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ARTICLE

Synthesis of (Difluoromethyl)naphthalenes by Ring Construction Strategy: C–C Bond Formation on the Central Carbon of 1,1-Difluoroallenes via Pd-Catalyzed Insertion

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The insertion of 1,1-difluoroallenes was carried out to form a C–C bond exclusively on their central carbon. *o*-Bromophenyl-bearing 1,1-difluoroallenes underwent intramolecular insertion in the presence of a palladium catalyst. Regioselective C–C bond formation occurred to construct a six-membered carbocycle, leading to pharmaceutically and agrochemically promising difluoromethylated naphthalenes.

Introduction

The difluoromethyl (CHF_2) group as a fluorinated functional group has attracted considerable attention. Its unique properties are attributed to the steric and electronic characteristics of fluorine.[1] The CHF_2 group is a bioisostere of a hydroxyl group and serves as a hydrogen donor for hydrogen bonding while simultaneously exhibiting hydrophobicity.[2–4] On the basis of these facts, the number of difluoromethylated biologically active substances is definitely increasing.

Among the difluoromethylated compounds, (difluoromethyl)arenes have been extensively investigated in terms of their synthesis, due to their abundance in bioactive compounds.[5] Typical methods to synthesize (difluoromethyl)arenes include the (i) deoxyfluorination of aromatic aldehydes or their derivatives[6] (ii) double C–H fluorination of methylarenes,[7] and (iii) difluoromethylation of (pseudo)haloarenes[8] or arylmetals[9] by cross coupling reaction.[10] However, all these methods require aromatic rings in the starting materials. From a synthetic point of view, a process for simultaneous formation of an aromatic nuclei and installation of a difluoromethyl group is desirable.

In the past years, our group has developed metal-catalyzed

or

-mediated reactions of 1,1-difluoroallenes,[11] involving the C–C bond formation at the positions α and γ to the fluorine substituents, respectively (Scheme 1). (a) With respect to the regioselective C–C bond formation at the α position, 1,1-difluoroallenes were treated with an indium(III) catalyst.[12–14] Metallated allylic CF_2 cations, stabilized by the α-fluorine substituents,[1] were generated and subsequently underwent

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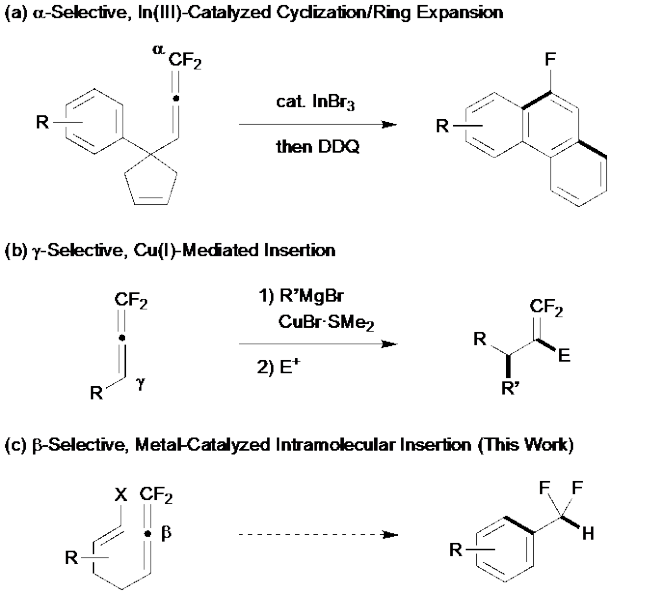
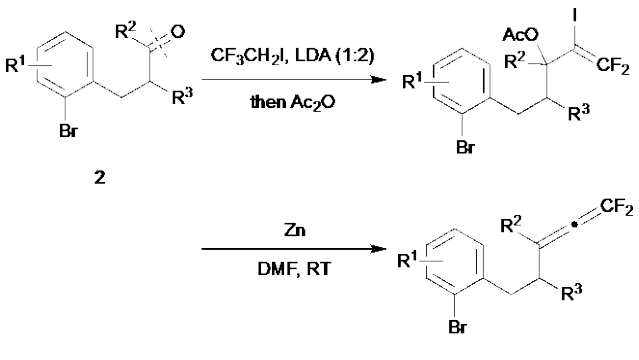


Scheme 1 α-, γ-, and β-Selective C–C bond formations of 1,1-difluoroallenes by metal complexes (DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone).



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Electronic supplementary information (ESI) available: Copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra of compounds. See DOI:

Scheme 2. Preparation of 1,1-difluoroallenes.

Friedel–Crafts-type cyclization/ring expansion, affording regioselectively monofluorinated PAHs (pinpoint-fluorinated PAHs), which are soluble p-type semiconducting materials.[15] Notably, the fluorination and construction of aromatic rings were simultaneously achieved during the synthesis of fluoroarenes. (b) The formation of a C–C bond at the γ position was achieved using a stoichiometric amount of organocopper(I) reagents.[16] 1,1-Difluoroallenes underwent regioselective insertion, forming a C–C bond at the position γ to the fluorine substituents to afford γ-branched 1,1-difluoroalkenes.[17] On the basis of the above-mentioned two reactions: (a) ring construction of arenes and (b) insertion with organometallics, the intramolecular insertion of 1,1-difluoroallenes was envisioned to facilitate the synthesis of (difluoromethyl)arenes via ring construction,[17] which permits the rare formation of C–C bonds at the position β to the fluorine substituents.[18]

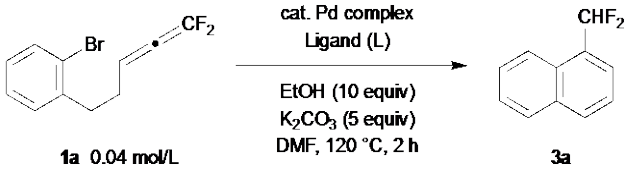
In this study, (difluoromethyl)naphthalenes were synthesized by the palladium(0)-catalyzed regioselective insertion of *o*-bromophenyl-bearing 1,1-difluoroallenes. Although the Pd-catalyzed intramolecular insertion of fluorine-free allenes has been previously reported,[19,20] the reactivities of 1,1-difluoroallenes are typically changed by the two fluorines, and their C–C bond formation via transition-metal-catalyzed insertion has never been investigated. Thus, through the synthesis of (difluoromethyl)arenes, the unexplored insertion of difluoroallenes was achieved.

Results and discussion

For the difluorovinylidenation of carbonyl compounds, our protocol was adopted to prepare 1,1-difluoroallenes **1** (Scheme 2).[21] *o*-Bromophenyl-bearing aldehydes or ketones **2** were treated with 2,2-difluoro-1-iodovinyllithium, which was generated from commercially available 1,1,1-trifluoro-2-iodoethane and LDA in a ratio of 1:2, followed by acetic anhydride, generating the corresponding iodoacetates. These acetates were subsequently treated with zinc metal, and IZnOAc was eliminated, affording the desired mono- or disubstituted 1,1-difluoroallenes **1**.

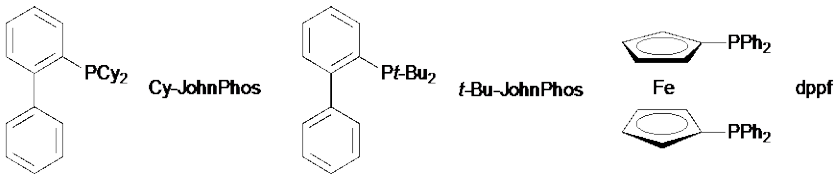
By using a model substrate **1a** (R^1–R^3 = H), the catalyst system was investigated in the presence of ethanol[20] (Table 1). Although palladium(II) acetate gave a complex mixture (entry 1), $Pd_2(dba)_3{\cdot}CHCl_3$ afforded the desired 1-(difluoromethyl)naphthalene **3a**, albeit in 5% yield (entry 2). Triphenylphosphine-ligated

Table 1. Effect of catalyst [a]



Entry	Pd complex, mol%	Ligand (L), mol%	Pd/L Ratio	Cone Angle (θ)	**3a** (%)
1 [b]	$Pd(OAc)_2$, 5	none	–	–	CM
2	$Pd_2(dba)_3{\cdot}CHCl_3$, 3	none	–	–	5
3 [c]	$PdCl_2(PPh_3)_2$, 5	none	–	–	21
4	$Pd(PPh_3)_4$, 5	none	–	–	32
5	$Pd_2(dba)_3{\cdot}CHCl_3$, 3	PPh_3, 6	1/1	145	23
6	$Pd_2(dba)_3{\cdot}CHCl_3$, 3	P*p*-Tol_3, 6	1/1	145 [d]	23
7	$Pd_2(dba)_3{\cdot}CHCl_3$, 3	$P(C_6H_4p\text{-}OMe)_3$, 6	1/1	145 [d]	30
8	$Pd_2(dba)_3{\cdot}CHCl_3$, 3	$P(C_6H_4p\text{-}CF_3)_3$, 6	1/1	149	25
9	$Pd_2(dba)_3{\cdot}CHCl_3$, 3	PAr_3, 6	1/1	175	38
10	$Pd_2(dba)_3{\cdot}CHCl_3$, 3	P*m*-Tol_3, 6	1/1	184	42
11	$Pd_2(dba)_3{\cdot}CHCl_3$, 3	P*m*-Tol_3, 12	1/2	184	24
12	$Pd_2(dba)_3{\cdot}CHCl_3$, 3	P*m*-Tol_3, 24	1/4	184	25
13	$Pd_2(dba)_3{\cdot}CHCl_3$, 3	P*o*-Tol_3, 6	1/1	193	12
14	$Pd_2(dba)_3{\cdot}CHCl_3$, 3	Cy-JohnPhos, 6	1/1	–	12
15	$Pd_2(dba)_3{\cdot}CHCl_3$, 3	*t*-Bu-JohnPhos, 6	1/1	–	0
16	$Pd_2(dba)_3{\cdot}CHCl_3$, 3	PCy_3, 6	1/1	170	24
17	$Pd_2(dba)_3{\cdot}CHCl_3$, 3	P*t*-Bu_3, 6	1/1	182	18
18	$Pd_2(dba)_3{\cdot}CHCl_3$, 3	$P(OEt)_3$, 6	1/1	109	14
19	$Pd_2(dba)_3{\cdot}CHCl_3$, 3	$P(OPh)_3$, 6	1/1	130	14

[a] ^{19}F NMR yield based on the internal standard $PhCF_3$. [b] 7 h. [c] 80 °C, 15 h. [d] Value of PPh_3. Ar = $C_6H_3$3,5-Me_2. Tol = tolyl. CM = complex mixture.

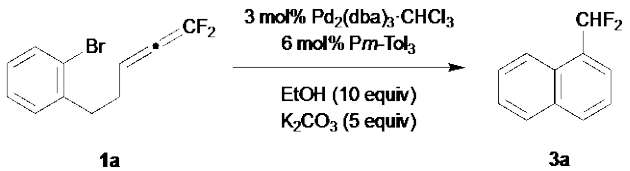


$PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$ afforded **3a** in 21% and 32% yields (entries 3 and 4), respectively. Thus, ring construction via insertion proceeded as expected and the insertion exhibited similar regioselectivity reported in the corresponding fluorine-free system, generating stable π-allylpalladium(II) intermediates (vide infra).

Yields of **3a** varied depending on the steric bulk of ligands L and the Pd/L ratio. By using triarylphosphines with $Pd_2(dba)_3{\cdot}CHCl_3$, yields of **3a** exhibited a correlation with the Tolman cone angle θ (Pd/L = 1/1, entries 5–10, Table 1). Thus, P*m*-Tol_3 with a large θ (184°) afforded **3a** in the highest yields (42%, entry 10), whereas extremely bulky ligands afforded poor results (entries 13–15). In addition, trialkylphosphines and phosphites afforded **3a** in 14–24% yields (entries 16–19). Notably, the yields of **3a** were also affected by the Pd/L ratio. The use of P*m*-Tol_3 with a Pd/L ratio of 1/1 afforded **3a** in the highest yield (42%, entry 10), whereas higher ligand loadings (Pd/L = 1/2 and 1/4) led to lower yields of **3a** (24% and 25% yields in entries 11 and 12), respectively. Relatedly, the use of bidentate ligands [3 mol% $Pd_2(dba)_3{\cdot}CHCl_3$, 6 mol% $Ph_2P(CH_2)_nPPh_2$ (n = 1–4) or 6 mol% dppf, Pd/P = 1/2] also afforded poor yields of **3a** (9–16% yields, not shown).

The concentration of **1a** strongly affected the product yield (Table 2). Higher concentrations (0.5 and 0.1 mol/L, entries 1 and 2) led to decreased yields of **3a** to 4% and 19%, respectively, affording a complex reaction mixture. Reaction using higher concentrations presumably caused undesired intermolecular reactions. On the other hand, the reaction conducted using lower concentration (0.01 mol/L) led to the increased yield of **3a** to 49% (entry 4), whereas highly diluted conditions (0.001 mol/L) afforded a lower yield (10%, entry 5). The survey of solvents revealed that DMF is the most suitable solvent for this insertion reaction (entries 6–9). Use of 50 equiv of ethanol led to generation of **3a** in the highest 76% yield (entry 10).

Table 2. Effect of substrate concentration and solvent [a]



Entry	Conditions	**1a** (mol/L)	**3a** (%)	**1a** (%) [b]
1	DMF, 120 °C, 2 h	0.5	4	–
2	DMF, 120 °C, 2 h	0.1	19	–
3 [c]	DMF, 120 °C, 2 h	0.04	42	–
4	DMF, 120 °C, 2 h	0.01	49	–
5	DMF, 120 °C, 2 h	0.001	10	–
6	DMA, 110 °C, 2 h	0.04	12	–
7	DMSO, 110 °C, 2 h	0.04	31	–
8	1,4-Dioxane, 100 °C, 1 h	0.04	–	75
9	Toluene, 110 °C, 2 h	0.04	–	–
10 [d]	DMF, 120 °C, 2 h	0.01	76	–

[a] ^{19}F NMR yield based on the internal standard $PhCF_3$. [b] Recovery. [c] Table 1, Entry 10. [d] EtOH 50 equiv. DMA = *N*,*N*-dimethylacetamide.

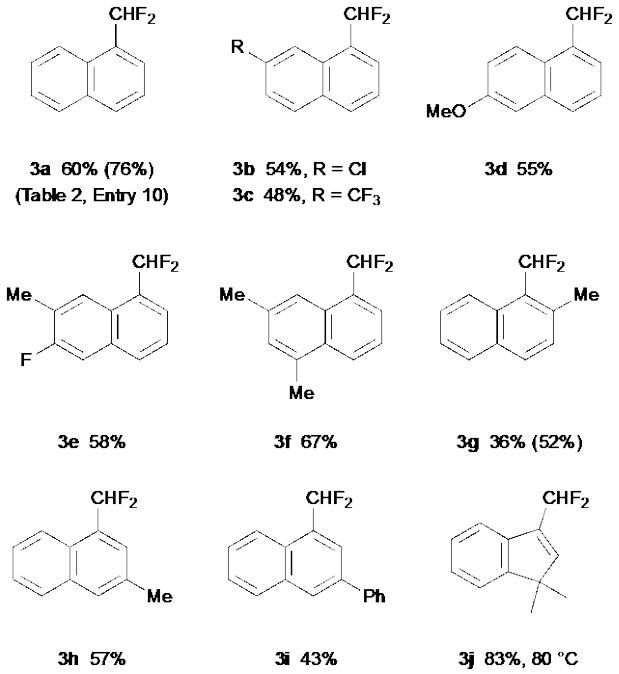
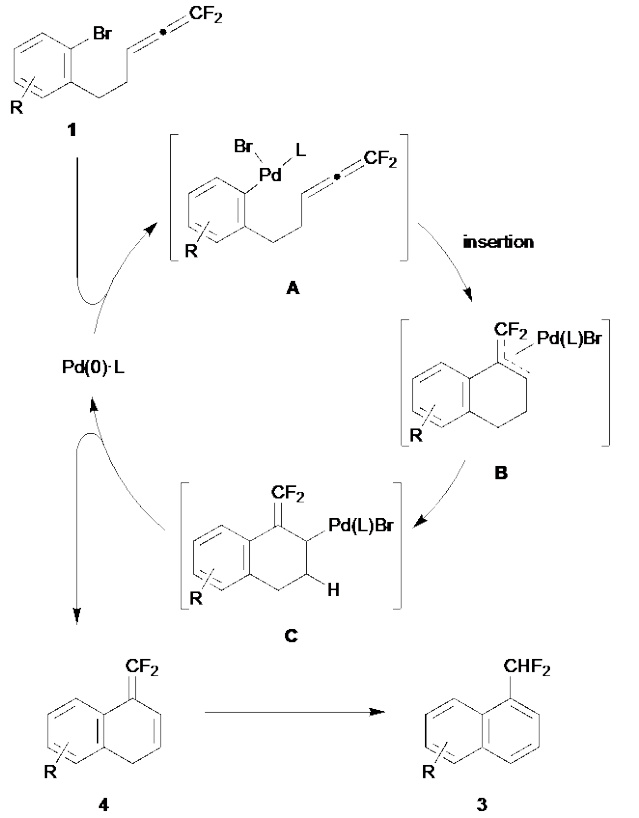


Fig. 1 Synthesis of (difluoromethyl)naphthalenes [^{19}F NMR yield based on the internal standard $PhCF_3$ in parentheses; conditions: **1** (0.01 M), 3 mol% $Pd_2(dba)_3{\cdot}CHCl_3$, 6 mol% P*m*-Tol_3, EtOH 50 equiv, K_2CO_3 5.0 equiv, DMF, 120 °C, 2 h].

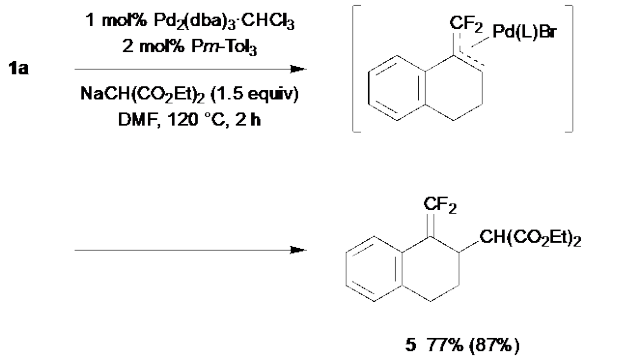
(Difluoromethyl)naphthalenes were synthesized under the optimized conditions (Fig. 1). Electron-withdrawing and -donating groups on the tethered benzene ring did not affect the reaction. Thus, (difluoromethyl)naphthalenes **3a–f** were isolated in 48–67% yields. In addition, disubstituted difluoroallenes participated in the reaction, affording naphthalene **3g** in a decreased yield (52% by ^{19}F NMR). 1,1-Difluoroallenes bearing a methyl or phenyl group at the position δ to the fluorine substituents afforded corresponding

products **3h** and **3i** in 57% and 43% yields, respectively. This intramolecular insertion was applicable not only for six-membered ring construction but also for five-membered ring construction. 1,1-Difluoroallene, having a CMe_2 tether instead of an ethyelene tether afforded the corresponding **3j** in 83% yield.[22]

The plausible mechanism is described in Scheme 3. Bromoallenes **1** undergo oxidative addition to palladium(0), affording arylpalladium(II) bromides **A**. Intermediates **A** undergo regioselective insertion to generate more stable π-allylpalladium(II) intermediates **B**, forming a C–C bond at the position β to the fluorine substituents.[23] Taking the effects of the steric bulk of the ligand and the Pd/L ratio (1/1) into consideration (Table 1), it is supposed that the Pd(0)·L complex is the catalytically active species, and the steric bulk of the ligand can suppress the formation of Pd(0)·L_n complexes (n > 1), which must be less reactive for the coordination and insertion of the difluoroallene moiety in **A**. β-Hydrogen elimination from σ-allylpalladium(II) intermediates **C** affords cyclic 1,1-difluoro-1,3-dienes **4**, whose isomerization provides **3**. Shibasaki has reported that the use of pinacol as an additive for the Heck reaction of alkenyl triflates leads to the



Scheme 3. Proposed catalytic cycle.



Scheme 4 The Tsuji–Trost reaction of difluorinated π-allylpalladium(II) intermediate (^{19}F NMR yield based on the internal standard $PhCF_3$ in parentheses).

stabilization of a reactive Pd(0)·L_2 complex.[24,25] In the present system, ethanol might stabilize the reactive Pd(0)·L complex via coordination.

This is the first example to generate terminally fluorinated π-allylpalladium(II) intermediates not through oxidative addition but insertion.[26] The π-allylpalladium(II) intermediates thus-formed underwent Tsuji–Trost reaction at the position γ to the fluorine substituents (Scheme 4) and the corresponding alkylation product **5** was obtained in 77% yield.[26b]

Conclusion

In this study, the palladium-catalyzed C–C bond formation via intramolecular insertion of 1,1-difluoroallenes was accomplished for the first time. When *o*-bromophenyl-bearing 1,1-difluoroallenes were treated with a Pd(0) complex, C–C bond formation at the position β to the fluorine substituents occurred, affording pharmaceutically and agrochemically promising (difluoromethyl)naphthalenes. Thus, the β-selective C–C bond formation reaction has newly joined the existing α- and γ-selective bond formation reactions of 1,1-difluroallenes.

Experimental

Preparation of 1,1-difluoroallenes

1,1-Difluoroallenes **1a–j** were prepared by our reported method.[21]

5-(2-Bromo-4-chlorophenyl)-1,1-difluoropenta-1,2-diene (**1b**): ^1H NMR (500 MHz; $CDCl_3$; $SiMe_4$): δ 2.51–2.59 (m, 2H), 2.87 (dd, *J* = 22.6, 7.6 Hz, 1H), 2.89 (t, *J* = 7.7 Hz, 1H), 6.48 (tt, *J* = 6.0 Hz, J_{HF} = 2.5 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.23 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.56 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (101 MHz; $CDCl_3$; $SiMe_4$): δ 31.9, 33.5, 120.6 (t, J_{CF} = 5 Hz), 124.5, 127.7, 131.0, 132.5, 132.8, 138.5, 152.9 (t, J_{CF} = 260 Hz), 170.5 (t, J_{CF} = 36 Hz); ^{19}F NMR (470 MHz; $CDCl_3$; C_6F_6): δ 60.4 (br s); IR (neat): ν 2015, 1464, 1201, 818 cm^{-1}; HRMS (EI): *m/z* calcd. for $C_{11}H_8BrClF_2$ $[M]^+$: 291.9466; Found: 291.9453.

5-[2-Bromo-4-(trifluoromethyl)phenyl]-1,1-difluoropenta-1,2-diene (**1c**): ^{1}H NMR (500 MHz; $CDCl_3$; $SiMe_4$): δ 2.55–2.63 (m, 2H), 2.98 (t, *J* = 8.0 Hz, 2H), 6.49 (tt, *J* = 5.5 Hz, J_{HF} = 2.5 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.81 (s, 1H); ^{13}C NMR (126 MHz; $CDCl_3$; $SiMe_4$): δ 31.7, 34.1, 120.3 (t, J_{CF} = 6 Hz), 123.2 (q, J_{CF} = 273 Hz), 124.4 (q, J_{CF} = 4 Hz), 124.5, 130.0 (q, J_{CF} = 6 Hz), 130.5 (q, J_{CF} = 33 Hz), 130.6, 144.1, 153.0 (t, J_{CF} = 262 Hz), 170.9 (t, J_{CF} = 36 Hz); ^{19}F NMR (470 MHz, $CDCl_3$; C_6F_6): δ 60.6 (br s, 2F), 99.1 (s, 3F); IR (neat): ν 2941, 2011, 1462, 1321, 1122, 1171, 1078, 829 cm^{-1}; HRMS (EI): *m/z* calcd. for $C_{12}H_8BrF_5$ [M]$^+$: 325.9730; Found: 325.9731.

5-(2-Bromo-5-methoxylphenyl)-1,1-difluoropenta-1,2-diene (**1d**): ^{1}H NMR (400 MHz; $CDCl_3$; $SiMe_4$): δ 2.55 (m, 2H), 2.86 (t, *J* = 7.8 Hz, 2H), 3.76 (s, 3H), 6.48 (tt, *J* = 6.0 Hz, J_{HF} = 2.4 Hz, 1H), 6.64 (dd, *J* = 8.8, 3.0 Hz, 1H), 6.75 (d, *J* = 3.0 Hz, 1H), 7.40 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (101 MHz; $CDCl_3$; $SiMe_4$): δ 32.0, 34.3, 55.3, 113.6, 114.7, 116.1, 121.0 (t, J_{CF} = 5 Hz), 133.4, 140.8, 152.8 (t, J_{CF} = 260 Hz), 159.0, 170.2 (t, J_{CF} = 36 Hz); ^{19}F NMR (376 MHz, $CDCl_3$; C_6F_6): δ 60.3–60.4 (m); IR (neat): ν 2937, 2837, 2011, 1460, 1240, 1190, 1055, 802 cm^{-1}; HRMS (EI): *m/z* calcd. for $C_{12}H_{11}BrF_2O$ [M]$^+$: 287.9961; Found: 287.9949.

5-(2-Bromo-5-fluoro-4-methylphenyl)-1,1-difluoropenta-1,2-diene (**1e**): ^{1}H NMR (400 MHz; $CDCl_3$; $SiMe_4$): δ 2.22 (s, 3H), 2.50–2.59 (m, 2H), 2.86 (t, *J* = 7.8 Hz, 2H), 6.47 (tt, *J* = 6.0 Hz, J_{HF} = 2.6 Hz, 1H), 6.87 (d, J_{HF} = 10.0 Hz, 1H), 7.35 (d, *J* = 6.8 Hz, 1H); ^{13}C NMR (101 MHz; $CDCl_3$; $SiMe_4$): δ 13.9 (d, J_{CF} = 3 Hz), 31.9, 33.8, 116.7 (d, J_{CF} = 24 Hz), 117.8 (d, J_{CF} = 3 Hz), 120.7 (t, J_{CF} = 5 Hz), 125.0 (d, J_{CF} = 18 Hz), 135.1 (d, J_{CF} = 6 Hz), 139.0 (d, J_{CF} = 7 Hz), 152.9 (t, J_{CF} = 260 Hz), 160.4 (d, J_{CF} = 244 Hz), 170.5 (t, J_{CF} = 36 Hz); ^{19}F NMR (376 MHz, $CDCl_3$; C_6F_6): δ 42.5 (ddq, J_{HF} = 10, 7, 1 Hz, 1F), 60.4 (td, J_{FH} = 6, 3 Hz, 2F); IR (neat): ν 2931, 2866, 2011, 1485, 1460, 1192, 1134, 881 cm^{-1}; HRMS (EI): *m/z* calcd. for $C_{12}H_{10}BrF_3$ [M]$^+$: 289.9918; Found: 289.9922.

5-(2-Bromo-4,6-dimethylphenyl)-1,1-difluoropenta-1,2-diene (**1f**): ^{1}H NMR (400 MHz; $CDCl_3$; $SiMe_4$): δ 2.25 (s, 3H), 2.31 (s, 3H), 2.37–2.49 (m, 2H), 2.92 (t, *J* = 8.0 Hz, 2H), 6.48–6.55 (m, 1H), 6.91 (s, 1H), 7.23 (s, 1H); ^{13}C NMR (101 MHz; $CDCl_3$; $SiMe_4$): δ 20.4, 20.5, 30.7, 31.1, 121.4 (t, J_{CF} = 5 Hz), 125.1, 130.5, 131.2, 135.2, 137.5, 137.7, 152.8 (t, J_{CF} = 259 Hz), 169.9 (t, J_{CF} = 36 Hz); ^{19}F NMR (376 MHz, $CDCl_3$; C_6F_6): δ 60.2–60.3 (m); IR (neat): ν 2951, 2920, 2009, 1460, 1190, 955, 850 cm^{-1}; HRMS (EI): *m/z* calcd. for $C_{13}H_{13}BrF_2$ [M]$^+$: 286.0169; Found: 286.0181.

5-(2-Bromophenyl)-3-methyl-1,1-difluoropenta-1,2-diene (**1g**): ^{1}H NMR (500 MHz; $CDCl_3$; $SiMe_4$): δ 1.98 (t, J_{HF} = 5.0 Hz, 3H), 2.48 (tt, *J* = 8.0 Hz, J_{HF} = 5.5 Hz, 2H), 2.89 (t, *J* = 8.0 Hz, 2H), 7.07 (ddd, *J* = 7.8, 7.0, 2.1 Hz, 1H), 7.18–7.25 (m, 2H), 7.53 (dd, *J* = 7.0, 1.2 Hz, 1H); ^{13}C NMR (126 MHz; $CDCl_3$; $SiMe_4$): δ 22.9, 33.9, 37.0, 124.3, 127.5, 127.9, 130.3, 132.0 (t, J_{CF} = 6 Hz), 132.9, 140.3, 150.4 (t, J_{CF} = 260 Hz), 163.2 (t, J_{CF} = 35 Hz); ^{19}F NMR (470 MHz, $CDCl_3$; C_6F_6): δ 61.6 (tq, J_{FH} = 5.5, 5.0 Hz); IR (neat): ν 2993, 2922, 2004, 1479, 1176, 1159, 748 cm^{-1}; HRMS (EI): *m/z* calcd. for $C_{12}H_{11}BrF_2$ [M]$^+$: 272.0012; Found: 272.0005.

5-(2-Bromophenyl)-4-methyl-1,1-difluoropenta-1,2-diene (**1h**): ^{1}H NMR (400 MHz; $CDCl_3$; $SiMe_4$): δ 1.06–1.14 (m, 3H), 2.65–2.88 (m, 2H), 2.88–3.00 (m, 1H), 6.45 (ddd, *J* = 7.6, 5.2, 2.4 Hz, 1H), 7.02–7.13 (m, 1H), 7.13–7.20 (m, 1H), 7.20–7.32 (m, 1H), 7.54 (dd, *J* = 8.4, 3.6 Hz, 1H); ^{13}C NMR (101 MHz; $CDCl_3$; $SiMe_4$): δ 18.5, 36.7, 42.0, 124.7, 126.5 (dd, J_{CF} = 5, 5 Hz), 127.3, 128.1, 131.4, 133.0, 138.9, 153.4 (dd, J_{CF} = 259, 259 Hz), 168.9 (dd, J_{CF} = 36, 36 Hz); ^{19}F NMR (376 MHz, $CDCl_3$; C_6F_6): δ 60.1 (dm, *J* = 121 Hz, 1F), 60.5 (dm, *J* = 121 Hz, 1F); IR (neat): ν 2968, 2931, 2009, 1446, 1238, 1194, 746 cm^{-1}; HRMS (EI): *m/z* calcd. for $C_{12}H_{11}BrF_2$ [M]$^+$: 272.0012; Found: 272.0005.

5-(2-Bromophenyl)-4-phenyl-1,1-difluoropenta-1,2-diene (**1i**): ^{1}H NMR (500 MHz; $CDCl_3$; $SiMe_4$): δ 3.03 (dd, *J* = 14.0, 7.5 Hz, 1H), 3.32 (dd, *J* = 14.0, 7.5 Hz, 1H), 3.91–3.99 (m, 1H) 6.62 (ddd, *J* = 6.5 Hz, J_{HF} = 2.5, 2.5 Hz, 1H), 6.86 (d, *J* = 7.5 Hz, 1H), 7.03 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.08 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.23 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.29 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.52 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (126 MHz; $CDCl_3$; $SiMe_4$): δ 41.7, 48.0, 123.9 (dd, J_{CF} = 6, 6 Hz), 124.6, 127.1, 127.2, 128.0, 128.1, 128.6, 131.6, 132.8, 138.3, 140.6, 153.4 (dd, J_{CF} = 263, 263 Hz), 170.4 (dd, J_{CF} = 37, 37 Hz); ^{19}F NMR (470 MHz, $CDCl_3$; C_6F_6): δ 60.7 (ddd, *J* = 119 Hz, J_{FH} = 4, 3 Hz, 1F), 61.5 (ddd, *J* = 119 Hz, J_{FH} = 5, 3 Hz, 1F); IR (neat): ν 3030, 2925, 2009, 1450, 1194, 744, 698 cm^{-1}; HRMS (EI): *m/z* calcd. for $C_{17}H_{13}BrF_2$ [M]$^+$: 334.0169; Found: 334.0173.

4-(2-Bromophenyl)-4-methyl-1,1-difluoropenta-1,2-diene (**1j**): ^{1}H NMR (500 MHz; $CDCl_3$; $SiMe_4$): δ 1.62 (s, 6H), 6.75 (t, J_{HF} = 2.4 Hz, 1H) 7.11 (ddd, *J* = 7.6, 7.6, 1.6 Hz, 1H), 7.30 (ddd, *J* = 7.6, 7.6, 1.6 Hz, 1H), 7.43 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.61 (dd, *J* = 7.6, 1.6 Hz, 1H); ^{13}C NMR (101 MHz; $CDCl_3$; $SiMe_4$): δ 28.1, 43.8, 123.2, 127.4, 128.0, 128.5, 130.7 (t, J_{CF} = 6 Hz), 135.5, 144.5, 153.2 (t, J_{CF} = 260 Hz), 167.6 (t, J_{FC} = 36 Hz); ^{19}F NMR (470 MHz, $CDCl_3$; C_6F_6): δ 60.9 (d, J_{FH} = 2 Hz); IR (neat): ν 2974, 2009, 1435, 1192, 752 cm^{-1}; HRMS (EI): *m/z* calcd. for $C_{12}H_{11}BrF_2$ [M]$^+$: 272.0012; Found: 272.0018.

Synthesis of (difluoromethyl)naphthalenes and (difluoromethyl)indenes

Synthesis of **3a** is described as a typical procedure. The mixture of $Pd_2(dba)_3$·$CHCl_3$ (4.0 mg, 3.9 mol%), P*m*-Tol_3 (2.4 mg, 7.8 mol%), K_2CO_3 (89.9 mg, 0.650 mmol), ethanol (0.380 ml, 6.50 mmol) in DMF (10 mL) was stirred for 15 min at room temperature under argon. A solution of **1a** (33.6 mg, 0.130 mmol) in DMF (3 mL) was added to the mixture, and then heated to 120 °C. After stirring for 2 h at the same temperature, the mixture was cooled to room temperature, and then $PhCF_3$ (16.2 mg, 0.111 mmol) was added as an internal standard. (Difluoromethyl)naphthalene **3a** was obtained in 76% yield that determined by ^{19}F NMR. The reaction was quenched with aq. NaOH (2 mol/L, 15 mL), and the organic products were extracted with Et_2O. The combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (pentane). 1-(Difluoromethyl)naphthalene **3a** was obtained as a colorless liquid (14.0 mg, 60%). The spectral data of **3a** met complete agreement with those in literature.[8b]

7-Chloro-1-(difluoromethyl)naphthalene (**3b**): ^{1}H NMR (500 MHz; $CDCl_3$; $SiMe_4$): δ 7.06 (t, J_{HF} = 55.0 Hz, 1H), 7.47–7.53 (m, 2H), 7.70 (dd, *J* = 7.1, 1.0 Hz, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 7.94 (d, *J* = 8.3 Hz, 1H), 8.16 (s, 1H); ^{13}C NMR (126 MHz; $CDCl_3$; $SiMe_4$): δ 115.2 (t, J_{CF} = 239 Hz), 122,88, 122.90, 124.9, 125.9 (t, J_{CF} = 9 Hz), 127.4, 128.9 (t,

J_{CF} = 21 Hz), 130.2, 131.3, 132.0, 133.3; ^{19}F NMR (470 MHz, $CDCl_3$; C_6F_6): δ 51.0 (d, J_{FH} = 55 Hz); IR (neat): ν 3059, 2974, 1583, 1502, 1176, 1113, 1092, 1020, 829, 750 cm^{-1}; HRMS (EI): *m/z* calcd. for $C_{11}H_7ClF_2$ [M]$^+$: 212.0204; Found: 212.0199.

1-Difluoromethyl-7-(trifluoromethyl)naphthalene (**3c**): ^{1}H NMR (500 MHz; $CDCl_3$; $SiMe_4$): δ 7.13 (t, J_{HF} = 54.8 Hz, 1H), 7.64 (dd, *J* = 7.7 Hz, 1H), 7.74 (dd, *J* = 8.7, 1.4 Hz, 1H), 7.78 (d, *J* = 7.0 Hz, 1H), 8.03 (d, *J* = 8.7 Hz, 2H) 8.49 (s, 1H); ^{13}C NMR (126 MHz; $CDCl_3$; $SiMe_4$): δ 115.1 (t, J_{CF} = 240 Hz), 121.6 (q, J_{CF} = 5 Hz), 122.2 (q, J_{CF} = 3 Hz), 124.1 (q, J_{CF} = 273 Hz), 126.2 (t, J_{CF} = 9 Hz), 126.9, 128.7, 129.1 (q, J_{CF} = 32 Hz), 129.8, 130.7 (t, J_{CF} = 21 Hz), 131.4, 135.0; ^{19}F NMR (470 MHz, $CDCl_3$; C_6F_6): δ 51.4 (d, J_{FH} = 55 Hz, 2F), 99.3 (s, 3F); IR (neat): ν 1315, 1165, 1122, 1076, 1028, 839 cm^{-1}; HRMS (EI): *m/z* calcd. for $C_{12}H_7F_5$ [M]$^+$: 246.0468; Found: 246.0477.

1-Difluoromethyl-6-methoxynaphthalene (**3d**): ^{1}H NMR (400 MHz; $CDCl_3$; $SiMe_4$): δ 3.91 (s, 3H), 7.05 (t, J_{HF} = 55.2 Hz, 1H), 7.18 (d, *J* = 2.6 Hz, 1H), 7.24 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.43 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.83 (d, *J* = 7.6 Hz, 1H), 8.07 (d, *J* = 9.2 Hz, 1H); ^{13}C NMR (101 MHz; $CDCl_3$; $SiMe_4$): δ 55.3, 106.7, 115.6 (t, J_{CF} = 237 Hz), 119.8, 122.6 (t, J_{CF} = 9 Hz), 125.0, 125.15, 125.23, 129.6 (t, J_{CF} = 21 Hz), 130.3, 135.3, 157.8; ^{19}F NMR (376 MHz, $CDCl_3$; C_6F_6): δ 51.5 (d, J_{FH} = 55 Hz); IR (neat): ν 2960, 2933, 1630, 1518, 1261, 1105, 1022 cm^{-1}; HRMS (EI): *m/z* calcd. for $C_{12}H_{10}F_2O$ [M]$^+$: 208.0700; Found: 208.0697.

1-Difluoromethyl-6-fluoro-7-methylnaphthalene (**3e**): ^{1}H NMR (500 MHz; $CDCl_3$; $SiMe_4$): δ 2.48 (s, 3H), 7.05 (t, J_{HF} = 55.1 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.46 (d, *J* = 9.0, 1H), 7.59 (d, *J* = 7.5 Hz, 1H), 7.84 (d, *J* = 9.0 Hz, 1H), 7.98 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (126 MHz; $CDCl_3$; $SiMe_4$): δ 15.6 (d, J_{CF} = 4 Hz), 111.4 (d, J_{CF} = 22 Hz), 115.6 (t, J_{CF} = 239 Hz), 124.2 (td, J_{CF} = 9, 2 Hz), 124.8, 126.0 (d, J_{CF} = 6 Hz), 127.4 (d, J_{CF} = 21 Hz), 128.0 (d, J_{CF} = 10 Hz), 129.1 (t, J_{CF} = 21 Hz), 130.5 (d, J_{CF} = 5 Hz), 133.7 (d, J_{CF} = 10 Hz), 160.2 (d, J_{CF} = 249 Hz); ^{19}F NMR (470 MHz, $CDCl_3$; C_6F_6): δ 44.1 (dd, *J* = 9, 9 Hz, 1F), 51.5 (d, J_{FH} = 55 Hz, 2F); IR (neat): ν 2966, 1514, 1250, 1095, 1026, 870 cm^{-1}; HRMS (EI): *m/z* calcd. for $C_{12}H_9F_3$ [M]$^+$: 210.0656; Found: 210.0663.

1-Difluoromethyl-5,7-dimethylnaphthalene (**3f**): ^{1}H NMR (400 MHz; $CDCl_3$; $SiMe_4$): δ 2.51 (s, 3H), 2.68 (s, 3H), 7.13 (t, J_{HF} = 55.2 Hz, 1H), 7.24 (s, 1H), 7.46 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.77 (s, 1H), 8.08 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (101 MHz; $CDCl_3$; $SiMe_4$): δ 19.7, 22.1, 115.4 (t, J_{CF} = 237 Hz), 120.6, 123.6, 124.4 (t, J_{CF} = 9 Hz), 127.3, 129.2 (t, J_{CF} = 21 Hz), 129.5, 130.3, 131.2, 134.8, 136.7; ^{19}F NMR (376 MHz, $CDCl_3$; C_6F_6): δ 50.7 (d, J_{FH} = 55 Hz); IR (neat): ν 2974, 1383, 1134, 1016, 810, 758, 748 cm^{-1}; HRMS (EI): *m/z* calcd. for $C_{13}H_{12}F_2$ [M]$^+$: 206.0907; Found: 206.0912.

1-Difluoromethyl-2-methylnaphthalene (**3g**): ^{1}H NMR (500 MHz; $CDCl_3$; $SiMe_4$): δ 2.64 (t, *J* = 1.9 Hz, 3H), 7.29 (d, *J* = 8.5 Hz, 1H), 7.37 (t, J_{HF} = 54.0 Hz, 1H), 7.47 (dd, *J* = 7.2 Hz, 1H), 7.55 (ddd, *J* = 8.4, 7.2, 1.4 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 2H), 8.34 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR (126 MHz; $CDCl_3$; $SiMe_4$): δ 19.5, 114.7 (t, J_{CF} = 236 Hz), 124.3 (t, J_{CF} = 3 Hz), 125.5, 126.2, 127.0, 128.5, 129.0, 130.4, 131.2, 132.7, 135.4 (t, J_{CF} = 7 Hz); ^{19}F NMR (470 MHz, $CDCl_3$; C_6F_6): δ 52.6 (d, *J* = 54 Hz); IR (neat): ν 2927, 1818, 1512, 1186, 1099, 1036, 1011, 814, 742 cm^{-1}; HRMS (EI): *m/z* calcd. for $C_{12}H_{10}F_2$ [M]$^+$: 192.0751; Found: 192.0730.

1-Difluoromethyl-3-methylnaphthalene (**3h**): ^{1}H NMR (500 MHz; $CDCl_3$; $SiMe_4$): δ 2.53 (s, 3H), 7.10 (t, J_{HF} = 55.3 Hz, 1H), 7.50–7.55 (m, 3H), 7.72 (s, 1H), 7.80–7.84 (m, 1H), 8.08–8.13 (m, 1H); ^{13}C NMR (126 MHz; $CDCl_3$; $SiMe_4$): δ 21.5, 115.4 (t, J_{CF} = 239 Hz), 123.3, 126.2, 126.4, 127.0 (t, J_{CF} = 9 Hz), 127.9, 128.1 (t, J_{CF} = 13 Hz), 129.3 (t, J_{CF} = 21 Hz), 130.3, 134.1, 134.4; ^{19}F NMR (470 MHz, $CDCl_3$; C_6F_6): δ 50.8 (d, J_{FH} = 55 Hz); IR (neat): ν: 2966, 1514, 1346, 1111, 1018, 877, 748 cm^{-1}; HRMS (EI): *m/z* calcd. for $C_{12}H_{10}F_2$ [M]$^+$: 192.0751; Found: 192.0758.

1-Difluoromethyl-3-phenylnaphthalene (**3i**): ^{1}H NMR (500 MHz; $CDCl_3$; $SiMe_4$): δ 2.51 (s, 3H), 2.68 (s, 3H), 7.13 (t, J_{HF} = 55.2 Hz, 1H), 7.24 (s, 1H), 7.46 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.77 (s, 1H), 8.08 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (126 MHz; $CDCl_3$; $SiMe_4$): δ 115.4 (t, J_{CF} = 239 Hz), 123.4, 124.6 (t, J_{CF} = 9 Hz), 126.8, 127.2, 127.3, 127.8, 128.8, 129.0, 129.1, 130.1 (t, J_{CF} = 21 Hz), 134.2, 137.6, 140.1; ^{19}F NMR (470 MHz, $CDCl_3$; C_6F_6): δ 50.7 (d, J_{FH} = 55 Hz); IR (neat): ν 3060, 2924, 1603, 1346, 1246, 1113, 1022, 889 cm^{-1}; HRMS (EI): *m/z* calcd. for $C_{17}H_{12}F_2$ [M]$^+$: 254.0907; Found: 254.0919.

3-Difluoromethyl-1,1-dimethylindene (**3j**): ^{1}H NMR (500 MHz; $CDCl_3$; $SiMe_4$): δ 1.35 (s, 6H), 6.60 (t, J_{HF} = 3.0 Hz, 1H), 6.62 (t, J_{HF} = 55.3 Hz, 1H), 7.21–7.30 (m, 2H), 7.32–7.37 (m, 1H), 7.43–7.48 (m, 1H); ^{13}C NMR (126 MHz; $CDCl_3$; $SiMe_4$): δ 24.0, 49.0, 112.8 (t, J_{CF} = 234 Hz), 120.9, 121.5, 126.2, 126.7, 134.5 (t, J_{CF} = 23 Hz), 137.8, 147.1 (t, J_{CF} = 9 Hz), 153.5; ^{19}F NMR (470 MHz, $CDCl_3$; C_6F_6): δ 47.2 (dd, J_{FH} = 55, 3 Hz); IR (neat): ν 2962, 2925, 2856, 1469, 1375, 1022, 818, 771 cm^{-1}; HRMS (EI): *m/z* calcd. for $C_{12}H_{12}F_2$ [M]$^+$: 194.0907; Found: 194.0905.

1-Difluoromethylidene-2-di(ethoxycarbonyl)methyl-1,2,3,4-tetrahydronaphthalene (**5**): ^{1}H NMR (500 MHz; $CDCl_3$; $SiMe_4$): δ 1.22 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.97–2.09 (m, 2H), 2.81 (ddd, *J* = 17.7, 5.9, 3.8 Hz, 1H), 2.88 (ddd, *J* = 17.7, 10.7, 6.9 Hz, 1H), 3.43 (d, *J* = 11.1 Hz, 1H), 3.61–3.67 (m, 1H), 4.13 (dq, *J* = 10.9, 7.1 Hz, 1H), 4.17 (dq, *J* = 10.9, 7.1 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 7.11–7.15 (m, 1H), 7.18 (dd, *J* = 3.5, 3.5 Hz, 1H), 7.19 (dd, *J* = 3.5, 3.5 Hz, 1H), 7.43 (ddd, *J* = 5.7, 3.5, 3.5 Hz, 1H); ^{13}C NMR (126 MHz; $CDCl_3$; $SiMe_4$): δ 13.9, 14.0, 25.1, 25.3, 32.7, 52.9, 61.4, 61.5, 90.0 (dd, J_{CF} = 22, 11 Hz), 126.3, 127.2, 127.4 (dd, J_{CF} = 4, 4 Hz), 128.0, 128.1, 129.0, 135.49, 135.53, 152.9 (dd, J_{CF} = 293, 286 Hz); ^{19}F NMR (470 MHz, $CDCl_3$; C_6F_6): δ 73.5 (d, *J* = 36 Hz, 1F), 76.8 (d, *J* = 36 Hz, 1F); IR (neat): ν 2981, 2937, 1755, 1728, 1240, 1032, 766 cm^{-1}; HRMS (EI): *m/z* calcd. for $C_{18}H_{20}F_2O_4$ [M]$^+$: 338.1330; Found: 338.1325.

Conflicts of interest

There are no conflicts to declare.

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