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Facile Synthesis of Unsymmetrical 1,1-Diaryl-2,2-difluoroethenes via Stepwise Coupling of 1,1-Dibromo-2,2-difluoroethenes

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Abstract
Unsymmetrical 1,1-diaryl-2,2-difluoroethenes were synthesized from 1,1-dibromo-2,2-difluoroethene, which is commercially available, via the Suzuki–Miyaura coupling in a stepwise fashion. Suitable ligands for each coupling process were used to achieve selective synthesis of these diaryldifluoroethenes.

Keywords: Difluoroalkene, Diarylethene, Suzuki–Miyaura coupling, Dibromoethene, Arylboronic acid, Palladium, Ligand

1. Introduction
1,1-Diaryl-2,2-difluoroethenes are an important class of gem-difluoroalkenes, which have the potential to be used for a wide range of purposes, including functional materials and medicines such as photoreceptors [1], anticancer drugs [2], and dermatological agents [3]. These compounds are also expected to be bioisosteres of biologically active diarylketones [4]. Despite their versatility, the supply of 1,1-diaryl-2,2-difluoroethenes has been limited because of difficulties involved in synthesizing them (Scheme 1) [5,6]. Conventional synthetic methods, especially for unsymmetrically disubstituted 1,1-diaryl-2,2-difluoroethenes, have mostly required difluorovinylidene species to be synthesized as key intermediates, bearing both a metal functional group and a halogen (or pseudohalogen) substituent at the carbon β to the fluorine substituents [6]. This is due to selective introduction of two different aryl groups. The preparation of such intermediates is troublesome and requires extra synthetic steps.
Scheme 1. Conventional synthesis of 1,1-diaryl-2,2-difluoroethenes.

A straightforward synthesis of unsymmetrical 1,1-diaryl-2,2-difluoroethenes might be achieved simply with two reactivity-controlled coupling reactions, starting from 1,1-difluoro-2,2-dihaloethenes. However, there are only a few examples of the monoarylation of symmetric gem-dihaloethenes [7], because this type of selective reaction requires steric and/or electronic effects of vinylic substituents [8]. Although the monoarylation of symmetric gem-dichloroethenes has been reported, the low reactivities of their chlorine substituents might prevent a second arylation toward diarylated ethenes. Using highly reactive coupling partners of the arylating agents and/or vinyl halides (or pseudohalides) would easily induce double arylation, leading to undesirable symmetrical byproducts. Therefore, the selective synthesis of unsymmetrically disubstituted 1,1-diaryl-2,2-difluoroethenes is a significant challenge.

To solve these synthetic problems, we sought to find an appropriate ligand for each coupling step, preventing the formation of symmetrical 1,1-diaryl-2,2-difluoroethenes 3. We eventually achieved the selective synthesis of unsymmetrical 1,1-diaryl-2,2-difluoroethenes 4 by choosing ligands to control the reactivities in the first and second arylations of 1,1-dibromo-2,2-difluoroethene (1), which is commercially available (Scheme 2) [9].
Scheme 2. Strategy for the synthesis of unsymmetrical 1,1-diaryl-2,2-difluoroethenes 4 via stepwise coupling of 1,1-dibromo-2,2-difluoroethene (1).

2. Results and discussion

2.1. The first coupling: Selective synthesis of 1-aryl-1-bromo-2,2-difluoroethene 2 from 1,1-dibromo-2,2-difluoroethene (1)

To synthesize unsymmetrically disubstituted 1,1-diaryl-2,2-difluoroethenes 4, we first sought suitable conditions for selective monoarylation in the Suzuki–Miyaura coupling between 1,1-dibromo-2,2-difluoroethene (1) and phenylboronic acid, using cesium fluoride as a base (Table 1). The choice of ligands used with Pd\(_2\text{dba}_3\cdot\text{CHCl}_3\) (dba = dibenzylideneacetone) was found to be critical for the yield of the monoarylated product, 1-bromo-1-phenyl-2,2-difluoroethene (2a, Entries 1–8). Among the ligands that were screened, 1,1-bis(diphenylphosphino)methane (dppm) gave the highest yield of 2a (Entry 8), suppressing the formation of the diarylated product 3a. Co-solvents used with water (Entries 9–14) at different ratios (Entries 15–16) were subsequently examined. Ether-type solvents typically gave good yield and selectivity of 2a (Entries 9–11), and dioxane gave the highest yield of 2a in a short reaction time (Entry 11). Finally, we found that the optimum dioxane/water ratio was 2:1 (Entry 16), which gave, almost exclusively, bromodifluorostyrene 2a in 80% yield.

Table 1. Effects of the ligand and solvent used in the first Suzuki–Miyaura coupling
Once the optimal conditions had been determined, we investigated the scope of the substrate (Table 2). Monoarylation with several para-functionalized (Me, Ph, OMe, and F) phenylboronic acids was successfully achieved, providing bromodifluorostyrenes 2a–2e. To the best of our knowledge, this is the first example of the selective monoarylation of symmetrical gem-dibromoalkenes.

Table 2. Monoarylation of 1,1-dibromo-2,2-difluoroethylene (1)
2.2. The second coupling: Synthesis of unsymmetrically substituted 1,1-diaryl-2,2-difluoroethenes 4 from 1-aryl-1-bromo-2,2-difluoroethenes 2

The ligand used for the second coupling in the synthesis of unsymmetrically
disubstituted 1,1-diaryl-2,2-difluoroethenes 4 was examined next, and the ligands were screened in the Suzuki–Miyaura coupling of monoarylated bromodifluorostyrene 2c with 4-fluorophenylboronic acid, at higher temperatures than in the first step. The second coupling proceeded most effectively using triphenylphosphine, yielding 1,1-diaryl-2,2-difluoroethenes 4c in 72% yield (Entry 1). The low yield obtained using dppm indicated that dppm, although highly suitable for the first coupling, effectively suppressed the second coupling (Entry 4).

Table 3. Effects of the ligand in the second Suzuki–Miyaura coupling

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand 2</th>
<th>x / mol%</th>
<th>4c / %a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PPh3</td>
<td>2</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>AsPh3</td>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>dpf</td>
<td>1</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>dppm</td>
<td>1</td>
<td>27</td>
</tr>
</tbody>
</table>

a 19F NMR yield based on PhCF3.

The synthesis of several unsymmetrically disubstituted 1,1-diaryl-2,2-difluoroethenes 4 was examined under the conditions described above (Table 4). Both para-substituted (Me, OMe, and F; Entries 1–3) and ortho-substituted (Me; Entry 4) phenylboronic acids readily participated in the reaction, affording the desired difluoroethenes 4a–d in high yields.

Table 4. Synthesis of unsymmetrical 1,1-diaryl-2,2-difluoroethenes 4
3. Conclusion

We synthesized unsymmetrically disubstituted 1,1-diaryl-2,2-difluoroethenes 4 via stepwise Suzuki–Miyaura coupling reactions, starting from 1,1-dibromo-2,2-difluoroethene (1). The key to success was using the most appropriate
ligand in each coupling step. These protocols provide a versatile method for synthesizing 1,1-diaryl-2,2-difluoroethenes, involving the direct coupling of 1,1-dibromo-2,2-difluoroethylene. We expect 1,1-diaryl-2,2-difluoroethenes formed using this method to be biologically active compounds and important intermediates for further chemical transformations.

4. Experimental

4.1 General Information

IR spectra were recorded on a Horiba FT-300S spectrometer. NMR spectra were recorded on a Bruker Avance 500 spectrometer in CDCl₃ at 500 MHz (¹H NMR), at 126 MHz (¹³C NMR), and at 470 MHz (¹⁹F NMR). Chemical shifts were given in ppm relative to internal Me₄Si (for ¹H NMR: δ = 0.00), CDCl₃ (for ¹³C NMR: δ = 77.0), and C₆F₆ (for ¹⁹F NMR: δ = 0.0). High resolution mass spectroscopy (HRMS) was conducted with a JMS-T100GCV spectrometer.

1,1-Dibromo-2,2-difluoroethylene, purchased from SynQuest Labs, Inc., was used without further purification. Unless otherwise noted, materials were obtained from commercial sources and used directly without further purification. Column chromatography was performed on silica gel (Kanto, spherical and neutral, 63–210 mesh).

Spectral data for compounds 2a [10,11], 2b [12], 2d [12], and 2e [11] showed good agreement with the literature data. As for compounds 2a, 2b, 2d, and 2e, we present only NMR data in this section.

4.2 Synthesis of 1-aryl-1-bromo-2,2-difluoroethenes 2

4.2.1 Typical procedure for the synthesis of 1-aryl-1-bromo-2,2-difluoroethenes 2

In a pyrex-glass tube were placed phenylboronic acid (61 mg, 0.50 mmol), CsF (152 mg, 1.0 mmol), Pd₂dba₃·CHCl₃ (2.6 mg, 2.5 µmol), and dppm (1.9 mg, 4.9 µmol). After the tube was purged with nitrogen, a pre-degassed mixed solvent (2.5 mL, 1,4-dioxane/water = 2:1) and 1,1-dibromo-2,2-difluoroethylene (1, 48 µL, 0.50 mmol) was added to the tube. After stirring for 3 h at 60 °C, the mixture was quenched with NH₄Cl aq., and organic materials were extracted with ether three times. The combined
extracts were washed with brine and dried over Na$_2$SO$_4$. After removal of solvent under reduced pressure, the residue was purified by column chromatography on silica gel (pentane) to give 2a (95 mg, 86%) as a colorless oil.

4.2.2 Spectra data of 1-aryl-1-bromo-2,2-difluoroethenes 2

4.2.2.1 1-Bromo-1-phenyl-2,2-difluoroethene (2a)

Colorless oil. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.33 (tt, $J = 7.3$, 1.3 Hz, 1H), 7.39 (dd, $J = 7.4$, 7.3 Hz, 2H), 7.48−7.51 (m, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 79.9 (dd, $J_{CF} = 35$, 26 Hz), 128.5, 128.80, 128.84 (dd, $J_{CF} = 4$ Hz) 131.6 (dd, $J_{CF} = 3$ Hz), 153.1 (dd, $J_{CF} = 295$, 287 Hz). $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ 77.1 (dd, $J_{FF} = 28$ Hz), 83.3 (dd, $J_{FF} = 28$ Hz).

4.2.2.2 1-Bromo-1-(4-methylphenyl)-2,2-difluoroethene (2b)

Colorless oil. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 2.37 (s, 3H), 7.19 (d, $J = 7.8$ Hz, 2H), 7.37 (d, $J = 7.8$ Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 21.2, 79.9 (dd, $J_{CF} = 35$, 26 Hz), 128.7 (dd, $J_{CF} = 4$, 4 Hz), 129.2, 130.8 (dd, $J_{CF} = 4$, 4 Hz), 139.0, 153.0 (dd, $J_{CF} = 294$, 286 Hz). $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ 76.5 (dd, $J_{FF} = 32$ Hz), 82.6 (dd, $J_{FF} = 32$ Hz).

4.2.2.3 1-(Biphenyl-4-yl)-1-bromo-2,2-difluoroethene (2c)

White solid. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.30 (tt, $J = 7.3$, 1.3 Hz, 1H), 7.38 (dd, $J = 7.7$, 7.7 Hz, 2H), 7.49−7.55 (m, 6H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 79.8 (dd, $J_{CF} = 34$, 26 Hz), 127.1, 127.2, 127.8, 128.9, 129.2 (dd, $J_{CF} = 4$, 4 Hz), 130.5 (d, $J_{CF} = 4$ Hz), 140.1, 141.7, 153.2 (dd, $J_{CF} = 295$, 287 Hz). $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ 77.5 (d, $J_{FF} = 30$ Hz), 83.8 (d, $J_{FF} = 30$ Hz). IR (neat): $\nu$ = 1709, 1290, 984, 841, 764, 692 cm$^{-1}$. HRMS (EI): $m/z$ calcd. for C$_{14}$H$_9$F$_2$Br$^+$ ([M$^+$]): 293.9856; Found: 293.9863.

4.2.2.4 1-Bromo-2,2-difluoro-1-(4-methoxyphenyl)ethene (2d)

Colorless oil. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 3.83 (s, 3H), 6.90 (d, $J = 9.0$ Hz, 2H), 7.41 (d, $J = 9.0$ Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 55.5, 79.6 (dd, $J_{CF} = 35$, 26
10

Hz), 113.9, 123.8 (d, \( J_{CF} = 3 \) Hz), 130.2 (dd, \( J_{CF} = 3, 3 \) Hz), 152.8 (dd, \( J_{CF} = 293, 286 \) Hz), 159.9. \(^{19}\)F NMR (470 MHz, CDCl\(_3\)): \( \delta \) 75.7 (d, \( J_{FF} = 36 \) Hz), 81.9 (d, \( J_{FF} = 36 \) Hz).

4.2.2.5 1-Bromo-2,2-difluoro-1-(4-fluorophenyl)ethene (2e)

Colorless oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 7.08 (dd, \( J = 8.7, 8.7 \) Hz, 2H), 7.45–7.49 (m, 2H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \( \delta \) 78.8 (dd, \( J_{CF} = 35, 27 \) Hz), 115.6 (d, \( J_{CF} = 22 \) Hz), 127.7 (dd, \( J_{CF} = 3 \) Hz), 130.8 (ddd, \( J = 9, 3, 3 \) Hz), 153.1 (dd, \( J_{CF} = 294, 287 \) Hz), 162.7 (d, \( J_{CF} = 250 \) Hz). \(^{19}\)F NMR (470 MHz, CDCl\(_3\)): \( \delta \) 49.9–50.0 (m), 76.9 (d, \( J_{FF} = 31 \) Hz), 83.2 (d, \( J_{FF} = 31 \) Hz).

4.3 Synthesis of unsymmetrical 1,1-diaryl-2,2-difluoroethenes 4

4.3.1 Typical procedure for the synthesis of 1,1-diaryl-2,2-difluoroethenes 4

In a pyrex-glass tube were placed 1-bromo-1-(biphenyl-4-yl)-2,2-difluoroethene (2c, 89 mg, 0.30 mmol), 4-methylphenylboronic acid (45 mg, 0.33 mmol), CsF (91 mg, 0.60 mmol), Pd\(_2\)dba\(_3\)-CHCl\(_3\) (1.6 mg, 1.5 \( \mu \)mol), and PPh\(_3\) (1.6 mg, 6.1 \( \mu \)mol). After the tube was purged with nitrogen, a pre-degassed mixed solvent (3.0 mL, 1,4-dioxane/water = 2:1) was added to the tube. After stirring for 12 h at 120 °C, the mixture was quenched with NH\(_4\)Cl aq., and organic materials were extracted with ether three times. The combined extracts were washed with brine and dried over Na\(_2\)SO\(_4\). After removal of solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexane/EtOAc = 50:1) to give 4a (86 mg, 93%) as a colorless oil.

4.3.2 Spectra data of 1,1-diaryl-2,2-difluoroethenes 4

4.3.2.1 1-(Biphenyl-4-yl)-2,2-difluoro-1-(4-methylphenyl)ethene (4a)

White solid. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 2.40 (s, 3H), 7.19 (s, 4H), 7.33–7.37 (m, 3H), 7.44 (dd, \( J = 7.7, 7.7 \) Hz, 2H), 7.57 (d, \( J = 8.4 \) Hz, 2H), 7.60 (d, \( J = 7.1 \) Hz, 2H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \( \delta \) 21.4, 96.0 (dd, \( J_{CF} = 18, 18 \) Hz), 127.20, 127.20, 127.6, 129.0, 129.3, 129.8 (dd, \( J_{CF} = 3, 3 \) Hz), 130.1 (dd, \( J_{CF} = 3, 3 \) Hz), 131.4 (dd, \( J_{CF} = 3, 3 \) Hz).
Hz), 133.7 (dd, $J_{CF} = 4, 4$ Hz), 137.6, 140.4, 140.7, 153.9 (dd, $J_{CF} = 294, 294$ Hz). $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ 73.7 (d, $J_{FF} = 33$ Hz), 74.1 (d, $J_{FF} = 33$ Hz). IR (neat): $\nu^r$ = 2924, 1699, 1242, 982, 820, 766, 692 cm$^{-1}$. HRMS (EI): $m/z$ calcd. for C$_{21}$H$_{16}$F$_2$ ([M]$^+$): 306.1220; Found: 306.1217.

4.3.2.2 1-(Biphenyl-4-yl)-2,2-difluoro-1-(4-methoxyphenyl)ethene (4b)

White solid. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 3.83 (s, 3H), 6.91 (d, $J = 9.1$ Hz, 2H), 7.23 (d, $J = 9.1$ Hz, 2H), 7.33–7.39 (m, 3H), 7.45 (dd, $J = 7.6, 7.6$ Hz, 2H), 7.57 (d, $J = 8.4$ Hz, 2H), 7.60 (d, $J = 8.4$ Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 55.4, 95.6 (dd, $J_{CF} = 19, 19$ Hz), 114.0, 126.5 (dd, $J_{CF} = 4, 4$ Hz), 127.16, 127.16, 127.6, 128.9, 130.0 (dd, $J_{CF} = 3, 3$ Hz), 131.0 (dd, $J_{CF} = 3, 3$ Hz), 133.7 (dd, $J_{CF} = 4, 4$ Hz), 140.4, 140.7, 153.8 (dd, $J_{CF} = 293, 293$ Hz), 159.1. $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ 73.2 (d, $J_{FF} = 33$ Hz), 73.6 (d, $J_{FF} = 33$ Hz). IR (neat): $\nu^r$ = 2960, 1699, 1512, 1246, 1178, 984, 835, 766 cm$^{-1}$. HRMS (EI): $m/z$ calcd. for C$_{21}$H$_{16}$F$_2$O ([M]$^+$): 322.1169; Found: 322.1169.

4.3.2.3 1-(Biphenyl-4-yl)-2,2-difluoro-1-(4-fluorophenyl)ethene (4c)

White solid. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.07 (dd, $J = 8.7, 8.7$ Hz, 2H), 7.28, (dd, $J = 8.9, 1.0$ Hz, 2H), 7.32 (dd, $J = 8.5, 1.2$ Hz, 2H), 7.36 (tt, $J = 7.4, 1.2$ Hz, 1H), 7.45 (dd, $J = 7.6, 7.6$ Hz, 2H), 7.57–7.61 (m, 4H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 95.2 (dd, $J_{CF} = 19, 19$ Hz), 114.0, 126.5 (dd, $J_{CF} = 4, 4$ Hz), 127.16, 127.16, 127.6, 128.9, 130.0 (dd, $J_{CF} = 3, 3$ Hz), 131.0 (dd, $J_{CF} = 3, 3$ Hz), 133.7 (dd, $J_{CF} = 4, 4$ Hz), 140.4, 140.7, 153.8 (dd, $J_{CF} = 293, 293$ Hz), 159.1. $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ 73.2 (d, $J_{FF} = 33$ Hz), 73.6 (d, $J_{FF} = 33$ Hz). IR (neat): $\nu^r$ = 2960, 1699, 1512, 1246, 1178, 984, 835, 766 cm$^{-1}$. HRMS (EI): $m/z$ calcd. for C$_{20}$H$_{13}$F$_3$ ([M]$^+$): 310.0969; Found: 310.0965.

4.3.2.4 1-(Biphenyl-4-yl)-2,2-difluoro-1-(2-methylphenyl)ethene (4d)

White solid. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 2.19 (s, 3H), 7.25–7.29 (m, 6H), 7.34 (t, $J = 7.4$ Hz, 1H), 7.43 (dd, $J = 7.7, 7.7$ Hz, 2H), 7.54 (d, $J = 8.4$ Hz, 2H), 7.57 (d, $J = 8.2$ Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 19.6, 94.5 (dd, $J_{CF} = 23, 15$ Hz), 126.1, 127.0,
127.1, 127.4, 128.4, 128.5 (dd, $J_{CF} = 6, 3$ Hz), 128.8, 130.5, 131.0 (dd, $J_{CF} = 2, 2$ Hz),
132.8 (d, $J_{CF} = 4$ Hz), 132.9 (d, $J_{CF} = 4$ Hz), 137.7 (d, $J_{CF} = 3$ Hz), 139.8, 140.5, 153.4
(dd, $J_{CF} = 299, 288$ Hz). $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ 73.1 (d, $J_{FF} = 31$ Hz), 78.2 (d, $J_{FF} = 31$ Hz).
IR (neat): $\nu \approx 1705, 1487, 1244, 984, 841, 764, 696$ cm$^{-1}$. HRMS (EI): $m/z$ calcd. for C$_{21}$H$_{16}$F$_2$ ([M]$^+$): 306.1220; Found: 306.1207.

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