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Ligand Promoted Olefination of Anilides for Indirectly Introducing Fluorinated Functional Groups via Palladium Catalyst

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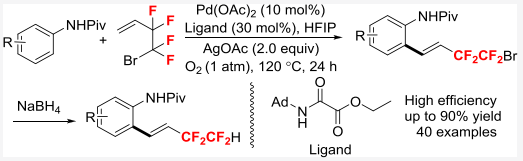
ABSTRACT: We report a palladium-catalyzed, ligand promoted, C−H fluorine-containing olefination of anilides with 4-bromo-3,3,4,4-tetrafluorobutene as the fluorinated reagent, which has a potential transformation into other compounds due to its -CF_2CF_2Br functional group. -CF_2CF_2H was obtained by using the mild reducing agent sodium borohydride. Bioactive compounds such as aminoglutethimide derivative and propham were well-tolerated in this reaction, both of which highlight the synthetic importance of this method.

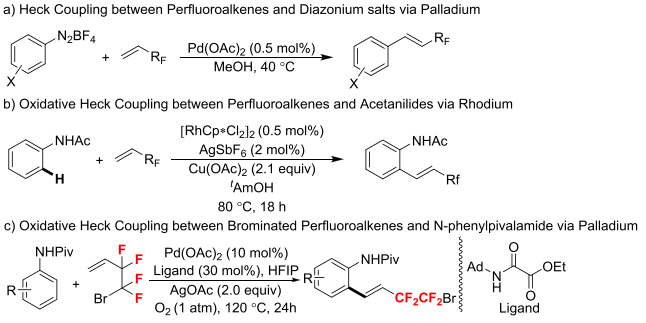


INTRODUCTION

Organofluorinated compounds have important applications in pharmaceuticals, agrochemicals, and in material science.[1] Due to the unique electronic characteristics of the fluorine atom/ion, it affects the distribution of the electron cloud within a molecule as well as the dipole moment, acidity, and alkalinity. Incorporation of fluorine makes agriculture products more productive and drugs more efficient; a specific example includes the antitumor drug epothilone B. In 2003, Danishefsky and coworkers reported the synthesis of the 12-trifluoromethyl derivative of epothilone B from trifluoromethyl building blocks. Studies have shown that the trifluoromethylated derivatives of epothilone B have higher antitumor activity.[2] Consequently, the development of efficient methods for introducing organofluorine compounds is extremely valuable in synthetic chemistry.

Several methodologies for introducing fluorine groups to aromatics and heterocyclics have been extensively explored.[3] Functional groups such as **F**,[4] $\mathbf{CF_3}$,[5] $\mathbf{CF_2CONR_2}$,[6] and $\mathbf{CF_2COOR}$[7] are immensely popular fluorinated moieties to introduce onto prefunctionalized arenes or alkenes and rely on metal-mediated cross-coupling reactions. These groups have great appeal for researchers because of the significant potential for postfunctionalization. In 2001 Genêt demonstrated an efficient access to introduce perfluorinated tails onto aromatic rings by Heck reaction between perfluoroalkenes and arenediazonium salts catalyzed by palladium, followed by hydrogenation of the double bond[8] (Scheme 1a). In 2016, Uchiyama and colleagues[9] developed an efficient Rh-catalyzed (perfluoroalkyl) olefination reaction of acetanilides under slightly modified Glorius[10] olefination conditions. R_F-anilides with the saturated C2 spacer were obtained in the presence of a catalytic amount of Pd/C under atmospheric pressure of H_2 gas (Scheme 1b). Aniline is usually the key skeleton of a variety of important compounds and often plays an important role in dye work, drug production, and pesticide synthesis. As impressed by Uchiyama's work, looking for R_F-anilides with potential transformations is important and attractive. One relatively inexpensive fluorinated reagent, 4-bromo-3,3,4,4-tetrafluorobutene, reported by Maiti[11] previously, has potential application due to its -CF_2CF_2Br functional group that could ring on other kinds of compounds.[12]

Scheme 1. Synthetic Approaches towards Organofluorinated Compounds



Although ortho-selective olefination of anilides via palladium catalysis has been studied previously by de Vries and van Leeuwen,[13] the introduction of fluorine groups onto aromatic compounds via a palladium-catalyzed C−H fluorine-containing olefination[14] of anilides has not been reported. Herein, we report the development of a synthetic pathway for the introduction of fluorine groups onto aromatic compounds via a palladium-catalyzed, ligand promoted C−H fluorine-containing olefination of anilides with 4-bromo-3,3,4,4-tetrafluorobutene as the coupling reagent. Various anilides

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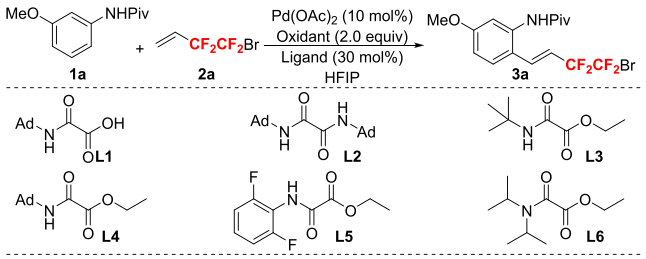
were treated and showed good tolerance, yielding the corresponding fluorinated products in moderate to good yields. More importantly, some molecules possessing drug activity, such as aminoglutethimide and propham, were fluorinated by 4-bromo-3,3,4,4-tetrafluorobutene; this indicated that such an indirect fluorination approach might have broad potential in pharmaceutical research.

RESULTS AND DISCUSSION

We began our study by investigating the role of different ligands; we selected *N*-(3-methoxyphenyl)pivalamide (**1a**) as the model substrate, 4-bromo-3,3,4,4-tetrafluorobutene as the fluorinated reagent, palladium acetate as the catalyst, and AgOAc as the oxidant, and the reaction ran for 24 h at 120 °C in HFIP. To our delight, **3a** was obtained in 41% yield (Table 1, entry 1). Several acid additives such as PivOH, MesCOOH, and $(BuO)_2POOH$ were tested; however, none improved the yield of **3a** (Table 1, entries 2−4). Using the well-known ligand *N*-Ac-Gly-OH[15] improved the yield to 45%, while Ad-substituted oxalic amide with a free carboxylic acid group (ligand 1) afforded **3a** in 48% yield (Table 1, entries 5 and 6). Inspired by these results, ligands derived from oxalyl chloride were examined, and the result showed that ligand 4 proceeded smoothly for this transformation (Table 1, entries 7−11), leading to the desired product **3a** in 61% yield. Next, oxidants like Ag_2CO_3, $Cu(OAc)_2$, and PhIOAc were examined (Table 1, entries 12−14), but none afforded a higher yield than AgOAc. Interestingly, a slightly improved yield of **3a** was obtained when the reaction was performed under oxygen (Table 1, entries 15 and 16). This might be because oxygen acted as a co-oxidant to oxidize Pd(0) to Pd(II) during the catalytic cycle.[16] However, when copper with oxygen or Cu/AgOAc with oxygen was used as oxidant, we could hardly obtain the target product (Table 1, entries 17 and 18). A control experiment showed that the palladium catalyst played a crucial role in this transformation along with the recovered starting material (Table 1, entry 19).

With the optimized reaction conditions in hand, we subsequently examined the substrate scope of various substituted *N*-phenylpivalamides (Table 2) under optimized conditions: catalyst, $Pd(OAc)_2$; oxidant, AgOAc; **L4** as the ligand in HFIP at 120 °C for 24 h under oxygen atmosphere. A wide variety of *N*-phenylpivalamides were well-tolerated, leading to the corresponding fluorinated products in moderate to good yields. Both electron-withdrawing and electron-donating functional groups such as Me, MeO, F, Cl, CF_3, and COOMe all worked well for this reaction. The para-substituted *N*-phenylpivalamides (**1b**−**1h**) reacted well, affording the corresponding products in moderate to good yields (**3b**−**3h**, 51−79%) along with recovery of the starting material. It is worth noting the diolefinated product (**3h**) can be obtained when the sterically hindered functional group *tert*-butyl was applied. The fluorine-containing alkenylation

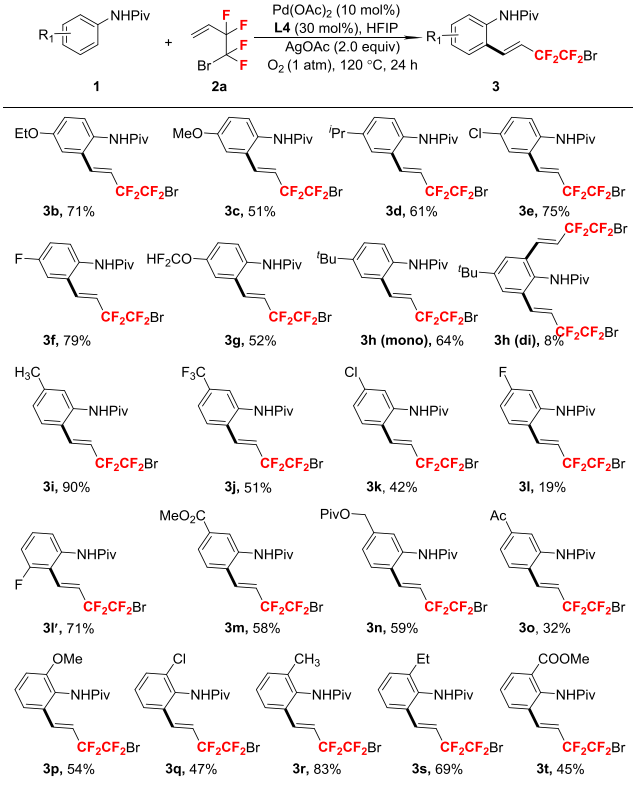
Table 1. Optimization of Reaction Conditions[a]



entry	oxidant	ligand	yield (%)
1	AgOAc		41
2	AgOAc	PivOH	43
3	AgOAc	MesCOOH	15
4	AgOAc	$(BuO)_2POOH$	nr
5	AgOAc	*N*-Ac-Gly-OH	45
6	AgOAc	**L1**	48
7	AgOAc	**L2**	56
8	AgOAc	**L3**	48
9	AgOAc	**L4**	61
10	AgOAc	**L5**	47
11	AgOAc	**L6**	45
12	PhIOAc	**L4**	trace
13	Ag_2CO_3	**L4**	35
14	$Cu(OAc)_2$	**L4**	trace
15[b]	$Cu(OAc)_2$	**L4**	31
16[b]	AgOAc	**L4**	72
17[b]	Cu	**L4**	nr
18[b]	Cu/AgOAc	**L4**	trace
19[c]	AgOAc	**L4**	nr

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $Pd(OAc)_2$(10 mol %), oxidant (2 equiv), ligand (30 mol %), solvent (0.5 mL) at 120 °C in an oil bath for 24 h in a sealed tube. [b]O_2 (1 atm) was added. [c]No $Pd(OAc)_2$. Key: pivalic acid (PivOH), 2,4,6-trimethylbenzoic acid (MesCOOH), *N*-acetylglycine (*N*-Ac-Gly-OH), hexafluoroisopropanol (HFIP), $AdNH_2$ = diamantadine.

Table 2. Substrate Scope of Monosubstituted Anilines[a]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $Pd(OAc)_2$ (10 mol %), AgOAc (2 equiv), **L4** (30 mol %), in HFIP (0.5 mL) at 120 °C in an oil bath for 24 h under O_2 atm in a sealed tube.

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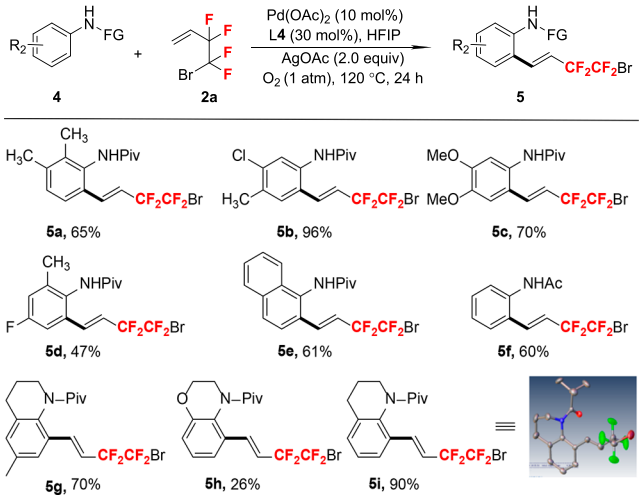
products were obtained in reasonable to good yields for substrates containing either electron-donating or -withdrawing groups at the meta position of the benzene ring (**3i**–**3o**) with the highest yield obtained using a methyl functional group (**3i**, 90%). It is worth noting that when the functional group was F, the fluoroolefin could be introduced onto the C2 position (**3l′**) in 71% yield and the C6 position (**3l**) in 19% yield. Further studies revealed that ortho-substituted (**3p**–**3t**) products performed equally well and led to the fluorine-containing alkenylation products in 45–83% yields.

We subsequently broadened the scope of aniline substrates to disubstituted *N*-phenylpivalamides, *N*-phenylacetamide, and tetrahydroquinolines (Table 3), and to our delight, they all

Table 3. Substrate Scope of Disubstituted and Other Anilines[a]

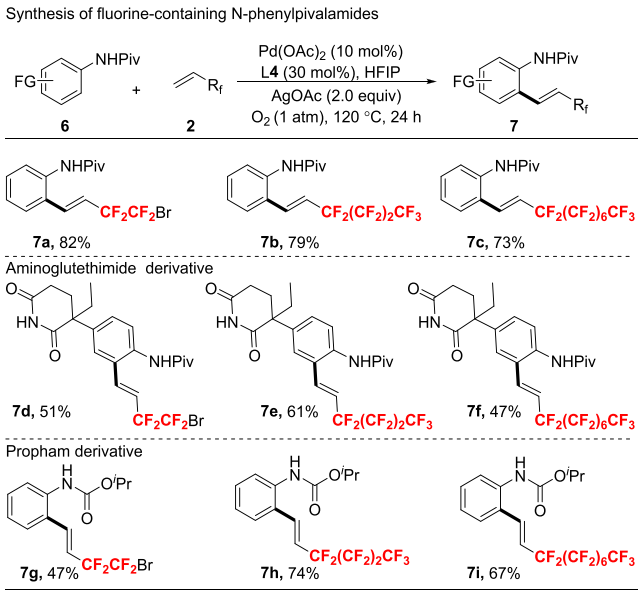


[a]Reaction conditions: **4** (0.2 mmol), **2a** (0.4 mmol), $Pd(OAc)_2$(10 mol %), AgOAc (2 equiv), **L4** (30 mol %), in HFIP (0.5 mL) at 120 °C in an oil bath for 24 h under O_2 atmosphere in a sealed tube.

worked well under these optimized reaction conditions. Disubstituted *N*-phenylpivalamides gave corresponding fluorinated products in moderate to good yields (**5a**–**5d**) along with the recovered starting material. For *N*-(naphthalen-1-yl)-pivalamide (**5e**) and *N*-phenylacetamide (**5f**), the fluorinated olefin products were obtained in 61 and 60% yields, respectively. Finally, tetrahydroquinolines were examined for their tolerance to this reaction due to their great value in medicinal chemistry;[17] they serve as intermediates in medicinal, pesticide, and chemical industries and some are also found in several well-known drugs such as oxamniquine and argatroban. Therefore, we selected several tetrahydroquinolines as substrates for fluorine-containing alkenylation. To our relief, tetrahydroquinoline substrates with a trimethylacetyl group as the protecting group smoothly underwent fluorine-containing alkenylation. Among them, a trimethylacetyl-protected tetrahydroquinoline (**4i**) resulted in the target product (**5i**) with a yield of 90% and afforded a crystal of **5i** which was used to unambiguously confirm its structure and the transformation. Unfortunately, a trimethylacetyl-protected benzomorpholine only formed **5h** in poor yield (26%).

We further investigated the substrate scope concerning various fluoroolefins by reacting them with *N*-phenylpivalamide under standard conditions (Scheme 2). As expected, olefins with varying fluoroalkyl chains were compatible and led

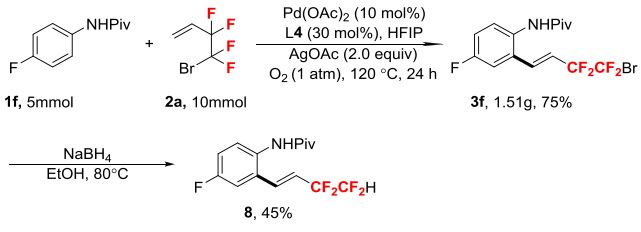
Scheme 2. Substrate Scope of Fluoroolefins



to the formation of the corresponding products in good yields (73–82%). Substrates like perfluorobutylethylene and perfluorooctylethylene performed well in this reaction, and those reactions yielded the corresponding products in 79% (**7b**) and 73% (**7c**) yields, respectively. In addition, drugs like aminoglutethimide and propham were also examined. Aminoglutethimide[18] is a kind of adrenal cortex hormone inhibitor and antitumor drug; it inhibits the lyase system that converts cholesterol to pregnenolone, thereby blocking the synthesis of adrenal cortex hormones. Furthermore, it inhibits the production of estrogen by blocking aromatase, thereby reducing the promoting effect of estrogen on breast cancer and inhibiting tumor growth. Propham is a kind of pesticide[19] that is widely used to control annual gramineous weeds in soybean, sugar beet, cotton, vegetable, and tobacco fields. To our delight, the aminoglutethimide derivative and propham were both compatible with this reaction. The aminoglutethimide took place under standard reaction conditions and afforded the desired fluorinated products in yields ranging from 47 to 61%. Subsequent testing indicated yields of the corresponding fluorinated products as 47% (**7g**), 74% (**7h**), and 67% (**7i**) when propham was used under those same standard conditions.

To further demonstrate the synthetic utility of our procedure, a gram-scale reaction was explored (Scheme 3), and a yield of 75% was obtained (1.51 g) of the corresponding fluorinated product (**3f**) when *N*-(4-fluorophenyl)pivalamide (**1f**) was used as the substrate under standard conditions. The next step in this reaction yielded the target product *N*-(4-

Scheme 3. Gram-Scale Reaction Conditions



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fluoro-2-(3,3,4,4-tetrafluorobut-1-en-1-yl)phenyl)-pivalamide (**8**) in 45% yield using the mild reducing agent sodium borohydride.

CONCLUSIONS

In conclusion, we report a C−H fluorine-containing olefination of anilides with the fluorocarbon compound 4-bromo-3,3,4,4-tetrafluorobutene and catalyzed by palladium(II). This reaction is atom-economic, and a variety of fluorinated products were obtained in high yields based on this process. Compounds like aminoglutethimide and propham were modified by fluorinated olefins from this reaction which have potential application in pharmaceutical research due to the -CF_2CF_2Br functional group. Also, -CF_2CF_2H can be obtained from -CF_2CF_2Br by using the mild reducing agent, sodium borohydride, and more transformations may be conducted using the -CF_2CF_2Br functional group.

EXPERIMENTAL SECTION

General. Unless otherwise noted, all reagents were purchased from commercial suppliers and used without further purification. Column chromatography purifications were performed using 200−300 mesh silica gel. NMR spectra were recorded on Varian Inova 400 MHz, Inova 300 MHz, Bruker DRX 400, or Bruker DRX 500 instruments and calibrated using residual solvent peaks as internal reference. Multiplicities are recorded as s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, td = triplet of doublets, m = multiplet. HRMS analysis was carried out using a Bruker microTOF-Q instrument or a TOF-MS instrument. X-ray crystallographic data were collected with a Bruker D8 Quest CCD instrument equipped with graphite-monochromated Mo Kα radiation.

General Procedure for the Compounds ***1a−1t, 4b−4i, 6a, and 6d.***[20] To a stirred solution of anilines (5 mmol, 1.0 equiv) and triethylamine (15 mmol, 2.1 mL, 3.0 equiv) in anhydrous CH_2Cl_2 (10 mL), pivaloyl chloride (6 mmol, 0.74 mL, 1.2 equiv) was added dropwise under an ice bath at 0 °C. After stirring at room temperature, the mixture was quenched with water and extracted by CH_2Cl_2. The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure to afford the crude compounds. The crude products were purified by column chromatography to obtain the desired products. (Note: for synthesis of **1n**, double pivaloyl chloride was added.)

General Procedure for the Synthesis of the Compound ***4a.***[21] The reactions were carried out in a one-neck round-bottom flask. 2,3-Dimethylaniline (5.0 mmol, 0.6 mL, 1.0 equiv) and Na_2CO_3 (10.0 mmol, 1.06 g 2.0 equiv) were added to a vigorously stirred mixture of CH_2Cl_2 (5 mL) and H_2O (5 mL). A reflux condenser was attached to the flask, and pivaloyl chloride (10.0 mmol, 1.2 mL, 2.0 equiv) was slowly added by syringe through the condenser while maintaining vigorous stirring. The flask was lowered into an oil bath heated to 80 °C, and the reaction mixture was stirred for 2 h. After cooling to room temperature, CH_2Cl_2 (10 mL) and 1 N NaOH (10 mL) were added. The layers were separated, and the organic layer was washed with H_2O (2 × 10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was subsequently purified by silica gel chromatography (PE/EA = 10/1) or recrystallization.

General Procedure for the Synthesis of ***L1, L3, and L4.***[22] Diamantadine hydrochloride or *tert*-butylamine (5 mmol, 1.0 equiv) and triethylamine (15 mmol, 2.1 mL, 3.0 equiv) were added to dichloromethane (20 mL) solution, and the reaction was stirred in an ice bath for 10 min. A mixture of ethyl oxalyl monochloride (6 mmol, 0.67 mL, 1.2 equiv) and dichloromethane (5 mL) was then added to the solution slowly under cooling with an ice−water bath, and the resulting mixture was stirred at room temperature overnight. Then, water (20 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was washed with brine (2 × 5 mL) and dried over anhydrous Na_2SO_4, and all of the volatiles were evaporated under reduced pressure. The resulting residue was purified by column chromatography (PE/EA = 10/1) on silica gel to give the product.

L4 (2 mmol, 0.56 g, 1.0 equiv) was dissolved into EtOH (5 mL) and H_2O (5 mL), and NaOH (2.4 mmol, 96 mg, 1.2 equiv) was added. The reaction was stirred for 3 h at room temperature, detected by TLC. Then, the mixture was acidified by 4 M HCl and extracted by CH_2Cl_2 (3 × 5 mL). The combined organic extract was washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give the product (**L1**).

General Procedure for the Synthesis of ***L2.***[23] Diamantadine hydrochloride (21 mmol, 4.53 g, 2.1 equiv) and triethylamine (50 mmol, 6.9 mL, 5.0 equiv) were added to dichloromethane (50 mL) solution, and the reaction was stirred in an ice bath for 10 min. A mixture of oxaloyl chloride (10 mmol, 0.85 mL, 1.0 equiv) and dichloromethane (20 mL) was then added to the solution slowly under cooling with an ice−water bath, and the resulting mixture was stirred at room temperature overnight. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was washed with brine (2 × 5 mL) and dried over anhydrous Na_2SO_4, and all of the volatiles were evaporated under reduced pressure. The resulting residue was purified by column chromatography (PE/EA = 10/1) on silica gel to give the product.

General Procedure for the Synthesis of ***L5.***[24] 2,6-Difluoroaniline (20 mmol, 2.2 mL, 1.0 equiv) and dry triethylamine (40 mmol, 5.6 mL, 2.0 equiv) were dissolved in dry THF (10 mL) under nitrogen. This solution was cooled to 0 °C, and ethyl chlorooxoacetate (24 mmol, 2.7 mL, 1.2 equiv) was added dropwise. Precipitation of a white solid (triethylamonium chloride) occurred immediately upon addition. The suspension was allowed to stir for 16 h, warming to room temperature. The solid was filtered off and washed with diethyl ether (40 mL), and the combined organic layer was washed with an aqueous saturated NH_4Cl solution until pH 6. This organic layer was then washed with brine (30 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure, leaving a yellow solid that was washed with hexanes (3 × 3 mL) to afford a yellowish crystalline solid.

General Procedure for the Synthesis of ***L6.***[25] *N,N*-Diisopropylethylamine (1 mmol, 165 μL), ethanol (1 mL), and 10 mol % Pd/C as a catalyst in a 100 mL stainless steel autoclave. Then, 9 mL of acetonitrile was added as a solvent, and the autoclave was closed tightly and pressurized with oxygen (1 atm) and CO (5 atm) at 100 °C for 24 h. The mixture was stirred with a mechanical stirrer with 450 rpm. After the completion of the reaction, the autoclave cooled to room temperature, and the remaining pressure was removed carefully. The reactor vessel was opened, and the catalyst was separated using a centrifuge tube. Then, the residue was concentrated by a rotary evaporator. Finally, the crude product was purified by column chromatography.

General Procedure for the Synthesis of Compounds ***3, 5, and 7.*** A mixture of *N*-phenylpivalamides (0.2 mmol, 1.0 equiv), fluorinated olefin (0.4 mmol, 2.0 equiv), $Pd(OAc)_2$ (0.02 mmol, 4.5 mg, 10 mol %), AgOAc (0.4 mmol, 67 mg, 2.0 equiv), **L4** (0.06 mmol, 8.4 mg, 0.3 equiv), and HFIP (0.5 mL) in a 15 mL glass vial sealed under oxygen atmosphere was heated at 120 °C in an oil bath for 24 h. The reaction mixture was cooled to room temperature, filtered through a pad of Celite, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to give the pure product.

General Procedure for Gram-Scale Reaction. A mixture of **1f** (5 mmol, 1.0 equiv, 0.98g), **2** (10 mmol, 2.0 equiv, 1.5 mL), $Pd(OAc)_2$ (10 mol %, 0.11g), AgOAc (10 mmol, 2.0 equiv, 1.67g), Ligand 4 (1.5 mmol, 0.3 equiv, 0.38g) and HFIP (15 mL) in a 100 mL round bottomed flask glass was refluxed at 120 °C in an oil bath for 48 h under oxygen. After cooling to room temperature, the reaction mixture was filtered through a pad of Celite and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to give the pure product **3f** (1.51 g, 75%).

General Procedure for the Synthesis of Compounds ***8.*** A mixture of **3f** (0.4 mmol, 1.0 equiv, 0.16g), $NaBH_4$ (3.2 mmol, 8.0 equiv, 0.12

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g), and anhydrous EtOH (2 mL) in a 15 mL sealed glass vial were heated at 80 °C in an oil bath for 48 h, detected by TLC. After cooling to room temperature, the reaction mixture was concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to give the pure product **8** (57.8 mg, 45%).

*N-(4-Ethoxyphenyl)pivalamide (**1b**).* Light green crystalline solid, PE/EtOAc (10:1) as the eluent, 1.08 g, 98%. Mp: 104−105 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.44−7.36 (m, 1H), 7.31 (s, 1H), 6.88−6.76 (m, 2H), 4.10−3.90 (m, 2H), 1.41−1.36 (m, 3H), 1.30−1.28 (m, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 176.6, 155.8, 131.2, 122.1, 114.8, 63.8, 39.5, 27.8, 14.9. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{20}NO_2$ 222.1494; Found: 222.1492.

*N-(4-Isopropylphenyl)pivalamide (**1d**).* Light crystalline orange solid, PE/EtOAc (10:1) as the eluent, 1.08 g, 99%. Mp: 143−144 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.44 (d, J = 8.4 Hz, 2H), 7.33 (s, 1H), 7.17 (d, J = 8.3 Hz, 2H), 2.87 (hept, J = 6.8 Hz, 1H), 1.31 (s, 9H), 1.23 (d, J = 6.9 Hz, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 176.6, 145.0, 135.8, 126.9, 120.3, 39.6, 33.7, 27.8, 24.2. HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{14}H_{21}NONa$ 242.1521; Found: 242.1515.

*N-(4-(Difluoromethoxy)phenyl)pivalamide (**1g**).* Dark brown crystalline solid, PE/EtOAc (10:1) as the eluent, 1.19g, 98%. Mp: 105−106 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.59 (s, 1H), 7.48 (d, J = 9.0 Hz, 2H), 7.01 (d, J = 8.9 Hz, 2H), 6.43 (t, J = 74.1 Hz, 1H), 1.27 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 177.0, 147.3 (C−F, $^1J_{C-F}$ = 2.9 Hz), 135.6, 121.8, 120.2, 118.7, 116.1, 113.5, 39.6, 27.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −80.6. HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{12}H_{15}NO_2Na$ 266.0969; Found: 266.0979.

*Methyl 3-Pivalamidobenzoate (**1m**).* White crystalline solid, PE/EtOAc (10:1) as the eluent, 1.15 g, 98%. Mp: 111−112 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.00 (s, 1H), 7.76 (d, J = 9.2 Hz, 2H), 7.63 (d, J = 7.7 Hz, 1H), 7.24 (m, 1H), 3.77 (s, 3H), 0.61 (d, J = 487.3 Hz, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 177.1, 166.8, 138.4, 130.6, 128.9, 125.1, 124.9, 121.2, 52.1, 39.6, 27.5. HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{13}H_{17}NO_3Na$ 258.1106; Found: 258.1100.

*3-Pivalamidobenzyl pivalate (**1n**).* White crystalline solid, PE/EtOAc (10:1) as the eluent, 1.41 g, 97%. Mp: 111−112 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.60 (s, 1H), 7.46 (s, 1H), 7.38 (d, J = 8.1 Hz, 1H), 7.16 (m, 1H), 6.96 (d, J = 7.6 Hz, 1H), 4.94 (s, 2H), 1.20 (s, 9H), 1.12 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 178.2, 176.8, 138.3, 137.1, 129.0, 123.3, 119.9, 119.7, 65.8, 39.5, 38.7, 27.5, 27.1. HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{17}H_{25}NO_3Na$ 314.1732; Found: 314.1736.

*N-(3-Chloro-4-methylphenyl)pivalamide (**4b**).* White crystalline solid, PE/EtOAc (10:1) as the eluent, 1.07 g, 95%. Mp: 160−161 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.63 (d, J = 1.9 Hz, 1H), 7.28−7.25 (m, 2H), 7.14 (d, J = 8.2 Hz, 1H), 2.31 (s, 3H), 1.29 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 176.7, 136.9, 134.6, 131.9, 131.0, 120.7, 118.3, 39.8, 27.73, 19.6. HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{12}H_{16}ClNONa$ 226.0999; Found: 226.0988.

*N-(4-Fluoro-2-methylphenyl)pivalamide (**4d**).* Pink crystalline solid, PE/EtOAc (10:1) as the eluent, 1.02 g, 98%. Mp:94−95 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.59−7.56 (m, 1H), 7.21 (s, 1H), 6.86 (d, J = 9.1 Hz, 2H), 2.19 (s, 3H), 1.31−1.30 (m, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 176.9, 160.1 (C−F $^1J_{C-F}$ = 244.0 Hz,), 132.8 (C−F, $^3J_{C-F}$ = 8.2 Hz,), 131.8 (C−F, $^3J_{C-F}$ = 2.6 Hz,), 125.7 (C−F, $^4J_{C-F}$ = 8.5 Hz,), 117.0 (C−F, $^2J_{C-F}$ = 22.5 Hz,), 113.2 (C−F, $^2J_{C-F}$ = 22.0 Hz,), 40.0, 27.7, 17.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −117.6. HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{12}H_{16}FNONa$ 232.1114; Found: 232.1117.

*N-(4-(3-Ethyl-2,6-dioxopiperidin-3-yl)phenyl)pivalamide (**6d**).* White crystalline solid, PE/EtOAc (5:1) as the eluent, 1.55 g, 98%. Mp:204−205 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.25 (s, 1H), 7.54 (d, J = 8.7 Hz, 2H), 7.44 (s, 1H), 7.20 (d, J = 8.7 Hz, 2H), 2.63−2.53 (m, 1H), 2.43−2.31 (m, 2H), 2.23−2.15 (m, 1H), 2.01 (tt, J = 14.7, 7.5 Hz, 1H), 1.88 (dq, J = 14.6, 7.4 Hz, 1H), 1.30 (s, 9H), 0.84 (t, J = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.9, 175.3, 172.4, 137.6, 134.4, 126.9, 120.5, 50.8, 39.8, 33.0, 29.4, 27.7, 27.1, 9.1. HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{18}H_{24}N_2O_3Na$ 339.1685; Found: 339.1674.

*2-((Adamantan-1-yl)amino)-2-oxoacetic acid (**L1**).* White crystalline solid, 0.48 g, 95%. Mp: 61−62 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.08 (s, 1H), 2.19 (s, 1H), 1.86 (s, 2H), 1.66 (q, J = 11.9 Hz, 4H), 1.49−1.08 (m, 6H), 0.87 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 54.6, 50.5, 47.0, 42.5, 39.6, 32.6, 30.1. HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{14}H_{21}NO_3Na$ 274.1419; Found: 274.1418.

*Ethyl 2-((Adamantan-1-yl)amino)-2-oxoacetate (**L4**).* White crystalline solid, PE/EtOAc (10:1) as the eluent, 1.37 g, 98%. Mp: 52−53 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.83 (s, 1H), 4.27 (q, J = 7.1 Hz, 2H), 2.14 (dt, J = 6.2, 3.1 Hz, 1H), 1.84 (d, J = 1.4 Hz, 2H), 1.64 (q, J = 12.2 Hz, 4H), 1.42−1.23 (m, 7H), 1.20−1.07 (m, 2H), 0.83 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 161.6, 155.4, 63.2, 54.2, 50. 6, 47.0, 42.6, 39.5, 32.5, 30.1, 14.1. HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{16}H_{25}NO_3Na$ 302.1732; Found: 302.1735.

*N-(2-(4-Bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-5-methoxyphenyl)pivalamide (**3a**).* White crystalline solid, PE/EtOAc (40:1) as the eluent, 59.2 mg, 72%. Mp: 81−82 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.47 (d, J = 2.6 Hz, 1H), 7.41 (d, J = 8.7 Hz, 1H), 7.33 (s, 1H), 7.18 (dt, J = 15.9, 2.1 Hz, 1H), 6.78 (dd, J = 8.7, 2.6 Hz, 1H), 6.09 (dt, J = 16.0, 11.5 Hz, 1H), 3.86 (s, 3H), 1.36 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 177.0, 161.6, 137.1, 134.7 (C−F, $^3J_{C-F}$ = 9.2 Hz,), 128.5, 119.5, 115.5 (C−F, $^2J_{C-F}$ = 23.8 Hz), 112.8, 109.1, 55.7, 40.0, 27.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −65.69 (t, J = 6.4 Hz), −108.77 (t, J = 6.3 Hz,). HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{16}H_{18}BrF_4NO_2Na$ 434.0355; Found: 434.0340.

*N-(2-(4-Bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-4-ethoxyphenyl)pivalamide (**3b**).* White crystalline solid, PE/EtOAc (20:1) as the eluent, 60.4 mg, 71%. Mp: 102−103 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.36(d, J = 8.8 Hz, 1H), 7.18 (dt, J = 15.8, 2.1 Hz, 2H), 6.97 (d, J = 2.8 Hz, 1H), 6.90 (dd, J = 8.8, 2.8 Hz, 1H), 6.13 (dt, J = 16.1, 11.5 Hz, 1H), 4.04 (q, J = 7.0 Hz, 2H), 1.42 (t, J = 7.0 Hz, 3H), 1.31 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 177.6, 157.4, 135.8 (C−F, $^3J_{C-F}$ = 9.1 Hz), 130.6, 128.6, 128.2, 116.9 (C−F, $^2J_{C-F}$ = 23.9 Hz), 116.6, 112.4, 64.0, 39.4, 27.6, 14.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −65.70 (t, J = 6.3 Hz), −109.12 (t, J = 6.3 Hz,). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{21}BrF_4NO_2$ 426.0692; Found: 426.0687.

*N-(2-(4-Bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-4-methoxyphenyl)pivalamide (**3c**).* White crystalline solid, PE/EtOAc (10:1) as the eluent, 41.8 mg, 51%. Mp: 108−109 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.32 (s, 1H), 7.28 (d, J = 8.8 Hz, 1H), 7.16 (dt, J = 16.1, 2.1 Hz, 1H), 6.92 (d, J = 2.8 Hz, 1H), 6.87 (dd, J = 8.7, 2.8 Hz, 1H), 6.10 (dt, J = 16.1, 11.5 Hz, 1H), 3.81 (s, 3H), 1.28 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 177.6, 157.9, 135.7 (C−F, $^3J_{C-F}$ = 9.2 Hz), 130.6, 128.6, 128.2, 116.8 (C−F, $^2J_{C-F}$ = 23.9 Hz), 116.1, 111.5, 55.5, 39.3, 27.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −65.69 (t, J = 6.3 Hz,), −109.07 (t, J = 6.3 Hz). HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{16}H_{18}BrF_4NO_2Na$ 434.0355; Found: 434.0343.

*N-(2-(4-Bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-4-isopropylphenyl)pivalamide (**3d**).* White crystalline solid, PE/EtOAc (80:1) as the eluent, 51.6 mg, 61%. Mp: 138−139 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.55 (d, J = 8.3 Hz, 1H), 7.30 (d, J = 1.9 Hz, 1H), 7.27−7.21 (m, 2H), 7.20 (s, 1H), 6.17 (dt, J = 16.1, 11.5 Hz, 1H), 2.92 (m, 1H), 1.32 (s, 9H), 1.25 (d, J = 6.9 Hz, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 177.1, 147.1, 136.0 (C−F, $^3J_{C-F}$ = 9.1 Hz), 133.4, 128.8, 128.2, 125.8, 125.2, 117.3 (C−F, $^2J_{C-F}$ = 23.9 Hz), 39.7, 33.9, 27.7, 24.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −65.64 (t, J = 6.2 Hz,), −108.97 (t, J = 6.2 Hz,). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{23}BrF_4NO$ 424.0899; Found: 424.0891.

*N-(2-(4-Bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-4-chlorophenyl)pivalamide (**3e**).* White crystalline solid, PE/EtOAc (60:1) as the eluent, 62.2 mg, 75%. Mp: 146−147 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.58 (d, J = 8.6 Hz, 1H), 7.41 (d, J = 2.4 Hz,

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1H), 7.36−7.27 (m, 2H), 7.14 (dt, J = 16.0, 2.1 Hz, 1H), 6.17 (dt, J = 16.0, 11.3 Hz, 1H), 1.31 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 177.2, 134.5 (C−F, $^3J_{C-F}$ = 9.2 Hz), 134.2, 131.7, 130.5, 129.8, 127.0, 118.9 (C−F, $^2J_{C-F}$ = 24.1 Hz), 39.7, 27.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −65.8 (t, J = 6.2 Hz, 1H), −109.3 (t, J = 6.2 Hz, 2H). HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{15}BrClF_4NONa$ 437.9859; Found: 437.9864.

*N-(2-(4-Bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-4-fluorophenyl)-pivalamide (**3f**).* White crystalline solid, PE/EtOAc (100:1) as the eluent, 63.0 mg, 79%. Mp: 136−137 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.49 (s, 1H), 7.33 (dd, J = 8.8, 5.2 Hz, 1H), 7.21−7.06 (m, 2H), 7.05−6.96 (m, 1H), 6.10 (dt, J = 16.1, 11.4 Hz,1H), 1.27 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 177.6, 160.6 (C−F, $^1J_{C-F}$ = 246.6 Hz), 134.6 (C−F, $^3J_{C-F}$ = 9.1 Hz), 131.6 (C−F, $4J_{C-F}$= 2.8 Hz), 131.0 (C−F, $3J_{C-F}$ = 8.0 Hz), 128.5 (C−F, $3J_{C-F}$= 8.4 Hz), 118.0 (C−F, $2J_{C-F}$= 24.1 Hz), 117.3 (C−F, $2J_{C-F}$ = 22.5 Hz), 113.2 (C−F, $2J_{C-F}$= 23.6 Hz), 39.4, 27.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −65.8, −109.3 (dt, J = 11.2, 5.3 Hz), −111.7, −117.5. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{15}BrF_5NONa$ 422.0155; Found: 422.0143.

*N-(2-(4-Bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-4-(difluoromethoxy)phenyl)pivalamide (**3g**).* White crystalline solid, PE/EtOAc (40:1) as the eluent, 46.6 mg, 52%. Mp: 94−95 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.51 (s, 1H), 7.41 (d, J = 8.8 Hz, 1H), 7.24−6.98 (m, 6H). 6.50 (t, J = 73.4 Hz, 1H), 6.12 (dt, J = 15.9, 11.4 Hz, 1H), 1.27 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 177.8 (C−F, $2J_{C-F}$ = 9.7 Hz), 148.9 (C−F, $^1J_{C-F}$ = 2.7 Hz), 134.8 (C−F, $3J_{C-F}$= 9.2 Hz), 133.1, 130.7 (C−F, $3J_{C-F}$ = 12.5 Hz), 128.0 (C−F, $2J_{C-F}$ = 11.9 Hz), 121.6 (C−F, $2J_{C-F}$ = 5.7 Hz), 119.0−117.9, 115.8, 39.5 (C−F, $3J_{C-F}$ = 3.2 Hz), 27.5 ppm (C−F, $4J_{C-F}$ = 2.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −65.8 (t, J = 6.0 Hz,), −81.1 (d, J = 10.4 Hz), −109.3 (q, J = 6.3 Hz). HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{16}BrF_6NO_2Na$ 470.0166; Found: 470.0164.

*N-(2-(4-Bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-4-(tert-butyl)-phenyl)pivalamide (**3h$_{mono}$**).* White crystalline solid, PE/EtOAc (150:1) as the eluent, 55.8 mg, 64%. Mp: 130−131 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.57 (d, J = 8.3 Hz, 1H), 7.42 (d, J = 7.8 Hz, 2H), 7.24 (dd, J = 17.2, 4.8 Hz, 2H), 6.16 (dt, J = 16.0, 11.5 Hz, 1H), 1.33 (d, J = 3.5 Hz, 18H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 177.1, 149.4, 136.3 (C−F, $^3J_{C-F}$ = 9.1 Hz), 133.1, 128.0, 127.8, 125.4, 124.0, 117.2 (C−F, $^2J_{C-F}$ = 23.8 Hz), 39.6, 34.7, 31.4, 27.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −65.6 (t, J = 6.1 Hz), −108.9 (t, J = 6.2 Hz). HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{24}BrF_4NONa$ 460.0875; Found: 460.0860.

*N-(2,6-Bis((E)-4-bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-4-(tert-butyl)phenyl)pivalamide (**3h$_{di}$**).* White crystalline solid, PE/EtOAc (150:1) as the eluent, 41.2 mg (0.8 mmol), 8%. Mp: 253−254 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.57 (s, 2H), 7.39−7.09 (m, 2H), 6.97 (s, 1H), 6.17 (dt, J = 16.1, 11.4 Hz, 2H), 1.36 ppm (d, J = 8.4 Hz, 18H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 177. 6, 151.5, 136.2 (C−F, $^3J_{C-F}$ = 9.2 Hz), 132.6, 131.6, 125.5, 117.4 (C−F, $^2J_{C-F}$ = 23.9 Hz), 39.5, 35.0, 31.3, 27.6 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −65.6 (C−F, J = 6.2 Hz), −109.0 (C−F, J = 6.2 Hz). HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{25}Br_2F_8NONa$ 666.0052; Found: 666.0036.

*N-(2-(4-Bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-5-methylphenyl)pivalamide (**3i**).* White crystalline solid, PE/EtOAc (80:1) as the eluent, 71.0 mg, 90%. Mp: 88−89 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.39 (d, J = 15.3 Hz, 2H), 7.32 (d, J = 8.0 Hz, 1H), 7.15 (d, J = 16.1 Hz, 1H), 7.01 (d, J = 7.9 Hz, 1H), 6.08 (dt, J = 15.9, 11.6 Hz, 1H), 2.33 (s, 3H), 1.29 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 177.3, 141.0, 136.9−134.4, 127.2, 126.9, 126.5, 125.7, 116.0 (C−F, $^2J_{C-F}$ = 23.8 Hz), 39.6, 27.6, 21.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −65.66 (t, J = 6.4 Hz), −108.92 (t, J = 6.3 Hz). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{16}H_{19}BrF_4NO$ 396.0586; Found: 396.0599.

*N-(2-(4-Bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-5-(trifluoromethyl)phenyl)pivalamide (**3j**).* White crystalline solid, PE/EtOAc (120:1) as the eluent, 45.8 mg, 51%. Mp: 171−172 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.93 (s, 1H), 7.61−7.47 (m, 2H), 7.42 (d, J = 8.1 Hz, 1H), 7.18 (d, J = 16.1 Hz, 1H), 6.20 (dt, J = 16.0, 11.3 Hz, 1H), 1.31 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 177.4, 136.1, 134.6 (C−F, $^3J_{C-F}$ = 9.1 Hz), 132.4 (C−F, $^1J_{C-F}$ = 33.1 Hz), 131.4, 127.8, 124.9, 123.3−121.6, 119.9 (C−F, $2J_{C-F}$ = 24.1 Hz), 39.8, 27.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −62.9, −65.9 (t, J = 6.2 Hz), −109.5 (t, J = 6.2 Hz). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{16}H_{16}BrF_7NO$ 450.0303; Found: 450.0313.

*N-(2-(4-Bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-5-chlorophenyl)pivalamide (**3k**).* White crystalline solid, PE/EtOAc (200:1) as the eluent, 34.8 mg, 42%. Mp: 124−125 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.84 (d, J = 2.1 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H). 7.28 (s, 1H), 7.22−7.11 (m, 2H), 6.17 (dt, J = 16.0, 11.3 Hz, 1H), 1.33 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 177.0, 136.6, 136.4, 134.5 (C−F, $^3J_{C-F}$ = 9.2 Hz), 128.4, 126.2, 126.0, 125.0, 118.5 (C−F, $^2J_{C-F}$ = 24.1 Hz), 39.9, 27.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −65.8 (t, J = 6.3 Hz), −109.3 (t, J = 6.3 Hz). HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{15}BrClF_4NONa$ 437.9859; Found: 437.9869.

*N-(2-(4-Bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-5-fluorophenyl)-pivalamide (**3l**).* White crystalline solid, PE/EtOAc (80:1) as the eluent, 15.2 mg, 19%. Mp: 130−131 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.56 (d, J = 8.2 Hz, 1H), 7.38 (s, 1H), 7.31 (m, 1H), 7.03 (dt, J = 16.5, 2.3 Hz, 1H), 6.99−6.90 (m, 1H), 6.38 (dt, J = 16.5, 11.3 Hz, 1H), 1.32 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 177.1 (C−F, $^2J_{C-F}$ = 3.7 Hz), 160.93 (C−F, $^1J_{C-F}$ = 251.1 Hz), 137.1 (C−F, $^3J_{C-F}$ = 4.6 Hz), 130.9 (C−F, $^2J_{C-F}$ = 10.3 Hz), 129.5 (C−F, $^3J_{C-F}$ = 9.8 Hz), 122.3−121.4, 120.7, 113.4−112.5, 39.9, 27.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −60.5, −70.3, −110.0 (t, J = 6.2 Hz), −112.2. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{15}BrF_5NONa$ 422.0155; Found: 422.0142.

*N-(2-(4-Bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-3-fluorophenyl)-pivalamide (**3l′**).* White crystalline solid, PE/EtOAc (300:1) as the eluent, 56.6 mg, 71%. Mp: 99−100 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.71 (dd, J = 10.4, 2.6 Hz, 1H), 7.41 (dd, J = 8.6, 6.1 Hz, 1H), 7.31 (s, 1H), 7.17 (d, J = 16.0 Hz, 1H), 6.92 (m, 1H), 6.14 (dt, J = 16.0, 11.4 Hz, 1H), 1.33 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 177.1 (C−F, $^2J_{C-F}$ = 3.8 Hz), 163.7 (C−F, $^2J_{C-F}$ = 250.1 Hz), 137.3 (C−F, $^3J_{C-F}$ = 11.2 Hz), 134.5 (C−F, $^2J_{C-F}$ = 9.1 Hz,), 128.8 (C−F, $^3J_{C-F}$ = 9.4 Hz), 123.4 (C−F, $^3J_{C-F}$ = 9.1, 3.1 Hz), 118.5−117.4, 113.1 (C−F, $^2J_{C-F}$ = 22.1, 2.5 Hz), 112.1 (C−F, $^2J_{C-F}$ = 25.5, 7.4 Hz), 39.9 (C−F, $^3J_{C-F}$ = 1.2 Hz), 27.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −65.8 (t, J = 6.2 Hz), −108.3, −109.2 (t, J = 6.3 Hz). HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{15}BrF_5NONa$ 422.0155; Found: 422.0144.

*Methyl-4-(4-bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-3-pivalamidobenzoate (**3m**).* White crystalline solid, PE/EtOAc (40:1) as the eluent, 50.8 mg, 58%. Mp: 114−115 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.24 (d, J = 1.6 Hz, 1H), 7.87 (dd, J = 8.1, 1.5 Hz, 1H), 7.52 (d, J = 8.2 Hz, 1H), 7.35 (s, 1H), 7.22 (dt, J = 16.1, 2.1 Hz, 1H), 6.25 (dt, J = 16.1, 11.3 Hz, 1H), 3.92 (s, 3H), 1.34 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 177.2, 166.2, 135.8, 135.0 (C−F, $^3J_{C-F}$ = 9.1 Hz), 132.8, 132.1, 127.3 126.9, 119.5 (C−F, $^2J_{C-F}$ = 24.1 Hz), 52.5, 39.7, 27.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −65.8 (t, J = 6.2 Hz), −109.4 (t, J = 6.2 Hz). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{19}BrF_4NO_3$ 440.0484; Found: 440.0488.

*4-(4-Bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-3-pivalamidobenzylpivalate (**3n**).* White crystalline solid, PE/EtOAc (10:1) as the eluent, 58.4 mg, 59%. Mp: 112−113 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.56 (s, 1H), 7.45 (dd, J = 17.6, 11.1 Hz, 2H), 7.23−7.13 (m, 2H), 6.14 (dt, J = 16.0, 11.5 Hz, 1H), 5.05 (s, 2H), 1.30 (s, 9H), 1.21 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 178.3, 177.2, 139.3, 135.8, 135.2 (C−F, $^3J_{C-F}$ = 9.1 Hz), 127.9, 127.5, 125.3, 124.9, 117.6 (C−F, $^2J_{C-F}$ = 23.9 Hz), 65.3, 39.7, 38.9, 27.6, 27.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −65.8 (t, J = 6.2 Hz), −109.2 (t, J = 6.2 Hz). HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{26}BrF_4NO_3Na$ 518.0930; Found: 518.0920.

*N-(5-Acetyl-2-(4-bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)phenyl)-pivalamide (**3o**).* Yellow crystalline solid, PE/EtOAc (10:1) as the eluent, 27.0 mg, 32%. Mp: 135−136 °C. ^1H NMR (400 MHz,

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$CDCl_3$): δ (ppm) 8.24 (d, J = 1.7 Hz, 1H), 7.80 (dd, J = 8.1, 1.6 Hz, 1H), 7.55 (d, J = 8.1 Hz, 1H), 7.37 (s, 1H), 7.23 (d, J = 16.1 Hz, 1H), 6.26 (dt, J = 16.1, 11.3 Hz, 1H), 2.61 (s, 3H), 1.35 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 197.3, 177.3, 138.7, 136.0, 134.8 (C−F, $^3J_{C-F}$ = 9.2 Hz), 132.6, 127.6, 125.6, 119.7 (C−F, $^3J_{C-F}$ = 24.1 Hz), 39.8, 27.6, 26.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −65.8 (t, J = 6.2 Hz), −109.4 (t, J = 6.2 Hz). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{19}BrF_4NO_2$ 424.0535; Found: 424.0547.

*N-(2-(4-Bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-6-methoxyphenyl)pivalamide (**3p**).* White crystalline solid, PE/EtOAc (60:1) as the eluent, 44.2 mg, 54%. Mp: 102−103 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.23 (m, 1H), 7.20−7.13 (m, 3H), 6.92 (dd, J = 8.1, 1.0 Hz, 1H), 6.15 (dt, J = 16.1, 11.6 Hz, 1H), 3.84 (s, 3H), 1.34 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 177.7, 153.8, 137.0 (C−F, $^3J_{C-F}$ = 9.3 Hz), 132.1, 127.3, 125.2, 118.6, 115.4 (C−F, $^2J_{C-F}$ = 23.9 Hz), 111.9, 56.1, 39.6, 27.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −65.5 (t, J = 6.3 Hz), −109.0 (t, J = 6.3 Hz). HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{18}BrF_4NO_2Na$ 434.0355; Found: 434.0340.

*N-(2-(4-Bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-6-chlorophenyl)pivalamide (**3q**).* White crystalline solid, PE/EtOAc (40:1) as the eluent, 39.0 mg, 47%. Mp: 154−155 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.43 (m, 2H), 7.34 (s, 1H), 7.22 (m, 1H), 7.13 (dt, J = 16.2, 2.0 Hz, 1H), 6.15 (dt, J = 16.1, 11.5 Hz, 1H), 1.34 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 177.3, 136.3 (C−F, $^3J_{C-F}$ = 9.4 Hz), 133.9, 133.2, 132.0, 130.7, 128.0, 125.4, 116.8 (C−F, $^2J_{C-F}$ = 24.0 Hz), 39.7, 27.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −65.6 (t, J = 6.3 Hz), −109.2 (ddd, J = 8.7, 6.8, 3.3 Hz). HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{15}BrClF_4NONa$ 437.9859; Found: 437.9866.

*N-(2-(4-Bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-6-methylphenyl)pivalamide (**3r**).* White crystalline solid, PE/EtOAc (80:1) as the eluent, 65.6 mg, 83%. Mp: 165−166 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.34 (s, 1H), 7.31 (dd, J = 6.3, 2.8 Hz, 1H), 7.15 (dd, J = 9.2, 5.1 Hz, 3H), 6.06 (dt, J = 16.1, 11.6 Hz, 1H), 2.08 (s, 3H), 1.25 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 177.4, 137.9−135.9, 134.5, 132.1, 127.6, 124.3, 115.9 (C−F, $^2J_{C-F}$ = 23.8 Hz), 39.3, 27.6, 18.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −65.6 (t, J = 6.2 Hz), −109.0 (t, J = 6.3 Hz). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{16}H_{19}BrF_4NO$ 396.0586; Found: 396.0585.

*N-(2-(4-Bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-6-ethylphenyl)-pivalamide (**3s**).* White crystalline solid, PE/EtOAc (80:1) as the eluent, 56.4 mg, 69%. Mp: 159−160 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.36 (m, 1H), 7.28 (s, 1H), 7.23 (d, J = 4.9 Hz, 2H), 7.17 (dt, J = 16.1, 2.0 Hz, 1H), 6.08 (dt, J = 16.1, 11.6 Hz, 1H), 2.48 (q, J = 7.6 Hz, 2H), 1.26 (s, 9H), 1.12 (t, J = 7.6 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 177.6, 142.1, 136.8 (C−F, $^3J_{C-F}$ = 9.2 Hz), 134.0, 132.5, 130.3, 127.9, 124.4, 115.9 (C−F, $^2J_{C-F}$ = 23.8 Hz), 39.3, 27.6, 24.7, 14.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −65.6 (t, J = 6.3 Hz), −109.0 (ddd, J = 11.1, 6.6, 4.8 Hz). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{21}BrF_4NO$ 410.0743; Found: 410.0756.

*Methyl 3-(4-Bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-2-pivalamidobenzoate (**3t**).* White crystalline solid, PE/EtOAc (40:1) as the eluent, 39.4 mg, 45%. Mp: 77−78 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.74 (s, 1H), 8.01 (dd, J = 7.9, 1.4 Hz, 1H), 7.74 (dd, J = 7.8, 1.3 Hz, 1H), 7.29 (d, J = 7.8 Hz, 1H), 7.07 (dt, J = 16.1, 2.1 Hz, 1H), 6.17 (dt, J = 16.1, 11.5 Hz, 1H), 3.92 (s, 3H), 1.35 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 177.7, 167.6, 138.4, 137.2 (C−F, $^3J_{C-F}$ = 9.3 Hz), 132.0, 131.7, 131.5, 125.3, 123.0, 115.0 (C−F, $^2J_{C-F}$ = 24.1 Hz), 52.7, 39.9, 27.5 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −65.5 (t, J = 6.3 Hz), −108.9 (t, J = 6.4 Hz). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{19}BrF_4NO_3$ 440.0484; Found: 440.0479.

*N-(6-(4-Bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-2,3-dimethylphenyl)pivalamide (**5a**).* White crystalline solid, PE/EtOAc (40:1) as the eluent, 53.2 mg, 65%. Mp: 137−138 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.29 (s, 1H), 7.24 (d, J = 7.9 Hz, 1H), 7.15 (dt, J = 16.1, 2.0 Hz, 1H), 7.07 (d, J = 8.0 Hz, 1H), 6.04 (dt, J = 16.1, 11.7 Hz, 1H), 2.26 (s, 3H), 2.00 (s, 3H), 1.28 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 177.3, 139.6, 136.6 (C−F, $^3J_{C-F}$ = 9.1 Hz), 135.1, 134.1, 129.6, 129.1, 123.4, 114.8 (C−F, $^2J_{C-F}$ = 23.6, 5.1 Hz), 39.2, 27.5, 20.6, 14.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −65.5 (t, J = 5.7 Hz), −108.8 (t, J = 6.1 Hz). HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{20}BrF_4NONa$ 432.0562; Found: 432.0569.

*N-(2-(4-Bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-5-chloro-4-methylphenyl)pivalamide (**5b**).* White crystalline solid, PE/EtOAc (200:1) as the eluent, 82.2 mg, 96%. Mp: 158−159 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.63 (s, 1H), 7.29 (d, J = 10.2 Hz, 2H), 7.11 (dt, J = 16.1, 2.1 Hz, 1H), 6.13 (dt, J = 16.1, 11.4 Hz, 1H), 2.35 (s, 3H), 1.31 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 177.2, 136.2, 134.6 (C−F, $^3J_{C-F}$ = 9.1 Hz), 134.1 (C−F, $^2J_{C-F}$ = 4.3 Hz), 128.8, 126.7, 126.1, 117.8−117.0, 39.6, 27.5, 19.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −65.7 (t, J = 6.2 Hz), −109.2 (t, J = 6.3 Hz). HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{17}BrClF_4NONa$ 452.0016; Found: 452.0007.

*N-(2-(4-Bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-4,5-dimethoxyphenyl)pivalamide (**5c**).* Yellow crystalline solid, PE/EtOAc (5:1) as the eluent, 61.8 mg, 70%. Mp: 156−157 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.25 (s, 1H), 7.15 (d, J = 14.6 Hz, 2H), 6.88 (s, 1H), 6.03 (dt, J = 16.0, 11.5 Hz, 1H), 3.89 (d, J = 3.8 Hz, 6H), 1.33 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 177.4, 151.0, 147.4, 134.8 (C−F, $^3J_{C-F}$ = 9.2 Hz), 129.8, 120.3, 114.8 (C−F, $^2J_{C-F}$ = 23.9 Hz), 109.2, 108.7, 56.3, 56.2, 39.7, 27.7 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −65.6 (t, J = 6.2 Hz), −108.5 (t, J = 6.2 Hz). HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{20}BrF_4NO_3Na$ 464.0460; Found: 464.0461.

*N-(2-(4-Bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-4-fluoro-6-methylphenyl)pivalamide (**5d**).* White crystalline solid, PE/EtOAc (40:1) as the eluent, 38.8 mg, 47%. Mp: 158−159 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.51 (s, 1H), 7.04 (d, J = 16.0 Hz, 1H), 6.93 (dd, J = 8.9, 2.6 Hz, 1H), 6.81 (dd, J = 8.7, 2.5 Hz, 1H), 6.02 (dt, J = 16.1, 11.4 Hz, 1H), 2.00 (s, 3H), 1.23 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 177.9, 161.2 (C−F, ^1J = 246.4 Hz), 139.3 (C−F, $^3J_{C-F}$ = 8.6 Hz), 135.6 (C−F, $^3J_{C-F}$ = 9.1 Hz), 133.7 (C−F, $^3J_{C-F}$ = 8.7 Hz), 130.6 (C−F, $^4J_{C-F}$ = 2.5 Hz), 118.6 (C−F, $^2J_{C-F}$ = 22.2 Hz), 117.0 (C−F, $^2J_{C-F}$ = 24.0 Hz), 110.5 (C−F, $^2J_{C-F}$ = 23.3 Hz), 39.3, 27.5, 18.1 (C−F, $^3J_{C-F}$ = 1.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −65.7 (dd, J = 13.4, 7.2 Hz), −109.1 (dt, J = 11.3, 6.1 Hz), −114.5 (d, J = 45.5 Hz). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{16}H_{18}BrF_5NO$ 414.0492; Found: 414.0499.

*N-(2-(4-Bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)naphthalen-1-yl)pivalamide (**5e**).* White crystalline solid, PE/EtOAc (50:1) as the eluent, 52.4 mg, 61%. Mp: 166−167 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.72 (d, J = 8.0 Hz, 1H), 7.65 (s, 1H), 7.58 (dd, J = 16.1, 8.5 Hz, 2H), 7.50−7.36 (m, 2H), 7.31 (d, J = 8.7 Hz, 1H), 7.19 (d, J = 16.2 Hz, 1H), 6.06 (dt, J = 16.1, 11.6 Hz, 1H), 1.30 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 178.1, 135.9 (C−F, $^3J_{C-F}$ = 9.2 Hz), 134.5, 132.3, 130.6, 128.5, 128.3, 128.0, 127.1, 123.2, 122.5, 115.8 (C−F, $^2J_{C-F}$ = 23.8 Hz), 39.5, 27.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −65.5 (t, J = 6.2 Hz), −108.8 (t, J = 6.2 Hz). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{19}BrF_4NO$ 432.0586; Found: 432.0580.

*N-(2-(4-Bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)phenyl)-acetamide (**5f**).* White crystalline solid, PE/EtOAc (10:1) as the eluent, 40.7 mg, 60%. Mp: 116−117 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.86 (s, 1H), 7.43 (m, 1H), 7.30 (d, J = 7.4 Hz, 1H), 7.18 (dd, J = 17.4, 9.8 Hz, 2H), 6.29−5.88 (m, 1H), 2.12 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 169.8, 137.9−134.1, 130.4, 128.4, 126.8, 126.5−126.4, 116.4 (C−F, $^2J_{C-F}$ = 23.8 Hz), 23.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −65.7 (t, J = 6.3 Hz), −109.0 (t, J = 6.3 Hz). HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{10}BrF_4NONa$ 361.9780; Found: 361.9783.

*1-(8-(4-Bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-6-methyl-3,4-dihydroquinolin-1(2H)-yl)-2,2-dimethylpropan-1-one (**5g**).* White crystalline solid, PE/EtOAc (180:1) as the eluent, 60.9 mg, 70%. Mp: 117−118 °C. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.20 (s, 1H), 7.00 (s, 2H), 6.15 (dd, J = 23.7, 10.9 Hz, 1H), 4.42 (s, 1H), 3.23 (s, 1H), 2.72 (s, 2H), 2.21 (d, J = 97.3 Hz, 3H), 2.04 (d, J = 40.8 Hz, 2H), 1.36 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 178.7, 138.4, 136.5, 130.6, 129.7, 124.6, 120.6, 118.4−116.7, 114.5

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(C−F, $^2J_{C-F}$ = 40.7, 22.2 Hz), 45.4, 39.8, 28.5, 25.6, 24.5, 21.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −59.93, −74.24, −108.75. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{22}BrF_4NONa$ 458.0719; Found: 458.0722.

*1-(5-(4-Bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-2,2-dimethylpropan-1-one (**5h**).* White crystalline solid, PE/EtOAc (40:1) as the eluent, 22.0 mg, 26%. Mp: 144−145 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.16−7.01 (m, 2H), 6.99−6.78 (m, 2H), 6.15 (dt, J = 16.0, 11.7 Hz, 1H), 4.96−3.14 (m, 4H), 1.37 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 178.5, 148.7, 136.4 (C−F, $^3J_{C-F}$ = 9.4 Hz), 130.8, 126.7, 118.7, 118.5, 114.7 (C−F, $^2J_{C-F}$ = 23.7 Hz), 67.0, 44.6, 40.2, 28.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −65.5 (dd, J = 11.1, 5.5 Hz), −108.8 (dt, J = 23.3, 5.5 Hz). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{19}BrF_4NO_2$ 424.0535; Found: 424.0545.

*1-(8-(4-Bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-3,4-dihydroquin-olin-1(2H)-yl)-2,2-dimethylpropan-1-one (**5i**).* White crystalline solid, PE/EtOAc (180:1) as the eluent, 75.8 mg, 90%. Mp: 132−133 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.49−7.37 (m, 1H), 7.17 (dd, J = 8.4, 5.2 Hz, 2H), 7.05 (d, J = 15.3 Hz, 1H), 6.16 (dd, J = 27.4, 11.9 Hz, 1H), 4.42 (s, 1H), 3.28 (s, 1H), 2.76 (s, 2H), 2.04 (s, 2H), 1.35 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 178.8, 141.0, 138.5−135.7, 130.2, 130.0, 126.1, 124.2, 115.6−114.1, 45.4, 40.0, 28.6, 25.7, 24.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −65.5 (td, J = 6.0, 3.2 Hz), −103.1, −117.7. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{21}BrF_4NO$ 422.0743; Found: 422.0737.

*N-(2-(4-Bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)phenyl)-pivalamide (**7a**).* White crystalline solid, PE/EtOAc (60:1) as the eluent, 62.5 mg, 82%. Mp: 106−107 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.58 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 7.8 Hz, 1H), 7.35 (dd, J = 12.2, 4.6 Hz, 1H), 7.25−7.14 (m, 2H), 6.15 (dt, J = 16.0, 11.5 Hz, 1H), 1.31 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 177.2, 135.7 (C−F, $^3J_{C-F}$ = 9.1 Hz), 130.6, 128.4, 127.2, 126.3, 125.8, 117.4 (C−F, $^2J_{C-F}$ = 23.9 Hz), 39.6, 27.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −65.7 (t, J = 6.3 Hz), −109.1 (t, J = 6.4 Hz). HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{16}BrF_4NONa$ 404.0249; Found: 404.0248.

*N-(2-(3,3,4,4,5,5,6,6,6-Nonafluorohex-1-en-1-yl)phenyl)-pivalamide (**7b**).* White crystalline solid, PE/EtOAc (60:1) as the eluent, 66.5 mg, 79%. Mp: 81−82 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.52 (d, J = 8.0 Hz, 1H), 7.48−7.39 (m, 2H), 7.38−7.30 (m, 1H), 7.24−7.15 (m, 2H), 6.10 (dt, J = 16.0, 11.9 Hz, 1H), 1.30 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 177.3, 135.8 (C−F, $^3J_{C-F}$ = 4.8 Hz), 135.7, 130.7, 128.6, 127.2, 126.4, 126.0, 117.1 (C−F, $^2J_{C-F}$ = 23.1 Hz), 39.6, 27.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −74.2, −84.3, −111.5 (dd, J = 17.4, 7.2 Hz), −124.1 (dt, J = 16.5, 4.7 Hz), −125.1, −127.0. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{16}F_9NONa$ 444.0980; Found: 444.0964.

*N-(2-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodec-1-en-1-yl)phenyl)pivalamide (**7c**).* White crystalline solid, PE/EtOAc (60:1) as the eluent, 90.7 mg, 73%. Mp: 88−89 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.53 (s, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.30 (t, J = 7.5 Hz, 1H), 7.24−7.12 (m, 2H), 6.07 (dt, J = 15.7, 11.9 Hz, 1H), 1.27 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 177.5, 135.9, 135.7 (C−F, $^3J_{C-F}$ = 9.9 Hz), 130.6, 128.8, 127.1, 126.4, 126.2, 117.1 (C−F, $^2J_{C-F}$ = 23.0 Hz), 39.5, 27.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −81.1, −111.4, −121.5, −122.1, −123.1 (d, J = 123.2 Hz), −125.9, −127.0. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{16}F_{17}NONa$ 644.0858; Found: 644.0855.

*N-(2-(4-Bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-4-(3-ethyl-2,6-dioxopiperidin-3-yl)phenyl)pivalamide (**7d**).* White crystalline solid, PE/EtOAc (5:1) as the eluent, 52.1 mg, 51%. Mp: 248−249 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.94 (s, 1H), 7.83 (d, J = 9.2 Hz, 1H), 7.37−7.30 (m, 2H), 7.21 (d, J = 16.1 Hz, 1H), 6.15 (dt, J = 16.1, 11.2 Hz, 1H), 2.64 (dd, J = 16.1, 3.3 Hz, 1H), 2.49−2.33 (m, 2H), 2.31−2.19 (m, 1H), 2.06 (m, 1H), 1.91 (m, 1H), 1.32 (s, 9H), 0.88 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 177.0, 174.7, 171.9, 136.5, 135.4 (C−F, $^3J_{C-F}$ = 9.3 Hz), 135.1, 128.3, 128.1, 125.5, 125.3, 119.1 (C−F, $^2J_{C-F}$ = 24.0 Hz), 50.9, 39.9, 33.1, 29.4, 27.7, 27.0, 9.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −65.7 (t, J = 5.9 Hz), −109.0 (t, J = 5.9 Hz). HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{22}H_{25}BrF_4N_2O_3Na$ 543.0882; Found: 543.0883.

*N-(4-(3-Ethyl-2,6-dioxopiperidin-3-yl)-2-(3,3,4,4,5,5,6,6,6-nonafluorohex-1-en-1-yl)phenyl)pivalamide (**7e**).* White crystalline solid, PE/EtOAc (5:1) as the eluent, 62 mg, 61%. Mp: 170−171 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.00 (s, 1H), 7.80 (d, J = 9.2 Hz, 1H), 7.38−7.29 (m, 2H), 7.24−7.16 (m, 1H), 6.13 (dt, J = 16.0, 11.7 Hz, 1H), 2.72−2.54 (m, 1H), 2.49−2.32 (m, 2H), 2.31−2.20 (m, 2H), 2.14−1.98 (m, 1H), 1.91 (m, 1H), 1.32 (s, 9H), 0.88 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 177.1, 174.8, 172.0, 136.6, 135.5 (C−F, $^3J_{C-F}$ = 9.8 Hz), 135.2, 128.4, 128.1, 125.5, 118.8 (C−F, $^2J_{C-F}$ = 23.2 Hz), 50.9, 39.8, 33.1, 29.3, 27.6, 26.9, 9.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −80.1, −82.2, −111.5 (t, J = 11.5 Hz), −123.8 (dd, J = 17.3, 9.6 Hz), −124.8, −126.7. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{25}F_9N_2O_3Na$ 583.1619; Found: 583.1618.

*N-(4-(3-Ethyl-2,6-dioxopiperidin-3-yl)-2-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodec-1-en-1-yl)phenyl)pivalamide (**7f**).* White crystalline solid, PE/EtOAc (5:1) as the eluent, 71 mg, 47%. Mp: 159−160 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.09 (s, 1H), 7.79 (d, J = 9.2 Hz, 1H), 7.36−7.27 (m, 3H), 7.20 (d, J = 16.1 Hz, 1H), 6.13 (dt, J = 16.0, 11.6 Hz, 1H), 2.80−2.54 (m, 1H), 2.50−2.33 (m, 2H), 2.33−2.18 (m, 1H), 2.05 (dt, J = 14.7, 7.3 Hz, 1H), 2.02−1.87 (m, 1H), 1.32 (s, 9H), 0.88 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 177.0, 174.7, 171.9, 136.5, 135.4 (C−F, $^3J_{C-F}$ = 9.7 Hz), 135.1, 128.3, 128.0, 125.3, 118.7 (C−F, $^2J_{C-F}$ = 23.0 Hz), 50.7, 39.7, 32.9, 29.2, 27.4, 26.8, 9.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −80.8 (t, J = 9.8 Hz), −111.3 (t, J = 12.9 Hz), −121.3, −121.9), −122.8 (d, J = 11.1 Hz), −126.1 (d, J = 13.6 Hz). HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{28}H_{25}F_{17}N_2O_3Na$ 783.1491; Found: 783.1492.

*Isopropyl-(2-(4-bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)phenyl)-carbamate (**7g**).* White crystalline solid, PE/EtOAc (400:1) as the eluent, 36.0 mg, 47%. Mp: 58−59 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.70 (d, J = 8.1 Hz, 1H), 7.46 (dd, J = 7.8, 1.2 Hz, 1H), 7.41−7.36 (m, 1H), 7.33 (dt, J = 16.1, 2.3 Hz, 1H), 7.18 (t, J = 7.5 Hz,1H), 6.41 (s, 1H), 6.19 (dt, J = 16.0, 11.7 Hz, 1H), 5.02 (m, 1H), 1.31 (d, J = 6.3 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 153.8, 135.9, 135.2 (C−F, $^3J_{C-F}$ = 8.9 Hz), 130.8, 129.2, 127.4, 125.4, 123.9, 117.5 (C−F, $^2J_{C-F}$ = 23.7 Hz), 69.6, 22.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −65.7 (t, J = 6.5 Hz), −109.2 (t, J = 6.3 Hz). HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{14}BrF_4NO_2Na$ 406.0042; Found: 406.0041.

*Isopropyl-(2-(3,3,4,4,5,5,6,6,6-nonafluorohex-1-en-1-yl)phenyl)-carbamate (**7h**).* White crystalline solid, PE/EtOAc (400:1) as the eluent, 62.6 mg, 74%. Mp: 80−81 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.70 (d, J = 7.4 Hz, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.43−7.36 (m, 1H), 7.32 (dt, J = 15.9, 2.2 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 6.39 (s, 1H), 6.16 (dt, J = 15.9, 12.1 Hz, 1H), 5.02 (m, 1H), 1.31 (d, J = 6.3 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 153.8, 136.0, 135.3 (C−F, $^3J_{C-F}$ = 9.5 Hz), 130.9, 129.2, 127.4, 125.4, 124.0, 117.3 (C−F, $^2J_{C-F}$ = 23.1 Hz), 69.6, 22.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −74.8, −85.7, −111.5 (t, J = 11.4 Hz), −124.1 (dd, J = 16.8, 8.8 Hz), −124.9, −127.2. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{14}F_9NO_2Na$ 446.0779; Found: 446.0779.

*Isopropyl-(2-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodec-1-en-1-yl)phenyl)carbamate (**7i**).* White crystalline solid, PE/EtOAc (400:1) as the eluent, 83.5 mg, 67%. Mp: 89−90 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.70 (d, J = 7.2 Hz, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.43−7.36 (m, 1H), 7.32 (d, J = 16.0 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 6.40 (s, 1H), 6.17 (dt, J = 15.9, 12.1 Hz, 1H), 5.02 (m, 1H), 1.31 ppm (d, J = 6.3 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 153.8, 136.0, 135.3 (C−F, $^3J_{C-F}$ = 9.6 Hz), 130.9, 127.4, 125.4, 124.0, 117.4 (C−F, $^2J_{C-F}$ = 22.9 Hz), 69.6, 22.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −80.8 (t, J = 10.0 Hz), −111.2 (t, J = 12.6 Hz), −121.3, −121.9, −122.7, −123.1 (d, J = 11.7 Hz), −125.4, −127.6. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{20}H_{14}F_{17}NO_2Na$ 646.0645; Found: 646.0630.

*N-(4-Fluoro-2-(3,3,4,4-tetrafluorobut-1-en-1-yl)phenyl)-pivalamide (**8**).* Yellow liquid, PE/EtOAc (100:1) as the eluent, 57.8

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mg, 45%. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.54 (dd, J = 8.9, 5.3 Hz, 1H), 7.24 (s, 1H), 7.15 (d, J = 2.9 Hz, 1H), 7.13−7.00 (m, 2H), 6.12 (dt, J = 16.2, 11.6 Hz, 1H), 5.83 (m, 1H), 1.32 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 177.4, 160.6 (C−F, $^1J_{C-F}$ = 246.1 Hz), 133.6 (C−F, $^3J_{C-F}$ = 9.8 Hz), 131.5, 130.9 (C−F, $^3J_{C-F}$ = 8.0 Hz), 127.9 (C−F, $^3J_{C-F}$ = 8.3 Hz), 119.6 (C−F, $^2J_{C-F}$ = 23.9 Hz), 117.2 (C−F, $^2J_{C-F}$ = 22.5 Hz), 113.6 (C−F, $^2J_{C-F}$ = 23.7 Hz), 39.6, 27.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −113.2 (d, J = 3.0 Hz), −115.4, −134.1 (d, J = 2.4 Hz). HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{16}F_5NONa$ 344.1050; Found: 344.1061.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02701.

^{1}H, ^{13}C and ^{19}F NMR spectra for all compounds (PDF)

FAIR data, including the primary NMR FID files, for compounds **1b**, **1d**, **1g**, **1m**, **1n**, **4b**, **4d**, **6d**, **2a**, **3a**−**3t** (**3h** includes **3h** (mono) and **3h** (di)), **3l** includes **3l** and **3l′**), **5a**−**5i**, **7a**−**7i**, **8**, **L1**, and **L4** (ZIP)

Accession Codes

CCDC 2035074 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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