

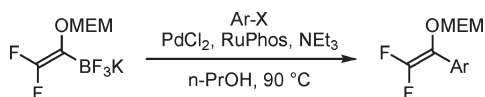
## Preparation of a Stable Trifluoroborate Salt for the Synthesis of 1-Aryl-2,2-difluoro-enoethers and/or 2,2-Difluoro-1-aryl-ketones via Palladium-Mediated Cross-Coupling

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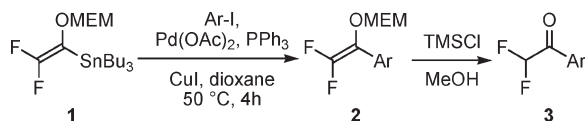
Received August 18, 2009



A bench-stable potassium trifluoroborate enol ether reagent has been prepared. This reagent is suitable for the incorporation of 2,2-difluoroenoethers into aryl and heteroaryl systems via palladium-mediated cross-coupling with suitable halide coupling partners.

Introduction of fluorine into organic molecules is often used in medicinal chemistry to affect a wide range of properties, such as desirable  $pK_a$ , drug metabolism, and distribution *in vivo*.<sup>1</sup> In a recent medicinal chemistry program, the synthesis of a targeted compound required an  $\alpha$ -gem-difluoro ketone as a key intermediate. The initial approach utilized chemistry described by Percy for the preparation of the difluoroenolstannane reagent **1**, followed by a cross-coupling with aryl iodides under Stille conditions (Scheme 1, **1**  $\rightarrow$  **2**).<sup>2,3</sup>

### Scheme 1. Initial Approach to Difluoroketone 3



To enhance the practical value of this precedent, a side-project was initiated to explore variations of this chemistry that avoid problems arising from the use of tin reagents, such as removal of the tin byproducts from the reaction mixture and potential toxicity associated with exposure to tin. The major focus of this effort was to test the feasibility of employing the corresponding boronic acid or ester

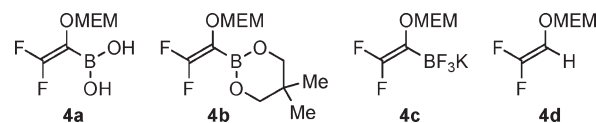
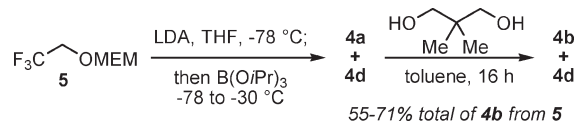


FIGURE 1. Enol boron analogues of **1**.

(Figure 1, **4a** and **4b** respectively) in a cross-coupling using the common Suzuki–Miyaura conditions. Surprisingly, given the extensive use of alkenyl boronates in modern organic synthesis, there have only been a few reports of 1-alkoxyalkenyl boronic esters or acids in the literature. Most reported examples focus on the preparation of the 3,4-dihydro-2*H*-pyran-6-yl-boronic esters, where the enol ether is contained in a ring system.<sup>4</sup> However, encouraging precedent was established by both Matteson's preparation of a (1-methoxyvinyl) boronic ester<sup>5</sup> and the preparation of 1-ethoxy-butadienyl boronic esters by Venturello and Prandi and their subsequent cross-coupling with aryl halides.<sup>6</sup>

Adapting the procedure described by Percy for the formation of **1**, 2-(methoxy)ethoxymethyl (MEM) protected trifluoroethanol **5** was treated with 2 equiv of LDA at  $-78$  °C and quenched with triisopropyl borate (Scheme 2).<sup>2,7</sup>

### Scheme 2. Preparation of Boronic Ester 4b



Following workup, the boronic acid **4a** was isolated from the crude reaction mixture, along with varying amounts of enol ether **4d** (typically  $\sim 7\%$ ) and diisopropyl amine. However, boronic acid **4a** proved relatively unstable and therefore was not an effective partner in our initial cross-coupling reactions.<sup>8</sup> Consequently, **4a** was immediately converted to the more stable boronic ester **4b**, which was isolated as an oil. Although **4b** was normally used within 24 h for subsequent cross-couplings, a toluene solution of **4b** could be stored at  $4$  °C for  $> 6$  months, with no decomposition observed.

Gratifyingly, initial experiments with the key boronic ester **4b** proved it to be an effective cross-coupling partner for the Suzuki–Miyaura protocol. The desired coupling product **2** could be obtained in excellent yield (91%) under conditions employing 2 equiv of **4b**, 10% Pd<sub>2</sub>dba<sub>3</sub>, 20% P(*o*-tol)<sub>3</sub>, and 1

(4) (a) Bower, J. F.; Guillauneux, D.; Nguyen, T.; Wong, P. L.; Snieckus, V. *J. Org. Chem.* **1998**, *63*, 1514. (b) Beckett, R. P.; Foster, R.; Henault, C.; Ralbovsky, J. L.; Gauss, C. M.; Gustafson, G. R.; Luo, Z.; Campbell, A.; Shelekhin, T. E. WO 2008/157751 A2, **2008**. (c) Allen, J. R.; Biwas, K.; Cao, G.-Q.; Golden, J. E.; Mercede, S.; Peterkin, T.; Reed, A.; Tegley, C. M. WO 2008/076425 A1, **2008**. (d) Kikuchi, T.; Takagi, J.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **2008**, *37*, 664.

(5) Matteson, D. S.; Beedle, E. C. *Heteroat. Chem.* **1990**, *1*, 135.

(6) Tivola, P. B.; Deagostino, A.; Prandi, C.; Venturello, P. *Org. Lett.* **2002**, *4*, 1275.

(7) (a) For a general review of  $\alpha$ -metalated vinyl ethers, see: Friesen, R. W. *J. Chem. Soc., Perkins Trans. 1* **2001**, 1969. (b) After this work was complete, a report was published describing the condensation of tosyloxydifluorovinyl-lithium reagent with diisopropyl iodomethylboronate: Ramachandran, P. V.; Chatterjee, A. *Org. Lett.* **2008**, *10*, 1195.

(8) The presence of **4d** does not appear to interfere with subsequent cross-couplings.

(1) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359.

(2) Patel, S. T.; Percy, J. M.; Wilkes, R. D. *Tetrahedron* **1995**, *51*, 9201.

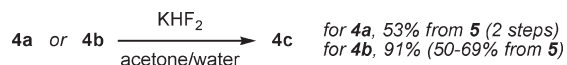
(3) DeBoos, G. A.; Fullbrook, J. J.; Percy, J. M. *Org. Lett.* **2001**, *3*, 2859.

M  $K_2CO_3$ (aq) in 1,4-dioxane at ambient temperature for 4 h.<sup>6</sup> While not extensively optimized, the use of either the corresponding aryl bromide, higher reaction temperatures, lower catalyst loadings, or fewer equivalents of the boronic ester **4b** resulted in lower conversions and isolated yields of **2**. Furthermore, it appeared that boronic ester **4b** was not particularly stable under these reaction conditions (temperature and/or base). Indeed, a toluene solution of the boronic ester **4b** stored over granular  $K_2CO_3$  at 4 °C decomposed overnight.

Whereas the cross-coupling with boronic ester **4b** proved adequate for the delivery of material for our internal program, there were several characteristics of this reagent that limited its' broader utility. In particular, physical properties (i.e., oil) made it inconvenient to prepare large quantities and dispense aliquots for intermittent use.<sup>9</sup> In addition, the instability of the reagent under a variety of reaction conditions was seen as a potential limitation to the substrate scope. Molander and co-workers have demonstrated that alkyl and aryltrifluoroborate salts often have superior reactivity compared to that of the corresponding boronic acids and esters and have the additional advantage of often being bench-stable solids.<sup>10</sup> Therefore, the preparation of the related trifluoroborate salt **4c** was investigated.

Initially, with ample quantities of the boronic ester in hand, trifluoroborate salt **4c** was prepared by treating the boronic ester **4b** with  $KHF_2$  (Scheme 3). Workup and

### SCHEME 3. Formation of Trifluoroborate Salt **4c**



recrystallization from acetonitrile/ether delivered **4c** in 91% yield (50–69% over 3 steps from **5**). Similarly, the salt could be generated more directly from the boronic acid **4a**, delivering **4c** in a comparable 53% yield over two steps from **5**. Pleasingly, trifluoroborate salt **4c** was a solid that has proven to be stable when stored for > 6 months in a vial on the benchtop (ambient light and temperature).

Turning to the Suzuki–Miyaura cross-coupling, optimization of the reaction conditions was explored using the 1-halo-naphthyl system (Table 1). Typical conditions for the Suzuki–Miyaura cross-coupling of potassium trifluoroborate salts (entry 1) delivered the desired product **7** in a moderate 70% isolated yield.<sup>10</sup> However, unlike the couplings with boronic ester **4b**, only 1.1 equiv of **4c** was required for complete conversion.<sup>11</sup> In addition, the coupling with trifluoroborate salt **4c** required heating at 90 °C for at least 6 h to go to completion.<sup>11,12</sup>

Although the  $PdCl_2(dppf)$  system proved adequate, additional catalyst–ligand combinations were screened to identify a more effective system. Not surprisingly, the use of  $PPh_3$

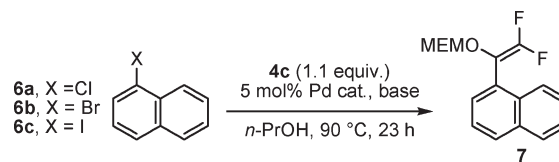
(9) Although we have prepared large batches of the toluene solution, syringed out aliquots as needed, and removed the toluene *in vacuo*, this is not ideal.

(10) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275 and references therein.

(11) For a full list of these results, please refer to Table S1 in Supporting Information. In addition, microwave conditions were briefly explored using the optimal conditions. The Supporting Information contains a brief account of these efforts.

(12) Although the reactions were mostly complete at 8 h, they were typically allowed to go for 23 h for convenience.

TABLE 1. Optimization of Reaction Conditions for Cross-Coupling of **4c** with 1-Naphthyl Halides



entry	X	catalyst system	Base	isolated yield (%)
1	Br	$PdCl_2(dppf) \cdot CH_2Cl_2$	$NEt_3$	70
2	Br	$PdCl_2/PPh_3$ (1:2)	$NEt_3$	39
3	Br	$PdCl_2/X-Phos$ (1:3)	$NEt_3$	86
4	Br	$PdCl_2/Ru-Phos$ (1:3)	$NEt_3$	91
5	Br	$Pd(OAc)_2/Ru-Phos$ (1:3)	$NEt_3$	86
6	Br	$Pd_2dba_3/Ru-Phos$ (1:3)	$NEt_3$	69
7	Br	$PdCl_2/Ru-Phos$ (1:3)	$CS_2CO_3$	0
8	Br	$PdCl_2/Ru-Phos$ (1:3)	KOAc	36
9	Br	$PdCl_2/Ru-Phos$ (1:3)	$K_3PO_4$	53
10	Br	$PdCl_2/Ru-Phos$ (1:3)	$K_2HPO_4$	64
11	Br	$PdCl_2/Ru-Phos$ (1:3)	$KH_2PO_4$	6
12	Br	$PdCl_2/Ru-Phos$ (1:3)	$NEt_3$	25 <sup>a</sup>
13	Br	$PdCl_2/Ru-Phos$ (1:3)	$NEt_3$	66 <sup>b</sup>
14	Cl	$PdCl_2/Ru-Phos$ (1:3)	$NEt_3$	78
15	I	$PdCl_2/Ru-Phos$ (1:3)	$NEt_3$	48

<sup>a</sup>Experiment was conducted using boronic ester **4b**. <sup>b</sup>Experiment was initiated with 1.1 equiv of boronic ester **4b**. After 2 h, an additional 1.1 equiv of boronic ester **4b** was added.

as a ligand resulted in a much lower yield (entry 2); however, using either the X-Phos or Ru-Phos<sup>13</sup> ligands delivered the coupled product **7** with a substantial increase in yield (entries 3 and 4).<sup>14</sup> Given the success with Ru-Phos, it was decided to use this ligand for future optimization of the cross-coupling reaction. We next evaluated the source of palladium, as up to this point, only  $PdCl_2$  had been used as a precatalyst. However, screening other palladium sources did not improve the yield relative to  $PdCl_2$  (entries 5 and 6).

Originally,  $NEt_3$  was selected as the base of choice, given the potential instability issues of the boronic ester in the presence of an inorganic base, as seen with potassium carbonate (*vide supra*). Similarly, the coupling with  $CS_2CO_3$  proceeded poorly, with no desired product isolated from the reaction mixture (entry 7). However, switching to the less basic KOAc delivered the coupled product in 36% yield (entry 8). A further examination using tri-, di-, and mono-basic potassium phosphates (entries 9–11) revealed that choosing an inorganic base with an appropriate  $pK_a$  leads to the formation of **7** in a moderate 64% yield.<sup>15</sup>

As a final comparison between the reactivity of the boronic ester **4b** and the trifluoroborate salt **4c**, the cross-coupling of **4b** under the optimal conditions was examined in the context of the 1-naphthyl system (entries 12 and 13). The reaction of **6b** with 1.1 equiv of boronic ester **4b** resulted in a low 25% yield of coupling product (entry 12). Given the propensity for the ester reagent to decompose at these elevated temperatures, a separate experiment was conducted where an additional 1.1 equiv of **4b** was added to the reaction mixture after 2 h (entry 13). This modification resulted in a much improved yield (66%) of

(13) RuPhos = 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl; X-Phos = 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl.

(14) Molander, G. A.; Brown, A. R. *J. Org. Chem.* **2006**, *71*, 9681.

(15) These results suggest that  $pK_a \approx 7-10$  could be an optimal range.

the coupling product, suggesting that the rate of decomposition of **4b** at the optimized coupling conditions is competitive with the rate of the cross-coupling reaction.

Finally, the coupling of the trifluoroborate salt **4c** with the 1-chloro- and 1-iodo-naphthyl analogues revealed that both aryl chlorides and aryl iodides are competent coupling partners (entries 14 and 15). The chloro analogue delivered the product in an acceptable 78% yield, while the iodo analogue proceeded in a lower 48% yield.

The results of the cross-coupling of trifluoroborate salt **4c** with a number of aryl and heteroaryl bromides is presented in Table 2. The cross-coupling with a variety of *ortho*

TABLE 2. Cross-Coupling of **4c** with Aryl and Heteroaryl Bromides

Entry	Ar-Br	Isolated Yield (%) <sup>a</sup>
1		74
2		70
3		72
4		78
5		85
6		82
7		58 + compd <b>10</b> (29) <sup>b</sup>
8		0 (41) <sup>b</sup>
9		76
10		65
11		0 + compd <b>11</b>

<sup>a</sup>Reported yields are an average of two runs. <sup>b</sup>Reaction was conducted using the boronic ester **4b** instead of the trifluoroborate salt **4c**.

alkyl-substituted aryl bromides reveals that the efficiency of the cross-coupling is not dependent on the degree of substitution about the halide (entries 1–3). Additionally, the conditions are tolerant to various electron-donating and electron-withdrawing substituents on the aryl halides (entries 4–7). However, the coupling of **4c** with a nitro-substituted analogue did not afford any of the desired product (entry 8). The cross-coupling was also shown to work with several heteroaryl bromides, such as the 3-pyridyl (entry 9) and 7-indolyl (entry 10) analogues. Similar to the observations in the aryl series, not all heteroaryl bromides were competent coupling partners in the Suzuki–Miyaura reaction (entry 11).

It is interesting to note that in the case of the keto analogues (Table 2, entries 7 and 11), the trifluoromethyl MEM ether side products **10** and **11** were also isolated from the reaction mixture (Figure 2).<sup>16</sup> One report in the patent

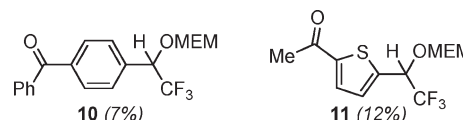


FIGURE 2. Side-products isolated from coupling reactions.

literature describes a similar addition of HF to a related *gem*-difluoroenoether in the presence of fluoride salts in protic media.<sup>17,18</sup> Therefore, it was postulated that **10** and **11** similarly arose as a result of the addition of fluoride into the enoether, followed by protonation of the intermediate from the *n*-propanol solvent. Indeed, when boronic ester **4b** was used in the cross-coupling with benzophenone (entry 7), where no fluoride is present, only the desired enol ether was isolated, albeit in a 29% yield.<sup>19</sup> In the thiophene example (entry 11), use of the boronic ester **4b** did not result in the formation of any desired product.

Building upon the result from entry 7, when the 3-nitro-bromobenzene analogue was reacted with the boronic ester **4b**, the desired product was isolated in 41% yield (entry 8). Thus, although the trifluoroborate salt **4c** proved effective for most of the attempted cross-couplings, the use of the boronic ester **4b** can be explored in some cases as a secondary strategy.

Whereas the 2,2-difluoroenoethers **9** are potentially synthetically useful intermediates for more complex couplings and rearrangements,<sup>18</sup> simple deprotection of the MEM protecting group reveals the originally desired *gem*-difluoroketone (Scheme 1, **3**). As a representative example, the naphthyl derived enoether **7** was treated with TMSCl in MeOH (Scheme 4), to reveal the *gem*-difluoroketone **12** in 91% isolated yield.<sup>3</sup>

In conclusion, the bench-stable potassium trifluoroborate salt **4c** has been prepared to enable practical incorporation of 2,2-difluoroenoethers and difluoroketone functionality.

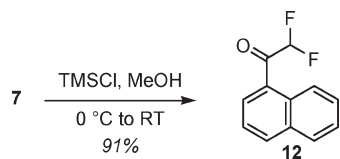
(16) A similar product was also observed in the 4-acetophenone derivative as well (data not shown).

(17) Ohtsuka, T. Y.; Kuroki, Y.; Suzuki, A.; Sugiyama, A. WO2007/142110, 2007.

(18) In addition, difluoroenoethers have previously been shown to be electrophiles at the *gem*-difluoro position for a variety of reactions, such as (a) oxidative cross coupling: Uneyama, K.; Tanaka, H.; Kobayashi, S.; Shioyama, M.; Amii, H. *Org. Lett.* 2004, 6, 2733 and (b) 2,3-Wittig rearrangements: Miles, J. A. L.; Mitchell, L.; Percy, J. M.; Singh, K.; Uneyama, E. *J. Org. Chem.* 2007, 72.

(19) As with the naphthyl system described in Table 1, entry 13, the yield likely could be increased by the addition of extra **4b** 2 h into the reaction.

## SCHEME 4. Removal of MEM Protecting Group



This reagent is suitable for cross-coupling reactions with a range of aryl and heteroaryl halides. In certain cases where side reactions were observed, the use of the related boronic ester reagent **4b** allows for isolation of the desired products. Current work is focused on expanding the scope of this reagent into other types of chemical transformations common to potassium trifluoroborate salts.

## Experimental Section

**Synthesis of Boronic Ester 4b.** Butyllithium (2.5 M in hexanes, 179 mL, 446 mmol) was added dropwise via addition funnel to a solution of diisopropylamine (63.6 mL, 446 mmol) in THF (240 mL) at  $-78\text{ }^{\circ}\text{C}$ , such that the internal temperature remained below  $-65\text{ }^{\circ}\text{C}$ . After the addition was complete, the funnel was rinsed with 10 mL of THF, and the solution was allowed to stir at  $-78\text{ }^{\circ}\text{C}$  for 10 min. A solution of 1,1,1-trifluoro-2-[(2-methoxyethoxy)methoxy]ethane (40.0 g, 213 mmol) in 40 mL of THF was then added dropwise via addition funnel so that the internal temperature remained below  $-65\text{ }^{\circ}\text{C}$  (ca. 2 h). The reaction mixture initially formed a yellow-green solution and then turned to a brownish-orange slurry by the end of the addition. After the addition was complete, the reaction mixture was held at  $-78\text{ }^{\circ}\text{C}$  for 30 min, followed by the addition of triisopropyl borate (99 mL, 425 mmol) dropwise via addition funnel at a rate to keep the internal temperature below  $-65\text{ }^{\circ}\text{C}$  (ca. 2 h). The resulting dark red-brown solution was allowed to warm to  $-30\text{ }^{\circ}\text{C}$  over 2 h, then was quenched by the addition of 200 mL of saturated  $\text{NH}_4\text{Cl}$  (aq), and allowed to warm to ambient temperature. The reaction mixture was partitioned between  $\text{Et}_2\text{O}$  (800 mL) and water (400 mL), and the layers were separated. The organic layer was washed with 200 mL of water, and the combined aqueous layers were adjusted to pH 5 with concentrated HCl. The aqueous layer was then extracted with  $\text{Et}_2\text{O}$  ( $3 \times 300\text{ mL}$ ), and these combined  $\text{Et}_2\text{O}$  layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to give 63.9 g of an orange oil containing {2,2-difluoro-1-[(2-methoxyethoxy)methoxy]ethenyl}boronic acid **4a**.

The crude reaction mixture was then dissolved in toluene (1 L) and THF (100 mL), 2,2-dimethyl-1,3-propanediol (22.1 g, 213 mmol) was added, and the mixture was allowed to stir at ambient temperature overnight. The reaction mixture was then concentrated to approximately 200 mL, diluted in  $\text{Et}_2\text{O}$  (1.2 L), and washed with water (200 mL) and brine (300 mL). The aqueous layer was back extracted with  $\text{Et}_2\text{O}$  (300 mL), and the combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to give 42.6 g of **4b** (152 mmol, 71% yield) as a colorless oil contaminated with the protonated byproduct **4d** (7% by  $^1\text{H NMR}$ ):  $^1\text{H NMR}$  (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  4.78 (s, 2H), 3.62–3.68 (m, 6H), 3.40–3.45 (m, 2H), 3.18 (s, 3H), 0.90 (s, 6H).

**Synthesis of Potassium Trifluoroborate Salt 4c from Ester 4b.** Potassium hydrogen fluoride (10.1 g, 129 mmol) was added to a solution of **4b** (6.03 g, 21.5 mmol) in water (70 mL)/acetone (175 mL), and the mixture was allowed to stir for 2 h. The solvents were removed *in vacuo*, and then excess water was removed by azeotroping three times with toluene and once with acetone to give a colorless solid. The solid was suspended in boiling acetone, filtered, and concentrated. The resulting solid was dissolved in acetonitrile (40 mL) and  $\text{Et}_2\text{O}$  (100 mL) was slowly added to precipitate a colorless solid. The slurry was then cooled to  $0\text{ }^{\circ}\text{C}$ , and the solid was collected by filtration and rinsed with cold diethyl ether to give 5.34 g of **4c** (19.5 mmol, 91%) as a colorless solid.  $^1\text{H NMR}$  (500 MHz, acetone- $d_6$ )  $\delta$  4.87 (s, 2H), 3.65–3.75 (m, 2H), 3.45–3.55 (m, 2H), 3.30 (s, 3H);  $^{19}\text{F NMR}$  (470 MHz, acetone- $d_6$ )  $\delta$   $-99.5$  (br d, 1F,  $J = 74.7\text{ Hz}$ ),  $-115.3$  (dq, 1F,  $J = 9.0, 74.7\text{ Hz}$ ),  $-141.1$  (3F, 1:1:1:1 q,  $J = 33.0\text{ Hz}$ );  $^{13}\text{C NMR}$  (125 MHz, acetone- $d_6$ )  $\delta$  159.2, 119.0, 94.8, 71.7, 67.1, 58.0. LRMS calcd for  $\text{C}_6\text{H}_9\text{BF}_3\text{O}_3 [\text{M} - \text{K}]^-$  235.1, found, 235.1.

**Representative Coupling Procedure: 1-(2,2-Difluoro-1-((2-methoxyethoxy)methoxy)vinyl)naphthalene (7).** Trifluoroborate salt **4c** (150.0 mg, 0.550 mmol), palladium(II) chloride (4.4 mg, 0.03 mmol), and 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (35.0 mg, 0.075 mmol) were added to a flask, and the vessel was sparged with Ar for 5 min. 1-Bromo-naphthalene (70.0  $\mu\text{L}$ , 0.500 mmol), triethylamine (209  $\mu\text{L}$ , 1.50 mmol), and *n*-PrOH (2.5 mL) were added, and the mixture was sparged with Ar for 10 min. The reaction mixture was heated to  $90\text{ }^{\circ}\text{C}$  and allowed to stir for 23 h. The reaction mixture was diluted in EtOAc, washed with saturated aqueous  $\text{NaHCO}_3$  and brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (EtOAc/hexanes gradient, 0–14%) to give 133.6 mg (0.454 mmol, 91%) of **7** as a colorless oil.  $R_f = 0.18$  (7.5% EtOAc/92.5% hexanes);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.10 (d,  $J = 8.0\text{ Hz}$ , 1H), 7.94–7.84 (m, 2H), 7.60–7.44 (m, 4H), 4.71 (d,  $J = 1.0\text{ Hz}$ , 2H), 3.83–3.75 (m, 2H), 3.53–3.48 (m, 2H), 3.36 (s, 3H);  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  155.3 (dd,  $J = 290.3, 281.0\text{ Hz}$ ), 133.9, 132.1 (app. d,  $J = 3.3\text{ Hz}$ ), 130.4, 129.8, 128.6, 127.0, 126.5, 126.1 (dd,  $J = 4.2, 1.9\text{ Hz}$ ), 125.5, 125.4, 114.3 (dd,  $J = 40.9, 18.6\text{ Hz}$ ), 94.1–93.7 (m), 71.8, 68.1, 59.2 (d,  $J = 2.8\text{ Hz}$ );  $^{19}\text{F NMR}$  (470 MHz,  $\text{CDCl}_3$ )  $\delta$   $-101.2$  (d,  $J = 61.3\text{ Hz}$ , 1F),  $-108.7$  (d,  $J = 61.3\text{ Hz}$ , 1F); HRMS calcd for  $\text{C}_{16}\text{H}_{17}\text{F}_2\text{O}_3 [\text{M} + \text{H}]^+$  295.1146, found 295.1158.

**Acknowledgment.** Part of this work was completed as part of the Co-Op Education Program with Northeastern University, Boston, MA (B.T.L.). We thank Bruce Adams and Bridget Becker for assistance with NMR spectra and Adam Beard for obtaining HRMS data.

**Supporting Information Available:** Supplemental Table S1, exploration of microwave experiments, experimental procedures (**4c** from **4a**, **12**, microwave conditions) and characterization data for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.