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Selective Perfluoro- and Polyfluoroarylation of Meldrum's Acid

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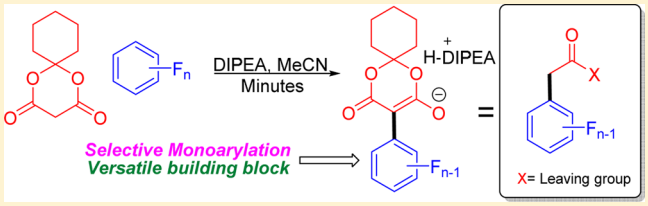
Supporting Information

ABSTRACT: This work describes the facile and monoselective per- and polyfluoroarylation of Meldrum's acid to generate a versatile synthon for highly fluorinated α-phenyl acetic acid derivatives, which provide straightforward access to fluorinated building blocks. The reaction takes place quickly, and most products were isolated without the need for chromatography. Importantly, this method provides an alternative strategy to access α-arylated Meldrum's acids, which avoids the need for aryl-Pb(IV) salts or diaryliodonium salts. Furthermore, we demonstrate the synthetic versatility and utility of the Meldrum's acid products by subjecting our products to several derivatizations of the Meldrum's acid products as well as photocatalytic hydrodefluorination.



INTRODUCTION

Meldrum's acid was initially discovered in 1908 by Meldrum;[1] however, the structure was misidentified for the next 40 years until it was correctly assigned by Davidson.[2] Because of its anomalous acidity (pK_a = 7.3 in DMSO),[3] Meldrum's acid has a long and rich history as an activated nucleophile,[4] and, contrary to its malonate cousin, it can be hydrolyzed easily under acidic conditions, which can allow for facile elaboration not possible with malonates. While strategies for the selective alkylation of Meldrum's acid have been well developed such as the reductive alkylation of aldehydes,[5] coupling and reduction of carboxylic acids,[6] addition to Michael acceptors,[7] substitution of Mitsunobu reagents,[8] substitution of alkyl halides,[7] and the addition to cationic metal allyls,[9]the corresponding arylation is far less developed.

In contrast to alkylation of Meldrum's acid, very few methods exist for the direct α-arylation of Meldrum's acid.[10] In fact, most commonly this motif is achieved via acetal or ketal formation of an α-phenyl malonic acid or its ketene derivative.[11] A more direct approach would be to α-arylate an already existing Meldrum's acid unit. Toward this goal, Chen and Stang[12] have shown that diaryliodonium salts can afford direct arylation of Meldrum's acid (eq 1, Scheme 1). Furthermore, Pinhey[13] has shown that aryl-leadtriacetates undergo facile coupling with Meldrum's acid (eq 2, Scheme 1).

Comparison to Previous Arylations of Meldrum's Acid. Unfortunately, neither of these methods allows for selective monoarylation as the reaction always leads to the fully quaternerized product. Thus, methods that allow for the selective monoarylation of Meldrum's acid are needed to be able to access the Meldrum's acid that possesses a tertiary center or unsymmetric quaternerized center.

Recently, our group has taken an interest in increasing the number of fluorinated arene building blocks as well as methods for their further elaboration. A method for direct per(poly)-fluoroarylation of Meldrum's acid would be particularly ideal given the versatility of Meldrum's acid.

Given perfluoroarenes are known to readily undergo nucleophilic aromatic substitution (S_NAr),[14] we were surprised to find that the addition of Meldrum's acid had never been reported (eq 3, Scheme 1), and we set about to develop this reaction.[15] We hoped to determine whether Meldrum's acid is a competent nucleophile for S_NAr reactions of highly fluorinated arenes. Herein, we report conditions that allow for clean, rapid, and operationally simple monoarylation of Meldrum's acid and its derivatives with a number of highly fluorinated arenes. Furthermore, we demonstrate that these adducts are easily functionalizable and undergo typical reactions expected of Meldrum's acid.

RESULTS AND DISCUSSION

We initiated our investigation using pentafluoropyridine and 1,5-dioxaspiro[5.5]undecane-2,4-dione (MA) along with diisopropylethylamine (DIPEA) in acetonitrile (Table 1). In this analogue, the normal [2,2] dimethyl group has been replaced with a cyclohexyl group. Consequently, it is more soluble[16] in most organic solvents and displays a greater hydrolytic stability[17] than simple Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione), which can be prone to hydrolysis over prolonged time periods. With routine optimization, several trends became clear. First, polar aprotic solvents worked well (entries 1−3), while protic- (entry 4), halogenated- (entry 5), aromatic- (entry 6), and ethereal-solvents (entry 7) were found to be inferior. Acetonitrile was used for further studies because its comparatively greater volatility facilitated isolation. Additionally, both triethylamine (entry 8) and K_2CO_3 (entry 9) were screened as bases. While triethylamine gave conversions similar to those of the standard reaction (entry 1), it also

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Scheme 1. Previous Direct Arylations of Meldrum's Acid

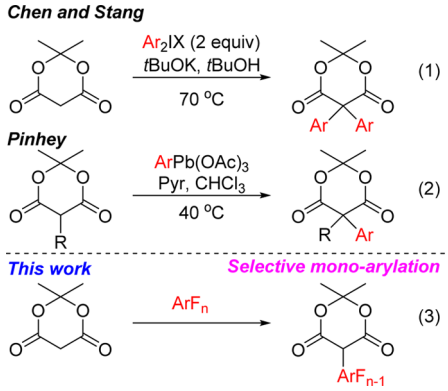
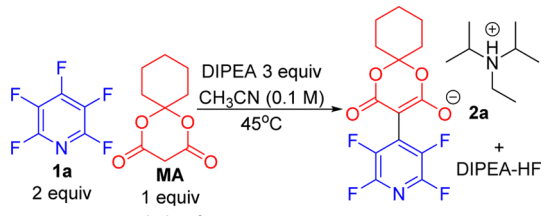


Table 1. Optimization of Reaction Conditions



entry	deviation from standard conditions	time (min)	% conv.[a]
1	none	120/300	93/100
2	DMSO	120/300	100/100
3	DMA	120/300	100/100
4	IPA	120/300	3/6
5	DCM	120/300	17/28
6	Tol	120/300	ND[b]
7	THF	120/300	13/23
8	TEA instead of DIPEA	120/300	87/100
9	K_2CO_3 instead of DIPEA	120/300	10/15
10	0.05 M in MeCN	270	45
11	0.1 M in MeCN	270	73
12	0.2 M in MeCN	270	100
13	1.0 M in MeCN	20	100

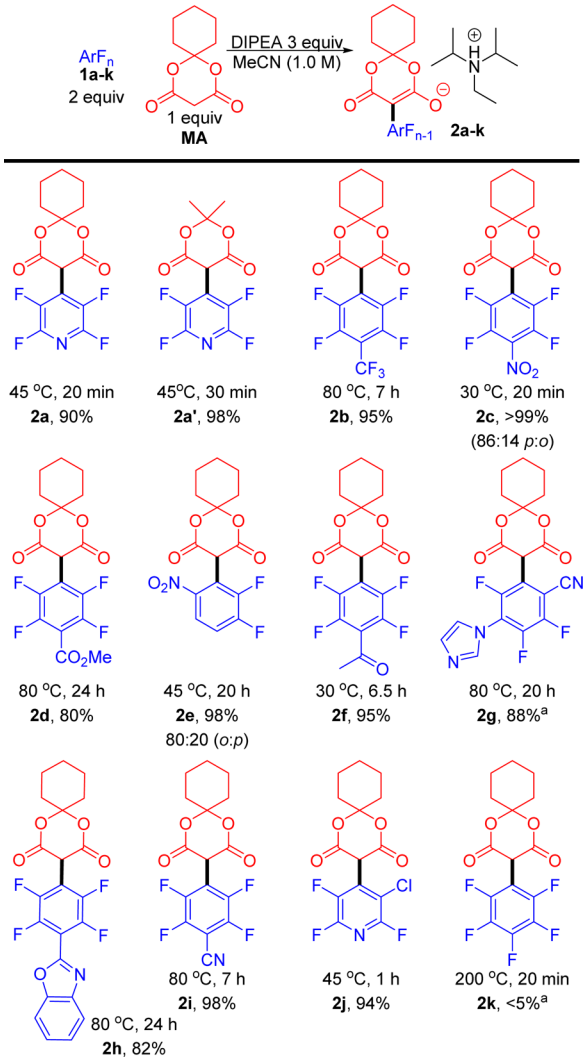
[a]Conversions determined by ^{19}F NMR. [b]ND = not detected.

yielded an undesirable *N*-arylated side-product.[18] Thus, DIPEA was used for further studies. Finally, the effect of concentration was briefly examined (entries 10−13). The rate of the reaction displayed a dependency on the concentration, and thus the reactions were run at 1 M concentration to shorten the reaction times.

With conditions in hand that provided product with remarkable speed and were essentially free of unwanted side products, we next sought to develop workup conditions that would allow us to isolate the DIPEA-adduct salt from left-over perfluoroarene, DIPEA, and DIPEA-HF salt. Fortuitously, we were able to accomplish this through a series of evaporations, solvent changes, and washings, which resulted in pure products.[19] The workups allow rapid isolation in high yield with no need for column chromatography, which should facilitate its implementation on a larger scale.[20]

With reaction and workup conditions in hand, we began to evaluate the scope of the reaction. In general, this reaction works extremely well for fluoroarenes that possess an activating functional group (i.e., an electron-withdrawing group) (Table 2).

Table 2. Addition of Unsubstituted MA to Fluorinated Arenes



[a]μ-wave heating.

Specifically, the reaction worked well for pyridines (**1a**, **1a**′, and **1j**), nitro-substituted substrates (**1c** and **1e**), ketones (**1f**), nitriles (**1g** and **1i**), and esters (**1d**), as well as trifluoromethyl groups (**1b**) and heterocycle substituted substrates (**1g** and **1h**). Only in the case of the nitroarenes **1c** and **1e** were regioisomers observed. Selective addition to the C-4 (fluorine bearing) of 3-chloro-2,4,5-trifluoropyridine (**1j**) is consistent with the S_NAr mechanism. The absolute control of mono-arylation versus diarylation is remarkable considering that the previous methods were unable to selectively monoarylate.[12,13]

Unfortunately, the reaction would not work for simple hexafluorobenzene even at elevated temperatures (200 °C) where it remained mostly unchanged. It did, however, demonstrate the robustness of MA at high temperatures under basic conditions, as no decomposition products could be detected. Speculating that the lack of reactivity of hexafluorobenzene (**1k**) could be attributed to an insurmountable reaction barrier, we reasoned that it might be overcome by increasing the reactivity of the nucleophile. To accomplish this, we turned to the malonate ester, which is significantly more basic (diethyl malonate pK_a = 16.4 in DMSO)[21] and correspondingly more nucleophilic.[22] We were pleased to find

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that use of the malonate did indeed lead to clean substitution of even the least activated of the perfluoroarenes (Table 3). While we would have liked to have used Meldrum's acid as the nucleophile due to its synthetic versatility, ultimately we were able to obtain the 1,3-diester motif using diethyl malonate for hexafluorobenzene (**3k**), decafluorobiphenyl (**3l**), and perfluoronaphthalene (**3m**).[15a,23]

Next, we sought to fully quaternerize the remaining activated methine via alkylation. However, after several failed attempts to methylate **2a** via standard alkylation techniques, we were forced to reevaluate our strategy. The lack of alkylation could be due to either steric or electronic inhibition (or alternatively a combination of both). However, we suspected that the additional stabilization of the MA-carbanion by the perfluoroarene significantly reduced the nucleophilicity of the carbanion and that the rate of alkylation (and subsequent arylation) was slow due more to the electronics than the steric inhibition of the transition state. Steric inhibition seems less likely given that there are numerous examples of quaternerized Meldrum's acid compounds that were achieved via alkylation,[24] although admittedly there are no examples of alkylations of α-(2,6-disubstituted aryl)-Meldrum's acid. Nonetheless, we were forced to reconsider our planned route to the fully quaternerized carbons.

In an attempt to quaternerize the MA, we next reversed the order of events. Using α-alkylated Meldrum's acid derivatives, we were able to facilitate the S_NAr reaction to arrive at the desired fully substituted Meldrum's acid derivatives (Table 4). We were pleased to find that the additions took place smoothly with no alterations from the initial conditions despite the fact that the reaction forms a quaternary center, hinting that the inability to alkylate **2a** is an electronic rather than a steric issue. As can be seen from Table 4, the yields range from good to excellent. To the first approximation, the reactions take place with rates similar to those of the corresponding perfluoroarylation (i.e., Table 2).

Finally, we wanted to demonstrate the utility of the MA-adducts as highly functionalizable building blocks (Scheme 2). While our MA-adducts were stable under basic conditions, under acidic conditions they undergo facile hydrolysis[25] and nucleophilic addition.[26] Under acidic conditions, nucleophilic attack of the carbonyl group and ring opening take place along with decarboxylation. We have found that the decarboxylation is significantly accelerated by the presence of the perfluoroaryl group such that it takes place readily at methanolic reflux (and

Table 3. Addition of Diethylmalonate to Unactivated Perfluoroarenes

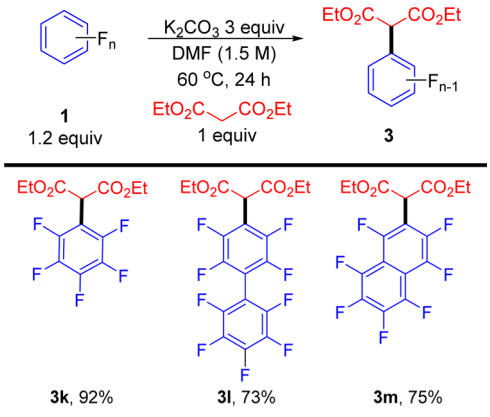
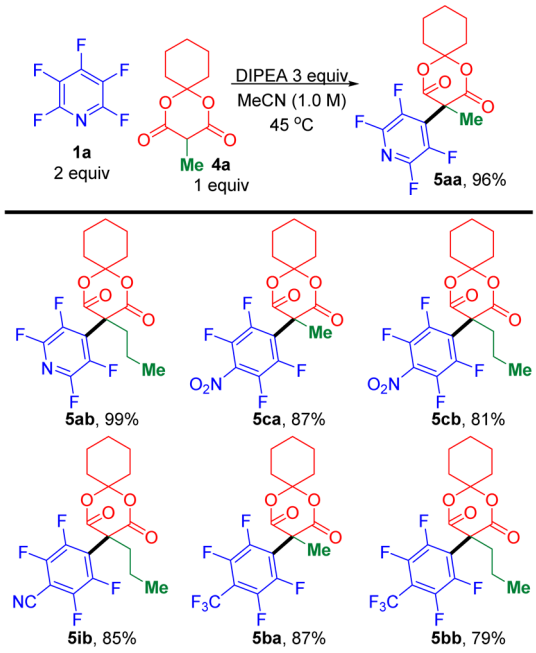
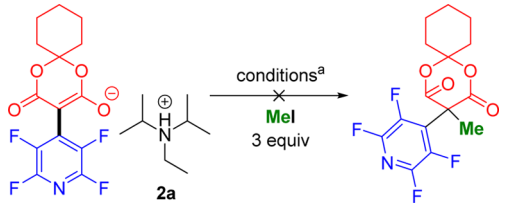


Table 4. Addition of α-Alkylated MAs to Perfluoroarenes



Scheme 2. Failed Direct Alkylation of the Adducts[a]



[a](a) See the Supporting Information for details on conditions tried.

even at room temperature)[19] rather than temperatures well over 100 °C[27] typical of the relevant diacids. Glycine ethyl ester underwent smooth acylation to afford the *N*-addition product (**6aa**, eq 1, Scheme 3). The Weinreb amide, which is a useful synthetic intermediate for the formation of ketones, was easily formed by the addition of its HCl salt with gentle heating (**6ac**, eq 2). Methanolysis of MA-adduct **2d** (eq 3) cleanly formed the dimethyl ester, which we subjected to photocatalytic hydrodefluorination (HDF) conditions (eq 4) recently developed in our lab.[28] By controlling the equivalents of reductant (the aliphatic amine) and the reaction time, selective formation of both the mono-HDF product (**6de**) and di-HDF (**6df**) was accomplished, which allowed access to a di- and trifluorinated arene that would be challenging to access by existing methods.

CONCLUSIONS

We have reported conditions that facilitate the addition of Meldrum's acid to perfluoro- and polyfluoroarenes to arrive at synthetically versatile highly fluorinated building blocks. Furthermore, we have shown that we can take advantage of the relatively acidic nature of the products to prevent over arylation and to facilitate isolation. We also have shown that fully quaternerized carbons can be synthesized by reversing the order of events, which leverages the wealth of methods that exist for selective alkylation to circumvent the problematic alkylation. Given the increasing demand for fluorine incorpo-

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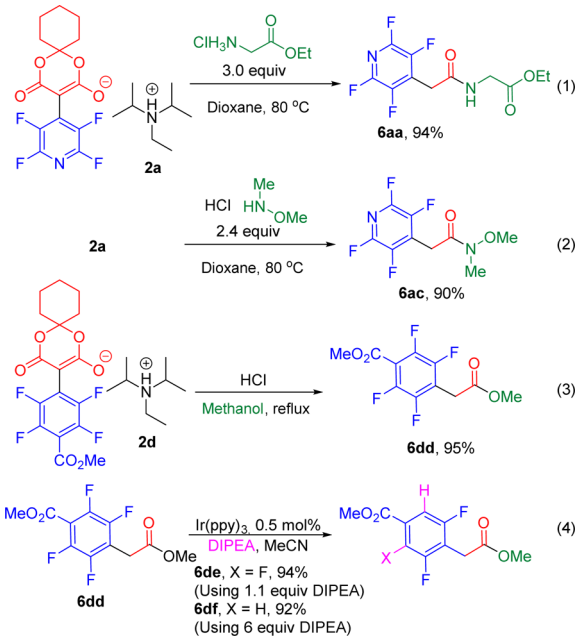
Scheme 3. Utility of the MA-Adducts

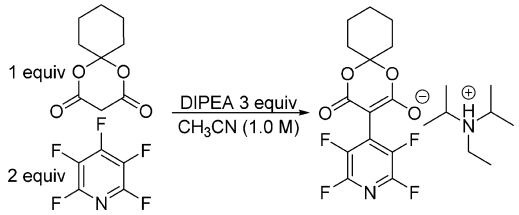


ration into molecules of disparate fields, we suspect that this simple method for construction of fluorinated building blocks will be of value for a broad spectrum of chemists.

EXPERIMENTAL SECTION

All reagents were obtained from commercial suppliers and used without further purification unless otherwise noted. Acetonitrile (CH_3CN) was dried over molecular sieves. Photocatalyst tris-(2-phenylpyridinato-C^2,N)iridium(III), 99% (purity) ($Ir(ppy)_3$), was obtained from a chemical supplier. Methyl-2,3,4,5,6-pentafluorobenzoate (**1d**),[28] 2-(perfluorophenyl)benzo[*d*]oxazole (**1h**),[28] 2,3,5,6-tetrafluoro-4-(1*H*-imidazol-1-yl)benzonitrile[29] (**1g**), and cyclohexyl-Meldrum's acid, MA,[16] were synthesized according to literature procedures. NMR spectra were obtained on 400 MHz spectrometers. ^1H and ^{13}C NMR chemical shifts are reported in ppm relative to the residual protio solvent peak (^1H, ^{13}C). Melting points were reported uncorrected. HRMS data were obtained using a LTQ (linear trap quadrupole) Orbitrap XL mass spectrometer. Isolations were carried out using an automated chromatography system using normal phase silica (4, 12 , 24, or 40 g) with product detection at 254, 280 nm and using an evaporative light scattering detector (ELSD). Substrate syntheses reactions were monitored by thin layer chromatography (TLC), with UV254, glass backed, 250 μm, and were visualized with ultraviolet light or potassium permanganate.

General Procedure A: Fluoroarylation of Unsubstituted-MA.



For the monitoring purposes, these reactions were carried out in NMR tubes and monitored via ^{19}F NMR. An NMR tube was charged with cyclohexyl-Meldrum's acid (1 equiv), then CH_3CN (1.0 M), followed by *N*,*N*-diisopropylethylamine (3 equiv), and fluorinated starting material **1a**−**k** (1.2 or 2 equiv) were added, and a sealed glass capillary containing C_6D_6 was placed in the NMR tube for locking purposes. The NMR tube then was placed in a sand bath and maintained at the appropriate temperature (30, 45, or 80 °C). The NMR tube was occasionally removed from the sand bath, and the progress was checked by ^{19}F NMR.

General Workup Method B for the Isolation of the Fluoroarylated-MA Adduct (for Volatile Starting Materials). After reaction completion as judged by ^{19}F NMR, CH_3CN and excess volatile starting material were removed via rotavap, and the residue was dissolved in DCM (2 mL) and washed with deionized water (2 mL) to selectively remove DIPEA-HF salt. The organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo to yield the title compound.

General Workup Method C for the Isolation of the Fluoroarylated-MA Adduct (for Nonvolatile Per- and Polyfluoroarene Starting Materials). In the case of less volatile fluoroarene starting materials, purification of the crude material was done by using the following purification method. After reaction completion as judged by ^{19}F NMR, CH_3CN was removed via rotavap, and the residue was dissolved in DCM (2 mL) and washed with deionized water (2 mL) to remove DIPEA-HF salt. The organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The compound was purified via trituration. In a borosilicate test tube, the sample was dissolved in a minimal amount (~0.5 mL) of ethyl acetate, and pentane (~5.0 mL) was slowly added along the wall of the test tube resulting in the formation of two layers. The test tube then was capped with a rubber septum and allowed to sit overnight, which resulted in the selective dissolution of the excess fluoroarene starting material (typically 1.2 equiv used) and the ethyl acetate into the pentane layer, leaving behind the product as a solid or oil. The product was then separated by simple decantation of the pentane layer, which contained the excess starting material. Finally, the product was placed in a vacuum to remove any left-over pentane to yield the title compound.

General Procedure D: Fluoroarylation of Diethyl Malonate. These reactions were carried out in 0.5−2.0 mL microwave vials. A microwave vial was charged with diethyl malonate (1 equiv), DMF (1.6 M), fluorinated starting material (1.2 equiv), and K_2CO_3 (3.0 equiv), and then a magnetic stir bar was added. The microwave vial was placed in a sand bath and maintained at 60 °C. The reaction was monitored by ^{19}F NMR by pulling out small aliquots using a syringe and a needle. After the completion of the reaction, the residue was dissolved in DCM (~4 × the vol of DMF) and washed with deionized water (3 × 5 mL) to remove K_2CO_3 and DMF. The organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by normal phase chromatography with hexanes and ethyl acetate.

General Procedure E: Fluoroarylation of Substituted-MA. For monitoring purposes, these reactions were carried out in NMR tubes and monitored via ^{19}F NMR. An NMR tube was charged with alkylated-Meldrum's acid (1 equiv), and then CH_3CN (1.0 M), fluorinated starting material **1a**−**c** (2 equiv), and *N*,*N*-diisopropylethylamine (3 equiv) were added, and a sealed glass capillary containing C_6D_6 was placed in the NMR tube for locking purposes. The NMR tube then was placed in a sand bath and maintained at the appropriate temperature (30, 45, or 80 °C). The reaction was monitored by ^{19}F NMR.

General Procedure F: Photocatalytic Hydrodefluorination Reaction. This reaction was carried out following the literature procedure.[1] In an NMR tube capped with NMR septum was charged tris-(2- phenylpyridinato-C^2,N) iridium(III) ($Ir(ppy)_3$) (1 mL of a 0.5 mM solution in MeCN). Fluorinated starting material **6dd** (1.0 equiv) and *N*,*N*-diisopropylethylamine (1.1 or 6.0 equiv) were added, and a sealed glass capillary containing C_6D_6 was added for locking purposes before degassing. The reaction then was degassed through the septum via Ar bubbling for 5−10 min at 0 °C (to avoid evaporation of *N*,*N*-diisopropylethylamine). The NMR tube was placed in a light bath, and the lower portion of the tube was submerged under the water bath, which was maintained at 45 °C. The reaction was periodically monitored by ^{19}F NMR. After the reaction completion, CH_3CN was removed via rotavap, and the residue was treated with deionized water (2 mL) and extracted with EtOAc (5 × 1 mL). The combined organic

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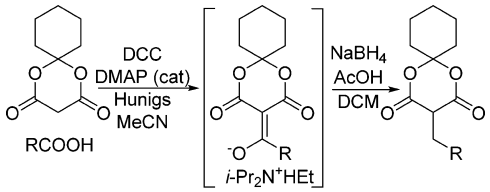
portions were dried with anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by normal phase chromatography.

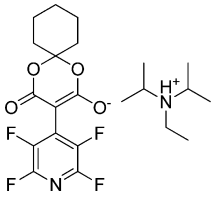
General Procedure G: Alkylation of MA.



These reactions were carried out in a one-pot, two-step procedure.[30] In a 100 mL round-bottom flask, the corresponding carboxylic acid (1.0 equiv) and MeCN (0.2 M) were added followed by cyclohexyl-Meldrum's acid (1.1 equiv). To the stirring mixture was added DMAP (4-dimethylaminopyridine) (0.1 equiv) followed by the dropwise addition of *N*,*N*-diisopropylethylamine (2.15 equiv). Next, DCC (*N*,*N*′-dicyclohexylcarbodiimide) (1.1 equiv) was added, and the reaction was stirred at room temperature for 14 h. MeCN then was evaporated in vacuo, and the crude material was taken onto the next step without further purification. In the second step, the crude material was dissolved in DCM (0.2 M), cooled to 0 °C, and acetic acid (10 equiv) was added followed by the portion-wise addition of $NaBH_4$ (2.5 equiv). The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was then diluted with water (20 mL), acidified with 1 M HCl. The organic layer was separated, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resultant crude residue was purified by automated flash chromatography to give the product.

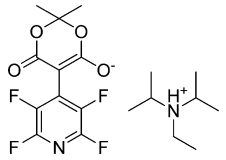
General Procedure H: Aminolysis Reaction of the Fluoroarylated-MA Adduct. For monitoring purposes, these reactions were carried out in NMR tubes and monitored via ^{19}F NMR. An NMR tube charged with **2a** (1.0 equiv) and the amine-HCl salt (2.4 or 3.0 equiv) and dioxane (0.1 M) was added, and sealed glass capillary containing C_6D_6 was placed in the NMR tube for locking purposes. The NMR tube then was placed in a sand bath and maintained at 80 °C. The reaction was periodically monitored by ^{19}F NMR. After the completion of the reaction, the residue was dissolved in DCM (2 mL) and washed with deionized water (3 × 5 mL) to remove dioxane. The organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo to obtain the title compound.

Synthesis of *N*-Ethyl-*N*-isopropylpropan-2-aminium 4-Oxo-3-(perfluoropyridin-4-yl)-1,5-dioxaspiro[5.5]undec-2-en-2-olate (2a).



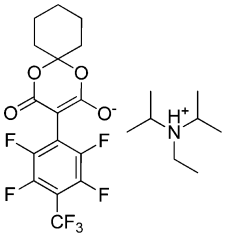
The general procedure A was followed using pentafluoropyridine (220 μL, 2.0 mmol, 2.0 equiv), cyclohexyl-Meldrum's acid, MA (184 mg, 1.0 mmol, 1.0 equiv), *N*,*N*-diisopropylethylamine (522 μL, 3.0 mmol, 3.0 equiv), and CH_3CN (1.0 mL). After the completion of the reaction, the workup method B was used to isolate **2a** in 90% yield as a light yellow solid (416.0 mg, 0.9 mmol). ^{19}F NMR (376 MHz, $CDCl_3$): δ −96.5 to −96.8 (m, 2F), −138.6 to −138.9 (m, 2F). ^1H NMR (400 MHz, $CDCl_3$): δ 3.64−3.50 (m, 2H), 3.04 (qd, *J* = 7.4, 4.0 Hz, 2H), 2.08−1.98 (m, 4H), 1.65 (p, *J* = 6.6 Hz, 4H), 1.50−1.32 (m, 17H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 164.2, 144.8−141.9 (m), 142.1−138.5 (m), 131.9 (ddd, *J* = 20.1, 16.8, 3.5 Hz), 103.1, 67.7, 54.4, 42.7, 34.8, 25.0, 22.7, 18.4, 17.0, 12.4. mp 138−140 °C. FT-IR (neat): cm^{-1} 2935, 1605, 1254, 1368, 1466. HRMS (ESI) calcd, $C_{14}H_{10}F_4NO_4^-$ 332.0551; observed, 332.0532.

Synthesis of *N*-Ethyl-*N*-isopropylpropan-2-aminium 2,2-Dimethyl-4-oxo-5-(perfluoropyridin-4-yl)-4*H*-1,3-dioxin-6-olate (2a′).



The general procedure A was followed using pentafluoropyridine (110 μL, 1.0 mmol, 2.0 equiv), simple-Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) (72.0 mg, 0.5 mmol, 1.0 equiv), *N*,*N*-diisopropylethylamine (261 μL, 1.5 mmol, 3.0 equiv), and CH_3CN (0.5 mL). After the completion of the reaction, the workup method B was used to isolate **2a**′ in 98% yield as a white solid (207.0 mg, 0.49 mmol). ^{19}F NMR (376 MHz, $CDCl_3$): δ −95.6 to −95.9 (m, 2F), −138.2 to −138.4 (m, 2F). ^1H NMR (400 MHz, $CDCl_3$): δ 3.47 (hept, *J* = 13.0, 6.5 Hz, 2H), 3.04−2.90 (m, 2H), 1.60 (s, 6H), 1.31−1.21 (m, 15H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 164.5, 144.9−141.9 (m), 142.0−138.9 (m), 131.8 (tt, *J* = 16.6, 3.4 Hz), 102.5, 67.6 (d, *J* = 4.6 Hz), 54.4, 42.7, 26.0, 18.4, 17.1, 12.4. mp 102−104 °C. FT-IR (neat): cm^{-1} 2992, 2958, 1600, 1266. HRMS (ESI) calcd, $C_{11}H_6F_4NO_4^-$ 292.0238; observed, 292.0217.

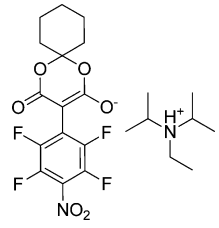
Synthesis of *N*-Ethyl-*N*-isopropylpropan-2-aminium 4-Oxo-3-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-1,5-dioxaspiro[5.5]undec-2-en-2-olate (2b).



The general procedure A was followed using octafluorotoluene (283 μL, 2.0 mmol, 2.0 equiv), cyclohexyl-Meldrum's acid (184.0 mg, 1.0 mmol, 1.0 equiv), *N*,*N*-diisopropylethylamine (522 μL, 3.0 mmol, 3.0 equiv), and CH_3CN (1.0 mL). After the completion of the reaction, the workup method C was used to isolate **2b** in 95% yield as a sticky white solid (502.7 mg, 0.95 mmol). ^{19}F NMR (376 MHz, $CDCl_3$): δ −56.0 (t, *J* = 21.6, 6.8 Hz, 3F), −135.2 to −135.4 (m, 2F), −144.7 to −145.1 (m, 2F). ^1H NMR (400 MHz, $CDCl_3$): δ 3.5−3.3 (m, 2H), 3.0−2.9 (m, 2H), 2.0−1.8 (m, 4H), 1.5 (p, *J* = 5.9 Hz, 4H), 1.4−1.1 (m, 17H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 164.4, 146.8−143.7 (m), 143.7 (dd, *J* = 255.7, 17.5 Hz), 122.6 (d, *J* = 19.5 Hz), 121.2 (d, *J* = 234.0 Hz), 105.0 (qt, *J* = 33.8, 12.8 Hz), 102.7, 66.4, 54.1, 42.4, 34.5, 24.8, 22.4, 18.1, 16.7, 12.1. mp 100−101 °C. FT-IR (neat): cm^{-1} 2936, 2706, 1593, 1286. HRMS (ESI) calcd, $C_{16}H_{10}F_7O_4^-$ 399.0473; observed, 399.0448.

Note: Complete removal of DCM was not accomplished due to the extreme stickiness of the product. The yield was calculated taking the DCM into account.

Synthesis of *N*-Ethyl-*N*-isopropylpropan-2-aminium 4-Oxo-3-(2,3,5,6-tetrafluoro-4-nitrophenyl)-1,5-dioxaspiro[5.5]-undec-2-en-2-olate (2c).



The general procedure A was followed using pentafluoronitrobenzene (66.7 μL, 0.55 mmol, 1.1 equiv), cyclohexyl-Meldrum's acid (92.0 mg, 0.5 mmol, 1.0 equiv), *N*,*N*-diisopropylethylamine (260 μL, 1.5 mmol, 3.0 equiv), and CH_3CN (0.5 mL). After the completion of the reaction, the workup method C was used to isolate **2c** in >99% yield as

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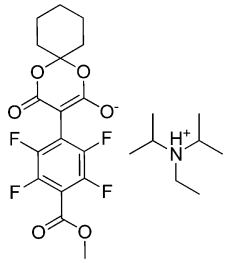
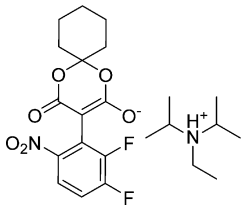
a brown sticky solid (253 mg, 0.5 mmol). The isolated product contained *para* and *ortho* substituted compounds in 7.1:1 ratio as determined by the ^{19}F NMR of the isolated material. ^{19}F NMR of the mixture (376 MHz, $CDCl_3$): δ −132.2 (minor, dd, J = 23.6, 9.5 Hz, 1F), −133.3 to −133.5 (major, m, 2F), −149.9 (minor, ddd, J = 21.7, 9.3, 4.1 Hz, 1F), −150.5 (major, td, J = 15.4, 14.7, 10.0 Hz, 2F), −152.1 to −152.4 (minor, m, 1F), −159.1 (minor, t, J = 21.2 Hz, 1F). ^1H NMR (400 MHz, $CDCl_3$): δ 3.58 (h, J = 10.2, 6.6, 3.7 Hz, 2H), 3.10−2.99 (m, 2H), 2.08−2.00 (m, 4H), 1.66 (p, J = 6.7 Hz, 4H), 1.52−1.34 (m, 17H). $^{13}C\{^1H\}$ NMR of the mixture (101 MHz, $CDCl_3$): δ 164.6, 164.2, 146.5 (d, J = 6.3 Hz), 144.9 (ddd, J = 243.9, 10.5, 7.0 Hz), 142.7−139.6 (m), 140.2 (dd, J = 258.3, 18.8 Hz), 135.7−135.3 (m), 126.8 (t, J = 12.8 Hz), 123.4 (t, J = 18.5 Hz), 118.7 (dd, J = 20.4, 4.2 Hz), 102.8, 67.4, 66.6, 54.1, 53.5, 42.4, 35.1, 34.6, 34.0, 24.8, 22.4, 18.2, 16.8, 12.2. mp 85−86 °C. FT-IR (neat): cm^{-1} 2947, 1594, 1479, 1345. HRMS (ESI) calcd, $C_{15}H_{10}F_4NO_6^-$ 376.0450; observed, 376.0424.

Synthesis of *N*-Ethyl-*N*-isopropylpropan-2-aminium 4-Oxo-3-(2,3,5,6-tetrafluoro-4-(methoxycarbonyl)phenyl)-1,5-dioxaspiro[5.5]undec-2-en-2-olate (2d).



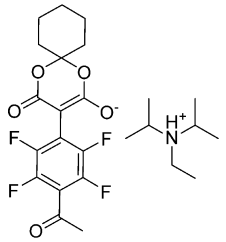
The general procedure A was followed using methyl-2,3,4,5,6-pentafluorobenzoate (124.3 μL, 0.55 mmol, 1.1 equiv), cyclohexyl-Meldrum's acid, MA (92.0 mg, 0.5 mmol, 1.0 equiv), *N*,*N*-diisopropylethylamine (260 μL, 1.5 mmol, 3.0 equiv), and CH_3CN (0.5 mL). After the completion of the reaction, the workup method C was used to isolate **2d** in 80% yield as colorless crystals (207.6 mg, 0.4 mmol). ^{19}F NMR (376 MHz, $CDCl_3$): δ −136.2 to −136.3 (m, 2F), −142.8 to −143.0 (m, 2F). ^1H NMR (400 MHz, $CDCl_3$): δ 3.93 (s, 3H), 3.58 (hept, J = 6.5 Hz, 2H), 3.09−2.99 (m, 2H), 2.09−1.98 (m, 4H), 1.71−1.56 (m, 4H), 1.45−1.29 (m, 17H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 164.5, 161.1, 146.7−143.7 (m), 146.1−143.0 (m), 121.6 (t, J = 18.7 Hz), 108.0 (t, J = 15.4 Hz), 102.5, 66.7, 54.0, 52.7, 42.3, 34.6, 24.9, 22.5, 18.2, 16.9, 12.1. mp 119−121 °C. FT-IR (neat): cm^{-1} 2991, 2953, 1744, 1595, 1300. HRMS (ESI) calcd, $C_{17}H_{13}F_4O_6^-$ 389.0654; observed, 389.0629.

Synthesis of *N*-Ethyl-*N*-isopropylpropan-2-aminium 3-(2,3-Difluoro-4-nitrophenyl)-4-oxo-1,5-dioxaspiro[5.5]undec-2-en-2-olate (2e).



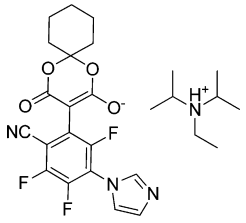
The general procedure A was followed using 1,2,3-trifluoro-4-nitrobenzene (63.2 μL, 0.55 mmol, 1.1 equiv), cyclohexyl-Meldrum's acid, MA (92.0 mg, 0.5 mmol, 1.0 equiv), *N*,*N*-diisopropylethylamine (260 μL, 1.5 mmol, 3.0 equiv), and CH_3CN (0.5 mL). After the completion of the reaction, the workup method C was used to isolate **2e** in 98% yield as orange crystals (230.0 mg, 0.49 mmol). The isolated product contained *ortho* and *para* substituted compounds in 4.1:1 ratio as determined by the ^{19}F NMR of the isolated material. ^{19}F NMR of the mixture (376 MHz, $CDCl_3$): δ −129.5 (major, d, J = 22.5 Hz, 1F), −130.3 (minor, d, J = 27.1 Hz, 1F), −130.6 (major, d, J = 8.4 Hz, 1F), −144.6 (minor, d, J = 15.1 Hz, 1F). ^1H NMR (400 MHz, $CDCl_3$): δ 7.65−7.63 (minor, m, 2H), 7.57 (major, ddd, J = 9.1, 4.8, 1.8 Hz, 1H), 7.05−6.92 (major, m, 1H), 3.66−3.48 (major, m, 2H), 3.02 (major, q, J = 7.2 Hz, 2H), 2.16−1.95 (major, m, 4H), 1.72−1.57 (major, m, 4H), 1.50−1.27 (major, m, 17H). $^{13}C\{^1H\}$ NMR of the mixture (101 MHz, $CDCl_3$): δ 164.64, 164.55, 152.0 (dd, J = 407.5, 13.2 Hz), 152.0−147.2 (m), 151.8−147.1 (m), 151.7−147.2 (m), 149.5−146.7 (m), 149.4−149.1 (m), 146.9−146.8 (m), 146.2, 146.8−143.8 (m), 136.6 (d, J = 11.3 Hz), 132.8 (d, J = 4.0 Hz), 125.9, 124.3 (d, J = 15.8 Hz), 119.9 (dd, J = 8.3, 3.7 Hz), 118.6, 112.8 (d, J = 19.4 Hz), 102.4, 101.8, 73.7, 69.7, 53.9, 42.2, 35.3, 34.7, 34.0, 24.9, 22.5, 22.4, 22.4,, 18.2, 16.9, 12.1. mp 130−133 °C. FT-IR (neat): cm^{-1} 2991, 1678, 1592, 1213. HRMS (ESI) calcd, $C_{15}H_{12}F_2NO_6^-$ 340.0638; observed, 340.0619.

Synthesis of *N*-Ethyl-*N*-isopropylpropan-2-aminium 3-(4-Acetyl-2,3,5,6-tetrafluorophenyl)-4-oxo-1,5-dioxaspiro[5.5]-undec-2-en-2-olate (2f).



The general procedure A was followed using 2′,3′,4′,5′,6′-pentafluoroacetophenone (142.3 μL, 1.0 mmol, 2.0 equiv), cyclohexyl-Meldrum's acid, MA (92.0 mg, 0.5 mmol, 1.0 equiv), *N*,*N*-diisopropylethylamine (260 μL, 1.5 mmol, 3.0 equiv), and CH_3CN (0.5 mL). After the completion of the reaction, the workup method C was used to isolate **2f** in 95% yield as a yellow solid (239 mg, 0.48 mmol). ^{19}F NMR (376 MHz, $CDCl_3$): δ −136.1 to −136.4 (m, 2F), −144.8 to −145.0 (m, 2F). ^1H NMR (400 MHz, $CDCl_3$): δ 3.56 (hept, J = 6.6 Hz, 2H), 3.01 (q, J = 7.4 Hz, 2H), 2.07−2.01 (m, 4H), 2.00 (s, 3H), 1.66 (p, J = 6.4 Hz, 4H), 1.51−1.19 (m, 17H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 193.0, 164.5, 146.7−143.7 (m), 143.9 (dddd, J = 251.3, 16.3, 7.0, 4.0 Hz), 121.2 (t, J = 18.7 Hz), 115.4 (t, J = 16.1 Hz), 102.6, 66.8, 54.1, 42.4, 34.6, 32.4, 24.9, 22.5, 18.2, 16.8, 12.2. mp 58−60 °C. FT-IR (neat): cm^{-1} 2943, 1599, 1314. HRMS (ESI) calcd, $C_{17}H_{13}F_4O_5^-$ 373.0705; observed, 373.0677.

Synthesis of *N*-Ethyl-*N*-isopropylpropan-2-aminium 3-(2-Cyano-3,4,6-trifluoro-5-(1*H*-imidazol-1-yl)phenyl)-4-oxo-1,5-dioxaspiro[5.5]undec-2-en-2-olate (2g).



The general procedure A was followed using 2,3,5,6-tetrafluoro-4-(1*H*-imidazol-1-yl)benzonitrile (132.5 mg, 0.55 mmol, 1.1 equiv), cyclohexyl-Meldrum's acid, MA (92.0 mg, 0.5 mmol, 1.0 equiv), *N*,*N*-diisopropylethylamine (260 μL, 1.5 mmol, 3.0 equiv), and CH_3CN (0.5 mL). After the completion of the reaction, the workup method C was used to isolate **2g** in 88% yield as a brown solid (236 mg, 0.44 mmol). ^{19}F NMR (376 MHz, $CDCl_3$): δ −118.2 (d, J = 13.2 Hz, 1F), −134.9 (dd, J = 21.2, 13.2 Hz, 1F), −146.5 (d, J = 21.2 Hz, 1F). ^1H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 2.0 Hz, 1H), 7.21 (d, J = 1.5 Hz, 1H), 7.19 (s, 1H), 3.62 (hept, J = 6.7 Hz, 2H), 3.07 (q, J = 7.4 Hz, 2H), 2.15−1.90 (m, 4H), 1.75−1.11 (m, 21H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 164.5, 151.2, 148.7, 149.8−142.5 (m), 147.1−140.0 (m), 129.3, 127.6 (dd, J = 20.9, 3.8 Hz), 120.1, 119.7 (dd, J = 19.9, 11.4 Hz), 112.2 (t, J = 3.6 Hz), 105.0 (dd, J = 10.5, 5.5 Hz), 102.7, 70.4, 53.9, 42.2, 34.6 (d, J = 14.7 Hz), 24.7, 22.4, 18.3, 17.0, 12.1. mp 80−82 °C. FT-IR (neat): cm^{-1} 2938, 1681, 1589, 1482. HRMS (ESI) calcd, $C_{19}H_{13}F_3N_3O_4^-$ 404.0864; observed, 404.0852.

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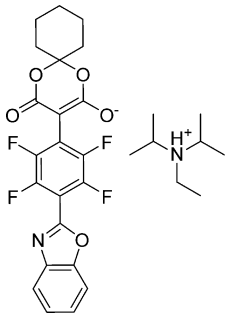
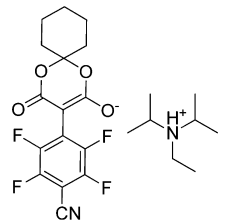
Synthesis of *N*-Ethyl-*N*-isopropylpropan-2-aminium 3-(4-(2,7*a*-Dihydrobenzo[*d*]oxazol-2-yl)-2,3,5,6-tetrafluorophenyl)-4-oxo-1,5-dioxaspiro[5.5]undec-2-en-2-olate (2h).



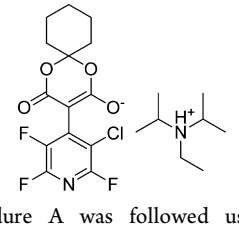
The general procedure A was followed using 2-(perfluorophenyl)-benzo[*d*]oxazole (156.8 mg, 0.55 mmol, 1.1 equiv), cyclohexyl-Meldrum's acid, MA (92.0 mg, 0.5 mmol, 1.0 equiv), *N*,*N*-diisopropylethylamine (260 μL, 1.5 mmol, 3.0 equiv), and CH_3CN (0.5 mL). After the completion of the reaction, the workup method C was used to isolate **2h** in 82% yield as a yellow oil (237 mg, 0.41 mmol). ^{19}F NMR (376 MHz, $CDCl_3$): δ −135.9 to −136.0 (m, 2F), −141.6 to −141.7 (m, 2F). ^1H NMR (400 MHz, $CDCl_3$): δ 7.89−7.61 (m, 2H), 7.46−7.35 (m, 2H), 3.61 (hept, *J* = 6.8, 6.3 Hz, 2H), 3.05 (q, *J* = 7.3 Hz, 2H), 2.11−2.04 (m, 4H), 1.67 (m, 4H), 1.47−1.33 (m, 17H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 164.4, 154.2, 150.1, 145.5 (dddd, *J* = 244.3, 11.3, 6.2, 3.3 Hz), 144.7 (ddt, *J* = 255.5, 16.7, 4.9 Hz), 141.0, 125.8, 124.7, 121.3 (t, *J* = 18.7 Hz), 120.2, 110.6, 103.6 (t, *J* = 13.7 Hz), 102.5, 66.9, 54.0, 42.3, 34.5, 24.8, 22.4, 18.1, 16.7, 12.1. FT-IR: cm^{-1} 2942, 1686, 1597, 1488, 1304. HRMS (ESI) calcd, $C_{22}H_{16}F_4NO_5^-$ 450.0970; observed, 450.0950.

Synthesis of *N*-Ethyl-*N*-isopropylpropan-2-aminium 3-(4-Cyano-2,3,5,6-tetrafluorophenyl)-4-oxo-1,5-dioxaspiro[5.5]-undec-2-en-2-olate (2i).



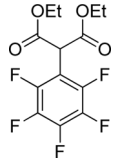
This reaction was carried out in a borosilicate test tube. The general procedure A was followed using 2,3,4,5,6-pentafluorobenzonitrile (1.0 g, 5.42 mmol, 2.0 equiv), cyclohexyl-Meldrum's acid, MA (0.5 g, 2.71 mmol, 1.0 equiv), *N*,*N*-diisopropylethylamine (1.41 mL, 8.1 mmol, 3.0 equiv), and CH_3CN (27 mL). After the completion of the reaction, the workup method C was used to isolate **2i** in 98% yield as a yellow solid (1.3 g, 2.66 mmol). ^{19}F NMR (376 MHz, $CDCl_3$): δ −133.3 to −133.6 (m, 2F), −136.4 to −136.7 (m, 2F). ^1H NMR (400 MHz, $CDCl_3$): δ 3.60 (hept, *J* = 10.0, 6.5, 3.2 Hz, 2H), 3.05 (qd, *J* = 7.4, 3.6 Hz, 2H), 2.06−2.00 (m, 4H), 1.66 (p, *J* = 6.7 Hz, 4H), 1.44−1.34 (m, 17H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 163.5, 147.7−144.5 (m), 145.8−142.9 (m), 125.2 (t, *J* = 18.2 Hz), 108.2, 102.2, 88.3, 66.7, 53.7, 42.0, 34.1, 24.3, 21.9, 17.6, 16.2, 11.7. mp 72−74 °C. FT-IR: cm^{-1} 2948, 1594, 1481, 1291. HRMS (ESI) calcd, $C_{16}H_{10}F_4NO_4^-$ 356.0551; observed, 356.0521.

Synthesis of *N*-Ethyl-*N*-isopropylpropan-2-aminium 3-(3-Chloro-2,5,6-trifluoropyridin-4-yl)-4-oxo-1,5-dioxaspiro[5.5]-undec-2-en-2-olate (2j).



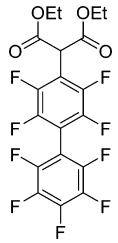
The general procedure A was followed using 3-chloro-2,4,5,6-tetrafluoropyridine (22.6 μL, 0.2 mmol, 2.0 equiv), cyclohexyl-Meldrum's acid, MA (18.42 mg, 0.1 mmol, 1.0 equiv), *N*,*N*-diisopropylethylamine (52.0 μL, 0.3 mmol, 3.0 equiv), and CH_3CN (0.5 mL). After the completion of the reaction, the workup method B was used to isolate **2j** in 94% yield as a colorless oil (45.0 mg, 0.09 mmol). ^{19}F NMR (376 MHz, $CDCl_3$): δ −76.6 to −77.0 (m, 1F), −93.4 to −93.6 (m, 1F), −138.1 (t, *J* = 24.6 Hz, 1F). ^1H NMR (400 MHz, $CDCl_3$): δ 3.64−3.50 (m, 2H), 3.04 (qd, *J* = 7.4, 4.0 Hz, 2H), 2.08−1.98 (m, 4H), 1.65 (p, *J* = 6.6 Hz, 4H), 1.50−1.32 (m, 17H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 164.0, 150.8 (ddd, *J* = 239.2, 13.7, 2.5 Hz), 146.9 (ddd, *J* = 243.2, 18.9, 15.2 Hz), 141.5 (ddd, *J* = 252.6, 24.4, 5.9 Hz), 115.4 (dd, *J* = 31.1, 5.9 Hz), 103.0, 71.2, 54.1, 42.4, 35.7, 33.8, 25.0, 22.6 (d, *J* = 22.6 Hz), 18.4, 17.1, 12.2. FT-IR: cm^{-1} 2942,2 1599, 1434, 1216. HRMS (ESI) calcd, $C_{14}H_{10}ClF_3NO_4^-$ 348.0256; observed, 348.0248.

Synthesis of Diethyl 2-(Perfluorophenyl)malonate (3k).



The general procedure D was followed using hexafluorobenzene (138 μL, 1.2 mmol, 1.2 equiv), diethyl malonate (153 μL, 1.0 mmol, 1.0 equiv), K_2CO_3 (414 mg, 3.0 mmol, 3.0 equiv), and DMF (0.6 mL). The crude material was purified by flash chromatography using hexane:ethyl acetate (0% EtOAc for 0−4 cv, 0−10% EtOAc for 4−9 cv, 10% EtOAc for 9−11 cv, 10−100% EtOAc for 11−16 cv, then held at 100% EtOAc 16−18 cv), on 4 g silica column to afford **3a** in 92% yield (300 mg, 0.92 mmol) as a colorless liquid. ^{19}F NMR (376 MHz, $CDCl_3$): δ −139.9 to −140.1 (m, 2F), −153.4 (ddd, *J* = 21.0, 19.1, 1.7 Hz, 1F), −161.6 to −161.8 (m, 2F). ^1H NMR (400 MHz, $CDCl_3$): δ 4.93 (s, 1H), 4.27 (qd, *J* = 7.1, 2.0 Hz, 4H), 1.29 (t, *J* = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 165.3, 145.4 (dtt, *J* = 249.8, 7.6, 3.7 Hz), 141.2 (dtd, *J* = 254.9, 13.4, 6.8 Hz), 139.1−136.0 (m), 108.4 (td, *J* = 17.0, 3.9 Hz), 62.5, 46.9, 13.6. FT-IR: cm^{-1} 2987, 1751, 1508, 1307, 1224. HRMS (ESI) calcd, $C_{13}H_{11}F_5O_4$ 326.0577; observed, 326.0562.

Synthesis of Diethyl 2-(Perfluoro-[1,1′-biphenyl]-4-yl)-malonate (3l).



The general procedure D was followed using decafluorobiphenyl (80.2 mg, 0.24 mmol, 1.2 equiv), diethyl malonate (30.5 μL, 0.2 mmol, 1.0 equiv), K_2CO_3 (83 mg, 0.6 mmol, 3.0 equiv), and DMF (0.6 mL). The crude material was purified by flash chromatography using hexane:ethyl acetate (0% EtOAc for 0−5 cv, 0%−9% EtOAc for 5−10 cv, 9% EtOAc for 10−15 cv, 9%−17% EtOAc for 15−18 cv, 17% EtOAc for 18−22 cv, 17%−100% EtOAc for 22−25 cv, then held at 100% EtOAc 25−27 cv), on 4 g silica column to afford **3l** in 73% yield (69.0 mg, 0.15 mmol) as white crystals. ^{19}F NMR (376 MHz, $CDCl_3$): δ −137.0 (dddd, *J* = 17.4, 11.8, 8.7, 5.8 Hz, 2F), −137.9 to −138.1 (m, 2F), −139.1 to −139.3 (m, 2F), −150.0 (tt, *J* = 20.8, 3.1 Hz, 1F), −160.3 to −160.5 (m, 2F). ^1H NMR (400 MHz, $CDCl_3$): δ 5.05 (s, 1H), 4.32 (qq, *J* = 7.0, 3.6 Hz, 4H), 1.33 (t, *J* = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 165.3, 146.7−143.7 (m), 146.0−143.0 (m), 144.0 (ddt, *J* = 252.0, 14.9, 4.4 Hz), 139.6−138.7 (m), 141.5−136.2 (m), 115.4 (t, *J* = 16.6 Hz), 107.0−101.7 (m), 67.1, 62.8, 47.6, 13.9. mp 83−84 °C. FT-IR: cm^{-1} 2989, 2926, 1739, 1477. HRMS (ESI) calcd, $C_{19}H_{11}F_9O_4$ 474.0514; observed, 474.0523.

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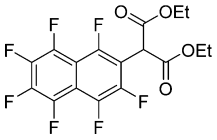
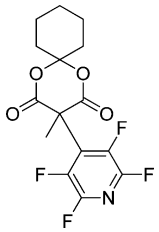
Synthesis of Diethyl 2-(Perfluoronaphthalen-2-yl)malonate (3m).



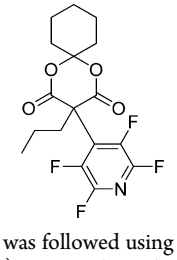
The general procedure D was followed using octafluoronaphthalene (65.3 mg, 0.24 mmol, 1.2 equiv), diethyl malonate (30.5 μL, 0.2 mmol, 1.0 equiv), K_2CO_3 (83 mg, 0.6 mmol, 3.0 equiv), and DMF (0.6 mL). The crude material was purified by flash chromatography using hexane:ethyl acetate (0% EtOAc for 0−4 cv, 0−10% EtOAc for 4−9 cv, 10% EtOAc for 9−11 cv, 10−100% EtOAc for 11−16 cv, then held at 100% EtOAc 16−18 cv), on 4 g silica column to afford **3m** in 75% yield (69.0 mg, 0.15 mmol) as a colorless liquid. ^{19}F NMR (376 MHz, $CDCl_3$): δ −118.8 to −119.3 (m, 1F), −135.2 to −135.5 (m, 1F), −143.3 to −143.8 (m, 1F), −145.6 to −146.1 (m, 1F), −148.1 to −148.6 (m,1F), −152.6 (q, *J* = 20.8 Hz, 1F), −155.2 (d, *J* = 19.4 Hz, 1F). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.13 (s, 1H), 4.30 (q, *J* = 7.3, 6.5 Hz, 4H), 1.30 (t, *J* = 7.1 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 165.6, 152.4−148.9 (m), 147.9−142.6 (m), 145.2−142.2 (m), 141.5−141.0 (m), 140.1−140.0 (m), 140.4−139.7 (m), 139.0−137.0 (m), 112.3−111.7 (m), 152.2−149.2 (m), 111.7−107.4 (m), 62.7, 47.5, 13.9. FT-IR: cm^{-1} 2987, 2942, 1745, 1655, 1497, 1441, 1409, 1181. HRMS (ESI) calcd, $C_{17}H_{11}F_7O_4$ 412.0546; observed, 474.0541.

Synthesis of 3-Methyl-3-(perfluoropyridin-4-yl)-1,5-dioxaspiro[5.5]undecane-2,4-dione (5aa).



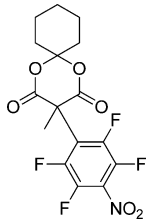
The general procedure E was followed using pentafluoropyridine (54.9 μL, 0.5 mmol, 2.0 equiv), 3-methyl-1,5-dioxaspiro[5.5]undecane-2,4-dione (49.25 mg, 0.25 mmol, 1.0 equiv), *N*,*N*-diisopropylethylamine (130.4 μL, 0.75 mmol, 3.0 equiv), and CH_3CN (0.5 mL). After the completion of the reaction, the workup method B was used to isolate **5aa** in 96% yield as a white solid (83.6 mg, 0.24 mmol). The isolated product contained a mixture of the *para* and *ortho* isomers in 25:1 ratio as determined by the ^{19}F NMR of the isolated material. ^{19}F NMR (376 MHz, $CDCl_3$): δ −89.1 − −89.3 (m, 2F), −138.9 to −139.2 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.25 (t, *J* = 3.0 Hz, 3H), 2.05 (m, 4H), 1.87−1.74 (m, 4H), 1.60−1.50 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 165.6, 145.5−142.5 (m), 142.6−139.5 (m), 129.2 (tt, *J* = 11.7, 2.2 Hz), 109.0, 53.7, 37.5, 24.0 (t, *J* = 6.5 Hz), 23.8, 22.2 (d, *J* = 8.1 Hz). mp 100−101 °C. FT-IR: cm^{-1} 2998, 2947, 1741, 1453, 1261. HRMS (ESI) calcd, $C_{15}H_{13}F_4NO_4$ 347.0781; observed, 347.0772.

Synthesis of 3-(Perfluoropyridin-4-yl)-3-propyl-1,5-dioxaspiro[5.5]undecane-2,4-dione (5ab).



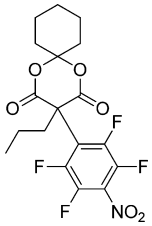
The general procedure E was followed using pentafluoropyridine (54.9 μL, 0.5 mmol, 2.0 equiv), 3-propyl-1,5-dioxaspiro[5.5]undecane-2,4-dione (56.57 mg, 0.25 mmol, 1.0 equiv), *N*,*N*-diisopropylethylamine (130.4 μL, 0.75 mmol, 3.0 equiv), and CH_3CN (0.5 mL). After the completion of the reaction, the workup method B was used to isolate **5ab** in >99% yield as a colorless liquid (94 mg, 0.25 mmol). The isolated product contained a mixture of the *para* and *ortho* isomers in 25:1 ratio as determined by the ^{19}F NMR of the isolated material. ^{19}F NMR (376 MHz, $CDCl_3$): δ −89.0 to −89.5 (m, 2F), −137.5 (dd, *J* = 35.0, 14.9 Hz, 2F). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.60−2.49 (m, 2H), 2.02 (m, 4H), 1.85−1.70 (m, 4H), 1.58−1.41 (m, 4H), 1.01 (t, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR of the mixture (101 MHz, $CDCl_3$): δ 161.8, 160.7, 141.8−138.8 (m), 138.7−135.5 (m), 124.6 (t, *J* = 11.5 Hz), 105.0, 101.7, 35.2 (t, *J* = 5.3 Hz), 34.4 (t, *J* = 2.4 Hz), 33.4, 33.0, 32.1, 20.1, 19.9, 18.6, 18.5, 18.1, 17.8, 16.0, 15.5, 10.0, 9.7. FT-IR: cm^{-1} 2944, 2874, 1746, 1469, 1259. HRMS (ESI) calcd, $C_{17}H_{17}F_4NO_4$ 375.1094; observed, 375.1063.

Synthesis of 3-Methyl-3-(2,3,5,6-tetrafluoro-4-nitrophenyl)-1,5-dioxaspiro[5.5]undecane-2,4-dione (5ca).



The general procedure E was followed using pentafluoronitrobenzene (33.3 μL, 0.275 mmol, 1.1 equiv), 3-methyl-1,5-dioxaspiro[5.5]-undecane-2,4-dione (49.32 mg, 0.25 mmol, 1.0 equiv), *N*,*N*-diisopropylethylamine (130.4 μL, 0.75 mmol, 3.0 equiv), and CH_3CN (0.5 mL). After the completion of the reaction, the workup method B was followed. The crude material was purified by flash chromatography using hexane:ethyl acetate (0% EtOAc for 0−2 cv, 0−10% EtOAc for 2−6 cv, 10% EtOAc for 6−11 cv, 10−100% EtOAc for 11−16 cv, then held at 100% EtOAc 16−18 cv), on 4 g silica column to afford **5ca** in 87% yield (85.0 mg, 0.21 mmol) as a colorless oil. ^{19}F NMR (376 MHz, $CDCl_3$): δ −134.3 (m, 2F), −145.3 to −145.5 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.2 (t, *J* = 3.1 Hz, 3H), 2.1−2.0 (m, 4H), 1.9−1.8 (m, 4H), 1.6−1.5 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 166.0, 146.1 (ddt, *J* = 254.0, 12.9, 5.6 Hz), 140.6 (ddd, *J* = 263.2, 17.5, 3.7 Hz), 120.5 (t, *J* = 13.1 Hz), 109.1, 51.2, 38.1, 37.6, 24.3 (t, *J* = 7.0 Hz), 24.0, 22.4 (d, *J* = 8.6 Hz). FT-IR: cm^{-1} 2947, 1743, 1554, 1305. HRMS (ESI) calcd, $C_{16}H_{13}F_4NO_6$ 391.0679; observed, 391.0665.

Synthesis of 3-Propyl-3-(2,3,5,6-tetrafluoro-4-nitrophenyl)-1,5-dioxaspiro[5.5]undecane-2,4-dione (5cb).



The general procedure E was followed using pentafluoronitrobenzene (33.3 μL, 0.275 mmol, 1.1 equiv), 3-propyl-1,5-dioxaspiro[5.5]-undecane-2,4-dione (49.32 mg, 0.25 mmol, 1.0 equiv), *N*,*N*-diisopropylethylamine (130.4 μL, 0.75 mmol, 3.0 equiv), and CH_3CN (0.5 mL). After the completion of the reaction, the workup method B was followed. The crude material was purified by flash chromatography using hexane:ethyl acetate (0% EtOAc for 0−3 cv, 0−10% EtOAc for 3−7 cv, 10% EtOAc for 7−11 cv, 10−30% EtOAc for 11−15 cv, 30−100% EtOAc for 15−16, then held at 100% EtOAc 16−18 cv), on 4 g silica column to afford **5cb** in 81% yield (84.2 mg, 0.20 mmol) as yellow crystals. ^{19}F NMR (376 MHz, $CDCl_3$): δ −130.9 to −131.7 (m, 2F), −133.3 to −133.7 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.58−2.46 (m, 2H), 2.11−1.92 (m, 4H), 1.86−1.71 (m, 4H), 1.59−1.43 (m, 4H), 1.03 (t, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 165.0, 146.1 (ddt, *J* = 253.7, 13.0, 5.8 Hz), 142.5−139.1 (m), 120.0 (t, *J* = 13.0 Hz), 109.1, 39.3 (t, *J* = 5.7 Hz), 38.4 (t, *J* = 2.3 Hz), 37.5, 24.0, 22.6, 22.2, 19.6, 13.7. mp 99−100 °C. FT-IR: cm^{-1} 2953, 1737, 1253. HRMS (ESI) calcd, $C_{18}H_{17}F_4NO_6H$ 420.1070; observed, 420.1051.

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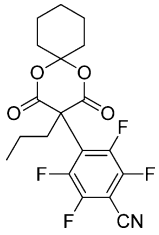
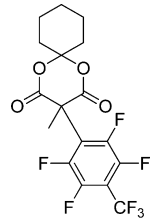
Synthesis of 4-(2,4-Dioxo-3-propyl-1,5-dioxaspiro[5.5]-undecan-3-yl)-2,3,5,6-tetrafluorobenzonitrile (5ib).



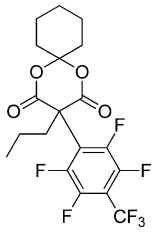
The general procedure E was followed using pentafluorobenzonitrile (34.7 μL, 0.275 mmol, 1.1 equiv), 3-propyl-1,5-dioxaspiro[5.5]-undecane-2,4-dione (49.32 mg, 0.25 mmol, 1.0 equiv), *N*,*N*-diisopropylethylamine (130.4 μL, 0.75 mmol, 3.0 equiv), and CH_3CN (0.5 mL). After the completion of the reaction, the workup method B was followed. The crude material was purified by flash chromatography using hexane:ethyl acetate (0% EtOAc for 0−5 cv, 0−10% EtOAc for 5−25 cv, 10% EtOAc for 25−40 cv, 10−40% EtOAc for 40−60 cv, 40−100% EtOAc for 60−65, then held at 100% EtOAc 65−67 cv), on 4 g silica column to afford **5ib** in 85% yield (85.0 mg, 0.21 mmol) as a colorless oil. ^{19}F NMR (376 MHz, $CDCl_3$): δ −126.7 to −136.0 (m, 2F), −142.2 to −151.4 (m, 2F). ^1H NMR (400 MHz, $CDCl_3$): δ 2.57−2.47 (m, 2H), 2.12−1.95 (m, 4H), 1.87−1.73 (m, 4H), 1.60−1.43 (m, 4H), 1.03 (t, J = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 164.8, 147.5 (ddt, J = 262.8, 17.8, 3.8 Hz), 145.9 (ddt, J = 252.3, 12.6, 5.3 Hz), 122.1 (d, J = 12.9 Hz), 108.9, 106.7 (t, J = 3.7 Hz), 39.1 (t, J = 5.7 Hz), 38.3, 37.4, 23.9, 22.5, 22.1, 19.5, 13.6. FT-IR: cm^{-1} 2944, 1744, 1491. HRMS (ESI) calcd, $C_{19}H_{17}F_4NO_4$ 399.1094; observed, 399.1081.

Synthesis of 3-Methyl-3-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-1,5-dioxaspiro[5.5]undecane-2,4-dione (5ba).



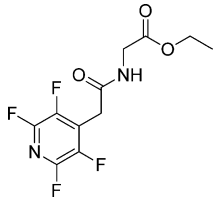
The general procedure E was followed using octafluorotoluene (70.8 μL, 0.50 mmol, 2.0 equiv), 3-methyl-1,5-dioxaspiro[5.5]undecane-2,4-dione (49.32 mg, 0.25 mmol, 1.0 equiv), *N*,*N*-diisopropylethylamine (130.4 μL, 0.75 mmol, 3.0 equiv), and CH_3CN (0.5 mL). After the completion of the reaction, the workup method B was followed. The crude material was purified by flash chromatography using hexane:ethyl acetate (0% EtOAc for 0−6 cv, 0−10% EtOAc for 6−23 cv, 10% EtOAc for 23−35 cv, 10−100% EtOAc for 35−45 cv, then held at 100% EtOAc 45−47 cv), on 4 g silica column to afford **5ba** in 80% yield (83.0 mg, 0.20 mmol) as a white solid. ^{19}F NMR (376 MHz, $CDCl_3$): δ −56.6 (t, J = 21.4 Hz, 3F), −136.0 to −136.2 (m, 2F), −139.2 to −139.5 (m, 2F). ^1H NMR (400 MHz, $CDCl_3$): δ 2.24 (t, J = 3.0 Hz, 3H), 2.12−2.00 (m, 4H), 1.86−1.75 (m, 4H), 1.58−1.50 (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 166.1, 146.0 (ddt, J = 251.2, 14.8, 5.2 Hz), 144.4 (dd, J = 261.6, 17.5 Hz), 121.8, 120.4 (t, J = 13.0 Hz), 119.0, 108.8, 37.9, 37.6, 24.2 (t, J = 6.9 Hz), 23.9, 22.2 (d, J = 8.2 Hz). mp 100−102 °C. FT-IR: cm^{-1} 2944, 2856, 1736, 1142. HRMS (ESI) calcd, $C_{17}H_{13}F_7O_4H$ 415.0780; observed, 414.0792.

Synthesis of 3-Propyl-3-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-1,5-dioxaspiro[5.5]undecane-2,4-dione (5bb).



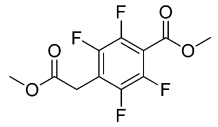
The general procedure E was followed using octafluorotoluene (70.8 μL, 0.50 mmol, 2.0 equiv), 3-propyl-1,5-dioxaspiro[5.5]undecane-2,4-dione (49.32 mg, 0.25 mmol, 1.0 equiv), *N*,*N*-diisopropylethylamine (130.4 μL, 0.75 mmol, 3.0 equiv), and CH_3CN (0.5 mL). After the completion of the reaction, the workup method B was followed. The crude material was purified by flash chromatography using hexane:ethyl acetate (0% EtOAc for 0−2 cv, 0−10% EtOAc for 2−6 cv, 10% EtOAc for 6−8 cv, 10−15% EtOAc for 8−10 cv, 15−100% EtOAc for 10−12 cv, then held at 100% EtOAc 12−14 cv), on 4 g silica column to afford **5bb** in 79% yield (88.3 mg, 0.19 mmol) as a colorless oil. ^{19}F NMR (376 MHz, $CDCl_3$): δ −56.7 (t, J = 21.3 Hz, 3F), −134.4 to −134.9 (m, 2F), −139.0 to −139.6 (m, 2F). ^1H NMR (400 MHz, $CDCl_3$): δ 2.53−2.41 (m, 2H), 2.05−1.89 (m, 4H), 1.82−1.65 (m, 4H), 1.53−1.36 (m, 4H), 0.96 (t, J = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 165.3, 147.7−144.6 (m), 146.4−143.0 (m), 120.0 (t, J = 12.9 Hz), 111.1−110.2 (m), 108.9, 39.4 (t, J = 5.6 Hz), 38.4 (t, J = 2.5 Hz), 37.6, 24.1, 22.6, 22.2, 19.6, 13.8. FT-IR: cm^{-1} 2946, 2875, 1747, 1492, 13334. HRMS (ESI) calcd, $C_{19}H_{17}F_7O_4H$ 443.1093; observed, 443.1095.

Synthesis of Ethyl 2-(2-(Perfluoropyridin-4-yl)acetamido)-acetate (6aa).



The general procedure E was followed using **2a** (46.2 mg, 0.1 mmol, 1.0 equiv) and ethyl 2-aminoacetate hydrochloride (41.9 mg, 0.3 mmol, 3.0 equiv) and dioxane (1.0 mL) to obtain **6aa** in 94% yield (55.0 mg, 0.09 mmol) as an off-white solid. ^{19}F NMR (376 MHz, $CDCl_3$): δ −91.0 to −91.3 (m, 2F), −143.4 to −143.6 (m, 2F). ^1H NMR (400 MHz, $CDCl_3$): δ 4.20 (q, J = 7.2 Hz, 2H), 4.03 (d, J = 5.1 Hz, 2H), 3.81 (s, 2H), 1.26 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 169.7, 166.1, 144.8−141.7 (m), 142.4−141.8 (m), 128.0 (tt, J = 16.7, 2.9 Hz), 61.9, 41.8, 30.4, 14.1. mp 90−92 °C. FT-IR: cm^{-1} 3316, 2997, 1741, 1459, 1225. HRMS (ESI) calcd, $C_{11}H_{10}F_4N_2O_3$ 294.0628; observed, 294.0642.

Synthesis of Methyl 2,3,5,6-Tetrafluoro-4-(2-methoxy-2-oxoethyl)benzoate (6dd).



For the monitoring purposes, this reaction was carried out in an NMR tube and monitored via ^{19}F NMR. An NMR tube was charged with **2d** (100 mg, 0.2 mmol, 1.0 equiv), and HCl (36% w/v, 20.6 μL, 0.24 mmol, 1.2 equiv) and methanol (0.5 mL) were added, and a sealed glass capillary containing C_6D_6 was placed in the NMR tube for locking purposes. The NMR tube then was placed in a sand bath and maintained at 80 °C. The reaction was periodically monitored by ^{19}F NMR. After the completion of the reaction, methanol was removed in vacuo, and the resulting residue was dissolved in DCM (2 mL) and washed with deionized water (3 × 5 mL). The organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo to obtain

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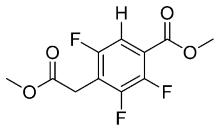
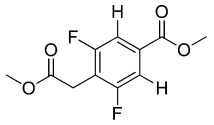
the title compound **6dd** in 95% yield (53.0 mg, 0.19 mmol) as a colorless liquid. ^{19}F NMR (376 MHz, $CDCl_3$): δ −139.7 to −139.9 (m, 2F), −141.4 to −141.5 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.98 (s, 3H), 3.80 (t, J = 1.6 Hz, 2H), 3.75 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 168.2, 160.0, 145.1 (ddt, J = 248.6, 14.3, 5.1 Hz), 144.4 (ddt, J = 256.5, 15.4, 4.6 Hz), 116.5 (t, J = 18.2 Hz), 111.8 (t, J = 15.9 Hz), 53.2, 52.7, 28.2. FT-IR: cm^{-1} 2960, 1742, 1485, 1310. HRMS (ESI) calcd, $C_{11}H_8F_4O_4$ 280.0359; observed, 280.0382.

Synthesis of Methyl 2,3,5-Trifluoro-4-(2-methoxy-2-oxoethyl)benzoate (6de).



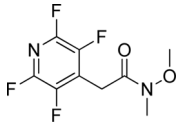
The general procedure F was followed using methyl 2,3,5,6-tetrafluoro-4-(2-methoxy-2-oxoethyl)benzoate (**6dd**) (28.0 mg, 0.1 mmol, 1.0 equiv) and *N*,*N*-diisopropylethylamine (19.2 μL, 0.11 mmol, 1.1 equiv). After the completion of the reaction, the crude material was purified by flash chromatography using hexane:ethyl acetate (0% EtOAc for 0−1 cv, 0−11% EtOAc for 1−3 cv, 11% EtOAc for 3−4 cv, 11−22% EtOAc for 4−5 cv, 22−100% EtOAc for 5−8 cv, then held at 100% EtOAc 8−10 cv), on 4 g silica column to afford **6de** in 94% yield (25.0 mg, 0.09 mmol) as a colorless oil. The isolated product also contained 2% starting material and 4% dihydrodefluorinated product. ^{19}F NMR (376 MHz, $CDCl_3$): δ −118.7 to −118.8 (m, 1F), −135.0 (d, J = 20.3 Hz, 1F), −139.0 (ddd, J = 20.7, 16.1, 5.1 Hz, 1F). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43−7.36 (m, 1H), 3.88 (s, 3H), 3.71 (s, 2H), 3.67 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 168.7, 163.0 (q, J = 3.4 Hz), 155.6 (ddd, J = 246.5, 6.5, 3.5 Hz), 149.9 (ddd, J = 251.4, 15.0, 8.1 Hz), 147.0 (ddd, J = 259.8, 14.5, 3.8 Hz), 119.3 (t, J = 8.9 Hz), 117.2 (dd, J = 22.2, 16.8 Hz), 112.3 (dd, J = 26.1, 3.8 Hz), 52.9, 52.6, 28.4−28.3 (m). FT-IR: cm^{-1} 2958, 1742, 1468, 1265. HRMS (ESI) calcd, $C_{11}H_9F_3O_4$ 262.0453; observed, 262.0469.

Synthesis of Methyl 3,5-Difluoro-4-(2-methoxy-2-oxoethyl)-benzoate (6df).



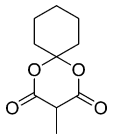
The general procedure F was followed using methyl-2,3,5,6-tetrafluoro-4-(2-methoxy-2-oxoethyl)benzoate (**6dd**) (26.5 mg, 0.09 mmol, 1.0 equiv) and *N*,*N*-diisopropylethylamine (99.0 μL, 0.57 mmol, 6.0 equiv). After the completion of the reaction, the crude material was purified by passing through a short silica plug to afford **6df** in 92% yield (23.2 mg, 0.08 mmol) as a colorless oil. ^{19}F NMR (376 MHz, $CDCl_3$): δ −112.9 (d, J = 7.3 Hz, 2F). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60−7.54 (m, 2H), 3.92 (s, 3H), 3.75 (s, 2H), 3.72 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 164.8 (t, J = 3.3 Hz), 161.1 (dd, J = 249.6, 7.9 Hz), 131.6 (t, J = 9.5 Hz), 115.5 (t, J = 20.4 Hz), 112.4 (d, J = 27.1 Hz), 112.4 (d, J = 12.5 Hz), 52.6, 52.5, 28.0. FT-IR: cm^{-1} 2957, 1730, 1586, 1430. HRMS (ESI) calcd, $C_{11}H_{10}F_2O_4$ 244.0547; observed, 244.0529.

Synthesis of *N*-Methoxy-*N*-methyl-2-(perfluoropyridin-4-yl)-acetamide (6ac).



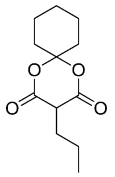
The general procedure E was followed using **2a** (23.1 mg, 0.05 mmol, 1.0 equiv) and *N*,*O*-dimethylhydroxylamine hydrochloride (11.8 mg, 0.12 mmol, 2.4 equiv) and dioxane (0.5 mL) to obtain **6ac** in 90% yield (11.3 mg, 0.04 mmol) as a yellow liquid. ^{19}F NMR (376 MHz, $CDCl_3$): δ −91.0 to −91.3 (m, 2F), −143.6 to −143.9 (m, 2F). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.98 (s, 2H), 3.81 (s, 3H), 3.25 (s, 3H). FT-IR: cm^{-1} 2937, 1710, 1471, 1047. HRMS (ESI) calcd, $C_9H_8F_4N_2O_2$ 252.0522; observed, 252.0529.

Synthesis of 3-Methyl-1,5-dioxaspiro[5.5]undecane-2,4-dione (4a).



The general procedure G was followed using formic acid (186 μL, 4.93 mmol), cyclohexyl-Meldrum's acid (1.0 g, 5.43 mmol), DMAP (60 mg, 0.49 mmol), *N*,*N*-diisopropylethylamine (1.8 mL, 10.6 mmol), DCC (1.4 g, 5.43 mmol), acetic acid (2.8 mL, 49.3 mmol), $NaBH_4$ (466 mg, 12.3 mmol), and MeCN (25 mL). The crude material was purified by flash chromatography using hexane:ethyl acetate (0% EtOAc for 0−5 cv, 0−12% EtOAc for 5−15 cv, 12% EtOAc for 15−25 cv, 12−50% EtOAc for 25−30 cv, 50−100% EtOAc for 30−37 cv, then held at 100% EtOAc 37−39 cv), on 40 g silica column to afford **4a** in 71% yield (971 mg, 3.5 mmol) as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.61 (q, J = 7.1 Hz, 1H), 2.07−1.91 (m, 4H), 1.84−1.64 (m, 4H), 1.63−1.46 (m, 5H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 166.1, 105.6, 41.4, 36.9, 35.1, 24.0, 22.5, 21.8, 10.6, which matched with the literature.[31]

Synthesis of 3-Propyl-1,5-dioxaspiro[5.5]undecane-2,4-dione (4b).



The general procedure G was followed using propionic acid (369 μL, 4.93 mmol), cyclohexyl-Meldrum's acid (1.0 g, 5.43 mmol), DMAP (60 mg, 0.49 mmol), *N*,*N*-diisopropylethylamine (1.8 mL, 10.6 mmol), DCC (1.4 g, 5.43 mmol), acetic acid (2.8 mL, 49.3 mmol), and $NaBH_4$ (466 mg, 12.3 mmol). The crude material was purified by flash chromatography using hexane:ethyl acetate (0% EtOAc for 0−3 cv, 0−9% EtOAc for 3−11 cv, 9% EtOAc for 11−30 cv, 9−35% EtOAc for 30−37 cv, 35% EtOAc for 37−45 cv, 35−70% EtOAc for 45−50 cv, 70% EtOAc for 50−55 cv, 70−100% EtOAc for 55−65 cv, then held at 100% EtOAc 65−67 cv), on 40 g silica column to afford **4b** in 92% yield (1.0 g, 4.5 mmol) as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.51 (t, J = 5.1 Hz, 1H), 2.11−2.03 (m, 2H), 2.03−1.89 (m, 4H), 1.83−1.62 (m, 4H), 1.55−1.39 (m, 4H), 0.96 (t, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 165.6, 105.5, 46.1, 36.8, 35.7, 28.6, 24.0, 22.5, 21.7, 19.7, 13.8, which matched with the literature.[31]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Spectra and additional experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(18) Our tentative assignment of the N-arylated product is one in which the amine has undergone arylation and dealkylation. The N-substitution occurs at the same site as the MA addition.
(19) For details, please see the Supporting Information.
(20) Substrate **2i** was performed on a 1 g scale, ∼5× the scale of **2a**, and the product was obtained in an excellent yield, suggesting that the reaction may scale well.
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