

Communication

Palladium-Catalyzed Cross-Coupling of *Gem*-Bromofluoroalkenes with Alkylboronic Acids for the Synthesis of Alkylated Monofluoroalkenes

Laëtitia Chausset-Boissarie * , Nicolas Cheval and Christian Rolando *

Univ. Lille, CNRS, USR 3290—MSAP—Miniaturisation Pour la Synthèse, l'Analyse et la Protéomique, F-59000 Lille, France; nicolas.cheval@gmail.fr

* Correspondence: laetitia.boissarie@univ-lille.fr (L.C.-B.); christian.rolando@univ-lille.fr (C.R.)

Academic Editors: Vito Capriati and Yurii Yagupolskii

Received: 15 October 2020; Accepted: 19 November 2020; Published: 25 November 2020



Abstract: Monofluoroalkenes are versatile fluorinated synthons in organic synthesis, medicinal chemistry and materials science. In light of the importance of alkyl-substituted monofluoroalkenes efficient synthesis of these moieties still represents a synthetic challenge. Herein, we described a mild and efficient methodology to obtain monofluoroalkenes through a stereospecific palladium-catalyzed alkylation of *gem*-bromofluoroalkenes with primary and strained secondary alkylboronic acids under mild conditions. This novel strategy gives access to a wide range of functionalized tri- and tetrasubstituted monofluoroalkenes in high yield, with good functional group tolerance, independently from the *gem*-bromofluoroalkenes geometry.

Keywords: monofluoroalkenes; *gem*-bromofluoroalkenes; alkylboronic acids; Suzuki–Miyaura–cross-coupling

1. Introduction

The incorporation of fluorine atoms into bioactive molecules hugely impacts their physicochemical and pharmacokinetic properties, prevents oxidative metabolism and, more important, modulates their overall biological activities [1,2]. Accordingly, fluorinated compounds are abundant scaffolds found in a large variety of materials, agrochemicals and pharmaceuticals [3–8]. In particular, monofluoroalkenes are highly valuable fluorinated synthons in organic synthesis, in high-performance materials and in medicinal chemistry as they are excellent peptide bond mimics with enhanced stability towards proteases and stable conformation, improving the molecule stability and lipophilicity [9,10]. Despite the importance of alkylated monofluoroalkenes, limited methodologies have been developed for their modular synthesis. Pioneering studies to obtain alkyl-substituted monofluoroalkenes were focused on classical olefination (Wittig, Horner–Wadsworth–Emmons or Julia Kocienski reaction) [11,12], electrophilic fluorination or fluorination of alkynes [13–16]. More recently, transition metal-catalyzed defluorinative alkylation of *gem*-difluoroalkenes [17–21] or *gem*-difluorocyclopropanes [22–24] with various carbon nucleophiles has proven to be efficient strategies to access alkylated monofluoroalkenes. In the meantime, photoredox monofluoroalkenylation of *gem*-difluoroalkenes has also been successfully applied for their syntheses [25–28]. Despite these remarkable achievements, defluorinative cross-coupling towards the C(*sp*³)-C(*sp*²) bond formation is still limited by the use of expensive catalytic systems, moderate *Z/E* selectivity, air-sensitive reagents or specific alkyl sources bearing a heteroatom at the α -position. *Gem*-bromofluoroalkenes, which are easily accessible, starting materials from aldehyde or ketones via a Wittig–Burton reaction, can also be efficient substrates for the selective formation of alkyl-substituted monofluoroalkenes [29,30]. In this regard, Pannecoucke's group reported the selective synthesis of stereo-defined butylated *Z*-(fluoro)alkene by Pd-catalyzed

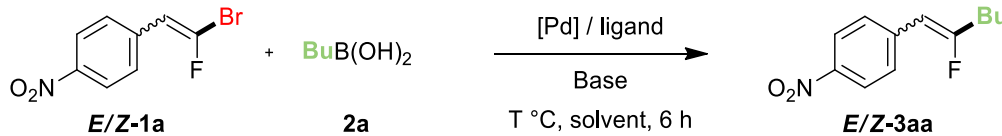
cross-coupling of (*E/Z*)-*gem*-bromofluoroalkenes with an in situ-generated organozinc intermediate [31]. Following up, the group of Wnuk reported an elegant pallado-catalyzed Negishi cross-coupling of *gem*-bromofluoroalkenes with alkyl organozinc derivatives as coupling partners to selectively produce (*Z*)-monofluoroalkenes [32]. Nevertheless, one of the drawbacks of these pathways is a low functional group tolerance and the use of sensitive reagents. Therefore, despite great successes achieved, the development of mild and practical methodologies to monofluoroalkenes, especially 2-fluoroalkyl scaffolds, remains an appealing task. Continuing our research directed towards the development of new methodology for the synthesis of functionalized monofluoroalkenes [33–36] Herein, we report the first example of a stereospecific Suzuki-Miyaura-cross-coupling reaction with readily available alkyl boronic acids that is adaptable across a range of *gem*-bromofluoroalkenes providing a large array of alkylated monofluoroalkenes with retention of configuration and in good yields under mild conditions.

2. Results and Discussion

At the outset of the study, coupling reactions were investigated with the easily accessible (*E/Z*)-1-(2-bromo-2-fluorovinyl)-4-nitrobenzene **1a** [31] and butylboronic acid **2a**.

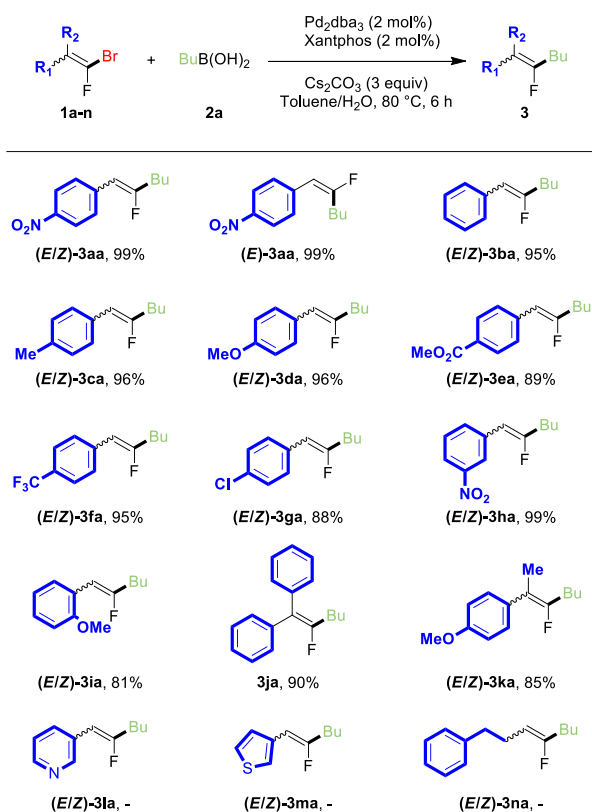
To establish the best reaction conditions, a broad range of palladium catalyst precursors, bases, solvents, temperatures and phosphine ligands were evaluated (Table 1). An initial survey demonstrated that the use of PdCl₂dppf as catalyst gave the desired product as a mixture of *E/Z* isomers in 95% yield (entries 1–3). Among the bases, Cs₂CO₃ proved to be the most effective (entries 3–7). Subsequently, the solvents were screened, and the original biphasic mixture of toluene/H₂O (9:1) was the best of choice (entries 3, 8–10). Further examination revealed that a decrease in the reaction temperature reduces the reaction efficiency (entries 11–12). Common ligands of palladium were tested (entries 13–17), and bidentate bisphosphines and, above all, those with large P-Pd-P bite angles appeared to be essentials [37]. Under some conditions, (*E*)-isomer reacts faster than the corresponding (*Z*)-isomers in Pd-catalyzed coupling reactions (entries 3, 5, 16). The best catalytic system was found to be Pd₂(dba)₃ (2 mol%) with xantphos (2 mol%) as the catalyst and Cs₂CO₃ as the base in a mixture of toluene/H₂O (9:1) at 80 °C under nitrogen affording the desired product in almost quantitative yield (entry 15).

With the optimized conditions in hand, we investigated the substrate scope of the cross-coupling reaction on the *gem*-bromofluoroalkene part (Scheme 1). A large range of (*E/Z*)-*gem*-bromofluoroalkenes was successfully cross-coupled to afford the related *Z* and *E* monofluoroalkenes in good to excellent isolated yield. The electronic effects of the substituents on the aromatics rings showed no obvious influence on this transformation since (*E/Z*)-*gem*-bromofluoroalkenes possessing electron neutral (**3ba–ca**), electron-donating (**3da**) and electron-withdrawing groups (**3ea–ga**) provided the (*E/Z*)-monofluoroalkenes in high yields. Several sensitive or valuable functional groups, notably for further post-functionalizations, such as esters, trifluoromethyl and nitro groups, were well tolerated throughout the coupling reactions. In all cases, no stereodifferentiation was observed since a mixture of the corresponding *E/Z* isomers was obtained with the same isomeric composition of the starting material. The cross-coupling reaction of isomerically pure (*Z*)-1-bromo-1-fluoroalkene **1a** led stereospecifically to a corresponding (*E*)-monofluoroalkene **3aa** with complete retention of the stereochemistry confirming the stereospecificity of the reaction. Interestingly, *gem*-bromofluoroalkene that are meta-substituted (**3ha**) or sterically hindered at the ortho position (**3ia**) were suitable coupling partners for the reaction albeit, aryl *gem*-bromofluoroalkenes bearing substituents in the para position showed better reactivity. Gratifyingly, in the case of symmetric and unsymmetric *gem*-bromofluoroalkenes derived from ketones, the corresponding tetrasubstituted monofluoroalkenes **3ja** and **3ka** are obtained in excellent isolated yield. Unfortunately, the reaction is not compatible with nitrogen or sulfur hetaryl *gem*-bromofluoroalkenes (**3la–ma**) mainly due to the degradation of the starting material. In addition, when alkylated *gem*-bromofluoroolefin **1n** was used as the substrate, the reaction also failed to give any coupling product.

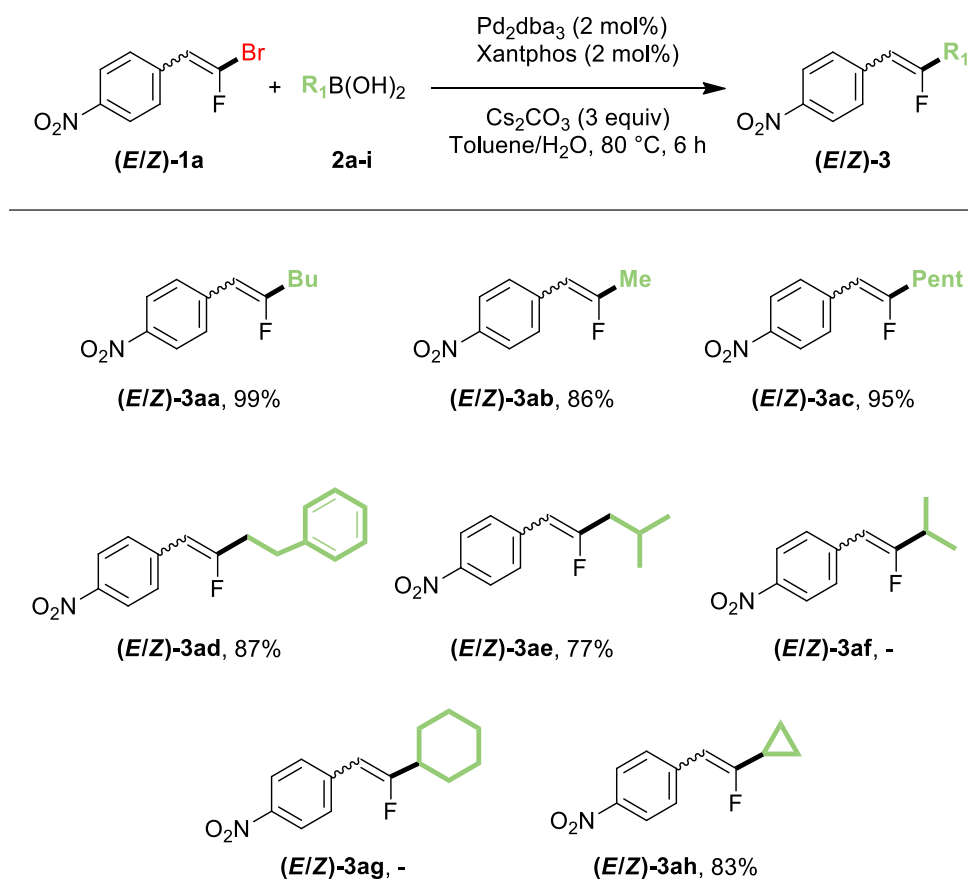
Table 1. Optimization of the cross-coupling between *E/Z*-1a and butylboronic acid 2a ^a.


Entry	<i>E/Z</i> 1a ^b	[Pd]	Ligand	Base	Solvent	T (°C)	<i>Z/E</i> 3aa ^b	Yield (%) ^c
1	55:45	Pd(Ph ₃) ₄	-	Cs ₂ CO ₃	toluene/H ₂ O	80	-	-
2	55:45	Pd ₂ dba ₃ ·CHCl ₃	-	Cs ₂ CO ₃	toluene/H ₂ O	80	-	-
3	56:44	PdCl ₂ dppf	-	Cs ₂ CO ₃	toluene/H ₂ O	80	58:42	95
4	55:45	PdCl ₂ dppf	-	K ₂ CO ₃	toluene/H ₂ O	80	46:54	76
5	55:45	PdCl ₂ dppf	-	Na ₂ CO ₃	toluene/H ₂ O	80	57:43	44
6	55:45	PdCl ₂ dppf	-	K ₃ PO ₄	toluene/H ₂ O	80	51:49	93
7	55:46	PdCl ₂ dppf	-	Ba(OH) ₂	toluene/H ₂ O	80	-	-
8	39:61	PdCl ₂ dppf	-	Cs ₂ CO ₃	toluene	80	38:62	89
9	39:61	PdCl ₂ dppf	-	Cs ₂ CO ₃	Dioxane	80	-	-
10	39:61	PdCl ₂ dppf	-	Cs ₂ CO ₃	THF	80	-	-
11	55:45	PdCl ₂ dppf	-	Cs ₂ CO ₃	toluene/H ₂ O	RT	-	-
12	55:45	PdCl ₂ dppf	-	Cs ₂ CO ₃	toluene/H ₂ O	60	45:55	51
13	55:45	Pd ₂ dba ₃ ·CHCl ₃	Dppf	Cs ₂ CO ₃	toluene/H ₂ O	80	51:49	91
14	48:52	Pd ₂ dba ₃ ·CHCl ₃	Dppe	Cs ₂ CO ₃	toluene/H ₂ O	80	48:52	41
15	48:52	Pd ₂ dba ₃ ·CHCl ₃	Xantphos	Cs ₂ CO ₃	toluene/H ₂ O	80	49:51	99
16	48:52	Pd ₂ dba ₃ ·CHCl ₃	Xphos	Cs ₂ CO ₃	toluene/H ₂ O	80	60:40	35
17	48:52	Pd ₂ dba ₃ ·CHCl ₃	TFP	Cs ₂ CO ₃	toluene/H ₂ O	80	42:58	78

^a All reactions unless specified were carried out using **1a** (1 eq), **2a** (1.2 eq), Pd source (2 mol%), ligand (2 mol%) and base (3 eq), in solvent (0.09 M) under N₂ for 6 h. ^b Ratio determined by ¹H NMR. ^c Yield was determined using 1,3,5-trimethoxybenzene as an internal standard. Pd₂dba₃ = tris(dibenzylideneacetone)dipalladium. Dppf = 1,1'-bis(diphenylphosphino)ferrocene. Dppe = 1,2-bis(diphenylphosphino)ethane. Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene. Xphos = 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl. TFP = tri(2-furyl)phosphine.

**Scheme 1.** Palladium-catalyzed cross-coupling of butylboronic acid **2a** with various *gem*-bromoalkenes **1a-n**.

We then examined the coupling reactions with different primary and secondary alkyl boronic acids and (*E/Z*)-1-(2-bromo-2-fluorovinyl)-4-nitrobenzene **1a** using the same set of reaction conditions developed (Scheme 2). All of the primary aliphatic alkyl boronic acids **2a–e** provided the desired product **3aa–ae** in good to excellent isolated yields. In the case of secondary alkyl substituents such as isopropyl or cyclohexyl boronic acids **2f–g**, no reaction occurred; only starting materials were recovered. Cyclopropyl boronic acid **2h** was shown to undergo a cross-coupling reaction giving the product in 83% yield. This could be due to the geometry of the substrate, which suppresses β -hydride elimination.



Scheme 2. Palladium-catalyzed cross-coupling of (*E/Z*)-1-(2-bromo-2-fluorovinyl)-4-nitrobenzene **1a** with various alkyl boronic acids **2a–i**.

3. Materials and Methods

3.1. General Methods

All reagents were purchased from commercial suppliers and were used without further purification unless otherwise indicated. Thin-layer chromatography (TLC) was performed on silica gel 60 F254 plates (Merck, Pfizer, Sanofi) and visualized under UV (254 nm) or by staining with potassium permanganate or phosphomolybdic acid. The purification of the obtained products was performed by flash chromatography using silica gel (230–400 mesh, 0.040–0.063 mm).

NMR spectra were recorded on a Bruker AVANCE 300 spectrometer (Bruker Corporation, Billerica, MA, USA) at 300 MHz (75 MHz). Chemical shifts are given in parts per million relative to the solvent signal. Multiplicities of the signals are reported using the standard abbreviations: singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). Coupling constants are reported in hertz (Hz). Coupling constants (*J*) are reported in hertz (Hz). High-resolution mass spectra (HRMS) were performed on a ThermoFisher Scientific LTQ Orbitrap XL mass spectrometer (Thermo Fischer Scientific, Bremen, Germany) using electrospray ionization (ESI).

3.2. Synthesis of Gem-Bromofluoroalkenes 1

Gem-bromofluoroalkenes **1a–n** were synthesized according to known procedures reported by Pannecoucke's group³¹ from the appropriate aldehyde and tribromofluoromethane.

3.3. General Procedure for the Synthesis of Monofluoroalkenes 3

In a Schlenk tube, gem-bromofluoroalkene **1** (1.0 equiv), boronic acid **2** (1.2 equiv), Pd₂dba₃·CHCl₃ (2 mol%), xantphos (2 mol%) and Cs₂CO₃ (3 equiv) were added. The vial was flushed under nitrogen, then filled with a mixture of toluene/H₂O (9:1) (0.09 M). The reaction mixture was heated for 6 h at 80 °C then cooled to r.t., filtered through Celite® and washed with EtOAc. The filtrate was concentrated under vacuum, and the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 100:0 to 95:5) to afford the pure product **3**. ¹H-, ¹³C- and ¹⁹F-NMR spectra of products can be found in Supplementary Materials.

3.3.1. (E/Z)-1-(2-fluorohex-1-en-1-yl)-4-nitrobenzene (**3aa**)

(E/Z)-1-(2-bromo-2-fluorovinyl)-4-nitrobenzene **1a** (0.23 mmol, 56.32 mg), butyl boronic acid **2a** (0.28 mmol, 28.45 mg), Pd₂dba₃·CHCl₃ (4.710⁻³ mmol, 4.25 mg), xantphos (4.710⁻³ mmol, 2.69 mg), Cs₂CO₃ (0.70 mmol, 227.10 mg), toluene/H₂O (2.53 mL) were reacted according to general procedure. The crude product was purified by silica gel column chromatography (petroleum ether/EtOAc = 100:0 to 95:5) affording compound **3aa** in 99% yield (50.80 mg) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 8.09 (t, *J* = 9.1 Hz, 2.0H), 7.51 (d, *J* = 8.9 Hz, 0.8 H), 7.26 (d, *J* = 8.4 Hz, 1.2H), 6.15 (d, *J*^E_{H-F} = 21.1 Hz, 0.6H), 5.49 (d, *J*^Z_{H-F} = 38.1 Hz, 0.4H), 2.47–2.23 (m, 2.0H), 1.59–1.50 (m, 2.0H), 1.37–1.27 (m, 2.0H), 0.90–0.81 (m, 3.0H). ¹³C NMR (75 MHz, CDCl₃): δ 164.1 (d, *J*^E_{C-F} = 257.5 Hz), 163.6 (d, *J*^Z_{C-F} = 271.8 Hz), 145.3 (2), 140.5 (d, *J*^E_{C-F} = 14.8 Hz), 139.6 (d, *J*^Z_{C-F} = 2.7 Hz), 127.9 (2), 127.7, 127.6, 122.8 (2), 122.7 (2), 106.1 (d, *J*^E_{C-F} = 31.0 Hz), 103.5 (d, *J*^E_{C-F} = 8.2 Hz), 31.9 (d, *J*^Z_{C-F} = 25.6 Hz), 28.0 (d, *J*^E_{C-F} = 26.6 Hz), 27.3 (2), 21.2, 21.0, 12.7 (2). ¹⁹F NMR (282.5 MHz, CDCl₃): δ –99.23 (q, *J*^E = 23.2 Hz), –101.65 (dt, *J*^Z = 39.7, 18.1 Hz). HRMS (ESI): *m/z* [M + H]⁺ calc. for C₁₂H₁₅FNO₂, 224.1081 found 224.1080.

3.3.2. (E)-1-(2-fluorohex-1-en-1-yl)-4-nitrobenzene (**E-3aa**)

(Z)-1-(2-bromo-2-fluorovinyl)-4-nitrobenzene **1a** (0.23 mmol, 56.32 mg), butyl boronic acid **2a** (0.28 mmol, 28.45 mg), Pd₂dba₃·CHCl₃ (4.710⁻³ mmol, 4.25 mg), xantphos (4.710⁻³ mmol, 2.69 mg), Cs₂CO₃ (0.70 mmol, 227.10 mg), toluene/H₂O (2.53 mL) were reacted according to general procedure. The crude product was purified by silica gel column chromatography (petroleum ether/EtOAc = 100:0 to 95:5) affording compound **E-3aa** in 99% yield (50.80 mg) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 8.09 (t, *J* = 9.1 Hz, 2.0H), 7.51 (d, *J* = 8.9 Hz, 2.0 H), 6.15 (d, *J*^E_{H-F} = 21.1 Hz, 1.0H), 2.47–2.23 (m, 2.0H), 1.59–1.50 (m, 2.0H), 1.37–1.27 (m, 2.0H), 0.90–0.81 (m, 3.0H). ¹³C NMR (75 MHz, CDCl₃): δ 164.1 (d, *J*^E_{C-F} = 257.5 Hz), 145.3, 140.5 (d, *J*^E_{C-F} = 14.8 Hz), 127.9, 127.7, 122.8, 122.7, 103.5 (d, *J*^E_{C-F} = 8.2 Hz), 28.0 (d, *J*^E_{C-F} = 26.6 Hz), 27.3, 21.2, 12.7. ¹⁹F NMR (282.5 MHz, CDCl₃): δ –99.23 (q, *J*^E = 23.2 Hz). HRMS (ESI): *m/z* [M + H]⁺ calc. for C₁₂H₁₅FNO₂, 224.1081 found 224.1082.

3.3.3. (E/Z)-(2-fluorohex-1-en-1-yl)benzene (**3ba**)

(E/Z)-1-(2-bromo-2-fluorovinyl)-benzene **2b** (0.23 mmol, 46.39 mg), butyl boronic acid **2a** (0.28 mmol, 28.45 mg), Pd₂dba₃·CHCl₃ (4.710⁻³ mmol, 4.25 mg), xantphos (4.710⁻³ mmol, 2.69 mg), Cs₂CO₃ (0.70 mmol, 227.10 mg), toluene/H₂O (2.53 mL) were reacted according to general procedure. The crude product was purified by silica gel column chromatography (petroleum ether/EtOAc = 100:0 to 95:5) affording compound **3ba** in 95% yield (39.25 mg) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 7.43–7.34 (m, 1.00H), 7.28–7.20 (m, 2.00H), 7.16–7.05 (m, 2.00H), 6.10 (d, *J*^E_{H-F} = 22.0 Hz, 0.53H), 5.38 (d, *J*^Z_{H-F} = 39.5 Hz, 0.47H), 2.43–2.19 (m, 2.00H), 1.57–1.46 (m, 2.00H), 1.31 (ddd, *J* = 15.1, 9.5, 7.4 Hz, 2.00H), 0.87 (t, *J* = 6.3 Hz, 1.40H), 0.82 (t, *J* = 6.4 Hz, 1.60H). ¹³C NMR (75 MHz, CDCl₃): δ 162.8 (d,

$^1J_{C-F}^E = 251.3$ Hz), 161.3 (d, $^1J_{C-F}^Z = 265.1$ Hz), 134.5 (d, $^3J_{C-F}^E = 14.1$ Hz), 134.0 (d, $^3J_{C-F}^Z = 2.5$ Hz), 128.6, 128.6 (3), 128.5 (2), 128.4, 128.3, 126.7 (2), 108.1 (d, $^2J_{C-F}^Z = 28.6$ Hz), 105.7 (d, $^2J_{C-F}^E = 8.8$ Hz), 32.8 (d, $^2J_{C-F}^Z = 26.3$ Hz), 28.7 (d, $^2J_{C-F}^E = 29.2$ Hz), 28.5 (2), 22.3, 22.1, 13.8 (2).¹⁹ F NMR (282 MHz, CDCl₃): δ - 98.35 (dd, $J^E = 45.7, 23.4$ Hz), -100.61 (dt, $J^Z = 39.4, 18.0$ Hz). HRMS (ESI): m/z [M + H]⁺ calc. for C₁₂H₁₆F 179.1230, found 179.1233.

3.3.4. (E/Z)-1-(2-fluorohex-1-en-1-yl)-4-methylbenzene (3ca)

(E/Z)-1-(2-bromo-2-fluorovinyl)-4-methylbenzene **2c** (0.23 mmol, 49.64 mg), butyl boronic acid **2a** (0.28 mmol, 28.45 mg), Pd₂dba₃·CHCl₃ (4.710⁻³ mmol, 4.25 mg), xantphos (4.710⁻³ mmol, 2.69 mg), Cs₂CO₃ (0.70 mmol, 227.10 mg), toluene/H₂O (2.53 mL) were reacted according to general procedure. The crude product was purified by silica gel column chromatography (petroleum ether/EtOAc = 100:0 to 95:5) affording compound **3ca** in 96% yield (42.79 mg) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 7.39 (d, $J = 8.2$ Hz, 1.00H), 7.21–7.08 (m, 3.00H), 6.18 (d, $J_{H-F}^E = 22.1$ Hz, 0.51H), 5.45 (d, $J_{H-F}^Z = 39.8$ Hz, 0.49H), 2.54–2.29 (m, 2.00H), 2.36 (s, 1.47H), 2.35 (s, 1.53H), 1.64–1.56 (m, 2.00H), 1.47–1.37 (m, 2.00H), 0.98 (t, $J = 5.5$ Hz, 1.47H), 0.93 (t, $J = 5.5$ Hz, 1.53H). ¹³C NMR (75 MHz, CDCl₃): δ 162.5 (d, $^1J_{C-F}^E = 250.2$ Hz), 160.9 (d, $^1J_{C-F}^Z = 263.9$ Hz), 136.4 (2), 131.6 (d, $^3J_{C-F}^E = 14.0$ Hz), 131.3 (d, $^3J_{C-F}^Z = 2.5$ Hz), 129.3 (3), 129.2, 128.5, 128.4, 128.3, 128.2, 108.0 (d, $^2J_{C-F}^Z = 28.6$ Hz), 105.6 (d, $^2J_{C-F}^E = 9.0$ Hz), 32.9 (d, $^2J_{C-F}^Z = 26.4$ Hz), 28.9 (d, $^2J_{C-F}^E = 28.6$ Hz), 28.7 (2), 22.5, 22.2, 21.3, 21.2, 13.9 (2).¹⁹ F NMR (282 MHz, CDCl₃): δ - 99.23 (q, $J^E = 23.2$ Hz), -101.65 (dt, $J^Z = 39.7, 18.1$ Hz). HRMS (ESI): m/z [M + H]⁺ calc. for C₁₃H₁₈F 193.1387, found 193.1388.

3.3.5. (E/Z)-1-(2-fluorohex-1-en-1-yl)-4-methoxybenzene (3da)

(E/Z)-1-(2-bromo-2-fluorovinyl)-4-methoxybenzene **2d** (0.23 mmol, 53.35 mg), butyl boronic acid **2a** (0.28 mmol, 28.45 mg), Pd₂dba₃·CHCl₃ (4.710⁻³ mmol, 4.25 mg), xantphos (4.710⁻³ mmol, 2.69 mg), Cs₂CO₃ (0.70 mmol, 227.10 mg), toluene/H₂O (2.53 mL) were reacted according to general procedure. The crude product was purified by silica gel column chromatography (petroleum ether/EtOAc = 100:0 to 95:5) affording compound **3da** in 96% yield (46.35 mg) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 7.42 (d, $J = 8.9$ Hz, 0.96H), 7.13 (d, $J = 8.3$ Hz, 1.04H), 6.90–6.84 (m, 2.00H), 6.14 (d, $J_{H-F}^E = 22.0$ Hz, 0.52H), 5.41 (d, $J_{H-F}^Z = 39.8$ Hz, 0.48H), 3.81 (s, 3.00H), 2.49–2.28 (m, 2.00H), 1.64–1.56 (m, 2.00H), 1.45–1.36 (m, 2.00H), 0.96 (t, $J = 5.4$ Hz, 1.44H), 0.92 (t, $J = 5.5$ Hz, 1.56H). ¹³C NMR (75 MHz, CDCl₃): δ 162.1 (d, $^1J_{C-F}^E = 249.3$ Hz), 160.1 (d, $^1J_{C-F}^Z = 262.2$ Hz), 158.6, 158.4, 129.7, 129.6 (2), 129.5, 126.9 (d, $^3J_{C-F}^E = 13.9$ Hz), 126.8 (d, $^3J_{C-F}^Z = 2.3$ Hz), 114.0 (4), 107.6 (d, $^2J_{C-F}^Z = 28.9$ Hz), 105.1 (d, $^2J_{C-F}^E = 9.2$ Hz), 55.4 (2), 32.9 (d, $^2J_{C-F}^Z = 26.5$ Hz), 28.8 (d, $^2J_{C-F}^E = 27.1$ Hz), 28.7 (2), 22.4, 22.2, 13.9 (2). ¹⁹ F NMR (282 MHz, CDCl₃): δ - 100.27 (dd, $J^E = 45.9, 23.2$ Hz), -103.58 (dt, $J^Z = 39.8, 18.3$ Hz). HRMS (ESI): m/z [M + H]⁺ calc. for C₁₃H₁₈FO, 209.1336 found 209.1336.

3.3.6. (E/Z)-methyl 4-(2-fluorohex-1-en-1-yl)benzoate (3ea)

(E/Z)-methyl 4-(2-bromo-2-fluorovinyl)benzoate **2e** (0.23 mmol, 59.84 mg), butyl boronic acid **2a** (0.28 mmol, 28.45 mg), Pd₂dba₃·CHCl₃ (4.710⁻³ mmol, 4.25 mg), xantphos (4.710⁻³ mmol, 2.69 mg), Cs₂CO₃ (0.70 mmol, 227.10 mg), toluene/H₂O (2.53 mL) were reacted according to general procedure. The crude product was purified by silica gel column chromatography (petroleum ether/EtOAc = 100:0 to 95:5) affording compound **3ea** in 89% yield (48.75 mg) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 7.90 (dd, $J = 8.4, 6.0$ Hz, 2.00H), 7.43 (d, $J = 8.5$ Hz, 0.92H), 7.17 (d, $J = 8.1$ Hz, 1.08H), 6.12 (d, $J_{H-F}^E = 21.6$ Hz, 0.54H), 5.43 (d, $J = 38.9$ Hz, 0.46H), 3.83 (s, 1.62H), 3.82 (s, 1.38H), 2.44–2.21 (m, 2.00H), 1.57–1.48 (m, 2.00H), 1.36–1.24 (m, 2.00H), 0.87 (t, $J = 7.0$ Hz, 1.38H), 0.81 (t, $J = 7.3$ Hz, 1.62H). ¹³C NMR (75 MHz, CDCl₃): δ 167.0 (2), 164.2 (d, $^1J_{C-F}^E = 254.7$ Hz), 163.3 (d, $^1J_{C-F}^Z = 269.0$ Hz), 139.5 (d, $^3J_{C-F}^E = 14.3$ Hz), 138.7 (d, $^3J_{C-F}^Z = 2.6$ Hz), 129.9 (3), 129.8 (3), 128.4 (2), 128.2, 128.1, 107.8 (d, $^2J_{C-F}^Z = 29.7$ Hz), 105.3 (d, $^2J_{C-F}^E = 8.5$ Hz), 52.2, 52.1, 33.0 (d, $^2J_{C-F}^Z = 26.0$ Hz), 29.0 (d, $^2J_{C-F}^E = 26.8$ Hz), 28.5 (2), 22.4, 22.2, 13.9, 13.8. ¹⁹ F NMR (282 MHz, CDCl₃): δ - 94.29 (dd, $J^E = 45.3, 23.4$ Hz), -96.35 (dt, $J^Z = 38.8, 18.3$ Hz). HRMS (ESI): m/z [M + H]⁺ calc. for C₁₄H₁₈FO₂, 237.1285 found 237.1287.

3.3.7. (*E/Z*)-1-(2-fluorohex-1-en-1-yl)-4-(trifluoromethyl)benzene (**3fa**)

(*E/Z*)-1-(2-bromo-2-fluorovinyl)-4-trifluoromethylbenzene **2f** (0.23 mmol, 62.16 mg), butyl boronic acid **2a** (0.28 mmol, 28.45 mg), Pd₂dba₃·CHCl₃ (4.710⁻³ mmol, 4.25 mg), xantphos (4.710⁻³ mmol, 2.69 mg), Cs₂CO₃ (0.70 mmol, 227.10 mg), toluene/H₂O (2.53 mL) were reacted according to general procedure. The crude product was purified by silica gel column chromatography (petroleum ether/EtOAc = 100:0 to 95:5) affording compound **3fa** in 95% yield (54.24 mg) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 7.35–7.26 (m, 3.00H), 7.00 (d, *J* = 8.6 Hz, 1.00H), 5.93 (t, *J*^E_{H-F} = 15.5 Hz, 0.47H), 5.22 (d, *J*^Z_{H-F} = 38.6 Hz, 0.53H), 2.20–2.00 (m, 2.00H), 1.38–1.28 (m, 2.00H), 1.17–1.06 (m, 2.00H), 0.67 (t, *J* = 6.6 Hz, 1.41H), 0.62 (t, *J* = 6.6 Hz, 1.59H). ¹³C NMR (75 MHz, CDCl₃): δ 164.2 (d, ¹*J*^E_{C-F} = 254.7 Hz), 163.3 (d, ¹*J*^Z_{C-F} = 268.2 Hz), 138.4 (d, ³*J*^E_{C-F} = 15.2 Hz), 137.7 (d, ³*J*^Z_{C-F} = 1.2 Hz), 129.7, 129.3, 128.8 (4), 128.5 (2), 128.4 (2), 125.5 (dq, *J* = 7.7, 3.8 Hz, 2), 107.4 (d, ²*J*^Z_{C-F} = 30.0 Hz), 104.9 (d, ²*J*^E_{C-F} = 8.5 Hz), 33.0 (d, ²*J*^Z_{C-F} = 25.9 Hz), 29.0 (d, ²*J*^E_{C-F} = 26.8 Hz), 28.5 (2), 22.4, 22.2, 13.9 (2). ¹⁹F NMR (282 MHz, CDCl₃): δ -62.54 (s), -94.83 (dd, *J*^E = 44.9, 23.2 Hz), -97.08 (dt, *J*^Z = 36.8, 18.1 Hz). HRMS (ESI): *m/z* [M + H]⁺ calc. for C₁₃H₁₅F₄, 247.1104 found 247.1103.

3.3.8. (*E/Z*)-1-chloro-4-(2-fluorohex-1-en-1-yl)benzene (**3ga**)

(*E/Z*)-1-(2-bromo-2-fluorovinyl)-4-chlorobenzene **2g** (0.23 mmol, 54.27 mg), butyl boronic acid **2a** (0.28 mmol, 28.45 mg), Pd₂dba₃·CHCl₃ (4.710⁻³ mmol, 4.25 mg), xantphos (4.710⁻³ mmol, 2.69 mg), Cs₂CO₃ (0.70 mmol, 227.10 mg), toluene/H₂O (2.53 mL) were reacted according to general procedure. The crude product was purified by silica gel column chromatography (petroleum ether/EtOAc = 100:0 to 95:5) affording compound **3ga** in 88% yield (43.29 mg) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 7.30 (d, *J* = 8.6 Hz, 1.00H), 7.19 (dd, *J* = 11.7, 4.6 Hz, 2.00H), 7.03 (d, *J* = 8.3 Hz, 1.00H), 6.04 (d, *J*^E_{H-F} = 21.5 Hz, 0.55H), 5.34 (d, *J*^Z_{H-F} = 39.0 Hz, 0.45H), 2.40–2.20 (m, 2.00H), 1.56–1.47 (m, 2.00H), 1.38–1.26 (m, 2.00H), 0.87 (t, *J* = 6.5 Hz, 1.35H), 0.81 (d, *J* = 7.3 Hz, 1.65H). ¹³C NMR (75 MHz, CDCl₃): δ 163.3 (d, ¹*J*^E_{C-F} = 252.7 Hz), 161.9 (d, ¹*J*^Z_{C-F} = 265.9 Hz), 133.1 (d, ³*J*^E_{C-F} = 14.3 Hz), 132.6 (d, ³*J*^Z_{C-F} = 2.4 Hz), 132.3, 132.2, 129.9, 129.8, 129.7, 129.6, 128.7 (2), 128.6 (2), 107.3 (d, ²*J*^Z_{C-F} = 29.5 Hz), 104.8 (d, ²*J*^E_{C-F} = 8.8 Hz), 32.9 (d, ²*J*^Z_{C-F} = 26.0 Hz), 28.8 (d, ²*J*^E_{C-F} = 27.0 Hz), 28.6 (2), 22.4, 22.2, 13.9 (2). ¹⁹F NMR (282 MHz, CDCl₃): δ -97.15 (dd, *J*^E = 45.0, 23.2 Hz), -99.62 (dt, *J*^Z = 39.0, 18.2 Hz). HRMS (ESI): *m/z* [M + H]⁺ calc. for C₁₂H₁₅ClF, 213.0841 found 213.0842.

3.3.9. (*E/Z*)-1-(2-fluorohex-1-en-1-yl)-3-nitrobenzene (**3ha**)

(*E/Z*)-1-(2-bromo-2-fluorovinyl)-3-nitrobenzene **2h** (0.23 mmol, 56.82 mg), butyl boronic acid **2a** (0.28 mmol, 28.45 mg), Pd₂dba₃·CHCl₃ (4.710⁻³ mmol, 4.25 mg), xantphos (4.710⁻³ mmol, 2.69 mg), Cs₂CO₃ (0.70 mmol, 227.10 mg), toluene/H₂O (2.53 mL) were reacted according to general procedure. The crude product was purified by silica gel column chromatography (petroleum ether/EtOAc = 100:0 to 95:5) affording compound **3ha** in 99% yield (51.24 mg) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 8.30 (s, 0.49H), 8.14–7.99 (m, 1.50H), 7.76 (d, *J* = 7.8 Hz, 0.51H), 7.51–7.43 (m, 1.50H), 6.22 (d, *J*^E_{H-F} = 20.8 Hz, 0.51H), 5.55 (d, *J*^Z_{H-F} = 37.8 Hz, 0.49H), 2.54–2.32 (m, 2.00H), 1.66–1.57 (m, 2.00H), 1.42 (dd, *J* = 15.2, 7.8 Hz, 2.00H), 0.96 (t, *J* = 6.5 Hz, 1.50H), 0.91 (t, *J* = 6.5 Hz, 1.50H). ¹³C NMR (75 MHz, CDCl₃): δ 164.7 (d, ¹*J*^E_{C-F} = 256.0 Hz), 163.7 (d, ¹*J*^Z_{C-F} = 269.1 Hz), 148.6 (2), 136.4 (d, ³*J*^E_{C-F} = 14.9 Hz), 135.7 (d, ³*J*^Z_{C-F} = 2.2 Hz), 134.5 (d, *J*_{C-F} = 2.7 Hz), 134.1 (d, *J*_{C-F} = 7.9 Hz), 129.5, 129.3, 123.2 (d, *J*_{C-F} = 2.8 Hz), 123.0 (d, *J*_{C-F} = 8.1 Hz), 121.6, 121.4 (d, *J*_{C-F} = 1.9 Hz), 106.7 (d, ²*J*^Z_{C-F} = 31.3 Hz), 104.2 (d, ²*J*^E_{C-F} = 8.4 Hz), 32.9 (d, ²*J*^Z_{C-F} = 25.8 Hz), 28.9 (d, ²*J*^E_{C-F} = 26.9 Hz), 28.4 (2), 22.4, 22.2, 13.9 (2). ¹⁹F NMR (282 MHz, CDCl₃): δ -93.83 (td, *J*^E = 23.2, 20.9 Hz), -96.00–-96.53 (m). HRMS (ESI): *m/z* [M + H]⁺ calc. for C₁₂H₁₅FNO₂, 224.1081 found 224.1079.

3.3.10. (E/Z)-1-(2-fluorohex-1-en-1-yl)-2-methoxybenzene (3ia)

(E/Z)-1-(2-bromo-2-fluorovinyl)-2-methoxybenzene **2i** (0.23 mmol, 53.35 mg), butyl boronic acid **2a** (0.28 mmol, 28.45 mg), Pd₂dba₃·CHCl₃ (4.710⁻³ mmol, 4.25 mg), xantphos (4.710⁻³ mmol, 2.69 mg), Cs₂CO₃ (0.70 mmol, 227.10 mg), toluene/H₂O (2.53 mL) were reacted according to general procedure. The crude product was purified by silica gel column chromatography (petroleum ether/EtOAc = 100:0 to 95:5) affording compound **3ia** in 81% yield (39.11 mg) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 7.67 (dt, *J* = 8.2, 4.1 Hz, 0.41H), 7.18–7.05 (m, 1.59H), 6.86–6.71 (m, 2.00H), 6.15 (d, ¹*J*_{H-F} = 21.9 Hz, 0.59H), 5.79 (d, ¹*J*_{H-F} = 40.6 Hz, 0.41H), 3.74 (s, 3.00H), 2.38–2.23 (m, 2.00H), 1.53 (ddd, *J* = 8.2, 7.2, 5.2 Hz, 2.00H), 1.31 (dd, *J* = 14.9, 7.6 Hz, 2.00H), 0.87 (t, *J* = 7.3 Hz, 1.23H), 0.81 (t, *J* = 7.3 Hz, 1.77H). ¹³C NMR (75 MHz, CDCl₃): δ 162.6 (d, ¹*J*_{C-F} = 250.6 Hz), 161.4 (d, ¹*J*_{C-F} = 264.4 Hz), 157.2 (d, *J*_{C-F} = 2.7 Hz), 156.0, 129.9 (d, *J*_{C-F} = 12.7 Hz), 129.7 (d, *J*_{C-F} = 1.6 Hz), 128.3, 127.8 (d, *J*_{C-F} = 1.7 Hz), 123.5 (d, ³*J*_{C-F} = 13.8 Hz), 122.8 (d, ³*J*_{C-F} = 2.7 Hz), 120.7, 120.5, 110.6 (2), 103.7 (d, ²*J*_{C-F} = 30.4 Hz), 99.1 (d, ²*J*_{C-F} = 7.4 Hz), 55.7, 55.6, 33.2 (d, ²*J*_{C-F} = 26.7 Hz), 28.9 (d, ²*J*_{C-F} = 27.2 Hz), 28.7 (2), 22.5, 22.2, 13.9 (2). ¹⁹F NMR (282 MHz, CDCl₃): δ -98.74 (q, *J*^E = 22.7 Hz), -102.28 (dt, *J*^Z = 40.6, 18.0 Hz). HRMS (ESI): *m/z* [M + H]⁺ calc. for C₁₃H₁₈FO, 209.1336 found 209.1333.

3.3.11. (2-Bromo-2-fluoroethene-1,1-diyl)dibenzene (3ja)

1-(2-bromo-2-fluorovinyl)-2-methoxybenzene **2j** (0.23 mmol, 64.03 mg), butyl boronic acid **2a** (0.28 mmol, 28.45 mg), Pd₂dba₃·CHCl₃ (4.710⁻³ mmol, 4.25 mg), xantphos (4.710⁻³ mmol, 2.69 mg), Cs₂CO₃ (0.70 mmol, 227.10 mg), toluene/H₂O (2.53 mL) were reacted according to general procedure. The crude product was purified by silica gel column chromatography (petroleum ether/EtOAc = 100:0 to 95:5) affording compound **3ja** in 90% yield (53.06 mg) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 7.39–7.13 (m, 10H), 2.40–2.21 (m, 2H), 1.64–1.52 (m, 2H), 1.31 (dt, *J* = 14.6, 7.4 Hz, 2H), 0.85 (t, *J* = 7.3 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 158.5 (d, ¹*J*_{C-F} = 261.1 Hz), 139.3 (d, ³*J*_{C-F} = 8.3 Hz), 137.9, 130.4 (d, *J*_{C-F} = 2.6 Hz), 129.7 (d, *J*_{C-F} = 4.9 Hz), 128.5 (3), 128.1 (3), 127.2, 126.8, 120.4 (d, ²*J*_{C-F} = 15.2 Hz), 30.3 (d, ²*J*_{C-F} = 27.4 Hz), 29.0, 22.3, 13.9. ¹⁹F NMR (282 MHz, CDCl₃): δ -106.14 (t, *J* = 23.0 Hz). HRMS (ESI): *m/z* [M + H]⁺ calc. for C₁₈H₂₀F, 255.1543 found 255.1541.

3.3.12. (E/Z)-1-(3-fluorohept-2-en-2-yl)-4-methoxybenzene (3ka)

(E/Z)-1-(1-bromo-1-fluoroprop-1-en-2-yl)-4-methoxybenzene **2k** (0.23 mmol, 56.60 mg), butyl boronic acid **2a** (0.28 mmol, 28.45 mg), Pd₂dba₃·CHCl₃ (4.710⁻³ mmol, 4.25 mg), xantphos (4.710⁻³ mmol, 2.69 mg), Cs₂CO₃ (0.70 mmol, 227.10 mg), toluene/H₂O (2.53 mL) were reacted according to general procedure. The crude product was purified by silica gel column chromatography (petroleum ether/EtOAc = 100:0 to 95:5) affording compound **3ka** in 90% yield (43.80 mg) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 7.31 (dd, *J* = 8.9, 1.1 Hz, 1.0H), 7.11 (d, *J* = 8.6 Hz, 1.0H), 6.87 (dd, *J* = 8.9, 2.2 Hz, 2.0H), 3.82 (s, 1.5H), 3.81 (s, 1.5H), 2.40 (dt, *J* = 24.0, 7.3 Hz, 1.0H), 2.28–2.07 (m, 1.0H), 2.07–1.81 (m, 3.0H), 1.60–1.26 (m, 4.0H), 0.96 (t, *J* = 7.2 Hz, 1.5H), 0.85 (t, *J* = 7.3 Hz, 1.5H). ¹³C NMR (75 MHz, CDCl₃): 158.5, 158.3, 157.1 (d, ¹*J*_{C-F} = 248.6 Hz), 155.6 (d, ¹*J*_{C-F} = 248.7 Hz), 133.0 (d, ³*J*_{C-F} = 9.3 Hz), 131.2, 129.6 (d, *J*_{C-F} = 2.7 Hz, 2), 129.4 (d, *J*_{C-F} = 4.2 Hz, 2), 113.8 (2), 113.5 (2), 111.3, (d, ²*J*_{C-F} = 13.8 Hz, 2), 55.4 (2), 29.3 (d, *J*_{C-F} = 19.6 Hz), 29.0 (d, *J* = 2.9 Hz), 29.0, 28.9, 22.3 (2), 17.4 (d, ³*J*_{C-F} = 4.7 Hz), 16.4 (d, ³*J*_{C-F} = 7.9 Hz), 14.0, 13.9. ¹⁹F NMR (282 MHz, CDCl₃): δ -107.87–-108.18 (m), -109.64 (ddd, *J* = 26.7, 19.6, 3.6 Hz). HRMS (ESI): *m/z* [M + H]⁺ calc. for C₁₄H₂₀FO, 223.1492 found 223.1490.

3.3.13. 1-(2-Fluoroprop-1-en-1-yl)-4-nitrobenzene (3ab)

(E/Z)-1-(2-bromo-2-fluorovinyl)-4-nitrobenzene **1a** (0.23 mmol, 56.32 mg), methyl boronic acid **2b** (0.28 mmol, 16.71 mg), Pd₂dba₃·CHCl₃ (4.710⁻³ mmol, 4.25 mg), xantphos (4.710⁻³ mmol, 2.69 mg), Cs₂CO₃ (0.70 mmol, 227.10 mg), toluene/H₂O (2.53 mL) were reacted according to general procedure. The crude product was purified by silica gel column chromatography (petroleum ether/EtOAc = 100:0 to 95:5) affording compound **3ab** in 86% yield (36.12 mg) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ

8.26–8.11 (m, 2.00H), 7.56 (t, $J = 8.5$ Hz, 1.26H), 7.35 (d, $J = 8.6$ Hz, 0.76H), 6.25 (d, $J = 20.7$ Hz, 0.37H), 5.58 (d, $J = 37.4$ Hz, 0.63H), 2.22–2.09 (m, 3.00H). ^{13}C NMR (75 MHz, CDCl_3): δ 164.1 (d, $^1J_{\text{C-F}} = 257.5$ Hz), 163.6 (d, $^1J_{\text{C-F}} = 271.8$ Hz), 145.3 (2), 140.5 (d, $^3J_{\text{C-F}} = 14.8$ Hz), 139.6 (d, $^3J_{\text{C-F}} = 2.7$ Hz), 129.2 (2), 129.1, 129.0, 124.2 (2), 123.9 (2), 111.8 (d, $^2J_{\text{C-F}} = 6.0$ Hz), 110.7 (d, $^2J_{\text{C-F}} = 26.1$ Hz), 19.40 (d, $^2J_{\text{C-F}} = 2.5$ Hz), 18.9 (d, $^2J_{\text{C-F}} = 24.9$ Hz). ^{19}F NMR (282 MHz, CDCl_3): δ –81.75 (tt, $J = 36.1, 18.0$ Hz), –87.75 (dq, $J = 37.5, 17.1$ Hz). HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calc. for $\text{C}_9\text{H}_8\text{FNO}_2$, 182.0612 found 182.0619.

3.3.14. 1-(2-Fluoropent-1-en-1-yl)-4-nitrobenzene (3ac)

(*E/Z*)-1-(2-bromo-2-fluorovinyl)-4-nitrobenzene **1a** (0.23 mmol, 56.32 mg), pentyl boronic acid **2c** (0.28 mmol, 24.51 mg), $\text{Pd}_2\text{dba}_3 \cdot \text{CHCl}_3$ (4.710^{-3} mmol, 4.25 mg), xantphos (4.710^{-3} mmol, 2.69 mg), Cs_2CO_3 (0.70 mmol, 227.10 mg), toluene/ H_2O (2.53 mL) were reacted according to general procedure. The crude product was purified by silica gel column chromatography (petroleum ether/ $\text{EtOAc} = 100:0$ to 95:5) affording compound **3ac** in 95% yield (46.08 mg) as a yellow solid. ^1H NMR (300 MHz, CDCl_3): δ 8.24–8.12 (m, 2.00H), 7.62–7.56 (m, 1.24H), 7.36–7.31 (m, 0.76H), 6.24 (d, $J_{\text{H-F}}^E = 21.1$ Hz, 0.38H), 5.57 (d, $J_{\text{H-F}}^Z = 38.1$ Hz, 0.62H), 2.51–2.30 (m, 2.00H), 1.67 (ddd, $J = 14.8, 7.4, 5.7$ Hz, 2.00H), 1.00 (dd, $J = 15.7, 7.7$ Hz, 3.00H). ^{13}C NMR (75 MHz, CDCl_3): δ 164.1 (d, $^1J_{\text{C-F}} = 257.5$ Hz), 163.6 (d, $^1J_{\text{C-F}} = 271.8$ Hz), 143.5 (2), 139.7 (d, $^3J_{\text{C-F}} = 14.9$ Hz), 138.8 (d, $^3J_{\text{C-F}} = 2.5$ Hz), 127.1 (2), 126.9, 126.8, 121.9 (4), 105.5 (d, $^2J_{\text{C-F}} = 31.1$ Hz), 102.8 (d, $^2J_{\text{C-F}} = 8.1$ Hz), 33.3 (d, $^2J_{\text{C-F}} = 25.7$ Hz), 29.3 (d, $^2J_{\text{C-F}} = 26.8$ Hz), 17.7 (2), 11.7, 11.5. ^{19}F NMR (282 MHz, CDCl_3): δ –91.24 (dd, $J^E = 44.6, 23.2$ Hz), –93.61––94.11 (m). HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calc. for $\text{C}_{11}\text{H}_{13}\text{FNO}_2$, 210.0925 found 210.0920.

3.3.15. 1-(2-Fluoro-4-phenylbut-1-en-1-yl)-4-nitrobenzene (3ad)

(*E/Z*)-1-(2-bromo-2-fluorovinyl)-4-nitrobenzene **1a** (0.23 mmol, 56.32 mg), phenethylboronic acid **2d** (0.28 mmol, 41.78 mg), $\text{Pd}_2\text{dba}_3 \cdot \text{CHCl}_3$ (4.710^{-3} mmol, 4.25 mg), xantphos (4.710^{-3} mmol, 2.69 mg), Cs_2CO_3 (0.70 mmol, 227.10 mg), toluene/ H_2O (2.53 mL) were reacted according to general procedure. The crude product was purified by silica gel column chromatography (petroleum ether/ $\text{EtOAc} = 100:0$ to 95:5) affording compound **3ad** in 87% yield (54.71 mg) as a yellow solid. ^1H NMR (300 MHz, CDCl_3): δ 8.16 (d, $J = 9.0$ Hz, 1.24H), 8.08 (d, $J_{\text{H-F}}^E = 8.9$ Hz, 0.76H), 7.57 (d, $J_{\text{H-F}}^Z = 8.9$ Hz, 1.24H), 7.35–7.15 (m, 5.00H), 7.07–7.00 (m, 0.76H), 6.25 (d, $J_{\text{H-F}}^E = 20.9$ Hz, 0.38H), 5.53 (d, $J_{\text{H-F}}^Z = 38.0$ Hz, 0.62H), 2.95 (dd, $J = 8.8, 6.9$ Hz, 2.00H), 2.70 (ddd, $J = 16.2, 10.9, 7.4$ Hz, 2.00H). ^{13}C NMR (75 MHz, CDCl_3): δ 163.4 (d, $^1J_{\text{C-F}} = 261.0$ Hz), 163.2 (d, $^1J_{\text{C-F}} = 266.8$ Hz), 146.2, 146.1, 141.1, 140.9, 140.3 (d, $^3J_{\text{C-F}} = 2.4$ Hz), 140.0 (d, $^3J_{\text{C-F}} = 10.6$ Hz), 129.0, 128.9, 128.8, 128.7 (2), 128.6 (4), 128.5, 128.4 (2), 126.6, 126.5, 123.7 (2), 123.7 (2), 108.1 (d, $^2J_{\text{C-F}} = 30.3$ Hz), 105.3 (d, $^2J_{\text{C-F}} = 7.9$ Hz), 35.2 (d, $^2J_{\text{C-F}} = 25.8$ Hz), 32.3 (d, $^2J_{\text{C-F}} = 36.5$ Hz), 31.5, 31.2. ^{19}F NMR (282 MHz, CDCl_3): δ –93.83 (dd, $J^E = 43.3, 22.6$ Hz), –95.15 (dt, $J^Z = 36.5, 18.0$ Hz). HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calc. for $\text{C}_{16}\text{H}_{15}\text{FNO}_2$, 272.1081 found 272.1082.

3.3.16. 1-(2-Fluoro-4-methylpent-1-en-1-yl)-4-nitrobenzene (3ae)

(*E/Z*)-1-(2-bromo-2-fluorovinyl)-4-nitrobenzene **1a** (0.23 mmol, 56.32 mg), isobutylboronic acid **2e** (0.28 mmol, 28.42 mg), $\text{Pd}_2\text{dba}_3 \cdot \text{CHCl}_3$ (4.710^{-3} mmol, 4.25 mg), xantphos (4.710^{-3} mmol, 2.69 mg), Cs_2CO_3 (0.70 mmol, 227.10 mg), toluene/ H_2O (2.53 mL) were reacted according to general procedure. The crude product was purified by silica gel column chromatography (petroleum ether/ $\text{EtOAc} = 100:0$ to 95:5) affording compound **3ae** in 77% yield (39.85 mg) as a yellow solid. ^1H NMR (300 MHz, CDCl_3): δ 8.18 (d, $J = 7.4$ Hz, 0.84H), 8.15 (d, $J = 7.5$ Hz, 1.16H), 7.59 (d, $J = 9.0$ Hz, 1.16H), 7.34 (d, $J = 8.4$ Hz, 0.84H), 6.27 (d, $J_{\text{H-F}}^E = 21.6$ Hz, 0.42H), 5.56 (d, $J_{\text{H-F}}^Z = 37.9$ Hz, 0.58H), 2.35 (dd, $J = 23.4, 7.2$ Hz, 0.84H), 2.23 (dd, $J = 21.4, 7.1$ Hz, 1.16H), 2.08–1.95 (m, 1.00H), 1.00 (dd, $J = 6.6, 0.5$ Hz, 3.48H), 0.96 (dd, $J = 6.7, 0.6$ Hz, 2.52H). ^{13}C NMR (75 MHz, CDCl_3): 164.3 (d, $^1J_{\text{C-F}} = 257.5$ Hz), 163.8 (d, $^1J_{\text{C-F}} = 272.2$ Hz), 141.5 (d, $^3J_{\text{C-F}} = 15.1$ Hz), 140.6 (d, $^3J_{\text{C-F}} = 2.6$ Hz), 129.1 (d, $J_{\text{C-F}} = 2.7$ Hz, 2), 128.7 (d, $J_{\text{C-F}} = 8.3$ Hz, 2), 123.8 (4), 108.0 (d, $^2J_{\text{C-F}} = 31.1$ Hz), 105.7 (d, $^2J_{\text{C-F}} = 8.3$ Hz), 42.5 (d, $^2J_{\text{C-F}} = 25.0$ Hz), 38.0 (d, $^2J_{\text{C-F}} = 25.9$ Hz), 26.2, 26.1, 22.3, 22.2. ^{19}F NMR (282 MHz, CDCl_3): δ –89.63 (q, $J^E = 22.9$ Hz), –93.10 (dt, $J^Z = 37.9, 21.4$ Hz). HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calc. for $\text{C}_{12}\text{H}_{15}\text{FNO}_2$, 224.1081 found 224.1080.

3.3.17. 1-(2-Cyclopropyl-2-fluorovinyl)-4-nitrobenzene (3ah)

(*E/Z*)-1-(2-bromo-2-fluorovinyl)-4-nitrobenzene **1a** (0.23 mmol, 56.32 mg), cyclopropylboronic acid **2h** (0.28 mmol, 23.95 mg), Pd₂dba₃·CHCl₃ (4.710⁻³ mmol, 4.25 mg), xantphos (4.710⁻³ mmol, 2.69 mg), Cs₂CO₃ (0.70 mmol, 227.10 mg), toluene/H₂O (2.53 mL) were reacted according to general procedure. The crude product was purified by silica gel column chromatography (petroleum ether/EtOAc = 100:0 to 95:5) affording compound **3ah** in 83% yield (39.87 mg) as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 8.12 (d, *J* = 8.9 Hz, 0.84H), 8.07 (d, *J* = 9.0 Hz, 1.16H), 7.47 (d, *J* = 9.0 Hz, 1.16H), 7.41 (d, *J* = 8.4 Hz, 0.84H), 6.16 (d, *J*^E_{H-F} = 19.9 Hz, 0.42H), 5.58 (d, *J*^Z_{H-F} = 37.9 Hz, 0.58H), 1.93–1.77 (v-1Hm, 0.42H), 1.69–1.54 (m, 0.58H), 0.92 (dt, *J* = 8.9, 3.2 Hz, 0.84H), 0.87–0.78 (m, 3.16H). ¹³C NMR (75 MHz, CDCl₃): 164.2 (d, ¹*J*_{C-F} = 266.7 Hz), 164.0 (d, ¹*J*_{C-F} = 252.9 Hz), 146.1, 147.5, 141.8 (d, ³*J*_{C-F} = 14.7 Hz), 140.8 (d, ³*J*_{C-F} = 3.3 Hz), 129.1 (d, *J*_{C-F} = 2.7 Hz, 2), 128.4 (d, *J*_{C-F} = 8.2 Hz, 2), 123.(4), 106.2 (d, ²*J*_{C-F} = 32.9 Hz), 102.9 (d, ²*J*_{C-F} = 9.9 Hz), 13.4 (d, ²*J*_{C-F} = 28.1 Hz), 10.3 (d, ²*J*_{C-F} = 26.6 Hz), 6.2, 6.1, 5.8 (2). ¹⁹F NMR (282 MHz, CDCl₃): δ - 108.50 (dd, *J* = 37.9, 22.7 Hz). HRMS (ESI): *m/z* [M + H]⁺ calc. for C₁₁H₁₁FNO₂, 208.0768 found 208.0765.

4. Conclusions

In conclusion, an efficient palladium-catalyzed carbon–carbon coupling reaction of readily available *gem*-bromofluoroalkenes with primary and strained secondary alkyl boronic acid derivatives was successfully achieved under mild conditions. This methodology demonstrates its applicability for the synthesis of alkyl trisubstituted or tetrasubstituted monofluoroalkenes with a broad range of *gem*-bromofluoroalkenes and alkyl boronic acids with good group compatibility, stereospecificity and excellent yields. Such reactions may be useful for the synthesis of fluorolefins of interest for life and material sciences.

Supplementary Materials: ¹H-, ¹³C- and ¹⁹F-NMR spectra of products associated with this article are available online.

Author Contributions: L.C.-B. and N.C. performed the experiments, L.C.-B. and C.R. designed and supervised the study and wrote the paper. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Acknowledgments: The authors gratefully acknowledge the CNRS for financial support. The NMR facilities used in this study were funded by the European Community (FEDER), Région Haut de France (France), the CNRS and Lille University.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Hagmann, W.K. The Many Roles for Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2008**, *51*, 4359–4369. [[CrossRef](#)] [[PubMed](#)]
2. Gillis, E.P.; Eastman, K.J.; Hill, M.D.; Donnelly, D.J.; Meanwell, N.A. Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2015**, *58*, 8315–8359. [[CrossRef](#)] [[PubMed](#)]
3. Müller, K.; Faeh, C.; Diederich, F. Fluorine in Pharmaceuticals: Looking Beyond Intuition. *Science* **2007**, *317*, 1881–1886. [[CrossRef](#)] [[PubMed](#)]
4. Purser, S.; Moore, P.R.; Swallow, S.; Gouverneur, V. Fluorine in medicinal chemistry. *Chem. Soc. Rev.* **2008**, *37*, 320–330. [[CrossRef](#)]
5. Wang, J.; Sánchez-Roselló, M.; Aceña, J.L.; Del Pozo, C.; Sorochinsky, A.E.; Fustero, S.; Soloshonok, V.A.; Liu, H. Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001–2011). *Chem. Rev.* **2014**, *114*, 2432–2506. [[CrossRef](#)]
6. Fujiwara, T.; O'Hagan, D. Successful fluorine-containing herbicide agrochemicals. *J. Fluor. Chem.* **2014**, *167*, 16–29. [[CrossRef](#)]
7. Berger, R.; Resnati, G.; Metrangolo, P.; Weber, E.; Hulliger, J. Organic fluorine compounds: A great opportunity for enhanced materials properties. *Chem. Soc. Rev.* **2011**, *40*, 3496–3508. [[CrossRef](#)]

8. Meanwell, N.A. Fluorine and Fluorinated Motifs in the Design and Application of Bioisosteres for Drug Design. *J. Med. Chem.* **2018**, *61*, 5822–5880. [[CrossRef](#)]
9. Couve-Bonnaire, S.; Cahard, D.; Pannecoucke, X. Chiral dipeptide mimics possessing a fluoroolefin moiety: A relevant tool for conformational and medicinal studies. *Org. Biomol. Chem.* **2007**, *5*, 1151–1157. [[CrossRef](#)]
10. Osada, S.; Sano, S.; Ueyama, M.; Chuman, Y.; Kodama, H.; Sakaguchi, K. Fluoroalkene modification of mercaptoacetamide-based histone deacetylase inhibitors. *Bioorganic Med. Chem.* **2010**, *18*, 605–611. [[CrossRef](#)]
11. Zajc, B.; Kumar, R. Synthesis of Fluoroolefins via Julia-Kocienski Olefination. *Synthesis* **2010**, *2010*, 1822–1836. [[CrossRef](#)]
12. Zhao, Y.; Jiang, F.; Hu, J. Spontaneous Resolution of Julia-Kocienski Intermediates Facilitates Phase Separation to Produce *Z*- and *E*-Monofluoroalkenes. *J. Am. Chem. Soc.* **2015**, *137*, 5199–5203. [[CrossRef](#)] [[PubMed](#)]
13. Akana, J.A.; Bhattacharyya, K.X.; Mueller, P.; Sadighi, J.P. Reversible C-F Bond Formation and the Au-Catalyzed Hydrofluorination of Alkynes. *J. Am. Chem. Soc.* **2007**, *129*, 7736–7737. [[CrossRef](#)]
14. Gorske, B.C.; Mbofana, C.T.; Miller, S.J. Regio- and Stereoselective Synthesis of Fluoroalkenes by Directed Au(I) Catalysis. *Org. Lett.* **2009**, *11*, 4318–4321. [[CrossRef](#)] [[PubMed](#)]
15. Liu, T.-L.; Wu, J.; Zhao, Y. Divergent reactivities in fluorination of allylic alcohols: Synthesis of *Z*-fluoroalkenes via carbon-carbon bond cleavage. *Chem. Sci.* **2017**, *8*, 3885–3890. [[CrossRef](#)] [[PubMed](#)]
16. Gauthier, R.; Mamone, M.; Paquin, J. Gold-Catalyzed Hydrofluorination of Internal Alkynes Using Aqueous HF. *Org. Lett.* **2019**, *21*, 9024–9027. [[CrossRef](#)] [[PubMed](#)]
17. Dai, W.; Shi, H.; Zhao, X.; Cao, S. Sterically Controlled Cu-Catalyzed or Transition-Metal-Free Cross-Coupling of *gem*-Difluoroalkenes with Tertiary, Secondary, and Primary Alkyl Grignard Reagents. *Org. Lett.* **2016**, *18*, 4284–4287. [[CrossRef](#)]
18. Lu, X.; Wang, Y.; Zhang, B.; Pi, J.-J.; Wang, X.-X.; Gong, T.-J.; Xiao, B.; Fu, Y. Nickel-Catalyzed Defluorinative Reductive Cross-Coupling of *gem*-Difluoroalkenes with Unactivated Secondary and Tertiary Alkyl Halides. *J. Am. Chem. Soc.* **2017**, *139*, 12632–12637. [[CrossRef](#)]
19. Yang, L.; Ji, W.-W.; Lin, E.; Li, J.-L.; Fan, W.-X.; Li, Q.; Zhang, S.-S. Synthesis of Alkylated Monofluoroalkenes via Fe-Catalyzed Defluorinative Cross-Coupling of Donor Alkenes with *gem*-Difluoroalkenes. *Org. Lett.* **2018**, *20*, 1924–1927. [[CrossRef](#)]
20. Yu, L.; Tang, M.-L.; Si, C.-M.; Meng, Z.; Liang, Y.; Han, J.; Sun, X. Zinc-Mediated Decarboxylative Alkylation of *gem*-Difluoroalkenes. *Org. Lett.* **2018**, *20*, 4579–4583. [[CrossRef](#)]
21. Zhou, L.; Zhu, C.; Bi, P.; Feng, C. Ni-catalyzed migratory fluoro-alkenylation of unactivated alkyl bromides with *gem*-difluoroalkenes. *Chem. Sci.* **2019**, *10*, 1144–1149. [[CrossRef](#)] [[PubMed](#)]
22. Xu, J.; Ahmed, E.-A.; Xiao, B.; Lu, Q.-Q.; Wang, Y.-L.; Yu, C.-G.; Fu, Y. ChemInform Abstract: Pd-Catalyzed Regioselective Activation of *gem*-Difluorinated Cyclopropanes: A Highly Efficient Approach to 2-Fluorinated Allylic Scaffolds. *Angew. Chem.* **2015**, *46*, 8231–8235. [[CrossRef](#)] [[PubMed](#)]
23. Wenz, J.; Rettenmeier, C.A.; Wadepohl, H.; Gade, L.H. ChemInform Abstract: Catalytic C-F Bond Activation of Geminal Difluorocyclopropanes by Nickel(I) Complexes via a Radical Mechanism. *Angew. Chem.* **2016**, *47*, 202–205. [[CrossRef](#)]
24. Ahmed, E.-A.M.A.; Suliman, A.M.Y.; Gong, T.-J.; Fu, Y. Palladium-Catalyzed Stereoselective Defluorination Arylation/Alkenylation/Alkylation of *gem*-Difluorinated Cyclopropanes. *Org. Lett.* **2019**, *21*, 5645–5649. [[CrossRef](#)]
25. Xie, J.; Yu, J.; Rudolph, M.; Rominger, F.; Hashmi, A.S.K. Monofluoroalkenylation of Dimethylamino Compounds through Radical-Radical Cross-Coupling. *Angew. Chem. Int. Ed.* **2016**, *55*, 9416–9421. [[CrossRef](#)] [[PubMed](#)]
26. Li, J.; Lefebvre, Q.; Yang, H.; Zhao, Y.; Fu, H. Visible light photocatalytic decarboxylative monofluoroalkenylation of α -amino acids with *gem*-difluoroalkenes. *Chem. Commun.* **2017**, *53*, 10299–10302. [[CrossRef](#)]
27. Yang, H.; Tian, C.; Qiu, D.; Tian, H.; An, G.-H.; Li, G.-M. Organic photoredox catalytic decarboxylative cross-coupling of *gem*-difluoroalkenes with unactivated carboxylic acids. *Org. Chem. Front.* **2019**, *6*, 2365–2370. [[CrossRef](#)]
28. Du, H.-W.; Sun, J.; Gao, Q.-S.; Wang, J.-Y.; Wang, H.; Xu, Z.; Zhou, M. Synthesis of Monofluoroalkenes through Visible-Light-Promoted Defluorinative Alkylation of *gem*-Difluoroalkenes with 4-Alkyl-1,4-dihydropyridines. *Org. Lett.* **2020**, *22*, 1542–1546. [[CrossRef](#)]

29. Chelucci, G. ChemInform Abstract: Synthesis and Metal-Catalyzed Reactions of *gem*-Dihalovinyl Systems. *Angew. Chem.* **2012**, *43*, 1344–1462. [[CrossRef](#)]
30. Landelle, G.; Bergeron, M.; Turcotte-Savard, M.-O.; Paquin, J.-F. Synthetic approaches to monofluoroalkenes. *Chem. Soc. Rev.* **2011**, *40*, 2867–2908. [[CrossRef](#)]
31. Lei, X.; Dutheuil, G.; Pannecoucke, X.; Quirion, J.-C. A Facile and Mild Method for the Synthesis of Terminal Bromofluoroolefins via Diethylzinc-Promoted Wittig Reaction. *Org. Lett.* **2004**, *6*, 2101–2104. [[CrossRef](#)] [[PubMed](#)]
32. Andrei, D.; Wnuk, S.F. Synthesis of the Multisubstituted Halogenated Olefins via Cross-Coupling of Dihaloalkenes with Alkylzinc Bromides. *J. Org. Chem.* **2006**, *71*, 405–408. [[CrossRef](#)] [[PubMed](#)]
33. Zemmouri, R.; Kajjout, M.; Castanet, Y.; Eddarir, S.; Rolando, C. Palladium-Catalyzed Stereoconvergent Formylation of (*E/Z*)- β -Bromo- β -fluorostyrenes: Straightforward Access to (*Z*)- α -Fluorocinnamic Aldehydes and (*Z*)- β -Fluorocinnamic Alcohols. *J. Org. Chem.* **2011**, *76*, 7691–7698. [[CrossRef](#)] [[PubMed](#)]
34. Eddarir, S.; Kajjout, M.; Rolando, C. Stereoselective cyanation of β -bromo- β -fluorostyrenes using potassium cyanide and promoted by $(\text{CH}_3\text{CN})_4\text{Cu}^+ \text{BF}_4^-$. *Tetrahedron* **2012**, *68*, 603–607. [[CrossRef](#)]
35. Kajjout, M.; Zemmouri, R.; Eddarir, S.; Rolando, C. An efficient access to (*Z*)- β -fluoroallyl alcohols based on the two carbon homologation of aromatic aldehydes by Horner-Wadsworth-Emmons reaction with 2-(diethoxyphosphinyl)-2-fluoro-ethanethioic acid, *S*-ethyl ester followed by reduction with sodium borohydride. *Tetrahedron* **2012**, *68*, 3225–3230. [[CrossRef](#)]
36. Kajjout, M.; Smietana, M.; Leroy, J.; Rolando, C. A new approach to the synthesis of (*Z*)-2-fluoro-2-alkenals via Wittig-type carbonyl condensation reactions of 2-(fluoromethyl)-4,4,6-trimethyl-1,3-oxazine phosphonium bromide. *Tetrahedron Lett.* **2013**, *54*, 1658–1660. [[CrossRef](#)]
37. Tan, Z.; Negishi, E.-I. Widely Applicable Pd-Catalyzed *trans*-Selective Monoalkylation of Unactivated 1,1-Dichloro-1-alkenes and Pd-Catalyzed Second Substitution for the Selective Synthesis of (*E*)- or (*Z*)-Trisubstituted Alkenes. *Angew. Chem.* **2006**, *37*, 762–765. [[CrossRef](#)]

Sample Availability: Samples of the compounds are available from the authors.

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



© 2020 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).