



Facile synthesis of unsymmetrical 1,1-diaryl-2,2-difluoroethenes via stepwise coupling of 1,1-dibromo-2,2-difluoroethenes



Takeshi Fujita, Naoto Suzuki, Tomohiro Ichitsuka, Junji Ichikawa*

Division of Chemistry, Faculty of Pure and Applied Sciences, University of Tsukuba, Tsukuba, Ibaraki 305-8571, Japan

ARTICLE INFO

Article history:

Received 17 April 2013

Received in revised form 12 June 2013

Accepted 20 June 2013

Available online 10 July 2013

Keywords:

Difluoroalkene

Diarylethene

Dibromoethene

Ligand

Suzuki–Miyaura coupling

Stepwise arylation

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.

© 2013 Elsevier B.V. All rights reserved.

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.

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].

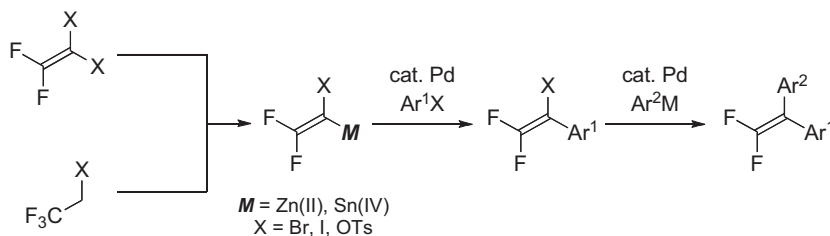
2. Results and discussion

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

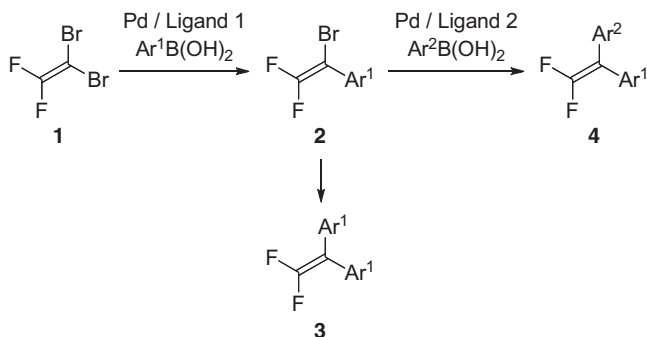
To synthesize unsymmetrically disubstituted 1,1-diaryl-2,2-difluoroethenes **4**, we first sought suitable conditions for selective monoarylation in the Suzuki–Miyaura coupling between 1,1-dibromo-2,2-difluoroethene (**1**) and phenylboronic acid, using

* Corresponding author. Tel.: +81 29 853 4237; fax: +81 29 853 4237.

E-mail addresses: junji@chem.tsukuba.ac.jp, junji@me.com (J. Ichikawa).



Scheme 1. Conventional synthesis of 1,1-diaryl-2,2-difluoroethenes.

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**).

cesium fluoride as a base (Table 1). The choice of ligands used with $\text{Pd}_2\text{dba}_3 \cdot \text{CHCl}_3$ (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 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.

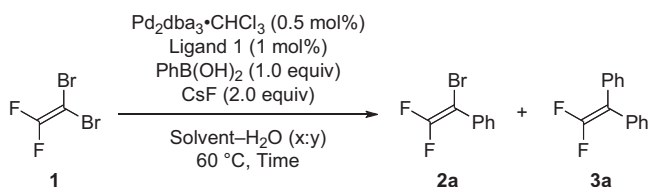
Once the optimal conditions had been determined, we the scope of the substrate (Table 2). Monoarylation with several *para*-functionalized (Me, Ph, OMe, and F) phenylboronic acids was successfully achieved, providing bromodifluorostyrenes **2a–2e**. To the best of our knowledge, this is the first example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

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 (Table 3). 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 by using dppm indicated that dppm, although highly suitable for the first coupling, effectively suppressed the second coupling (Entry 4).

Table 1

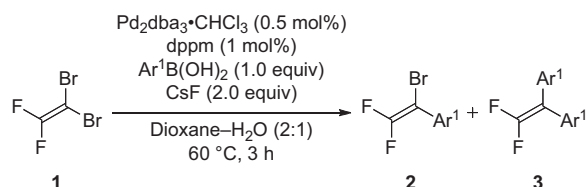
Effects of the ligand and solvent used in the first Suzuki–Miyaura coupling.



Entry	Ligand 1	Solvent (x:y)	Time (h)	2a (%) ^a	3a (%) ^a
1	PPh_3^b	THF (4:1)	6	51	Trace
2	$\text{P}(t\text{-Bu})_3^b$	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 ^{19}F NMR yield based on PhCF_3 .

^b 2 mol%.

Table 2Monoarylation of 1,1-dibromo-2,2-difluoroethene (**1**).

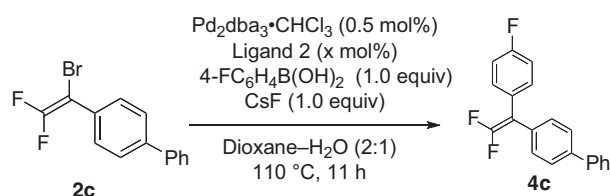
Ar ¹ B(OH) ₂	2 ^a	Yield (%) ^a
1 		2a , 86% (3a , 3%)
2 		2b , 69% (3b , 3%)
3 		2c , 83% (3c , 4%)
4 		2d , 59% (3d , 5%)
5 		2e , 68% (3e , 5%)

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

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

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.

acids readily participated in the reaction, affording the desired difluoroethenes **4a–d** in high yields.

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 Na₂SO₄. 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, CDCl₃): 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). ¹³C NMR (126 MHz, CDCl₃): δ 79.9 (dd, *J*_{CF} = 35, 26 Hz), 128.5, 128.80, 128.84 (d, *J*_{CF} = 4 Hz), 131.6 (d, *J*_{CF} = 3 Hz), 153.1 (dd, *J*_{CF} = 295, 287 Hz). ¹⁹F NMR (470 MHz, CDCl₃): δ 77.1 (d, *J*_{FF} = 28 Hz), 83.3 (d, *J*_{FF} = 28 Hz).

4.2.2.2. 1-Bromo-1-(4-methylphenyl)-2,2-difluoroethene (2b). Colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 2.37 (s, 3H), 7.19 (d, *J* = 7.8 Hz, 2H), 7.37 (d, *J* = 7.8 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃): δ

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

$ \begin{array}{c} \text{Pd}_2\text{dba}_3 \cdot \text{CHCl}_3 \text{ (0.5 mol\%)} \\ \text{PPh}_3 \text{ (2 mol\%)} \\ \text{Ar}^2\text{B(OH)}_2 \text{ (1.1 equiv)} \\ \text{CsF} \text{ (2.0 equiv)} \\ \text{Dioxane-H}_2\text{O (2:1)} \\ 120^\circ\text{C, 12 h} \end{array} $			
Entry	Ar ² B(OH) ₂	4	Yield (%)
1			4a , 93%
2			4b , 92%
3 ^a			4c , 72%
4			4d , 88%

^a 4-FC₆H₄B(OH)₂ (1.0 equiv).**4.2.2.4. 1-Bromo-2,2-difluoro-1-(4-methoxyphenyl)ethene**

(**2d**). Colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 3.83 (s, 3H), 6.90 (d, *J* = 9.0 Hz, 2H), 7.41 (d, *J* = 9.0 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃): δ 55.5, 79.6 (dd, *J*_{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. ¹⁹F NMR (470 MHz, CDCl₃): 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, CDCl₃): δ 7.08 (dd, *J* = 8.7, 8.7 Hz, 2H), 7.45–7.49 (m, 2H). ¹³C NMR (126 MHz, CDCl₃): 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*_{CF} = 9, 3, 3 Hz), 153.1 (dd, *J*_{CF} = 294, 287 Hz), 162.7 (d, *J*_{CF} = 250 Hz). ¹⁹F NMR (470 MHz, CDCl₃): 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), Pd₂dba₃·CHCl₃ (1.6 mg, 1.5 μmol), and PPh₃ (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 NH₄Cl aq., and organic materials were extracted with ether three times. The combined extracts were washed with brine and dried over Na₂SO₄. 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 white solid.

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, CDCl₃): 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). ¹³C NMR (126 MHz, CDCl₃): 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). ¹⁹F NMR (470 MHz, CDCl₃): 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 C₂₁H₁₆F₂ ([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, CDCl₃): 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). ¹³C NMR (126 MHz, CDCl₃): 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. ¹⁹F NMR (470 MHz, CDCl₃): 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 C₂₁H₁₆F₂O ([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, CDCl₃): 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). ¹³C NMR (126 MHz, CDCl₃): δ 95.2 (dd, *J*_{CF} = 19, 19 Hz), 115.5 (d, *J*_{CF} = 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),

21.2, 79.9 (dd, *J*_{CF} = 35, 26 Hz), 128.7 (dd, *J*_{CF} = 4, 4 Hz), 130.8 (dd, *J*_{CF} = 4, 4 Hz), 139.0, 153.0 (dd, *J*_{CF} = 294, 286 Hz). ¹⁹F NMR (470 MHz, CDCl₃): δ 76.5 (d, *J*_{FF} = 32 Hz), 82.6 (d, *J*_{FF} = 32 Hz).

4.2.2.3. 1-(Biphenyl-4-yl)-1-bromo-2,2-difluoroethene (**2c**). White solid. ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (126 MHz, CDCl₃): δ 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). ¹⁹F NMR (470 MHz, CDCl₃): δ 77.5 (d, *J*_{FF} = 30 Hz), 83.8 (d, *J*_{FF} = 30 Hz). IR (neat): $\tilde{\nu}$ = 1709, 1290, 984, 841, 764, 692 cm⁻¹. HRMS (EI): *m/z* calcd. for C₁₄H₉⁷⁹BrF₂ ([M]⁺): 293.9856; Found: 293.9863.

133.1 (dd, $J_{\text{CF}} = 3, 3$ Hz), 140.4, 140.5, 153.8 (dd, $J_{\text{CF}} = 294, 294$ Hz), 162.1 (d, $J_{\text{CF}} = 248$ Hz). ^{19}F NMR (470 MHz, CDCl_3): δ 47.7–47.6 (m), 74.2 (d, $J_{\text{FF}} = 32$ Hz), 74.3 (d, $J_{\text{FF}} = 32$ Hz). IR (neat): $\tilde{\nu} = 1707, 1508, 1247, 987, 835\text{ cm}^{-1}$. 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, $J_{\text{CF}} = 23, 15$ Hz), 126.1, 127.0, 127.1, 127.4, 128.4, 128.5 (dd, $J_{\text{CF}} = 6, 3$ Hz), 128.8, 130.5, 131.0 (dd, $J_{\text{CF}} = 2, 2$ Hz), 132.8 (d, $J_{\text{CF}} = 4$ Hz), 132.9 (d, $J_{\text{CF}} = 4$ Hz), 137.7 (d, $J_{\text{CF}} = 3$ Hz), 139.8, 140.5, 153.4 (dd, $J_{\text{CF}} = 299, 288$ Hz). ^{19}F NMR (470 MHz, CDCl_3): δ 73.1 (d, $J_{\text{FF}} = 31$ Hz), 78.2 (d, $J_{\text{FF}} = 31$ Hz). IR (neat): $\tilde{\nu} = 1705, 1487, 1244, 984, 841, 764, 696\text{ cm}^{-1}$. HRMS (EI): m/z calcd. for $\text{C}_{21}\text{H}_{16}\text{F}_2$ ($[\text{M}]^+$): 306.1220; Found: 306.1207.

References

- [1] N. Hirose, O. Sasaki, Y. Takizawa, Eur. Pat. Appl. 0153145 (1985) 64–95.
- [2] (a) S. Messaoudi, B. Tréguier, A. Hamze, O. Provot, J.-F. Peyrat, J.R. DeLosada, J.-M. Liu, J. Bignon, J. Wdziejczak-Bakala, S. Thoret, J. Dubois, J.-D. Brion, M. Alami, J. Med. Chem. 52 (2009) 4538–4542; (b) A.L. Ruchelman, H.-W. Man, R. Chen, W. Liu, L. Lu, D. Cedzik, L. Zhang, J. Leisten, A. Collette, R.K. Narla, H.K. Raymon, G.W. Muller, Bioorg. Med. Chem. 19 (2011) 6356–6374.
- [3] K.-L. Yu, P. Spinazze, J. Ostrowski, S.J. Currier, E.J. Pack, L. Hammer, T. Roalsvig, J.A. Honeyman, D.R. Tortolani, P.R. Reczek, M.M. Mansuri, J.E. Starret Jr., J. Med. Chem. 39 (1996) 2411–2421.
- [4] For recent papers and a review on uses of difluoroalkenes as bioisosteres of ketones, see: (a) I.A. McDonald, J.M. Lacoste, P. Bey, M.G. Palfreyman, M. Zreika, J. Med. Chem. 28 (1985) 186–193; (b) M. Bobek, I. Kavaï, E. De Clercq, J. Med. Chem. 30 (1987) 1494–1497; (c) W.R. Moore, G.L. Schatzman, E.T. Jarvi, R.S. Gross, J.R. McCarthy, J. Am. Chem. Soc. 114 (1992) 360–361; (d) P.M. Weintraub, A.K. Holland, C.A. Gates, W.R. Moore, R.J. Resvick, P. Bey, N.P. Peet, Bioorg. Med. Chem. 11 (2003) 427–431; (e) J.-M. Altenburger, G.Y. Lassalle, M. Matrougui, D. Galtier, J.-C. Jetha, Z. Bocskei, C.N. Berry, C. Lunven, J. Lorrain, J.-P. Herault, P. Schaeffer, S.E. O'Connor, J.-M. Herbert, Bioorg. Med. Chem. 12 (2004) 1713–1730; (f) J. Ichikawa, J. Synth. Org. Chem. Jpn. 68 (2010) 1175–1184.
- [5] For synthetic methods for symmetrical 1,1-diaryl-2,2-difluoroethenes, see: (a) M. Obayashi, E. Ito, K. Matsui, K. Kondo, Tetrahedron Lett. 23 (1982) 2323–2326; (b) R. Ocampo, W.R. Dolbier Jr., R. Paredes, J. Fluorine Chem. 88 (1998) 41–50; (c) G. Mlostoń, J. Romański, H. Heimgartner, Heterocycles 50 (1999) 403–410; (d) I. Nowak, M.J. Robins, Org. Lett. 7 (2005) 721–724; (e) S.Y. Han, H.Y. Lee, J.H. Jeon, I.H. Jeong, Tetrahedron Lett. 53 (2012) 1833–1836.
- [6] For synthetic methods for unsymmetrical 1,1-diaryl-2,2-difluoroethenes, see: (a) A. Raghavanpillai, D.J. Burton, J. Org. Chem. 71 (2006) 194–201; (b) J.H. Choi, I.H. Jeong, Tetrahedron Lett. 49 (2008) 952–955; (c) S.Y. Han, I.H. Jeong, Org. Lett. 12 (2010) 5518–5521.
- [7] J. Barluenga, P. Moriel, F. Aznar, C. Valdés, Adv. Synth. Catal. 348 (2006) 347–353.
- [8] (a) Y. Takeda, M. Shimizu, T. Hiyama, Angew. Chem. Int. Ed. 46 (2007) 8659–8661; (b) D. Alloatti, G. Giannini, W. Cabri, I. Lustrati, M. Marzi, A. Ciacci, G. Gallo, M.O. Tinti, M. Marcellini, T. Riccioni, M.B. Guglielmi, P. Carminati, C. Pisano, J. Med. Chem. 51 (2008) 2708–2721; (c) G. Chelucci, Chem. Rev. 112 (2012) 1344–1462 (and references cited therein).
- [9] Although synthesis of unsymmetrical 1,1-diaryl-2,2-difluoroethenes had been reported once by the Suzuki–Miyaura coupling of 1,1-dichloro-2,2-difluoroethene using a water-soluble phosphine ligand, the paper was retracted later, see: J. Pschierer, N. Perschek, H. Plenio, Green Chem. 12 (2010) 636–642. Retraction was endorsed by Sarah Ruthven, Editor, and published on 15th September 2010.
- [10] D.J. Burton, A.L. Anderson, R. Takei, H.F. Koch, T.L. Shih, J. Fluorine Chem. 16 (1980) 229–235.
- [11] R. Anilkumar, D.J. Burton, J. Fluorine Chem. 125 (2004) 561–566.
- [12] B.V. Nguyen, D.J. Burton, J. Org. Chem. 63 (1998) 1714–1715.