

Nickel-Catalyzed Cross-Coupling of Functionalized Difluoromethyl Bromides and Chlorides with Aryl Boronic Acids: A General Method for Difluoroalkylated Arenes**

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Dedicated to Professor Li-Xin Dai on the occasion of his 90th birthday

Abstract: Transition-metal-catalyzed difluoroalkylation of aromatics remains challenging despite the importance of difluoroalkylated arenes in medicinal chemistry. Herein, the first successful example of nickel-catalyzed difluoroalkylation of aryl boronic acids is described. The reaction allows access to a variety of functionalized difluoromethyl bromides and chlorides, and paves the way to highly cost-efficient synthesis of a wide range of difluoroalkylated arenes. The notable features of this protocol are its high generality, excellent functional-group compatibility, low-cost nickel-catalyst, and practicality for gram-scale production, thus providing a facile method for applications in drug discovery and development.

Fluorinated arenes are an important class of substituted aromatic compounds owing to their presence in numerous biologically active molecules and functional materials.^[1] Although great endeavors have been made in introducing fluoroalkylated groups onto aromatic rings and significant progress has been achieved over the past few years,^[2] developing reliable methods with high generality and practicality remains appealing in this area.^[3] Particularly, in the case of difluoroalkylation of arenes, only a few examples have been reported so far because of the lack of general and efficient strategies.^[4,5] In view of the unique properties of the difluoromethylene group (CF_2), which can serve as a bioisostere for an oxygen atom or a carbonyl group^[6] and has important applications in biologically active molecules,^[7] it is highly desirable to develop a general strategy and efficient methods for the preparation of such a valuable structural motif. In this context, the transition-metal-catalyzed difluoroalkylation of aromatics between fluoroalkyl halides ($\text{R}_f\text{-X}$) and aryl metals would be attractive, as the C–C bond formation catalyzed by transition metals has proven to be a powerful strategy owing to its high efficacy, broad substrate scope, and excellent functional-group compatibility. How-

ever, such a transformation remains challenging for the difluoroalkylation of arenes because: 1) some of the difluoroalkylated metal species formed from the reaction of a transition metal and $\text{R}_f\text{-X}$ are prone to decomposition and lead to difluoroalkanes, difluoroalkyl dimers, and/or other uncertain by-products;^[8] and 2) the reductive elimination of the transition-metal intermediate arylmetal fluoroalkyl $[\text{ArM}(\text{L}_n)\text{R}_f]$ is slower compared to its nonfluorinated counterpart.^[5f] As a result, it is difficult to control the catalytic cycle to obtain the desired difluoroalkylated arenes.

To date, the palladium-^[5d–g,9] and copper-catalyzed^[5a–c,10] fluoroalkylation of arenes have become two major methods to access fluoroalkylated arenes. However, the former method requires an expensive palladium catalyst and phosphine ligands, and the latter method is limited by substrate scope and/or expensive fluoroalkylated reagents. Yet the use of other abundant and cost-efficient transition metals as catalysts has been scarcely explored.^[11] Recently, the preparation of nickel(II) fluoroalkyl complexes has been documented.^[12] But all of these prepared nickel(II) species were thermally stable and failed to produce fluoroalkylated arenes under thermal conditions.^[12a] To the best of our knowledge, the nickel-catalyzed fluoroalkylation of arenes using aryl metals and $\text{R}_f\text{-X}$ ($\text{R}_f = \text{CF}_2\text{R}$, CF_3) have not been reported so far,^[13] and the nickel-catalyzed fluoroalkylation reactions remain underdeveloped, thus representing a great challenge. What is more, to date, although fluoroalkyl chlorides ($\text{R}_f\text{-Cl}$) are among one of the cheapest sources of R_f groups, the transition-metal-catalyzed cross-coupling between aryl metals and $\text{R}_f\text{-Cl}$ ($\text{R}_f = \text{CF}_2\text{R}$, CF_3) has never been reported because of their relatively stronger C–Cl bond.

As a part of ongoing efforts on the transition-metal-catalyzed direct introduction of fluorinated functional groups into organic molecules,^[5b–c,14] we herein demonstrate the first example of nickel-catalyzed difluoroalkylation of aryl boronic acids. The reaction provides a variety of functionalized difluoromethyl bromides and chlorides (RCF_2X , $\text{X} = \text{Br}$, Cl ; $\text{R} = \text{CO}_2\text{Et}$, CONR^3R^4 , COR^5 , heteroaryl), and paves the way for highly efficient synthesis of a wide range of difluoroalkylated arenes. This protocol has several notable advantages: 1) broad substrate scope; 2) excellent functional-group compatibility, even towards bromide; 3) 2.5–5 mol % $\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ as the catalyst; and 4) practical for gram-scale production. Therefore, this route represents a highly cost-efficient method for the general synthesis of difluoroalkylated arenes. To demonstrate the usefulness of this protocol, late-

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stage functionalization for the synthesis of difluoroalkylated bioactive molecules has been performed.

We began this study by choosing bromodifluoroacetate (**1a**) as one of the difluoroalkyl halides because of its low cost, ready availability, and the potential for various modifications of the CO₂Et moiety in subsequent transformations. Initially, when **1a** was treated with air-stable phenyl boronic acid (**2a**) in the presence of NiCl₂·DME (5 mol %), terpyridine (tpy) (5 mol %), and K₂CO₃ (2 equiv) in 1,4-dioxane at 80 °C, some unidentified by-products were detected instead of the desired product **3a** (Table 1, entry 1). In addition, the side-product

Table 1: Representative results for optimization of nickel-catalyzed cross-coupling of bromodifluoroacetate (**1a**) with phenyl boronic acid (**2a**)^[a]

Entry	[Ni] (x)	Ligand (y)	3a/4 Yield [%] ^[b]
1	NiCl ₂ ·DME (5)	tpy (5)	1/7
2	NiCl ₂ ·DME (5)	phen (5)	32/13
3	NiCl ₂ ·DME (5)	bpy (5)	86/2
4	NiCl ₂ ·DME (5)	L1 (5)	51/12
5	NiCl ₂ ·DME (5)	L2 (5)	13/8
6	NiCl ₂ ·DME (5)	L3 (5)	58/6
7	NiCl ₂ ·DME (5)	L4 (5)	0/2
8	NiCl ₂ ·DME (5)	L5 (5)	87/ < 1
9	Ni(NO ₃) ₂ ·6 H ₂ O (5)	bpy (5)	91/4
10 ^[c]	Ni(NO ₃) ₂ ·6 H ₂ O (2.5)	bpy (2.5)	98 (87)/2

[a] Reaction conditions (unless otherwise specified): **1a** (0.3 mmol, 1.0 equiv), **2a** (1.5 equiv), 1,4-dioxane (2 mL), 8 h. [b] Determined by ¹⁹F NMR spectroscopy using fluorobenzene as an internal standard and the number within parentheses represents the yield of the isolated product. [c] **1a** (0.6 mmol, 1.0 equiv), **2a** (1.5 equiv), 1,4-dioxane (4 mL) at 60 °C for 24 h. DME = dimethyl ether.

HCF₂CO₂Et (**4**; 7 % yield) and the homocoupled product (CF₂CO₂Et)₂ (**5**; 3 %) were also detected in the reaction. To suppress the competitive side reactions and improve the reaction efficiency, different tri-/diamine ligands were examined because the tri-/diamine ligands can stabilize the homogenous nickel complexes by chelation and increase electron density at the nickel center (Table 1, entries 2–8). Among the tested ligands, the triamine ligand pybox led to similar negative results (for details, see the Supporting Information). But the diamine ligand, 1,10-phenanthroline (phen) furnished **3a** in 32 % yield, albeit with the generation of 13 % yield of **4** (Table 1, entry 2). Importantly, the formation of the homocoupled by-product **5** was totally inhibited by using diamine ligands. To our delight, when bipyridine (bpy) was examined a dramatically improved yield of **3a** (86 %, determined by ¹⁹F NMR spectroscopy), along with 2 % yield of the protonated side-product **4**, was obtained (Table 1, entry 3). A comparable yield (87 % determined by

¹⁹F NMR spectroscopy) of **3a** was also obtained when 3,3'-dimethyl-2,2'-bipyridine (**L5**) was tested (Table 1, entry 8). However, other diamine ligands were less effective. Encouraged by these results, we investigated a variety of nickel catalysts, bases, and solvents, and found that the reaction was not sensitive to the nature of nickel salts (for details, see the Supporting Information), and low-cost Ni(NO₃)₂·6H₂O was the optimum precatalyst, thus providing **3a** in 91 % yield (determined by ¹⁹F NMR spectroscopy) along with 4 % yield of **4** (Table 1, entry 9). However, the choice of solvent and base are crucial for the reaction efficiency, and 1,4-dioxane and K₂CO₃ were the best choice (for details, see the Supporting Information). Other solvents and bases led to either lower yields or no product. Finally, the optimal reaction conditions were identified by decreasing the reaction temperature to 60 °C and using 2.5 mol % Ni(NO₃)₂·6H₂O and 2.5 mol % bpy for 24 hours, thus providing **3a** in 87 % yield upon isolation (Table 1, entry 10). No product was observed in the absence of the nickel catalyst or ligand, thus demonstrating that nickel does play a catalytic role to promote the reaction in a highly efficient way.

With the optimized reaction conditions, a wide range of difluoroacyl arenes were generated by this method (Table 2). Overall, aromatic boronic acids bearing either electron-rich

Table 2: Nickel-catalyzed difluoroalkylation of organoboronic acids with bromo/chlorodifluoroacetate.^[a]

[a] Reaction conditions (unless otherwise specified): **1** (0.6 mmol), **2** (1.5 equiv), 1,4-dioxane (4 mL), 24 h. [b] Reaction conducted at 80 °C. [c] **1** (0.6 mmol), **2** (2.0 equiv), Ni(NO₃)₂·6H₂O (5 mol %), bpy (5 mol %), PPh₃ (5 mol %), 80 °C. [d] Reaction carried out on a gram scale.

or electron-deficient substituents all led to **3** in moderate to high yields. Many important functional groups, such as the alkoxycarbonyl, enolizable ketone, nitrile, and methylsulfonyl, were quite well-tolerated (**3f–i**). Most remarkably, aromatic boronic acids bearing a bromide underwent reaction smoothly with yield as high as 95 % (**3k**). Even benzyl bromide, an active electrophile, was compatible with the present catalytic system, thus providing **3l** in good yield.

These results are in sharp contrast to those of previous palladium-catalyzed reactions, in which bromide-containing aryl boronic acids are unsuitable substrates.^[5d] Furthermore, the sterically hindered *o*-tolylboronic acid was also a competent coupling partner leading to high product yield (**3c**). On the contrary, no **3c** was provided when palladium was used as the catalyst. Thus, compared to previous methods,^[5a,d] the present nickel catalytic system not only features its low cost, but also exhibits a wide substrate scope towards the formation of difluoroalkylated arenes. It is also possible to prepare difluoroalkylated arenes on a gram scale. High yield was obtained for the gram-scale synthesis of **3k**, thus offering a reliable and practical access to highly functionalized difluoroalkylated arenes.

To demonstrate the generality of this catalytic system, the chlorodifluoroacetate (**1b**) was explored. To our delight, by increasing the amount of $\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ to 5 mol % in conjunction with PPh_3 (5 mol %) as a ligand, good yields of the difluoroacyl arenes were still obtained (**3a–e**). Although some functional groups containing aryl boronic acids led to low yields (**3f** and **3h**), this is the first example of transition-metal-catalyzed fluoroalkylation of aryl metals with $\text{R}_f\text{–Cl}$. We believe that this cross-coupling process will prompt the research in nickel-catalyzed fluoroalkylation reactions with $\text{R}_f\text{–Cl}$.

This advantage has been further demonstrated by extending the scope of the difluoroalkyl halides to bromo/chlorodifluoroacetamides and α -bromo/chloro- α,α -difluoroketones (Table 3). Good yields were obtained when bromo/chlorodifluoroacetamides were examined (**6a,b**). Importantly, the protic amide did not interfere with the reaction (**6b**). The α -bromo- α,α -difluoroacetophenones were also suitable substrates, thus providing their corresponding difluoroalkylated arenes with high efficiency (**6c–e**). This reactivity is noteworthy, as it has been demonstrated that the α -aryl- α,α -difluoroacetophenone products could be converted into various difluoroalkylated molecules.^[5f] It should be mentioned that the alkyl-substituted α -bromo- α,α -difluoroketone also reacted smoothly, thus providing **6f** in high yield (93 %). To the best of our knowledge, this is the first example to access such difluoroalkylated arenes through a transition-metal-catalyzed process, thus further highlighting the wide application scope of the present catalytic system. What is more, the α -chloro- α,α -difluoroketone was also a competent coupling partner, thus providing its corresponding product in good yield (**6c**).

The reaction was not restricted to bromo/chlorodifluoroacetate (**1a,b**) and their derivatives, as some other functionalized difluoromethyl bromides and chlorides were also investigated. Bromodifluoromethylbenzoxazole^[15] furnished the corresponding aryl(heteroaryl)difluoromethane in good yields (**6g–m**). The bromodifluoromethylated thiazole and benzimidazole^[15] were also applicable to the cross-coupling reactions, thus providing **6n** and **6o**, respectively, with high efficiency. This reactivity is noteworthy, as benzoxazole, benzimidazole, thiazole, and their derivatives are a class of prominent structural motifs in numerous pharmaceuticals and agrochemicals.^[16] Importantly, heteroaryl difluoromethyl chlorides also underwent the reactions smoothly, thus provid-

Table 3: Nickel-catalyzed difluoroalkylation of organoboronic acids with functionalized difluoromethyl bromides and chlorides.^[a]

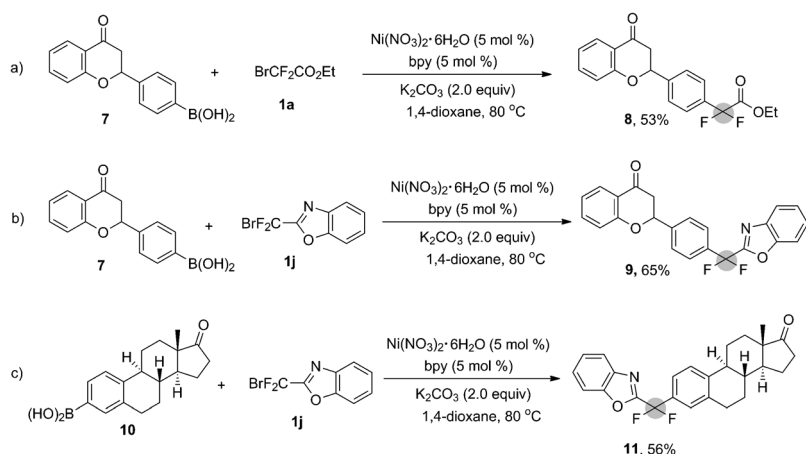
$\text{R}^1\text{--C}_6\text{H}_4\text{--B(OH)}_2 + \text{XCF}_2\text{R}^2 \xrightarrow[\text{K}_2\text{CO}_3 (2.0 \text{ equiv}), 1,4\text{-dioxane}, 80^\circ\text{C}]{\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O} (2.5\text{--}5 \text{ mol } \%), \text{bpy} (2.5\text{--}5 \text{ mol } \%)}$			$\text{R}^1\text{--C}_6\text{H}_4\text{--CF}_2\text{R}^2$
2	1	X = Br, Cl	6
	6a , X = Br, 73% X = Cl, 85% ^[b]		6b , X = Br, 88%
	6c , X = Br, 93% X = Cl, 65% ^[b]		6d , X = Br, 52% ^[c]
	6e , X = Br, 73%		6f , X = Br, 93%
	6g , X = Br, 87% ^[d] X = Cl, 88% ^[b]		6h , X = Br, 73% ^[d] X = Cl, 84% ^[b]
	6i , X = Br, 83% ^[d] X = Cl, 94% ^[b]		6j , X = Br, 62% ^[d] X = Cl, 95% ^[b]
	6k , X = Br, 87% ^[d] X = Cl, 86%		6l , X = Br, 93% ^[d] X = Cl, 87%
	6m , X = Br, 68% ^[d]		6n , X = Br, 85% ^[d]
	6o , X = Br, 69% ^[d] X = Cl, 77% ^[b]		

[a] Reaction conditions (unless otherwise specified): **1** (0.6 mmol), **2** (1.5 equiv), $\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ (2.5 mol %), bpy (2.5 mol %), 1,4-dioxane (4 mL), 24 h. [b] **1** (0.6 mmol), **2** (2.0 equiv), $\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ (5 mol %), bpy (5 mol %), PPh_3 (5 mol %). [c] $[\text{NiCl}_2(\text{dppe})]$ (2.5 mol %). [d] $\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ (5 mol %), bpy (5 mol %). dppe = 1,2-Bis(diphenylphosphino)ethane.

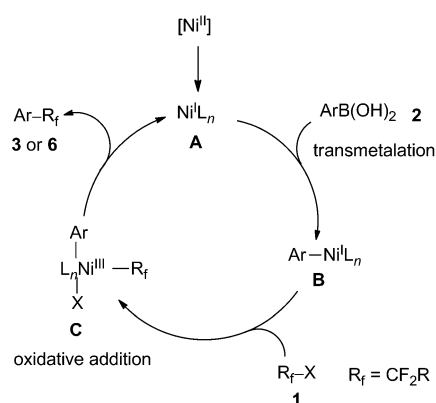
ing the corresponding products in even higher yields (**6g–l,o**). To date, however, there has been no efficient and reliable method to access such difluoroalkylated arenes.^[17] Thus, the present process provides a facile route for applications in drug discovery and development.

To demonstrate the importance and utility of this method, the late-stage difluoroalkylation of biologically active molecules was performed. As shown in Scheme 1 a–c, treatment of the flavanone-derived aryl boronic acid **7** with the difluoroalkyl bromides **1a** and **1j** afforded difluoroalkylated compounds **8** and **9**, respectively, with good efficiency (Scheme 1 a,b). This transformation provides a highly valuable possibility for drug discovery and development because of the significant bioactivities of flavanone, as well as unique characteristics of CF_2 group. Furthermore, the difluoroalkylated estrone derivative **11** was obtained in good yield, thus further highlighting the importance of this protocol (Scheme 1 c).

On the basis of previous reports,^[18] a plausible reaction mechanism involving a $\text{Ni}^{\text{I}}/\text{Ni}^{\text{III}}$ catalytic cycle was proposed (Scheme 2). The transmetalation between $[\text{Ni}^{\text{I}}\text{L}_n]$ (**A**) and



Scheme 1. Late-stage functionalization for synthesis of biologically active molecules.



Scheme 2. Proposed reaction mechanism.

aryl boronic acids might be the first step. As a consequence of oxidative addition of the fluoroalkyl halides **1** to the resulting $[(\text{Ar})\text{Ni}^{\text{II}}\text{L}_n]$ (**B**) species, an arylnickel fluoroalkyl complex $[(\text{Ar})(\text{R}_f)\text{Ni}^{\text{III}}\text{L}_n\text{X}]$ (**C**) was formed, which then underwent reductive elimination to produce **3** or **6**, and regenerated **A** simultaneously.

In conclusion, we demonstrated the first successful example of nickel-catalyzed difluoroalkylation of aryl boronic acids. Using the diamine ligand *bpy* is critical for the reaction efficiency. The reaction allows a variety of functionalized difluoromethyl bromides and chlorides, and provides a general method for efficient and practical synthesis of difluoroalkylated arenes. Because of the low cost of the nickel catalyst, as well as broad substrate scope and excellent functional-group compatibility of this method, we believe that it will not only be useful for drug discovery and development, but also prompt the research for nickel-catalyzed fluoroalkylation reactions, in particular with fluoroalkyl chlorides. Further studies to uncover the reaction mechanism and to develop derivative reactions are underway in our laboratory.

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