Letter

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Copper-Catalyzed Regioselective Borylfluoromethylation of Alkenes

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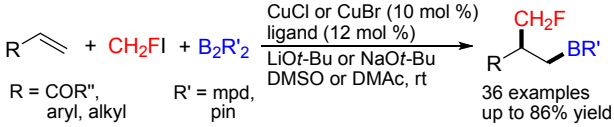
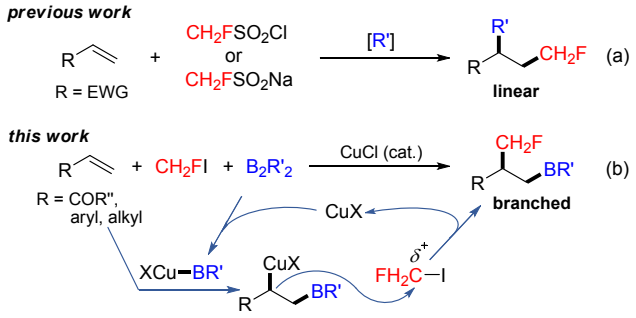


ABSTRACT: A copper-catalyzed borylfluoromethylation of alkenes with fluoromethyl iodide and diboron reagents was disclosed. This protocol afforded the previously unknown and synthetically useful borylfluoromethylated alkanes in good yields and excellent regioselectivity. Its synthetic application was illustrated through the derivatization of organoboron products and preparation of monofluorinated ibuprofen.

KEYWORDS: fluoromethylation, borylation, alkene, copper, regioselective

The presence of fluorine atom(s) in a group could affect its electronic and physicochemical properties.[1] For instance, fluoromethyl group (CH_2F) normally acts as a metabolically stable bioisostere for methyl group (CH_3). Furthermore, the CH_2F group is also considered as a CH_2OH group mimic.[2] As a consequence, the fluoromethylated compounds have widespread applications in agrochemicals, pharmaceuticals, and materials.[3] Conventionally, the fluoromethylated compounds are prepared via C–H fluorination of CH_3-containing compounds[4] or fluorination of functionalized substrates.[5] However, these methods have some limitations, such as narrow substrate scope, low regioselectivity, or prior installation of a functional group. Alternatively, the method of choice for the preparation of fluoromethylated compounds involves indirect fluoromethylation using fluoromethylating agents bearing a suitable auxiliary, followed by the removal of the auxiliary.[6] Compared to the indirect methods, the direct fluoromethylation through electrophilic,[7] nucleophilic,[8] and radial pathways[9] are more attractive due to the atom and step economy. Recently, the groups of Zhang,[10a] Hu,[10b] Wang,[10c] and Baran[10d] have also reported transition metal-catalyzed direct fluoromethylation of aryl boronic acids (esters), halides, and zinc reagents.

Alkenes are prevalent chemical feedstocks in organic synthesis. Recently, the difunctionalization of alkenes for the incorporation of both fluoroalkyl and another functional groups has been extensively studied for the synthesis of fluorine-containing compounds.[11] However, only three examples of fluoromethylation of alkenes have been reported (Scheme 1a).[12] In all these cases, the addition of CH_2F radical to electron-deficient alkenes gave the linear fluoromethylated products.

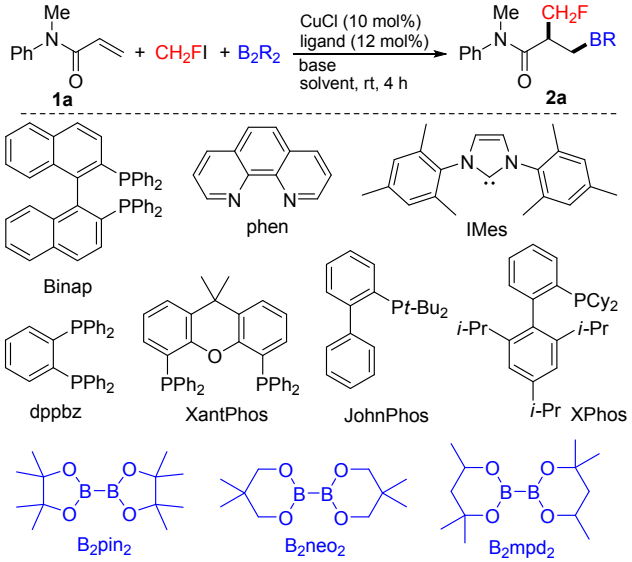


Scheme 1. Regioselective fluoromethylation of Alkenes

Organoboron compounds are versatile intermediates for organic synthesis. Recently, borylative difunctionalization of unsaturated carbon–carbon bonds has emerged as a powerful approach to highly functionalized alkylboranes.[13] Among them, copper-catalyzed arylborylation,[14] alkylborylation,[15] cyanoborylation,[16] and aminoborylation[17] of alkenes has been extensively investigated. Inspired by these works,[14-17] we envisioned that the borylcupration of alkenes, followed by electrophilic fluoromethylation, might serve as a novel method for fluoromethylation of alkenes.

Herein, we disclose a copper-catalyzed regioselective borylfluoromethylation of alkenes with fluoromethyl iodide and diboron reagents for the formation of the branched fluoromethylated compounds (Scheme 1b).[18]

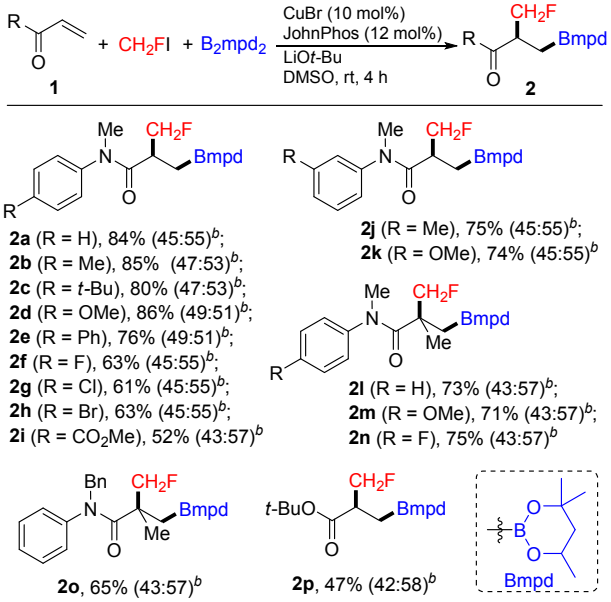
Table 1. Optimization of Reaction Conditions[a]



entry	ligand	base	solvent	B_2R_2	yield (%)[b]
1	Binap	NaO*t*-Bu	THF	B_2pin_2	trace
2	Binap	NaO*t*-Bu	toluene	B_2pin_2	0
3	Binap	NaO*t*-Bu	DMAc	B_2pin_2	41
4	Binap	NaO*t*-Bu	DMF	B_2pin_2	61
5	Binap	NaO*t*-Bu	DMSO	B_2pin_2	65
6	phen	NaO*t*-Bu	DMSO	B_2pin_2	48
7	IMes	NaO*t*-Bu	DMSO	B_2pin_2	52
8	dppbz	NaO*t*-Bu	DMSO	B_2pin_2	63
9	XantPhos	NaO*t*-Bu	DMSO	B_2pin_2	35
10	JohnPhos	NaO*t*-Bu	DMSO	B_2pin_2	70
11	XPhos	NaO*t*-Bu	DMSO	B_2pin_2	61
12	PPh_3	NaO*t*-Bu	DMSO	B_2pin_2	60
13	PCy_3	NaO*t*-Bu	DMSO	B_2pin_2	57
14	JohnPhos	KO*t*-Bu	DMSO	B_2pin_2	7
15	JohnPhos	LiO*t*-Bu	DMSO	B_2pin_2	78
16	JohnPhos	LiOMe	DMSO	B_2pin_2	0
17	JohnPhos	LiO*t*-Bu	DMSO	B_2neo_2	72
18	JohnPhos	LiO*t*-Bu	DMSO	B_2mpd_2	88
19[c]	JohnPhos	LiO*t*-Bu	DMSO	B_2mpd_2	93
20[d]	JohnPhos	LiO*t*-Bu	DMSO	B_2mpd_2	76

[a]Reaction conditions: **1a** (0.2 mmol), B_2R_2 (0.3 mmol), ICH_2F (0.3 mmol), CuCl (0.02 mmol), ligand (0.024 mmol), base (0.36 mmol), solvent (2.0 mL), rt, under N_2, 4 h. [b]Yields determined by ^{19}F NMR using fluorobenzene as an internal standard. [c]CuBr (0.02 mmol). [d]CuI (0.02 mmol).

We commenced our studies with the borylfluoromethylation of *N*-methyl-*N*-phenylacrylamide (**1a**) with CH_2FI and B_2pin_2 (Table 1). Only trace of the desired product **2a** was formed in the presence of CuCl, Binap, and NaO*t*-Bu in THF (entry 1). Screening of different solvents demonstrated that polar solvents including DMAc, DMF, and DMSO could promote this reaction, and DMSO was optimal to provide **2a** in 65% yield (entries 2-5). The effect of the ligand was then investigated. When nitrogen-based ligand phen or *N*-heterocyclic carbene (NHC) ligand IMes was employed, lower yields were obtained (entries 6 and 7). Other bidentate phosphine ligands such as dppbz and XantPhos were less effective (entries 8 and 9). In the cases of monodentate phosphine ligands, JohnPhos improved the yield to 70% (entry 10), whereas XPhos, PPh_3, and PCy_3 resulted in slightly lower yields (entries 11-13). The choice of an inorganic base had strong influence on the reaction. LiO*t*-Bu could slightly improve the yield to 78% (entry 15). In contrast, the yield was diminished sharply when KO*t*-Bu or LiOMe was used (entries 14 and 16). To our delight, after further investigation of the diboron reagents (entries 17 and 18) and copper salts (entries 19 and 20), the yield of **2a** was finally improved up to 93% when B_2mpd_2 and CuBr were used as the boron reagent and catalyst, respectively.



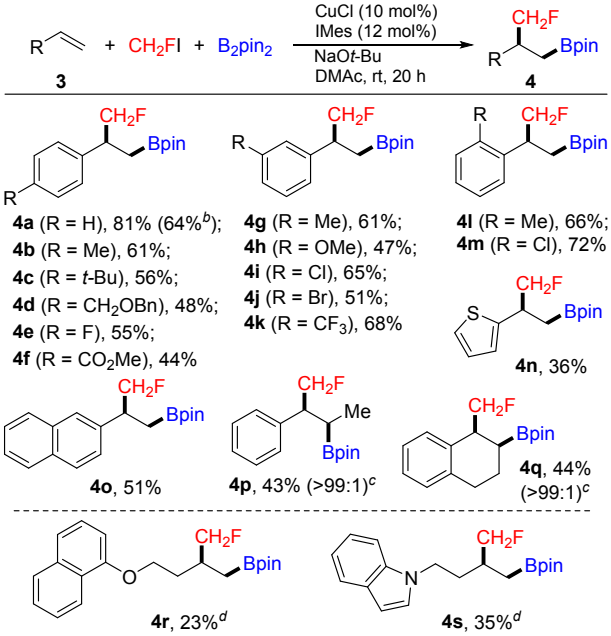
Scheme 2. Borylfluoromethylation of Acrylamides[a]

[a]Reaction conditions: **1** (0.2 mmol), B_2mpd_2 (0.3 mmol), ICH_2F (0.3 mmol), CuBr (0.02 mmol), JohnPhos (0.024 mmol), LiO*t*-Bu (0.36 mmol), DMSO (2.0 mL), rt, under N_2, 4 h, isolated yields. [b]The diastereomer ratios were determined by ^{19}F NMR of the crude products (the Bmpd contains a stereocenter).

Under the optimal conditions (Table 1, entry 19), the substrate scope of this reaction was then evaluated. As shown in Scheme 2, a variety of α-fluoromethyl-β-boryl carbonyl compounds (**2a-p**) were furnished in moderate to high yields as mixtures of diastereomers. An array of functionality including ether, ester, amide, fluoro, chloro, and bromo were well tolerated. In general, the electron-donating substitutions (**1b-e**) led to higher yields than the electron-withdrawing substitutions (**1f-i**). Steric hindrance of the substrates (**1j**,**k**) resulted in slightly lower yields. Acrylamides **1l-o** with methyl at the α-

carbon position were also suitable for this transformation. Furthermore, the reaction of α,β-unsaturated ester **1p** proceeded smoothly to give product **2p** in 47% yield.

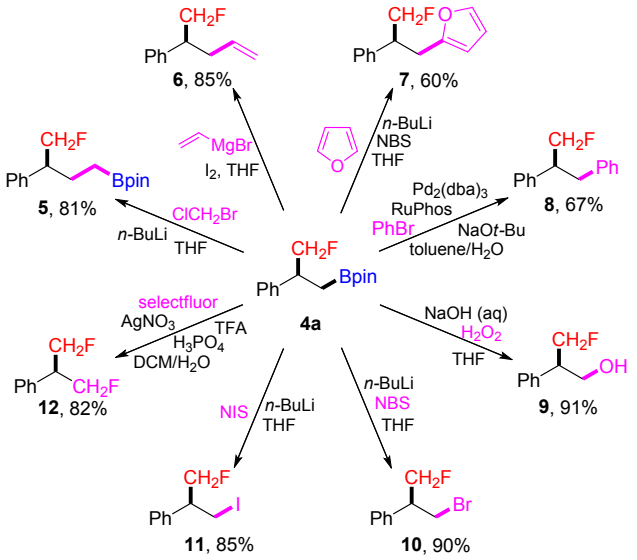
This borylfluoromethylation reaction was then extended to other alkenes. However, only moderate yield was observed when subjecting styrene **3a** to the optimized reaction conditions for acrylamides. After extensive screening of reaction conditions (For details, see SI), borylfluoromethylation of styrene **3a** with CH_2FI occurred efficiently using B_2pin_2 as the boron reagent, CuCl as the catalyst, IMes as the ligand, NaO*t*-Bu as the base, and DMAc as the solvent. Under these optimized reaction conditions, styrenes **3a**-**m** bearing different substituents were conveniently converted to borylfluoromethylated products **4a**-**m** (Scheme 3). 2-Thienyl (**3n**) and 2-naphthyl (**3o**) substituted alkenes showed lower reactivity than styrenes. The internal alkenes (**3p**,**q**) also provided the desired products in a regioselective manner, albeit in low yields. Notably, this reaction was easily scaled up to 8.0 mmol, providing 1.34 g of **4a** in 64% yield. However, the borylfluoromethylation of the unactivated alkenes **3r** and **3s** resulted in low yields.



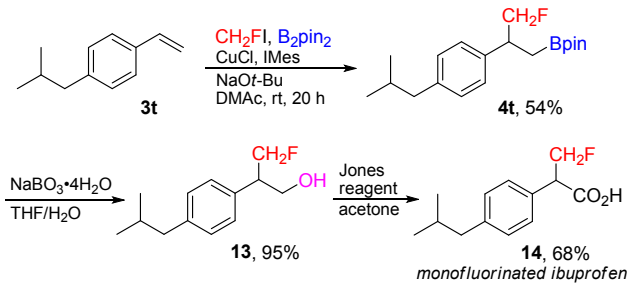
Scheme 3. Borylfluoromethylation of Alkenes[a]

[a]Reaction conditions: **3** (0.2 mmol), B_2pin_2 (0.3 mmol), ICH_2F (0.3 mmol), CuCl (0.02 mmol), IMes (0.024 mmol), NaO*t*-Bu (0.36 mmol), DMAc (2.0 mL), under N_2, 20 h, isolated yields. [b]Reaction was performed in 8.0 mmol. [c]The diastereomer ratios were determined by ^{19}F NMR of the crude products. [d]XantPhos (0.024 mmol) was employed as the ligand.

To illustrate the application of this protocol, the further transformations of the borylfluoromethylated product **4a** were surveyed (Scheme 4). Matteson homologation of **4a** with $ClCH_2Br$ and *n*-BuLi gave product **5** in 81% yield. Treatment of **4a** with vinylmagnesium bromide and I_2 afforded vinylated product **6** in 85% yield. The similar reaction of **4a** and furan in the presence of *n*-BuLi and NBS delivered compound **7** in 60% yield. Furthermore, the cross-coupling of **4a** and PhBr furnished arylated product **8** in high yield. Additionally, β-fluoromethyl alkylalcohol **9** was obtained in 91% yield after oxidation by H_2O_2. The formation of brominated and iodinated products was readily achieved by the reaction of **4a** and *n*-BuLi as well as NBS or NIS. Finally, silver-catalyzed fluorination with Selectfluor delivered novel bis(fluoromethylated) product **12**.



Scheme 4. Transformation of Compound 4a

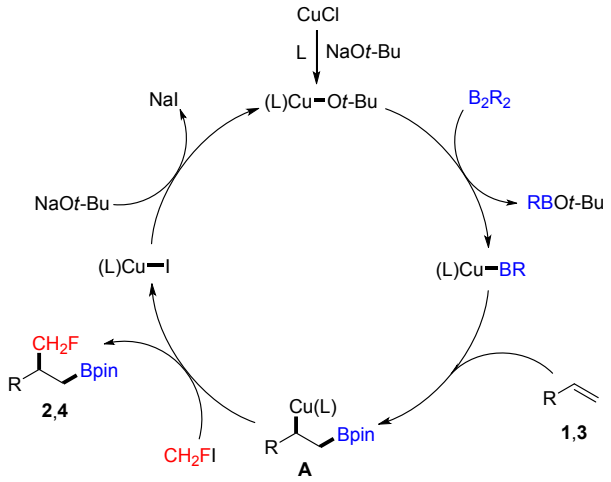


Scheme 5. Preparation of Monofluorinated Ibuprofen

The synthetic utility of this protocol was further highlighted through the preparation of monofluorinated analogue of ibuprofen, an anti-inflammatory drug.[19] As shown in Scheme 5, the reaction of styrene **3t**, CH_2FI, and B_2pin_2 under the standard conditions provided product **4t** in 54% yield. Compound **4t** was easily converted to the monofluorinated ibuprofen **14**[6c,20] through sequential oxidation with $NaBO_3{\cdot}4H_2O$ and Jones reagent (CrO_3-H_2SO_4-H_2O).[21]

Based on the literature data, a plausible mechanism for borylfluoromethylation is illustrated in Scheme 6. Initially, treatment of CuCl with NaO*t*-Bu and coordination of the ligand generates (L)Cu–O*t*-Bu.[22] Then, (L)Cu–O*t*-Bu reacts with B_2R_2 to afford borylcopper species (L)Cu–BR.[23] Subsequently, the insertion of the C–C double bond of alkene (**1**,**3**) into the Cu–B bond gives borylcuprated intermediate **A**,[24] which is captured by CH_2FI to furnish

borylfluoromethylated product (**2,4**).[15-17] At the same time, (L)Cu–I is formed and converted to (L)Cu–O*t*-Bu for the next catalytic cycle. However, the reason why two different reaction systems are needed for acrylamides and styrenes remains unclear.



Scheme 6. Proposed Catalytic Cycle

In summary, we have developed a copper-catalyzed regioselective borylfluoromethylation of acrylamides, styrenes, and unactivated alkenes with fluoromethyl iodide and diboron reagents. This reaction proceeded smoothly to deliver β-fluoromethyl alkylboronates in good yields. The resulting products are useful synthetic intermediates for various potentially valuable fluoromethylated compounds. Efforts to explore Cu-catalyzed difunctionalization reactions for the preparation of other fluoroalkylated compounds are ongoing in our laboratory.

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Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: XXX

Detailed experimental procedures, characterization data, and copies of ^{1}H, ^{19}F and ^{13}C NMR spectra.

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SYNOPSIS TOC.