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Copper-Catalyzed Allylation of α,α-Difluoro-Substituted Organozinc Reagents

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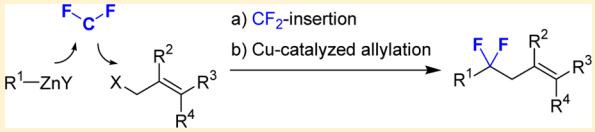
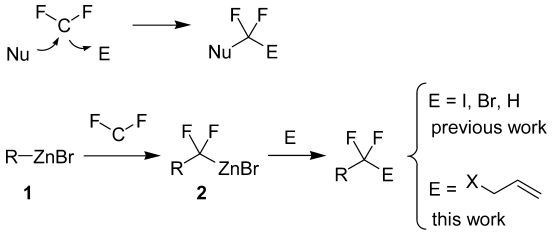
Supporting Information

ABSTRACT: A method for the coupling of organozinc reagents, difluorocarbene, and allylic electrophiles is described. The reaction involves insertion of difluorocarbene into the carbon−zinc bond followed by copper-catalyzed allylic substitution.



Because of the ability of the CF_2 fragment to serve as bioisostere of ether oxygen or a carbonyl group, compounds containing difluoromethylene units have gained increasing attention in medicinal chemistry.[1] At the same time, existing methodologies for the synthesis of organofluorine compounds of this type[2] suffer from a number of disadvantages such as hazardous/harsh reagents (deoxofluorination process)[3] or multistep synthetic sequences starting from widely available fluorinated chemicals.[4,5] Recently, we introduced a concept for assembling CF_2-containing products from three independent components: difluorocarbene, nucleophile, and electrophile[6] (Scheme 1). Organozinc reagents **1** were used as nucleophiles,

Scheme 1. Synthesis of CF_2-Containing Products

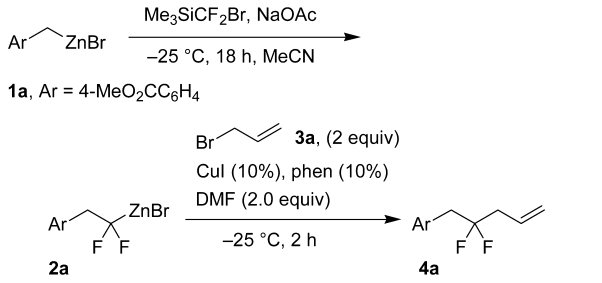


generating *gem*-difluorinated organozinc species **2**, which were quenched by halogen or a proton.[6] Herein we demonstrate the use of allylic electrophiles as the final component. Notably, this one-pot protocol for assembling fluorinated products from three parts involves the formation of two C−C bonds.[7]

Fluorinated organozinc reagents typically exhibit low reactivity toward various carbon-centered electrophiles.[8] However, the presence of copper(I) salts may induce zinc/copper exchange to generate fluorinated organocopper species, which are expected to undergo coupling with allylic electrophiles.[9−11]

(Bromodifluoromethyl)trimethylsilane (Me_3SiCF_2Br) in the presence of a basic activator was used as a source of difluorocarbene.[12] Organozinc reagent **2a** generated from 4-methoxycarbonylbenzylzinc bromide under typical conditions[6] was selected as a model substrate, and its reaction with allyl bromide (**3a**) was evaluated (Table 1). The coupling of **2a** and **3a** proceeded cleanly within 2 h at −25 °C in the presence of 10 mol

Table 1. Allylation of Reagent 1a



entry	deviation from standard conditions	yield of **4a** (%)
1	none	88
2	no CuI, phen, DMF	16[a]
3	no phen	41[a]
4	no DMF	68[a]
5	allyl chloride instead of **3a**	82

[a]Determined by ^{19}F NMR analysis with $PhCF_3$ as an internal standard.

% copper iodide/1,10-phenanthroline combination with 2 equiv of dimethylformamide as an additive, affording product **4a** in 88% yield (entry 1). 1,10-Phenanthroline (phen) is a typical ligand in copper-catalyzed processes,[13] whereas the role of dimethylformamide is to stabilize reagents **2** through coordination with zinc.[6] Allyl chloride can be used instead of allyl bromide, leading to the product in slightly reduced yield (entry 5). Interestingly, even in the absence of copper the coupling product was slowly formed (entry 2). Presumably, the copper-free reaction proceeds because of the Lewis acidic nature of the organozinc reagent.[14]

Under the optimized conditions, benzyl- and alkylzinc reagents were coupled with allyl bromides or chlorides (Table

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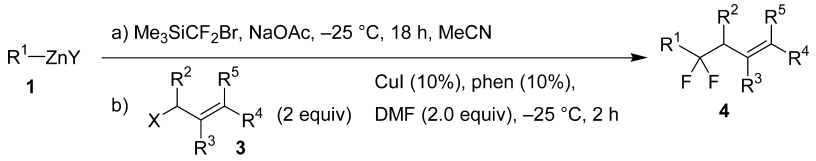
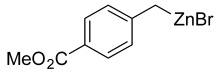
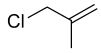
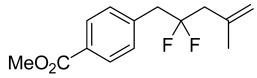
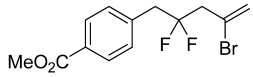
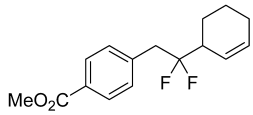
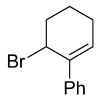
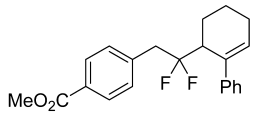
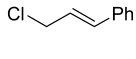
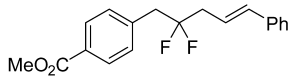
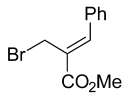
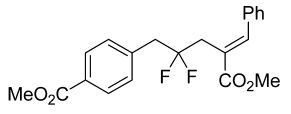
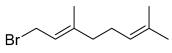
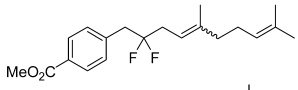
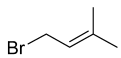
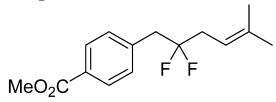
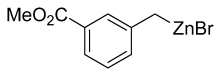
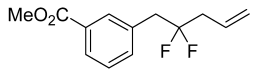
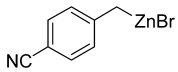
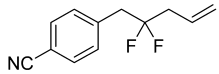
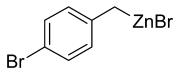
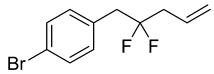
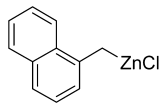
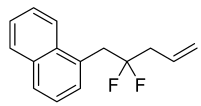
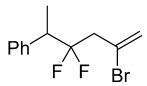
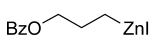
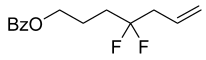
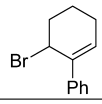
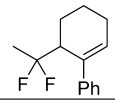
Table 2. Allylation of Organozinc Reagents



Entry	1	3		4		Yield of 4, %[a]
1		1a		3b		4b	76
2		1a		3c		4c	76
3		1a		3d		4d	90
4		1a		3e[b]		4e	76
5		1a		3f[b]		4f	75
6		1a		3g[b]		4g	66
7		1a		3h[b]		4h	71[c]
8		1a		3i		4i	80
9		1b		3a		4j	76
10		1c		3a		4k	80
11		1d		3a		4l	81
12		1e		3a		4m	78
13		1f		3c		4n	74
14		1g		3a		4o	70
15	Me—ZnI	1i		3e		4p	66[d]

[a]Based on organozinc halide. [b]1.33 equiv of allylating reagent was used. [c]3:1 mixture of geometrical isomers. [d]1.5 equiv of MeZnI relative to **3e**; the yield is based on **3e**.

2). The coupling tolerates ester and nitrile functional groups and provides products **4** in good yields. With respect to the allylic component, the reaction afforded products in which the fluorinated nucleophile is attached to the less substituted carbon (entries 5–8). It should be pointed out that (*E*)-geranyl bromide (**3h**) afforded product **4h** as an inseparable mixture of geometrical isomers in a ratio of 3:1 (assignment of the configurations of the components of **4h** was problematic because of overlap of the signals from the two isomers).

Concerning the reaction mechanism, we may propose the initial formation of organocopper intermediate **5** (Scheme 2).[15] The interaction of the copper center with the double bond leads

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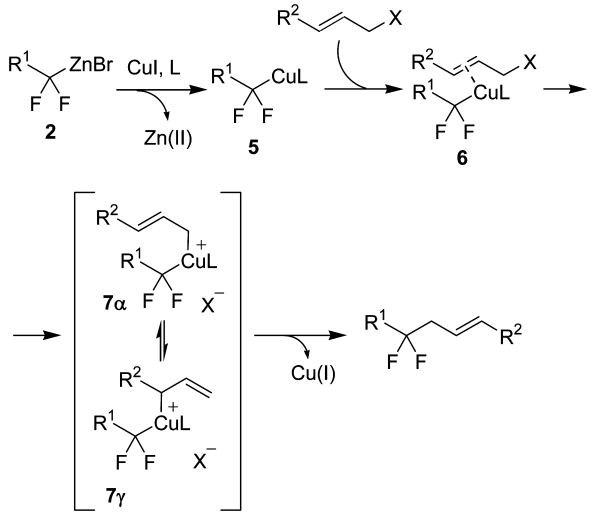
Scheme 2. Proposed Mechanism



to π-complex **6**, which is followed by slow generation of copper(III) species **7*α*** or **7*γ***. The formation of only one product may be associated either with rapid interconversion between **7*α*** and **7*γ*** or with exclusive formation of isomer **7*α***. Nevertheless, the loss of the double-bond geometry observed for (**3h**) supports the former pathway.[16]

In summary, a method for the synthesis of CF_2-containing compounds from three components—an organozinc reagent, difluorocarbene, and an allylic electrophile—has been described. The reaction is performed under mild reaction conditions and results in the formation of two C−C bonds within one synthetic step.

EXPERIMENTAL SECTION

General Methods. All reactions were performed in Schlenk flasks under an argon atmosphere. Column chromatography was carried out employing silica gel (230−400 mesh). Precoated F-254 silica gel plates were used for analytical thin-layer chromatography, visualizing with UV and/or aqueous $KMnO_4$ solution. For NMR measurements, $CDCl_3$ was distilled from CaH_2. Commercial allyl halides and methyl iodide were distilled prior to use. Organozinc reagents **1a**−**g**,[6] (bromodifluoromethyl)trimethylsilane,[7] methyl (2*Z*)-2-(bromomethyl)-3-phenylacrylate (**3g**),[17] and (2*E*)-1-bromo-3,7-dimethylocta-2,6-diene (**3h**)[18] were prepared according to literature procedures.

*2,3-Dibromoprop-1-ene (**3c**).* To a solution of allyl bromide (5.0 g, 41.3 mmol) in CCl_4 (40 mL) was added bromine (2.1 mL, 41.3 mmol) at a rate that did not cause the reaction temperature to exceed 30 °C. The solution was stirred for 2 h until complete decoloration, and then all of the volatile compounds were removed under reduced pressure, furnishing 1,2,3-tribromopropane (10.4 g, 90% yield) as a slightly yellow oil, which was used without further purification. Water (0.54 mL, 30.0 mmol) was added to the resulting 1,2,3-tribromopropane, and to the stirred mixture solid NaOH (4.0 g, 70.0 mmol) was slowly added at room temperature. The resulting suspension was stirred for 18 h, and then the product was distilled from the reaction flask under reduced pressure (65−75 °C, 70 mmHg). Subsequent recrystallization of the resulting oil from MeOH (5 mL) at −78 °C followed by distillation under reduced pressure (79−81 °C, 80 mmHg) gave 2.97 g (40% yield) of **3c** as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.20 (s, 2H), 5.65 (br, 1H), 6.04 (br, 1H).[19]

*(6-Bromocyclohex-1-en-1-yl)benzene (**3e**).* PhMgCl (1.9 M in THF, 25 mL, 47.5 mmol) was added to a solution of cyclohexanone (3.7 mL, 36.0 mmol) in THF (25 mL) at −30 °C. The cooling bath was removed, and the thick white suspension was stirred for 1 h at room temperature. Then water (10 mL) and hexane (40 mL) were added, and the biphasic mixture was vigorously shaken. The organic layer was separated, and the residual inorganic cake was extracted with hexane (2 × 20 mL). The combined organic phases were concentrated on a rotary evaporator, and the resulting solid was dissolved in toluene (30 mL). $TsOH·H_2O$ (20 mg) was added, and the mixture was refluxed with Dean−Stark trap for 1 h. Most of the toluene was evaporated at atmospheric pressure, and the residual toluene was evaporated under reduced pressure (15 mmHg). The crude 1-phenylcyclohex-1-ene was dissolved in acetone (60 mL) and water (30 mL), followed by addition of *N*-bromosuccinimide (6.41 g, 36.0 mmol), and the mixture was stirred for 3 h at 10 °C. Then acetone was evaporated under vacuum, and water (20 mL) was added. The mixture was extracted with hexane (3 × 30 mL), and the combined organic phases were successively washed with water and brine, dried over Na_2SO_4, and concentrated on a rotary evaporator. The crude bromohydrin was dissolved in hexane (10 mL), and the solution was added to a mixture of 20% H_2SO_4 (10 mL) and AcOH (40 mL). After the reaction mixture was stirred for 5 min, iced water (50 mL) was added, and the product was extracted with ether (3 × 30 mL). The combined organic phases were successively washed with water and a saturated solution of $NaHCO_3$ and concentrated on a rotary evaporator. The resulting oil was dissolved in hexane/CH_2Cl_2 (2/1) and cooled to 0 °C. The precipitate was filtered, affording compound **3e** (3.92 g, 46% yield) as a light-lilac solid. Mp 43−44 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.77−1.93 (m, 1H), 2.05−2.24 (m, 2H), 2.31−2.55 (m, 3H), 5.35 (t, 1H, *J* = 2.8 Hz), 6.21 (dd, 1H, *J* = 4.8, 3.1 Hz), 7.27−7.47 (m, 5H).[20]

General Procedure for the Difluorocarbene Insertion/Allylation Reaction. A freshly titrated THF solution of **1** (1.5 mmol)[6] was concentrated in vacuo until the solid or viscious residue was formed, and the residue was dissolved in freshly distilled MeCN (1.5 mL). To the resulting solution was added NaOAc (148 mg, 1.8 mmol for **1a**−**d**,**f**−**i** or 172 mg, 2.1 mmol for **1e**) at room temperature. The reaction flask was immersed in a cold bath at −25 °C, and the mixture was stirred for 10 min at this temperature. Then Me_3SiCF_2Br (365 mg, 1.8 mmol for **1a**−**d**,**f**−**i** or 426 mg, 2.1 mmol for **1e**) was added dropwise at −25 °C, and the reaction mixture was stirred at this temperature for 18 h (**1a**−**d**,**f**−**i**) or 21 h (**1e**). To the resulting white suspension at −25 °C were successively added DMF (231 μL, 3.0 mmol), allyl reagent **3** (3.0 mmol for **3a**−**d**,**g**,**i**; 2.0 mmol for **3e**,**f**,**h**; 1.0 mmol of **3e** for the **1i**/**3e** combination), 1,10-phenanthroline (27 mg, 0.15 mmol), and CuI (29 mg, 0.15 mmol), and the reaction mixture was stirred for 2 h at −25 °C. The cooling bath was removed, and the reaction was quenched with water (10 mL). The resulting suspension was extracted with hexane (3 × 10 mL) [or pentane (3 × 10 mL) in the cases of the volatile products **4n** and **4p**]. The combined organic phases were filtered through Na_2SO_4, concentrated under vacuum (or under ambient pressure for **4n** and **4p**). The residue was purified by column chromatography on silica gel.

*Methyl 4-(2,2-Difluoropent-4-enyl)benzoate (**4a**).* 317 mg (88%). Colorless crystals. Mp 52−54 °C. R_f = 0.24 (hexanes/EtOAc, 15/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.57 (td, 2H, *J* = 15.9, 7.2 Hz), 3.20 (t, 2H, *J* = 15.9 Hz), 3.93 (s, 3H), 5.20 (dd, 1H, *J* = 17.2, 1.5 Hz), 5.27 (dd, 1H, *J* = 10.3, 1.5 Hz), 5.84 (ddt, 1H, *J* = 17.2, 10.3, 7.2 Hz), 7.36 (d, 2H, *J* = 8.2 Hz), 8.01 (d, 2H, *J* = 8.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 40.6 (t, *J* = 25.6 Hz), 42.2 (t, *J* = 24.9 Hz), 52.0, 120.6, 122.7 (t, *J* = 244.6 Hz), 129.1, 129.2, 129.3, 129.6, 130.4, 138.3 (t, *J* = 4.3 Hz), 166.7. ^{19}F NMR (282 MHz, $CDCl_3$): δ −96.4 (tt, 2F, *J* = 15.9, 15.9 Hz). Anal. Calcd for $C_{13}H_{14}F_2O_2$ (240.25): C 64.99, H 5.87. Found: C 65.05, H 5.84.

*Methyl 4-(2,2-Difluoro-4-methylpent-4-enyl)benzoate (**4b**).* 290 mg (76%). Colorless oil. R_f = 0.33 (hexanes/EtOAc, 15/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.84 (s, 3H), 2.54 (t, 2H, *J* = 15.9 Hz), 3.21 (t, 2H, *J* = 15.9 Hz), 3.92 (s, 3H), 4.85 (d, 1H, *J* = 1.3 Hz), 5.01 (d, 1H, *J* = 1.3 Hz), 7.36 (d, 2H, *J* = 8.2 Hz), 8.00 (d, 2H, *J* = 8.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.4 (t, *J* = 2.2 Hz), 42.6 (t, *J* = 25.7 Hz), 44.4 (t, *J* = 25.9 Hz), 52.1, 117.0, 123.1 (t, *J* = 244.6 Hz), 129.3, 129.7, 130.6, 138.1 (t, *J* = 3.9 Hz), 138.6 (t, *J* = 3.9 Hz), 166.9. ^{19}F NMR (282 MHz, $CDCl_3$): δ −94.6 (tt, 2F, *J* = 15.9, 15.9 Hz). Anal. Calcd for $C_{14}H_{16}F_2O_2$ (254.27): C 66.13, H 6.34. Found: C 66.07, H 6.31.

*Methyl 4-(4-Bromo-2,2-difluoropent-4-enyl)benzoate (**4c**).* 364 mg (76%). Colorless crystals. Mp 40−42 °C. R_f = 0.19 (hexanes/EtOAc, 15/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.01 (t, 2H, *J* = 16.3 Hz), 3.31 (t, 2H, *J* = 16.3 Hz), 3.93 (s, 3H), 5.75 (d, 1H, *J* = 1.7 Hz), 5.82 (d, 1H, *J* =

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1.7 Hz), 7.39 (d, 2H, J = 8.4 Hz), 8.02 (d, 2H, J = 8.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 41.9 (t, J = 25.4 Hz), 46.8 (t, J = 26.8 Hz), 51.6, 121.0 (t, J = 245.7 Hz), 121.8 (t, J = 5.3 Hz), 122.8, 129.0, 129.2, 130.0, 137.2 (t, J = 3.6 Hz), 166.3. ^{19}F NMR (282 MHz, $CDCl_3$): δ −95.4 (tt, 2F, J = 16.3, 16.3 Hz). Anal. Calcd for $C_{13}H_{13}BrF_2O_2$ (319.14): C 48.92, H 4.11. Found: C 49.07, H 4.18.

*Methyl 4-(2-Cyclohex-2-en-1-yl-2,2-difluoroethyl)benzoate (**4d**).* 378 mg (90%). Pale-yellow crystals. Mp 74−76 °C. R_f = 0.24 (hexanes/EtOAc, 15/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.43−1.68 (m, 2H), 1.78−1.98 (m, 2H), 1.99−2.10 (m, 2H), 2.51−2.73 (m, 1H), 3.20 (t, 2H, J = 17.2 Hz), 3.92 (s, 3H), 5.71 (dd, 1H, J = 10.1, 2.5 Hz), 5.94 (ddd, 1H, J = 10.1, 3.6, 2.5 Hz), 7.37 (d, 2H, J = 8.2 Hz), 8.01 (d, 2H, J = 8.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.1, 23.0 (t, J = 4.4 Hz), 24.8, 40.3 (t, J = 26.0 Hz), 42.0 (t, J = 23.8 Hz), 52.1, 123.1 (t, J = 5.5 Hz), 124.4 (t, J = 245.5 Hz), 129.2, 129.6, 130.6, 131.3, 138.7 (t, J = 3.3 Hz), 167.0. ^{19}F NMR (282 MHz, $CDCl_3$): δ −102.7 (m, 2F). Anal. Calcd for $C_{16}H_{18}F_2O_2$ (280.31): C 68.56, H 6.47. Found: C 68.84, H 6.66.

*Methyl 4-[2,2-Difluoro-2-(2-phenylcyclohex-2-en-1-yl)ethyl]-benzoate (**4e**).* 406 mg (76%). Colorless crystals. Mp 74−75 °C. R_f = 0.21 (hexanes/EtOAc, 15/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.63−1.97 (m, 3H), 2.13−2.23 (m, 1H), 2.24−2.33 (m, 2H), 2.91 (ddd, 1H, J = 14.6, 13.8, 11.2 Hz), 3.01 (ddd, 1H, J = 14.6, 13.8, 11.2 Hz), 3.21−3.37 (m, 1H), 3.90 (s, 3H), 6.09 (t, 1H, J = 3.7 Hz), 7.16 (d, 2H, J = 8.2 Hz), 7.22−7.38 (m, 5H), 7.94 (d, 2H, J = 8.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.5 (t, J = 1.9 Hz), 23.7 (dd, J = 4.8, 3.5 Hz), 25.5, 42.2 (t, J = 22.7 Hz), 42.4 (t, J = 25.7 Hz), 52.2, 124.3 (t, J = 248.5 Hz), 126.7, 126.9, 128.4, 129.0, 129.4, 130.7, 132.7, 135.0 (t, J = 3.6 Hz), 138.7 (t, J = 3.0 Hz), 143.9, 167.1. ^{19}F NMR (282 MHz, $CDCl_3$): δ −96.2 (dddd, 1F, J = 243.7, 23.3, 14.6, 13.8 Hz), −94.5 (dddd, 1F, J = 243.7, 23.8, 14.6, 13.8 Hz). Anal. Calcd for $C_{22}H_{22}F_2O_2$ (356.41): C 74.14, H 6.22. Found: C 73.95, H 6.24.

*Methyl 4-[(4E)-2,2-Difluoro-5-phenylpent-4-enyl]benzoate (**4f**).* 356 mg (75%). Colorless crystals. Mp 85−86 °C. R_f = 0.23 (hexanes/EtOAc, 10/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.72 (td, 2H, J = 15.7, 7.7 Hz), 3.25 (t, 2H, J = 15.7 Hz), 3.94 (s, 3H), 6.19 (dt, 1H, J = 16.0, 7.7 Hz), 6.49 (d, 1H, J = 16.0 Hz), 7.24−7.44 (m, 7H), 8.04 (d, 2H, J = 8.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 40.1 (t, J = 26.0 Hz), 42.6 (t, J = 26.0 Hz), 52.2, 120.5 (t, J = 5.8 Hz), 123.1 (t, J = 244.1 Hz), 126.4, 127.9, 128.7, 129.5, 129.8, 130.6, 135.6, 136.8, 138.5 (t, J = 4.4 Hz), 166.9. ^{19}F NMR (282 MHz, $CDCl_3$): δ −95.8 (tt, 2F, J = 15.7, 15.7 Hz). Anal. Calcd for $C_{19}H_{18}F_2O_2$ (316.34): C 72.14, H 5.74. Found: C 72.16, H 5.84.

*Methyl 4-[(4E)-2,2-Difluoro-4-(methoxycarbonyl)-5-phenylpent-4-enyl]benzoate (**4g**).* 371 mg (66%). Colorless oil. R_f = 0.04 (hexanes/EtOAc, 15/1). Configuration determined by a NOESY experiment. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.19 (t, 2H, J = 16.3 Hz), 3.25 (t, 2H, J = 16.3 Hz), 3.83 (s, 3H), 3.92 (s, 3H), 7.29−7.33 (m, 5H), 7.32 (d, 2H, J = 8.2 Hz), 7.88 (s, 1H), 8.00 (d, 2H, J = 8.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.0 (t, J = 25.4 Hz), 43.5 (t, J = 25.4 Hz), 52.0, 52.2, 122.6 (t, J = 245.7 Hz), 124.7 (t, J = 3.3 Hz), 128.5, 128.9, 129.0 (t, J = 1.7 Hz), 129.3, 129.5, 130.5, 134.7, 138.1 (t, J = 3.9 Hz), 143.6, 166.8, 168.5. ^{19}F NMR (282 MHz, $CDCl_3$): δ −94.5 (tt, 2F, J = 16.3, 16.3 Hz). Anal. Calcd for $C_{21}H_{20}F_2O_4$ (374.38): C 67.37, H 5.38. Found: C 67.25, H 5.49.

*Methyl 4-(2,2-Difluoro-5,9-dimethyldeca-4,8-dienyl)benzoate (**4h**).* 358 mg (71%). Isolated as a 3:1 mixture of isomers. Colorless oil. R_f = 0.28 (hexanes/EtOAc, 25/1). ^{1}H NMR (300 MHz, $CDCl_3$): (major) δ 1.55 (s, 3H), 1.63 (s, 3H), 1.69 (s, 3H), 5.11 (t, 1H, J = 7.2 Hz); (minor) δ 1.58 (s, 3H), 1.67 (s, 3H), 1.77 (s, 3H), 5.06 (t, 1H, J = 7.2 Hz); (both isomers) δ 1.91−2.20 (m, 4H), 2.50 (td, 2H, J = 15.9, 7.2 Hz), 3.17 (t, 2H, J = 15.9 Hz), 3.92 (s, 3H), 5.21 (t, 1H, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): (both isomers) δ 16.4, 17.7, 17.8, 23.7, 25.7, 25.8, 26.3, 26.5, 32.2, 35.0 (t, J = 25.4 Hz), 35.1 (t, J = 25.4 Hz), 42.2 (t, J = 26.0 Hz), 42.5 (t, J = 26.0 Hz), 52.1, 110.1, 115.0 (t, J = 5.8 Hz), 115.4 (t, J = 5.8 Hz), 123.6 (t, J = 243.5 Hz), 123.8, 124.0 (t, J = 243.3 Hz), 124.1, 129.3, 129.7, 130.5, 131.8, 132.0, 138.7 (t, J = 4.2 Hz), 138.8 (t, J = 4.2 Hz), 140.5, 140.7, 167.0. ^{19}F NMR (282 MHz, $CDCl_3$): (major) δ −95.7 (tt, 2F, J = 15.9, 15.9 Hz); (minor) δ −96.3 (tt, 2F, J = 15.9, 15.9 Hz). Anal. Calcd for $C_{20}H_{26}F_2O_2$ (336.42): C 71.40, H 7.79. Found: C 71.19, H 7.55.

*Methyl 4-(2,2-Difluoro-5-methylhex-4-enyl)benzoate (**4i**).* 322 mg (80%). Colorless oil. R_f = 0.26 (hexanes/EtOAc, 15/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56 (s, 3H), 1.77 (s, 3H), 2.57 (td, 2H, J = 15.8, 7.2 Hz), 3.18 (t, 2H, J = 16.3 Hz), 3.92 (s, 3H), 5.15−5.25 (m, 1H), 7.34 (d, 2H, J = 8.2 Hz), 8.00 (d, 2H, J = 8.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.0, 25.9, 35.3 (t, J = 25.4 Hz), 42.3 (t, J = 26.0 Hz), 52.0, 115.0 (t, J = 5.8 Hz), 123.8 (t, J = 243.3 Hz), 129.3, 129.6, 130.5, 137.0, 138.8 (t, J = 4.4 Hz), 166.9. ^{19}F NMR (282 MHz, $CDCl_3$): δ −95.9 (tt, 2F, J = 16.3, 15.8 Hz). Anal. Calcd for $C_{15}H_{18}F_2O_2$ (268.30): C 67.15, H 6.76. Found: C 67.09, H 6.66.

*Methyl 3-(2,2-Difluoropent-4-enyl)benzoate (**4j**).* 274 mg (76%). Colorless oil. R_f = 0.26 (hexanes/EtOAc, 15/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.57 (dt, 2H, J = 15.8, 7.3 Hz), 3.19 (t, 2H, J = 15.8 Hz), 3.92 (s, 3H), 5.21 (dd, 1H, J = 17.4, 1.6 Hz), 5.27 (dd, 1H, J = 10.5, 1.7 Hz), 5.85 (ddt, 1H, J = 17.4, 10.5, 7.3 Hz), 7.40 (dd, 1H, J = 7.3, 7.3 Hz), 7.48 (d, 1H, J = 7.3 Hz), 7.96 (d, 1H, J = 1.5 Hz), 7.97 (dd, 1H, J = 7.3, 1.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 40.6 (t, J = 25.6 Hz), 42.0 (t, J = 25.6 Hz), 52.0, 120.5, 122.7 (t, J = 243.6 Hz), 128.4, 128.5, 129.2 (t, J = 5.8 Hz), 130.3, 131.4, 133.5 (t, J = 4.3 Hz), 134.8, 166.7. ^{19}F NMR (282, $CDCl_3$): δ −96.9 (tt, 2F, J = 15.8. 15.8 Hz). Anal. Calcd for $C_{13}H_{14}F_2O_2$ (240.25): C 64.99, H 5.87. Found: C 65.05, H 5.87.

*4-(2,2-Difluoropent-4-enyl)benzonitrile (**4k**).* 249 mg (80%). Colorless crystals. Mp 40−42 °C. R_f = 0.27 (hexanes/EtOAc, 15/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.60 (td, 2H, J = 15.6, 7.2 Hz), 3.20 (t, 2H, J = 16.2 Hz), 5.22 (dd, 1H, J = 17.4, 1.2 Hz), 5.28 (dd, 1H, J = 10.2, 1.2 Hz), 5.83 (ddt, 1H, J = 17.4, 10.2, 7.2 Hz), 7.40 (d, 2H, J = 7.8 Hz), 7.63 (d, 2H, J = 7.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 40.9 (t, J = 25.6 Hz), 42.3 (t, J = 25.9 Hz), 111.5, 118.6, 120.9, 122.5 (t, J = 243.9 Hz), 129.1 (t, J = 6.1 Hz), 131.3, 132.1, 138.6 (t, J = 4.0 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −96.8 (tt, 2F, J = 16.2, 15.6 Hz). Anal. Calcd for $C_{12}H_{11}F_2N$ (207.22): C 69.55, H 5.35, N 6.76. Found: C 69.59, H 5.38, N 6.69.

*1-Bromo-4-(2,2-difluoropent-4-enyl)benzene (**4l**).* 317 mg (81%). Colorless oil. R_f = 0.33 (hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.58 (td, 2H, J = 15.9, 7.1 Hz), 3.12 (t, 2H, J = 15.9 Hz), 5.22 (dd, 1H, J = 17.0, 1.5 Hz), 5.29 (dd, 1H, J = 10.1, 1.5 Hz), 5.86 (ddt, 1H, J = 17.0, 10.1, 7.1 Hz), 7.18 (d, 2H, J = 8.2 Hz), 7.49 (d, 2H, J = 8.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 40.5 (t, J = 25.6 Hz), 41.7 (t, J = 25.9 Hz), 120.5, 121.4, 122.7 (t, J = 243.6 Hz), 129.3 (t, J = 5.8 Hz), 131.5, 132.0, 132.1 (t, J = 5.0 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −96.8 (tt, 2F, J = 15.9, 15.9 Hz). Anal. Calcd for $C_{11}H_{11}BrF_2$ (261.11): C 50.60, H 4.25. Found: C 50.61, H 4.29.

*1-(2,2-Difluoropent-4-enyl)naphthalene (**4m**).* 272 mg (78%). Colorless oil. R_f = 0.24 (hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.70 (td, 2H, J = 15.9, 7.0 Hz), 3.68 (t, 2H, J = 15.9 Hz), 5.26 (dd, 1H, J = 17.8, 1.3 Hz), 5.32 (dd, 1H, J = 11.0, 1.3 Hz), 5.96 (ddt, 1H, J = 17.8, 11.0, 7.0 Hz), 7.42−7.65 (m, 4H), 7.82−7.90 (m, 1H), 7.92 (d, 1H, J = 7.8 Hz), 8.12 (d, 1H, J = 7.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 39.0 (t, J = 25.9 Hz), 41.1 (t, J = 25.6 Hz), 120.5, 123.5 (t, J = 243.9 Hz), 124.4 (t, J = 1.8 Hz), 125.3, 125.7, 126.2, 128.3, 128.8, 129.4, 129.6 (d, J = 5.5 Hz), 129.6, 132.9, 134.0. ^{19}F NMR (282 MHz, $CDCl_3$): δ −95.4 (tt, 2F, J = 15.9, 15.9 Hz). Anal. Calcd for $C_{15}H_{14}F_2$ (232.27): C 77.57, H 6.08. Found: C 77.17, H 5.55.

*(4-Bromo-2,2-difluoro-1-methylpent-4-enyl)benzene (**4n**).* 306 mg (74%). Colorless oil. R_f = 0.19 (pentane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.50 (d, 3H, J = 7.2 Hz), 2.85−2.99 (m, 2H), 3.30 (ddq, 1H, J = 19.6, 10.5, 7.2 Hz), 5.72 (d, 1H, J = 1.7 Hz), 5.74 (d, 1H, J = 1.7 Hz), 7.29−7.42 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4 (t, J = 5.3 Hz), 45.59 (dd, J = 24.2, 22.1 Hz), 45.62 (dd, J = 27.1, 25.4 Hz), 122.1 (dd, J = 5.2, 3.3 Hz), 122.3, 122.7 (t, J = 248.8 Hz), 127.0, 128.1, 128.2 (t, J = 1.4 Hz), 138.8 (d, J = 6.1 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −105.8 (ddt, 1F, J = 245.8, 19.6, 12.7 Hz), −101.7 (dtd, 1F, J = 245.8, 15.4, 10.5 Hz). Anal. Calcd for $C_{12}H_{13}BrF_2$ (275.13): C 52.39, H 4.76. Found: C 52.11, H 4.88.

*4,4-Difluorohept-6-enyl Benzoate (**4o**).* 267 mg, (70%). Colorless oil. R_f = 0.41 (hexanes/EtOAc 15/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.87−2.15 (m, 4H), 2.65 (td, 2H, J = 16.0, 7.3 Hz), 4.36 (t, 2H, J = 5.7 Hz), 5.23 (dd, 1H, J = 16.1, 1.2 Hz), 5.24 (dd, 1H, J = 10.3, 1.2 Hz), 5.82 (ddt, 1H, J = 16.0, 10.3, 7.3 Hz), 7.45 (dd, 2H, J = 7.9, 7.2 Hz), 7.57 (dd, 1H, J = 7.2 Hz), 8.06 (d, 2H, J = 7.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.8 (t, J = 4.6 Hz), 32.7 (t, J = 25.6 Hz), 41.4 (t, J = 26.2 Hz), 64.2,

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120.3, 123.9 (t, J = 241.8 Hz), 128.4, 129.5 (t, J = 6.1 Hz), 129.6, 130.3, 133.0, 166.4. ^{19}F NMR (282, $CDCl_3$): δ −98.6 (tt, 2F, J = 16.0, 16.0 Hz). Anal. Calcd for $C_{14}H_{16}F_2O_2$ (254.27): C 66.13, H 6.34. Found: C 66.09, H 6.38.

*[6-(1,1-Difluoroethyl)cyclohex-1-en-1-yl]benzene (**4p**).* 147 mg (66%). Colorless oil. R_f = 0.28 (pentane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39 (t, 3H, J = 18.8 Hz), 1.62−1.76 (m, 1H), 1.77−1.97 (m, 2H), 2.10−2.21 (m, 1H), 2.22−2.33 (m, 2H), 3.19−3.39 (m, 1H), 6.04−6.12 (m, 1H), 7.19−7.44 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.5 (dd, J = 2.8, 1.4 Hz), 23.2 (t, J = 28.2 Hz), 23.7 (dd, J = 5.0, 3.8 Hz), 25.5, 42.9 (t, J = 23.5 Hz), 125.4 (t, J = 243.5 Hz), 126.59, 126.62, 128.1, 132.2, 135.5 (t, J = 3.9 Hz), 143.8. ^{19}F NMR (282 MHz, $CDCl_3$): δ −90.4 (dqd, 1F, J = 243.0, 18.8, 17.0 Hz), −85.4 (dqd, 1F, J = 243.0, 18.8, 12.7 Hz). Anal. Calcd for $C_{14}H_{16}F_2$ (222.27): C 75.65, H 7.26. Found: C 75.59, H 7.21.

■ ASSOCIATED CONTENT

Supporting Information

Copies of NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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