Nickel-Catalyzed Difluoromethylation of Arylboronic Acids with Bromodifluoromethane

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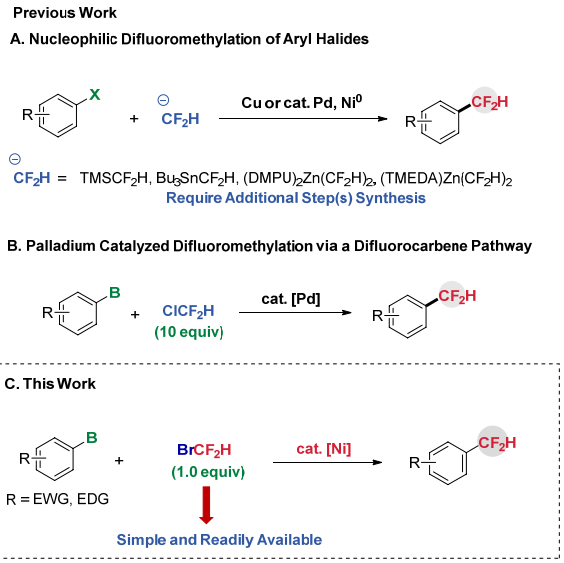
ABSTRACT Although bromodifluoromethane ($BrCF_2H$) is a simple and readily available fluorine source, direct formation of difluoromethylated arenes with $BrCF_2H$ has not been reported. Herein, we describe an efficient method to access difluoromethylated arenes through a nickel-catalyzed difluoromethylation of arylboronic acids with $BrCF_2H$. The reaction exhibits high efficiency, good functional group tolerance and broad substrate scope, thus providing an efficient route for applications in drug discovery and development. Preliminary mechanistic studies reveal that a difluoromethyl radical is involved in the reaction.

KEYWORDS arylboronic acids, bromodifluoromethane, cross-coupling, difluoromethylation, nickel

Introduction

Owing to the unique properties of the fluorine atom and/or C-F bonds, fluorinated compounds are of paramount importance in pharmaceuticals, agrochemicals, and materials science.[1] Although great progresses have been achieved in introduction of fluorine atom(s) into organic molecules,[2] utilization of abundant difluoromethyl halides (CF_2H-X) as the difluromethylating reagents remains challenging. For instance, bromodifluoromethane ($BrCF_2H$) is a simple and readily available fluorine source. However, except for its use as the refrigerant and fire-extinguisher,[3] $BrCF_2H$ has only been used as a difluorocarbene precursor for the preparation of aryl difluoromethyl ethers.[4] The direct introduction of CF_2H group onto aromatics using $BrCF_2H$ has not been reported thus far. Inspired by our recent work on transition-metal-catalyzed difluoroalkylations,[5] we envisioned the feasibility of a transition-metal-catalyzed difluoromethylation of aromatics with $BrCF_2H$.[6-11]

Although successful examples of transition-metal-mediated difluoromethylation of aromatics with nucleophilic difluoromethylating reagents have been reported (Scheme 1A), all the involved difluoromethylating reagents in these methods are expensive and require additional step(s) to prepare from fluoroalkyl halides.[6-12] Very recently, we have developed a palladium-catalyzed difluoromethylation of arylborons with an industrial raw material $ClCF_2H$ via a difluorocarbene pathway,[13] which provides an efficient method to access a wide range of difluoromethylated arenes (Scheme 1B). However, a noble metal palladium catalyst was used in this method. From the point of view of cost-efficiency, the use of abundant and more sustainable catalysts based on first-row transition metals to access difluoromethylated arenes would be more attractive. Herein, we describe a nickel-catalyzed cross-coupling between arylboronic acids and $BrCF_2H$ (Scheme 1C), a low-cost and readily available analogue of $ClCF_2H$.



Scheme 1 Strategies in transition-metal medicated direct difluoromethylation of aromatics.

Results and Discussion

We began our initial studies on the cross-coupling of (1,1-biphenyl)-4-boronic acid **1a** (1.5 equiv) with $BrCF_2H$ **2** (1.0 equiv) in the presence of $NiCl_2$·DME (5 mol%) with a variety of ligands in dioxane (Table 1, for details, see the Supporting Information). We found that the reaction was very sensitive to the nature of the ligands. Among the tested ligands, the diamine ligand bipyridyl (bpy) or 1,10-phenanthroline (phen) could provide the desired difluoromethylated arene **3** in 14% yield (entry 1), but terpyridyl and bidentate phosphane ligands, such as dppf and dppe, failed to afford **3**. A survey of the nickel catalysts with bpy as a ligand showed that a variety of nickel sources could provide **3** in a range of 8% to 55% yields (entries 2-6, for details, see the Supporting Information), in which $Ni(PPh_3)_2Br_2$ was proved to be the superior one, providing **3** in 55% yield along with 3% yield of

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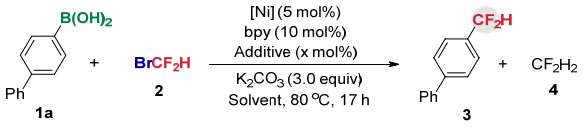
hydrodebrominated CF_2H_2 and 16% yield of unreacted $BrCF_2H$ (entry 6). An improved the yield (63%) of **3** was obtained by switching the solvent from dioxane to THF with 4.0 equiv of K_2CO_3 as a base (entry 7). However, the increased yields of byproduct **4** and unreacted **2** were also observed (entry 7). This outcome is probably a result of the low reactivity of $BrCF_2H$. Accordingly, a ligand combo system [(2+1), a bidentate ligand plus a monodentate ligand] was used to modulate the electronic and steric properties of the nickel center to facilitate the catalytic cycle.[5b, 5c, 14] We observed that when an extra electron-rich monodentate ligand 4-methoxypyridine (10 mol %) was used, the yield could be improved to 78% (entry 10). Remarkably, the use of more electron-rich DMAP (5 mol %) provided **3** in a yield as high as 92% upon isolation (entry 12). But electron-deficient 4-trifluoromethylpyridine led to a decreased yield (entry 9). It was also found that the use of PPh_3 showed beneficial effect, but led to lower yield (70%) than that of DMAP (90%) (entry 13). No product **3** was observed without nickel or bpy (entries 14 and 15), thus demonstrating the essential role of Ni/bpy in promotion of the reaction.

Table 1 Representative results for optimization of Ni-catalyzed difluoromethylation of **1a** with $BrCF_2H$ **2**.[a]

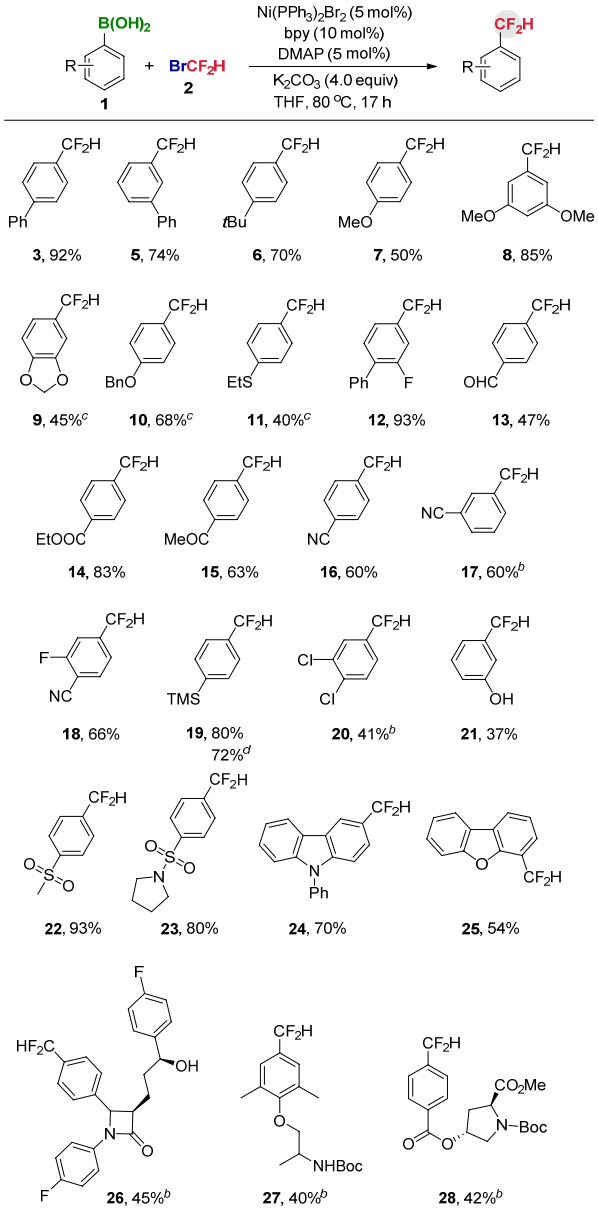


Entry	[Ni]	Additive (x)	Yield (%),[b] **3** / **4** / **2**
1	$NiCl_2$·DME	/	14 / nd / 68
2	$NiCl_2$	/	8 / 7 / 44
3	$Ni(NO_3)_2·6H_2O$	/	20 / -- / 59
4	$Ni(PPh_3)_2Cl_2$	/	18 / -- / 65
5	$Ni(dppf)Cl_2$	/	39 / 4 / 17
6	$Ni(PPh_3)_2Br_2$	/	55 / 3 / 16
7[c]	$Ni(PPh_3)_2Br_2$	/	63 / 16 / 29
8[c]	$Ni(PPh_3)_2Br_2$	Py (10)	65 / trace / nd
9[c]	$Ni(PPh_3)_2Br_2$	4-CF_3-Py (10)	61 / 5 / nd
10[c]	$Ni(PPh_3)_2Br_2$	4-MeO-Py (10)	78 / trace / nd
11[c]	$Ni(PPh_3)_2Br_2$	DMAP (10)	81 / 7 / nd
12[c]	$Ni(PPh_3)_2Br_2$	DMAP (5)	90 (92) / 5 / nd
13[c]	$Ni(PPh_3)_2Br_2$	PPh_3 (10)	70 / 3 / nd
14[c]	/	DMAP (5)	0 / 13 / 60
15[c, d]	$Ni(PPh_3)_2Br_2$	DMAP (5)	0 / 15 / 40

[a]Reaction conditions (unless otherwise specified): **1a** (0.45 mmol, 1.5 equiv), **2** (3 M in 1, 4-dioxane, 0.3 mmol, 1.0 equiv), K_2CO_3 (3.0 equiv), 1,4-dioxane (2.5 mL). [b]Determined by ^{19}F NMR using fluorobenzene as an internal standard and number in parenthesis is isolated yield. [c]K_2CO_3 (4.0 equiv) and THF (2.5 mL) were used. [d]Reaction run in the absence of bpy.

With the optimized reaction conditions in hand, a variety of arylboronic acids were examined (Scheme 2). Generally, arylboronic acids bearing both electron-donating and electron-withdrawing substituents all showed good reactivity towards $BrCF_2H$, providing the corresponding difluoromethylated arenes in good to high yields (**5**-**18**). This is in sharp contrast to previous nickel catalyzed nucleophilic difluoromethylation of aryl iodides, in which electron-rich aryl iodides led to no or poor yields.[10] The reaction exhibited high tolerance to functional groups. Many important functional groups including base or nucleophile-sensitive moieties, such as formyl, alkoxycarbonyl, enolizable ketone, cyano, silyl, sulfuryl, and thioether, even towards chloride (**13**-**23**, **11**) were compatible with the reactions. Remarkably, phenol-containing aryl boronic acids was also amenable to the reaction. Although 37% yield of **21** was obtained, it is difficult to access such a kind of structural motif through conventional methods. Although $BrCFH_2$ is a gas and only 1.0 equiv of it was used in the reaction, it is also possible to scale up the reaction.[15] For instance, 4 mmol-scale synthesis of compound **19** proceeded smoothly with a 72% yield obtained, thus highlighting the reliability and practicability of current process. Additionally, dibenzo[*b*,*d*]furan and carbazole-derived boronic acids also furnished the corresponding products in good yields (**24** and **25**). However, *ortho*-substituted arylboronic acids failed to provide corresponding product.

Scheme 2 Ni-catalyzed difluoromethylation of arylboronic acids with $BrCF_2H$.[a]



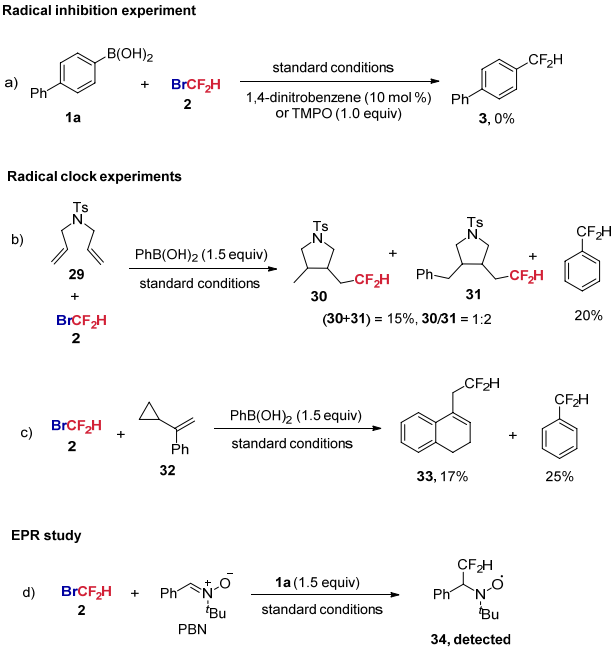
[a]Reaction conditions (unless otherwise specified): **1** (1.5 equiv), **2** (3 M in 1, 4-dioxane, 0.3 mmol, 1.0 equiv), THF (2.5 mL), 80 °C, 17 h. Yields of isolated products are given. [b]$Ni(PPh_3)_2Br_2$ (10 mol%), bpy (20 mol%), DMAP (10 mol%) were used. [c]5,5´-dibromo-2,2´-bipyridine (10 mol%) was used. [d]4

mmol-scale synthesis.

Most importantly, the current strategy can also provide straightforward approach to access valuable, difluoromethylated molecules at the end of a medicinal chemistry development effort. As shown in Scheme 2, late-stage difluoromethylation of ezetimibe derived arylboronic acid, a potent inhibitor of cholesterol absorption,[16] was successfully carried out without protection of the free hydroxyl (**26**). A non-selective voltage-gated sodium channel blocker mexiletine[17] derived boronic acid could also be transferred into the corresponding difluoromethyltated analogue **27** in a considerable yield, thus demonstrating the utility of this reaction in medicinal chemistry further. Moreover, the current nickel-catalyzed process was also applicable to direct difluoromethylation of proline containing arylboronic acid (**28**). Since fluoralkylated amino acids have important applications in chemical biology, it may open a new window to discover some interesting biologically active molecules.

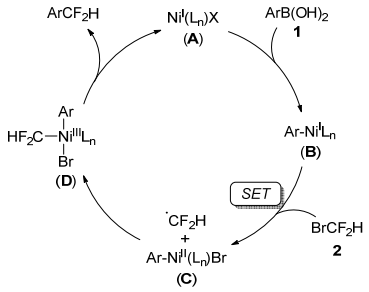
To gain some mechanistic insights into the current reaction, a series of experiments were conducted (Scheme 3). Radical inhibition experiment showed that the reaction could be readily inhibited by addition of catalytic amount of electron transfer scavenger 1,4-dinitrobenzene or 1.0 equiv of TMPO (Scheme 3a). A mixture of ring-closing products **30** and **31** were observed (**30**+**31**, 15% yield, **30**/**31** = 1:2) when the reaction of phenylboronic acid with $BrCF_2H$ was treated with *N*,*N*-diallyl-4-methylbenzenesulfonamide **29** under standard reaction conditions (Scheme 3b). In addition, the reaction of **2** with α-cycloproylstyrene **32**[18] led to a ring-expanded product **33** in a 17% yield (determined by ^{19}F NMR, Scheme 3c). Thus, these results indicate that a difluoromethyl radical is involved in the reaction. The formation of radical intermediate was further confirmed by the ESR study of reaction of $BrCF_2H$ with spin-trapping agent phenyl *tert*-butyl nitrone (PBN), in which a signal of spin adduct of trapped $HCF_2\cdot$ radical $HCF_2CHPhN(O\cdot)$-*t*-Bu **34** was observed (Scheme 3d, for details, see the Supporting Information), demonstrating that a difluoromethyl radical is generated in the reaction.

Scheme 3 Radical trapping experiments



On the basis of above results and previous reports,[19] a plausible mechanism via a Ni(I/III) catalytic cycle was proposed. As illustrated in Scheme 3, the initial step of the reaction would be the transmetalation between arylboronic acids and $[Ni^{I}L_nX]$ (**A**), which was supposed to be generated by comproportionation of *in situ* generated Ni^0 and the remaining Ni^{II} species.[20] Subsequently, the resulting arylnickel complex $[ArNi^{I}L_n]$ (**B**) would react with $BrCF_2H$ via a single electron transfer (SET) pathway to produce the arylnickel (difluoromethyl) complex $[(Ar)(CF_2H)Ni^{III}L_nX]$ (**D**). Finally, **D** would undergo reductive elimination to deliver products difluoromethylated arenes and regenerate $[Ni^{I}]$ simultaneously.

Scheme 4 Proposed mechanism



Conclusions

In conclusion, we have developed the first example of nickel-catalyzed cross-coupling of arylboronic acids with $BrCF_2H$. Although $BrCF_2H$ is prone to generation of difluorocarbene under basic conditions,[4] the current nickel-catalyzed process has circumvented this limitation and enables the reaction to carry out via a difluoromethyl radical pathway, thus complementing the applications of $BrCF_2H$ in organic synthesis. Further detailed mechanistic studies and related reaction are currently underway in our laboratory.

Experimental

General Procedure for Ni-Catalyzed Cross-Coupling of Arylboronic Acids 1 with $BrCF_2H$ 2. To a 25 mL of Schlenk tube was added arylboronic acid **1** (0.45 mmol, 1.5 equiv), $Ni(PPh_3)_2Br_2$ (5 mol%), bpy (10 mol%), DMAP (10 mol%), and K_2CO_3 (4.0 equiv) under air. The mixture was then evacuated and backfilled with argon (3 times). THF (2.5 mL) and $BrCF_2H$ **2** (3 M in 1, 4-dioxane, 100 μL, 0.3 mmol, 1.0 equiv) were added subsequently. The Schlenk tube was screw capped and put into a preheated oil bath (80 °C). After stirring for 17 h, the reaction mixture was cooled to room temperature. The reaction mixture was diluted with ethyl acetate and filtered with a pad of celite. The filtrate was concentrated, and the residue was purified with silica gel chromatography to give product.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

Acknowledgement (optional)

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[15] Although it is a gas, the solubility of $BrCFH_2$ in dioxane is good and the saturated solution of $BrCFH_2$ in dioxane is more than 4M. A control experiment by heating 0.3 mmol of $BrCFH_2$ (3 M in dioxane) in THF (2.5 mL) for 17 h at 80 °C in a 25 mL of sealed Schlenk tube was conducted, and only 2% weight of $BrCFH_2$ was lost.

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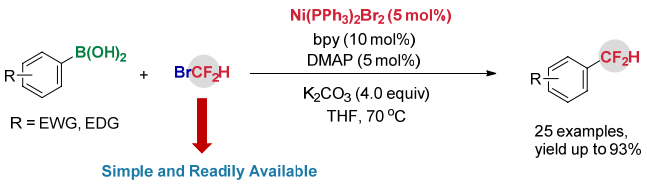

An efficient method to access difluoromethylated arenes through a nickel-catalyzed difluoromethylation of arylboronic acids with $BrCF_2H$ has been described. The reaction exhibits high efficiency, good functional group tolerance and broad substrate scope, thus providing an efficient route for applications in drug discovery and development.

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