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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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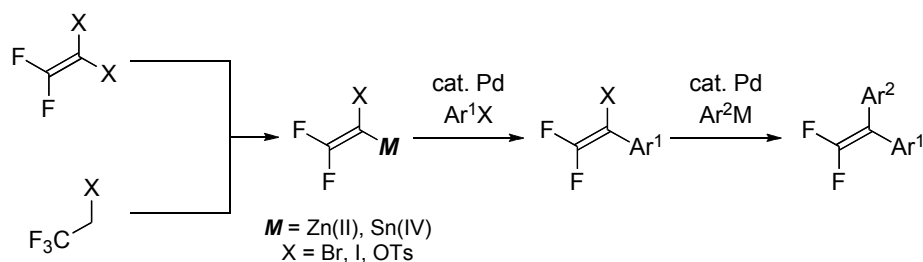
Abstract

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

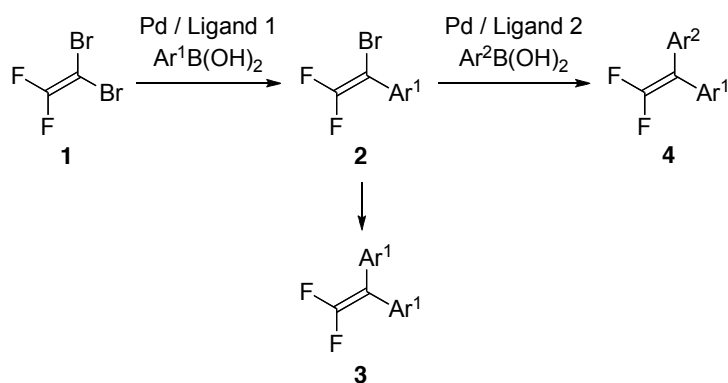
1,1-Diaryl-2,2-difluoroethenes are an important class of *gem*-difluoroalkenes, which have the potential to be used for a wide range of purposes, including functional materials and medicines such as photoreceptors [1], anticancer drugs [2], and dermatological agents [3]. These compounds are also expected 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].



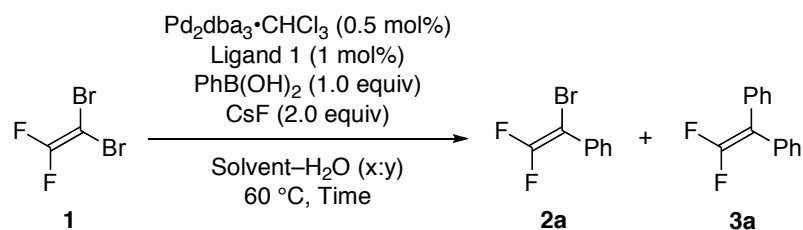
Scheme 2. Strategy for the synthesis of unsymmetrical 1,1-diaryl-2,2-difluoroethenes **4** via stepwise coupling of 1,1-dibromo-2,2-difluoroethene (**1**).

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 Pd₂dba₃·CHCl₃ (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

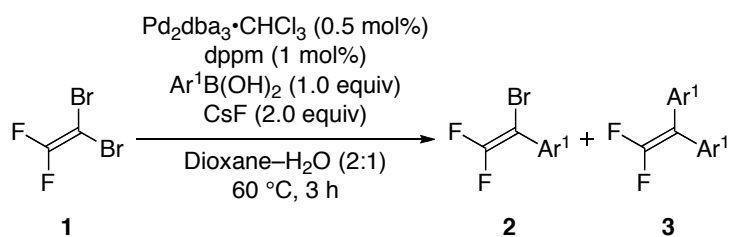


Entry	Ligand 1	Solvent (x:y)	Time / h	2a / % ^a	3a / % ^a
1	PPh_3^{b}	THF (4:1)	6	51	Trace
2	$\text{P}(t\text{-Bu})_3^{\text{b}}$	THF (4:1)	6	–	–
3	Cy-JohnPhos ^b	THF (4:1)	6	–	–
4	AsPh_3^{b}	THF (4:1)	6	24	Trace
5	Xantphos	THF (4:1)	6	8	12
6	dppf	THF (4:1)	6	40	1
7	dppb	THF (4:1)	6	14	Trace
8	dppm	THF (4:1)	6	54	Trace
9	dppm	THF (4:1)	3	36	2
10	dppm	DME (4:1)	3	49	1
11	dppm	Dioxane (4:1)	3	70	4
12	dppm	DMF (4:1)	3	10	4
13	dppm	MeCN (4:1)	3	36	4
14	dppm	Toluene (4:1)	3	23	Trace
15	dppm	Dioxane (8:1)	3	53	2
16	dppm	Dioxane (2:1)	3	80	3

^a ¹⁹F NMR yield based on PhCF_3 . ^b 2 mol%.

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-difluoroethene (**1**)



Entry	$\text{Ar}^1\text{B}(\text{OH})_2$	Product ^a
1		 2a , 86% (3a) , 3%
2		 2b , 69% (3b) , 3%
3		 2c , 83% (3c) , 4%
4		 2d , 59% (3d) , 5%
5		 2e , 68% (3e) , 5%

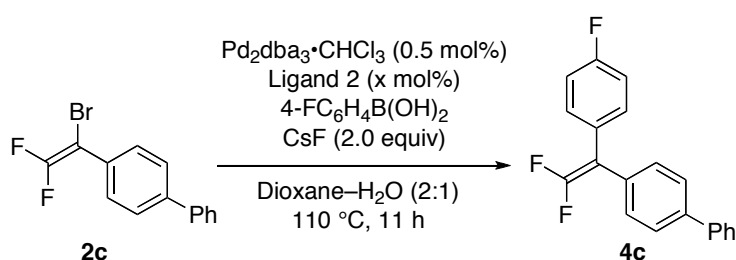
^a Isolated yield (in parentheses is shown ¹⁹F NMR yield based on PhCF₃).

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

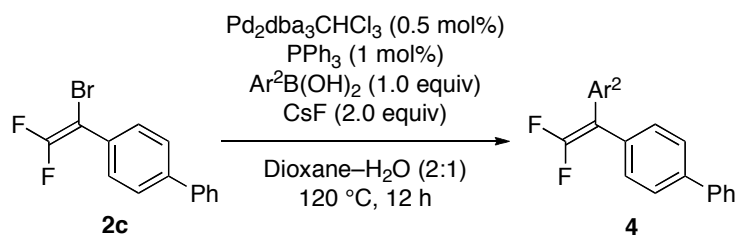


Entry	Ligand 2	x / mol%	4c / % ^a
1	PPh ₃	2	72
2	AsPh ₃	2	50
3	dppf	1	70
4	dppm	1	27

^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**



Entry	$\text{Ar}^2\text{B(OH)}_2$	Product
1		 4a , 93%
2		 4b , 92%
3		 4c , 72%
4		 4d , 88%

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-difluoroethene. 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-difluoroethene, 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_2SO_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. ^1H NMR (500 MHz, CDCl_3): δ 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): δ 79.9 (dd, $J_{\text{CF}} = 35, 26$ Hz), 128.5, 128.80, 128.84 (d, $J_{\text{CF}} = 4$ Hz), 131.6 (d, $J_{\text{CF}} = 3$ Hz), 153.1 (dd, $J_{\text{CF}} = 295, 287$ Hz). ^{19}F NMR (470 MHz, CDCl_3): δ 77.1 (d, $J_{\text{FF}} = 28$ Hz), 83.3 (d, $J_{\text{FF}} = 28$ Hz).

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

Colorless oil. ^1H NMR (500 MHz, CDCl_3): δ 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): δ 21.2, 79.9 (dd, $J_{\text{CF}} = 35, 26$ Hz), 128.7 (dd, $J_{\text{CF}} = 4, 4$ Hz), 129.2, 130.8 (dd, $J_{\text{CF}} = 4, 4$ Hz), 139.0, 153.0 (dd, $J_{\text{CF}} = 294, 286$ Hz). ^{19}F NMR (470 MHz, CDCl_3): δ 76.5 (d, $J_{\text{FF}} = 32$ Hz), 82.6 (d, $J_{\text{FF}} = 32$ Hz).

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

White solid. ^1H NMR (500 MHz, CDCl_3): δ 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): δ 79.8 (dd, $J_{\text{CF}} = 34, 26$ Hz), 127.1, 127.2, 127.8, 128.9, 129.2 (dd, $J_{\text{CF}} = 4, 4$ Hz), 130.5 (d, $J_{\text{CF}} = 4$ Hz), 140.1, 141.7, 153.2 (dd, $J_{\text{CF}} = 295, 287$ Hz). ^{19}F NMR (470 MHz, CDCl_3): δ 77.5 (d, $J_{\text{FF}} = 30$ Hz), 83.8 (d, $J_{\text{FF}} = 30$ Hz). IR (neat): $\tilde{\nu} = 1709, 1290, 984, 841, 764, 692$ cm^{-1} . HRMS (EI): m/z calcd. for $\text{C}_{14}\text{H}_9^{79}\text{BrF}_2$ ($[\text{M}]^+$): 293.9856; Found: 293.9863.

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

Colorless oil. ^1H NMR (500 MHz, CDCl_3): δ 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): δ 55.5, 79.6 (dd, $J_{\text{CF}} = 35, 26$

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): δ 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. ^1H NMR (500 MHz, CDCl_3): δ 7.08 (dd, $J = 8.7, 8.7$ Hz, 2H), 7.45–7.49 (m, 2H). ^{13}C NMR (126 MHz, CDCl_3): δ 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): δ 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), $\text{Pd}_2\text{dba}_3 \cdot \text{CHCl}_3$ (1.6 mg, 1.5 μmol), and PPh_3 (1.6 mg, 6.1 μmol). 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_4Cl aq., and organic materials were extracted with ether three times. The combined extracts were washed with brine and dried over Na_2SO_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. ^1H NMR (500 MHz, CDCl_3): δ 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): δ 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), 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): δ 73.7 (d, $J_{FF} = 33$ Hz), 74.1 (d, $J_{FF} = 33$ Hz). IR (neat): $\tilde{\nu} = 2924, 1699, 1242, 982, 820, 766, 692$ cm^{-1} . HRMS (EI): m/z calcd. for $\text{C}_{21}\text{H}_{16}\text{F}_2$ ($[\text{M}]^+$): 306.1220; Found: 306.1217.

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

White solid. ^1H NMR (500 MHz, CDCl_3): δ 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): δ 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): δ 73.2 (d, $J_{FF} = 33$ Hz), 73.6 (d, $J_{FF} = 33$ Hz). IR (neat): $\tilde{\nu} = 2960, 1699, 1512, 1246, 1178, 984, 835, 766$ cm^{-1} . HRMS (EI): m/z calcd. for $\text{C}_{21}\text{H}_{16}\text{F}_2\text{O}$ ($[\text{M}]^+$): 322.1169; Found: 322.1169.

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

White solid. ^1H NMR (500 MHz, CDCl_3): δ 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): δ 95.2 (dd, $J_{CF} = 19, 19$ Hz), 115.5 (d, $J = 22$ Hz), 127.0, 127.1, 127.5, 128.8, 129.8 (dd, $J_{CF} = 3, 3$ Hz), 130.1 (dd, $J_{CF} = 3, 3$ Hz), 131.4 (ddd, $J_{CF} = 8, 8, 3$ Hz), 133.1 (dd, $J_{CF} = 3, 3$ Hz), 140.4, 140.5, 153.8 (dd, $J_{CF} = 294, 294$ Hz), 162.1 (d, $J_{CF} = 248$ Hz). ^{19}F NMR (470 MHz, CDCl_3): δ 47.7–47.6 (m), 74.2 (d, $J_{FF} = 32$ Hz), 74.3 (d, $J_{FF} = 32$ Hz). IR (neat): $\tilde{\nu} = 1707, 1508, 1247, 987, 835$ cm^{-1} . HRMS (EI): m/z calcd. for $\text{C}_{20}\text{H}_{13}\text{F}_3$ ($[\text{M}]^+$): 310.0969; Found: 310.0965.

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

White solid. ^1H NMR (500 MHz, CDCl_3): δ 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): δ 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): δ 73.1 (d, $J_{FF} = 31$ Hz), 78.2 (d, $J_{FF} = 31$ Hz). IR (neat): $\tilde{\nu} = 1705, 1487, 1244, 984, 841, 764, 696$ cm^{-1} . HRMS (EI): m/z calcd. for $\text{C}_{21}\text{H}_{16}\text{F}_2$ ($[\text{M}]^+$): 306.1220; Found: 306.1207.

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