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Radical Perfluoroalkylation of Arenes via Carbanion Intermediates

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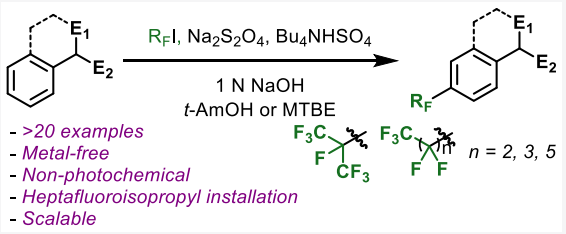
ABSTRACT: The use of sodium dithionite with perfluoroalkyl iodides under basic conditions facilitates the direct perfluoroalkylation of arenes with pendant benzylic electron-withdrawing groups. This occurs via attack of the arene on the electrophilic perfluoroalkyl radical, through the donation of electron density from a benzylic anion. The substrate scope was expanded beyond benzylic nitriles with cyclic substrates bearing electron-withdrawing groups at the benzylic position—enforcing donation of electron density to the aromatic ring and enabling attack on the perfluoroalkyl radical.



Perfluoroalkyl-substituted arenes have received significant interest from the synthetic chemistry community over the past few decades due to the prevalence of these moieties within a large array of clinical drug candidates.[1−12] One such clinical candidate recently reported by Bristol Myers Squibb was the heptafluoroisopropyl-substituted (HFP) **1**, which is shown to be a promising inverse agonist of RORγt (Figure 1).[2]

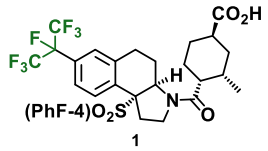


Figure 1. Recently reported inverse agonist of RORγt.

Although there are several reports utilizing transition metal catalysis to install polyfluorinated alkyl groups, incorporation of the HFP moiety has been limited and primarily achieved by (a) stoichiometric reductive processes mediated by activated copper,[3f] (b) copper-mediated processes requiring stoichiometric amounts of AgF,[3d] or (c) multistep sequences ending in substitution of a tertiary hydroxyl group with fluoride from DAST.[2e] Metal-catalyzed processes are scarce and often limited by the few available precursors of the heptafluoroisopropyl unit and the instability of the corresponding organometallic derivatives.[13] On this basis, our initial work toward compound **1** required several functional group manipulations and an expensive starting material.[2d,g] Because of these inefficiencies, we became interested in exploring other options to install the HFP group and other perfluorinated substituents. With the goal of improved simplicity and synthetic efficiency, we turned our attention toward radical-based processes.[14]

Radical perfluoroalkylation reactions are reported to have a broad substrate scope and employ inexpensive reagents and initiators.[1] Particularly, anilines (**2**) have been shown by Onishi and co-workers to be competent substrates for the installation of the HFP by employing heptafluoroisopropyl iodide (**3**) to afford *para*-perfluoroalkylated anilines like **4** (Figure 2).[9a] However, the synthetic operations that would be

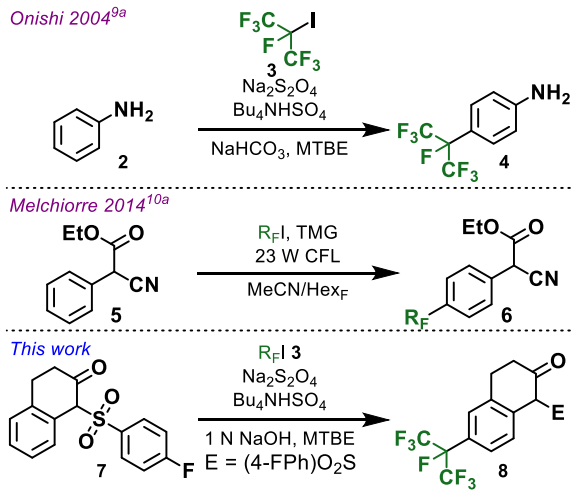


Figure 2. Previous reports from Onishi and Melchiorre that inspired this work.

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required to convert **4** to **1** would not be economical. Instead, we were intrigued by the 2014 report by Melchiorre and coworkers that directly introduced perfluoroalkyl groups through photochemical activation of the electron donor−acceptor (EDA) complex between perfluoroalkyl iodides and α-cyano arylacetates (**5**) to afford **6**.[10a] These substrates proceed through an intermediary benzylic carbanion that donates electron density to the aromatic ring, allowing for the substitution of the electrophilic perfluoroalkyl radical. Although the scope was limited to nitrile substituents and did not include the HFP group installation, we hypothesized that substrates that could form an intermediary benzylic carbanion similar to the α-cyano arylacetates could be viable in the reaction conditions developed by Onishi for anilines.[10b] Therefore, we began to investigate these types of substrates in the context of our ROR inverse agonist **1** and identified sulfonyl tetralone **7** as a suitable substrate for the radical perfluoroalkylation to furnish substituted **8**. Importantly, we were delighted to find that the newly developed process led to a significant cost reduction, as **7** could be derived from inexpensive β-tetralone in a single operation.[14] Given the limited examples of this type of transformation for the installation of the HFP group, we decided to evaluate if the method could be extended to other substrates and our efforts are described herein.

The optimized conditions found for the functionalization of **7** employed sodium dithionite (1.45 equiv) as a radical initiator, tetrabutylammonium hydrogensulfate (7.0 mol %) as a phase transfer catalyst, 1 N aqueous sodium hydroxide (3.15 equiv) as base, and *tert*-butyl methyl ether (MTBE) as the organic solvent, resulting in the formation of **8** in ∼80% yield (Table 1). Investigation into alternative EWGs found that the nature of the pendant functionality had a significant impact on the reaction yield. Removal of the *para*-fluoro group led to a diminished 59% yield of **9a**, whereas replacing the fluorine with chlorine gave **9b** in 80% yield. Interestingly, the methanesulfonyl variant (**9c**) provided only 25 area percent (AP) of the product by UHPLC-MS (UV),[15] with some decomposition observed. Attention was then turned to alternative perfluoroalkyl iodides. Contrary to the previous report,[10a] increased chain length improved yields for perfluoroalkyl iodides (**9d**−**9f**) and mixtures of constitutional isomers were not observed.

With the reaction in MTBE as solvent, significant quantities of alkylated enol ethers derived from the solvent would form in the perfluoroalkylation reaction.[16] Fortunately, the undesired byproduct could be hydrolyzed to the desired product with 6 N aqueous HCl. However, attempts to prepare α-cyano arylacetate **10** from **5** revealed the formation of alkylated **11a**, which could not by hydrolyzed to give the desired product (Scheme 1). Therefore, control of this alkylation side product was critical to expand the generality of this method. Of the solvents evaluated, 2-propanol (IPA) and *t*-AmOH (2-methyl-2-butanol) provided the product without any alkylation observed.

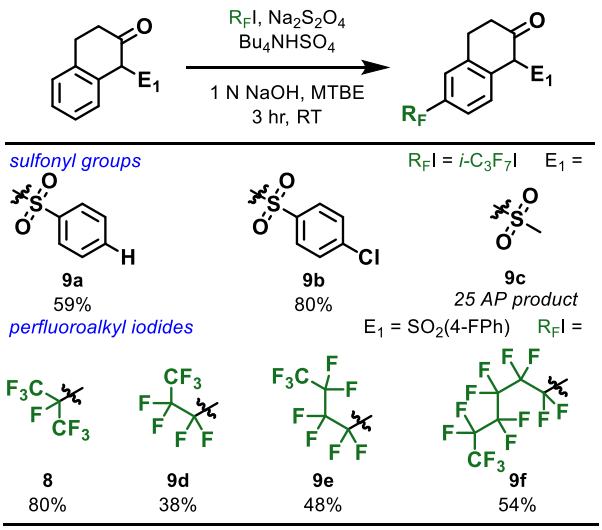
Using IPA as solvent, we performed additional optimization on cyanoacetate **5** and R_FI **3**. Initial conditions provided **10** in 57 AP (area percent by UHPLC-MS) of the product (Table 2, entry 1). Minimal impact to the yield was observed when increasing the equivalents of R_FI **3** (entries 3−5). Portion-wise addition of sodium dithionite provided a significant improvement in product formation (74 AP, entry 6). Increasing equivalents with portion-wise addition (entry 7) and the addition of sodium dithionite and R_FI **3** in portions (entry 8) resulted in decreased conversion.

As increasing the equivalents of initiator and R_FI **3** did not lead to improved yields, we hypothesized that the SO_2 generated in the reaction could be inhibiting conversion.[1f] Therefore, we reduced the $Na_2S_2O_4$ equivalents (entry 9) and observed a significant improvement in conversion to the product. As we were now employing sub-stiochiometric quantities of sodium dithionite and photochemical activation of the EDG complex between the perfluoroalkyl iodide and α-cyano arylacetates was known, light was excluded to ensure reactivity could be attributed to $Na_2S_2O_4$.[10]

Next, the equivalents of R_FI **3** were varied (entries 10−12), identifying 1.10 equiv as optimal (entry 12). Replacing IPA with *t*-AmOH (entry 13) provided complete conversion and 87 AP of the product. No product was observed with sodium bicarbonate as base (entry 14), implying that generation of the benzyl carbanion was necessary for reactivity.[18] Therefore, we selected the conditions from entry 13 to continue our studies.

The substrate scope for this transformation was explored with these optimized conditions (Scheme 2). While the yields for **8** and **9b** were diminished compared to the MTBE conditions, an improvement was observed with **9a** and **9c**.

Table 1. Substrate Scope I: Initial Conditions Employing MTBE as Solvent[a]



[a]Unless otherwise noted, reactions were performed on a 1.5 mmol scale relative to substrate, R_FI (1.45 equiv), $Na_2S_2O_4$ (1.45 equiv), Bu_4NHSO_4 (7.0 mol %), 1 N NaOH (3.15 equiv), MTBE (7.0 mL/g), rt, for 3 h. Conversion was monitored by UHPLC-MS. R_FI = perfluoroalkyl iodide. MTBE = *tert*-butyl methyl ether.

Scheme 1. Alkylation Byproducts in the Perfluoroalkylation of 5 with MTBE as Solvent

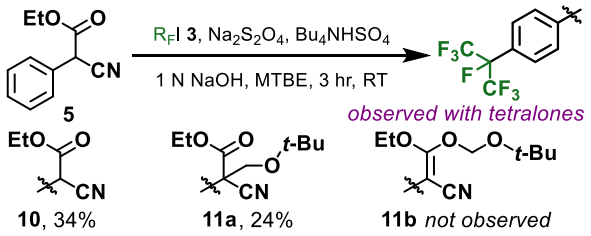


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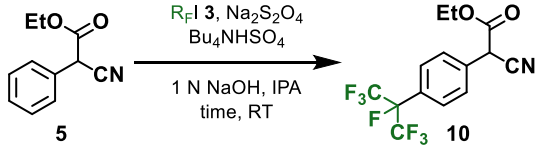
Table 2. Optimization of the Aromatic Perfluoroalkylation with Alcoholic Solvents[a]



entry	R_FI 3 equiv	$Na_2S_2O_4$ equiv	time	SM AP	Prdt AP
1	1.45	1.45	4.5 h	31	57
2	1.45	1.45	2 h	29	51
3	2.00	1.45	2 h	29	59
4	2.50	1.45	2 h	28	62
5	3.00	1.45	2 h	31	61
6[b]	1.45	1.45	2 h	10	75
7[b]	2.00	2.00	2 h	11	76
8[c]	2.00	2.00	2 h	27	63
9[d]	1.45	0.30	45 min	12	73
10[d]	1.10	0.30	45 min	12	75
11[d]	2.00	0.30	45 min	9	71
12[d]	2.50	0.30	45 min	9	67
13[d,e]	1.10	0.30	45 min	0	87
14[d,f]	1.10	0.30	45 min	100	0

[a]Unless otherwise noted, reactions were performed on a 0.30 mmol scale relative to substrate **5**, R_FI **3** (equiv), $Na_2S_2O_4$ (equiv), Bu_4NHSO_4 (7.0 mol %), 1 N NaOH (3.15 equiv), IPA (0.75M), rt, for a specified time. Conversion was monitored by UHPLC-MS. [b]$Na_2S_2O_4$ added in four portions. [c]$Na_2S_2O_4$ and R_FI **3** added in two portions. [d]Reaction run in the dark. [e]*t*-AmOH instead of IPA. [f]$NaHCO_3$ instead of NaOH. R_FI = perfluoroalkyl iodide.

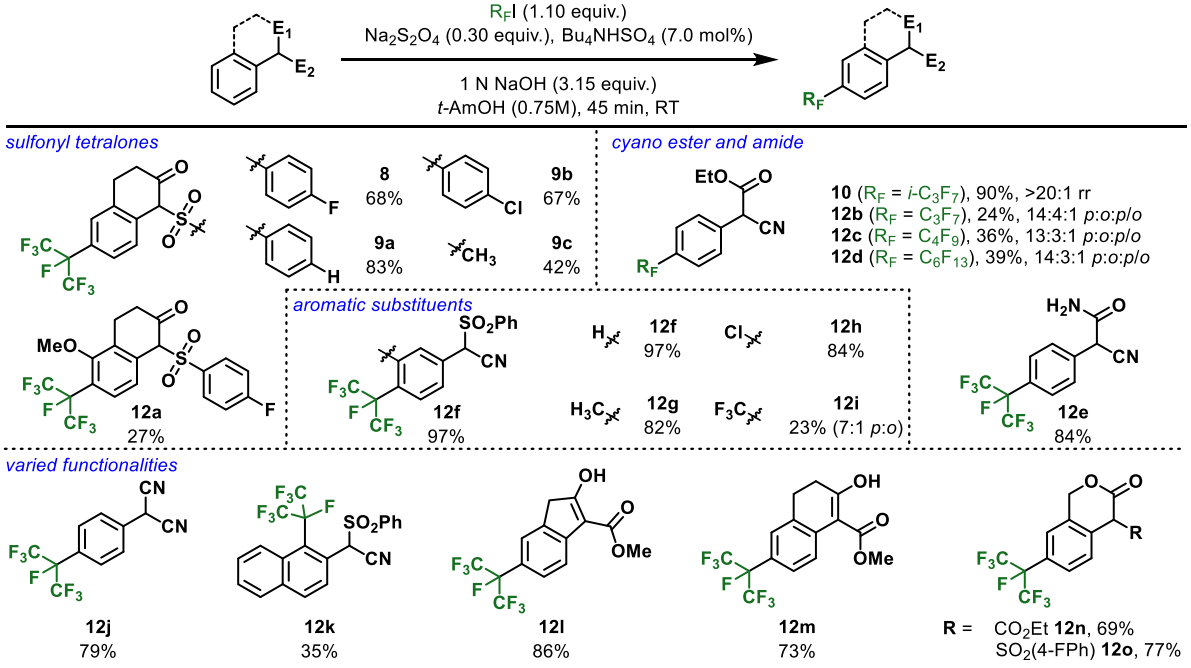
Installation of the electron-donating methoxy group diminished the yield, giving **12a** in 27% yield. In the case of cyano ester products derived from **7**, alternative R_FI reagents could be employed such as **12b**–**12d**. The HFP-containing product **10** was obtained in 90% isolated yield. Linear, alkyl chains (**12b**–**12d**) resulted in *p*:*o*:*p*/*o* isomers, albeit in improved ratios when compared to the previous literature report.[10a,19] Primary amides are also compatible with the reaction conditions, with the formation of **12e** in 84% yield.

Considering Melchiorre's substrate scope was limited to benzylic nitriles, the impact on the EWG that can promote a stabilized carbanion was then studied. Malononitrile **12j** was afforded in 79% yield, and a substituted naphthalene derivative could provide **12k** in 35% yield. By incorporating one of the EWGs into the benzylic position of a bicyclic system, perfluoroalkylation could occur without the need for nitrile substitution, as in the case of indanone **12l** and tetralone **12m**. This was further supported by isochormanones **12n** and **12o** that were isolated in 69 and 77% yield, respectively. Furthermore, without incorporating one of the EWGs into a bicyclic system, it was found that a nitrile was necessary to observe reactivity.[17] Notably, acyclic malonates and sulfonyl esters were not competent substrates in the reaction.

Our results are in agreement with Melchiorre's DFT experiments, which hypothesized that alternative EWGs would orient the intermediary anion perpendicular to the arene.[10b] Therefore, the crucial donation of electron density to the aromatic ring could not occur, preventing the attack on the highly electrophilic perfluoroalkyl radical. Considering the new scope of substrates, it can be concluded that incorporating one of the EWGs in a bicyclic system with the arene enforces the donation of electron density to the aromatic ring.

Based on these observations, the body of literature surrounding sodium dithionite in radical perfluoroalkylation reactions,[1f,8d] and Melchiorre's DFT studies,[10b] a plausible mechanism for the described transformation is depicted in Figure 3. Sodium dithionite under aqueous conditions is known to decompose to the SO_2 radical anion,[1f] which can

Scheme 2. Substrate Scope II: Optimized Conditions for the Radical Aromatic Perfluoroalkylation[a]



[a]Unless otherwise noted, reactions were performed on a 1.5 mmol scale relative to substrate, R_FI (1.10 equiv), $Na_2S_2O_4$ (0.30 equiv), Bu_4NHSO_4 (7.0 mol %), 1 N NaOH (3.15 equiv), *t*-AmOH (0.75M), rt, for 45 min. Conversion was monitored by UHPLC-MS. R_FI = perfluoroalkyl iodide.

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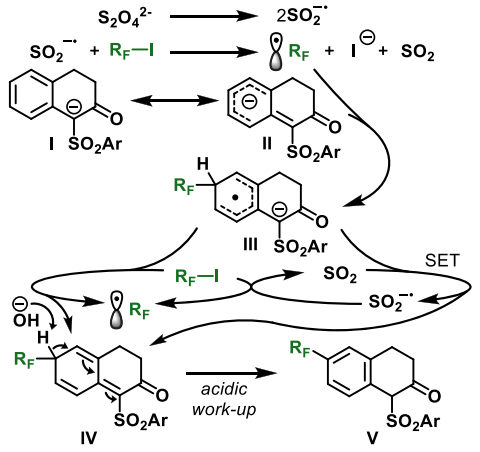

Figure 3. Proposed reaction mechanism.

then transfer an electron to the perfluoroalkyl iodide, generating the perfluoroalkyl radical. The enolate derived from the substrate could be represented with two resonance forms (**I** and **II**). The electron-rich aromatic ring could then react with the electrophilic perfluoroalkyl radical, forming radical anion **III**. Two modes of propagation could then potentially be operative; (a) **III** could reduce a second equivalent of perfluoroalkyl iodide, regenerating the radical, or (b) **III** could be oxidized by SO_2 in solution.[20] Finally, dearomatized intermediate **IV** could be deprotonated by the hydroxide in solution, leading to the desired product **V** after acidic workup.

In conclusion, we have developed conditions for the radical perfluoroalkylation of arenes via enolate intermediates employing sodium dithionite as the radical initiator. The use of *t*-AmOH as solvent enabled significant expansion of the substrate scope. Additionally, by incorporating one of the EWGs into a bicyclic system with the arene, the scope was expanded beyond nitrile-containing substrates. The ability to rapidly install HFP and other perfluoroalkyl groups will have a tremendous impact on the types of scaffolds that can be prepared for structure−activity relationship studies, as already demonstrated with our work in a pharmaceutical candidate,[11] as well as in other areas of research.[12]

EXPERIMENTAL SECTION

General Experimental Methods. Unless otherwise noted, all reactions were performed under ambient atmosphere at room temperature. All reagents were purchased from commercial sources. Standard benchtop techniques were employed for handling air-sensitive reagents. Analytical thin-layer chromatography was performed on Merck silica gel 60 F254 aluminum plates. Visualization was accomplished with UV light and/or potassium permanganate ($KMnO_4$). The retention factor (R_f) values reported were measured using a 5 × 2 cm^2 TLC plate in a developing chamber containing the solvent system described. Flash column chromatography was performed using a Teledyne ISCO using appropriately sized cartridges for the scale of the experiment. NMR spectra were recorded on a 400 or 500 MHz spectrometer. Spectra are referenced to residual chloroform (δ = 7.27 ppm, ^{1}H; 77.16 ppm, ^{13}C), residual benzene (δ = 7.16 ppm, ^{1}H; 128.06 ppm, ^{13}C), and residual DMSO (δ = 2.50 ppm, ^{1}H; 39.52 ppm, ^{13}C). Chemical shifts are reported in parts per million (ppm). Data are presented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad), coupling constant *J* (Hz), and integration. Melting points (°C) were measured on a Thomas-Hoover Unimelt and are uncorrected. HRMS samples were run on the Thermo LTQ-Orbitrap with Acquity Classic inlet. Data are reported in the form of *m*/*z* (intensity relative to the base peak = 100). Infrared spectra were measured neat on an Agilent Cary 630 FTIR spectrometer. Peaks are reported in cm^{-1} with indicated relative intensities: s (strong, 0−33% T); m (medium, 34−66% T), w (weak, 67−100% T), and br (broad). UHPLC was performed on a Shimadzu Nexera X2 spectrometer with monitoring at 220 nm using a gradient of 0 → 100% MeCN in H_2O with 0.1% TFA on an Ascentis Express C18 column.

Synthesis of Substrates. General Considerations. Substrates **5**, **S1** (**12f** precursor), **S2** (**12l** precursor), and **S3** (**12e** precursor) were purchased from commercial suppliers. Aryl substrates **S4** (**12g** precursor) and **S5** (**12h** precursor) were synthesized according to the literature procedure,[21] and all analytical data were in agreement with the previous reports.[22] Tetralone ester **S6** (**12m** precursor) was synthesized according to the literature procedure, and all analytical data were in agreement.[23] Substrate **S7** (**12j** precursor) was synthesized according to the literature procedure, and all analytical data were in agreement.[24]

General Procedure for the Synthesis of Sulfonyl Tetralone Substrates. The following procedure was adapted from the literature.[25] To a round-bottom flask equipped with a stir bar under a nitrogen atmosphere was added *β*-tetralone (1.00 equiv) followed by MeOH (20 vol). Et_3N (1.20 equiv) was then added followed by the requisite sulfinic acid sodium salt (1.20 equiv). Then, I_2 (1.00 equiv) was added as a single portion and the reaction was stirred at ambient temperature overnight. Upon complete disappearance of color and precipitation of the product, the reaction was filtered and washed with IPA (2 × 8.0 vol). The resultant cake was dried under a vacuum at 55 °C overnight to afford the sulfonylated product.

*1-((4-Fluorophenyl)sulfonyl)-3,4-dihydronaphthalen-2(1H)-one (**7**).* Following the general procedure employing *β*-tetralone (100 g, 670 mmol) and sodium 4-fluorobenzenesulfinate (154 g, 803 mmol) to afford the desired product as an off-white crystalline solid (108 g, 342 mmol, 51%). R_f = 0.28 (SiO_2, Hex:EtOAc = 3:1); mp = 172−174 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.76 (t, *J* = 6.4 Hz, 2H), 7.41−7.35 (m, 1H), 7.32−7.19 (m, 4H), 7.06 (d, *J* = 7.6 Hz, 1H), 4.82 (s, 1H), 3.64−3.56 (m, 1H), 3.01−2.90 (m, 2H), 2.58−2.48 (m, 1H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 201.0, 167.2, 165.1, 138.7, 133.6 (d, *J* = 3.6 Hz), 132.1, 132.1, 132.0, 129.8, 128.7, 127.0, 125.7, 116.5, 116.3, 77.5, 37.5, 27.0; ^{19}F NMR (376 MHz, chloroform-*d*) δ −102.08 to −102.19 (m); HRMS (CI-TOF, *m*/*z*) calcd. For $C_{16}H_{13}O_3SF$ $[M]^+$: calcd, 304.0569; found, 304.0564; IR (ATR, neat, cm^{-1}): 2933 (w), 1700 (m), 1588 (m), 1491 (m), 1323 (m), 1141 (s), 1077 (m), 839 (m).

*1-((4-Chlorophenyl)sulfonyl)-3,4-dihydronaphthalen-2(1H)-one (**S8**).* Following the general procedure employing *β*-tetralone (3.00 g, 20.1 mmol) and sodium 4-chlorobenzenesulfinate (4.14 g, 20.2 mmol) to afford the desired product as a yellow solid (4.22 g, 12.7 mmol, 63%). R_f = 0.31 (SiO_2, Hex:EtOAc = 3:1); mp = 173−175 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.70 (d, *J* = 8.5 Hz, 2H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.43−7.37 (m, 1H), 7.36−7.31 (m, 1H), 7.30−7.23 (m, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 4.83 (s, 1H), 3.68−3.55 (m, 1H), 3.06−2.89 (m, 2H), 2.60−2.48 (m, 1H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 200.9, 141.2, 138.7, 136.1, 132.1, 130.6, 129.8, 129.4, 128.7, 127.0, 125.5, 77.4, 37.5, 27.0; HRMS (CI-TOF, *m*/*z*) calcd. For $C_{16}H_{13}O_3SCl$ $[M]^+$: calcd, 320.0274; found, 320.0277; IR (ATR, neat, cm^{-1}): 3090 (w), 2937 (w), 1700 (m), 1569 (w), 1319 (s), 1141 (s), 1081 (s), 760 (s).

*1-(Phenylsulfonyl)-3,4-dihydronaphthalen-2(1H)-one (**S9**).* Following the general procedure employing *β*-tetralone (10.0 g, 67.0 mmol) and sodium benzenesulfinate (13.9 g, 80.4 mmol) to afford the desired product as a yellow crystalline solid (11.4 g, 39.5 mmol, 59%). R_f = 0.21 (SiO_2, Hex:EtOAc = 3:1); mp = 149−150 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.75 (d, *J* = 7.6 Hz, 2H), 7.72−7.66 (m, 1H), 7.57−7.51 (m, 2H), 7.40−7.33 (m, 1H), 7.33−7.28 (m, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 4.84 (s, 1H), 3.62−3.50 (m, 1H), 3.03−2.84 (m, 2H), 2.52 (ddd, *J* = 18.2, 11.4, 6.9 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 201.0, 138.7, 137.6, 134.3, 132.0, 129.7, 129.2, 129.1, 128.6, 126.9, 125.9, 77.5, 37.4, 27.1; HRMS (ESI-TOF, *m*/*z*) calcd. For $C_{16}H_{18}NO_3S$ $[M + NH_4]^+$: calcd,

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304.1002; found, 304.1006; IR (ATR, neat, cm^{-1}): 2937 (w), 1707 (m), 1446 (m), 1491 (m), 1312 (m), 1141 (s), 1077 (m), 753 (m).

*1-((4-Fluorophenyl)sulfonyl)-5-methoxy-3,4-dihydronaphthalen-2(1H)-one (**S10**).* Following the general procedure employing 5-OMe β-tetralone (5.00 g, 28.1 mmol) and sodium 4-fluorobenzenesulfinate (6.20 g, 34.0 mmol) to afford the desired product as an off-white solid (4.60 g, 13.5 mmol, 48%). R_f = 0.26 (SiO_2, Hex:EtOAc = 3:1); mp = 169−170 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.81−7.74 (m, 2H), 7.24−7.17 (m, 3H), 6.92 (d, *J* = 8.2 Hz, 1H), 6.66 (d, *J* = 7.8 Hz, 1H), 4.81 (s, 1H), 3.88 (s, 3H), 3.36−3.24 (m, 1H), 3.24−3.14 (m, 1H), 3.01 (ddd, *J* = 18.0, 6.5, 3.6 Hz, 1H), 2.47 (ddd, *J* = 18.0, 10.0, 7.5 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 201.3, 167.2, 165.1, 156.7, 133.7 (d, *J* = 3.6 Hz), 132.1 (d, *J* = 10.0 Hz), 127.6, 127.3 (d, *J* = 42.7 Hz), 123.7, 116.4 (d, *J* = 22.7 Hz), 111.1, 77.3, 55.6, 36.9, 20.1; ^{19}F NMR (376 MHz, chloroform-*d*) δ −98.26 to −104.30 (m); HRMS (ESI-TOF, *m*/*z*) calcd. For $C_{17}H_{19}NFO_4S$ $[M + NH_4]^+$: calcd, 352.1013; found, 352.1015; IR (ATR, neat, cm^{-1}): 2952 (w), 1711 (m), 1588 (m), 1465 (m), 1315 (m), 1141 (s), 1081 (m), 842 (m).

*1-(Methylsulfonyl)-3,4-dihydronaphthalen-2(1H)-one (**S11**).* Following the general procedure employing β-tetralone (10.0 g, 68.4 mmol) and sodium methanesulfinate (9.80 g, 82.0 mmol), the material was purified by flash chromatography (80 g of SiO_2 cartridge, 10 → 70% EtOAc in Hex over 30 min) to afford the desired product as a red solid (8.00 g, 35.6 mmol, 52%). R_f = 0.14 (SiO_2, Hex:EtOAc = 3:1); mp = 86−88 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.43−7.34 (m, 1H), 7.34−7.27 (m, 3H), 4.78 (s, 1H), 3.70−3.57 (m, 1H), 3.11 (s, 3H), 3.02−2.85 (m, 2H), 2.53 (ddd, *J* = 18.2, 12.1, 6.4 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 202.8, 138.6, 132.2, 129.5, 128.5, 126.8, 124.4, 74.7, 40.7, 37.7, 26.6; HRMS (CI-TOF, *m*/*z*) calcd. For $C_{11}H_{12}O_3S$ $[M]^+$: calcd, 224.0507; found, 224.0510; IR (ATR, neat, cm^{-1}): 2933 (w), 1703 (m), 1308 (s), 1126 (s), 1323 (m), 962 (m), 764 (m), 734 (m).

*4-((4-Fluorophenyl)sulfonyl)isochroman-3-one (**S12**).* Following the general procedure employing isochroman-3-one (992 mg, 6.70 mmol) and sodium 4-fluorobenzenesulfinate (1.50 g, 8.15 mmol) to afford the desired product as a white solid (1.10 g, 3.62 mmol, 54%). R_f = 0.52 (SiO_2, Hex:EtOAc = 2:1); mp = 173−174 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.99−7.86 (m, 2H), 7.56−7.48 (m, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.33−7.25 (m, 4H), 5.92 (d, *J* = 14.2 Hz, 1H), 5.29 (d, *J* = 14.2 Hz, 1H), 5.09 (s, 1H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 167.6, 165.5, 162.5, 132.8 (d, *J* = 3.6 Hz), 132.7, 132.3 (d, *J* = 10.0 Hz), 130.6 (d, *J* = 80.8 Hz), 128.9, 125.0, 122.9, 116.8 (d, *J* = 22.7 Hz), 71.7, 71.1; ^{19}F NMR (376 MHz, chloroform-*d*) δ −99.42 to −102.21 (m); HRMS (ESI-TOF, *m*/*z*) calcd. For $C_{15}H_{12}FO_4S$ $[M + H]^+$: calcd, 307.0435; found, 307.0435; IR (ATR, neat, cm^{-1}): 2948 (w), 1729 (m), 1587 (m), 1490 (m), 1326 (m), 1144 (s), 1081 (m), 838 (m).

General Procedure for the Synthesis of Sulfonyl Acetonitrile Substrates. The following procedure was adapted from the literature.[21] To a 40 mL scintillation vial equipped with an X-shaped stir bar was added benzenesulfonylacetonitrile (962 mg, 5.20 mmol, 1.30 equiv), and the headspace was purged with nitrogen. DME (20 mL) was then added followed by NaH (60% in mineral oil, 480 mg, 12.0 mmol, 3.00 equiv) in portions under a stream of nitrogen. The reaction was stirred until hydrogen evolution ceased. Then, PPh_3 (126 mg, 0.48 mmol, 12 mol %) and $Pd_2(dba)_3{\cdot}CHCl_3$ (83.0 mg, 0.08 mmol, 2.0 mol %) were added and the solution was sparged with nitrogen for 10 min. Then, the requisite halo-arene (4.00 mmol, 1.00 equiv) was added and the reaction was heated at 70 °C under a positive pressure of nitrogen overnight. Upon completion by TLC, the reaction was cooled to 0 °C with an ice bath and carefully quenched with NaCl (sat. aq., 15 mL) and 5 drops of conc. HCl were added. The phases were separated, and the aqueous phase was extracted with EtOAc (3 × 5.0 mL). The combined organics were dried over $MgSO_4$, filtered, concentrated over Celite under a vacuum, and purified by flash chromatography (24 g SiO_2 cartridge, 0 → 60% EtOAc in Hex over 20 min).

*2-(Phenylsulfonyl)-2-(3-(trifluoromethyl)phenyl)acetonitrile (**S13**).* Following the general procedure employing 1-iodo-3-(trifluoromethyl)benzene (1.09 g) to afford the desired product as a yellow solid (1.24 g, 3.81 mmol, 95%). Chromatography = 24 g SiO_2 cartridge, 0 → 100% EtOAc in Hex over 20 min. R_f = 0.30 (SiO_2, Hex:EtOAc = 3:1); mp = 102−104 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.78−7.69 (m, 4H), 7.62−7.52 (m, 4H), 7.43 (s, 1H), 5.32 (s, 1H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 135.6, 133.7, 133.1, 131.3 (q, *J* = 32.7 Hz), 129.8, 129.7, 129.3, 127.42−126.10 (m), 124.2, 122.1, 112.9, 62.3; ^{19}F NMR (376 MHz, chloroform-*d*) δ −62.92; HRMS (CI-TOF, *m*/*z*) calcd. For $C_{15}H_{10}NO_2SF_3$ $[M + H]^+$: calcd, 326.0463; found, 326.0475; IR (ATR, neat, cm^{-1}): 2937 (w), 1450 (w), 1323 (s), 1152 (s), 1129 (s), 1073 (s), 764 (m), 719 (m).

*2-(Naphthalen-2-yl)-2-(phenylsulfonyl)acetonitrile (**S14**).* Following the general procedure employing 2-bromonaphthalene (828 mg) to afford the desired product as a brown solid (1.05 g, 3.40 mmol, 85%). Product isolated as an inseparable mixture with methylene starting material; all spectral peaks reported. Chromatography = 24 g SiO_2 cartridge, 0 → 100% EtOAc in Hex over 20 min. R_f = 0.23 (SiO_2, Hex:EtOAc = 3:1); mp = 165−167 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.05 (d, *J* = 7.8 Hz, 2H), 7.91−7.83 (m, 2H), 7.79 (br d, *J* = 7.2 Hz, 2H), 7.76−7.70 (m, 4H), 7.69−7.64 (m, 2H), 7.62−7.53 (m, 2H), 7.53−7.48 (m, 2H), 7.36 (dd, *J* = 8.5, 1.7 Hz, 1H), 5.43−5.11 (m, 1H), 5.32 (s, 1H), 4.08 (s, 2H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 136.7, 135.4, 135.3, 134.2, 133.7, 132.7, 131.0, 130.1, 129.8, 129.7, 129.5, 129.2, 129.0, 128.9, 128.7, 128.3, 127.8, 127.1, 125.9, 122.6, 113.5, 110.3, 63.3, 45.7; HRMS (ESI-TOF, *m*/*z*) calcd. For $C_{18}H_{17}N_2O_2S$ $[M + NH_4]^+$: calcd, 325.1005; found, 325.1006; IR (ATR, neat, cm^{-1}): 2926 (w), 1446 (w), 1334 (m), 1312 (m), 1151 (s), 1081 (m), 827 (m), 757 (m).

*Ethyl 3-Oxoisochromane-4-carboxylate (**S15**).* To a solution of LHMDS (1.0 M, 10 mL, 10.0 mmol, 1.00 equiv) at −78 °C under an inert atmosphere in a 40 mL vial equipped with an X-shaped stir bar was added isochroman-3-one (1.48 g, 10.0 mmol, 1.00 equiv) in 2-methyltetrahydrofuran (14 mL) slowly. The solution was stirred for 30 min at the same temperature before the addition of ethyl chloroformate (2.4 mL, 12.5 mmol, 2.50 equiv). The reaction was left in the dry ice bath and allowed to warm to ambient temperature overnight. On completion by TLC, the reaction was quenched with NH_4Cl (20 mL) and diluted with EtOAc (20 mL). The phases were separated, and the organic layer was dried over $MgSO_4$, filtered, concentrated over Celite under a vacuum, and purified by flash chromatography (80 g SiO_2 cartridge, 0 → 100% EtOAc in Hex over 20 min). The product was isolated as a colorless oil (1.01 g, 4.59 mmol, 46%). Chromatography = 24 g SiO_2 cartridge, 0 → 100% EtOAc in Hex over 20 min. R_f = 0.59 (SiO_2, Hex:EtOAc = 2:1); ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.38−7.30 (m, 3H), 7.26−7.21 (m, 1H), 5.68−5.59 (m, 1H), 5.30−5.17 (m, 1H), 4.75−4.64 (m, 1H), 4.30−4.09 (m, 2H), 1.36−1.17 (m, 3H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 166.6, 166.4, 131.0, 129.1, 128.9, 128.4, 127.8, 124.8, 70.2, 62.4, 53.2, 13.8; HRMS (ESI-TOF, *m*/*z*) calcd. For $C_{12}H_{12}O_4Na$ $[M + Na]^+$: calcd, 243.0628; found, 243.0639; IR (ATR, neat, cm^{-1}): 2981 (w), 1722 (s), 1461 (m), 1390 (m), 1286 (m), 1189 (m), 1021 (m), 753 (m).

Synthesis of Perfluoroalkylation Products. *General Procedure A: Perfluoroalkylation with MTBE.* In a 20 mL scintillation vial equipped with an X-shaped stir bar was added the substrate (1.50 mmol, 1.00 equiv) and Bu_4NHSO_4 (36.0 mg, 0.105 mmol, 7.00 mol %). The solids were then dissolved in MTBE (7 vol), and stirring was commenced. To the stirred solution was added NaOH (1.0 N, 4.73 mL, 4.73 mmol, 3.15 equiv), and the biphasic mixture was stirred at a rate to ensure adequate mixing of the phases for 10 min. $Na_2S_2O_4$ (379 mg, 2.18 mmol, 1.45 equiv) was then added in a single portion followed by the requisite perfluoroalkyl iodide (2.18 mmol, 1.45 equiv), and the reaction was stirred for 3 h. A sample was then taken for UHPLC analysis, and upon verification of complete conversion, the stirring was stopped and the phases were allowed to separate. The lower aqueous phase was removed, and the organic phase was washed with NaCl (sat. aq., 7.0 vol). The phases were separated, HCl (6.0 N, 10 vol) was added, and stirring was commenced. The biphasic mixture was stirred with monitoring by UHPLC to observe disappearance of

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the MTBE adduct (ca. 3 h). Upon complete hydrolysis, the stirring was stopped and the phases were separated. The organic phase was washed with NaCl (sat. aq., 7.0 vol), dried over $MgSO_4$, filtered, concentrated over Celite under reduced pressure, and purified by flash chromatography.

General Procedure B: Perfluoroalkylation with t-AmOH. In a 20 mL scintillation vial equipped with an X-shaped stir bar was added the substrate (1.50 mmol, 1.00 equiv) and Bu_4NHSO_4 (36.0 mg, 0.105 mmol, 7.00 mol %). The solids were then dissolved in *t*-AmOH (2.00 mL), and stirring was commenced. To the stirred solution was added NaOH (1.0 N, 4.73 mL, 4.73 mmol, 3.15 equiv) and the biphasic mixture was stirred at a rate to ensure adequate mixing of the phases for 10 min. $Na_2S_2O_4$ (78.0 mg, 0.45 mmol, 0.30 equiv) was then added in a single portion followed by the requisite perfluoroalkyl iodide (1.65 mmol, 1.10 equiv), and the reaction was stirred for 45 min. A sample was then taken for UHPLC analysis, and upon verification of complete conversion, the reaction was quenched with HCl (2.0 N, 3.00 mL, 6.00 mmol, 4.00 equiv) and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 5.00 mL), and the combined organics were dried over $MgSO_4$, filtered, concentrated over Celite under reduced pressure, and purified by flash chromatography.

Characterization of Perfluoroalkylation Products. In many cases, the products were isolated as a mixture of keto:enol tautomers. For clarity, only the major tautomer spectral data is described. The major tautomer is depicted in the manuscript.

*1-((4-Fluorophenyl)sulfonyl)-6-(perfluoropropan-2-yl)-3,4-dihydronaphthalen-2(1H)-one (**8**).* Following general procedure A employing **7** (457 mg, 1.50 mmol) and heptafluoroisopropyl iodide (0.31 mL, 2.18 mmol) to obtain the desired product as a white solid (567 mg, 1.20 mmol, 80%).

Following general procedure B employing **7** (457 mg, 1.50 mmol) and heptafluoroisopropyl iodide (0.23 mL, 1.65 mmol) to obtain the desired product as a white solid (482 mg, 1.02 mmol, 68%). Chromatography = 12 g SiO_2 cartridge, 0 → 60% EtOAc in Hex over 15 min. R_f = 0.29 (SiO_2, Hex:EtOAc = 3:1); mp = 99−101 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.72−7.66 (m, 2H), 7.48 (s, 1H), 7.42 (br d, J = 8.2 Hz, 1H), 7.20−7.11 (m, 3H), 4.78 (s, 1H), 3.64−3.51 (m, 1H), 2.97−2.87 (m, 2H), 2.52−2.42 (m, 1H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 199.8, 167.4, 165.3, 139.6 (d, J = 2.7 Hz), 133.2 (d, J = 3.6 Hz), 132.7 (d, J = 1.8 Hz), 132.1 (d, J = 10.0 Hz), 129.2, 128.2 (d, J = 20.0 Hz), 125.1 (dd, J = 218.9, 10.9 Hz), 120.4 (dd, J = 287.0, 28.2 Hz), 116.6 (d, J = 22.7 Hz), 92.73−89.58 (m), 76.8, 37.1, 27.2; ^{19}F NMR (376 MHz, chloroform-*d*) δ −75.48 (d, J = 6.8 Hz), −101.37 to −101.50 (m), −182.35 to −182.42 (m); HRMS (CI-TOF, m/z) calcd. For $C_{19}H_{12}O_3SF_8Na$ [M + Na]$^+$: calcd, 495.0272; found, 495.0262; IR (ATR, neat, cm^{-1}): 2948 (w), 1715 (m), 1592 (m), 1495 (m), 1290 (m), 1211 (s), 1141 (s), 980 (s).

*6-(Perfluoropropan-2-yl)-1-(phenylsulfonyl)-3,4-dihydronaphthalen-2(1H)-one (**9a**).* Following general procedure A employing **S9** (429 mg, 1.50 mmol) and heptafluoroisopropyl iodide (0.31 mL, 2.18 mmol) to obtain the desired product as a yellow solid (400 mg, 0.88 mmol, 59%).

Following general procedure B employing **S9** (429 mg, 1.50 mmol) and heptafluoroisopropyl iodide (0.23 mL, 1.65 mmol) to obtain the desired product as a yellow solid (566 mg, 1.25 mmol, 83%). Chromatography = 12 g SiO_2 cartridge, 0 → 50% EtOAc in Hex over 15 min. R_f = 0.34 (SiO_2, Hex:EtOAc = 3:1); mp = 105−108 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.74 (dd, J = 8.2, 1.1 Hz, 2H), 7.71−7.67 (m, 1H), 7.58−7.51 (m, 3H), 7.46 (br d, J = 8.2 Hz, 1H), 7.22 (d, J = 8.2 Hz, 1H), 4.89 (s, 1H), 3.69−3.57 (m, 1H), 3.06−2.94 (m, 2H), 2.55 (ddd, J = 18.5, 11.5, 6.9 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 199.7, 139.6 (d, J = 1.8 Hz), 137.1, 134.6, 132.6 (d, J = 1.8 Hz), 129.5, 129.3, 129.2, 128.1 (d, J = 20.9 Hz), 126.7, 126.05−116.57 (m), 105.2, 91.2 (ddt, J = 203.2, 66.3, 33.3 Hz), 76.8, 37.0, 27.2; ^{19}F NMR (376 MHz, chloroform-*d*) δ −73.84 to −77.56 (m), −182.41 (quin, J = 7.2 Hz); HRMS (ESI-TOF, m/z) calcd. For $C_{19}H_{17}NO_3SF_7$ [M + NH$_4$]$^+$: calcd, 472.0812; found, 472.0808; IR (ATR, neat, cm^{-1}): 2948 (w), 1718 (m), 1446 (w), 1278 (m), 1208 (s), 1141 (s), 980 (s), 719 (s).

*1-((4-Chlorophenyl)sulfonyl)-6-(perfluoropropan-2-yl)-3,4-dihydronaphthalen-2(1H)-one (**9b**).* Following general procedure A employing **S8** (481 mg, 1.50 mmol) and heptafluoroisopropyl iodide (0.31 mL, 2.18 mmol) to obtain the desired product as a brown solid (589 mg, 1.20 mmol, 80%).

Following general procedure B employing **S8** (481 mg, 1.50 mmol) and heptafluoroisopropyl iodide (0.23 mL, 1.65 mmol) to obtain the desired product as a brown solid (490 mg, 1.00 mmol, 67%). Chromatography = 12 g SiO_2 cartridge, 0 → 60% EtOAc in Hex over 15 min. R_f = 0.29 (SiO_2, Hex:EtOAc = 3:1); mp = 104−106 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.60−7.54 (m, 2H), 7.46 (s, 1H), 7.42−7.35 (m, 3H), 7.15 (d, J = 8.1 Hz, 1H), 4.81 (s, 1H), 3.63−3.49 (m, 1H), 2.95−2.83 (m, 2H), 2.42 (ddd, J = 18.3, 11.6, 6.9 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 199.7, 141.4, 139.6 (d, J = 1.8 Hz), 135.6, 132.7 (d, J = 1.8 Hz), 130.6, 129.6, 129.4, 129.2, 128.50−127.98 (m), 125.0 (br dd, J = 221.6, 10.9 Hz), 123.94−116.66 (m), 91.1 (dquin, J = 202.9, 33.1 Hz), 76.5, 37.0, 27.1; ^{19}F NMR (376 MHz, chloroform-*d*) δ −73.61 to −77.33 (m), −182.42 (quin, J = 7.2 Hz); HRMS (ESI-TOF, m/z) calcd. For $C_{19}H_{16}NO_3SF_7Cl$ [M + NH$_4$]$^+$: calcd, 506.0422; found, 506.0416; IR (ATR, neat, cm^{-1}): 2960 (w), 1718 (m), 1580 (w), 1476 (w), 1305 (m), 1207 (s), 1141 (s), 980 (s).

*1-(Methylsulfonyl)-6-(perfluoropropan-2-yl)-3,4-dihydronaphthalen-2(1H)-one (**9c**).* Following general procedure B employing **S11** (337 mg, 1.50 mmol) and heptafluoroisopropyl iodide (0.23 mL, 1.65 mmol) to obtain the desired product as an orange solid (249 mg, 0.63 mmol, 42%). Chromatography = 12 g SiO_2 cartridge, 0 → 10% MeOH in CH_2Cl_2 over 15 min. R_f = 0.18 (SiO_2, Hex:EtOAc = 3:1); mp = 125−127 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.61−7.55 (m, 2H), 7.48 (d, J = 8.1 Hz, 1H), 4.80 (s, 1H), 3.78−3.65 (m, 1H), 3.20 (s, 3H), 3.09−2.97 (m, 2H), 2.60 (ddd, J = 18.6, 12.1, 6.9 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 201.8, 139.7 (d, J = 1.8 Hz), 133.1 (d, J = 1.8 Hz), 128.2 (d, J = 20.0 Hz), 127.8, 125.9 (br d, J = 10.9 Hz), 124.3 (br d, J = 10.9 Hz), 124.10−116.31 (m), 91.2 (dt, J = 202.5, 33.2 Hz), 74.4, 41.1, 37.5, 27.1; ^{19}F NMR (376 MHz, chloroform-*d*) δ −75.42 (d, J = 8.2 Hz), −181.26 to −184.05 (m); HRMS (ESI-TOF, m/z) calcd. For $C_{14}H_{15}NO_3SF_7$ [M + NH$_4$]$^+$: calcd, 410.0655; found, 410.0651; IR (ATR, neat, cm^{-1}): 2941 (w), 1722 (m), 1305 (m), 1278 (m), 1211 (s), 1125 (s), 980 (m), 719 (m).

*1-((4-Fluorophenyl)sulfonyl)-6-(perfluoropropyl)-3,4-dihydronaphthalen-2(1H)-one (**9d**).* Following general procedure A employing **7** (457 mg, 1.50 mmol) and perfluoropropyl iodide (0.31 mL, 2.18 mmol) to obtain the desired product as a yellow oil (269 mg, 0.57 mmol, 38%). Chromatography = 12 g SiO_2 cartridge, 0 → 50% EtOAc in Hex over 15 min. R_f = 0.33 (SiO_2, Hex:EtOAc = 3:1); ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.75−7.64 (m, 2H), 7.46 (s, 1H), 7.40 (d, J = 8.1 Hz, 1H), 7.20−7.12 (m, 3H), 4.79 (s, 1H), 3.64−3.53 (m, 1H), 2.99−2.87 (m, 2H), 2.55−2.38 (m, 1H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 199.7, 167.4, 165.4, 139.5, 133.3 (d, J = 3.6 Hz), 132.5, 132.2 (d, J = 10.0 Hz), 130.1, 127.17−126.86 (m), 125.3 (t, J = 6.8 Hz), 123.3, 116.6 (d, J = 22.7 Hz), 108.6 (q, J = 39.1 Hz), 76.9, 37.0, 27.1; ^{19}F NMR (376 MHz, chloroform-*d*) δ −79.84 to −79.98 (m), −79.93 (t, J = 10.2 Hz), −101.13 to −101.60 (m), −111.89 (q, J = 9.5 Hz), −126.16; HRMS (CI-TOF, m/z) calcd. For $C_{19}H_{16}F_8O_3SN$ [M + NH$_4$]$^+$: calcd, 490.0718; found, 4490.0712; IR (ATR, neat, cm^{-1}): 2926 (w), 1722 (m), 1592 (m), 1495 (m), 1227 (m), 1144 (s), 1114 (s), 731 (s).

*1-((4-Fluorophenyl)sulfonyl)-6-(perfluorobutyl)-3,4-dihydronaphthalen-2(1H)-one (**9e**).* Following general procedure A, and scaling all reagents appropriately, employing **7** (500 mg, 1.64 mmol) and perfluorobutyl iodide (0.41 mL, 2.38 mmol) to obtain the desired product as a yellow solid (410 mg, 0.79 mmol, 48%). Chromatography = 12 g SiO_2 cartridge, 0 → 60% EtOAc in Hex over 15 min. R_f = 0.28 (SiO_2, Hex:EtOAc = 3:1); mp = 86−89 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.74−7.64 (m, 2H), 7.46 (s, 1H), 7.40 (d, J = 8.1 Hz, 1H), 7.21−7.11 (m, 3H), 4.79 (s, 1H), 3.64−3.51 (m, 1H), 3.00−2.88 (m, 2H), 2.51−2.40 (m, 1H); ^{13}C{^{1}H} NMR (126 MHz,

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chloroform-*d*) δ 199.7, 167.4, 165.4, 139.5, 133.2 (d, *J* = 2.7 Hz), 132.5, 132.2 (d, *J* = 10.0 Hz), 130.84−129.95 (m), 129.7, 127.1 (t, *J* = 6.4 Hz), 125.4 (br t, *J* = 6.4 Hz), 118.5 (t, *J* = 33.2 Hz), 117.33−115.93 (m), 115.82−114.67 (m), 111.44−107.99 (m), 76.9, 37.0, 27.1; ^{19}F NMR (376 MHz, chloroform-*d*) δ −79.42 to −82.45 (m), −101.43 (tt, *J* = 8.5, 4.4 Hz), −111.15 (br t, *J* = 13.6 Hz), −122.54 (q, *J* = 9.5 Hz), −124.53 to −126.39 (m); HRMS (ESI-TOF, *m*/*z*) calcd. For $C_{20}H_{16}NO_3SF_{10}$ $[M + NH_4]^+$: calcd, 540.0686; found, 540.0675; IR (ATR, neat, cm^{-1}): 2956 (w), 1730 (w), 1588 (w), 1491 (w), 1234 (m), 1193 (w), 1129 (s), 831 (m).

1-((4-Fluorophenyl)sulfonyl)-6-(perfluorohexyl)-3,4-dihydronaphthalen-2(1H)-one (**9f**). Following general procedure A, and scaling all reagents appropriately, employing **7** (500 mg, 1.64 mmol) and perfluorohexyl iodide (0.52 mL, 2.38 mmol) to obtain the desired product as a yellow solid (550 mg, 0.88 mmol, 54%). Chromatography = 12 g SiO_2 cartridge, 0 → 60% EtOAc in Hex over 15 min. R_f = 0.26 (SiO_2, Hex:EtOAc = 3:1); mp = 104−106 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.81−7.75 (m, 2H), 7.55 (s, 1H), 7.47 (d, *J* = 8.1 Hz, 1H), 7.32−7.17 (m, 3H), 4.90 (s, 1H), 3.73−3.61 (m, 1H), 3.08−3.02 (m, 1H), 3.02−2.97 (m, 1H), 2.60−2.49 (m, 1H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 199.7, 167.4, 165.4, 133.2 (d, *J* = 3.6 Hz), 132.5, 132.2 (d, *J* = 10.0 Hz), 130.2, 130.3 (br t, *J* = 24.5 Hz), 129.7 (d, *J* = 10.0 Hz), 127.1 (br t, *J* = 6.4 Hz), 125.3 (br t, *J* = 5.9 Hz), 118.3 (br t, *J* = 33.2 Hz), 117.38−115.46 (m), 116.30−114.86 (m), 114.26−112.02 (m), 111.48−109.69 (m), 109.49−107.50 (m), 76.9, 37.0, 27.1; ^{19}F NMR (376 MHz, chloroform-*d*) δ −81.01 (br t, *J* = 10.2 Hz), −101.16 to −102.21 (m), −110.99 (br t, *J* = 14.3 Hz), −121.51 (br s), −121.68 (br t, *J* = 13.6 Hz), −122.91 (br d, *J* = 4.1 Hz), −126.27 (ddd, *J* = 23.5, 9.2, 4.1 Hz); HRMS (ESI-TOF, *m*/*z*) calcd. For $C_{22}H_{16}NO_3SF_{14}$ $[M + NH_4]^+$: calcd, 640.0622; found, 640.0604; IR (ATR, neat, cm^{-1}): 2956 (w), 1729 (w), 1588 (w), 1491 (w), 1290 (m), 1189 (s), 1140 (s), 831 (m).

Ethyl 2-Cyano-2-(4-(perfluoropropan-2-yl)phenyl)acetate (**10**). Following general procedure B employing **5** (0.26 mL, 1.50 mmol) and heptafluoroisopropyl iodide (0.23 mL, 1.65 mmol) to obtain the desired product as a yellow oil (481 mg, 1.35 mmol, 90%). Chromatography = 12 g SiO_2 cartridge, 0 → 30% EtOAc in Hex over 15 min. R_f = 0.49 (SiO_2, Hex:EtOAc = 3:1); ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.63−7.58 (m, 2H), 7.58−7.53 (m, 2H), 4.75 (s, 1H), 4.18 (q, *J* = 6.2 Hz, 2H), 1.20 (br t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 164.2, 133.2, 128.6 (d, *J* = 2.7 Hz), 127.9 (d, *J* = 20.9 Hz), 126.7 (br d, *J* = 10.9 Hz), 120.4 (qd, *J* = 286.0, 27.7 Hz), 114.9, 91.2 (dquin, *J* = 202.8, 33.1 Hz), 63.6, 43.2, 13.7; ^{19}F NMR (376 MHz, chloroform-*d*) δ −75.77 (d, *J* = 8.2 Hz), −182.64 (t, *J* = 6.8 Hz); HRMS (CI-TOF, *m*/*z*) calcd. For $C_{14}H_{11}NO_2F_7$ $[M + H]^+$: calcd, 358.0678; found, 358.0675; IR (ATR, neat, cm^{-1}): 1748 (m), 1279 (m), 1203 (s), 1167 (m), 1099 (m), 984 (m), 954 (m), 708 (m).

Ethyl 3-(tert-Butoxy)-2-cyano-2-(4-(perfluoropropan-2-yl)phenyl)propanoate (**11a**). Following general procedure A employing **5** (0.26 mL, 1.50 mmol) and heptafluoroisopropyl iodide (0.23 mL, 1.65 mmol) to obtain the desired product as a yellow oil (160 mg, 0.361 mmol, 24%). **10** was also isolated (180 mg, 0.510 mmol, 34%). Due to the nature of the alkylated compound as an undesired byproduct, only the minimum analytical data required for identification was acquired. Chromatography = 12 g SiO_2 cartridge, 0 → 30% EtOAc in Hex over 15 min. ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.76 (d, *J* = 8.5 Hz, 2H), 7.66 (d, *J* = 8.5 Hz, 2H), 4.44−4.20 (m, 2H), 4.13 (d, *J* = 8.4 Hz, 1H), 3.73 (d, *J* = 8.4 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.19 (s, 9H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 166.2, 135.4, 127.9 (d, *J* = 20.9 Hz), 127.5 (d, *J* = 2.7 Hz), 126.6 (br d, *J* = 10.9 Hz), 117.5, 124.69−116.63 (m), 92.99−89.10 (m), 74.8, 67.1, 63.6, 55.6, 27.3, 14.0; ^{19}F NMR (376 MHz, chloroform-*d*) δ −75.64 (d, *J* = 6.8 Hz), −182.63 (dt, *J* = 14.7, 7.0 Hz).

1-((4-Fluorophenyl)sulfonyl)-5-methoxy-6-(perfluoropropan-2-yl)-3,4-dihydronaphthalen-2(1H)-one (**12a**). Following general procedure B employing **S10** (502 mg, 1.50 mmol) and heptafluoroisopropyl iodide (0.23 mL, 1.65 mmol) to obtain the desired product as a brown solid (206 mg, 0.41 mmol, 27%). Chromatography = 12 g SiO_2 cartridge, 0 → 50% EtOAc in Hex over 15 min. R_f = 0.30 (SiO_2, Hex:EtOAc = 3:1); mp = 78−80 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.85−7.73 (m, 2H), 7.48 (d, *J* = 8.2 Hz, 1H), 7.25 (t, *J* = 8.5 Hz, 2H), 7.01 (d, *J* = 8.5 Hz, 1H), 4.85 (s, 1H), 3.86 (s, 3H), 3.52−3.36 (m, 1H), 3.29 (ddd, *J* = 16.0, 6.9, 2.0 Hz, 1H), 3.05−2.94 (m, 1H), 2.44 (ddd, *J* = 18.6, 11.9, 6.9 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 199.8, 167.4, 165.4, 156.8 (br s), 133.9, 133.4 (d, *J* = 2.7 Hz), 132.1 (d, *J* = 10.0 Hz), 131.5, 127.7 (d, *J* = 2.7 Hz), 126.6 (br d, *J* = 15.4 Hz), 122.69−118.22 (m), 116.6 (d, *J* = 22.7 Hz), 92.6 (dt, *J* = 238.9, 34.1 Hz), 76.8, 62.1 (br s), 37.0, 21.2; ^{19}F NMR (376 MHz, chloroform-*d*) δ −73.50 to −74.24 (m), −74.88 (quin, *J* = 7.8 Hz), −100.97 to −101.87 (m); HRMS (CI-TOF, *m*/*z*) calcd. For $C_{20}H_{14}O_4SF_7$ $[M]^+$: calcd, 502.0485; found, 502.0480; IR (ATR, neat, cm^{-1}): 2941 (w), 1718 (w), 1588 (w), 1495 (w), 1237 (s), 1211 (s), 1141 (s), 976 (s).

Ethyl 2-Cyano-2-(4-(perfluoropropyl)phenyl)acetate (**12b**). Following general procedure B employing **5** (0.26 mL, 1.50 mmol) and perfluoropropyl iodide (0.24 mL, 1.65 mmol) to obtain the desired product as an orange oil (129 mg, 0.36 mmol, 24%). Careful analysis of the crude reaction mixture by ^{1}H NMR revealed a 14:4:1 ratio of *para*:*ortho*:*para*/*ortho* substitution. The isolated yield corresponds to the major *para*-product. Chromatography = 12 g SiO_2 cartridge, 0 → 40% MTBE in Hex over 15 min. R_f = 0.49 (SiO_2, Hex:EtOAc = 3:1); ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.70−7.62 (m, 4H), 4.82 (s, 1H), 4.28 (qd, *J* = 7.1, 1.0 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 164.2, 134.0, 129.9 (t, *J* = 24.5 Hz), 128.4, 127.8 (t, *J* = 6.4 Hz), 116.8 (td, *J* = 32.7, 13.6 Hz), 119.48−114.46 (m), 114.9, 108.6 (q, *J* = 38.1 Hz), 63.8, 43.5, 13.8; ^{19}F NMR (376 MHz, chloroform-*d*) δ −80.03 (t, *J* = 10.2 Hz), −112.01 (br d, *J* = 9.5 Hz), −126.35 (s); HRMS (CI-TOF, *m*/*z*) calcd. For $C_{14}H_{11}NO_2F_7$ $[M + H]^+$: calcd, 358.0678; found, 358.0670; IR (ATR, neat, cm^{-1}): 2989 (w), 1748 (m), 1349 (m), 1200 (s), 1178 (s), 1114 (s), 895 (m), 734 (m).

Ethyl 2-Cyano-2-(4-(perfluorobutyl)phenyl)acetate (**12c**). Following general procedure B employing **5** (0.26 mL, 1.50 mmol) and perfluorobutyl iodide (0.28 mL, 1.65 mmol) to obtain the desired product as an orange oil (220 mg, 0.54 mmol, 36%). Careful analysis of the crude reaction mixture by ^{1}H NMR revealed a 13:3:1 ratio of *para*:*ortho*:*para*/*ortho* substitution. The isolated yield corresponds to the major *para*-product. All characterization data were in agreement with the previous report.[10a]

Ethyl 2-Cyano-2-(4-(perfluorohexyl)phenyl)acetate (**12d**). Following general procedure B employing **5** (0.26 mL, 1.50 mmol) and perfluorohexyl iodide (0.36 mL, 1.65 mmol) to obtain the desired product as an orange solid (297 mg, 0.59 mmol, 39%). Careful analysis of the crude reaction mixture by ^{1}H NMR revealed a 14:3:1 ratio of *para*:*ortho*:*para*/*ortho* substitution. The isolated yield corresponds to the major *para*-product. All characterization data were in agreement with the previous report.[10a]

2-Cyano-2-(4-(perfluoropropan-2-yl)phenyl)acetamide (**12e**). Following general procedure B employing **S3** (240 mg, 1.50 mmol) and heptafluoroisopropyl iodide (0.23 mL, 1.65 mmol) to obtain the desired product as an off-white solid (413 mg, 1.26 mmol, 84%). Chromatography = 12 g SiO_2 cartridge, 0 → 10% MeOH in CH_2Cl_2 over 15 min. R_f = 0.24 (SiO_2, CH_2Cl_2:MeOH = 95:5); mp = 153−155 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.00 (s, 1H), 7.84−7.75 (m, 2H), 7.75−7.70 (m, 2H), 7.66 (s, 1H), 5.26 (s, 1H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 165.5, 136.7, 129.4 (d, *J* = 1.8 Hz), 126.7 (br d, *J* = 10.9 Hz), 125.7 (d, *J* = 20.0 Hz), 117.9, 120.6 (qd, *J* = 286.9, 27.7 Hz), 93.65−89.27 (m), 43.6; ^{19}F NMR (376 MHz, DMSO-d_6) δ −75.22 (d, *J* = 8.2 Hz), −180.56 to −183.58 (m); HRMS (CI-TOF, *m*/*z*) calcd. For $C_{12}H_7N_2OF_7$ $[M + H]^+$: calcd, 329.0525; found, 329.0522; IR (ATR, neat, cm^{-1}): 3384 (w), 3187 (w), 2262 (w), 1715 (s), 1278 (m), 1211 (s), 1103 (m), 984 (s).

2-(4-(Perfluoropropan-2-yl)phenyl)-2-(phenylsulfonyl)acetonitrile (**12f**). Following general procedure B employing **S1** (386 mg, 1.50 mmol) and heptafluoroisopropyl iodide (0.23 mL, 1.65 mmol) to obtain the desired product as a yellow solid (620 mg, 1.46 mmol, 97%). Chromatography = 12 g SiO_2 cartridge, 0 → 40% EtOAc in Hex over 15 min. R_f = 0.40 (SiO_2, Hex:EtOAc = 3:1); mp =

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93−95 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.75−7.68 (m, 3H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.55−7.45 (m, 4H), 5.34 (s, 1H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 135.5, 134.0, 130.2 (d, *J* = 1.8 Hz), 129.9, 129.3, 129.0 (d, *J* = 20.9 Hz), 128.8, 126.4 (br d, *J* = 10.0 Hz), 120.2 (qd, *J* = 286.7, 28.2 Hz), 112.9, 91.1 (ddt, *J* = 203.7, 66.8, 33.3 Hz), 62.3; ^{19}F NMR (376 MHz, chloroform-*d*) δ −75.69 (dq, *J* = 9.9, 5.3 Hz), −182.66 (dt, *J* = 14.6, 7.0 Hz); HRMS (CI-TOF, *m*/*z*) calcd. For $C_{17}H_{10}NO_2SF_7$ [M + H]$^+$: calcd, 425.0399; found, 426.0393; IR (ATR, neat, cm^{-1}): 2930 (w), 1282 (m), 1203 (s), 1151 (s), 1103 (m), 1085 (m), 984 (m), 950 (s).

*2-(3-Methyl-4-(perfluoropropan-2-yl)phenyl)-2-(phenylsulfonyl)-acetonitrile (**12g**).* Following general procedure B employing **S4** (407 mg, 1.50 mmol) and heptafluoroisopropyl iodide (0.23 mL, 1.65 mmol) to obtain the desired product as a white solid (540 mg, 1.23 mmol, 82%). Chromatography = 12 g SiO_2 cartridge, 0 → 40% EtOAc in Hex over 15 min. R_f = 0.40 (SiO_2, Hex:EtOAc = 3:1); mp = 101−104 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.79−7.68 (m, 3H), 7.58−7.51 (m, 2H), 7.48 (br d, *J* = 7.9 Hz, 1H), 7.25−7.19 (m, 2H), 5.21 (s, 1H), 2.49 (d, *J* = 9.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 140.0, 135.5, 134.7, 134.1, 129.9, 129.2, 128.2, 127.2, 127.1, 126.7 (br d, *J* = 19.1 Hz), 120.7 (qd, *J* = 287.5, 27.7 Hz), 112.9, 94.1 (ddt, *J* = 207.4, 64.6, 30.7 Hz), 62.2, 21.7 (br d, *J* = 16.3 Hz); ^{19}F NMR (376 MHz, chloroform-*d*) δ −74.75 (dt, *J* = 10.2, 5.8 Hz), −178.94 (br d, *J* = 4.1 Hz); HRMS (CI-TOF, *m*/*z*) calcd. For $C_{18}H_{12}NO_2SF_7$ [M + H]$^+$: calcd, 440.0555; found, 440.0555; IR (ATR, neat, cm^{-1}): 2907 (w), 1271 (m), 1226 (s), 1207 (s), 1136 (s), 1103 (m), 1084 (m), 961 (m).

*2-(3-Chloro-4-(perfluoropropan-2-yl)phenyl)-2-(phenylsulfonyl)-acetonitrile (**12h**).* Following general procedure B employing **S5** (438 mg, 1.50 mmol) and heptafluoroisopropyl iodide (0.23 mL, 1.65 mmol) to obtain the desired product as a white solid (578 mg, 1.26 mmol, 84%). Chromatography = 12 g SiO_2 cartridge, 0 → 40% EtOAc in Hex over 15 min. R_f = 0.40 (SiO_2, Hex:EtOAc = 3:1); mp = 120−121 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.81−7.72 (m, 3H), 7.62−7.52 (m, 3H), 7.46 (s, 1H), 7.38 (br s, 1H), 5.19 (s, 1H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 135.9, 135.53−135.01 (m), 134.4 (br s), 133.9, 130.0, 129.5, 129.2 (br d, *J* = 10.9 Hz), 127.8 (br s), 126.60−125.39 (m), 123.9 (br d, *J* = 25.4 Hz), 121.6 (br d, *J* = 28.2 Hz), 119.3 (br d, *J* = 28.2 Hz), 117.29−116.56 (m), 112.4, 92.7 (dquin, *J* = 211.4, 33.7 Hz), 61.7; ^{19}F NMR (376 MHz, chloroform-*d*) δ −71.13 to −72.62 (m), −74.01 (br s), −168.26 (br s), −179.68 (br s); HRMS (CI-TOF, *m*/*z*) calcd. For $C_{17}H_{10}NO_2SF_7Cl$ [M + H]$^+$: calcd, 460.0009; found, 460.0006; IR (ATR, neat, cm^{-1}): 2911 (w), 1267 (m), 1230 (s), 1211 (s), 1174 (s), 1137 (s), 976 (m), 954 (s).

*2-(4-(Perfluoropropan-2-yl)-3-(trifluoromethyl)phenyl)-2-(phenylsulfonyl)acetonitrile (**12i**).* Following general procedure B employing **S13** (488 mg, 1.50 mmol) and heptafluoroisopropyl iodide (0.23 mL, 1.65 mmol) to obtain the desired product as a brown solid (167 mg, 0.34 mmol, 23%). After isolation, it was found that this product was in a 7:1 ratio with its constitutional isomer as an inseparable mixture. Characterization data described for the major constitutional isomer for clarity. Chromatography = 12 g SiO_2 cartridge, 0 → 75% CH_2Cl_2 in Hex over 30 min. R_f = 0.35 (SiO_2, Hex:EtOAc = 3:1); mp = 102−104 °C; ^{1}H NMR (500 MHz, benzene-d_6) δ 7.37 (s, 1H), 7.30 (d, *J* = 7.6 Hz, 2H), 7.20−7.17 (m, 1H), 6.95 (br d, *J* = 8.5 Hz, 1H), 6.87−6.80 (m, 1H), 6.66 (t, *J* = 7.8 Hz, 2H), 4.12 (s, 1H); ^{13}C{^{1}H} NMR (126 MHz, benzene-d_6) δ 134.9, 133.6, 132.3, 130.3, 129.9 (quin, *J* = 5.7 Hz), 129.6, 128.7, 128.41−128.03 (m), 128.0 (br s), 126.5 (br s), 123.5, 121.75−118.95 (m), 112.5, 92.2 (dt, *J* = 211.4, 32.8 Hz), 61.5; ^{19}F NMR (376 MHz, benzene-d_6) δ −57.56 (br d, *J* = 51.8 Hz), −74.72 (br dd, *J* = 24.5, 6.8 Hz), −179.48 to −184.06 (m); HRMS (CI-TOF, *m*/*z*) calcd. For $C_{18}H_9NO_2SF_{10}$ [M + H]$^+$: calcd, 494.0273; found, 494.0279; IR (ATR, neat, cm^{-1}): 2915 (w), 1259 (m), 1215 (s), 1174 (s), 1137 (s), 1114 (s), 972 (m), 954 (m).

*2-(4-(Perfluoropropan-2-yl)phenyl)malononitrile (**12j**).* Following general procedure B employing **S7** (213 mg, 1.50 mmol) and heptafluoroisopropyl iodide (0.23 mL, 1.65 mmol) to obtain the desired product as a yellow oil (368 mg, 1.19 mmol, 79%). Chromatography = 12 g SiO_2 cartridge, 0 → 50% EtOAc in Hex over 15 min. R_f = 0.23 (SiO_2, Hex:EtOAc = 3:1); ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.79 (br d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.4 Hz, 2H), 5.23 (s, 1H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 129.5, 129.3 (d, *J* = 20.9 Hz), 127.9 (d, *J* = 1.8 Hz), 127.5 (br d, *J* = 10.9 Hz), 124.35−116.00 (m), 111.2, 91.1 (ddt, *J* = 203.5, 66.5, 33.5 Hz), 27.7; ^{19}F NMR (376 MHz, chloroform-*d*) δ −75.72 (d, *J* = 6.8 Hz), −180.56 to −184.28 (m); HRMS (CI-TOF, *m*/*z*) calcd. For $C_{12}H_5N_2F_7$ [M + H]$^+$: calcd, 311.0419; found, 311.0411; IR (ATR, neat, cm^{-1}): 2889 (w), 1278 (m), 1203 (s), 1167 (m), 1103 (m), 984 (m), 954 (m), 708 (m).

*2-(1-(Perfluoropropan-2-yl)naphthalen-2-yl)-2-(phenylsulfonyl)-acetonitrile (**12k**).* Following general procedure B employing **S14** (461 mg, 1.50 mmol) and heptafluoroisopropyl iodide (0.23 mL, 1.65 mmol) to obtain the desired product as a brown solid (248 mg, 0.52 mmol, 35%). Chromatography = 12 g SiO_2 cartridge, 0 → 60% EtOAc in Hex over 15 min. R_f = 0.27 (SiO_2, Hex:EtOAc = 3:1); mp = 136−139 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.21−8.13 (m, 2H), 8.10−8.05 (m, 1H), 8.02−7.94 (m, 3H), 7.82−7.74 (m, 1H), 7.69−7.62 (m, 4H), 6.14 (d, *J* = 10.2 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 136.5, 135.4, 134.3, 133.4, 130.8 (d, *J* = 6.4 Hz, 1C), 129.7, 129.6, 129.3, 128.1, 127.9, 126.8, 126.69−126.23 (m), 125.02−124.55 (m), 124.4 (d, *J* = 18.2 Hz), 120.9 (ddd, *J* = 289.1, 29.3, 10.4 Hz), 114.0 (d, *J* = 2.7 Hz), 99.63−96.46 (m), 60.8 (d, *J* = 32.7 Hz); ^{19}F NMR (376 MHz, chloroform-*d*) δ −65.71 to −68.50 (m), −73.09 (quin, *J* = 6.1 Hz), −157.56 (br d, *J* = 8.2 Hz); HRMS (ESI-TOF, *m*/*z*) calcd. For $C_{21}H_{16}N_2O_2SF_7$ [M + NH_4]$^+$: calcd, 493.0815; found, 493.0813; IR (ATR, neat, cm^{-1}): 3034 (w), 1346 (m), 1223 (s), 1155 (s), 1107 (m), 1058 (m), 969 (m), 924 (m).

*Methyl 2-Hydroxy-6-(perfluoropropan-2-yl)-1H-indene-3-carboxylate (**12l**).* Following general procedure B employing **S2** (285 mg, 1.50 mmol) and heptafluoroisopropyl iodide (0.23 mL, 1.65 mmol) to obtain the desired product as a white solid (463 mg, 1.29 mmol, 86%). Chromatography = 12 g SiO_2 cartridge, 0 → 60% EtOAc in Hex over 15 min. R_f = 0.28 (SiO_2, Hex:EtOAc = 3:1); mp = 134−136 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 11.11 (br s, 1H), 7.67 (br d, *J* = 7.8 Hz, 1H), 7.59−7.45 (m, 2H), 3.97 (s, 3H), 3.60 (s, 2H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 182.0, 168.9, 142.5, 133.7 (d, *J* = 2.7 Hz), 124.8 (br d, *J* = 10.9 Hz), 121.86−121.64 (m), 120.7 (br d, *J* = 11.8 Hz), 120.2 (d, *J* = 1.8 Hz), 124.41−117.09 (m), 104.8, 98.58−86.09 (m), 51.6, 37.7; ^{19}F NMR (376 MHz, chloroform-*d*) δ −75.83 (d, *J* = 8.2 Hz), −181.60 (t, *J* = 6.8 Hz); HRMS (CI-TOF, *m*/*z*) calcd. For $C_{14}H_9O_3SF_7$ [M]$^+$: calcd, 358.0440; found, 358.0456; IR (ATR, neat, cm^{-1}): 2963 (w), 1159 (m), 1588 (m), 1274 (m), 1211 (s), 1185 (s), 1159 (s), 977 (s).

*Methyl 6-(1-((Difluoro-λ^3-methyl)-λ^2-fluoraneyl)-1,2,2,2-tetrafluoroethyl)-2-hydroxy-3,4-dihydronaphthalene-1-carboxylate (**12m**).* Following general procedure B employing **S6** (261 mg, 1.50 mmol) and heptafluoroisopropyl iodide (0.23 mL, 1.65 mmol) to obtain the desired product as an orange solid (409 mg, 1.10 mmol, 73%). Chromatography = 12 g SiO_2 cartridge, 0 → 30% EtOAc in Hex over 15 min. R_f = 0.68 (SiO_2, Hex:EtOAc = 3:1); mp = 77−79 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 13.41 (s, 1H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.32 (br d, *J* = 8.5 Hz, 1H), 3.84 (s, 3H), 2.77 (t, *J* = 7.6 Hz, 2H), 2.49 (t, *J* = 7.6 Hz, 2H), 1.10 (s, 1H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 179.8, 172.1, 134.4, 133.84−133.54 (m), 126.20−125.80 (m), 124.47−123.56 (m), 123.12−122.56 (m), 122.09−119.32 (m), 99.3, 91.5 (dquin, *J* = 201.1, 32.8 Hz), 51.9, 29.2, 27.7, 26.9; ^{19}F NMR (376 MHz, chloroform-*d*) δ −75.75 (s), −75.77 (s), −182.51 to −182.65 (m); HRMS (CI-TOF, *m*/*z*) calcd. For $C_{15}H_{11}F_7O_3$ [M]$^+$: calcd, 372.0596; found, 372.0600; IR (ATR, neat, cm^{-1}): 2960 (w), 1625 (w), 1588 (w), 1450 (w), 1274 (m), 1211 (s), 1182 (s), 977 (s).

*Ethyl 7-(1-((Difluoro-λ^3-methyl)-λ^2-fluoraneyl)-1,2,2,2-tetrafluoroethyl)-3-oxoisochromane-4-carboxylate (**12n**).* Following general procedure B employing **S15** (330 mg, 1.50 mmol) and heptafluoroisopropyl iodide (0.23 mL, 1.65 mmol) to obtain the desired product as a colorless oil (404 mg, 1.03 mmol, 69%). Analysis of the mixture showed the product as an 8:1 mixture of keto:enol tautomers.

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For clarity, only the analytical data for the major isomer is reported. Chromatography = 24 g SiO_2 cartridge, 0 → 100% EtOAc in Hex over 20 min. R_f = 0.70 (SiO_2, Hex:EtOAc = 2:1); ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.65 (br d, J = 8.2 Hz, 1H), 7.55−7.46 (m, 2H), 5.70 (d, J = 14.2 Hz, 1H), 5.33 (d, J = 14.2 Hz, 1H), 4.78 (s, 1H), 4.31−4.17 (m, 2H), 4.17−4.09 (m, 1H), 1.32−1.25 (m, 3H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 165.8, 165.6, 132.7, 132.3 (d, J = 1.8 Hz), 128.7 (d, J = 2.7 Hz), 127.4 (d, J = 20.9 Hz), 126.4 (br d, J = 10.0 Hz), 122.6 (br d, J = 11.8 Hz), 120.4 (qd, J = 286.7, 26.3 Hz), 91.2 (dquin, J = 203.2, 33.2 Hz), 69.9, 63.0, 53.0, 13.9; ^{19}F NMR (376 MHz, chloroform-*d*) δ −74.86 to −76.17 (m), −181.32 to −183.13 (m); HRMS (ESI-TOF, m/z) calcd. For $C_{15}H_{12}F_7O_4$ [M + H]$^+$: calcd, 389.0618; found, 389.0606; IR (ATR, neat, cm^{-1}): 2986 (w), 1733 (m), 1303 (m), 1278 (m), 1204 (s), 1167 (s), 1103 (m), 980 (s).

*4-((4-Fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-isochroman-3-one (**12o**).* Following general procedure B employing **S12** (459 mg, 1.50 mmol) and heptafluoroisopropyl iodide (0.23 mL, 1.65 mmol) to obtain the desired product as a white solid (550 mg, 1.16 mmol, 77%). Chromatography = 24 g SiO_2 cartridge, 0 → 100% EtOAc in Hex over 20 min. R_f = 0.70 (SiO_2, Hex:EtOAc = 2:1); mp = 140−142 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.99−7.89 (m, 2H), 7.70 (br d, J = 8.2 Hz, 1H), 7.56 (s, 1H), 7.51 (d, J = 8.2 Hz, 1H), 7.33−7.24 (m, 2H), 5.98 (d, J = 14.5 Hz, 1H), 5.36 (d, J = 14.5 Hz, 1H), 5.13 (s, 1H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 167.8, 165.7, 161.7, 133.7 (d, J = 2.7 Hz), 132.4 (d, J = 10.0 Hz), 131.7 (d, J = 2.7 Hz), 129.0 (d, J = 20.9 Hz), 126.4, 126.2 (br d, J = 10.0 Hz), 122.6 (br d, J = 10.9 Hz), 120.3 (dd, J = 287.0, 27.2 Hz), 116.9 (d, J = 23.6 Hz), 92.88−89.66 (m), 71.2, 70.4; ^{19}F NMR (376 MHz, chloroform-*d*) δ −75.39 (br dd, J = 9.5, 6.8 Hz), −100.28 (t, J = 8.2 Hz), −182.19 (quin, J = 7.2 Hz); HRMS (ESI-TOF, m/z) calcd. For $C_{18}H_{11}F_8O_4S$ [M + H]$^+$: calcd, 475.0245; found, 475.0229; IR (ATR, neat, cm^{-1}): 2956 (w), 1737 (m), 1588 (w), 1495 (w), 1278 (m), 1211 (s), 1148 (s), 984 (s).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01296.

Additional optimization of reaction conditions, table of unsuccessful substrates, and NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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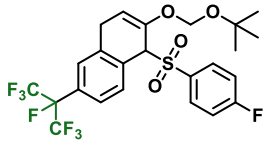
Diels-Alder Reaction of 1,3-Bis(silyloxy)-1,3-dienes with Aldehydes Catalyzed by Chiral Disulfonimide. *Angew. Chem., Int. Ed.* **2012**, *51*, 8859−8863. (c) Thomas, A. A.; Speck, K.; Kevlishvili, I.; Lu, Z.; Liu, P.; Buchwald, S. L. Mechanistically Guided Design of Ligands That Significantly Improve the Efficiency of CuH-Catalyzed Hydroamination Reactions. *J. Am. Chem. Soc.* **2018**, *140*, 13976−13984.

(13) Cross-coupling of ioodobenze and heptafluoroisopropyl zinc has been reported, but we have not been able to reproduce these results (ref 3e). The stability of nucleophilic organometallic reagents is limited: (a) Nair, H. K.; Burton, D. J. Perfluoroisopropylcadmium and copper: preparation, stability and reactivity. *J. Fluorine Chem.* **1992**, *56*, 341−351. (b) Chambers, R. D.; Musgrave, W. K. R.; Savory, J. Organometallic and metalloid compounds made from heptafluoro-2-iodopropane, and their properties. *J. Chem. Soc.* **1962**, 1993−1999.

(14) Details on the application of the methods herein described to the synthesis of **1** will be reported in due course.

(15) In keeping with standard industrial practice for optimization, in-process yields are assessed using "area percentage" (AP) yields. AP values are uncorrected for the difference in LC response factor for the starting material versus the desired product. These data, while approximate, give insight into general trends, aid in determining optimal conditions for lead reactions, and help approximate reaction conversion.

(16)



Proposed structure for the MTBE alkylation byproduct, based on UHPLC-MS and the fact that it hydrolyzes to **8**.

(17) See the Supporting Information for details.

(18) Presumably, the pK_a difference between the benzylic proton and bicarbonate is too great to facilitate deprotonation of the substrate—precluding access to the higher-energy-level HOMO of the delocalized enolate intermediate. This implies that the neutral substrate's HOMO is not sufficient in energy to trap the intermediary perfluoroalkyl radical. This marks an interesting distinction to anilines, as the electron-donating capabilities of the amine functionality increase the energy of the HOMO to a sufficient degree to achieve the desired reactivity.

(19) Melchiorre and co-workers observed mixtures of *para*, *ortho*, and *para/ortho* perfluoroalklyated products. With the HFP group, we did not observe this with the same cyanoacetate substrates. However, we did observe these constitutional isomers (and over-alkylated products) when linear perfluoroalkyl iodides were employed. In comparison to Melchiorre's results, our mixtures of isomers were improved, with the major product being the desired *para* isomer.

(20) This type of electrocatalytic chain propagation has been recently referred to as "upconversion of reductants": Syroeshkin, M. A.; Kuriakose, F.; Saverina, E. A.; Timofeeva, V. A.; Egorov, M. P.; Alabugin, I. V. Upconversion of Reductants. *Angew. Chem., Int. Ed.* **2019**, *58*, 5532−5550.

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