Flash Generation and Borylation of 1-(Trifluoromethyl)vinyllithium toward Synthesis of α-(Trifluoromethyl)styrenes

Takeshi Fujita,[a] Naruki Konno,[a] Yota Watabe,[a] Tomohiro Ichitsuka,[a] Aiichiro Nagaki,[b] Jun-ichi Yoshida,[b] Junji Ichikawa[a,*]

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

[b] Department of Synthetic and Biological Chemistry, Graduate School of Engineering, Kyoto University, Nishikyo-ku, Kyoto 615-8510, Japan

*Corresponding author. Fax: +81-29-853-4237

E-mail address: junji@chem.tsukuba.ac.jp (J. Ichikawa).

Dedicated to the memory of the late Professor George A. Olah for his outstanding scientific achievements

Abstract

Thermally unstable (3,3,3-trifluoroprop-1-en-2-yl)lithium was generated by lithiation of 2-bromo-3,3,3-trifluoroprop-1-ene and successively underwent borylation in a flow microreactor system. Direct use of the 1-(trifluoromethyl)vinylborate thus formed for the Suzuki–Miyaura coupling in a batch

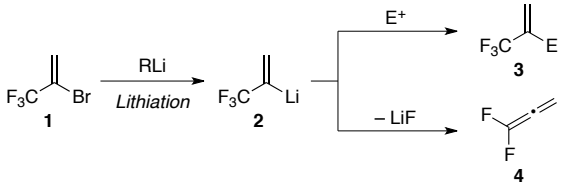
system afforded α-(trifluoromethyl)styrenes in high yields.

Keywords: Flow Microreactor, 1-(Trifluoromethyl)vinyl Compounds, Lithiation, Borylation, Suzuki–Miyaura Coupling, Palladium Catalyst

1. Introduction

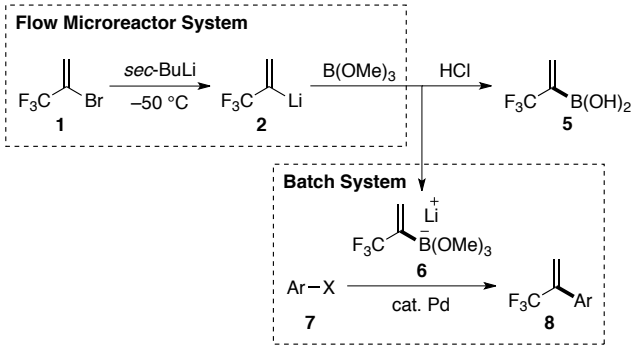
Since 1-(trifluoromethyl)vinyl compounds are highly electrophilic alkenes, they serve as versatile synthetic intermediates, which lead to a variety of fluorine-containing bioactive agents and functional materials [1]. Two modes of transition metal-catalyzed coupling are used as synthetic methods for the direct installation of a 1-(trifluoromethyl)vinyl group. First, (i) coupling of 1-(trifluoromethyl)vinylmetals with electrophiles was reported [2]. Second, (ii) coupling of 1-(trifluoromethyl)vinyl halides with organometallic nucleophiles emerged to avoid the use of thermally unstable 1-(trifluoromethyl)vinylmetals [3]. The latter coupling (ii) is achieved using the palladium-catalyzed reaction of volatile 2-bromo-3,3,3-trifluoroprop-1-ene (**1**) with arylmagnesium halides or arylboronic acids. However, the former coupling (i) could serve only as an alternative choice despite the high commercial availability of aryl halides, which is due to the difficulty in steady generation and/or use of 1-(trifluoromethyl)vinylmetals, including boronic acid and zinc reagents [4].

Tarrant adopted (3,3,3-trifluoroprop-1-en-2-yl)lithium (**2**), which is generated via lithiation of **1**, in the reaction with carbonyl compounds as electrophiles [5]. However, the yields of products **3** remained moderate, presumably because of the formation of 1,1-difluoroallene (**4**) via β-fluorine elimination from **2** [6], even though the reaction was performed by alternate addition of several aliquots of *n*-BuLi and carbonyl substrates at temperatures below –95 °C (Scheme 1). Further, Ichikawa overcame these difficulties using *sec*-BuLi instead of *n*-BuLi to improve the product yields, where the formation of **4** was suppressed, although this protocol required treatment using excess **1** and *sec*-BuLi at an even lower temperature (–105 °C) [7].



Scheme 1. Generation and reaction of thermally unstable **2**

Recently, Yoshida reported on the effective generation of **2** and its application to the reaction with carbonyl compounds at –78 °C in a flow microreactor system [8], which enables strict control of reaction temperature and time [9]. During our studies on the reactions of **2**, we found that its borylation proceeded effectively even at –50 °C in a flow system to afford 1-(trifluoromethyl)vinylboronic acid **5** (Scheme 2). Furthermore, the intermediary borate **6** successfully underwent the palladium-catalyzed coupling with aryl halides **7**, through the direct introduction of **6** into a batch system from a flow system, to provide α-(trifluoromethyl)styrenes **8** in high yields. This protocol is amenable to their large scale preparation (Scheme 2).



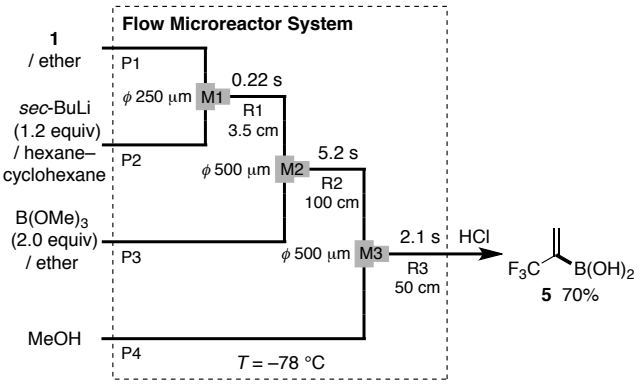
Scheme 2. Generation and borylation of **2** in a flow microreactor system and its application

2. Results and discussion

2.1. Lithiation and subsequent borylation starting from 2-bromo-3,3,3-trifluoroprop-1-ene

First, we tried the borylation of 1-(trifluoromethyl)vinyllithium **2** starting from 1-(trifluoromethyl)vinyl bromide **1** by using a flow microreactor system equipped with three T-shaped

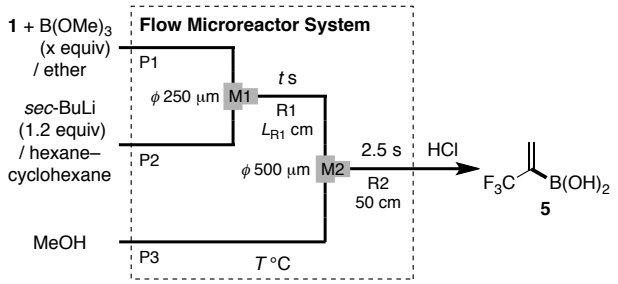
micromixers (M1: inner diameter ϕ = 250 μm; M2: ϕ = 500 μm; M3: ϕ = 500 μm), three microtube reactors (R1: inner diameter ϕ = 1.0 mm, length L = 3.5 cm, total flow rate = 7.5 mL min^{-1}; R2: ϕ = 1.0 mm, L = 100 cm, total flow rate = 9.0 mL min^{-1}; R3: ϕ = 1.0 mm, L = 50 cm, total flow rate = 11.0 mL min^{-1}), and four tube pre-cooling units (P1: inner diameter ϕ = 1.0 mm, length L = 50 cm; P2: ϕ = 1.0 mm, L = 150 cm; P3: ϕ = 1.0 mm, L = 50 cm; P4: ϕ = 1.0 mm, L = 50 cm) at –78 °C (Scheme 3). In this system, lithium–halogen exchange proceeded in M1/R1 to afford **2**, and subsequent borylation afforded borate **6** in M2/R2. Finally, boronic acid **5** was obtained by quenching with methanol followed by hydrolysis with aqueous HCl. The reaction using this system afforded boronic acid **5** in 70% yield.



Scheme 3. Preparation of **5** in a flow microreactor system equipped with three micromixers and three reactors

Next, we sought suitable conditions for borylation by using a premixed ether solution of 1-(trifluoromethyl)vinyl bromide **1** and $B(OMe)_3$ for the purpose of rapid mixing of 1-(trifluoromethyl)vinyllithium **2** with $B(OMe)_3$, using two micromixers (M1: ϕ = 250 μm; M2: ϕ = 500 μm), two reactors (R1: ϕ = 1.0 mm, $L = L_{R1}$ cm, total flow rate = 7.5 mL min^{-1}; R2: ϕ = 1.0 mm, L = 50 cm, total flow rate = 9.5 mL min^{-1}), and three pre-cooling units (P1: inner diameter ϕ = 1.0 mm, length L = 50 cm; P2: ϕ = 1.0 mm, L = 150 cm; P3: ϕ = 1.0 mm, L = 50 cm). The residence time for a lithium–bromine exchange process in R1 was first optimized in the presence of 1.0 equiv. of $B(OMe)_3$ at –78 °C

(Scheme 4, Figure 1). When the residence time was reduced to 0.22 s by using 3.5 cm reactor R1, the yield of boronic acid **5** increased to 55% (Table 1, entry 3). The use of 2.0 equiv. of $B(OMe)_3$ improved the yield of **5** to 79% (entry 4). Finally, raising the temperature to –50 °C afforded **5** in 81% yield (entry 5).



Scheme 4. Preparation of **5** in a flow microreactor system equipped with two micromixers and two reactors

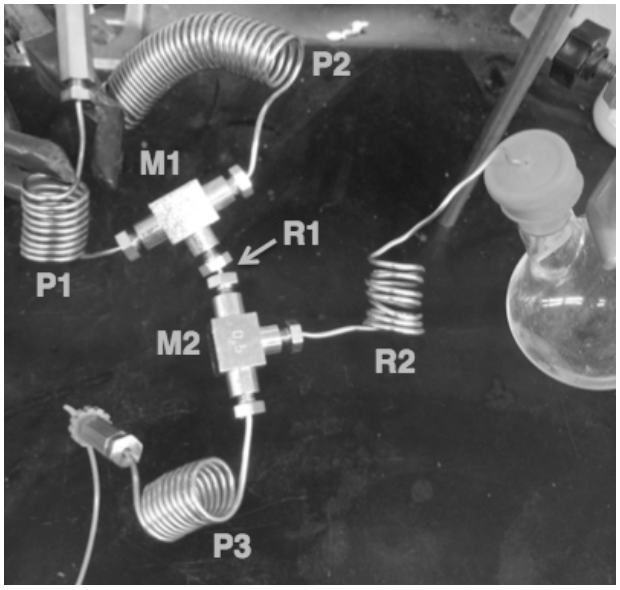


Figure 1. Flow microreactor system equipped with two micromixers and two reactors

Table 1. Screening of conditions for preparation of **5**

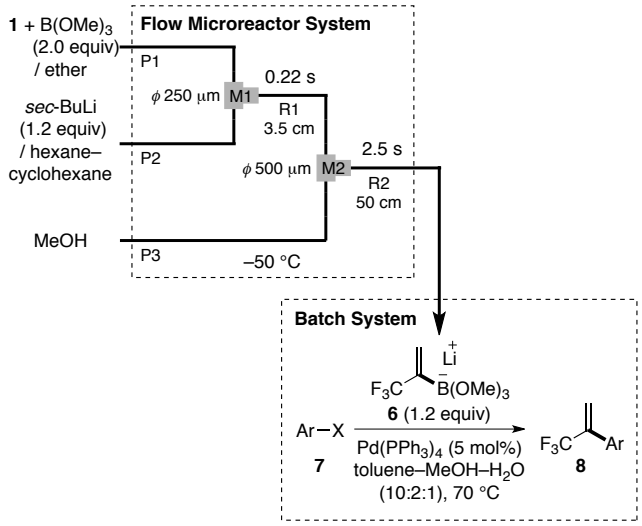
entry	t / L_{R1}	x (equiv)	T (°C)	**5** (%) [a]
1	6.3 s / 100 cm	1.0	–78	32
2	3.1 s / 50 cm	1.0	–78	42

3	0.22 s / 3.5 cm	1.0	–78	55
4	0.22 s / 3.5 cm	2.0	–78	79
5	0.22 s / 3.5 cm	2.0	–50	81
6	0.22 s / 3.5 cm	2.0	–41	71

[a] Yield was determined by ^{19}F NMR measurement using $PhCF_3$ as an internal standard.

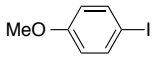
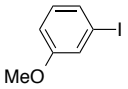
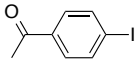
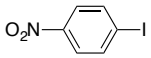
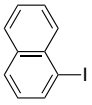
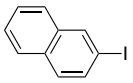
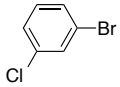
2.2. Direct Suzuki–Miyaura coupling using 1-(trifluoromethyl)vinylborate: Synthesis of α-(Trifluoromethyl)styrenes

With the optimized conditions for borylation of **1** in hand, borate **6** was directly used in the Suzuki–Miyaura coupling by transfer from a flow system to a batch system (Scheme 5). In the presence of 5 mol% of $Pd(PPh_3)_4$, treatment of aryl halides **7** with 1.2 equiv. of borate **6** successfully afforded the corresponding α-(trifluoromethyl)styrenes **8** (Table 2). This cross-coupling reaction proceeded without further addition of base, which is usually required for activating boronic acids or boronates in a typical Suzuki–Miyaura coupling, because borate **6** was already in an activated form. Aryl iodides **7a**–**7c** bearing a methoxy group effectively underwent coupling with **6** at 70 °C, regardless of the position of the substituent, to afford the corresponding styrenes **8a**–**8c** in 80%, 80%, and 82% yields, respectively (entries 1–3). Reactions of iodoarenes **7d**–**7f** bearing electron-withdrawing 4-acetyl, 4-nitro, and 3-fluoro substituents proceeded faster (entries 4–6). Both 1- and 2-iodonaphthalenes **7g** and **7h** participated in the reaction to afford the corresponding [1-(trifluoromethyl)vinyl]naphthalenes **8g** and **8h** in 85% and 82% yields, respectively (entries 7 and 8). In the case of 1-bromo-3-chlorobenzene (**7i**), the bromine substituent reacted exclusively to afford α-(trifluoromethyl)styrene **8i** bearing a chlorine substituent at the *meta* position in 78% yield (entry 9).



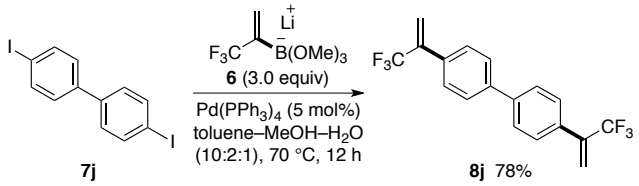
Scheme 5. Direct use of **6** for Pd-catalyzed coupling with **7**

Table 2. Synthesis of α-(trifluoromethyl)styrenes **8** via Pd-catalyzed coupling of **6** with **7**

entry	**7**		time (h)	**8** (yield %) [a]
1		**7a**	12	**8a** (80)
2		**7b**	14	**8b** (80)
3		**7c**	12	**8c** (82)
4		**7d**	7	**8d** (88)
5		**7e**	6	**8e** (69)
6		**7f**	6	**8f** (69)
7		**7g**	11	**8g** (85)
8		**7h**	6	**8h** (82)
9		**7i**	7	**8i** (78)

[a] Isolated yield.

In addition, this protocol enabled bis(trifluoromethyl)vinylation by using a diiodinated compound (Scheme 6). In the presence of a palladium catalyst, treatment of 4,4'-diiodobiphenyl (**7j**) with 3.0 equiv. of borate **6**, generated by a flow microreactor system, afforded **8j** in 78% yield as a sole coupling product.



Scheme 6. Bis(trifluoromethyl)vinylation of **7j** with **6**

3. Conclusion

We demonstrated an efficient method for borylation of 2-bromo-3,3,3-trifluoroprop-1-ene via lithiation and subsequent transmetalation in a flow microreactor system equipped with two micromixers and two reactors at –50 °C. Furthermore, we also succeeded in the Suzuki–Miyaura coupling with a broad substrate scope by using the resulting borate without further addition of base. This protocol would enable the mass production of α-(trifluoromethyl)styrenes, which serve as key intermediates for pharmaceuticals, agrochemicals, and functional polymers.

4. Experimental

4.1. General

^{1}H NMR, ^{13}C NMR, and ^{19}F NMR were recorded on a Bruker Avance 500 or a JEOL ECS-400 spectrometer. Chemical shift values are given in ppm relative to internal Me_4Si (for ^{1}H NMR: δ = 0.00 ppm), $CDCl_3$ (for ^{13}C NMR: δ = 77.0 ppm), and C_6F_6 (for ^{19}F NMR: δ = 0.0 ppm). IR spectra were

recorded on a Horiba FT-300S spectrometer by the attenuated total reflectance (ATR) method. Mass spectra were measured on a JEOL JMS-T100GCV spectrometer.

Column chromatography and preparative thin-layer chromatography were conducted on silica gel (Silica Gel 60 N, Kanto Chemical Co., Inc. for column chromatography and Wakogel B-5F, Wako Pure Chemical Industries, Ltd. for PTLC). Diethyl ether, hexane, and toluene were purified by a solvent-purification system (GlassContour) equipped with columns of activated alumina and supported-copper catalyst (Q-5) before use. Methanol was distilled from Mg and I_2 and stored over activated molecular sieves 3A. Unless otherwise noted, materials were obtained from commercial sources and used directly without further purifications.

Stainless steel (SUS304) T-shaped micromixers with inner diameter of 250 or 500 μm were manufactured by Sanko Seiki Co., Inc. Stainless steel (SUS316) microtube reactors with inner diameter of 1000 μm purchased from GL Sciences were used. The micromixers and microtube reactors were connected with stainless steel fittings (GL Sciences Inc., 1/16 OUW). The flow microreactor system was dipped in a cooling bath to control the temperature. Solutions were introduced to the flow microreactor system using syringe pumps, YMC-301, equipped with gastight syringes purchased from SGE Analytical Science Pty. Ltd.

*4.2. Preparation of 1-(trifluoromethyl)vinylboronic acid **5***

*4.2.1. Experimental procedure for preparation of 1-(trifluoromethyl)vinylboronic acid **5***

A flow microreactor system consisting of two T-shaped micromixers (M1: ϕ = 250 μm; M2: ϕ = 500 μm), two microtube reactors (R1: ϕ = 1.0 mm, L = 3.5 cm; R2: ϕ = 1.0 mm, L = 50 cm), and three tube pre-cooling units (P1: inner diameter ϕ = 1.0 mm, length L = 50 cm; P2: ϕ = 1.0 mm, L = 150 cm; P3: ϕ = 1.0 mm, L = 50 cm) was used. A Et_2O solution of 2-bromo-3,3,3-trifluoroprop-1-ene (**1**) and trimethoxyborane (0.10 M and 0.20 M, respectively, flow rate: 6.0 mL min^{-1}) and a hexane/cyclohexane (45:55) solution of *sec*-BuLi (0.48 M, flow rate: 1.5 mL min^{-1}) were introduced to M1 by syringe pumps.

The resulting solution was passed through R1 (t = 0.22 s) and was mixed with methanol (flow rate: 2.0 mL min^{-1}) in M2. The resulting solution was passed through R2 (t = 2.6 s). After a steady state was reached, the product solution was directly poured into aqueous HCl solution (2 M, 1 mL) for 30 s. The reaction mixture was analyzed by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard (81%).

*4.2.2. Spectral data of (3,3,3-trifluoroprop-1-en-2-yl)boronic acid (**5**)*

^{19}F NMR (470 MHz, C_6D_6) δ 98.4 (s). The NMR spectral data described above showed good agreement with the literature data [2b].

*4.3. Synthesis of α-(trifluoromethyl)styrenes **8** via the Suzuki–Miyaura coupling of borate **6** with aryl halides **7***

*4.3.1. Typical procedure for the synthesis of α-(trifluoromethyl)styrenes **8***

A flow microreactor system consisting of two T-shaped micromixers (M1: ϕ = 250 μm; M2: ϕ = 500 μm), two microtube reactors (R1: ϕ = 1.0 mm, L = 3.5 cm; R2: ϕ = 1.0 mm, L = 50 cm), and three tube pre-cooling units (P1: inner diameter ϕ = 1.0 mm, length L = 50 cm; P2: ϕ = 1.0 mm, L = 150 cm; P3: ϕ = 1.0 mm, L = 50 cm) was used. A Et_2O solution of 2-bromo-3,3,3-trifluoroprop-1-ene (**1**) and trimethoxyborane (0.10 M and 0.20 M, respectively, flow rate: 6.0 mL min^{-1}) and a hexane/cyclohexane (45:55) solution of *sec*-BuLi (0.48 M, flow rate: 1.5 mL min^{-1}) were introduced to M1 by syringe pumps. The resulting solution was passed through R1 (t = 0.22 s) and was mixed with methanol (flow rate: 2.0 mL min^{-1}) in M2. The resulting solution was passed through R2 (t = 2.6 s). After a steady state was reached, the product solution of borate **6** was directly poured into aqueous HCl solution (2 M). The concentration of the solution of **6** was determined by analyzing the resulting solution of boronic acid **5** using ^{19}F NMR spectroscopy.

Another aliquot of solution of **6** (0.18 mmol) was collected into a 2-necked flask. The solvent was removed under reduced pressure (30 mmHg). To the residue were added $Pd(PPh_3)_4$ (8.7 mg, 7.5

μmol), 2-iodonaphthalene **7h** (38 mg, 0.15 mmol), toluene (5.0 mL), and H_2O (0.5 mL). After stirring at 70 °C for 6 h, the reaction was quenched with saturated aqueous NH_4Cl (3 mL). The organic materials were extracted with diethyl ether for three times. The combined organic extracts were washed with brine and dried over Na_2SO_4. After the solvent was removed under reduced pressure, residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1) to give 2-(3,3,3-trifluoroprop-1-en-2-yl)naphthalene (**8h**, 27 mg, 82%) as a colorless liquid.

*4.3.2. Spectral data of α-(trifluoromethyl)styrenes **8***

*4.3.2.1. 1-Methoxy-4-(3,3,3-trifluoroprop-1-en-2-yl)benzene (**8a**)*

80% yield, a colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.83 (s, 3H), 5.70 (s, 1H), 5.86 (s, 1H), 6.91 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$): δ 98.1 (s, 3F). The NMR spectral data described above showed good agreement with the literature data [3b].

*4.3.2.2. 1-Methoxy-3-(3,3,3-trifluoroprop-1-en-2-yl)benzene (**8b**)*

80% yield, a colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.82 (s, 3H), 5.77 (s, 1H), 5.95 (s, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.98 (s, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 7.33 (dd, *J* = 8.0, 8.0 Hz, 1H). ^{9}F NMR (470 MHz, $CDCl_3$): δ 98.3(s, 3F). The NMR spectral data described above showed good agreement with the literature data [3b].

*4.3.2.3. 1-Methoxy-2-(3,3,3-trifluoroprop-1-en-2-yl)benzene (**8c**)*

82% yield, a colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.82 (s, 3H), 5.64 (s, 1H), 6.08 (s, 1H), 6.93–6.98 (m, 2H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.33 (d, *J* = 7.6 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ 97.3 (s, 3F). The NMR spectral data described above showed good agreement with the literature data [3b].

*4.3.2.4. 1-[4-(3,3,3-Trifluoroprop-1-en-2-yl)phenyl]ethan-1-one (**8d**)*

88% yield, a pale yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.63 (s, 3H), 5.88 (s, 1H), 6.06 (s, 1H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.98 (d, *J* = 8.0 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$): δ 98.5 (s, 3F). The NMR spectral data described above showed good agreement with the literature data [2a].

*4.3.2.5. 1-Nitro-4-(3,3,3-trifluoroprop-1-en-2-yl)benzene (**8e**)*

69% yield, a pale yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.93 (s, 1H), 6.15 (s, 1H), 7.64 (d, *J* = 8.8 Hz, 2H), 8.26 (d, *J* = 8.8 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$): δ 98.4 (s, 3F). The NMR spectral data described above showed good agreement with the literature data [2a].

*4.3.2.6. 1-Fluoro-3-(3,3,3-trifluoroprop-1-en-2-yl)benzene (**8f**)*

69% yield, a colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.80 (s, 1H), 5.99 (s, 1H), 7.07–7.11 (m, 1H), 7.17 (d, *J* = 8.4 Hz, 1H), 7.22 (s, 1H), 7.32–7.38 (m, 1H). The NMR spectral data described above showed good agreement with the literature data [10].

*4.3.2.7. 1-(3,3,3-Trifluoroprop-1-en-2-yl)naphthalene (**8g**)*

85% yield, a colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.66 (s, 1H), 6.33 (s, 1H), 7.42–7.52 (m, 4H), 7.86–7.94 (m, 3H). ^{19}F NMR (470 MHz, $CDCl_3$): δ 96.2 (s, 3F). The NMR spectral data described above showed good agreement with the literature data [2a,3a].

*4.3.2.8. 2-(3,3,3-Trifluoroprop-1-en-2-yl)naphthalene (**8h**)*

82% yield, a colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90 (s, 1H), 6.04 (s, 1H), 7.50–7.52 (m, 2H), 7.56 (d, *J* = 8.8 Hz, 1H), 7.86 (d, *J* = 8.8 Hz, 3H), 7.94 (s, 1H). ^{19}F NMR (470 MHz, $CDCl_3$): δ

98.4 (s, 3F). The NMR spectral data described above showed good agreement with the literature data [2a].

*4.3.2.9. 1-Chloro-4-(3,3,3-trifluoroprop-1-en-2-yl)benzene (**8i**)*

78% yield, a colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.79 (s, 1H), 6.00 (s, 1H), 7.29–7.32 (m, 1H), 7.35–7.40 (m, 2H), 7.44 (s, 1H). ^{19}F NMR (470 MHz, $CDCl_3$): δ 98.1 (s, 3F). The NMR spectral data described above showed good agreement with the literature data [3a,10].

*4.3.2.10. 1,4-Bis(3,3,3-trifluoroprop-1-en-2-yl)benzene (**8j**)*

78% yield, a white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.83 (d, J = 1.6 Hz, 2H), 5.99 (d, J = 1.6 Hz, 2H), 7.55 (d, J = 8.4 Hz, 4H), 7.62 (d, J = 8.4 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 120.4 (q, J_{CF} = 6 Hz), 123.3 (q, J_{CF} = 273 Hz), 127.2, 127.9, 132.9, 138.5 (q, J_{CF} = 30 Hz), 140.8. ^{19}F NMR (376 MHz, $CDCl_3$): δ 98.3 (s). IR (neat): 1354, 1194, 1167, 1120, 1082, 953, 827, 766 cm^{-1}. HRMS (EI+): *m/z* Calcd for $C_{18}H_{12}F_6$ $[M]^+$: 342.0843; Found: 342.0845.

Acknowledgments

This work was financially supported by JSPS KAKENHI Grant Number JP16H04105 in Grant-in-Aid for Scientific Research (B) (J.I.), JSPS KAKENHI Grant Number JP16H01002 in Precisely Designed Catalysts with Customized Scaffolding (J.I.), and JSPS KAKENHI Grant Number JP16K20939 in Grant-in-Aid for Young Scientists (B) (T.F.). We acknowledge Tosoh Finechem Co. for a generous gift of 2-bromo-3,3,3-trifluoroprop-1-ene.

References

[1] For reviews on transformations of 1-(trifluoromethyl)vinyl compounds, see:
(a) H. Amii, K. Uneyama, Chem. Rev. 109 (2009) 2119–2183.
(b) J. Ichikawa, J. Synth. Org. Chem. Jpn. 68 (2010) 1175–1184.

(c) T. Ahrens, J. Kohlmann, M. Ahrens, T. Braun, Chem. Rev. 115 (2015) 931–972.

(d) T. Unzner, T. Magauer, Tetrahedron Lett. 56 (2015) 877–883.

(e) Q. Shen, Y.-G. Huang, C. Liu, J.-C. Xiao, Q.-Y. Chen, Y. Guo, J. Fluorine Chem. 179 (2015) 14–22.

(f) X. Zhang, S. Cao, Tetrahedron Lett. 58 (2017) 375–392.

[2] (a) B. Jiang, Y. Xu, J. Org. Chem. 56 (1991) 7336–7340.

(b) B. Jiang, Q.-F. Wang, C.-G. Yang, M. Xu, Tetrahedron Lett. 42 (2001) 4083–4085.

(c) S. B. Lang, R. J. Wiles, C. B. Kelly, G. A. Molander, Angew. Chem. Int. Ed. 56 (2017) 15073–15077.

[3] (a) R.-q. Pan, X.-x. Liu, M.-z. Deng, J. Fluorine Chem. 95 (1999) 167–170.

(b) O. Kobayashi, D. Uraguchi, T. Yamakawa, J. Mol. Catal. A: Chem. 258 (2009) 7–10.

(c) O. Kobayashi, D. Uraguchi, T. Yamakawa, J. Fluorine Chem. 130 (2009) 591–594.

(d) J. Walkowiak, T. M. del Campo, B. Ameduri, V. Gouveneur, Synthesis (2010) 183–1890.

For most recent reports on palladium-catalyzed trifluoromethylvinylation using 2-bromo-3,3,3-trifluoroprop-1-ene via C–H bond functionalization, see:

(e) Q. Zhao, T. Besset, T. Poisson, J.-P. Bouillon, X. Pannecoucke, Eur. J. Org. Chem. (2016) 76–82.

(f) Q. Zhao, V. Tognetti, L. Joubert, T. Besset, X. Pannecoucke, J.-P. Bouillon, T. Poisson, Org. Lett. 19 (2017) 2106–2109.

[4] 1-(Trifluoromethyl)vinylboronic acid was prepared via the reaction of 1-(trifluoromethyl)vinylmagnesium bromide generated in situ with trimethyl borate (see ref. 2b). We modified this protocol to increase reproducibility. See: T. Mori, J. Ichikawa, Chem. Lett. 33 (2004) 1206–1207.

[5] F. G. Drakesmith, O. J. Stewart, P. Tarrant, J. Org. Chem. 33 (1968) 280–285.

[6] (a) W. R. Dolbier, Jr., C. R. Burkholder, C. A. Piedrahita, J. Fluorine Chem. 20 (1982) 637–647.

(b) D. Ristic-Petrovic, D. J. Anderson, J. R. Torkelson, M. J. Ferguson, R. McDonald, M. Cowie, Organometallics 24 (2005) 3711–3724.

(c) T. Fujita, S. Sanada, Y. Chiba, K. Sugiyama, J. Ichikawa, Org. Lett. 16 (2014) 1398–1401.

[7] (a) R. Nadano, J. Ichikawa, Synthesis (2006) 128–132.

(b) R. Nadano, J. Ichikawa, Chem. Lett. 36 (2007) 22–23.

(c) R. Nadano, K. Fuchibe, M. Ikeda, H. Takahashi, J. Ichikawa, Chem. Asian J. 5 (2010) 1875–1883.

[8] A. Nagaki, S. Tokuoka, J. Yoshida, Chem. Commun. 50 (2014) 15079–15081.

[9] For recent reviews on flow microreactor synthesis, see:

(a) D. T. McQuade, P. H. Seeberger, J. Org. Chem. 78 (2013) 6384–6389.
(b) K. S. Elvira, X. C. Solvas, R. C. R Wootton, A. J. DeMello, Nat. Chem. 5 (2013) 905–915.
(c) J. C. Pastre, D. L. Browne, S. V. Ley, Chem. Soc. Rev. 42 (2013) 8849–8869.
(d) I. R. Baxendale, J. Chem. Technol. Biotechnol. 88 (2013) 519–552.
(e) J. Yoshida, A. Nagaki, D. Yamada, Drug Discovery Today Technol. 10 (2013) e53–e59.
(f) H. Amii, A. Nagaki, J. Yoshida, Beilstein J. Org. Chem. 9 (2013) 2793–2802.
(g) T. Fukuyama, T. Totoki, I. Ryu, Green Chem. 16 (2014) 2042–2050.
[10] T. Fujita, M. Takazawa, K. Sugiyama, N. Suzuki, J. Ichikawa, Org. Lett. 19 (2017) 588–591.