–25.1	–20.2	–35.7	9.9	10.6
15	–6.2	–21.6	–18.6	–35.7	12.4	14.1

[a] B3LYP/6-31+G* geometry optimization and vibrational analysis were performed using the IEFP-PCM model for DMSO solvent within the Q-Chem 5.0 software package.[40]

It is noteworthy that a nitro group at the *meta* position (**12**) cannot stabilize the fragmentation of trifluoroacetate as well as a nitro group at the para position (**1**). As shown in Figure 4, this difference occurs because the lowest unoccupied orbital of the *meta*-nitro group overlaps less with the highest occupied orbitals on the arylated difluoromethyl carbanion, and thus withdraws few electrons. The net electrostatic-potential-derived (ESP) charges on the nitro groups in the product derived from the fragmentation of trifluoroacetate were found to be –0.85 for **1** and –0.23 for **12**. This difference leads to a less significant reaction free energy (–24.3 kcal/mol) for the fragmentation of trifluoroacetate from molecule **12**. Consequently, the product of **12** derived from the cleavage of trifluoroacetate becomes less stable than the products produced from the release of fluoroform (which retain the same reaction free energy of –32.4 kcal/mol as **1**).

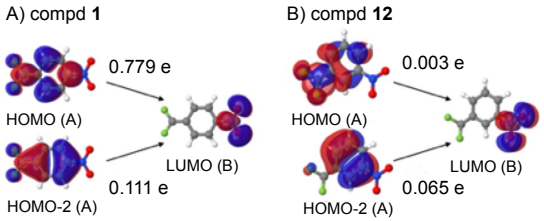
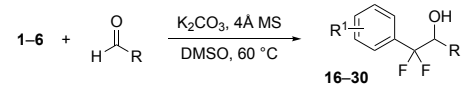
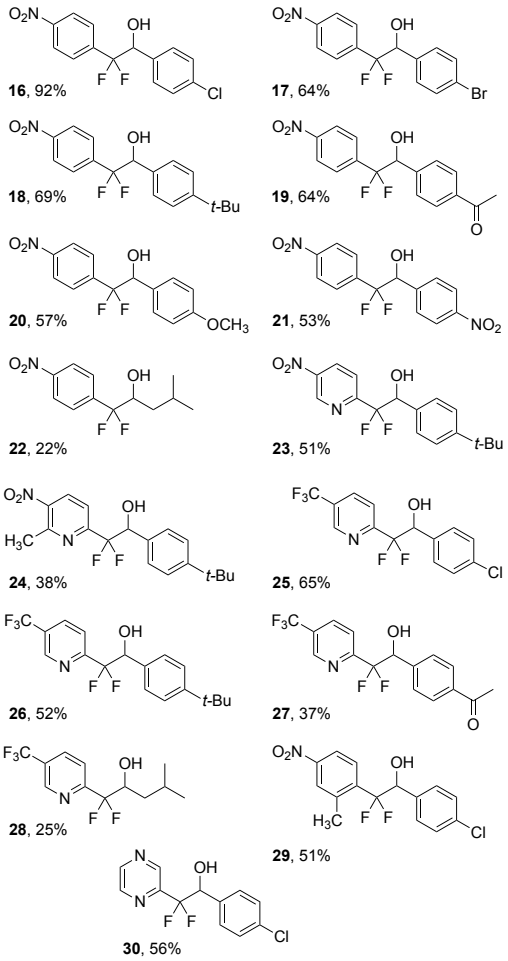


Figure 4. Intramolecular charge transfer within the fragmentation product of *para*-nitrophenyl pentafluoro *gem*-diol **1** and *meta*-nitrophenyl pentafluoro *gem*-diol **12** with the release of trifluoroacetate using a frontier orbital analysis[41] at the B3LYP/6-31+G* level of theory.

The goal of developing a process to form the α,α-difluorobenzyl carbanions is to use them in synthetic reactions with suitable electrophiles. Aldehydes were determined to be compatible with this class of carbanion, and the optimal conditions were five equivalents of K_2CO_3 in the presence of molecular sieves in DMSO at 60 °C (Table 6). The reaction was typically completed in two hours, but some substrates required up to five hours. The *para*-nitrobenzene **1** reacted with many aldehydes with a substantial range of isolated yields (22–93%) as shown in Table 6. Benzaldehydes with bromo, chloro, *tert*-butyl, acetyl, methoxy, and nitro-substituents participated with good to excellent isolated yields for the respective products **16**–**21**. An alkyl aldehyde, isovaleraldehyde, is compatible but provided the lowest isolated yield for the product **22** of the series at 22%. Substituted pyridines (e.g., **2, 3,** and **5**) display a similar reactivity profile as the nitrobenzenes **1** and **4** across the aryl and alkyl aldehydes. Pyrazine **6** reacts with *para*-chlorobenzaldehyde to make the difluorinated product **30** in 56% isolated yield. The results demonstrate a synthetic application of the selective fragmentation of the pentafluorinated-*gem*-diols through the release of trifluoroacetate.

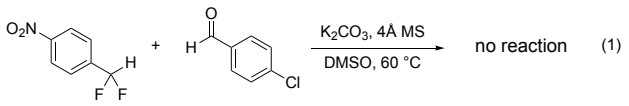
Table 6. Fragmentations of **1**–**6** in the Presence of Aldehydes [a]





[a] Isolated yields.

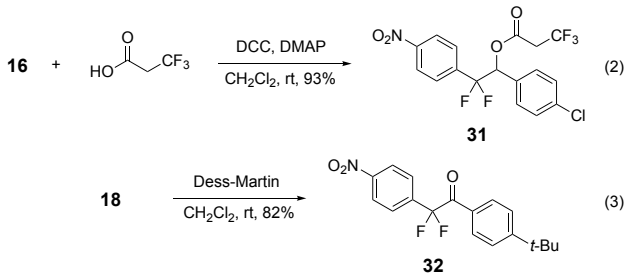
Additional experiments were performed to probe the mechanism of this synthetic transformation. Although we hypothesized that the creation of the α,α-difluorobenzyl carbanions would result from the fragmentation of the pentafluorinated-*gem*-diols, we still investigated if the electron-deficient α,α-difluoromethylarenes could be deprotonated under the reaction conditions and participate in coupling with the electrophile. Accordingly, the 1-difluoromethyl-4-nitrobenzene and *para*-chlorobenzaldehyde in DMSO was treated with K_2CO_3 and heated to 60 °C (eq 1). After six hours, only unreacted starting material was observed by ^{19}F NMR.



(1)

These mechanistic data serve to highlight the process of the release of trifluoroacetate to generate valuable reactive intermediates, such as α,α-difluorobenzyl carbanions. The necessity of only the mild base, K_2CO_3, is a significant advancement, because the usual reagents to create potassium-based carbanions in synthesis are the strong bases KH or KHMDS.

The fluorinated alcohols obtained from the fragmentation process can be used in the common synthetic reactions of alcohols. For example, alcohol **16** is esterified to **31** in 93% yield using DCC and DMAP (eq 2). Also, the alcohol **18** is oxidized to the ketone **32** using Dess-Martin periodinane in 82% yield (eq 3). These transformations demonstrate the additional synthetic potential of these difluorinated alcohols.



(2) (3)

CONCLUSIONS

In summary, we have demonstrated the cleavage of carbon–carbon bonds to generate α,α-difluorobenzyl carbanions by the selective release of trifluoroacetate. Our approach provides a method to synthesize α,α-difluoromethyl arenes and heteroarenes using the mild base K_2CO_3. This approach is compatible with electron-deficient aromatic and heteroaromatics pentafluoro-*gem*-diols with alkyl and aryl aldehydes. These findings demonstrated another application of the selective release of trifluoroacetate to access organic compounds that display difluoromethylarenes.

EXPERIMENTAL SECTION

Representative Reaction Procedure for Preparation of Pentafluoro *gem*-Diols.[42] The copper-mediated coupling of bromoethyldifluoroacetate with aryl halides was conducted according to the literature method.[33] Briefly, a mixture of 1-iodo-4-nitrobenzene (500 mg, 2.01 mmol) and copper (510 mg, 8.03 mmol) in DMSO (5.0 mL) was stirred at rt, and then ethyl 2-bromo-2,2-difluoroacetate (309 μL, 2.41 mmol) was added. The mixture was warmed to 51 °C in an oil bath for 9 h, cooled to rt, and quenched with saturated aqueous NH_4Cl (6 mL). The mixture was extracted with CH_2Cl_2 (6 mL × 5). The organics were dried over Na_2SO_4 and concentrated under reduced pressure. SiO_2 flash chromatography (100% $CHCl_3$) provided the ethyl 2,2-difluoroacetate-2-(4-nitrophenyl)acetate[33] (445 mg). Next, to a solution of ethyl 2,2-difluoroacetate-2-(4-nitrophenyl)acetate (96 mg, 0.39 mmol) in CH_3CN (1.0 mL) at rt was added trifluoromethyltrimethylsilane (88 μL, 0.59 mmol). The mixture was stirred for 3 min and then treated with a solution of CsF (30 mg, 0.2 mmol) in CH_3CN (2.0 mL). The reaction mixture was stirred for 24 h at rt. Then, the mixture was quenched with saturated aqueous NH_4Cl (2 mL), extracted with CH_2Cl_2 (2 mL × 5), dried over Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was treated with TBAF (0.5 mL, 1.0 M in THF) in CH_2Cl_2 (1 mL) and stirred for 40 min at rt. Next, the mixture was quenched with saturated aqueous NH_4Cl (2 mL), extracted with CH_2Cl_2 (2 mL × 5), dried over Na_2SO_4, and concentrated under reduced pressure. SiO_2 flash chromatography (100% $CHCl_3$→8:2 hexanes/EtOAc) afforded 1,1,1,3,3-pentafluoro-3-(4-nitrophenyl)propane-2,2-diol as a colorless solid (82 mg) in 44% yield (two steps).

1,1,1,3,3-Pentafluoro-3-(4-nitrophenyl)propane-2,2-diol (1). See representative reaction. Recrystallization from a solution of hexanes and CH2Cl2 (by slow evaporation) provided a crystalline solid suitable for X-ray structure analysis: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, J = 9.0 Hz, 2H), 7.83 (d, J = 8.9 Hz, 2H), 3.84 (br s, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 149.4, 137.6 (t, J_{CF} = 25.0 Hz, 1C), 128.6 (t, J_{CF} = 6.3 Hz, 2C), 123.2 (2), 121.2 (q, J_{CF} = 286.3 Hz, 1C), 117.1 (t, J_{CF} = 253.8 Hz, 1C), 92.6 (app sextet, J_{CF} = 32.5 Hz, 1C); ^{19}F NMR (282 MHz, $CDCl_3$) δ –81.17 (t, J_{FF} = 9.6 Hz, 3F), –110.95 (q, J_{FF} = 9.3 Hz, 2F); IR (film) ν_{max} 3391, 1531, 1192, 1177, 1064 cm^{-1}; HRMS (CI–Q) m/z calcd for $C_9H_5F_5NO_3$ $(M+H–H_2O)^+$ 270.0184, found 270.0193; mp 86–88 °C.

1,1,1,3,3-Pentafluoro-3-(5-nitropyridin-2-yl)propane-2,2-diol (2). See representative reaction. The reaction mixture was warmed to 70 °C in an oil bath for 72 h, and ethyl 2,2-difluoro-2-(5-nitropyridin-2-yl)acetate[43] was isolated. See representative reaction. 4Å molecular sieves were added prior to treatment with CsF. The reaction mixture was stirred –30 °C to 0 °C 1 h. SiO_2 flash chromatography (20% EtOAc in hexanes) afforded the title compound **2** as colorless solid (37% yield, two steps): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.46 (d, J = 2.5 Hz, 1H), 8.78 (dd, J = 8.6, 2.5 Hz, 1H), 8.08 (dd, J = 8.6, 0.6 Hz, 1H), 5.58 (br s, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 157.1 (t, J_{CF} = 28.4 Hz, 1C), 145.2, 143.9, 133.9, 122.2 (t, J_{CF} = 3.8 Hz, 1C), 121.1 (q, J_{CF} = 287.5 Hz, 1C), 112.6 (t, J_{CF} = 255.0 Hz, 1C), 93.3 (qt, J_{CF} = 28.8, 3.8 Hz, 1C); ^{19}F NMR (282 MHz, $CDCl_3$) δ –81.9 (t, J_{FF} = 10.8 Hz, 3F), –113.2 (q, J_{FF} = 10.8 Hz, 2F); IR (film) ν_{max} 3218, 1614, 1539, 1361, 1201 cm^{-1}; HRMS (EI–BE) m/z calcd for $C_8H_3F_5N_2O_3$ $(M–H_2O)^+$ 270.0058, found 270.0060; mp 66–68 °C.

1,1,1,3,3-Pentafluoro-3-(5-(trifluoromethyl)pyridin-2-yl)propane-2,2-diol (3). See representative reaction. The reaction mixture was warmed to 70 °C in an oil bath for 72 h. SiO_2 flash chromatography (100% $CHCl_3$) afforded ethyl 2,2-difluoro-2-(5-(trifluoromethyl)pyridin-2-yl)acetate as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.12 (dd, J = 8.3, 2.1 Hz, 1H), 7.89 (d, J = 8.3 Hz, 1H), 4.37 (q, J = 7.2 Hz, 2H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 162.7 (t, J_{CF} = 32.1 Hz, 1C), 155.0 (t, J_{CF} = 28.2 Hz, 1C), 146.5, 134.9, 128.5 (q, J_{CF} = 33.2 Hz, 1C), 122.8 (q, J_{CF} =

270.6 Hz, 1C), 120.5, 111.5 (t, J_{CF} = 250.8 Hz, 1C), 63.5, 13.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ –63.7 (s, 3F), –106.7 (s, 2F); IR (film) ν_{max} 1779, 1332, 1138, 1017 cm^{-1}; HRMS (CI–Q) *m/z* calcd for $C_{10}H_9F_5NO_2$ $(M+H)^+$, 270.0554, found 270.0551. See representative reaction. SiO_2 flash chromatography (100% $CHCl_3$ to 1:1 hexanes:EtOAc) afforded the title compound **3** as colorless solid (77% yield, two steps): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.24 (dd, *J* = 8.3, 1.9 Hz, 1H), 8.00 (d, *J* = 8.3 Hz, 1H), 5.74 (br s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 155.6 (t, J_{CF} = 28.3 Hz, 1C), 145.3 (q, J_{CF} = 3.9 Hz, 1C), 136.1 (q, J_{CF} = 3.4 Hz, 1C), 129.1 (q, J_{CF} = 33.7 Hz, 1C), 122.5 (q, J_{CF} = 271.3 Hz, 1C), 121.4 (t, J_{CF} = 4.9 Hz, 1C), 121.2 (q, J_{CF} = 286.4 Hz, 1C), 112.5 (t, J_{CF} = 254.1 Hz, 1C), 93.2 (qt, *J* = 32.5, 4.5 Hz 1C); ^{19}F NMR (282 MHz, $CDCl_3$) δ –63.7 (s, 3F), –82.0 (t, J_{FF} = 11.1 Hz, 3F), –113.4 (q, J_{FF} = 11.0 Hz, 2F); IR (film) ν_{max} 3392, 1615, 1204, 1083 cm^{-1}; HRMS (EI–BE) *m/z* calcd for $C_9H_4F_8NO$ $(M+H–H_2O)^+$ 294.0160, found 294.0168; mp 79–81 °C.

1,1,1,3,3-Pentafluoro-3-(2-methyl-4-nitrophenyl)propane-2,2-diol (4). See representative reaction. The reaction mixture was warmed to 55 °C in an oil bath for 18 h. SiO_2 flash chromatography (5% Et_2O in hexanes) afforded ethyl 2,2-difluoro-2-(2-methyl-4-nitrophenyl)acetate as a yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.7 Hz, 1H), 8.10 (s, 1H), 7.79 (d, *J* = 8.5 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 2.52 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 163.2 (t, J_{CF} = 34.1 Hz, 1C), 149.3, 138.9, 137.4 (t, J_{CF} = 23.6 Hz, 1C), 127.8 (t, J_{CF} = 9.0 Hz, 1C), 126.6, 121.1, 113.3 (t, J_{CF} = 253.1 Hz, 1C), 63.8, 20.0 (t, J_{CF} = 2.8 Hz, 1C), 14.0; ^{19}F NMR (471 MHz, $CDCl_3$) δ –103.16 (s, 2F); IR (film) ν_{max} 1761, 1531, 1351 cm^{-1}. See representative reaction. 4Å molecular sieves were added prior to treatment with CsF. The reaction mixture was stirred –30 °C to 0 °C 1 h. SiO_2 flash chromatography (10–20% EtOAc in hexanes) afforded the title compound **4** as colorless solid (58% yield, two steps): ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 8.02 (s, 1H), 8.01 (d, *J* = 9.2 Hz, 1H), 7.75 (d, *J* = 9.4 Hz, 1H), 7.20 (br s, 1H), 3.81 (br s, 1H), 2.65 (t, *J* = 3.6 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $(CD_3)_2CO$) δ 147.4, 139.6, 135.6 (t, J_{CF} = 23.6 Hz, 1C), 129.6 (t, J_{CF} = 8.9 Hz, 1C), 124.6, 121.3 (q, J_{CF} = 288.1 Hz, 1C), 118.9 (t, J_{CF} = 257.6 Hz, 1C), 118.3, 91.7 (app sextet, J_{CF} = 31.2 Hz, 1C), 19.3 (t, J_{CF} = 5.1 Hz, 1C); ^{19}F NMR (471 MHz, $CDCl_3$) δ –81.3 (t, J_{FF} = 10.4 Hz, 3F), –106.4 (q, J_{FF} = 10.3 Hz, 2F); IR (film) ν_{max} 3390, 2986, 2864, 1525, 1352, 1254, 1163, 1058 cm^{-1}; HRMS (ESI–TOF) *m/z* calcd for $C_{10}H_7F_5NO_4$ $[M–H]^-$ 300.0295, found 300.0291; mp 111–113 °C.

1,1,1,3,3-Pentafluoro-3-(6-methyl-5-nitropyridin-2-yl)propane-2,2-diol (5). See representative reaction. The reaction mixture was warmed to 55 °C in an oil bath for 10 h. SiO_2 flash chromatography (5% EtOAc in hexanes) afforded ethyl 2,2-difluoro-2-(6-methyl-5-nitropyridin-2-yl)acetate as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 8.4 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 4.37 (q, *J* = 7.2 Hz, 2H), 2.83 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.6 (t, J_{CF} = 32.3 Hz, 1C), 154.4 (t, J_{CF} = 28.7 Hz, 1C), 154.1, 146.7, 134.1, 119.1 (t, J_{CF} = 3.5 Hz, 1C), 111.3 (t, J_{CF} = 253.2 Hz, 1C), 63.6, 23.6, 14.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ –106.47 (s, 2F); IR (film) ν_{max} 1774, 1531, 1299 cm^{-1}; HRMS (ESI–TOF) *m/z* calcd for $C_{10}H_{11}F_2N_2O_4$ $[M+H]^+$ 261.0687, found 261.0683. See representative reaction. 4Å molecular sieves were added prior to treatment with CsF. The reaction mixture was stirred –30 °C to 0 °C 1 h. SiO_2 flash chromatography (20% EtOAc in hexanes) afforded the title compound **5** as colorless solid (55% yield, two steps): ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 8.60 (d, *J* = 8.5 Hz, 1H), 7.92 (d, *J* = 8.5 Hz, 1H), 2.96, (br s, 2H), 2.83 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $(CD_3)_2CO$) δ 155.6 (t, J_{CF} = 27.6 Hz), 154.2, 148.4, 135.8, 123.5 (q, J_{CF} = 286.7 Hz, 1C), 122.0 (t, J_{CF} = 4.8 Hz, 1C), 116.2 (t, J_{CF} = 256.1 Hz, 1C), 94.3 (qt, *J* = 28.6, 2.8 Hz, 1C), 23.9; ^{19}F NMR (471 MHz, $(CD_3)_2CO$) δ –81.40 (t, J_{FF} = 11.2 Hz, 3F), –113.78 (q, J_{FF} = 10.8 Hz, 2F); IR (film) ν_{max} 3331, 3105, 2928, 2853, 1741, 1610,1537, 1278, 1207, 1168, 1068 cm^{-1}; HRMS (ESI–TOF) *m/z* calcd for $C_9H_6F_5N_2O_4$ $[M–H]^-$ 301.0248, found 301.0233; mp 126–128 °C.

1,1,1,3,3-Pentafluoro-3-(pyrazin-2-yl)propane-2,2-diol (6). See representative reaction. The reaction mixture was warmed to 55 °C in an oil bath for 16 h and ethyl 2,2-difluoro-2-(pyrazin-2-yl)acetate[44] was isolated. See representative reaction. 4Å molecular sieves were added prior to treatment with CsF. The reaction mixture was stirred –30 °C to 0 °C 1 h. SiO_2 flash chromatography (20% acetone in hexanes) afforded the title compound **6** as colorless solid (55% yield, two steps): ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 8.97 (s, 1H), 8.81 (s, 1H), 8.74 (s, 1H), 3.40 (br s, 2H); ^{13}C{^{1}H} NMR (125 MHz, $(CD_3)_2CO$) δ 147.1 (t, J_{CF} = 27.0 Hz, 1C), 146.5, 143.8 (t, J_{CF} = 5.0 Hz, 1C), 143.5, 122.2 (q, J_{CF} = 289.1 Hz, 1C), 115.8 (t, J_{CF} = 255.4 Hz, 1C), 92.6 (app sextet, J_{CF} = 31.4 Hz, 1C); ^{19}F NMR (471 MHz, $(CD_3)_2CO$) δ –81.3 (t, J_{FF} = 10.7 Hz, 3F), –114.7 (q, J_{FF} = 10.7 Hz, 2F); IR (film) ν_{max} 3199, 2923, 2852, 1665,1583, 1413, 1298, 1204, 1176 cm^{-1}; HRMS (ESI–TOF) *m/z* calcd for $C_7H_4F_5N_2O_2$ $[M–H]^-$ 243.0193, found 243.0203; mp 129–131°C.

1,1,3,3,3-Pentafluoro-3-(5-cyanopyridin-2-yl)propane-2,2-diol (7). See representative reaction. The reaction mixture was warmed to 70 °C in an oil bath for 72 h. SiO_2 flash column chromatography (100% $CHCl_3$) afforded ethyl 2-(5-cyanopyridin-2-yl)-2,2-difluoroacetate as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.17 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.89 (dd, *J* = 8.1, 0.9 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 162.3 (t, J_{CF} = 31.5 Hz, 1C), 154.6 (t, J_{CF} = 28.7 Hz, 1C), 151.9, 141.0, 120.6 (t, J_{CF} = 3.6 Hz, 1C), 115.5, 112.0, 111.1 (t, J_{CF} = 252.0 Hz, 1C), 63.6, 13.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ –107.0 (s, 2F); IR (film) ν_{max} 2239, 1774, 1120, 1019 cm^{-1}; HRMS (CI–Q) *m/z* calcd for $C_{10}H_9F_2N_2O_2$ $(M+H)^+$, 227.0632; found, 227.0639. See representative reaction. SiO_2 flash column chromatography (100% $CHCl_3$ to 1:1 hexanes/EtOAc) afforded the title compound **7** as colorless solid (57% yield, two steps): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.27 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.99 (dd, *J* = 8.0, 1.0 Hz, 1H), 5.60 (br s, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 155.4 (t, J_{CF} = 28.4 Hz, 1C), 150.7, 142.2, 121.6 (t, J_{CF} = 3.8 Hz, 1C), 121.1 (q, J_{CF} = 286.3 Hz, 1C), 114.9, 112.6, 112.5 (t, J_{CF} = 253.8 Hz, 1C), 93.3 (app sextet, *J* = 28.4 Hz, 1C); ^{19}F NMR (282 MHz, $CDCl_3$) δ –81.9 (t, J_{FF} = 11.0 Hz, 3F), –113.7 (q, J_{FF} = 11.0 Hz, 2F); IR (film) ν_{max} 3368, 2239, 1203, 1118 cm^{-1}; HRMS (EI–BE) *m/z* calcd for $C_9H_3F_5N_2O$ $(M–H_2O)^+$ 250.0160, found, 250.0164; mp 90–92 °C.

1,1,3,3,3-Pentafluoro-3-(4-cyanophenyl)-propane-2,2-diol (8). See representative reaction. The reaction mixture was warmed to 80 °C in an oil bath for 48 h, and ethyl 2-(4-cyanophenyl)-2,2-difluoroacetate[45] was isolated. See representative reaction. SiO_2 flash column chromatography (100% $CHCl_3$ to 1:1 hexanes/EtOAc) afforded the title compound **8** as colorless solid (71% yield, two steps): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (s, 4H), 3.73 (br s, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 135.9 (t, J_{CF} = 25.0 Hz, 1C), 131.9 (2), 128.1 (t, J_{CF} = 6.6 Hz, 2C), 121.2 (q, J_{CF} = 286.3 Hz, 1C), 117.1 (t, J_{CF} = 253.5 Hz, 1C), 115.0, 92.6 (app sextet, J = 32.2 Hz, 1C); ^{19}F NMR (282 MHz, $CDCl_3$) δ –81.3 (t, J_{FF} = 9.3 Hz, 3F), –111.5 (q, J_{FF} = 9.5 Hz, 2F); IR (film) ν_{max} 3272, 2249, 1278, 1195, 1071 cm^{-1}; HRMS (EI–BE) *m/z* calcd for $C_{10}H_5F_5NO$ $(M+H–H_2O)^+$ 250.0286, found 250.0295; mp 98–100 °C.

1,1,3,3,3-Pentafluoro-3-(4-acetylphenyl)-propane-2,2-diol (9). See representative reaction. The reaction mixture was warmed to 80 °C in an oil bath for 48 h, and ethyl 2-(4-acetylphenyl)-2,2-difluoroacetate[46] was isolated. See representative reaction. SiO_2 flash column chromatography (100% $CHCl_3$ to 1:1 hexanes/EtOAc) afforded the title compound **9** as colorless solid (26% yield, two steps): ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 8.07 (d, *J* = 8.2 Hz, 2H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.07 (s, 2H), 2.63 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $(CD_3)_2CO$) δ 197.7, 139.7, 137.7 (t, J_{CF} = 25.0 Hz, 1C), 128.7 (t, J_{CF} = 6.7 Hz, 2C), 128.4 (2C), 123.5 (q, J_{CF} = 287.7 Hz, 1C), 119.6 (t, J_{CF} = 252.5 Hz, 1C), 93.5 (q, J_{CF} = 31.3 Hz, 1C), 26.9; ^{19}F NMR (376 MHz, $(CD_3)_2CO$) δ –79.9 (t, J_{FF} = 11.1 Hz, 3F), –109.7 (q, J_{FF} = 11.6 Hz, 2F); IR (film) ν_{max} 3391, 1679, 1277, 1198 cm^{-1}; HRMS (CI–Q) *m/z* calcd for $C_{11}H_8F_5O_2$ $(M+H–H_2O)^+$ 267.0439, found 267.0448; mp 106–108 °C.

1,1,1,3,3-Pentafluoro-3-(pyridin-2-yl)propane-2,2-diol (10). See representative reaction. The reaction mixture was warmed to 70 °C in an oil bath for 72 h, and ethyl 2,2-difluoro-2-(pyridin-2-yl)acetate[44] was isolated. See representative reaction. SiO_2 flash column chromatography (100% $CHCl_3$ to 7:3 hexanes/EtOAc) afforded the title compound **10** as colorless solid (46% yield, two steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 4.0 Hz, 1H), 7.98 (td, *J* = 7.8, 1.6 Hz, 1H), 7.84 (d, *J* = 7.9 Hz, 1H), 7.54 (dd, *J* = 7.2, 5.2 Hz, 1H), 6.22 (br s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.3 (t, J_{CF} = 28.8 Hz, 1C), 147.8, 138.8, 126.0, 121.4 (t, J_{CF} = 286.6 Hz, 1C), 121.3 (J_{CF} = 4.8 Hz, 1C), 112.6 (t, J_{CF} = 254.5 Hz, 1C), 93.6 (qt, *J* = 32.3, 4.3 Hz, 1C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –81.0 (t, J_{FF} = 10.9 Hz, 3F), –112.2 (q, J_{FF} = 10.9 Hz, 2F); IR (film) ν_{max} 3351, 1203, 1169, 1081 cm^{-1}; HRMS (EI–BE) *m/z* calcd for $C_8H_4F_5NO$ $(M–H_2O)^+$ 225.0208, found 225.0219; mp 47–48 °C.

1,1,1,3,3-Pentafluoro-3-(4-(trifluoromethyl)phenyl)propane-2,2-diol (11). See representative reaction. The reaction mixture was warmed to 80 °C in an oil bath for 24 h, and ethyl 2,2-difluoro-2-(4-(trifluoromethyl)phenyl)acetate[46] was isolated. See representative reaction. SiO_2 flash column chromatography (100% $CHCl_3$ to 1:1 hexanes/EtOAc) afforded the title compound **11** as colorless solid (84% yield, two steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.7 Hz, 2H), 7.73 (d, *J* = 8.7 Hz, 2H), 3.44 (br s, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 134.7 (t, J_{CF} = 25.4 Hz, 1C), 133.1 (q, J_{CF} = 34.0 Hz, 1C), 127.8 (t, J_{CF} = 6.5 Hz, 2C), 125.2 (q, J_{CF} = 4.0 Hz, 2C), 123.5 (q, J_{CF} = 271.3 Hz, 1C), 121.3 (q, J_{CF} = 286.4 Hz, 1C), 117.3 (t, J_{CF} = 253.1 Hz, 1C), 92.6 (app sextet, J_{CF} = 32.0 Hz, 1C); ^{19}F NMR (282 MHz, $CDCl_3$) δ –64.1 (s, 3F), –81.3 (t, J_{FF} = 9.6 Hz, 3F), –110.0 (q, J_{FF} = 9.6 Hz, 2F); IR (film) ν_{max} 3435, 1416, 1329, 1138, 1071 cm^{-1}; HRMS (EI–BE) *m/z* calcd for $C_{10}H_6F_7O_2$ $(M–F)^+$ 291.0251, found 291.0251; mp 56–58 °C.

1,1,1,3,3-Pentafluoro-3-(3-nitrophenyl)propane-2,2-diol (12). See representative reaction. The reaction mixture was warmed to 62 °C in an oil bath for 24 h. SiO_2 flash column chromatography (100% $CHCl_3$) afforded ethyl 2,2-difluoro-2-(3-nitrophenyl)acetate as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.38 (d, *J* = 8.2 Hz, 1H), 7.96 (d, *J* = 7.4 Hz, 1C), 7.69 (t, *J* = 8.0 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 163.1 (t, J_{CF} = 34.2 Hz, 1C), 148.2, 134.8 (t, J_{CF} = 26.3 Hz, 1C), 131.5 (t, J_{CF} = 5.8 Hz, 1C), 130.0, 125.9, 121.1 (t, J_{CF} = 6.4 Hz, 1C), 112.1 (t, J_{CF} = 252.5 Hz, 1C), 63.7, 13.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ –104.9 (s, 2F); IR (film) ν_{max} 1769, 1539, 1353, 1096, 717 cm^{-1}; HRMS (EI–BE) *m/z* calcd for $C_{10}H_{10}F_2NO_4$ $(M+H)^+$, 246.0578, found 246.0576. SiO_2 flash column chromatography (100% $CHCl_3$ to 8:2 hexanes/EtOAc) afforded the title compound **12** as colorless solid (67% yield, two steps). Recrystallization from a solution of hexanes and CH2Cl2 (by slow evaporation) provided a crystalline solid suitable for X-ray structure analysis: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (t, *J* = 1.8 Hz, 1H), 8.40 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.68 (t, *J* = 8.0 Hz, 1H), 3.57 (br s, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 147.9, 133.3 (t, J_{CF} = 26.0 Hz, 1C), 133.1 (t, J_{CF} = 6.3 Hz, 1C), 129.4, 125.9, 122.7 (t, J_{CF} = 7.1 Hz, 1C), 121.2 (q, J_{CF} = 286.4 Hz, 1C), 116.9 (t, J_{CF} = 253.5 Hz, 1C), 92.6 (sextet, J_{CF} = 32.3 Hz, 1C); ^{19}F NMR (282 MHz, $CDCl_3$) δ –81.3 (t, J_{FF} = 9.6 Hz, 3F), –110.6 (q, J_{FF} = 9.6 Hz, 2F); IR (film) ν_{max} 3367, 1534, 1356, 1197, 715 cm^{-1}; HRMS (EI–BE) *m/z* calcd for $C_9H_5F_5NO_3$ $(M+H–H_2O)^+$ 270.0184, found 270.0193; mp 93–95 °C.

1,1,1,3,3-Pentafluoro-3-(3-(trifluoromethyl)phenyl)propane-2,2-diol (13). See representative reaction. The reaction mixture was warmed to 62 °C in an oil bath for 48 h, and ethyl 2,2-difluoro-2-(3-(trifluoromethyl)phenyl)acetate[47] was isolated. See representative reaction. SiO_2 flash column chromatography (100% $CHCl_3$ to 1:1 hexanes/EtOAc) afforded the title compound **13** as colorless oil (36% yield, two steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.81 (t, *J* = 8.3 Hz, 2H), 7.61 (t, *J* = 7.9 Hz, 1H), 3.44 (br s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 132.5 (t, J_{CF} = 25.6 Hz, 1C), 130.8 (q, J_{CF} = 32.7 Hz, 1C), 130.5 (t, J_{CF} = 6.8 Hz, 1C), 128.6, 127.7 (m, 1C), 124.3 (m, 1C), 123.6 (q, J_{CF} = 270.7 Hz, 1C), 121.4 (q, J_{CF} = 286.3 Hz, 1C), 117.5 (t, J_{CF} = 252.7 Hz, 1C), 92.5 (q, J_{CF} = 31.9 Hz, 1C); ^{19}F NMR (282 MHz, $CDCl_3$) δ –64.4 (s, 3F), –81.8 (t, J_{FF} = 9.7 Hz, 3F), –111.3 (q, J_{FF} = 9.7 Hz, 2F); IR (film) ν_{max} 3446, 1339, 1259, 1135 cm^{-1}; HRMS (EI–BE) *m/z* calcd for $C_{10}H_5F_8O$ $(M+H–H_2O)^+$ 293.0207, found 293.0219.

1,1,1,3,3-Pentafluoro-3-(naphthalen-1-yl)propane-2,2-diol (14). See representative reaction. The reaction mixture was warmed to 60 °C in an oil bath for 96 h, and ethyl 2,2-difluoro-2-(naphthalen-1-yl)acetate[48] was isolated. See

representative reaction. SiO_2 flash column chromatography (100% $CHCl_3$ to 8:2 hexanes/EtOAc) afforded the title compound **14** as colorless oil (27% yield, two steps): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (d, *J* = 9.2 Hz, 1H), 8.06* (d, *J* = 8.3 Hz, 1H), 8.03 (d, *J* = 8.2 Hz, 1H), 7.94* (d, *J* = 11.0 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.83 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.63–7.53 (m, 3H), 3.35 (br s, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 180.3* (q, J_{CF} = 36.6 Hz, 1C), 134.2, 133.9*, 133.3*, 132.7, 130.5*, 129.2, 128.8, 128.1 (t, J_{CF} = 9.7 Hz, 1C), 127.2*, 126.7*, 126.3 (2C), 126.2, 126.1*, 126.0*, 124.6, 124.3, 123.6*, 121.7* (q, J_{CF} = 286.8 Hz, 1C), 121.3 (q, J_{CF} = 287.6 Hz, 1C), 116.3* (t, J_{CF} = 257.0 Hz, 1C), 115.8 (t, J_{CF} = 253.1 Hz, 1C), 93.1 (sextet, J_{CF} = 32.3 Hz, 1C); ^{19}F NMR (282 MHz, $CDCl_3$) δ –73.8* (t, J_{FF} = 7.6 Hz, 3F), –81.1 (t, J_{FF} = 11.2 Hz, 3F), –102.5* (q, J_{FF} = 7.3 Hz, 2F), –104.4 (q, J_{FF} = 11.1Hz, 2F); IR (film) ν_{max} 3519, 1202, 1049, 796 cm^{-1}; HRMS (EI–BE) *m/z* calcd for $C_{13}H_7F_5O$ $(M–H_2O)^+$ 274.0412, found 274.0424.* denotes the minor keto-form of the product.

1,1,1,3,3-Pentafluoro-3-(4-methoxyphenyl)propane-2,2-diol (15). See representative reaction. The reaction mixture was warmed to 55 °C in an oil bath for 24 h, and ethyl 2,2-difluoro-2-(4-methoxyphenyl)acetate[33] was isolated. See representative reaction. SiO_2 flash column chromatography (100% $CHCl_3$ to 8:2 hexanes/EtOAc) afforded the title compound **15** as colorless oil (67% yield, two steps): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 8.9 Hz, 2H), 3.85 (s, 3H), 2.57 (br s, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 161.7, 128.7 (t, J_{CF} = 6.4 Hz, 2C), 122.7 (t, J_{CF} = 25.0 Hz, 1C), 121.5 (q, J_{CF} = 286.3 Hz, 1C), 118.20 (t, J_{CF} = 252.5 Hz, 1C), 113.7 (2C), 92.5 (sextet, J_{CF} = 31.3 Hz, 1C), 55.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ –81.2 (t, J_{FF} = 10.2 Hz, 3F), –109.8 (q, J_{FF} = 10.8 Hz, 2F); IR (film) ν_{max} 3368, 1195, 1057, 831 cm^{-1}; HRMS (EI–BE) *m/z* calcd for $C_{10}H_7F_5O_2$ $(M–H_2O)^+$ 254.0361, found 254.0372; mp 85–87 °C.

Representative Reaction Procedure for Preparation α,α-Difluoromethyl Arenes. A solution of 1,1,1,3,3-pentafluoro-3-(4-nitrophenyl)propane-2,2-diol **1** (10 mg, 0.04 mmol) in DMSO (0.8 mL) at rt was treated with 4Å molecular sieves (100 mg) and K_2CO_3 (30 mg, 0.2 mmol). Then, a solution of 4-chlorobenzaldehyde (8.0 mg, 0.06 mmol) in DMSO (0.2 mL) was added dropwise and the reaction mixture was stirred at rt for 15 min. Next, the reaction mixture was heated to 60 °C in an oil bath for 2 h, cooled to rt, and quenched with saturated aqueous NH_4Cl (2 mL). The mixture was diluted with EtOAc (20 mL) and filtered through celite. The organics were washed with saturated aqueous NaCl (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by preparative TLC (15% EtOAc in hexanes) afforded 1-(4-chlorophenyl)-2,2-difluoro-2-(4-nitrophenyl)ethan-1-ol as a colorless solid (10 mg, 92%).

1-(4-Chlorophenyl)-2,2-difluoro-2-(4-nitrophenyl)ethan-1-ol (16). See representative reaction: ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 8.28 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.7 Hz, 2H), 7.34 (s, 4H), 5.71 (d, *J* = 5.0 Hz, 1H), 5.31 (dd, *J* = 11.8, 8.2 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $(CD_3)_2CO$) δ 149.9, 141.5 (t, J_{CF} = 26.4 Hz, 1C), 137.0, 134.6, 130.5 (2C), 129.0 (t, J_{CF} = 6.6 Hz, 2C), 128.8 (2C), 123.8 (2C), 121.5 (t, J_{CF} = 246.5 Hz, 1C), 75.4 (t, J_{CF} = 30.6 Hz, 1C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –105.8 (dd, J_{FF} = 252.2, J_{HF}= 9.0 Hz, 1F), –108.2 (dd, J_{FF} = 252.2, J_{HF} = 8.6 Hz, 1F); IR (film) ν_{max} 3515, 3115, 2907, 2849, 1608, 1519, 1353, 1074 cm^{-1}; HRMS (EI–TOF) *m/z* calcd for $C_{14}H_{10}Cl_2F_2NO_3$ $[M+Cl]^+$ 348.0006, found 348.0004; mp 154–155 °C.

1-(4-Bromophenyl)-2,2-difluoro-2-(4-nitrophenyl)ethan-1-ol (17). See representative reaction. Benzophenone (25 mg, 0.14 mmol) was added, and the reaction mixture was heated to 60 °C in an oil bath for 5 h. Purification by preparative TLC (5% EtOAc in $CHCl_3$) afforded the title compound **17** as a colorless solid (64%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.6 Hz, 2H), 7.42 (dd, *J* = 8.7, 2.6 Hz, 4H), 7.06 (d, *J* = 8.1 Hz, 2H), 5.13 (td, *J* = 9.0, 3.4 Hz, 1H), 2.61 (d, *J* = 3.9 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CD_3)_2CO$) δ 150.0, 141.5 (t, J_{CF} = 26.3 Hz, 1C), 137.5, 131.8 (2C), 130.8 (2C), 129.0 (t, J_{CF} = 6.3 Hz, 2C), 123.9 (2C), 122.9, 121.5 (t, J_{CF} = 248.6 Hz, 1C), 75.5 (t, J_{CF} = 30.5 Hz, 1C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –105.7 (dd, J_{FF} = 252.8, J_{HF} = 9.1 Hz, 1F), –108.2 (dd, J_{FF} = 252.3, J_{HF} = 8.6 Hz, 1F); IR (film) ν_{max} 3521, 2922, 2853, 1607, 1519, 1489, 1353, 1260, 1072 cm^{-1}; HRMS (EI–TOF) *m/z* calcd for $C_{14}H_{10}BrClF_2NO_3$ $[M+Cl]^+$ 391.9501, found 391.9507; mp 169–170 °C.

1-(4-(*tert*-Butyl)phenyl)-2,2-difluoro-2-(4-nitrophenyl)ethan-1-ol (18). See representative reaction. Benzophenone (16 mg, 0.088 mmol) was added, and the reaction mixture was heated to 60 °C in an oil bath for 5 h. Purification by preparative TLC (20% EtOAc in hexanes) afforded the title compound **18** as a colorless solid (69%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.5 Hz, 2H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 5.11 (t, *J* = 9.4 Hz, 1H), 2.55 (s, 1H), 1.30 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.3, 148.9, 140.1 (t, J_{CF} = 26.5 Hz, 1C), 132.2, 127.9 (t, J_{CF} = 6.2 Hz, 2C), 127.3 (2C), 125.2 (2C), 122.9 (2C), 120.3 (t, J_{CF} = 248.9 Hz, 1C), 76.3 (t, J_{CF} = 30.9 Hz, 1C), 34.6, 31.2 (3C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –105.7 (dd, J_{FF} = 251.3, J_{HF} = 9.5 Hz, 1F), –108.5 (dd, J_{FF} = 251.3, J_{HF} = 9.5 Hz, 1F); IR (film) ν_{max} 3457, 2963, 2905, 2870, 1610, 1528, 1410, 1350, 1076 cm^{-1}; HRMS (EI–TOF) *m/z* calcd for $C_{18}H_{19}ClF_2NO_3$ $[M+Cl]^+$ 370.1022, found 370.1028; mp 157–159 °C.

2-(4-Acetylphenyl)-1-2,2-difluoro-2-(4-nitrophenyl)ethan-1-ol (19). See representative reaction. Purification by preparative TLC (30% EtOAc in hexanes) afforded the title compound **19** as a colorless solid (69%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.5 Hz, 2H), 7.87 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 5.23 (t, *J* = 9.0 Hz, 1H), 2.85 (s, 1H), 2.59 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CD_3)_2CO$) δ 197.9, 149.9, 143.1, 141.5 (t, J_{CF} = 26.4 Hz, 1C), 138.0, 129.0 (2C), 128.9 (t, J_{CF} = 6.4 Hz, 2C), 128.5 (2C), 123.8 (2C), 121.5 (t, J_{CF} = 249.0 Hz, 1C), 75.3 (t, J_{CF} = 30.4 Hz, 1C), 26.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ –105.2 (dd, J_{FF} = 252.3 Hz, J_{HF} = 8.9 Hz, 1F), –108.1 (dd, J_{FF} = 252.4, J_{HF} = 8.4 Hz, 1F); IR (film) ν_{max} 3504, 3117, 2921, 1682, 1609, 1527, 1411, 1354, 1268, 1072 cm^{-1}; HRMS (ESI–TOF) *m/z* calcd for $C_{16}H_{12}F_2NO_4$ $[M–H]^-$ 320.0740, found 320.0740; mp 166–168 °C.

2,2-Difluoro-1-(4-methoxyphenyl)-2-(4-nitrophenyl)ethan-1-ol (20). See representative reaction.

Benzophenone (36 mg, 0.20 mmol) was added, and the reaction mixture was heated to 60 °C in an oil bath for 5 h. Purification by preparative TLC (20% EtOAc in hexanes) afforded the title compound **20** as a pale yellow solid (57%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 8.6 Hz, 2H), 7.07 (d, J = 8.5 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 5.09 (t, J = 9.2 Hz, 1H), 3.79 (s, 1H), 2.59 (br s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $(CD_3)_2CO$) δ 160.3, 149.3, 141.5 (t, J_{CF} = 26.5 Hz, 1C), 129.6, 129.5 (2C), 128.5 (t, J_{CF} = 6.2 Hz, 2C), 123.2 (2C), 121.4 (t, J_{CF} = 247.7 Hz, 1C), 113.6 (2C), 75.3 (t, J_{CF} = 30.3 Hz, 1C), 55.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ –105.5 (dd, J_{FF} = 250.8, J_{HF} = 9.9 Hz), –107.0 (dd, J_{FF} = 250.7, J_{HF} = 8.7 Hz, 1F); IR (film) ν_{max} 3477, 2916, 1611, 1525, 1514, 1351, 1252, 1075 cm^{-1}; HRMS (EI–TOF) m/z calcd for $C_{15}H_{13}ClF_2NO_4$ $[M+Cl]^+$ 344.0501, found 344.0516; mp 137–139 °C.

2,2-Difluoro-1,2-bis(4-nitrophenyl)ethan-1-ol (21). See representative reaction. Purification by preparative TLC (10% EtOAc in $CHCl_3$) afforded the title compound **21** as a colorless solid (53%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, J = 8.6 Hz, 2H), 8.16 (d, J = 8.8 Hz, 2H), 7.45 (d, J = 8.7 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 5.30 (t, J = 9.6 Hz, 1H), 2.81 (br s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 149.1, 148.3, 141.9, 138.9 (t, J_{CF} = 26.1 Hz, 1C), 128.5 (2C), 127.7 (t, J_{CF} = 6.0 Hz, 2C), 123.3 (2C), 123.2 (2C), 119.8 (t, J_{CF} = 248.6 Hz, 1C), 75.5 (t, J_{CF} = 31.3 Hz, 1C); ^{19}F NMR (282 MHz, $CDCl_3$) δ –104.5 (dd, J_{FF} = 253.8, J_{HF} = 8.2 Hz, 1F), –108.6 (dd, J_{FF} = 253.8, J_{HF} = 9.0 Hz, 1F); IR (film) ν_{max} 3497, 1519, 1347, 1080 cm^{-1}; HRMS (CI–Q) m/z calcd for $C_{14}H_{11}F_2N_2O_5$ $[M+H]^+$ 325.0636, found, 325.0634; mp 188–190 °C.

1,1-Difluoro-4-methyl-1-(4-nitrophenyl)pentan-2-ol (22). See representative reaction. Purification by preparative TLC (10% EtOAc in $CHCl_3$) afforded the title compound **22** as a colorless oil (22%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 8.6 Hz, 2H), 4.09 (m, 1H), 2.04 (br s, 1H), 1.84 (septet, J = 6.8 Hz, 1H), 1.32 (m, 2H), 0.94 (d, J = 6.4 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 148.9, 140.7 (t, J_{CF} = 26.6 Hz, 1C), 127.5 (t, J_{CF} = 6.3 Hz, 2C), 123.4 (2C), 120.9 (t, J_{CF} = 247.6 Hz, 1C), 72.3 (t, J_{CF} = 29.7 Hz, 1C), 38.8, 24.1, 23.6. 21.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ –105.4 (dd, J_{FF} = 253.5, J_{HF} = 8.4 Hz), –110.8 (dd, J_{FF} = 253.5, J_{HF} = 10.5 Hz); IR (film) ν_{max} 3444, 2959, 2924, 2872, 1719, 1611, 1529, 1469, 1352, 1288 1131, 1071 cm^{-1}; HRMS (EI–TOF) m/z calcd for $C_{12}H_{15}ClF_2NO_3$ $[M+Cl]^+$ 294.0709, found 294.0707.

1-(4-(*tert*-Butyl)phenyl)-2,2-difluoro-2-(5-nitropyridin-2-yl)ethan-1-ol (23). See representative reaction. Purification by preparative TLC (3% EtOAc in $CHCl_3$) afforded the title compound **23** as a colorless oil (51%): ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 9.48 (d, J = 2.5 Hz, 1H), 8.74 (dd, J = 8.6, 2.6 Hz, 1H), 7.95 (d, J = 8.6 Hz, 1H), 7.41 (s, 4H), 5.47 (dt, J = 18.4, 6.0 Hz, 1H), 5.40 (d, J = 5.6 Hz, 1H), 1.31 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $(CD_3)_2CO$) δ 159.8 (dd, J_{CF} = 31.5, 25.5 Hz, 1C), 151.9, 145.9, 145.4, 135.0, 133.3, 128.8 (2C), 125.6 (2C), 123.0 (dd, J_{CF} = 5.5, 3.5 Hz, 1C), 119.8 (dd, J_{CF} = 248.5, 244.5 Hz, 1C), 74.4 (dd, J_{CF} = 31.0, 24.0 Hz, 1C), 62.9, 35.1, 31.6 (3C); ^{19}F NMR (471 MHz, $CDCl_3$) δ –105.0 (d, J_{FF} = 262.4 Hz, 1F), –114.7 (dd, J_{FF} = 262.3, J_{HF} = 15.7 Hz, 1F); IR (film) ν_{max} 3416, 2963, 2927, 2867, 1735, 1606, 1532, 1469, 1357, 1275, 1179, 1077 cm^{-1}; HRMS (EI–TOF) m/z calcd for $C_{17}H_{18}F_2N_2O_3$ $[M]^+$ 336.1285, found 336.1285.

1-(4-(*tert*-Butyl)phenyl)-2,2-difluoro-2-(6-methyl-5-nitropyridin-2-yl)ethan-1-ol (24). See representative reaction. Purification by preparative TLC (3% EtOAc in $CHCl_3$) afforded the title compound **24** as a colorless oil (38%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J = 8.4 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.38 (d, J = 8.5 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H), 5.44 (dd, J = 16.1, 4.2 Hz, 1H), 3.57 (br s, 1H), 2.94 (s, 3H), 1.32 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 156.7 (dd, J_{CF} = 31.2, 28.2 Hz, 1C), 153.5, 151.9, 146.2, 133.8, 132.4, 127.6 (2C), 125.2 (2C), 119.9 (t, J_{CF} = 4.1 Hz, 1C), 117.2 (dd, J_{CF} = 248.7, 245.2 Hz, 1C), 74.7 (dd, J_{CF} = 29.8, 25.5 Hz, 1C), 34.6, 31.3 (3C), 23.8; ^{19}F NMR (471 MHz, $CDCl_3$) δ –105.6 (d, J_{FF} = 263.4 Hz, 1F), –114.3 (dd, J_{FF} = 263.6, J_{HF} = 15.9 Hz, 1F); IR (film) ν_{max} 3474, 2928, 2856, 1742, 1602, 1531, 1459, 1370, 1222, 1175, 1052 cm^{-1}; HRMS (EI–TOF) m/z calcd for $C_{18}H_{19}F_2N_2O_3$ $[M–H]^-$ 349.1369, found 349.1387.

1-(4-Chlorophenyl)-2,2-difluoro-2-(5-(trifluoromethyl)pyridin-2-yl)ethan-1-ol (25). See representative reaction. The reaction mixture was heated to 60 °C in an oil bath for 5.5 h. Purification by preparative TLC (20% EtOAc in hexanes) afforded the title compound **25** as a colorless solid (65%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (s, 1H), 8.07 (d, J = 8.9 Hz, 1H), 7.72 (d, J = 8.2 Hz, 1H), 7.36 (d, J = 8.6 Hz, 2H), 7.32 (d, J = 8.6 Hz, 2H), 5.46 (dd, J = 15.8, 6.4 Hz, 1H), 3.99 (s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $(CD_3)_2CO$) δ 158.3 (dd, J_{CF} = 31.6, 26.6 Hz, 1C), 147.1 (dd, J_{CF} = 6.5, 3,7 Hz, 1C), 137.1, 135.6 (q, J_{CF} = 3.5 Hz, 1C), 134.5, 130.7 (2C), 128.8 (2C), 128.0 (q, J_{CF} = 33.3 Hz, 1C), 124.4 (q, J_{CF} = 272.5 Hz, 1C), 122.5 (dd, J_{CF} = 5.9, 3.6 Hz, 1C), 119.6 (dd, J_{CF} = 250.7, 245.6 Hz, 1C), 73.9 (dd, J_{CF} = 30.7, 24.6 Hz, 1C); ^{19}F NMR (471 MHz, $CDCl_3$) δ –62.8 (3F), –104.5 (d, J_{FF} = 266.9, 1F), –133.5 (dd, J_{FF} = 266.7, J_{HF} = 15.8 Hz, 1F); IR (film) ν_{max} 3332, 2916, 2850, 1610, 1492, 1395, 1328, 1137, 1081 cm^{-1}; HRMS (EI–TOF) m/z calcd for $C_{14}H_9ClF_5NO$ $[M]^+$ 337.0293, found 337.0263; mp 105–107 °C.

1-(4-(*tert*-Butyl)phenyl)-2,2-difluoro-2-(5-(trifluoromethyl)pyridin-2-yl)ethan-1-ol (26). See representative reaction. The reaction mixture was heated to 60 °C in an oil bath for 4.5 h. Purification by preparative TLC (3% EtOAc in $CHCl_3$) afforded the title compound **26** as a colorless solid (52%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (s, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 8.2 Hz, 1H), 7.38 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 5.44 (dd, J = 16.4, 6.5 Hz, 1H), 3.71 (s, 1H), 1.31 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $(CD_3)_2CO$) δ 157.3 (t, J_{CF} = 29.5 Hz, 1C), 151.8, 145.9 (q, J_{CF} = 3.6 Hz, 1C), 134.6 (q, J_{CF} = 3.4 Hz, 1C), 132.5, 128.1 (q, J_{CF} = 33.6 Hz, 1C), 127.6 (2C), 125.2 (2C), 122.9 (q, J_{CF} = 273.3 Hz, 1C), 121.4 (t, J_{CF} = 4.2 Hz, 1C), 117.4 (dd, J_{CF} = 250.2, 246.6 Hz, 1C), 74.7 (dd, J_{CF} = 30.0, 25.4 Hz, 1C), 34.6, 31.3 (3C); ^{19}F NMR (471 MHz, $CDCl_3$) δ –62.6 (s, 3F), –104.1 (d, J_{FF} = 264.7 Hz, 1F), –114.7 (dd, J_{FF} = 264.4, J_{HF} = 16.5 Hz, 1F); IR (film) ν_{max} 3318, 2965, 2909, 2874, 1609, 1583, 1392, 1332, 1165, 1139, 1081 cm^{-1}; HRMS (EI–TOF) m/z calcd for $C_{18}H_{18}F_5NO$ $[M]^+$ 359.1309, found 359.1309; mp 135–136 °C.

1-(4-Acetylphenyl)-2,2-difluoro-2-(5-(trifluoromethyl)pyridin-2-yl)ethan-1-ol (27). See representative

reaction. The reaction mixture was heated to 60 °C in an oil bath for 4.5 h. Purification by preparative TLC (10% EtOAc in $CHCl_3$) afforded the title compound **27** as a colorless solid (37%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.95 (s, 1H), 8.08 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.94 (d, *J* = 8.3 Hz, 2H), 7.73 (d, *J* = 8.2 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 2H), 5.55 (d, *J* = 16.2 Hz, 1H), 4.09 (s, 1H), 2.61 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $(CD_3)_2CO$) δ 197.8, 158.2 (dd, J_{CF} = 31.3, 26.3 Hz, 1C), 147.1 (q, J_{CF} = 3.8 Hz, 1C), 143.1, 138.1, 135.7 (q, J_{CF} = 3.8 Hz, 1C), 129.3 (2C), 128.6 (2C), 128.0 (q, J_{CF} = 33.1 Hz, 1C), 124.4 (q, J_{CF} = 273.0 Hz, 1C), 122.6 (dd, J_{CF} = 5.6, 3.6 Hz, 1C), 119.8 (dd, J_{CF} = 250.2, 246.1 Hz, 1C), 74.3 (dd, J_{CF} = 30.8, 24.5 Hz, 1C), 26.8; ^{19}F NMR (471 MHz, $CDCl_3$) δ –62.6 (s, 3F), –104.1 (d, J_{FF} = 264.7 Hz, 1F), –114.7 (dd, J_{FF} = 267.3, J_{HF} = 16.3 Hz, 1F); IR (film) ν_{max} 3392, 3032, 2916, 2846, 1683, 1610, 1579, 1396, 1329, 1271, 1170, 1135, 1081 cm^{-1}; HRMS (EI–TOF) *m/z* calcd for $C_{16}H_{12}F_5NO_2$ [M]$^+$ 345.0788, found 345.0798; mp 152–154 °C.

1,1-Difluoro-4-methyl-1-(5-(trifluoromethyl)pyridin-2-yl)pentan-2-ol (28). See representative reaction. Purification by preparative TLC (15% EtOAc in hexanes) afforded the title compound **28** as a colorless oil (25%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.11 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.84 (d, *J* = 8.3 Hz, 1H), 4.42 (m, 1H), 2.98 (d, *J* = 6.2 Hz, 1H), 1.93 (m, 1H), 1.59–1.53 (m, 2H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 157.6 (t, J_{CF} = 29.8 Hz, 1C), 145.9 (q, J_{CF} = 3.6 Hz, 1C), 134.8 (q, J_{CF} = 3.4 Hz, 1C), 127.9 (q, J_{CF} = 31.9 Hz, 1C), 122.9 (q, J_{CF} = 271.1 Hz, 1C), 121.3 (t, J_{CF} = 4,0 Hz, 1C), 118.3 (t, J_{CF} = 246.5 Hz, 1C), 71.0 (t, J_{CF} = 27.1 Hz, 1C), 38.2, 29.7, 24.1, 23.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.7 (s, 3F), –105.9 (d, J_{FF} = 273.3 Hz, 1F), –115.2 (dd, J_{FF} = 266.3, J_{HF} = 15.1 Hz, 1F); IR (film) ν_{max} 3406, 2960, 2927, 2873, 1722, 1610, 1583, 1469, 1329, 1276, 1169, 1136, 1081 cm^{-1}; HRMS (EI–TOF) *m/z* calcd for $C_{12}H_{14}F_5NO$ [M]$^+$ 283.0996, found 283.0995.

1-(4-Chlorophenyl)-2,2-difluoro-2-(2-methyl-4-nitrophenyl)ethan-1-ol (29). See representative reaction. Purification by preparative TLC (3% EtOAc in $CHCl_3$) afforded the title compound **29** as a colorless oil (51%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.98 (d, *J* = 8.7 Hz, 1H), 7.38 (d, *J* = 8.6 Hz, 1H), 7.29 (d, *J* = 8.5 Hz, 2H), 7.16 (d, *J* = 8.3 Hz, 2H), 5.14 (td, *J* = 10.3, 3.4 Hz, 1H), 2.62 (d, *J* = 4.1 Hz, 1H), 2.38 (t, *J* = 3.0 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $(CD_3)_2CO$) δ 149.5, 140.2 (t, J_{CF} = 2.3 Hz, 1C), 140.0 (t, J_{CF} = 24.5 Hz, 1C), 137.1, 134.7, 130.7 (2C), 130.5 (t, J_{CF} = 8.7 Hz, 1C), 128 .8 (2C), 126.9, 122.7 (dd, J_{CF} = 249.2, 247.1 Hz, 1C), 120.9, 75.5 (dd, J_{CF} = 30.8, 28.6 Hz, 1C), 20.8 (t, J_{CF} = 4.6 Hz, 1C); ^{19}F NMR (471 MHz, $CDCl_3$) δ –103.1 (dd, J_{FF} = 254.9, J_{HF} = 8.6 Hz, 1F), –104.2 (dd, J_{FF} = 254.7, J_{HF} = 8.1 Hz, 1F); IR (film) ν_{max} 3510, 3098, 2926, 2857, 1597, 1527, 1494, 1350, 1240, 1081 cm^{-1}; HRMS (EI–TOF) *m/z* calcd for $C_{15}H_{12}ClF_2NO_3$ [M]$^+$ 327.0474, found 327.0474.

1-(4-Chlorophenyl)-2,2-difluoro-2-(pyrazin-2-yl)ethan-1-ol (30). See representative reaction. The reaction mixture was heated to 60 °C in an oil bath for 4 h. Purification by preparative TLC (30% EtOAc in $CHCl_3$) afforded the title compound **30** as a colorless solid (56%): ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 8.80 (s, 1H), 8.72 (d, *J* = 12.0 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 5.74 (d, *J* = 5.4 Hz, 1H), 5.42 (dt, *J* = 17.1, 6.1 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz $(CD_3)_2CO$) δ 149.7 (dd, J_{CF} = 30.1, 26.2 Hz, 1C), 147.1, 145.0, 143.5 (dd, J_{CF} = 5.9, 4.3 Hz, 1C), 137.0, 134.5, 130.7 (2C), 128.8 (2C), 119.7 (dd, J_{CF} = 249.7, 246.1 Hz, 1C), 73.9 (dd, J_{CF} = 30.8, 25.0 Hz, 1C); ^{19}F NMR (471 MHz, $CDCl_3$) δ –105.9 (d, J_{FF} = 268.3 Hz, 1F), –114.4 (dd, J_{FF} = 268.0, J_{HF} = 15.0 Hz, 1F); IR (film) ν_{max} 329, 3084, 2930, 1598, 1492, 1410, 1347, 1289, 1195, 11092, 1016 cm^{-1}; HRMS (ESI–TOF) *m/z* calcd for $C_{12}H_8ClF_2N_2O$ [M–H]$^-$ 269.0299, found 269.0316; mp 137–138 °C.

1-(4-Chlorophenyl)-2,2-difluoro-2-(4-nitrophenyl) ethyl 3,3,3-trifluoropropanoate (31). To a solution of **16** (9.7 mg, 0.031 mmol) in CH_2Cl_2 (2 mL) was added dicyclohexylcarbodiimide (10.2 mg, 0.049 mmol) and 3,3,3-trifluoropropionic acid (0.09 mL, 0.049 mmol), and the reaction mixture was stirred at rt for 15 min. Next, the mixture was treated with N,N-dimethylaminopyridine (0.76 mg, 6.2 μmol) and stirred at rt for 24 h. Then, the mixture was diluted with pentane (2 mL), filtered through celite, and washed with pentane (2 mL). The organics were washed with water (5 mL × 3), 5% aqueous acetic acid solution (10 mL × 3), water (15 mL), dried with Na_2SO_4, and concentrated under reduced pressure. Purification by preparative TLC (30% EtOAc in hexanes) afforded the title compound **31** as colorless oil (12 mg, 93%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.13 (d, *J* = 8.1 Hz, 2H), 6.21 (t, *J* = 10.1 Hz, 1H), 3.27 (q, *J* = 9.9 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.1, 149.3, 139.0 (t, J_{CF} = 26.1 Hz, 1C), 136.1, 129.8, 129.4 (2C), 128.9 (2C), 127.6 (t, J_{CF} = 6.2 Hz, 2C), 123.4 (2C), 122.9 (q, J_{CF} = 274.8 Hz, 1C), 118.5 (t, J_{CF} = 248.9 Hz, 1C), 76.4 (t, J_{CF} = 31.7 Hz, 1C), 39.9 (q, J_{CF} = 31.8 Hz, 1C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –63.0 (t, J_{HF} = 9.9 Hz), –105.2 (dd, J_{FF} = 254.7 Hz, J_{HF} = 9.9 Hz, 1F), –106.3 (dd, J_{FF} = 254.9 Hz, J_{HF} = 9.8 Hz); IR (film) ν_{max} 2922, 1767, 1530, 1353, 1269, 1090 cm^{-1}; HRMS (ESI–TOF) m/z calcd for $C_{17}H_{10}ClF_5NO_4$ [M–H]$^-$ 422.0213, found 422.0222.

1-(4-(*tert*-Butyl)phenyl)-2,2-difluoro-2-(4-nitrophenyl)ethan-1-one (32). A mixture of **18** (10 mg, 0.03 mmol) and DMP (21.2 mg, 0.0435 mmol) in CH_2CI_2 (1 mL) and H2O (0.017 mL) was stirred for 24 h at rt. The mixture was quenched with 1 M aqueous NaOH (1 mL) and extracted with CH_2Cl_2 (3 mL × 3). The organics were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by preparative TLC (1% MeOH in CH_2CI_2) afforded the title compound **32** as a yellow oil (8.1 mg, 82%): ^{1}H NMR (400 MHz, CDCl3) δ 8.33 (d, *J* = 8.4 Hz, 2H), 8.01 (d, *J* = 7.9 Hz, 2H), 7.80 (d, *J* = 8.6 Hz, 2H), 7.51 (d, *J* = 8.7 Hz, 2H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.4 (t, J_{CF} = 23.8 Hz, 1C), 159.0, 149.4, 139.4 (t, J_{CF} = 25.4 Hz, 1C), 130.3 (2C), 128.9 (t, J_{CF} = 7.7 Hz, 1C), 127.3 (t, J_{CF} = 6.2 Hz, 2C), 125.9 (2C), 123.8 (2C), 116.3 (t, J_{CF} = 254.3 Hz, 1C), 35.4, 30.9 (3C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –97.8 (s, 2F); IR (film) ν_{max} 2960, 2927, 2870, 1727, 1699, 1531, 1351, 1250, 1105 cm^{-1}; HRMS (APCI–TOF) m/z calcd for $C_{18}H_{17}F_2NO_3$ [M]$^-$ 333.1176, found 333.1178.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Spectroscopic data from ^{1}H, ^{19}F, and ^{13}C NMR spectra and X-ray experiments and data (PDF).

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H.R.K. conducted the synthetic experiments and mechanistic studies. C.H. performed the bond-cleavage experiments and synthesized the substrates. A.T.A. and M.D.A. performed additional synthetic experiments and contributed equally to the work.[#] E.L. and X.P. conducted the computational studies. All authors wrote the manuscript and designed the approach.

Notes

The authors declare no competing financial interests.

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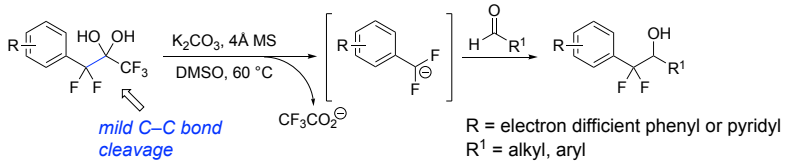
R
HO
OH
CF3
F F
K2CO3, 4Å MS
DMSO, 60 °C
CF3CO2
F
F
O
H
R1
OH
mild C–C bond cleavage
R = electron difficient phenyl or pyridyl
R1 = alkyl, aryl