Stereoselective synthesis of 4-fluoro-1,3-alkadienylboronates and their application in the stereoselective synthesis of fluoropolyenes

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Abstract \((1E, 3E)\)- and \((1E, 3Z)\)-4-Fluoro-1,3-alkadienylboronates were stereoselectively prepared by the Heck-reaction of a vinylboronate with \((E)\)- or \((Z)\)-2-fluoro-1-alkenyliodonium salts, and applied to the Suzuki-Miyaura coupling reaction for the synthesis of fluoropolyenes.

Keywords: Heck-reaction, Fluoroalkadienylboronates, Suzuki-Miyaura coupling, Fluoropolyene, Fluoroalkenyliodonium salts

1. Introduction

Polyene natural products that exhibit significant bioactivities are widely known in nature [1, 2]. The fluorinated analogs of the polyene are of great interest for studying their actions \emph{in vivo} and the modification of their activities [3-8]. Fluorodienylmetals (1) are effective as building blocks for the synthesis of polyene analogs with fluorine attached to the double bonds [5, 8]. Although fluorodienylboronates (1, M = B in scheme 1) can be used as building blocks for the synthesis of various fluoropolyenes by the Suzuki-Miyaura coupling reaction [9], they have not yet been synthesized.

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Alkadienylboronates are synthesized by the Heck reaction of vinylboronates (4) with haloalkenes and used for polyene synthesis [10, 11]. Recently, we succeeded in the stereoselective synthesis of (E)- and (Z)-2-fluoro-1-iodoalkenes (2) and 2-fluoroalkenyliodonium salts (3) [12-14]. For the synthesis of fluoroalkadienylboronates (5) and their application in the synthesis of fluoropolyenes (6), we examined the Heck reaction of vinylboronates (4) with 2-fluoro-1-iodoalkenes 2 and 2-fluoroalkenyliodonium salts 3 (Scheme 2).

2. Result and discussion

In the Heck-reaction of the vinylboronates with haloalkenes, the Suzuki-Miyaura coupling reaction competes to give dienes and the yield of the desired dienylboronates decreases [10]. Recently, Whiting et al. successfully depressed the undesired Suzuki-Miyaura coupling using 4,4,6-trimethyl-2-vinyl-1,3,2-dioxaborinane as the vinylboronate and performing the reaction at a high temperature [11]. However, under
the same conditions, the Heck reaction of \((E)-2\text{-fluoro-1-iodoalkenes (2)}\) with vinylboronates such as 4,4,6-trimethyl-2-vinyl-1,3,2-dioxaborinane or 4,4,5,5-tetramethyl-2-vinyl-[1,3,2]-dioxaborolane (7) proceeded non-selectively to give a mixture of products, e.g. \((E)\)- and \((Z)\)-fluorodienylboronates, and the Suzuki-Miyaura coupling product. Alkenyliodonium salts are more reactive than the corresponding iodides in the cross-coupling reaction [15, 16], and therefore, the Heck reaction of \((E)-2\text{-fluoro-1-dodecenyl iodonium salt (3a)}\) with 4,4,5,5-tetramethyl-2-vinyl-[1,3,2]-dioxaborolane (7) was examined (Table 1). As expected, the reaction proceeded at room temperature and the desired \((1E,\ 3E)\)-4-fluoro-1,3-tetradecadienylboronate (5a) was obtained stereoselectively (>95%). Under those conditions, (2-tolylvinyl)boronate (9), the Heck reaction product with a tolyl group on 3a, and 4-fluoro-1,3-tetradecadiene (8), the Suzuki-Miyaura coupling product, were also formed as by-products [17]. As reported previously, amine is superior to \(\text{K}_2\text{CO}_3\) as a base to selectively obtain the Heck product (entries 2 and 4) [18]. When the reaction was carried out using \(\text{Bu}_3\text{N}\) as a base and 2.4 eq of 7 to 3a, 5a was obtained in 65% yield (entry 5). Under these conditions, 8 (5% yield) and 9 (3% yield), which can be separated from 5a by silica gel column chromatography, were also formed.
Table 1
Synthesis of fluoroalkadienylboronate by Heck reaction using fluoroalkenyliodonium salt a

![Chemical structures]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Base</th>
<th>Yield of 5a (%) b</th>
<th>Yield of 8 (%)</th>
<th>Yield of 9 (%) c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>toluene</td>
<td>Bu3N</td>
<td>40 (97)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>DMF</td>
<td>Bu3N</td>
<td>60 (96)</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>Bu3N</td>
<td>60 (97)</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>DMF</td>
<td>K2CO3</td>
<td>19 (96)</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>DMF</td>
<td>Bu3N</td>
<td>65 (96) d</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

a If otherwise not mentioned, the reaction was carried out using 1.2 eq of 7, 1.2 eq of base, and 5 mol% of Pd(OAc)2.

b Isolated yield base on 3a. In parentheses, stereoselectivity, and a \((1E, 3Z)\)-isomer was formed as by-product.

c Determined by GC.

d 2.4 eq of 7 was used.

Various 2-fluoroalkenyliodonium salts (3a-f) were used in the synthesis of 4-fluoro-1,3-alkadienylboronates 5a-f (Table 2). When \((E)\)-fluoroalkenyliodonium salts (3a-e) were used, the corresponding \((1E, 3E)\)-4-fluoro-1,3-alkadienylboronates (5a-e) were obtained in 55-65% yield with good stereoselectivity (94-98%). Functional groups such as ketone and ester can tolerate these reaction conditions, and functionalized fluoroalkadienylboronates (5c-e) were obtained (entries 3-5). On the other hand, the reaction with \((Z)\)-fluoroalkenyliodonium salt (3f) proceeded less selectively, and the desired \((1E, 3Z)\)-4-fluoro-1,3-alkadienylboronate (5f) was obtained.
in lower yield (46%) with a significant amount of the Suzuki-Miyaura coupling product (20%) (Entry 6) [17].

Table 2
Synthesis of fluoroalkadienylboronates by Heck reaction using various fluoroalkenyliodonium salt

<table>
<thead>
<tr>
<th>Entry</th>
<th>Fluoroalkenyliodonium salt 3</th>
<th>Product 5</th>
<th>Yield of 5 (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{C}<em>{10}\text{H}</em>{21})BF4</td>
<td>(\text{C}<em>{10}\text{H}</em>{21})BF4</td>
<td>65 (96)</td>
</tr>
<tr>
<td>2</td>
<td>(\text{C}<em>{10}\text{H}</em>{21})BF4</td>
<td>(\text{C}<em>{10}\text{H}</em>{21})BF4</td>
<td>57 (95)</td>
</tr>
<tr>
<td>3</td>
<td>AcO-(CH2)9BF4</td>
<td>AcO-(CH2)9BF4</td>
<td>60 (97)</td>
</tr>
<tr>
<td>4</td>
<td>MeOOC-(CH2)8BF4</td>
<td>MeOOC-(CH2)8BF4</td>
<td>60 (98)</td>
</tr>
<tr>
<td>5</td>
<td>(\text{tBuC}-(\text{CH2})_{8})BF4</td>
<td>(\text{tBuC}-(\text{CH2})_{8})BF4</td>
<td>55 (95)</td>
</tr>
<tr>
<td>6</td>
<td>AcO-(CH2)9BF4</td>
<td>AcO-(CH2)9BF4</td>
<td>46 (94)</td>
</tr>
</tbody>
</table>

\(3\) If otherwise not mentioned, the reaction was carried out using 2.4eq of 7, 1.2 eq of Bu3N, and 5 mol% of Pd(OAc)2.

\(b\) Isolated yield base on 3. In parenthese, stereoselectivity determined by \(^{19}\)FNMR.
The resulting fluoroalkadienylboronates 5 can be used for fluoropolyene synthesis by the Suzuki-Miyaura coupling reaction. When 5a was subjected to the coupling reaction with ethyl 4-iodobenzoate (10), arylated (1E, 3E)-4-fluorotetradecadiene (12) was obtained in good yield. Similarly, (1E, 3E, 5E)-1-phenyl-6-fluorohexadecatriene (13) was obtained by the coupling reaction with β-bromostyrene (11) (Scheme 3).

\[
\begin{align*}
5a & \quad + \quad \text{I} \quad \text{Ph} \quad \text{COOEt}  \\
& \quad \text{P(PPh}_3\text{)}_4, \text{K}_2\text{CO}_3  \\
& \quad 80 \text{ °C, 20h}  \\
& \quad 85\%  \\
\end{align*}
\]

\[
\begin{align*}
5a & \quad + \quad \text{Br} \quad \text{Ph}  \\
& \quad \text{P(PPh}_3\text{)}_4, \text{KO}_2  \\
& \quad 50 \text{ °C, 2h}  \\
& \quad 70\%  \\
\end{align*}
\]

Scheme 3

3. Conclusion

In conclusion, various (1E, 3E)- and (1E, 3Z)-4-fluoro-1,3-alkadienylboronates were stereoselectively prepared by the Heck-reaction of 4,4,5,5-tetramethyl-2-vinyl-[1,3,2]-dioxaborolane with (E)- or (Z)-2-fluoro-1-alkenyliodonium salts. The reaction proceeded at room temperature and the pure fluoroalkadienylboronates were isolated by column chromatography. The resulting fluoroalkadienylboronates can be used for the synthesis of fluoropolyenes by the Suzuki-Miyaura coupling reaction with aryl or alkenyl halides.
4. Experimental

4.1. General methods

The IR spectra were recorded using a JASCO FT/IR-410 spectrophotometer. The $^1$H NMR (400 MHz) spectra, $^{19}$F NMR (376 MHz) spectra and $^{13}$C NMR (100 MHz) spectra were recorded in CDCl$_3$ on a JEOL JNM-A400II FT NMR spectrometer and the chemical shift, $\delta$, are referred to TMS ($^1$H, $^{13}$C) and CFCl$_3$ ($^{19}$F), respectively. The EI-high-resolution mass spectra were measured on a JEOL JMS-700TZ spectrometer.

(E)-2-Fluoroalkenyliodonium salts 3a-e were prepared from the corresponding alkynes and iodotoluene difluoride according to a literature [13]. (Z)-2-Fluoroalkenyliodonium salt 3f was prepared from the corresponding 1-alkyne in two steps according to the literatures [14]. 4,4,5,5-Tetramethyl-2-vinyl-[1,3,2]-dioxaborolane 7 was purchased from Aldrich or prepared according to the literature [19].

4.2. Synthesis of fluoroalkadienylboronates

4.2.1. (1E,3E)-2-(4-Fluoro-1,3-tetradecadienyl)-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (5a)

A mixture of Pd(OAc)$_2$ (11 mg, 0.05 mmol), Bu$_3$N (110 mg, 0.6 mmol), 3a (238 mg, 0.5 mmol), and 7 (185 mg, 1.2 mmol) in DMF (1.5 ml) was stirred under N$_2$ atmosphere at room temperature for 2h. Then, the mixture was poured into water and extracted with ether three times. The combined organic layers were dried over MgSO$_4$ and
concentrated under reduced pressure. Purification by column chromatography (silica gel/hexane-ether) gave 5a (110 mg, 0.33 mmol) in 65% yield. IR (neat) 2927, 1665, 1145 cm\(^{-1}\). \(^1\)H NMR \(\delta\) 0.88 (t, \(J = 6.8\) Hz, 3H), 1.27 (s, 12H), 1.27 – 1.31 (m, 14H), 1.52 – 1.54 (m, 2H), 2.42 (dt, \(J = 23.4, 7.3\) Hz, 2H), 5.48 (d, \(J = 17.5\) Hz, 1H), 5.82 (dd, \(J = 19.8, 11.2\) Hz, 1H), 6.97 (dd, \(J = 17.5, 11.3\) Hz, 1H). \(^1^9\)F NMR \(\delta\) - 95.64 (dt, \(J = 19.6, 23.3\) Hz, 1F). \(^{13}\)C NMR \(\delta\) 14.10, 22.67, 24.73 (4C), 26.32, 28.64 (d, \(J = 25.9\) Hz), 28.98, 29.29, 29.31, 29.46, 29.55, 31.88, 83.15 (2C), 110.62 (d, \(J = 26.5\) Hz), 142.99 (d, \(J = 12.4\) Hz), 166.10 (d, \(J = 261.2\) Hz). HRMS (EI): calc. for C\(_{20}\)H\(_{36}\)O\(_2\)FB: 338.2792, found 338.2794.

4.2.2. \((1E,3E)-2-(5\text{-Cyclohexyl-4-fluoro-1,3-pentadienyl})-4,4,5,5\text{-tetramethyl-}[1,3,2]\text{-dioxaborolane (5b). IR (neat) 2926, 1663, 1608, 1331, 1146 cm}^{-1\text{. \(^1\)H NMR \(\delta\) 1.16 – 1.26 (m, 10H), 1.28 (s, 12H), 1.64 – 1.72 (m, 1H), 2.31 (dd, \(J = 24.5, 7.1\) Hz, 2H), 5.47 (d, \(J = 17.5\) Hz, 1H), 5.87 (dd, \(J = 20.1, 11.2\) Hz, 1H), 6.93 (dd, \(J = 17.5, 11.2\) Hz, 1H). \(^1^9\)F NMR \(\delta\) - 93.15 (dt, \(J = 20.2, 24.4\) Hz, 1.1F). \(^{13}\)C NMR \(\delta\) 24.73 (4C), 26.13 (2C), 26.25, 32.86 (2C), 35.40, 36.33 (d, \(J = 26.0\) Hz), 83.13 (2C), 111.73 (d, \(J = 26.6\) Hz), 143.00 (d, \(J = 12.1\) Hz), 164.99 (d, \(J = 261.2\) Hz). HRMS (EI): calc. for C\(_{17}\)H\(_{28}\)O\(_2\)FB: 294.2166, found 294.2149.

4.2.3. \((1E,3E)-2-(13\text{-Acetoxy-4-fluoro-1,3-tridecadienyl})-4,4,5,5\text{-tetramethyl-}[1,3,2]\text{-dioxaborolane (5c). IR (neat) 2931, 1741, 1664, 1608, 1335, 1240, 1146 cm}^{-1\text{. \(^1\)H NMR \(\delta\) 1.27 (s, 12H), 1.27 – 1.30 (m, 10H), 1.55 – 1.62 (m, 4H), 2.05 (s, 3H), 2.42 (dt, \(J = 23.4, 7.6\) Hz, 2H), 4.05 (t, \(J = 6.7\) Hz, 2H), 5.48 (d, \(J = 17.5\) Hz, 1H), 5.82 (dd, \(J = 19.8, 11.3\) Hz, 1H), 6.96 (dd, \(J = 17.6, 11.4\) Hz, 1H). \(^1^9\)F NMR \(\delta\) - 95.70 (dt, \(J = 19.5, 23.2\) Hz, 1F). \(^{13}\)C NMR \(\delta\) 20.81, 24.59 (4C), 25.73, 26.14, 28.43. 28.50 (d, \(J = 26.2\) Hz), 28.75, 29.03, 29.09, 29.17, 64.45, 83.01 (2C), 110.53 (d, \(J = 26.2\) Hz), 142.79 (d, \(J = 12.4\) Hz), 165.84 (d, \(J = 261.3\) Hz), 171.04. HRMS (EI): calc. for C\(_{21}\)H\(_{36}\)O\(_4\)FB:
4.2.4. Methyl (10E,12E)-10-fluoro-13-(4,4,5,5-tetramethyl-[1,3,2]-dioxaborolan-2-yl)-10, 12-tridecadienoate (5d). IR (neat) 2932, 1740, 1664, 1608, 1335 cm\(^{-1}\). \(^1\)H NMR δ 1.27 (s, 12H), 1.27 – 1.31 (m, 8H), 1.43 – 1.62 (m, 4H), 2.30 (t, \(J = 7.6\) Hz, 2H), 2.42 (dt, \(J = 23.4, 7.6\) Hz, 2H), 3.67 (s, 3H), 5.48 (d, \(J = 17.6\) Hz, 1H), 5.82 (dd, \(J = 19.7, 11.2\) Hz, 1H), 6.96 (dd, \(J = 17.6, 11.2\) Hz, 1H). \(^{19}\)F NMR δ - 95.71 (dt, \(J = 20.2, 23.2\) Hz, 1F). \(^{13}\)C NMR δ 24.63 (4C), 24.77, 26.16, 28.54 (d, \(J = 26.5\) Hz), 28.75, 28.94 (2C), 29.01, 33.92, 51.28, 83.03 (2C), 110.56 (d, \(J = 26.5\) Hz), 142.80 (d, \(J = 12.4\) Hz), 165.86 (d, \(J = 261.3\) Hz), 174.10. HRMS (EI) calc. for C\(_{20}\)H\(_{34}\)O\(_4\)FB: 368.2534, found 368.2526.

4.2.5. (12E,14E)-12-Fluoro-2,2-dimethyl-15-(4,4,5,5-tetramethyl-[1,3,2]-dioxaborolan-2-yl)-12, 14-pentadecadien-3-one (5e). IR (neat) 2931, 1705, 1664, 1608, 1334 cm\(^{-1}\). \(^1\)H NMR δ 1.13 (s, 9H), 1.27 (s, 12H), 1.27 – 1.30 (m, 8H), 1.54 – 1.55 (m, 4H), 2.37 – 2.48 (m, 4H), 5.48 (d, \(J = 17.5\) Hz, 1H), 5.82 (dd, \(J = 19.8, 11.2\) Hz, 1H), 6.96 (dd, \(J = 17.6, 11.4\) Hz, 1H). \(^{19}\)F NMR δ - 95.67 (dt, \(J = 19.9, 23.5\) Hz, 1F). \(^{13}\)C NMR δ 23.85, 24.72 (4C), 26.28, 26.37 (3C), 28.66 (d, \(J = 26.5\) Hz), 28.91, 29.20, 29.22, 29.31, 36.35, 44.05, 83.13 (2C), 110.62 (d, \(J = 26.6\) Hz), 142.93 (d, \(J = 12.4\) Hz), 166.02 (d, \(J = 261.5\) Hz), 216.08. HRMS (EI) calc. for C\(_{23}\)H\(_{40}\)O\(_3\)FB: 394.3054, found 394.3056.

4.2.6. (1E,3Z)-2-(13-Acetoxy-4-fluoro-1,3-tridecadienyl)-4,4,5,5-tetramethyl-[1,3,2]-dioxaborole (5f). IR (neat) 2930, 1740, 1360 cm\(^{-1}\). \(^1\)H NMR δ 1.24 – 1.32 (m, 10H), 1.27 (s, 12H), 1.51 – 1.63 (m, 4H), 2.05 (s, 3H), 2.21 (dt, \(J = 17.6, 7.4\) Hz, 2H), 4.05 (t, \(J = 6.7\) Hz, 2H), 5.35 (dd, \(J = 35.0, 10.9\) Hz, 1H), 5.42 (d, \(J = 18.1\) Hz, 1H), 7.29 (dd, \(J = 17.9, 10.9\) Hz, 1H). \(^{19}\)F NMR δ - 98.26 (dt, \(J = 36.4, 17.7\) Hz, 1F). \(^{13}\)C
NMR δ 20.98, 24.72 (4C), 25.85, 25.95, 28.55, 28.81, 29.15, 29.29 (2C), 32.21(d, J = 25.7 Hz), 64.58 (2C), 83.11, 108.72 (d, J = 11.4 Hz), 141.42 (d, J = 5.7 Hz), 163.14 (d, J = 269.9 Hz), 171.19.

4.3. **Suzuki-Miyaura reaction using 5a**

4.3.1. *Ethyl 4-{(1E,3E)-4-fluoro-1,3-tetradecadienyl}benzoate (12)*

A mixture of Pd(PPh₃)₄ (28.8 mg, 0.025 mmol), ethyl p-iodobenzoate (166 mg, 0.6 mmol), 5a (169 mg, 0.5 mmol), aq K₂CO₃ (0.6 ml of 2M solution), and EtOH (0.6 ml) in toluene (5 ml) was stirred under N₂ atmosphere at 80 °C for 20h. The mixture was poured into water and extracted with ether three times. Combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. Purification by column chromatography (silica gel/hexane-ether) gave 12 (153 mg, 0.43 mmol) in 85% yield. IR (neat) 2926, 2855, 1718, 1665, 1604, 1276 cm⁻¹. ¹H NMR δ 0.87 (t, J = 7.1 Hz, 3H), 1.26 – 1.43 (m, 14H), 1.40 (t, J = 7.1 Hz, 3H), 1.55 – 1.61 (m, 2H), 2.46 (dt, J = 23.4, 7.4 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H), 5.93 (dd, J = 19.5, 11.3 Hz, 1H), 6.49 (d, J = 15.5 Hz, 1H), 6.78 (dd, J = 15.1, 11.5 Hz, 1H), 7.41 (d, J = 8.4 Hz, 2H), 7.98 (d, J = 8.3 Hz, 2H). ¹⁹F NMR δ -96.81 (dt, J = 19.9, 23.1 Hz, 1F). ¹³C NMR δ 14.01, 14.22, 22.59, 26.30, 28.62 (d, J = 26.8 Hz), 28.87, 29.24, 29.26, 29.44, 29.52, 31.81, 60.72, 108.56 (d, J = 28.4 Hz), 124.53 (d, J = 11.2 Hz), 125.66 (2C), 128.79, 129.58 (d, J = 10.1 Hz), 129.82 (2C), 141.72, 164.80 (d, J = 259.4 Hz), 166.20. HRMS(EI) calc. for C₂₃H₃₅FO₂: 360.2464, found: 360.2470.

4.3.2. *(1E,3E,5E)-6-Fluoro-1-phenyl-1,3,5-hexadecatriene (13)*

A mixture of Pd(PPh₃)₄ (28.8 mg, 0.025 mmol), (E)-β-bromostyrene (165 mg, 0.9
mmol), **Sa** (169 mg, 0.5 mmol), aq KOH (0.6 ml of 2M solution), and EtOH (0.6 ml) in toluene (5 ml) was stirred under N₂ atmosphere at 50 °C for 2h. The mixture was poured into water and extracted with ether three times. Combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. Purification by column chromatography (silica gel/hexane-ether) gave **13** (110 mg, 0.35 mmol) in 70% yield. IR (neat) 2926, 2854, 1663, 1604, 984 cm⁻¹. ¹H NMR δ 0.87 (t, J = 6.5 Hz, 3H), 1.26 (brs, 14H), 1.31 – 1.58 (m, 2H), 2.39 (dt, J = 23.4, 7.3 Hz, 2H), 5.84 (dd, J = 19.6, 10.1 Hz, 1H), 6.22 – 6.35 (m, 2H), 6.51 (d, J = 15.6 Hz, 1H), 6.83 (dd, J = 15.4, 9.5 Hz, 1H), 7.21 – 7.40 (m, 5H). ¹⁹F NMR δ - 98.91 (dt, J = 19.9, 23.1 Hz, 1F). ¹³C NMR δ 14.11, 22.68, 26.41, 28.65 (d, J = 27.1 Hz), 28.98, 29.32, 29.33, 29.51, 29.58, 31.89, 108.69 (d, J = 28.2 Hz), 126.21 (2C), 126.35 (d, J = 10.8 Hz), 127.34, 128.60 (2C), 129.06, 131.44, 131.50 (d, J = 7.2 Hz), 137.39, 163.81 (d, J = 258.0 Hz). HRMS (EI): calc. for C₂₂H₃₁F: 314.2410, found: 314.2415.

**References**