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Radical Addition of Polyhaloalkanes to 2-Ethynyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

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Radical addition of bromotrichloromethane to 2-ethynyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane takes place in the presence of a radical initiator in refluxing benzene. Perfluoroalkyl iodides undergo similar addition reactions. The addition reactions proceed in an anti fashion. The corresponding 1-halo-1-alkenylboronic esters are useful intermediates that undergo cross-coupling reactions.

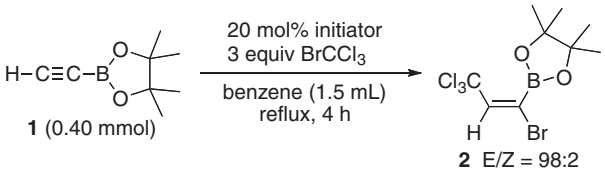
Radical addition of polyhaloalkanes to alkynes is an important reaction for the synthesis of alkenyl halides.[1] We envisioned that similar radical addition to an ethynylboronic ester would yield 1-halo-1-alkenylboronic esters, which would serve as useful building blocks in organic synthesis.[2] In the literature,[3] radical addition reactions of polyhaloalkanes to bis(diisopropylamino)(ethynyl)borane or dibutoxy(ethynyl)-borane have been reported. However, the starting borane and the product were sensitive to moisture. Here we report the use of 2-ethynyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane[4] (**1**) as a radical acceptor that is stable and easy to handle.

Radical addition of bromotrichloromethane to **1** proceeded in the presence of a radical initiator in refluxing benzene (Table 1). Thermally degradable dilauroyl peroxide (DLP), α,α-azobis(isobutyronitrile) (AIBN), and α,α-azobis(cyclohexanecarbonitrile) (ACCN) were effective.[5] Among them, ACCN was the best initiator (Entry 3), although the difference of the efficiency of the initiators was small. A prolonged reaction time improved the yield of **2** (Entry 4). The reactions yielded **2** with high regio- and stereoselectivities and were likely to proceed in an anti fashion predominantly to yield the E isomer with excellent selectivity (vide infra).

Radical addition of tridecafluorohexyl iodide with the aid of DLP did not proceed in refluxing benzene or chlorobenzene at 80 °C (Table 2, Entry 1). The reaction required an elevated temperature as high as 132 °C (Entry 2). Di-*t*-butyl peroxide (DBP) is known to be a suitable initiator at such a high temperature.[5] DBP initiated the reaction as efficiently as DLP without significant improvement (Entry 3). Benzoyl peroxide (BPO) proved to be more efficient (Entry 4). However, a higher loading of BPO resulted in a lower yield of **3a** (Entry 5). We envisaged that the rate of the homolysis of BPO would be too rapid at the high temperature and that the BPO added was consumed within 1.5 h. We thus performed the reaction for 3 h, charging 20 mol % of BPO twice at the beginning and after 1.5 h (Entry 6). Gratifyingly, the reaction afforded **3a** in 84% yield. The regio- and stereoselectivities of the reactions were perfect, providing **3a** as a sole isomer. Other primary perfluoroalkyl iodides reacted with **1** as smoothly as tridecafluorohexyl iodide (Entries 7–10). However, secondary heptafluoroisopropyl iodide was less reactive, and even with a larger amount of the starting iodide, the reaction afforded **3f** in moderate yield (Entry 11). Unfortunately, attempts to employ tetrachloromethane and tetrabromomethane failed.

Attempted radical addition to internal alkynylboronic esters, including phenylethynyl- and 1-octynylboronic esters, resulted in failure. Other active organic halides such as benzyl iodoacetate, diethyl bromomalonate, and α-iodo-γ-butyrolactone were far less reactive, and virtually no reactions with **1** took place.

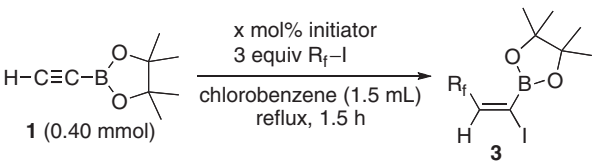
Table 1. Radical Addition of Bromotrichloromethane to **1**



Entry	Initiator	Yield/%
1	DLP	66
2	AIBN	62
3	ACCN	70
4	ACCN	82[a)]

a) Performed for 7 h.

Table 2. Radical Addition of Perfluoroalkyl Iodides to **1**



Entry	Initiator	x/mol %	R_f	**3**	Yield/%
1	DLP	20	C_6F_{13}	**3a**	0[a)]
2	DLP	20	C_6F_{13}	**3a**	44
3	DBP	20	C_6F_{13}	**3a**	47
4	BPO	20	C_6F_{13}	**3a**	72
5	BPO	30	C_6F_{13}	**3a**	55
6	BPO	20 + 20[b)]	C_6F_{13}	**3a**	84
7	BPO	20 + 20[b)]	C_4F_9	**3b**	78
8	BPO	20 + 20[b)]	C_8F_{17}	**3c**	79
9	BPO	20 + 20[b)]	C_3F_7	**3d**	72
10	BPO	20 + 20[b)]	$C_{10}F_{21}$	**3e**	77
11	BPO	20 + 20[b)]	i-C_3F_7[c)]	**3f**	55

a) Performed in refluxing benzene or chlorobenzene at 80 °C. b) Performed for 3 h. See Experimental Section. c) 6 equiv of i-C_3F_7I was used.

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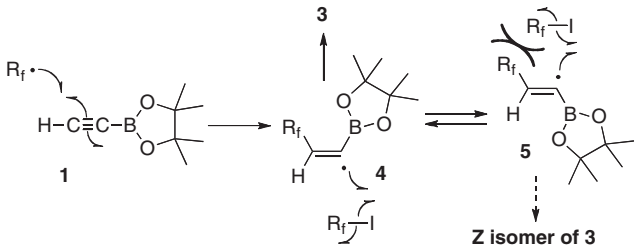
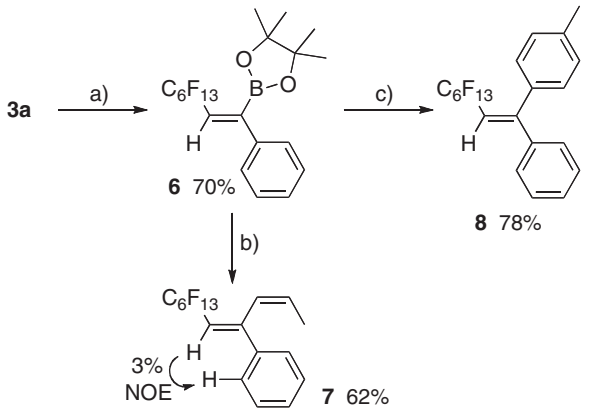


Scheme 1. Rationale of regio- and stereoselectivities.



Scheme 2. Use of **3a** in cross-coupling reactions. a) 5 mol % $Pd(PPh_3)_4$, 2 equiv PhZnCl, THF, 25 °C, 6 h; b) 10 mol % $Pd(PPh_3)_4$, 5 equiv (*Z*)-1-bromopropene, 2 equiv K_3PO_4, benzene/methanol = 20:1, 60 °C, 2 h; c) 10 mol % $Pd(PPh_3)_4$, 5 equiv 4-bromotoluene, 2 equiv K_2CO_3, benzene/methanol = 20:1, 60 °C, 21 h.

The regio- and stereoselectivity are controlled according to the conventional rules for radical addition reactions (Scheme 1).[3a,6] The radical addition of polyhaloalkyl radical to **1** occurs at the less hindered terminal carbon. The subsequent halogen abstraction proceeds mainly from radical **4** since polyhaloalkyl iodide could approach **4** more efficiently than it does radical **5**.

The products are useful intermediates that undergo cross-coupling reactions. For instance, treatment of **3a** with phenylzinc chloride under palladium catalysis afforded the corresponding α-borylstyrene derivative **6** in good yield (Scheme 2).[7] Alkenylboron compound **6** reacted with (*Z*)-1-bromopropene or 4-bromotoluene in the presence of a base and a catalytic amount of tetrakis(triphenylphosphine)palladium to provide the corresponding cross-coupling product **7** or **8** in good yield.[8] The NOE analysis of **7** verified the stereochemistry of **3** as well as **7** itself, given that the sequential cross-coupling reactions proceeded with retention of configuration.[9]

In summary, 2-ethynyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane serves as a good radical acceptor in radical addition reactions of polyhaloalkanes. The adducts are useful intermediates for the synthesis of multisubstituted alkenes.

Experimental

Instrumentation and Chemicals. ^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra were taken on a Varian UNITY INOVA 500 spectrometer and were obtained in $CDCl_3$ with tetramethylsilane as an internal standard. IR spectra were determined on a SHIMADZU FTIR-8200PC spectrometer. Elemental analyses were carried out at the Elemental Analysis Center of Kyoto University. Mass spectra were determined on a JEOL MStation 700 spectrometer. TLC analyses were performed on commercial glass plates bearing a 0.25-mm layer of Merck Silica gel $60F_{254}$. Silica gel (Wakogel C-200) or neutral silica gel (Kanto Chemical, silica gel 60N) was used for column chromatography.

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Boronic ester **1** was prepared according to the literature.[4c] Benzene was stored over slices of sodium. THF was purchased from Kanto Chemical Co., stored under argon, and used as is. Zinc chloride was purchased from Wako Pure Chemicals and was handled in a glove box under argon. Tetrakis(triphenylphosphine)palladium was obtained from Kanto Chemical Co., and stored under argon.

Addition of Bromotrichloromethane. Under argon, 2-ethynyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**1**, 61 mg, 0.40 mmol), bromotrichloromethane (0.24 g, 1.2 mmol), and ACCN (20 mg, 0.08 mmol) were dissolved in benzene (1.5 mL) in a reaction flask. The mixture was heated at reflux for 7 h. After the mixture was cooled to ambient temperature, the solvent was removed under reduced pressure. Chromatographic purification on neutral silica gel (hexane/ethyl acetate = 30:1) by using a dry ice/acetone-jacketed chromatographic column afforded **2** in 82% yield (0.11 g, 0.33 mmol).

Addition of Perfluoroalkyl Iodide. Under argon, 2-ethynyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**1**, 61 mg, 0.40 mmol), tridecafluorohexyl iodide (0.54 g, 1.2 mmol), and BPO (19 mg, 0.08 mmol) were dissolved in chlorobenzene (1.5 mL) in a reaction flask. The mixture was heated at reflux for 1.5 h. After the mixture was cooled to room temperature, an additional BPO (19 mg, 0.08 mmol) was added. The mixture was stirred at reflux for an additional 1.5 h. The solvent was removed under reduced pressure. Chromatographic purification on neutral silica gel (hexane/ethyl acetate = 30:1) by using a dry ice/acetone-jacketed chromatographic column afforded **2** in 84% yield (0.20 g, 0.34 mmol).

Cross-Coupling Reaction of 3a. Phenyllithium in cyclohexane–diethyl ether (1.09 M, 1.8 mL, 2.0 mmol) was added to a solution of zinc chloride (0.33 g, 2.40 mmol) in THF (3.5 mL) at 0 °C under argon. The mixture was stirred for 15 min at room temperature. The phenylzinc reagent prepared above was then added to a solution of **3a** (0.60 g, 1.00 mmol) and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) in THF (0.5 mL) at 0 °C under argon. The mixture was stirred at room temperature for 6 h. The reaction was quenched with aqueous ammonium chloride solution and extracted with ethyl acetate. After removal of the solvent, the residue was chromatographed (eluted with hexane/ethyl acetate = 20:1) on neutral silica gel to give **6** in 70% yield (0.38 g, 0.70 mmol).

Cross-Coupling Reaction of 6. Under argon, **6** (0.11 g, 0.20 mmol), 4-bromotoluene (0.17 g, 1.00 mmol), potassium carbonate (55 mg, 0.40 mmol), and $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) were dissolved in benzene (2.0 mL) and methanol (0.1 mL) in a reaction flask. The mixture was heated at 60 °C for 21 h. The reaction was quenched with water, and the product was extracted with ethyl acetate. After the solvent was removed, the residue was chromatographed (eluted with hexane) on silica gel to afford **8** in 78% yield (80 mg, 0.16 mmol).

(*E*)-2-(1-Bromo-3,3,3-trichloro-1-propenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2): IR (neat): 2984, 1635, 1496, 1384, 1240, 854, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.31 (s, 12H), 7.05 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 24.31, 85.19, 93.17, 144.00. HRMS

(FAB): Found: 348.9345 [(M + H)$^+$]; Calcd for $C_9H_{14}{}^{11}B^{79}Br^{35}Cl_3O_2$: 348.9336.

(*E*)-2-(3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluoro-1-iodo-1-octenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3a): IR (neat): 2984, 1683, 1652, 1363, 1241, 1145, 850, 709 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.29 (s, 12H), 6.84 (t, $J = 12.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 24.06, 85.27, 134.80 (t, $J = 22.9$ Hz). HRMS (EI): Found: 597.9853; Calcd for $C_{14}H_{13}{}^{11}BF_{13}IO_2$: 597.9846.

(*E*)-2-(3,3,4,4,5,5,6,6,6-Nonafluoro-1-iodo-1-hexenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3b): IR (neat): 2985, 1636, 1368, 1236, 1135, 850, 746 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.30 (s, 12H), 6.84 (t, $J = 12.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 24.12, 85.29, 134.72 (t, $J = 22.5$ Hz). HRMS (FAB): Found: 498.0015 [(M + H)$^+$]; Calcd for $C_{12}H_{14}{}^{10}BF_9IO_2$: 498.9988.

(*E*)-2-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluoro-1-iodo-1-decenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3c): IR (neat): 2985, 1640, 1384, 1368, 1343, 1243, 1212, 1147, 966, 852 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.30 (s, 12H), 6.85 (t, $J = 12.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 24.12, 85.29, 134.84 (t, $J = 22.4$ Hz). HRMS (FAB): Found: 698.9842 [M]; Calcd for $C_{16}H_{13}{}^{11}BF_{17}IO_2$: 698.9860.

(*E*)-2-(3,3,4,4,5,5,5-Heptafluoro-1-iodo-1-pentenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3d): IR (neat): 2985, 1639, 1383, 1367, 1351, 1229, 1178, 1142, 1118, 965, 851 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.30 (s, 12H), 6.84 (t, $J = 12.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 24.13, 85.29, 134.60 (t, $J = 23.0$ Hz). HRMS (FAB): Found: 447.9955; Calcd for $C_{11}H_{13}{}^{11}BF_7IO_2$: 447.9942.

(*E*)-2-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-Henicosafluoro-1-iodo-1-dodecenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3e): IR (nujol): 2953, 1635, 1376, 1366, 1339, 1243, 1151, 1141, 1117, 965, 846 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.30 (s, 12H), 6.85 (t, $J = 12.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 24.11, 85.28, 134.84 (t, $J = 23.4$ Hz); Anal. Found: C, 27.22; H, 1.36%. Calcd for $C_{18}H_{13}BF_{21}IO_2$: C, 27.09; H, 1.64%.

(*E*)-2-(3,4,4,4-Tetrafluoro-1-iodo-3-trifluoromethyl-1-butenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3f): IR (neat): 2984, 1652, 1637, 1473, 1374, 1302, 1228, 983 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.30 (s, 12H), 6.74 (d, $J = 22.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 24.10, 85.13, 131.41 (d, $J = 15.3$ Hz). HRMS (FAB): Found: 446.9965; Calcd for $C_{11}H_{13}{}^{10}BF_7IO_2$: 446.9978.

(*E*)-2-(3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluoro-1-phenyl-1-octenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6): IR (neat): 2984, 1496, 1412, 1112, 971, 854, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.33 (s, 12H), 6.13 (t, $J = 14.0$ Hz, 1H), 7.33–7.43 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 24.65, 84.80, 122.42 (t, $J = 22.0$ Hz), 126.84, 128.84, 128.92, 138.74. Anal. Found: C, 43.60; H, 3.25%. Calcd for $C_{20}H_{18}BF_{13}O_2$: C, 43.82; H, 3.31%.

(2*Z*,4*E*)-6,6,7,7,8,8,9,9,10,10,11,11,11-Tridecafluoro-4-phenyl-2,4-undecadiene (7): IR (neat): 3034, 1642, 1609, 1448, 1364, 1201, 1144, 848 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.37 (d, $J = 7.5$ Hz, 3H), 5.80 (t, $J = 15.0$ Hz, 1H), 5.92 (dq, $J = 11.5$, 7.5 Hz, 1H), 6.41 (d, $J = 11.5$ Hz, 1H), 7.35–7.45 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 15.30, 113.71 (t, $J = 22.0$ Hz), 125.09, 127.29, 128.66, 129.16, 132.28, 139.98, 150.40. HRMS (EI): Found: 462.0660; Calcd for $C_{17}H_{11}F_{13}$: 462.0653.

(*Z*)-3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluoro-1-(4-methylphenyl)-1-phenyl-1-octene (8): IR (neat): 3030, 1635, 1448, 1240, 1202, 1052, 824 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.40 (s, 3H), 6.06 (t, $J = 15.0$ Hz, 1H), 7.13 (d, $J = 8.0$ Hz, 2H), 7.19 (d, $J = 8.0$ Hz, 2H), 7.23–7.28 (m, 2H), 7.31–7.40 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 21.28, 112.46 (t, $J = 20.6$ Hz), 127.99, 128.44, 128.55, 129.00, 129.41, 134.55, 138.24, 141.07, 154.56; Anal. Found: C, 49.05; H, 2.80%. Calcd for $C_{21}H_{13}F_{13}$: C, 49.23; H, 2.56%.

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5 Ten hour half-life temperatures: DLP, 62 °C; AIBN, 65 °C; BPO, 74 °C; ACCN, 88 °C; DBP, 124 °C.

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7 The use of an excess amount of organozinc reagents is not a special case. For instance, see reference 2c.

8 The reason for the necessity of the excess organic halides is not clear. The reaction with 3 equiv of (*Z*)-1-bromopropene or 4-bromotoluene provided **7** or **8** in 42% or 53% yield, respectively.

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