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Copper-Catalyzed Regioselective Monodefluoroborylation of Polyfluoroalkenes en Route to Diverse Fluoroalkenes

Hironobu Sakaguchi,[†,§] Yuta Uetake,[‡,§] Masato Ohashi,[†] Takashi Niwa,*[,‡] Sensuke Ogoshi,*[,†] and Takamitsu Hosoya*[,‡,¶]

[†]Department of Applied Chemistry, Faculty of Engineering, Osaka University, 2-1 Yamada-oka, Suita, Osaka 565-0871, Japan

[‡]Chemical Biology Team, Division of Bio-Function Dynamic Imaging, RIKEN Center for Life Science Technologies (CLST), 6-7-3 Minatojima-minamimachi, Chuo-ku, Kobe 650-0047, Japan

[¶]Laboratory of Chemical Bioscience, Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University (TMDU), 2-3-10 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-0062, Japan

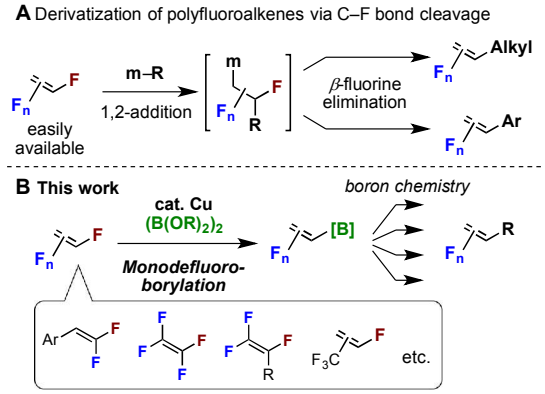
ABSTRACT: Monodefluoroborylation of polyfluoroalkenes has been achieved in a regioselective manner under mild conditions via copper catalysis. The method has showed an extremely broad scope of substrates, including (difluorovinyl)arenes, tetrafluoroethylene (TFE), (trifluorovinyl)arenes, and trifluoromethylated monofluoroalkenes. The choice of boron source was important for the efficient transformation of (difluorovinyl)arenes; $(Bpin)_2$ was suitable for substrates with an electron-deficient aryl group and $(Bnep)_2$ for those with an electron-rich aryl group. Derivatization of the (fluoroalkenyl)boronic acid esters to the corresponding potassium trifluoroborate salts has rendered the products easily isolable, which greatly improved the synthetic practicality of the monodefluoroborylation reaction. Stoichiometric experiments indicate that the fate of the regioselectivity depends on the mode of β-fluorine elimination, which depends on the substrate. Further transformation of the boryl group has allowed facile preparation of fluoroalkene derivatives as exemplified by the synthesis of a fluoroalkene mimic of atorvastatin, which potently inhibited the enzyme activity of HMG-CoA reductase.

INTRODUCTION

Organofluorine molecules have been widely applied in various research fields because of the unique properties of fluorine atoms.[1] In particular, fluoroalkenes have attracted considerable interest from medicinal chemists because fluoroalkene units are structurally similar to amide bonds. Fluoroalkene mimics of bioactive amides have been prepared to improve the pharmaceutical properties such as bioactivity, target specificity, and metabolic stability of the bioactive amides.[2] Highly fluorinated alkenes are also gaining much attention as promising monomers for preparing fluorine-containing polymers.[3] Nevertheless, only a limited range of fluoroalkenes can be prepared by the conventional methods,[4] and thus, a novel method that allows for the synthesis of diverse fluoroalkene derivatives is eagerly anticipated.

One of the most efficient approaches to fabricate fluoroalkenes is functionalization of highly fluorinated alkenes via C–F bond cleavage (Scheme 1A). This type of transformation has been achieved via 1,2-addition of organometallic species followed by β-fluorine elimination of the resulting fluoroethyl metal intermediates. For this purpose, strong nucleophiles such as organolithium or organomagnesium reagents have been used, largely limiting the scope of the substrate.[5] In this context, we recently found that a hard Lewis acid, such as a

Scheme 1. Synthesis of Fluoroalkenes from Polyfluoroalkenes



lithium salt, enhances the β-fluorine elimination step, which enables alkylative C–F bond cleavage of tetrafluoroethylene (TFE) with relatively weak nucleophiles such as organozinc reagents, expanding the scope of this approach.[6] To achieve global diversification from polyfluoroalkenes, we assumed that transition metal-catalyzed monodefluoroborylation would suit our purpose;[7,8] the resulting borylated fluoroalkenes[9] were

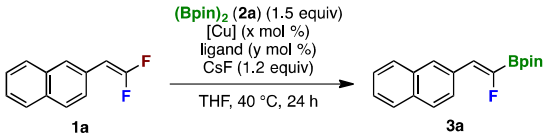
expected to serve as useful synthetic intermediates that take advantage of reliable transformations based on versatile organoboron chemistries (Scheme 1B). In this context, during our investigation on the transformation using TFE,[10] we found that weak copper(I) nucleophiles, such as arylcopper(I) reagents, were available for 1,2-addition to TFE under mild conditions; subsequent treatment of the products of carbocupration with a Lewis acid prompted the *β*-fluorine elimination to afford the corresponding trifluoroalkene derivatives.[11] Based on these previous studies, we conceived the idea of using borylcopper(I) to achieve borylative cleavage of polyfluoroalkenes via an addition–elimination mechanism. During preparation of this manuscript, Cao and co-workers reported a similar monodefluoroborylation reaction of *gem*-difluoroalkenes catalyzed by a (xantphos)Cu(I) complex (xantphos: 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene) to afford boryl(fluoro)alkenes.[12] Although they clearly demonstrated the synthetic utility of boryl(fluoro)alkenes, yields for monodefluoroborylation reactions were typically moderate and the scope of substrate was limited to *gem*-difluoroalkenes bearing a neutral or electron-rich aryl group. Herein, we describe a practical synthetic method for a diverse range of boryl(fluoro)alkenes, which has been achieved based on the copper-catalyzed regioselective borylative cleavage of C–F bond of various (poly)fluoroalkenes.[13]

RESULTS AND DISCUSSIONS

Optimization of the Reaction Conditions for Monodefluoroborylation of 2-(2,2-Difluorovinyl)arenes. From an extensive screen of conditions using 2-(2,2-difluorovinyl)naphthalene (**1a**) as a model substrate, we found a copper catalyst that efficiently promoted *trans*-selective monodefluoroborylation under mild conditions to give boryl(fluoro)alkene **3a**; heating a mixture of **1a**, bis(pinacolato)diboron (**2a**, $(Bpin)_2$, 1.5 equiv), copper(I) chloride (CuCl, 5 mol %), tricyclohexylphosphine (PCy_3, 10 mol %), and cesium fluoride (CsF, 1.2 equiv) in tetrahydrofuran (THF) at 40 °C for 24 h afforded borylated fluoroalkene **3a** in an excellent yield as a single stereoisomer (Table 1, entry 1). Among examined ligands (entries 1–13), electron-donating trialkylphosphines such as PCy_3 and tri(*n*-butyl)phosphine (P(*n*-Bu)$_3$) gave excellent results (entries 1 and 2). Several copper(I) sources other than CuCl were applicable for this transformation (entries 14–18). Reactions without either of the copper complex or ligand were totally impractical (entries 19 and 20). Pre-coordinated copper complexes, such as $(Cy_3P)_2CuCl$ and $[(Cy_3P)CuCl]_2$, which are air-stable and storable without special care, were available, thus enhancing the convenience of the method (entries 21 and 22). Furthermore, the amount of copper complex could be reduced to 1 mol % without a decrease in the yield of **3a** (entries 23–25).

Further screening of a base using $(Cy_3P)_2CuCl$ as the copper source showed that other bases are also employable (Table 2). In particular, an excellent result was obtained using potassium acetate instead of CsF that rendered the reaction conditions milder (entry 7). Lowering the reaction temperature to 30 °C slightly slowed the rate of the reaction (entry 11). In contrast to the Cao's report,[12] the use of a relatively strong base, such as *tert*-butoxide, was less efficient for our case (entries 5 and 8).

Table 1. Optimization of Ligand and Copper Source[a]

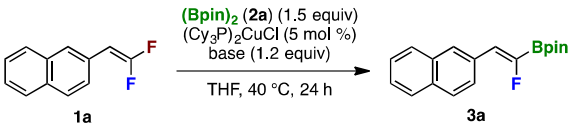


entry	[Cu] (x mol %)	ligand (y mol %)	yield (%)[b]	recovered **1a** (%)[b]
1	CuCl (5)	PCy_3 (10)	95	0
2	CuCl (5)	P(*n*-Bu)$_3$ (10)	93	0
3	CuCl (5)	PCy_2Ph (10)	92	8
4	CuCl (5)	CyJohnPhos (10)	65	28
5	CuCl (5)	PPh_3 (10)	25	68
6	CuCl (5)	dcpm (5)	83	10
7	CuCl (5)	dcpe (5)	61	9
8	CuCl (5)	dcpp (5)	57	25
9	CuCl (5)	dppf (5)	65	29
10	CuCl (5)	xantphos (5)	68	32
11	CuCl (5)	1,10-phen (5)	86	0
12	CuCl (5)	2,2′-bipyridine (5)	22	67
13	(IPr)CuCl (5)	–	40	54
14	CuBr (5)	PCy_3 (10)	92	0
15	CuI (5)	PCy_3 (10)	66	24
16	CuOAc (5)	PCy_3 (10)	94	0
17	CuCN (5)	PCy_3 (10)	75	19
18	$CuCl_2$ (5)	PCy_3 (10)	96	0
19	CuCl (5)	–	4	89
20	–	PCy_3 (10)	3	83
21	$(Cy_3P)_2CuCl$ (5)	–	96	0
22	$[(Cy_3P)CuCl]_2$ (2.5)	–	99	0
23	$(Cy_3P)_2CuCl$ (2)	–	98	0
24	$(Cy_3P)_2CuCl$ (1)	–	97	0
25	$(Cy_3P)_2CuCl$ (0.5)	–	93	4

[a]CyJohnPhos = 2-dicyclohexylphosphinobiphenyl; dcpm = bis(dicyclohexylphosphino)methane; dcpe = 1,2-bis(dicyclohexylphosphino)ethane; dcpp = 1,3-bis(dicyclohexylphosphino)propane; dppf = 1,1′-bis(diphenylphosphino)ferrocene; 1,10-phen = 1,10-phenanthroline; IPr = 1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene. [b]Yields were determined by ^{1}H NMR analysis.

The amount of potassium acetate could be reduced to 0.2 equiv by performing the reaction at a higher temperature (80 °C), whereas the reaction did not proceed without adding a base (Table 3, entries 1–3). These results suggest that only a catalytic amount of base is essential for this catalytic transformation. Indeed, the reaction using 1 mol % of copper(I) acetate with 2 mol % of PCy_3 at 80 °C (entry 4) gave a comparable result to that using 1 mol % of $(Cy_3P)_2CuCl$ with 0.2 equiv of potassium acetate (entry 2).

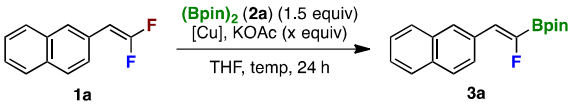
Table 2. Optimization of Base



entry	base	yield (%)[a]	recovered **1a** (%)[a]
1	CsF	97	0
2	Cs_2CO_3	58	0
3	CsOAc	95	0
4	KF	24	67
5	KO^{t}Bu	57	0
6	K_2CO_3	16	9
7	KOAc	96	0
8	NaO^{t}Bu	75	0
9	Na_2CO_3	10	79
10	NaOAc	2	91
11[b]	KOAc	72	24

[a]Yields were determined by ^{1}H NMR analysis. [b]Reaction was performed at 30 °C.

Table 3. Reactions with Reduced Amount of KOAc

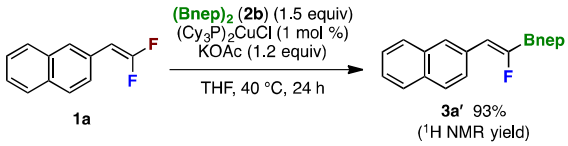


entry	[Cu] (mol %)	x (equiv)	temp (°C)	yield (%)[a]
1	$(Cy_3P)_2CuCl$ (1)	0.2	40	29
2	$(Cy_3P)_2CuCl$ (1)	0.2	80	77
3	$(Cy_3P)_2CuCl$ (1)	0	80	0
4	CuOAc (1) + PCy_3 (2)	0	80	62

[a]Yields were determined by ^{1}H NMR analysis.

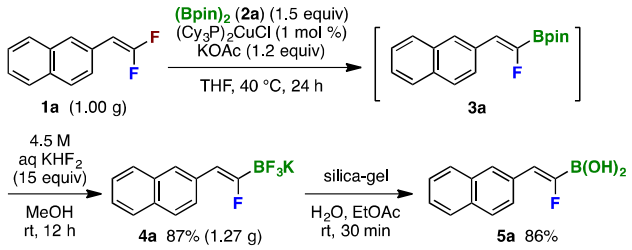
A wide range of solvents were employable for this reaction. In particular, ethereal solvents such as THF, 1,4-dioxane, and cyclopentyl methyl ether (CPME) gave efficient results (Table S1). Although no reaction proceeded when tetrahydroxy diboron was used instead of $(Bpin)_2$ (**2a**) probably because of poor solubility in THF, the use of bis(neopentyl glycolato)diboron (**2b**, $(Bnep)_2$) gave a comparable result to **2a** (Scheme 2). By using a similar catalyst, we recently achieved the defluoroborylation of fluoroarenes, wherein formation of a small amount of defluoroprotonated product was detected depending on the substrates.[7e] However, such protonation was not observed through this study. Moreover, neither a *cis*-isomer of boryl(fluoro)alkenes nor a diborylated byproduct via successive cleavage of two C–F bonds was observed, demonstrating that clean transformation proceeded under the optimized conditions.

Scheme 2. Monodefluoroborylation Using $(Bnep)_2$ (2b)



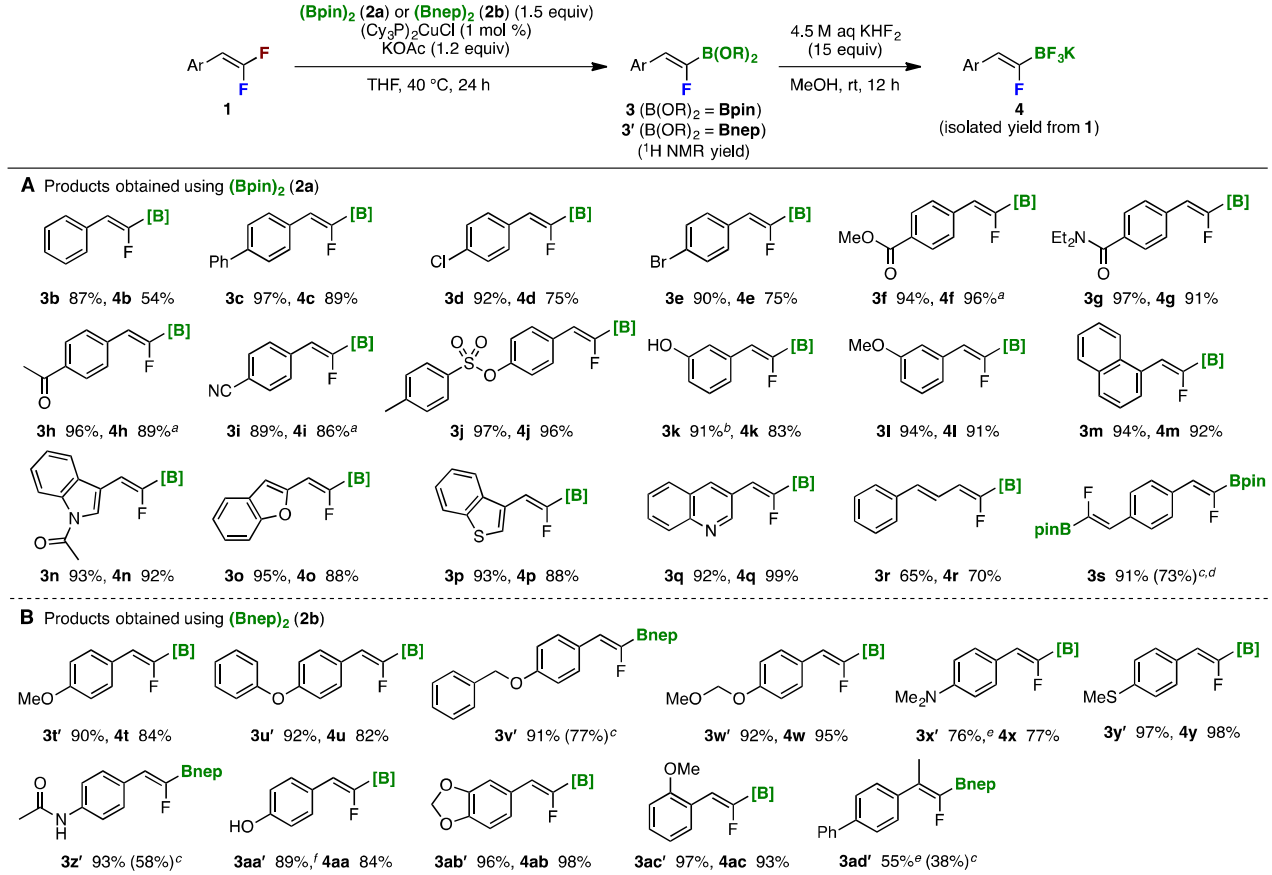
Isolation of Boryl(fluoro)alkenes. Boronic pinacol ester **3a** was difficult to purify without loss by using typical chromatographic techniques because of its high affinity to silica-gel. TLC analysis of **3b**, which is a phenyl analogue of **3a**, and protodefluorinated analogue of **3b**, *trans*-*β*-styrylboronic acid pinacol ester (**3b-deF**), indicated that the fluoro group was responsible for this behavior (Figure S1). Thus, to improve the synthetic practicality of the monodefluoroborylation reaction, we looked for an easy method to treat the borylated product before examining the scope of substrates. After extensive examinations, we found that sequential transformation of **3a** to the corresponding potassium trifluoroborate **4a** suited our purpose (Scheme 3); treatment of the crude reaction mixture containing **3a** with aqueous KHF_2 efficiently afforded **4a** as an air-stable solid even when the reaction was conducted using **1a** in gram-scale.[14] Subsequent defluorogenative hydrolysis of **4a** with a small amount of silica-gel gave the corresponding boronic acid **5a**. Using this scheme, borylated fluoroalkenes **4a** and **5a** were obtained in pure form using only a simple filtering procedure.

Scheme 3. Isolation of Borylated Fluoroalkenes



Substrate Scope for Monodefluoroborylation of 2-(2,2-Difluorovinyl)arenes. The optimized conditions for monodefluoroborylation (Table 2, entry 7) and the isolation procedure (Scheme 3) were applicable to transformation of a wide range of 2-(2,2-difluorovinyl)arenes **1** to the corresponding boryl(fluoro)alkenes **3** and **4** (Table 4). *β*,*β*-Difluorostyrene (**1b**) and its derivatives with an electron-withdrawing group at *para*-position of the phenyl group, such as **1c**–**j**, were smoothly borylated to give the desired products **4b**–**j** in good to excellent yields (Table 4A). Notably, our method was applicable to the substrates with a strong electron-withdrawing group such as cyano-substituted **1i**, which was reported unsuitable for the defluoroborylation under Cao's conditions.[12] Transformations of several boronates bearing an electron-withdrawing group, such as **3f**, **3h**, and **3i**, into the corresponding trifluoroborates **4f**, **4h**, and **4i**, respectively, required gentle heating (50 °C), probably due to their slow dissociation of pinacol from **3**.

Table 4. ***trans*-Selective Monodefluoroborylation of Various (Difluorovinyl)arenes**

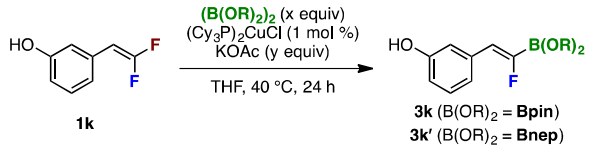


[a]The reactions with aqueous KHF_2 were performed at 50 °C. [b]2 equiv of **2a** was used. [c]Isolated yields as boronic esters **3** or **3′** in parentheses. [d]Two times the reagents were used. [e]The reaction was performed for 48 h. [f]2.5 equiv of **2b** was used.

A variety of substituents on the aromatic ring were tolerated; these include further transformable groups such as (pseudo)halogeno (**1d**, **1e**, and **1j**), cyano (**1i**),[15] and methylthio (**1y**)[16] groups. Notably, substrates having an unprotected phenolic hydroxy group, such as **1k**, were also applicable to afford the desired products in high yields. In the case of **1k**, whereas an acceptable result was obtained from the reaction conducted under the standard conditions (Table 5, entry 1), using an increased amount of **2a** (2.0 or 2.5 equiv) significantly improved the yield of **3k** (entries 4 and 5). The reactions of difluoroalkenes containing aromatic systems other than benzene, such as naphthalene (**1m**), indole (**1n**), benzofuran (**1o**), benzothiophene (**1p**), and quinoline (**1q**), as well as vinylogous *gem*-difluoro-1,3-butadienylbenzene (**1r**) proceeded uneventfully to afford the borylated products **4m**–**r** in high yields. Double defluoroborylation of 1,4-bis(difluorovinyl)benzene (**1s**) also efficiently took place using double the amounts of reagents to afford bisborylated **3s**, which was isolable as a bisboronate form.

Substrates bearing an electron-donating group resulted in low conversion under the standard conditions using $(Bpin)_2$ (**2a**) as the boron source. For example, *para*-benzyloxy-substituted substrate **1v** was monodefluoroborylated with **2a** to afford **3v** in a moderate yield (Table 6, entry 1). Whereas increasing the amount of reagents or prolongation of the reaction time did not improve the yield of **3v** (entries 2–4), significant improvement was obtained by using $(Bnep)_2$ (**2b**) instead of **2a** (entry 5). The same tendency was observed for *para*-methoxy substituted substrate **1t** (Table 7, entries 1 and 2). This finding allowed for efficient monodefluoroborylation of a wide range of other substrates bearing an electron-rich aryl group, such as **1t**–**ac**, affording the corresponding borylated products **3′** and **4** in high yields (Table 4B). Furthermore, fully substituted *gem*-difluoroalkene **1ad** was also monoborylated using **2b** to afford trisubstituted vinylboronate **3ad′**, although extending the reaction time to 48 h was needed to obtain the desired product in reasonable yield. In this case, the reaction also proceeded in a regioselective manner, where the fluorine atom at *trans*-position of the biaryl group was replaced with a boron atom (see the Supporting Information for structure determination of **3ad′**). Conversely, the use of $(Bnep)_2$ (**2b**) was less effective for the reaction of substrates bearing an electron-withdrawing group. For example, the borylation of *para*-methoxycarbonyl-substituted **1f** with **2b** resulted in a lower conversion than that with **2a** (Table 7, entries 3 and 4). These results indicated that there is a matched and mismatched combination between substrates and diborons. While this method demonstrated a broad scope for (difluorovinyl)arenes, the reactions of (difluorovinyl)alkane and (dichlorovinyl)arene resulted in no conversion (Figure S3).

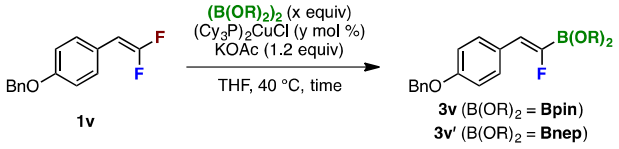
Table 5. Monodefluoroborylation of 1k Bearing a Hydroxy Group



entry	$(B(OR)_2)_2$ (x equiv)	y (equiv)	**3** or **3′**	yield (%)[a]
1	$(Bpin)_2$ (**2a**, 1.5)	1.2	**3k**	78
2	$(Bnep)_2$ (**2b**, 1.5)	1.2	**3k′**	77
3	$(Bpin)_2$ (**2a**, 1.5)	2.2	**3k**	78
4	$(Bpin)_2$ (**2a**, 2.0)	1.2	**3k**	91
5	$(Bpin)_2$ (**2a**, 2.5)	1.2	**3k**	90

[a]Yields were determined by ^{1}H NMR analysis.

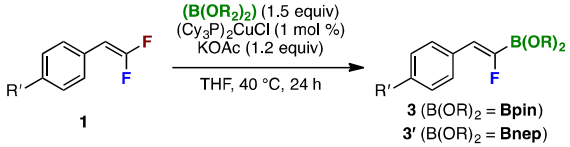
Table 6. Monodefluoroborylation of Electron-Rich Substrate 1v



entry	$(B(OR)_2)_2$ (x equiv)	y (mol %)	time (h)	**3** or **3′**	yield (%)[a]
1	$(Bpin)_2$ (**2a**, 1.5)	1	24	**3v**	42
2	$(Bpin)_2$ (**2a**, 2.0)	1	24	**3v**	45
3	$(Bpin)_2$ (**2a**, 1.5)	5	24	**3v**	50
4	$(Bpin)_2$ (**2a**, 1.5)	1	48	**3v**	65
5	$(Bnep)_2$ (**2b**, 1.5)	1	24	**3v′**	91

[a]Yields were determined by ^{1}H NMR analysis.

Table 7. Comparison of Monodefluoroborylation Using Different Diboron Reagents

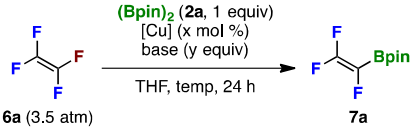


entry	R′	$(B(OR)_2)_2$	**3** or **3′**	yield (%)[a]	recovery of **1** (%)[a]
1	OMe (**1t**)	$(Bpin)_2$ (**2a**)	**3t**	35	48
2	OMe (**1t**)	$(Bnep)_2$ (**2b**)	**3t′**	90	2
3	CO_2Me (**1f**)	$(Bpin)_2$ (**2a**)	**3f**	94	0
4	CO_2Me (**1f**)	$(Bnep)_2$ (**2b**)	**3f′**	79[b]	11

[a]Yields were determined by ^{1}H NMR analysis. [b]Formation of a trace amount of (*Z*)-monofluoroalkene (<2% yield) in the reaction mixture was observed by ^{1}H NMR analysis (Figure S2).

Optimization of the Reaction Conditions for Monodefluoroborylation of TFE. Next, we examined to expand the method to monodefluoroborylation of polyfluoroalkenes. Since the reaction of TFE (**6a**) under the conditions similar to that for the monodefluoroborylation of (difluorovinyl)arenes **1** did not provide the desired monoborylated product **7a** (Table 8, entry 1), we rescreened the reaction conditions. Although simple elevation of the reaction temperature to 100 °C was not effective (entry 2), using CsF as a base afforded a small amount of **7a** (entry 3). Further screening revealed that the use of a copper(I) *tert*-butoxide complex significantly improved the yield (entry 4). Conclusively, the use of (IPr)CuO^{t}Bu (10 mol %) gave the best result affording **7a** quantitatively (entry 5). Using the pre-synthesized complex was important to achieve an efficient conversion; significant decrease of the yield of **7a** was observed when a mixture of (IPr)CuCl and sodium *tert*-butoxide was used (entries 6 and 7). The amount of the catalyst could be reduced to 5 mol %, which still afforded **7a** in an excellent yield (entry 8). Moreover, the reaction could be conducted at lower temperatures by extending the reaction time, which afforded **7a** in acceptable yields (entries 9–11).

Table 8. Screen of Conditions for Monodefluoroborylation of TFE (6a)



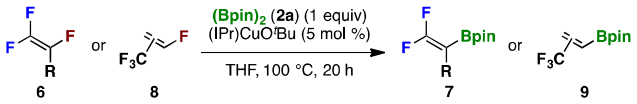
entry	[Cu] (x mol %)	base (y equiv)	temp (°C)	yield (%)[a]
1	$(Cy_3P)_2CuCl$ (10)	KOAc (1.2)	40	0
2	$(Cy_3P)_2CuCl$ (10)	KOAc (1.2)	100	0
3	$(Cy_3P)_2CuCl$ (10)	CsF (1.2)	100	8
4	CuO^{t}Bu (10)[b]	–	100	69
5	(IPr)CuO^{t}Bu (10)	–	100	>99
6	(IPr)CuCl (10)	NaO^{t}Bu (0.1)	100	37
7	(IPr)CuCl (10)	NaO^{t}Bu (1)	100	16
8	(IPr)CuO^{t}Bu (5)	–	100	93
9	(IPr)CuO^{t}Bu (5)	–	80	77 (90)[c]
10	(IPr)CuO^{t}Bu (5)	–	60	59 (89)[d]
11	(IPr)CuO^{t}Bu (5)	–	40	22 (69)[d]

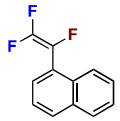
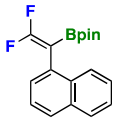
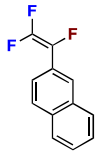
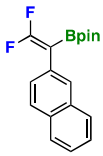
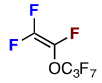
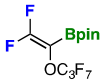
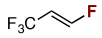
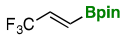
[a]Yields were determined by ^{19}F NMR analysis. [b]The reaction was performed in the presence of xantphos (10 mol %). [c]Yield of **7a** when the reaction was performed for 80 h in parentheses. [d]Yields of **7a** when the reaction was performed for 240 h in parentheses.

Substrate Scope for Monodefluoroborylation of Polyfluoroalkenes. The optimized conditions for monodefluoroborylation of TFE (**6a**) (Table 8, entry 5) could be applied to monodefluoroborylation of several polyfluoroalkenes, including (trifluorovinyl)arenes and trifluoromethylated monofluoroalkenes (Table 9). Due to water sensitivity of the products, structure identification and determination of the yields of products other than **7c** were conducted by ^{19}F NMR analysis (see the Supporting Information for details). The reactions of 1- and 2-(trifluorovinyl)naphthalene (**6b** and **6c**) proceeded selectively at the geminal position with respect to the aryl group to give **7b** and **7c** (entries 1 and 2). The reaction with heptafluoropropyl trifluorovinyl ether (**6d**) afforded only a trace amount of the desired product **7d**, and trifluorovinylborane **7a** was obtained in 7% yield (entry 3). This result indi-

cated that β-alkoxy elimination preferably occurred compared with the desired β-fluorine elimination. In this case, the desired **7d** was obtained in moderate yield using xantphos as the ligand. In addition to these polyfluoroalkenes, trifluoromethylated monofluoroalkenes **8a** and **8b**, which have fluorine atoms at the vinyl and allyl positions, respectively, were monodefluoroborylated selectively at the C(sp^2)–F bond moiety to afford borylated products **9a** and **9b** in high yields (entries 4 and 5).

Table 9. Regioselective Monodefluoroborylation of Various Tri- and Monofluoroalkenes

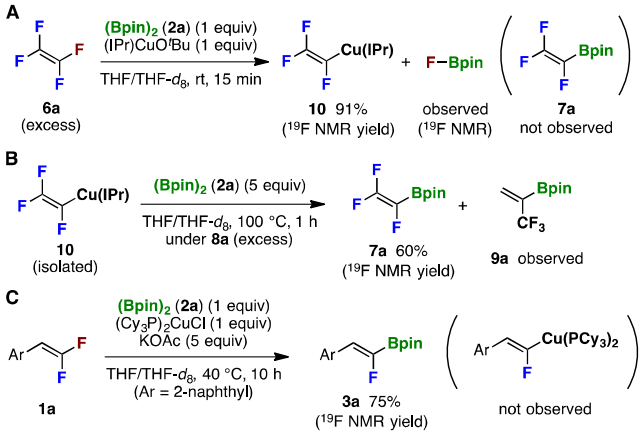


entry	substrate		product		yield (%)[a]
1[b]		**6b**		**7b**	21
2[b]		**6c**		**7c**	50 (42)[c]
3[d]		**6d**		**7d**	1 (+ **7a** 7%) (37%)[e]
4[f]		**8a**		**9a**	65
5[e,f]		**8b**		**9b**	87

[a]Yields were determined by ^{19}F NMR analysis. [b]1 equiv of **6b** or **6c** and 1.5 equiv of **2a** were used. [c]Isolated yield in the parentheses. [d]1.5 equiv of **6d** was used. [e]CuO^{t}Bu (5 mol %) and xantphos (5 mol %) were used instead of (IPr)CuO^{t}Bu. [f]Excess amount of **8a** or **8b** were used. See the Supporting Information for details.

Stoichiometric Reactions. Several stoichiometric reactions offered an insight into the reaction mechanism (Scheme 4). The reaction of the structurally characterized borylcopper(I) complex (IPr)CuBpin,[17] which was prepared by mixing (IPr)CuO^{t}Bu and diboron **2a** in situ, with an excess amount of TFE (**6a**) in THF at room temperature afforded a trifluorovinylcopper(I) complex **10** in 91% yield (Scheme 4A). The structure of **10** was unambiguously determined by X-ray diffraction analysis (Figure 1). In this reaction, generation of fluoroboronate (FBpin) was also observed, indicating that **10** was formed via 1,2-addition of the borylcopper(I) complex to TFE (**6a**) followed by elimination of FBpin, which was promoted by the thermodynamically favored B–F bond formation. The reaction of isolated **10** with diboron **2a** in the presence of **8a**, which was used as a borylcopper scavenger, proceeded at 100 °C to afford trifluorovinylboronate **7a** in 60% yield (Scheme 4B). In this reaction, formation of the borylated product **9a** was also observed, indicating that the borylcopper species was regenerated during the reaction. Conversely, the reaction of (difluorovinyl)arene **1a** with one equivalent of **2a** using stoichiometric amounts of $(Cy_3P)_2$CuCl and KOAc at 40 °C directly gave boryl(fluoro)alkene **3a** in 75% yield without observation of the corresponding vinylcopper(I) complex in the mixture (Scheme 4C).

Scheme 4. Stoichiometric Reactions



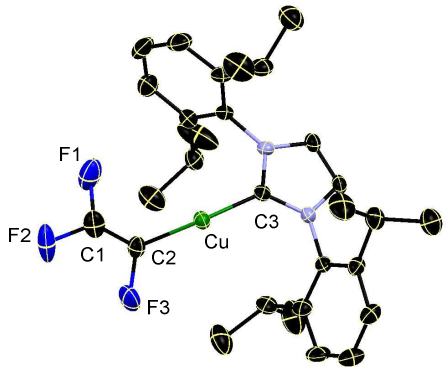
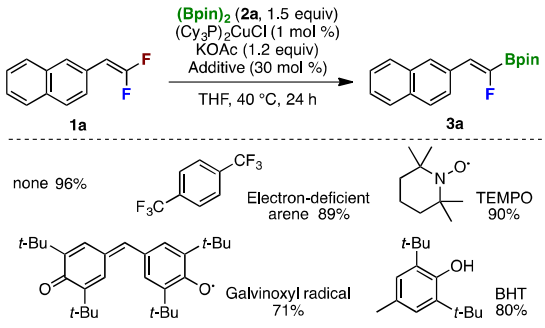


Figure 1. ORTEP drawing of **10** with thermal ellipsoids at the 30% probability level (H atoms have been omitted for clarity). Selected bond lengths (Å) and angles (deg): C1–C2 1.276(9), Cu–C2 1.902(6), Cu–C3 1.887(6), C2–Cu–C3 169.3(2), Cu–C2–C1 125.8(5), Cu–C2–F3 121.5(4), C1–C2–F3 111.9(5).

Scheme 5. Effects of Additives

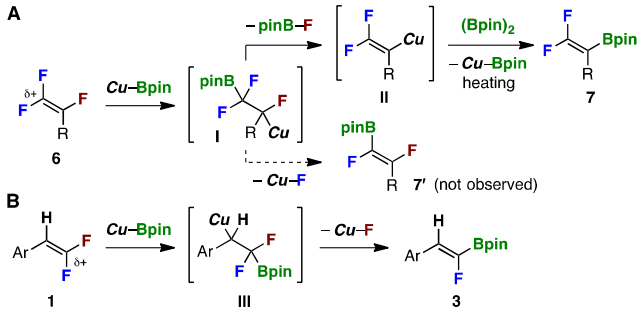


Effects of Additives. In our previous work on *ipso*-borylation of fluoroarenes that was achieved by means of a similar combination of $(Cy_3P)_2$CuCl and $(Bpin)_2$ (**2a**), the addition of electron-deficient arenes inhibited the reaction, which indicated the involvement of single electron-transfer (SET)

process from an electron-rich borylcopper(I) species.[7e] To check whether SET process or a radical species is involved in the monodefluoroborylation of **1a**, we examined the reaction in the presence of several additives, such as 1,4-bis(trifluoromethyl)benzene or radical scavengers (Scheme 5). In all cases, the reaction proceeded uneventfully to provide the desired **3a** in high yields, suggesting that the monodefluoroborylation does involve neither a SET process nor generation of free radical species as an intermediate.

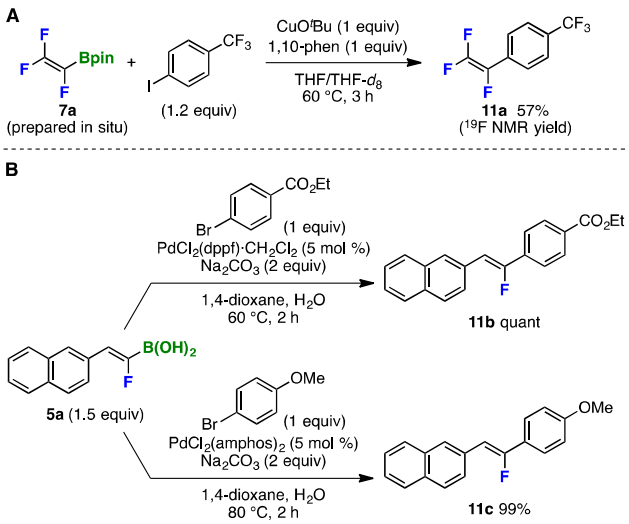
Plausible Mechanism. On the basis of experimental results, we currently consider that the monodefluoroborylation proceeds via addition-elimination pathway, and the regioselectivity originates in the mode of the *β*-fluorine elimination step, which depends on the substrates. In the case of TFE or trifluoroalkenes **6**, the reaction starts from 1,2-addition of the borylcopper(I) complex to form the C–B bond at the more electro-positive olefinic carbon in **6**, affording the alkylcopper(I) species **I** (Scheme 6A). Subsequent elimination of FBpin affords vinylcopper(I) complex **II**, which then reacts with **2a** under heating conditions to afford **7** with regeneration of the borylcopper(I) complex. Selective formation of **7b** and **7c** (R = 1- or 2-naphthyl) indicates faster elimination of FBpin than that of copper(I) fluoride, which affords isomer **7′** that was not observed in this study. In contrast, the reaction of the borylcopper(I) complex with *gem*-difluoroalkene **1** gives an alkylcopper(I) species **III** that has no fluorine atom at the vicinal position with respect to the introduced boron atom (Scheme 6B). Thus, in this case, elimination of copper(I) fluoride occurs to provide **3**, which could be accelerated by KOAc.[11] This mechanism, wherein the borylation proceeds without the formation of a vinylcopper(I) intermediate, is consistent with the fact that the reaction proceeded at a low temperature (40 °C).

Scheme 6. Plausible Mechanisms Depending on the Substrates



Synthetic Application of Monodefluoroborylated Compounds. The borylated products served as useful synthetic units for introduction of fluoroalkene moieties (Scheme 7 and Figure 2). For example, copper-mediated cross-coupling reaction of trifluorovinylborane **7a** with 4-iodobenzotrifluoride proceeded smoothly to give a trifluorostyrene derivative **11a** (Scheme 7A). The cross-coupling reaction of borylated monofluoroalkenes also took place efficiently (Scheme 7B); Suzuki–Miyaura coupling of boronic acid **5a** with aryl halides such as (4-ethoxycarbonyl)phenyl bromide and 4-bromoanisole afforded monofluorinated *trans*-stilbene derivatives **11b** and **11c**, respectively, in excellent yields.

Scheme 7. Cross-Coupling with Boryl(fluoro)alkenes



Finally, we demonstrated the utility of the method by the synthesis of a fluoroalkene mimic of a widely-used antihyperlipidemic drug, atorvastatin (Figure 2).[18] Suzuki–Miyaura cross-coupling of a boryl(fluoro)styrene unit **5b** with bromopyrrole **12** proceeded by using SPhosPdG3 as a precatalyst to give **13** in high yield (Figure 2A). Subsequent deprotections of isopropylidene acetal and *tert*-butyl ester moieties under standard acidic and basic conditions, respectively, afforded the desired fluoroalkene mimic **14**. Evaluation of the HMG-CoA reductase inhibitory effect of the mimic **14** using a commercial assay kit demonstrated that the replacement of amide moiety of atorvastatin to fluoroethylene structure did not significantly affect the activity the original compound; the mimic **14** showed a similar level of inhibition activity to that of atorvastatin (Figure 2B). This result indicates that replacing the amide moiety of the drug candidates would provide another promising candidate with favorable characters such as increased hydrophobicity and improved metabolic stability.[19]

CONCLUSION

We have developed a practical synthetic method for borylated fluoroalkenes via copper-catalyzed monodefluoroborylation of polyfluoroalkenes. The method has been successfully applied to a broad range of substrates, including (difluorovinyl)arenes, tetrafluoroethylene (TFE), (trifluorovinyl)arenes, and trifluoromethylated monofluoroalkenes. The mode of the *β*-elimination step, which occurs after the addition of borylcopper(I) species to the polyfluoroalkene, influences the fate of the regioselectivity depending on the substrates. Various fluoroalkenyl molecules, including a bioactive fluoroalkene mimic of an amide group-containing commercial drug, have become easily available by this method, which would facilitate the development of useful functional molecules in a broad fields, including drug discovery and materials science.

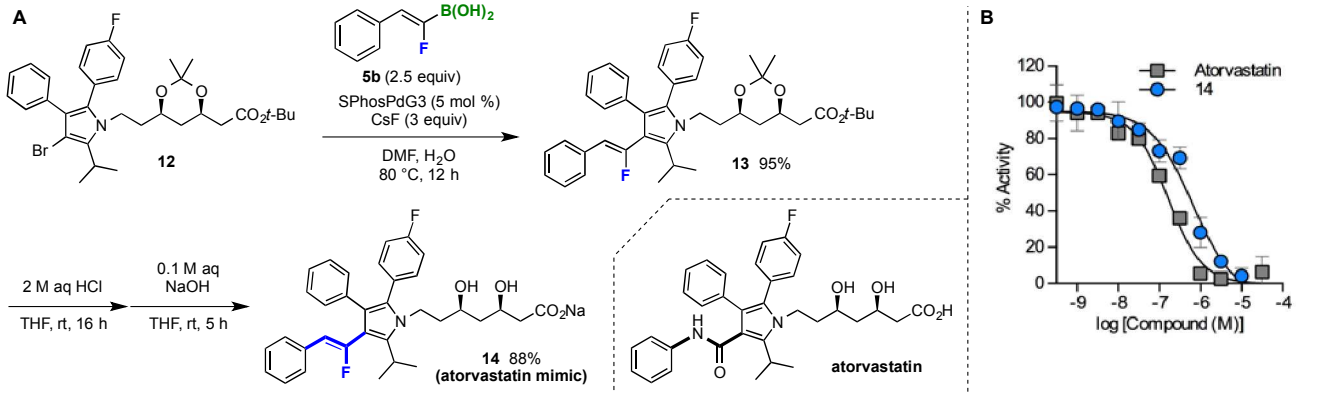


Figure 2. (A) Synthesis of a fluoroalkene mimic of atorvastatin **14** and evaluation of its HMG-CoA reductase inhibitory effect. (B) Dose-response curves with Hill slopes (252 sec after treatment of HMG-CoA reductase), showing that atorvastatin and **14** inhibited HMG-CoA reductase activity with IC_{50} values of 162 nM and 655 nM, respectively. See the Supporting Information for details.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experimental procedures, characterization for new compounds, including copies of NMR spectra.

■ AUTHOR INFORMATION

Corresponding Authors

*takashi.niwa@riken.jp
*ogoshi@chem.eng.osaka-u.ac.jp
*takamitsu.hosoya@riken.jp

Author Contribution

§H.S. and Y.U. contributed equally.

Notes

The authors declare no competing financial interest.

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