

## Preparation of $\alpha$ -Bromo- $\beta,\beta$ -difluorostyrenes

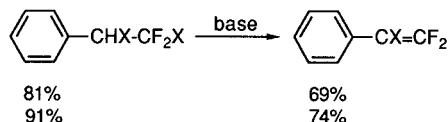
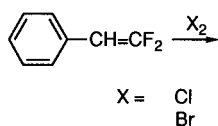
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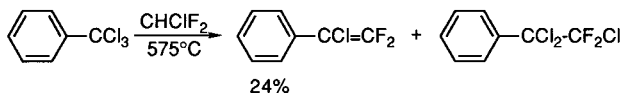
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### Introduction

$\alpha$ -Bromo- $\beta,\beta$ -difluorostyrenes (**II**) are building blocks in organofluorine chemistry due to the reactivity of the *gem*-difluoromethylene terminus toward nucleophilic reagents, and the  $\alpha$ -bromine provides a reaction site for further functionalization. Until now, no methods for the direct introduction of the  $\text{CF}_2=\text{CBr}$  group into organic molecules have been reported. Some synthetic strategies used to form  $\alpha$ -halo- $\beta,\beta$ -difluorostyrenes have been reported. The first approach was the addition of a halogen to  $\text{RCH}=\text{CF}_2$ <sup>1</sup> followed by dehydrohalogenation.<sup>2</sup> The success of the dehydrohalogenation process depended on the base employed. A more selective base was used to improve the yields and to avoid undesired byproducts.

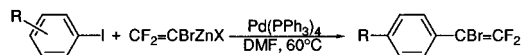


An alternative method<sup>3</sup> for the formation of  $\alpha$ -halo- $\beta,\beta$ -difluorostyrenes was to heat benzotrichlorides in the presence of chlorodifluoromethane at 575 °C. This method gives ( $\alpha,\alpha,\beta$ -trichloro- $\beta,\beta$ -difluoroethyl)benzene as a byproduct, and the total yields were low. The temperature was an important factor for the success of this reaction. For example, the reaction gives 18%, 24%, and 3% yields of  $\alpha$ -halo- $\beta,\beta$ -difluorostyrene at 635, 575, and 535 °C, respectively.



Recent reports from our laboratory have demonstrated the synthetic applications of  $\text{CF}_2=\text{CFZnX}^4$  and (*E*)- and (*Z*)- $\text{CF}_3\text{CF}=\text{CFZnX}^5$ . This success prompted us to examine the formation and synthetic applications of  $\text{F}_2\text{C}=\text{CBrZnX}$ . We now report the facile preparation of

**Table 1.** Reaction of Aryl Iodides with  $\text{CF}_2=\text{CBrZnX}$  Catalyzed by  $\text{Pd}(\text{PPh}_3)_4$  in DMF



Entry	R	Product	Yield % <sup>a</sup>
1	<i>o</i> -CH <sub>3</sub>		81
2	<i>m</i> -CH <sub>3</sub>		93
3	<i>p</i> -CH <sub>3</sub>		77
4	<i>o</i> -CF <sub>3</sub>		83
5	<i>p</i> -I		84
6	<i>m</i> -NO <sub>2</sub>		96
7	<i>p</i> -OCH <sub>3</sub>		93

<sup>a</sup> Isolated yields based on aryl iodides.

$\alpha$ -bromo- $\beta,\beta$ -difluorostyrenes by the palladium-catalyzed coupling reaction of  $\text{CF}_2=\text{CBrZnX}$  with aryl iodides.

### Results and Discussion

$\text{CF}_2=\text{CBrZnX}$  (**I**) is prepared by treatment of  $\text{CF}_2=\text{CBrX}$  ( $\text{X} = \text{I}, \text{Br}$ ) with acid-washed zinc in DMF. This exothermic reaction is completed in 20 min and gives <sup>19</sup>F NMR yields of 98% (vs internal  $\text{C}_6\text{H}_5\text{CF}_3$ ). Zinc reagent **I** reacted smoothly with aryl iodides in DMF in the presence of catalytic amounts of  $\text{Pd}(\text{PPh}_3)_4$  under mild conditions (Table 1). Methyl, trifluoromethyl, nitro, and methoxy groups substituted on the aryl iodides are tolerated under the reaction conditions. For example, **I** reacts with 1-iodotoluene at 60 °C in 5 h with 5 mol % of  $\text{Pd}(\text{PPh}_3)_4$  catalyst to form the corresponding coupled product 2-methyl- $\alpha$ -bromo- $\beta,\beta$ -difluorostyrene in 81% isolated yield (Table 1, entry 1). Reaction of 2.7 equiv of **I** with 1 equiv of 1,4-diiodobenzene gives 1,4-bis(1-bromo-2,2-difluoroethyl)benzene in 84% yield (Table 1, entry 5).

The  $\alpha$ -bromo- $\beta,\beta$ -difluorostyrenes and the starting aryl iodides have similar  $R_f$  values on silica gel. Thus, it is important to ensure that excess **I** is utilized so that the reaction goes to completion. The  $\alpha$ -bromo- $\beta,\beta$ -difluorostyrenes are stable indefinitely in solvents such as hexane, ether, and DMF; however, they are readily decomposed (hydrolyzed) in air when solvent is absent.

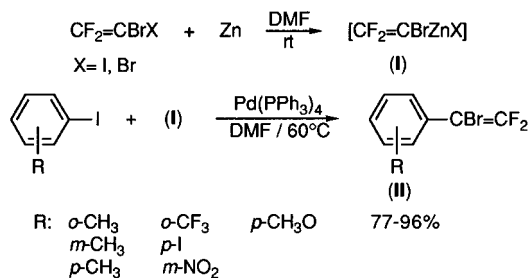
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### Conclusion

In conclusion, we have presented a new preparative method for  $\alpha$ -bromo- $\beta,\beta$ -difluorostyrenes via coupling of ( $\alpha$ -bromo- $\beta,\beta$ -difluoroethenyl)zinc reagent with aryl iodides catalyzed by  $\text{Pd(PPh}_3)_4$  in DMF under mild conditions. Since the zinc reagents can be produced in situ from 1,1-dibromodifluoroethene or from 1-bromo-1-iododifluoroethene, this route provides a convenient one-pot reaction and produces the desired products directly from commercially available materials.<sup>6</sup>

### Experimental Section

**General Methods.** All reactions were monitored by  $^{19}\text{F}$  NMR analysis of the reaction mixtures on a 90 MHz spectrometer. The  $^1\text{H}$ ,  $^{19}\text{F}$ , and  $^{13}\text{C}$  NMR spectra of final products were obtained on a 300 MHz spectrometer ( $\text{CDCl}_3$ ,  $\text{CFCl}_3$ , or TMS internal references). FT-IR spectra were recorded as  $\text{CCl}_4$  solutions in a 0.1 cm pathlength cell. Low-resolution mass spectra analyses were performed at 70 eV in the electron-impact mode on a single quadrupole instrument interfaced to a gas chromatograph fitted with an OV-101 column. High-resolution mass spectral analyses were performed by the University of Iowa High-Resolution Mass Spectrometry Facility at 70 eV in the electron impact mode. GLPC analyses were performed on a 5% OV-101 column and thermal conductivity detector. The aryl iodides were obtained from Aldrich and used directly.

**Preparation of  $\text{CF}_2=\text{CBrZnX}$  (I).** A 100 mL two-necked, round-bottomed flask equipped with a septum, a Teflon-coated magnetic stirbar, and  $\text{N}_2$  tee, which was connected to a mineral oil bubbler, was charged with 1.0 g (15 mmol) of acid-washed zinc, 8 mL of dry DMF, and 2.6 g (11.7 mmol) of  $\text{CF}_2=\text{CBr}_2$ . The reaction mixture was stirred for 20 min, and  $^{19}\text{F}$  NMR analysis showed two groups of signals:  $\delta$  -68.8 (d,  $J$  = 59.4 Hz, 0.3 F), -69.8 (d,  $J$  = 56.3 Hz, 0.7 F), and -84.9 (d,  $J$  = 56.9 Hz, 0.7 F), -85.8 (d,  $J$  = 59.2 Hz, 0.3 F). The NMR yield was 98% based on internal  $\text{C}_6\text{H}_5\text{CF}_3$ .

**Preparation of 2-(1-Bromo-2,2-difluoroethenyl)toluene (1).** A 50 mL, two-necked, round-bottomed flask equipped with a septum, a Teflon-coated magnetic stirbar, and  $\text{N}_2$  inlet, which was connected to a mineral oil bubbler, was charged with 0.87 g (4 mmol) of 2-iodotoluene, 5 mmol of  $\text{CF}_2=\text{CBrZnX}$ , and 5 mol % of  $\text{Pd(PPh}_3)_4$ . The reaction mixture was stirred at 60  $^\circ\text{C}$  under  $\text{N}_2$  atmosphere for 10 h. The reaction mixture was introduced onto a silica gel column and eluted with hexane to give 0.76 g (81%) of clear liquid **1**: GLPC purity >99%;  $^{19}\text{F}$   $\delta$  -83.2 (d,  $J$  = 32.8 Hz, 1F), -84.6 (d,  $J$  = 32.9 Hz, 1F);  $^1\text{H}$   $\delta$  7.2-7.1 (m, 4H), 2.3 (s, 3H);  $^{13}\text{C}$   $\delta$  152.9 (t,  $J$  = 288.7 Hz), 137.9 (s), 131.1 (s), 130.8 (d,  $J$  = 3.7 Hz), 130.6 (s), 130.0 (s), 126.4 (s), 77.1 (dd,  $J$  = 41.5, 25.6 Hz), 19.3 (s); FTIR ( $\text{cm}^{-1}$ ) 1724.5 (s), 1267.3 (s), 1238.4 (m); HRMS calcd for  $\text{C}_9\text{H}_7^{79}\text{BrF}_2$  231.9699, found 231.9709.

**Preparation of 3-(1-Bromo-2,2-difluoroethenyl)toluene (2).** Similarly, **2** was prepared from 0.87 g (4 mmol) of 3-iodotoluene, 5 mmol of  $\text{CF}_2=\text{CBrZnX}$ , and 5 mol % of  $\text{Pd(PPh}_3)_4$ . Purification of the reaction mixture by chromatography on silica gel with hexane as eluent given 0.87 g (93%) of clear liquid **2**: GLPC purity >99%;  $^{19}\text{F}$   $\delta$  -79.2 (d,  $J$  = 31.1 Hz, 1F), -85.2 (d,  $J$  = 31.4 Hz, 1F);  $^1\text{H}$   $\delta$  7.3-7.2 (m, 3H), 7.1 (m, 1H), 2.3 (s, 3H);

$^{13}\text{C}$   $\delta$  153.4 (dd,  $J$  = 293.9, 286.5 Hz), 138.4 (s), 134.0 (d,  $J$  = 19.7 Hz), 129.8 (s), 129.6 (m), 128.5 (s), 126.1 (t,  $J$  = 5.8 Hz), 80.4 (dd,  $J$  = 34.9, 25.6 Hz), 21.2 (s); FTIR ( $\text{cm}^{-1}$ ) 1709.0 (s), 1267.3 (s), 1172.8 (m); HRMS calcd for  $\text{C}_9\text{H}_7^{79}\text{BrF}_2$  231.9699, found 231.9717.

**Preparation of 4-(1-Bromo-2,2-difluoroethenyl)toluene (3).** Similarly, **3** was prepared from 1.1 g (5 mmol) of 4-iodotoluene, 7 mmol of  $\text{CF}_2=\text{CBrZnX}$ , and 5 mol % of  $\text{Pd(PPh}_3)_4$ . Purification of the reaction mixture by chromatography on silica gel with hexane as eluent gave 0.9 g (77%) of clear liquid **3**: GLPC purity >99%;  $^{19}\text{F}$   $\delta$  -79.6 (d,  $J$  = 32.4 Hz, 1F), -85.7 (d,  $J$  = 32.5 Hz, 1F);  $^1\text{H}$   $\delta$  7.3 (d,  $J$  = 7.5 Hz, 2H), 7.2 (d,  $J$  = 7.5 Hz, 2H), 2.3 (s, 3H);  $^{13}\text{C}$   $\delta$  153.3 (dd,  $J$  = 293.9, 285.7 Hz), 139.1 (s), 134.0 (d,  $J$  = 19.5 Hz), 129.4 (s), 128.9 (t,  $J$  = 5.6 Hz), 80.4 (dd,  $J$  = 34.3, 25.7 Hz), 21.1 (s); FTIR ( $\text{cm}^{-1}$ ) 1716.7 (s), 1276.9 (m), 1248.0 (m); HRMS calcd for  $\text{C}_9\text{H}_7^{79}\text{BrF}_2$  231.9699, found 231.9716.

**Preparation of 2-(1-Bromo-2,2-difluoroethenyl)benzotrifluoride (4).** Similarly, **4** was prepared from 1.4 g (5 mmol) of 2-iodobenzotrifluoride, 8 mmol of  $\text{CF}_2=\text{CBrZnX}$ , and 5 mol % of  $\text{Pd(PPh}_3)_4$ . Purification of the reaction mixture by chromatography on silica gel with hexane as eluent gave 1.2 g (83%) of clear liquid **4**: GLPC purity >99%;  $^{19}\text{F}$   $\delta$  -61.0 (s, 3F), -81.3 (m, 2F);  $^1\text{H}$   $\delta$  7.7 (d,  $J$  = 7.3 Hz, 1H), 7.6 (m, 1H), 7.5 (m, 2H);  $^{13}\text{C}$   $\delta$  124.6 (t,  $J$  = 181.0 Hz), 111.9 (m), 111.6 (s), 110.4 (s), 110.2 (s), 110.1 (s), 108.0 (q,  $J$  = 3.3 Hz), 106.2 (q,  $J$  = 170.9 Hz), 74.7 (dd,  $J$  = 25.2, 18.6 Hz); FTIR ( $\text{cm}^{-1}$ ) 1739.9 (s), 1311.7 (s), 1284.7 (s), 1230.7 (m), 1172.8 (s), 1130.4 (s), 1112.9 (s); HRMS calcd for  $\text{C}_9\text{H}_4^{79}\text{BrF}_5$  285.9416, found 285.9411.

**Preparation of 1,4-Bis(1-bromo-2,2-difluoroethenyl)benzene (5).** Similarly, **5** was prepared from 1.65 g (5 mmol) of 1,4-diiodobenzene, 13.6 mmol of  $\text{CF}_2=\text{CBrZnX}$ , and 5 mol % of  $\text{Pd(PPh}_3)_4$ . Purification of the reaction mixture by chromatography on silica gel with hexane as eluent gave 1.5 g (84%) of clear liquid **5**: GLPC purity >99%;  $^{19}\text{F}$   $\delta$  -77.3 (d,  $J$  = 27.8 Hz, 1F), -83.6 (d,  $J$  = 27.5 Hz, 1F);  $^1\text{H}$   $\delta$  7.5 (s);  $^{13}\text{C}$   $\delta$  153.7 (dd,  $J$  = 295.4, 288.0 Hz), 132.2 (d,  $J$  = 4.5 Hz), 128.9 (t,  $J$  = 3.6 Hz), 79.6 (dd,  $J$  = 33.0, 26.8 Hz); FTIR ( $\text{cm}^{-1}$ ) 1724.5 (s), 1290.4 (s), 1251.9 (s), 995.3 (s), 910.4 (m); HRMS calcd for  $\text{C}_{10}\text{H}_4^{79}\text{Br}_2\text{F}_4$  357.8615, found 357.8598.

**Preparation of 3-Nitro-(1-bromo-2,2-difluoroethenyl)benzene (6).** Similarly, **6** was prepared from 2.5 g (10 mmol) of 3-nitroiodobenzene, 13.2 mmol of  $\text{CF}_2=\text{CBrZnX}$ , and 5 mol % of  $\text{Pd(PPh}_3)_4$ . Purification of the reaction mixture by chromatography on silica gel with hexane/ether (80/20) as eluent gave 2.54 g (96%) of clear liquid **6**: GLPC purity >99%;  $^{19}\text{F}$   $\delta$  -75.6 (d,  $J$  = 24.8 Hz, 1F), -82.0 (d,  $J$  = 24.8 Hz, 1F);  $^1\text{H}$   $\delta$  8.4 (t,  $J$  = 1.8 Hz, 1H), 8.2 (dm,  $J$  = 8.2 Hz, 1H), 7.8 (dm,  $J$  = 7.9 Hz, 1H), 7.6 (t,  $J$  = 8.0 Hz, 1H);  $^{13}\text{C}$   $\delta$  154.0 (dd,  $J$  = 296.7, 288.3 Hz), 148.5 (s), 134.7 (t,  $J$  = 3.3 Hz), 133.5 (d,  $J$  = 4.7 Hz), 130.0 (s), 123.9 (m), 123.8 (s), 78.4 (dd,  $J$  = 33.0, 27.2 Hz); FTIR ( $\text{cm}^{-1}$ ) 1737.9 (s), 1535.4 (s), 1352.2 (s), 1305.9 (m), 1280.8 (m); HRMS calcd for  $\text{C}_8\text{H}_4^{79}\text{BrF}_2\text{NO}_2$  263.9383, found 263.9387.

**Preparation of 4-(1-Bromo-2,2-difluoroethenyl)anisole (7).** Similarly, **7** was prepared from 0.7 g (3 mmol) of 4-iodoanisole, 4.0 mmol of  $\text{CF}_2=\text{CBrZnX}$ , and 5 mol % of  $\text{Pd(PPh}_3)_4$ . Purification of the reaction mixture by chromatography on silica gel with hexane/ether (80/20) as eluent gave 0.75 g (93%) of clear liquid **7**: GLPC purity >99%;  $^{19}\text{F}$   $\delta$  -80.4 (d,  $J$  = 34.5 Hz, 1F), -86.6 (d,  $J$  = 34.5 Hz, 1F);  $^1\text{H}$   $\delta$  7.4 (dm,  $J$  = 8.1 Hz, 2H), 6.9 (dm,  $J$  = 8.9 Hz, 2H), 3.8 (s, 3H);  $^{13}\text{C}$   $\delta$  160.2 (s), 153.1 (dd,  $J$  = 292.7, 285.6 Hz), 130.3 (t,  $J$  = 3.0 Hz), 123.9 (d,  $J$  = 3.4 Hz), 114.1 (s), 80.0 (dd,  $J$  = 35.2, 25.8 Hz), 55.2 (s); FTIR ( $\text{cm}^{-1}$ ) 1722.5 (s), 1612.6 (s), 1302.0 (s), 1176.6 (s); HRMS calcd for  $\text{C}_9\text{H}_7^{79}\text{BrF}_2\text{O}$  248.9638, found 248.9727.

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**Supporting Information Available:**  $^{13}\text{C}$  NMR spectra of all compounds (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(6)  $\text{CF}_2=\text{CBr}_2$  is available from PCR or can be readily prepared from  $\text{F}_2\text{C}=\text{CH}_2$  via a succession of bromination, dehydrobromination reactions.  $\text{F}_2\text{C}=\text{CBrI}$  was prepared by quenching  $[\text{F}_2\text{C}=\text{CBrZnBr}]$  with  $\text{I}_2$ .