Monofluoromethylation

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Nickel-Catalyzed Monofluoromethylation of Aryl Boronic Acids**

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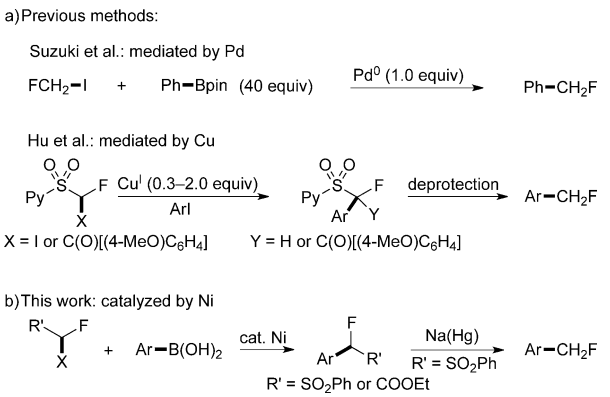
The incorporation of fluorine atoms into small organic molecules can often drastically enhance the metabolic stability, lipophilicity, and bioavailability, and can also increase the receptor-binding affinity and the selectivity relative to the parent molecule.[1] As a result, fluorine-containing compounds have been widely used in pharmaceutical and agrochemical products.[2] Recently, the selective introduction of monofluoromethyl groups into small organic molecules has emerged as a new strategy in drug design. Notably, many biologically active molecules, including the widely prescribed afloqualone, fluticasone propionate, and the anaesthetic sevoflurane, contain a CH_2F group as an essential motif.[3]

Although a variety of methods for the transition-metal-catalyzed trifluoromethylation[4] and difluoromethylation[3b,5] of arenes have been developed in the past several decades, the incorporation of methyl groups containing a single fluorine (CH_2F) into arenes has been studied to a lesser extent and remains a challenge.[6] The only example of a palladium-mediated direct monofluoromethylation of pinacol phenylboronate was reported by the Suzuki group in 2009.[7] Therein, a stoichiometric amount of palladium and a large excess of the boronic ester (40 equiv) were required, and the yield was modest (57%, Scheme 1). More recently, using fluoromethyl 2-pyridyl sulfone reagents, Hu and co-workers reported a copper-mediated monofluoromethylsulfonylation of aryl iodides.[8a,b] Herein, the requirement of the coordinating 2-pyridylsulfone group prohibits access to other stabilized monofluoromethylating groups. As in the report from Suzuki and co-workers, this reaction is also hampered by the high loading of a transition metal (0.3–2.0 equiv of copper), and also suffers from operational inconvenience imparted by the requisite stepwise addition of reagents. Herein, we report the first example of a nickel-catalyzed monofluoromethylation of aryl boronic acids, wherein the fluoromethylating reagents bear either a phenylsulfone or an ethoxycarbonyl moiety.[9–11]



Scheme 1. Transition-metal-promoted monofluoromethylation.

We commenced our study with phenylboronic acid (**1a**) as the pilot substrate and $PhSO_2CFHI$[8] (**2**) as the coupling partner in the presence of a catalytic amount of $[Ni(acac)_2]$ (5 mol%) in dichloromethane at 100°C. To our delight, the desired fluoro(phenylsulfonyl)methylated product **3a** was obtained in 45% yield when XantPhos (10 mol%) was used as the ligand (Table 1, entry 2). Furthermore, a careful survey of bases (entries 3–6) and solvents (see Table S2 in the Supporting Information) was then performed, which showed the combination of K_2CO_3 and dicholoromethane to be optimal. To improve the yield further, a variety of phosphine and diamine ligands were examined next. In contrast to previous reports on nickel-catalyzed reactions, in which diamine ligands are the most effective, phosphine ligands, including diphosphines (BINAP, dppe and dppf) and monophosphines (PPh_3), afforded the desired fluoromethylated product in up to 87% yield of isolated product (entry 20). Meanwhile, no improvement was found when the reaction temperature was changed (entry 21). Additionally, the investigation of aryl boron reagents showed that triphenylboroxine, usually in equilibrium with **1a**, gave the isolated products in slightly lower yield (75%, entry 23), while phenylboronic ester and trifluoroborate afforded no desired product (see Table S4 in the Supporting Information). Last, the control experiment indicated that none of the fluoromethylated product was obtained without nickel catalyst (entry 24).

With the optimized conditions in hand, we next investigated the scope of the procedure by testing various aryl boronic acids in reaction with **2**. As shown in Scheme 2, *para*-, *meta*-, and even *ortho*-substituted aryl boronic acids are all effective cross-coupling partners, affording the corresponding fluoromethylated arenes in good yields. Aryl boronic acids substituted with electron-donating groups are fluoromethylated smoothly to give the desired product with good yields (**3b–3i**). A range of halogenated boronic acids are also well-

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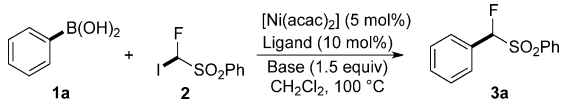
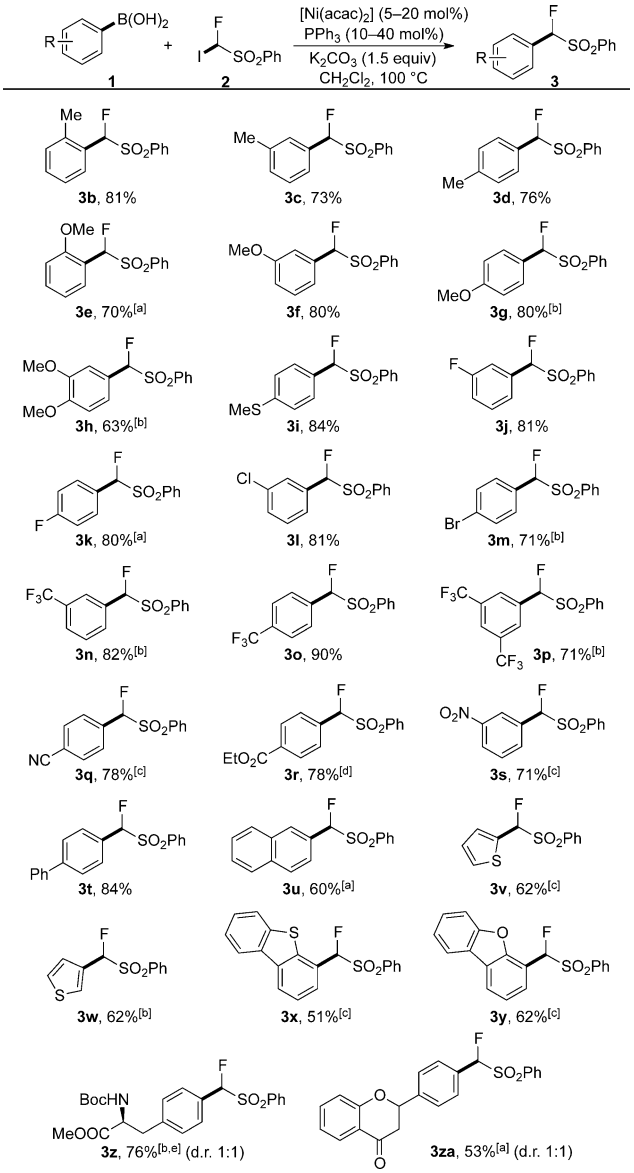
Table 1: Nickel-catalyzed monofluoromethylation of phenylboronic acids: optimization of reaction conditions.[a]



1a 2 3a

Entry	Ligand	Base	Yield [%][b]
1	XantPhos	No	0
2	XantPhos	Cs_2CO_3	45
3	XantPhos	K_2CO_3	48
4	XantPhos	KO*t*Bu	37
5	XantPhos	KOAc	0
6	XantPhos	DABCO	0
7[c]	XantPhos	K_2CO_3	7
8[d]	XantPhos	K_2CO_3	0
9[e]	XantPhos	K_2CO_3	28
10	XPhos	K_2CO_3	20
11	SPhos	K_2CO_3	0
12	BINAP	K_2CO_3	81
13	dppf	K_2CO_3	79
14	dppe	K_2CO_3	89
15	P(o-tol)$_3$	K_2CO_3	11
16	P(2-furyl)$_3$	K_2CO_3	31
17	bpy	K_2CO_3	0
18	TMEDA	K_2CO_3	27
19	DMEDA	K_2CO_3	41
20	PPh_3	K_2CO_3	97 (87[f])
21[g]	PPh_3	K_2CO_3	70
22[h]	PPh_3	K_2CO_3	53
23[i]	PPh_3	K_2CO_3	75[f]
24	PPh_3	K_2CO_3	0[j]

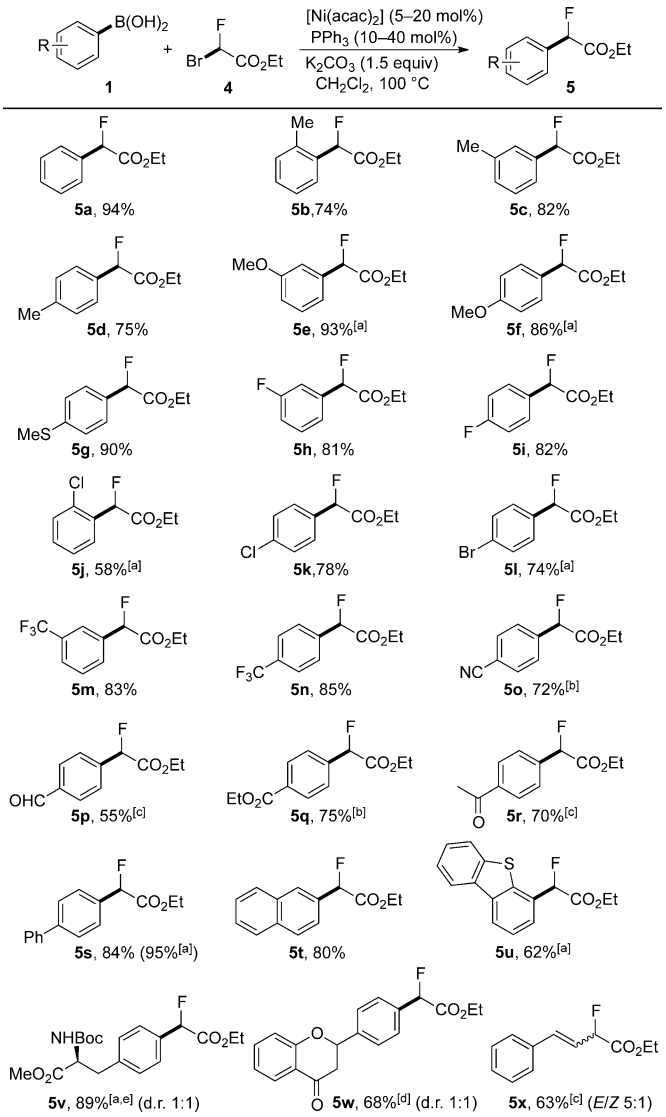
[a] Reaction conditions (unless otherwise noted): $PhSO_2CFHI$ (0.2 mmol, 1.0 equiv), **1a** (2.0 equiv), $[Ni(acac)_2]$ (5 mol%), ligand (10 mol%), base (1.5 equiv), CH_2Cl_2 (2.0 mL), 100°C, 24 h. [b] Yields determined by GC analysis. [c] $CHCl_3$ was used as solvent. [d] DMF was used as solvent. [e] Toluene was used as solvent. [f] Yield of isolated product. [g] Reaction at 80°C. [h] **1a** (1.0 equiv) was used. [i] Triphenylboroxine (1.0 equiv) was used instead of **1a**. [j] No $[Ni(acac)_2]$.



Scheme 2. Scope of substituted phenylboronic acid substrates. Reaction conditions (unless otherwise noted): $PhSO_2CFHI$ (0.2 mmol, 1.0 equiv), **1** (2.0 equiv), $[Ni(acac)_2]$ (5 mol%), PPh_3 (10 mol%), K_2CO_3 (1.5 equiv), CH_2Cl_2, 100°C, 24 h. Yields of isolated products are reported. [a] $[Ni(acac)_2]$ (20 mol%), PPh_3 (40 mol%). [b] $[Ni(acac)_2]$ (10 mol%), PPh_3 (20 mol%). [c] $[Ni(acac)_2]$ (20 mol%), PPh_3 (40 mol%), and **1** (2 equiv) were added in two batches (50% each time). [d] $[Ni(acac)_2]$ (10 mol%), PPh_3 (20 mol%), and **1** (2 equiv) were added in two batches (50% each time). [e] No racemization.

tolerated by this method (**3j**–**3m**). The presence of halo substituents in the products offers the potential for further synthetic elaboration through metal-catalyzed coupling reactions. In particular, aryl boronic acids containing electron-withdrawing groups, including trifluoromethyl (**3n**–**3p**), cyano (**3q**), ester (**3r**), and nitro groups (**3s**), were also fluoroalkylated with satisfactory yields in our catalytic system. Although a higher catalyst and ligand loading is typically required, these arenes are usually ineffective partners in nickel-catalyzed cross-coupling reactions.[10a,11] Additionally, boronic acids derived from polycyclic and heterocyclic arenes, such as *p*-biphenyl (**3t**), 2-naphthyl (**3u**), thiophene (**3v**–**3w**), dibenzothiophene (**3x**), and dibenzofuran (**3y**), are also compatible with the reaction conditions. Finally, even a tyrosine derivative and a flavanone derivative may be monofluoromethylated, leading to **3z** and **3za**, respectively, both in satisfactory yields.

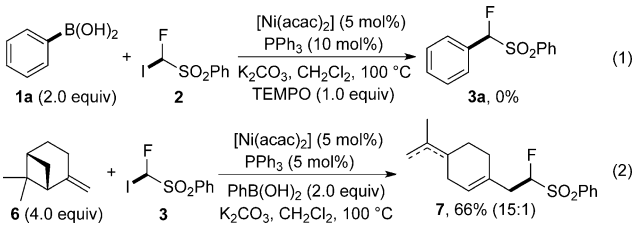
To test whether this method could be extended to fluoromethylating reagents other than sulfone **2**, we examined ethyl 2-bromo-2-fluoroacetate (**4**) as a fluoromethylator. To our excitement, phenylboronic acid was fluoroacetated in excellent yield (94%, Scheme 3, **5a**). The optimized reaction conditions were applied to a variety of boronic acids, furnishing 2-fluoro-2-aryl acetates in yields on par with those observed in the fluoro(phenylsulfonyl)methylations (Scheme 3). Both electron-donating groups, such as methyl, methoxy, and thiomethyl (**5b**–**5g**), and electron-withdrawing groups, such as fluoro, chloro, bromo, trifluoromethyl, cyano, ethoxycarbonyl, acyl, and even an aldehyde (**5h**–**5r**), are well-tolerated using this protocol. A dibenzothiophene-derived boronic acid is also a suitable coupling partner of this fluoroacetation, leading **5u** in a good yield. Again, biologically relevant tyrosine- and flavanone-derived boronic acids



Scheme 3. Scope of substituted phenylboronic acid substrates. Reaction conditions (unless otherwise noted): $EtO_2CCFHBr$ (0.2 mmol, 1.0 equiv), **1** (2.0 equiv), $[Ni(acac)_2]$ (5 mol%), PPh_3 (10 mol%), K_2CO_3 (1.5 equiv), CH_2Cl_2, 100°C, 24 h. Yields of isolated products are reported. [a] $[Ni(acac)_2]$ (10 mol%), PPh_3 (20 mol%). [b] $[Ni(acac)_2]$ (10 mol%), PPh_3 (20 mol%) and **1** (2 equiv) were added in two batches (50% each time). [c] $[Ni(acac)_2]$ (20 mol%), PPh_3 (40 mol%), and **1** (2 equiv) were added in two batches (50% each time). [d] $[Ni(acac)_2]$ (20 mol%), PPh_3 (40 mol%). [e] No racemization.

were monofluoromethylated smoothly under the reaction conditions to give the fluoroalkyl products **5v** and **5w**, respectively, with acceptable yields. Notably, a vinyl boronic acid was also compatible with this method, giving the product in an acceptable yield (63%, **5x**). While electron-deficient aryl- and heteroaryl boronic acids were not suitable coupling partners in the palladium-catalyzed method developed by Qing and co-workers,[9d] our nickel-catalyzed system enables these reagents to be useful coupling partners.

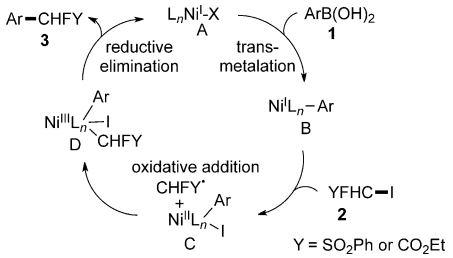
To gain insight into the mechanism of this transformation, a number of control experiments were carried out. First, when the reaction was performed in the presence of 1.0 equivalent of a radical scavenger, namely 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), the monofluoromethylated product **3a** was not obtained [Eq. (1), Scheme 4]. This observation is consis-



Scheme 4. Radical trapping experiments.

tent with reports that the oxidative addition step in nickel-catalyzed cross-couplings proceeds through a radical pathway.[12] We were also able to trap the $PhSO_2CHF\cdot$ radical using β-pinene **6** under our standard conditions, affording the ring-opened diene **7** as a mixture of isomers [Eq. (2), Scheme 4], which further implicated the generation of the fluoro(phenylsulfonyl)methyl radical in the catalytic cycle. Furthermore, catalytic (5 mol%) and stoichiometric amounts of $[Ni(PPh_3)_4]$ were subjected to the standard conditions, respectively, but gave none or only trace amounts of **3a**, thus indicating that the Ni^0 species might not be involved in the catalytic cycle (see the Supporting Information for a detailed discussion).

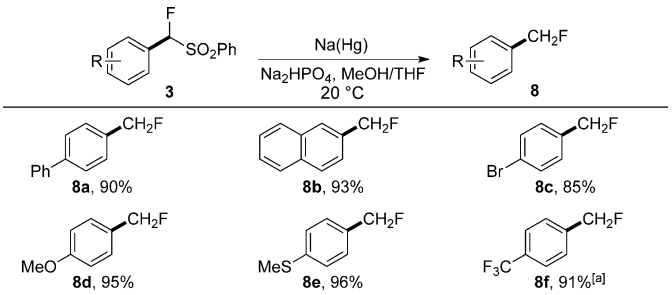
On the basis of the above results and previous reports,[13] a plausible mechanism involving a Ni^I/Ni^{III} catalytic cycle was proposed (Scheme 5). The transmetalation between aryl



Scheme 5. Possible mechanism.

boronic acid **1** and the initial Ni^I species **A**, which may be produced through the comproportionation reaction of in situ generated Ni^0 and the remaining Ni^{II} species,[13a,j] could generate Ni^I–Ar species **B**, which subsequently activates **2** through a single-electron transfer to afford Ni^{II} intermediate **C** and the corresponding alkyl radical. Intermediate **C** is then further oxidized to Ni^{III} species **D** through an oxidative radical addition, followed by reductive elimination to liberate the final monofluoromethylated product **3**.

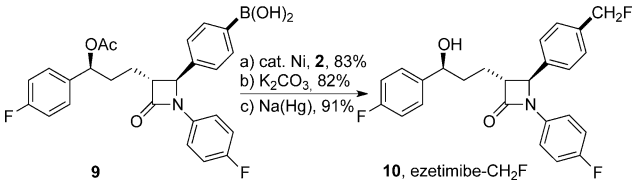
The reductive desulfonylation of **3** mediated by Na(Hg) proceeded smoothly with both electron-donating and electron-withdrawing substituents on the phenyl ring in MeOH/THF at −20°C,[14] affording the fluoromethyl arenes **8a**–**8f** in excellent yields (Scheme 6). In addition, the fluoroacetated arenes **5** can be hydrolyzed under very mild conditions to



Scheme 6. Reductive desulfonylation. Reaction conditions: **3** (0.1 mmol, 1.0 equiv), Na(Hg) (10.0 equiv), Na_2HPO_4, MeOH/THF, −20 °C. Yields of isolated products are reported. [a] ^{19}F NMR yield.

afford the corresponding α,α-fluoroarylethanoic acids in excellent yield (95% for **5s**, see the Supporting Information for details).[15]

To demonstrate both the potential pharmaceutical relevance and the functional-group tolerance of this method, we next attempted to perform a fluoromethylation of ezetimibe, a drug known to lower plasma cholesterol levels.[2c] As shown in Scheme 7, the monofluoromethylation of boronic acid **9**,



Scheme 7. Fluoro(phenylsulfonyl)methylation of ezetimibe derivative **9** and elaboration to ezetimibe-CH_2F **10**. Reaction conditions: [a] $PhSO_2CFHI$ (1.0 equiv), **9** (2.0 equiv), $[Ni(acac)_2]$ (10 mol%), PPh_3 (20 mol%), K_2CO_3 (1.5 equiv), CH_2Cl_2, 100 °C, 83%. [b] K_2CO_3, MeOH/THF, 82%. [c] Na(Hg), MeOH, 91%.

derived from acetated ezetimibe, proceeded smoothly to afford the fluoromethylated ezetimibe **10** in 62% overall yield after subsequent deacylation and desulfonylation. This type of late-stage modification could be highly useful for drug discovery and development as a straightforward method for the synthesis of fluorinated analogues.

In summary, we have developed novel monofluoromethylation and monofluoroacetation reactions of aryl boronic acids using nickel catalysis. Both electron-rich and electron-deficient aryl boronic acids were compatible with this new transformation. Mechanistic investigations indicated that a monofluoromethyl radical is involved in the catalytic cycle. Further examination of the mechanistic details of this catalytic cycle, and the application of this technology to the modification of complex molecules, are ongoing in our laboratory.

Keywords: aryl boronic acid · catalysis · monofluoromethylation · nickel · radicals

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