

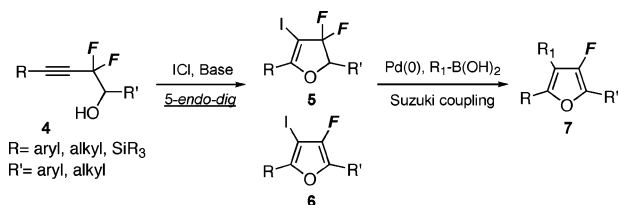
## Synthesis of 2,4,5-Trisubstituted 3-Fluorofurans via Sequential Iodocyclization and Cross-Coupling of *gem*-Difluorohomopropargyl Alcohols

Satoru Arimitsu, Jesse M. Jacobsen, and Gerald B. Hammond\*

Department of Chemistry, University of Louisville,  
Louisville, Kentucky 40292

gb.hammond@louisville.edu

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The iodocyclization of *gem*-difluorohomoallenyl and *gem*-difluorohomopropargyl alcohols with  $I_2$  and  $ICl$ , respectively, produced the corresponding fluorinated iodofuran analogues in good yields. The iodo substituent in fluorinated 4-iodofurans was utilized as a synthetic handle to prepare multi-substituted 3-fluorofurans using a Suzuki cross-coupling reaction. The yields of both iodocyclization of *gem*-difluorohomopropargyl alcohol and subsequent Suzuki coupling were dramatically enhanced by microwave irradiation.

The furan structure is a ubiquitous unit in a variety of natural products, active pharmaceuticals, agricultural compounds, fragrances, and synthetic precursors.<sup>1</sup> A concise synthetic methodology for multi-substituted furans remains an important task in modern organic chemistry.<sup>2</sup> A particularly underdeveloped area of furan chemistry is the synthesis of its fluorine congeners,<sup>3</sup> despite the fact that the presence of fluorine has often enhanced the pharmacokinetic properties of a parent molecule and that many current pharmaceuticals contain fluorine(s).<sup>4</sup>

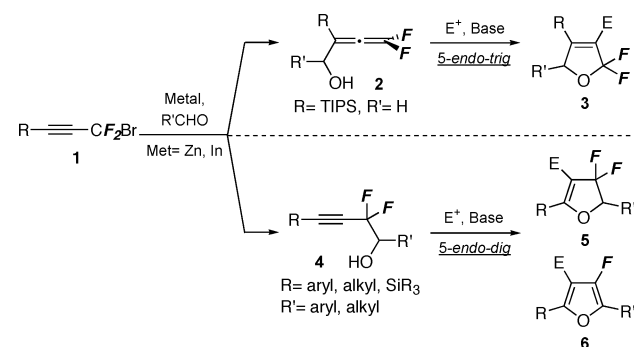
Our group has reported the indium-mediated selective synthesis of *gem*-difluorohomoallenyl alcohol **2** and *gem*-difluorohomopropargyl alcohol **4** from difluoropropargyl bromide **1**.<sup>5</sup> Both alcohols have demonstrated their usefulness as building blocks in the synthesis of fluorinated furan analogues under basic

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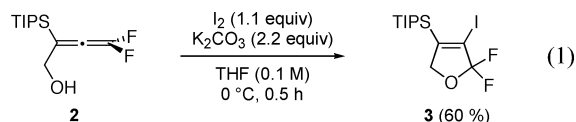
(2) (a) Babudri, F.; Cicco, S. R.; Farinola, G. M.; Lopez, L. C.; Naso, F.; Pinto, V. *Chem. Commun.* **2007**, 3756–3758. (b) Kirsch, S. F. *Org. Biomol. Chem.* **2006**, *4*, 2076–2080. (c) Minetto, G.; Raveglia, L. F.; Sega, A.; Taddei, M. *Eur. J. Org. Chem.* **2005**, *2*, 5277–5288. (d) Stauffer, F.; Neier, R. *Org. Lett.* **2000**, *2*, 3535–3537 and references cited therein.

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## SCHEME 1. Synthetic Access to Fluorinated Furans from Alcohols **2** and **4**



conditions (Scheme 1).<sup>6</sup> However, these methodologies use a proton ( $H^+$ ) electrophile, which does not permit installing a synthetic handle to access multi-substituted fluorinated furans. If instead we could use a halide electrophile, we would then be able to install this reactive halide on the furan structure, which could eventually be functionalized by further cross-coupling reactions. We are now pleased to report the synthesis of fluorinated iodofurans and their conversion into 2,4,5-trisubstituted 3-fluorofurans using a Suzuki coupling reaction.



As a point of entry to the ensuing discussions, the iodocyclization of *gem*-difluorohomoallenyl alcohol **2** produced 2,2-difluoro-3-iodo-2,5-dihydrofuran **3** under mild conditions (1 equiv). The expected—and observed—iodocyclization pattern<sup>7</sup> was driven by the high electrophilicity of the *gem*-difluorovinyl carbon.<sup>8</sup> In marked contrast, the lesser reactivity of the triple bond in *gem*-difluorohomopropargyl alcohol **4a** hindered its

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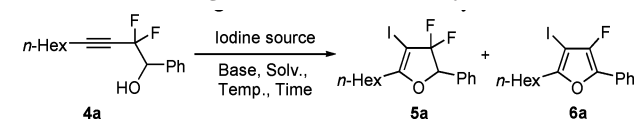
(5) For a review of *gem*-difluoroallenes, see: (a) Hammond, G. B. *J. Fluorine Chem.* **2006**, *127*, 476–488. For synthesis of *gem*-difluorohomopropargyl alcohols, see: (b) Arimitsu, S.; Jacobsen, J. M.; Hammond, G. B. *Tetrahedron Lett.* **2007**, *48*, 1625–1627. (c) Arimitsu, S.; Hammond, G. B. *J. Org. Chem.* **2006**, *71*, 8865–8868. (d) Kirihara, M.; Takuwa, T.; Takizawa, S.; Momose, T.; Nemoto, H.; *Tetrahedron* **2000**, *56*, 8275–8280. (e) Wang, Z.-G.; Hammond, G. B. *J. Org. Chem.* **2000**, *65*, 6547–2255.

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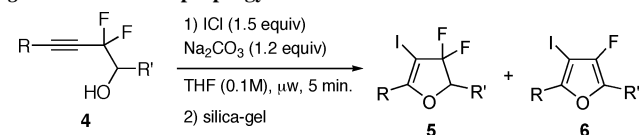
(8) Ichikawa, J. *Pure Appl. Chem.* **2000**, *72*, 1685–1689.

TABLE 1. Screening Conditions for the Iodocyclization of 4a



entry	base (1.2 equiv)	iodine source <sup>a</sup>	solvent (0.1 M)	temp (°C)	time	yields of 5a/6a (%) <sup>b</sup>
1	NaH	I <sub>2</sub>	THF	reflux	12 h	complex mixture
2	NaH	ICI	THF	reflux	12 h	0/36 (6)
3	<i>t</i> -BuOK	ICI	THF	reflux	12 h	0/46 (0)
4	Na <sub>2</sub> CO <sub>3</sub>	ICI	THF	reflux	12 h	54/0 (37)
5	K <sub>2</sub> CO <sub>3</sub>	ICI	THF	reflux	12 h	9/0 (76)
6 <sup>d</sup>	Na <sub>2</sub> CO <sub>3</sub>	ICI	THF	91	5 min	63/8 (0) [66] <sup>c</sup>
7 <sup>d</sup>	Na <sub>2</sub> CO <sub>3</sub>	ICI	DMF	91	5 min	50/trace (30)
8 <sup>d</sup>	Na <sub>2</sub> CO <sub>3</sub>	ICI	CH <sub>3</sub> CN	91	5 min	0/36 (0)
9 <sup>d</sup>	Na <sub>2</sub> CO <sub>3</sub>	ICI	CH <sub>2</sub> Cl <sub>2</sub>	91	5 min	complex mixture <sup>e</sup>
10 <sup>d</sup>	Na <sub>2</sub> CO <sub>3</sub>	ICI	toluene	91	5 min	trace/0 (64)
11 <sup>d</sup>	Na <sub>2</sub> CO <sub>3</sub>	ICI	ether	91	5 min	16/23 (13)

<sup>a</sup> 1.5 equiv was used. <sup>b</sup> Yield was determined by <sup>19</sup>F NMR, and the values in parentheses refer to the amount of recovered starting material 4a. <sup>c</sup> The value in brackets was the isolated yield of 6a after silica gel chromatography. <sup>d</sup> The reaction was carried out in a closed vial in a microwave reactor. <sup>e</sup> 6a isolated in 12% yield.

TABLE 2. Microwave-Mediated Iodocyclization of *gem*-Difluorohomopropargyl Alcohol 4


entry	R	R'	isolated yields of 5 or 6 (%)
1	<i>n</i> -Hex	Ph	66 (6a)
2	<i>n</i> -Hex	4-MeO-C <sub>6</sub> H <sub>4</sub>	62 (6b)
3	<i>n</i> -Hex	4-CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	76 (6c)
4	<i>n</i> -Hex	BnOCH <sub>2</sub>	46 (5d) <sup>a</sup>
5	BnOCH <sub>2</sub>	Ph	56 (5e) <sup>a</sup>
6	Ph	Ph	49 (5f) <sup>a</sup>

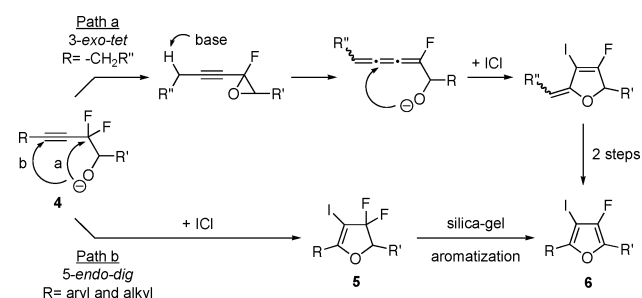
<sup>a</sup> Silica gel was deactivated by Et<sub>3</sub>N.

iodocyclization, as demonstrated by the fact that strong bases, such as NaH and *t*-BuOK, caused the decomposition of product or starting material (entries 1–3, Table 1), and no reaction occurred using K<sub>2</sub>CO<sub>3</sub> and a reactive electrophile (ICI) at reflux temperatures for 12 h (entry 5, Table 1). However, the combination of iodomonochloride (ICI) and Na<sub>2</sub>CO<sub>3</sub> gave the desired iodocyclization product 5a selectively, in moderate yield and with little decomposition (entry 4, Table 1).

The unreactive nature of 4a prompted us to investigate whether microwave irradiation would hasten the desired iodocyclization (entries 6–11, Table 1). Gratifyingly, 4a was quickly consumed to yield 5a as a major product in satisfactory yield after only 5 min of microwave irradiation. Following silica gel chromatography, the aromatic product 6a was obtained in 66% yield (entry 6, Table 1).

The scope of this reaction is shown in Table 2. Aryl substrates with electron-donating or -withdrawing groups at the homopropargyl position gave the corresponding 4-iodofuran 6 in good isolated yields (entries 1–3, Table 2). Interestingly, use of silica gel deactivated with triethylamine (Et<sub>3</sub>N) furnished 5 instead of the aromatized derivative 6 (entries 4–6, Table 2).<sup>9</sup>

SCHEME 2. Reaction Mechanism for the Iodocyclization of 4



The published syntheses of 2,5-substituted-3-fluorofurans do not permit functionalization at the 4-position of 3-fluorofurans.<sup>3</sup> Thus, a readily apparent useful synthetic transformation of 5 or 6 could be the replacement of iodine with a suitable substituent using a cross-coupling reaction. An obvious approach would be the Suzuki coupling<sup>10</sup> of arylboronic acids. Indeed, phenylboronic acid reacted with 6a to furnish 7aa in excellent yield in only 0.5 h (entry 1, Table 3). Microwave irradiation proved critical for the efficiency of this reaction since the same reaction at reflux not only failed to consume 6a after 12 h but also led to the formation of byproducts. Electron-rich or electron-deficient aryl boronic acids reacted with 6a in satisfactory yields (entries 2–6, Table 3). Furthermore, 3-thienylboronic acid (entry 7, Table 3) and (*E*)-cinnamylboronic acid (entry 8, Table 3) gave the corresponding sp<sup>2</sup>–sp<sup>2</sup> coupling products in good and moderate yields, respectively, with only a slight change in the reaction time. Notably, the Suzuki coupling of 5 spontaneously yielded only 7 (entries 11–13, Table 3), with no trace of the corresponding 4,5-dihydrofuran.

The two proposed mechanisms for the iodocyclization of 4 are depicted in Scheme 2. Initial deprotonation of 4 by a base gives rise to an oxyanion, which can then attack either on the CF<sub>2</sub> carbon in a 3-*exo-tet* fashion (Path a, Scheme 2)<sup>11</sup> or on the triple bond in a 5-*endo-dig* fashion (Path b, Scheme 2).<sup>12,13</sup> The conversion of acetylenic epoxide intermediates into furans via their cumulene intermediates, in the presence of bases, has been reported.<sup>14</sup> However, for this transformation to occur, alkyl substrates are required on R. Fortunately, we were able to recrystallize 5f and obtain an X-ray analysis (Figure 1), which, in turn, allowed us to use the <sup>19</sup>F NMR spectral data of crude 5 (prior to aromatization) to confirm that, in all cases, 3,3-difluoro-4-iodo-4,5-dihydrofuran 5 was produced, regardless of the substrates R and R'. This experimental fact shored up support for Path b as the most likely mechanism for our reaction. The

(9) The use of normal silica gel for isolation resulted in the decomposition of the benzyl ether group (entries 4 and 5, Table 2) and a difficult separation from byproducts (entry 6, Table 2).

(10) For reviews of the Suzuki–Miyaura cross-coupling, see: (a) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419–2440. (b) Kotha, S.; Lahiri, K.; Kaschinath, D. *Tetrahedron* **2002**, 58, 9633–9695. (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, 95, 2457–2483.

(11) A similar base-mediated cyclization of *gem*-difluorohomopropargyl alcohol was reported. This report claimed that 3-fluoro-2,5-substituted furans were obtained via a 3-*exo-tet* cyclization. See ref 3d.

(12) El-Taeb, G. M. M.; Evans, A. B.; Jones, S.; Knight, D. W. *Tetrahedron Lett.* **2001**, 42, 5945–5948.

(13) A cyclic iodonium ion intermediate has been proposed. See: Barluenga, J.; Rodríguez, M. A.; Campos, P. J. *J. Org. Chem.* **1990**, 55, 3104–3106 and references cited therein.

(14) (a) Marshall, J. A.; Dubay, W. J. *J. Am. Chem. Soc.* **1992**, 114, 1450–1456. (b) Marshall, J. A.; DuBay, W. J. *J. Org. Chem.* **1991**, 56, 1685–1687.

TABLE 3. Microwave-Mediated Suzuki Coupling of 5 or 6

entry	R	R'	R <sub>1</sub>	time <sup>a</sup> (h)	isolated yield of 7 (%)
1	<i>n</i> -Hex	Ph ( <b>6a</b> )	Ph	0.5	98 ( <b>7aa</b> )
2	<i>n</i> -Hex	Ph ( <b>6a</b> )	3,4-(OCH <sub>2</sub> O)-C <sub>6</sub> H <sub>3</sub>	0.5	78 ( <b>7ab</b> )
3	<i>n</i> -Hex	Ph ( <b>6a</b> )	4-CHO-C <sub>6</sub> H <sub>4</sub>	1.5	72 ( <b>7ac</b> )
4	<i>n</i> -Hex	Ph ( <b>6a</b> )	4-CN-C <sub>6</sub> H <sub>4</sub>	1.0	63 ( <b>7ad</b> )
5	<i>n</i> -Hex	Ph ( <b>6a</b> )	4-F-C <sub>6</sub> H <sub>4</sub>	0.5	66 ( <b>7ae</b> )
6	<i>n</i> -Hex	Ph ( <b>6a</b> )	4-CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	0.5	63 ( <b>7af</b> )
7	<i>n</i> -Hex	Ph ( <b>6a</b> )	3-thienyl	1.0	71 ( <b>7ag</b> )
8	<i>n</i> -Hex	Ph ( <b>6a</b> )	( <i>E</i> )-PhCHCH <sub>2</sub>	1.5	58 ( <b>7ah</b> )
9	<i>n</i> -Hex	4-MeO-C <sub>6</sub> H <sub>4</sub> ( <b>6b</b> )	Ph	2.0	85 ( <b>7ba</b> )
10	<i>n</i> -Hex	4-CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> ( <b>6c</b> )	Ph	1.0	75 ( <b>7ca</b> )
11	<i>n</i> -Hex	BnOCH <sub>2</sub> ( <b>5d</b> )	Ph	1.5	50 ( <b>7da</b> )
12	BnOCH <sub>2</sub>	Ph ( <b>5e</b> )	Ph	1.0	51 ( <b>7ea</b> )
13	Ph	Ph ( <b>5f</b> )	Ph	1.5	77 ( <b>7fa</b> )

<sup>a</sup> Reaction progress was monitored by TLC or GC-MS.

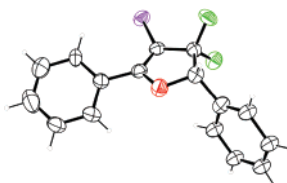


FIGURE 1. Single-crystal X-ray structure of 5f.

electronically deficient nature of the alkyne moiety in **4** had been verified through DFT calculations.<sup>3b</sup>

In summary, whereas the iodocyclization of *gem*-difluoro-homoallenyl alcohol **2** produced 2,2-difluoro-3-iodo-2,5-dihydrofuran **3** at low temperature, the iodocyclization of *gem*-difluorohomopropargyl alcohol **4** required use of microwave irradiation to yield 3,3-difluoro-4-iodo-4,5-dihydrofurans **5** or 3-fluoro-4-iodofurans **6** in satisfactory yields. This investigation clearly demonstrated that the iodocyclization proceeds via a 5-*endo-dig* mode on the electronically deficient triple bond. Finally, fluorinated 4-iodofuran analogues **5** and **6** were successfully used in the synthesis of fully substituted 3-fluorofurans **7** by microwave-mediated Suzuki coupling.

## Experimental Section

**2,2-Difluoro-3-iodo-4-triisopropylsilyl-2,5-dihydrofuran (3).** To a solution of I<sub>2</sub> (0.55 mmol, 1.1 equiv) and K<sub>2</sub>CO<sub>3</sub> (1.1 mmol, 2.2 equiv) in THF (4.0 mL) was added a solution of difluoro-homoallenyl alcohol **2** (0.5 mmol, 1.0 equiv) in THF (1.0 mL) at 0 °C. The resulting mixture was stirred for 0.5 h at 0 °C, then the reaction mixture was quenched by H<sub>2</sub>O (20 mL) and extracted by Et<sub>2</sub>O (10 mL × 3). The combined organic layer was washed by 5% aqueous solution of saturated sodium bisulfite (10 mL × 1) and then dried over MgSO<sub>4</sub>. The desired product was isolated by flash silica gel chromatography with hexane as an eluent, after which **3** (116 mg, 60%) was obtained as a white crystal: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.15 (s, 18H), 1.45 (m, 3H), 4.84 (t, *J* = 11.3 Hz, 2H); <sup>19</sup>F NMR (CDCl<sub>3</sub>) δ -61.18 (s); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 11.3, 18.6, 81.9, 92.2 (t, *J* = 38.0 Hz), 132.2 (t, *J* = 249.5 Hz), 151.7; IR (CCl<sub>4</sub>) 2949, 2870, 1577, 1461, 1348, 1257, 1174 cm<sup>-1</sup>; mp = 33–34 °C; MS *m/z* (%) 371 (100), 195 (5), 158 (5). Anal. Calcd for C<sub>13</sub>H<sub>23</sub>F<sub>2</sub>IOSi: C, 40.21; H, 5.97. Found: C, 40.49; H, 5.95.

**3-Fluoro-5-*n*-hexyl-4-iodo-2-phenylfuran (6a).** An oven-dried microwave vial (10 mL size) fitted with a stir bar, under argon atmosphere, was charged with sodium carbonate (0.6 mmol, 1.2 equiv) into which *gem*-difluorohomopropargyl alcohol **4a** (0.5 mmol) in THF (2.0 mL) was added via syringe. The mixture was stirred vigorously for 10 min before being cooled in an ice bath for 5 min followed by slow addition of iodine monochloride (0.75 mmol, 1.5 equiv) in THF (3.0 mL). The vial was then placed in a CEM Discover microwave synthesizer at 91 °C for 5 min (at 150 W, 250 psi max), and the temperature was monitored by the microwave-attached computer during the reaction. After cooling to room temperature, the reaction was quenched with aqueous sodium bisulfite (12.0 mL, 3/1 = water/saturated sodium bisulfite). The mixture was extracted with ether, and the combined organic extracts were washed with brine and dried over anhydrous MgSO<sub>4</sub>. The organic solvent was carefully removed in vacuo treating with ca. 1.0 g of silica gel to induce aromatization. The resulting powder was placed on top of a silica gel column chromatograph and eluted with hexane to furnish **6a** (122 mg, 66%) as a pale yellow oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.92–0.94 (m, 3H), 1.36–1.40 (m, 6H), 1.69–1.74 (m, 2H), 2.72 (dt, *J* = 2.0, 8.0 Hz, 2H), 7.27 (dt, *J* = 1.5, 6.5 Hz, 1H), 7.43 (dt, *J* = 2.0, 8.5 Hz, 2H), 7.67 (dd, *J* = 1.5, 7.0 Hz, 2H); <sup>19</sup>F NMR (CDCl<sub>3</sub>) δ -159.21 (s, 1F); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 14.1, 22.5, 27.8, 28.0, 28.6, 31.4, 57.6 (d, *J* = 24.1 Hz), 123.2 (d, *J* = 4.3 Hz), 127.0, 128.6, 128.7, 135.1 (d, *J* = 20.1 Hz), 149.7 (d, *J* = 253.8 Hz), 154.1 (d, *J* = 4.8 Hz); IR (neat) 3057, 2927, 2857, 1943, 1872, 1634, 1495, 1417, 1147, 1017, 759 cm<sup>-1</sup>; MS *m/z* (%) 373 (100, M<sup>+</sup> + H), 372 (14), 302 (44), 246 (3), 176 (6), 106 (9); HRMS (EI) calcd for C<sub>16</sub>H<sub>18</sub>FIO (M<sup>+</sup>) 372.0386, found 372.0375.

**3-Fluoro-5-*n*-hexyl-2,4-diphenylfuran (7aa).** An oven-dried microwave vial (10 mL size) fitted with a stir bar under argon atmosphere was charged with Pd(PPh<sub>3</sub>)<sub>4</sub> (0.035 mmol, 10 mol %) and phenylboronic acid (1.4 mmol, 4.0 equiv), into which 3-fluoro-4-iodofuran **6a** (0.35 mmol) was added along with EtOH (0.5 M relative to **6a**), 0.35 mL of aqueous Na<sub>2</sub>CO<sub>3</sub> (0.2 g/mL), and toluene (0.05 M). The vial was then capped under argon and placed in a CEM Discover microwave synthesizer at 115 °C for 30 min (at 150 W, 250 psi max), and the temperature was monitored by the microwave-attached computer during the reaction. After cooling to room temperature, the reaction mixture was quenched with saturated NH<sub>4</sub>Cl followed by extraction with ether. The combined organic layer was washed with brine and dried over anhydrous MgSO<sub>4</sub>. After evaporation of the solvent, the residue was purified on a silica gel column chromatograph eluted with hexane affording product **7aa** as a colorless oil (111 mg, 98% yield): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.92 (t, *J* = 7.0 Hz, 3H), 1.31–1.44 (m, 6H), 1.77

(quintet,  $J = 7.5$  Hz, 2H), 2.79 (t,  $J = 8.0$  Hz, 2H), 7.28 (t,  $J = 7.0$  Hz, 1H), 7.37–7.40 (m, 1H), 7.44–7.48 (m, 6H), 7.76 (d,  $J = 8.0$  Hz, 2H);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -166.21 (s, 1F);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  4.0 (d,  $J = 11.6$  Hz), 22.5, 27.2 (t,  $J = 11.5$  Hz), 28.2, 28.9, 31.5, 114.8 (d,  $J = 15.3$  Hz), 123.2 (d,  $J = 16.3$  Hz), 126.6 (d,  $J = 16.4$  Hz), 127.2 (d,  $J = 22.1$  Hz), 128.5, 128.7, 129.3 (d,  $J = 4.8$  Hz), 130.2, 134.3 (d,  $J = 20.3$  Hz), 141.2, 147.8 (d,  $J = 256.0$  Hz), 150.1 (d,  $J = 4.8$  Hz); IR (neat) 3058, 2954, 2927, 2856, 1945, 1872, 1802, 1749, 1645, 1499, 1421  $\text{cm}^{-1}$ ; MS  $m/z$  (%) 322 (2,  $\text{M}^+$ ), 254 (71), 233 (3), 205 (2), 106 (6). Anal. Calcd for  $\text{C}_{22}\text{H}_{23}\text{FO}$ : C, 81.95; H, 7.19. Found: C, 81.91; H, 7.31.

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**Supporting Information Available:** Analytical and spectroscopic data for **6b,6c**, **5d–5f**, **7ab–7ah**, and **7ba–7fa** and CIF information for **5f**. This material is available free charge via the Internet at <http://pubs.acs.org>.

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