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# Alkylations of Arylboronic Acids including Difluoroethylation/Trifluoroethylation *via* Nickel-Catalyzed Suzuki Cross-Coupling Reaction

Xiaofei Zhang[a] and Chunhao Yang[a,*]

[a] State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zu Chong Zhi Road, Shanghai 201203, People's Republic of China
E-mail: chyang@simm.ac.cn

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**Abstract:** An efficient alkylation method of functionalized alkyl halides under mild nickel-catalyzed C($sp^3$)–C($sp^2$) Suzuki cross-coupling conditions is described. The features of this approach are excellent functional group compatibility, low cost nickel catalyst, and the use of a mild base. This is also the first successful example of the nickel-catalyzed direct 2,2-difluoroethylation or 2,2,2-trifluoroethylation of aryl-/heteroarylboronic acids.

**Keywords:** C($sp^3$)–C($sp^2$) bond formation; 2,2-difluoroethylation; nickel catalyst; Suzuki cross-coupling; 2,2,2-trifluoroethylation

## Introduction

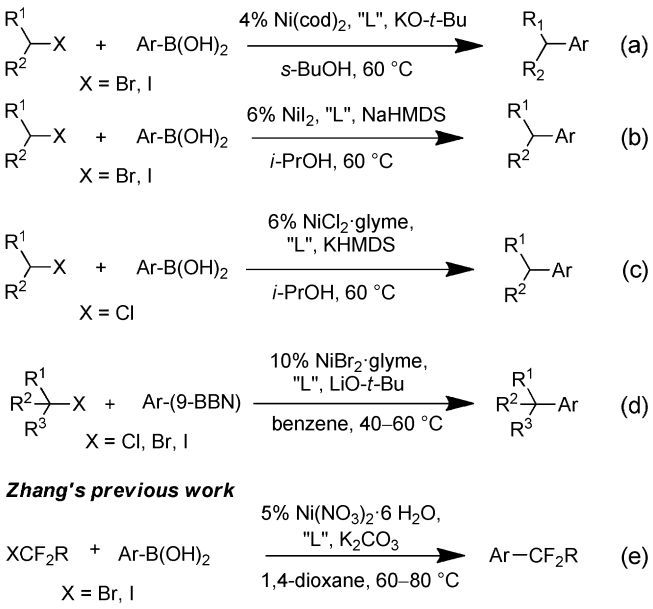
Transition metal-catalyzed C–C coupling reactions are ubiquitous in both academia and industry, and these protocols make it possible to build up complex structures quickly from readily available compounds. Among the C–C coupling reactions, aryl and vinyl electrophiles play an important role because of their high selectivity, high tolerance of functional groups and the wide availability of substrates.[1] Compared to aryl and alkenyl (pseudo) halides, alkyl halides and their equivalents also represent a prominent class of coupling reactions. However, alkyl electrophiles in these reactions are considered to be more challenging due to the difficulties in the oxidative addition step and side reactions, such as β-H elimination and hydrodehalogenation.[2] Since 1992, when the first palladium-catalyzed cross-coupling of alkyl iodides with arylborane reagents was reported by Suzuki and co-workers,[3] the development of C($sp^3$)–C($sp^2$) cross-coupling reactions of alkyl (pseudo) halides with prefunctionalized aryl compounds has gained much more attention. With different cross-coupling partners (aryl halides, Grignard and boronic reagents, etc.), the C ($sp^3$)-C ($sp^2$) formation betweern alkyl halides and aryl compounds can be achieved by Pd,[4] Ni,[5] Fe,[6] and Co[7] catalysts.

Among these transition metal-catalyzed cross-couplings such as Suzuki, Stille, Kumada, Negishi and Hiyama reactions, Suzuki cross-couplings are arguably the most powerful tool for the creation of C($sp^3$)–C($sp^2$) bonds. This may be attributed in a large part to the stable, commercially available boronic reagents and relatively mild reaction conditions. Over 30 years since the discovery of Suzuki cross-coupling in 1979,[8] palladium catalysts were the most frequently investigated until 2004, when the first nickel-catalyzed Suzuki cross-coupling of alkyl halides with arylboronic acids (Scheme 1, a) was described by Fu and coworkers.[5c] About two years later, the same group reported a more practical and robust method[5d] in which the replacement of $Ni(cod)_2$ by stable $NiI_2$ significantly simplified the process of the operation (Scheme 1, b). Furthermore they successfully enabled the cross-couplings of secondary and primary alkyl chlorides (Scheme 1, c)[5d] and unactivated tertiary alkyl halides (Scheme 1, d)[5k] with arylboronic reagents by employing an $NiCl_2$·glyme or $NiBr_2$·glyme complex.

Although the Ni(II)-catalyzed C($sp^3$)–C($sp^2$) Suzuki cross-coupling reactions were greatly promoted by Fu and other scientists, the inevitable application of strong bases like Li/KO-*t*-Bu, Na/KHMDS strictly limited the scope of substrates and the relevant functional groups. Recently, Zhang[9] and coworkers successfully achieved the nickel-catalyzed Suzuki cross-coupling reaction of arylboronic acids with difluoromethyl bromides and chlorides in the presence of $K_2CO_3$. This was one of the few reported examples of Ni(II)-catalyzed C($sp^3$)–C($sp^2$) Suzuki cross-couplings under relatively mild conditions. As

***Fu's previous work***




***Zhang's previous work***



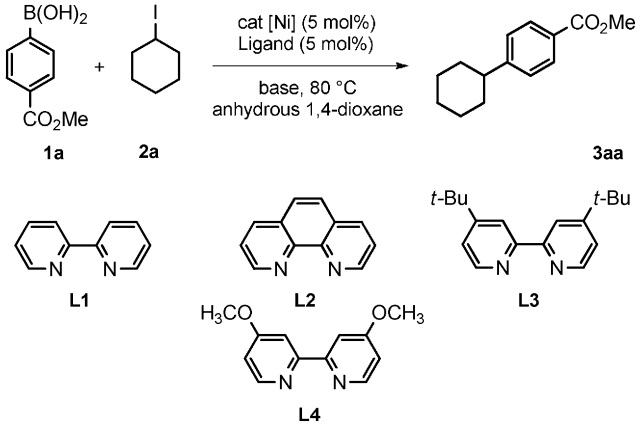

**Scheme 1.** Previous Ni-catalyzed C($sp^3$)–C($sp^2$) Suzuki cross-couplings reported by Fu and Zhang.

far as we know, very few functional groups were mentioned in previous works and the yields were relatively low. Many important functional groups in organic/medicinal chemistry were rarely reported in those literature reports, including aldehyde, lactone, vinyl and cyclopropyl groups. Meanwhile, maybe because of the alkaline conditions, the direct 2,2-difluoroethylation of arylboronic reagents with $ICH_2CF_2H$ still remains unexplored due to the high tendency for β-H elimination of $ICH_2CF_2H$. Moreover, 2,2,2-trifluoroethylation of $ICH_2CF_3$ was performed only by expensive palladium catalyst so far[10].

## Results and Discussion

As one part of our continuing efforts on the transition metal-catalyzed C–C bond construction,[11] and also because of the novel interesting features of target molecules in medicinal chemistry, we are keen about developing a cheap, mild and robust method for Suzuki cross-couplings of generally unactivated alkyl halides including functionalized alkyl halides. We first tested Zhang's optimized conditions for arylboronic acid and unactivated alkyl halides. 4-(Methoxycarbonyl)benzeneboronic acid (**1a**) and iodocyclohexane (**2a**) were used as model substrates. Not surprisingly, the desired cross-coupling product was obtained with only 16% yield under the optimized conditions (Table 1, entry 1). To suppress the side reactions and improve the reaction efficiency, different nickel catalysts and bipyridine (bpy) ligands which were commonly used in nickel-catalyzed Suzuki cross-coupling reactions were examined (Table 1, entries 2–12). $Ni(NO_3)_2{\cdot}6H_2O$ and 4,4′-di-*t*-Bubpy (**L3**) were found to be the most effective catalytic systems. Interestingly, water in the solvent decreased the yield of the reaction (Table 1, entry 3 *vs.* 4) while the crystal water in nickel catalyst was beneficial (Table 1, entry 4 *vs.* 5). In addition, compared to other bases and solvents, $K_2CO_3$ and anhydrous 1,4-dioxane were the best choice for this reaction. Finally, 5 mol% $Ni(NO_3)_2{\cdot}6H_2O$, 5 mol% 4,4′-di-*t*-Bubpy (**L3**) and $K_2CO_3$ (3.0 equiv.) in anhydrous 1,4-dioxane at 80 °C for 12 h under an argon atmosphere were identified

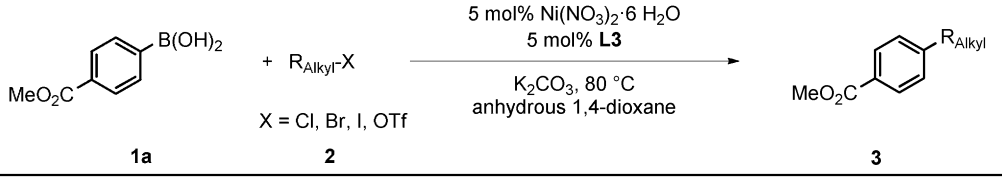
**Table 1.** Survey of reaction conditions[a]



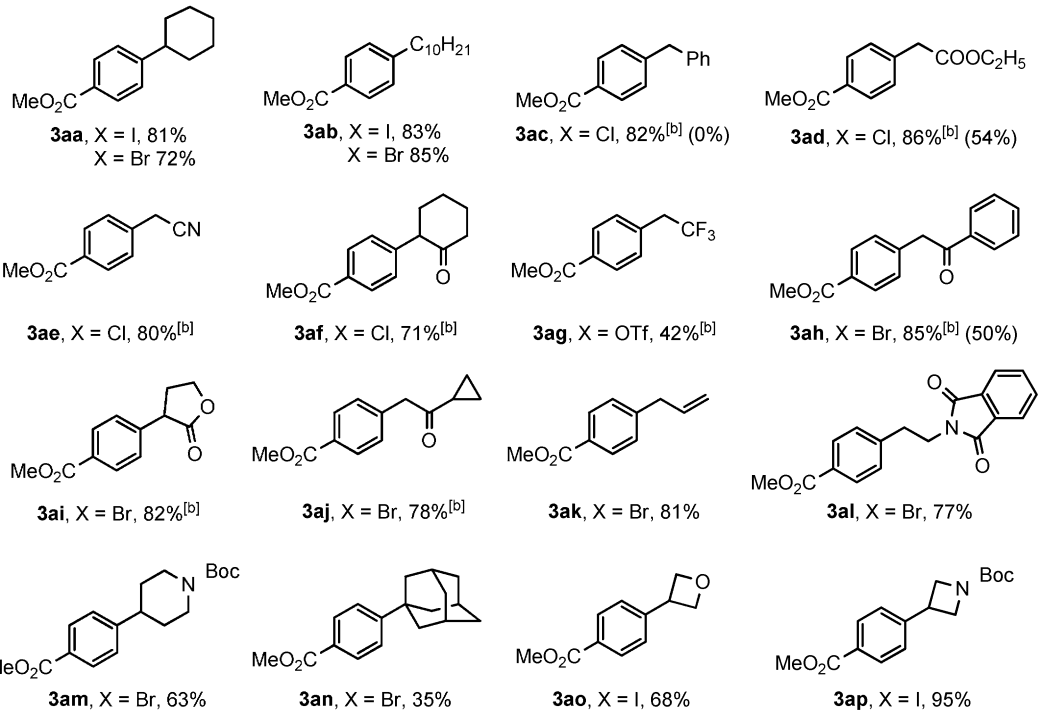

| Entry | Ni catalyst | Ligand | Base | Yield [%][b] |
|---|---|---|---|---|
| 1[c] | $Ni(NO_3)_2{\cdot}6H_2O$ | **L1** | $K_2CO_3$ | 16 |
| 2[d] | $NiCl_2{\cdot}DME$ | **L1** | $K_2CO_3$ | 21 |
| 3[d] | $NiCl_2{\cdot}6H_2O$ | **L1** | $K_2CO_3$ | 35 |
| 4 | $NiCl_2{\cdot}6H_2O$ | **L1** | $K_2CO_3$ | 45 |
| 5 | $NiCl_2$ | **L1** | $K_2CO_3$ | 13 |
| 6 | $Ni(PPh_3)_2Cl_2$ | **L1** | $K_2CO_3$ | 41 |
| 7 | $NiCl_2{\cdot}dppp$ | **L1** | $K_2CO_3$ | 27 |
| 8 | $Ni(OAc)_2{\cdot}6H_2O$ | **L1** | $K_2CO_3$ | trace |
| 9 | $Ni(NO_3)_2{\cdot}6H_2O$ | **L1** | $K_2CO_3$ | 55 |
| 10 | $Ni(NO_3)_2{\cdot}6H_2O$ | **L2** | $K_2CO_3$ | trace |
| 11 | $Ni(NO_3)_2{\cdot}6H_2O$ | **L3** | $K_2CO_3$ | 81 |
| 12 | $Ni(NO_3)_2{\cdot}6H_2O$ | **L4** | $K_2CO_3$ | 50 |
| 13 | $Ni(NO_3)_2{\cdot}6H_2O$ | **L3** | $Na_2CO_3$ | 22 |
| 14 | $Ni(NO_3)_2{\cdot}6H_2O$ | **L3** | $Cs_2CO_3$ | 58 |
| 15[e] | $Ni(NO_3)_2{\cdot}6H_2O$ | **L3** | $K_2CO_3$ | <30 |

[a] *Reaction conditions (unless stated otherwise):* **1a** (0.5 mmol, 1.0 equiv.), **2a** (1.0 mmol, 2.0 equiv.), base (1.5 mmol, 3.0 equiv.), anhydrous 1,4-dioxane (3 mL), 12 h.
[b] Yield of isolated product.
[c] **2a** (0.75 mmol, 1.5 equiv.), $K_2CO_3$ (1.0 mmol, 2.0 equiv.), commercially available 1,4-dioxane (3 mL), 60 °C, 24 h.
[d] Commercially available 1,4-dioxane (3 mL).
[e] Anhydrous toluene, tetrahydrofuran, *N*,*N*-dimethylformamide and dimethyl sulfoxide; DME = dimethyl ether, dppp = 1,3-bis(diphenylphosphino)propane.

**Table 2.** Nickel-catalyzed cross-couplings of **1a** with various alkyl halides[a]




**1a** **2** **3**




[a] *Reaction conditions (unless stated otherwise):* **1a** (0.5 mmol, 1.0 equiv.), **2** (1.0 mmol, 2.0 equiv.), $K_2CO_3$ (1.5 mmol, 3.0 equiv.), anhydrous 1,4-dioxane (3 mL), 12 h, isolated yield.
[b] NaI (0.25 mmol, 0.5 equiv.) was added and isolated yields without NaI are given in parentheses. Boc = *t*-butyloxycarbonyl.

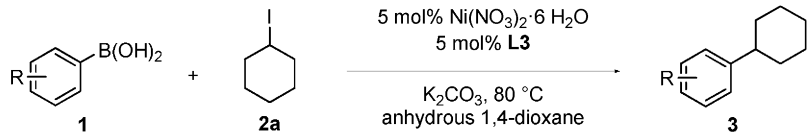
as the optimal conditions and the product was obtained in 81% yield (Table 1, entry 11) (for details, see the Supporting Information). No desired product was detected in the absence of the nickel catalyst or ligand.

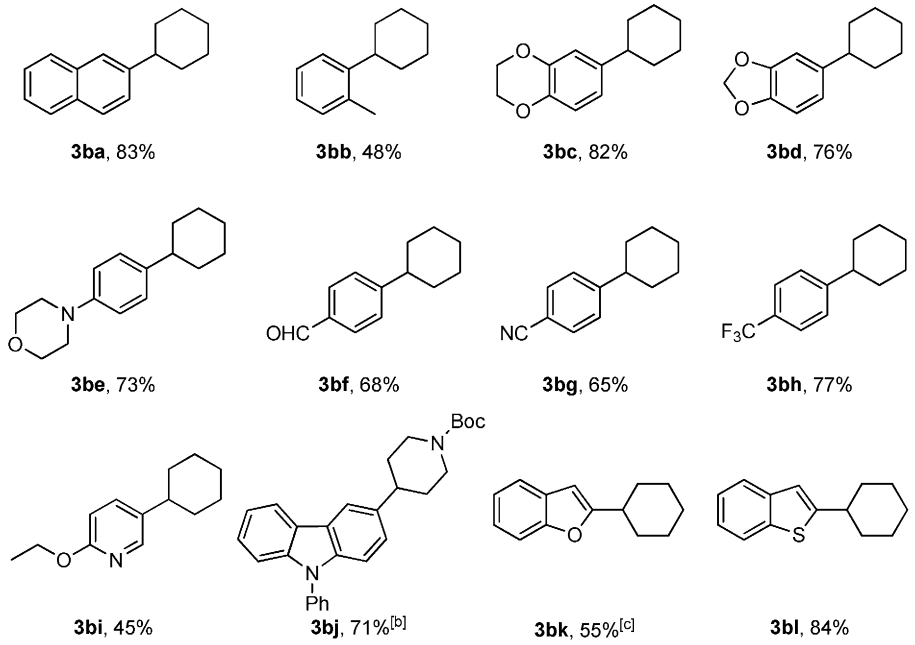
The substrate scope of the alkyl halides was then examined, and various unactivated/functionalized alkyl halides **2** were treated with **1a** under the optimal conditions (Table 2). Although the unactivated alkyl chlorides gave relatively poor yields (<30%) of unactivated alkyl bromides/iodides(**3aa**, **3ab**), the activated alkyl chlorides, such as benzyl chloride, ethyl chloroacetate, chloroacetonitrile and 2-chlorocyclohexanone, reacted smoothly with **1a** by addition of 0.5 equiv. NaI, and the corresponding products were obtained in good yields (**3ac**, **3ad**, **3ae** and **3af**). It is particularly worth noting that, with the addition of NaI, direct 2,2,2-trifluoroethylation of **1a** could be achieved by employing 2,2,2-trifluoroethyl trifluoromethanesulfonate in 42% yield (**3ag**). NaI was also beneficial for activated alkyl bromides but unnecessary for unactivated alkyl bromides and iodides. For $sp^3$ tertiary halides, the coupling could be especially challenging.[5k,12] Remarkably, 1-bromoadamantane afforded the coupling product **3an** in 35% yield. Above all, many important functional groups, like ester, cyano, ketone, lactone, cyclopropyl and vinyl groups, oxetane and N-Boc-azetidine were quite well tolerated. In comparison, we synthesized compound **3ai**, **3aj** and **3al** by employing Fu's method (Scheme 1, b), **3ai** was not detected in the reaction, and compounds **3aj** and **3al** were obtained with less than 30% yields.

To demonstrate the generality of boronic acids, a range of substituted aryl- and heteroarylboronic acids were employed with iodocyclohexane (**2a**) in this protocol (Table 3). The reactions of arylboronic acids that contain either electron-donating groups or electron-withdrawing groups afforded the desired products in 65–83% yield, and the electronic properties of the substituents on arylboronic acids had very limited influence over the yields of this reaction. Furthermore, the sterically hindered 2-tolylboronic acid

**Table 3.** Nickel-catalyzed cross-couplings of iodocyclohexane (**2a**) with various aryl- and heteroarylboronic acids[a]




[a] *Reaction conditions (unless stated otherwise):* **1** (0.5 mmol, 1.0 equiv.), **2a** (1.0 mmol, 2.0 equiv.), $K_2CO_3$ (1.5 mmol, 3.0 equiv.), anhydrous 1,4-dioxane (3 mL), 12 h, isolated yield.

[b] Due to the difficult purification of the product, *N*-Boc-4-iodopiperidine was used instead of **2a**.

[c] **2a** (1.5 mmol, 3.0 equiv.) was added.

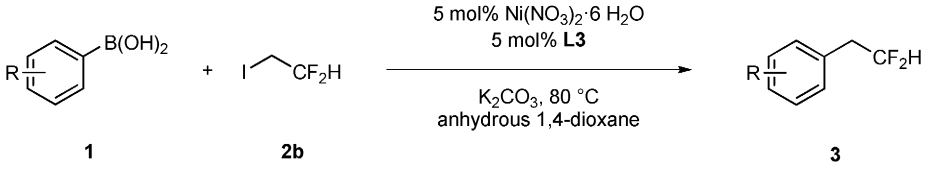
reacted well with bulky iodocyclohexane leading to an acceptable yield (**3bb**). This reaction was not restricted to arylboronic acids, and the heteroarylboronic acids were also investigated. This protocol was noteworthy because heteroaryl groups are very prominent structural motifs in pharmaceuticals and material science, such as pyridine (**3bi**), benzofuran (**3bk**) and benzothiophene **(3bl**). However, we failed in introducing a cyclohexyl group to the 2/3-position of indole and its derivatives by the same method.

As we all know, fluorinated moieties in organic molecules can powerfully modulate the biological activities of these molecules, and therefore, they have gained much attention in the strategy of drug design and life science research.[13] Among the fluorine-containing groups, the difluoromethylene and trifluoromethyl groups have proved to be very important moieties, this is owing to their lipophilic electron-withdrawing capacity and specific size.[14] For example, the difluoromethylene motif can serve as a bioisostere for a carbonyl group or an oxygen atom.[15] In contrast to many practical methods for introducing trifluoromethyl or difluoromethylene fragment into functionalized aromatic compounds, methods for the synthesis of (2,2-difluoroethyl)arenes or (2,2,2-trifluoroethyl)arenes are still limited.

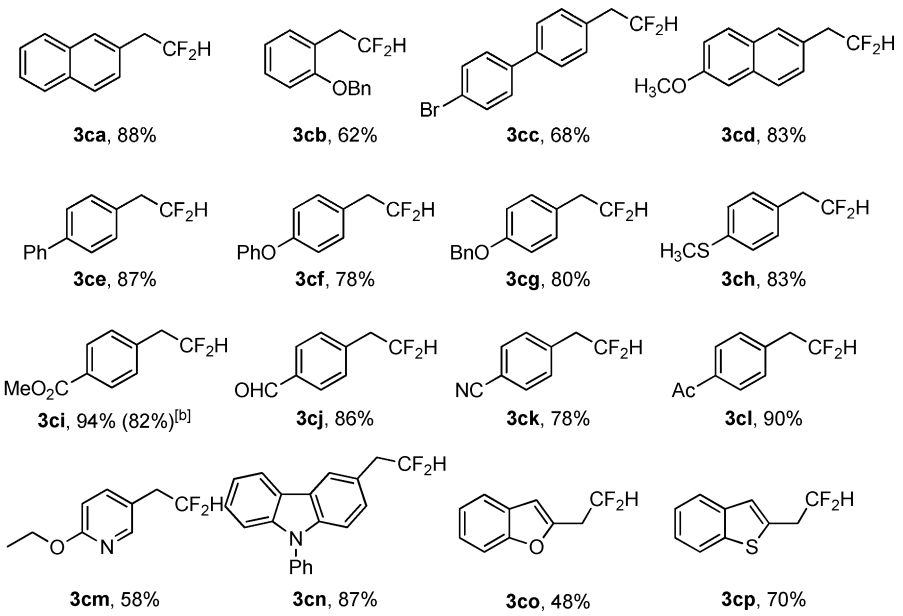
Inspired by product **3ag**, we tried to directly introduce 2,2-difluoroethyl and 2,2,2-trifluoroethyl groups to the aromatic rings by reacting aryl- and heteroarylboronic acids with $ICH_2CF_2H$ and $ICH_2CF_3$, respectively. To our delight, by applying this method, good to excellent yields of (2,2-difluoroethyl)arenes and (2,2,2-trifluoroethyl)arenes were obtained (Table 4 and Table 5). Importantly, the sterically hindered *o*-substituted and Br-substituted arylboronic acids only slightly affected the yields of target compounds (**3cb** and **3cc** in Table 4, **3db** and **3dc** in Table 5). The heteroarylboronic acids also underwent the reaction

**Table 4.** Nickel-catalyzed cross-couplings of $ICH_2CF_2H$ (**2b**) with various aryl- and heteroarylboronic acids[a]




**1** **2b** **3**

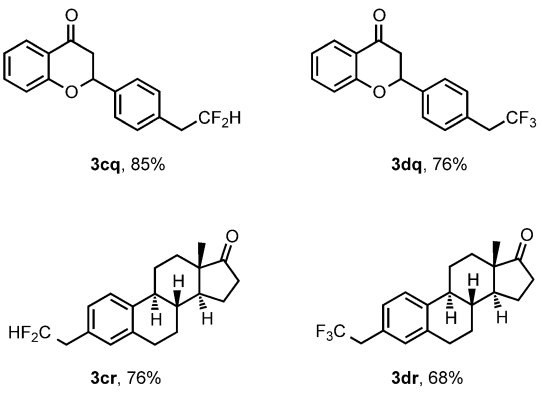



[a] *Reaction conditions (unless stated otherwise):* **1** (0.5 mmol, 1.0 equiv.), **2a** (1.0 mmol, 2.0 equiv.), $K_2CO_3$ (1.5 mmol, 3.0 equiv.), anhydrous 1,4-dioxane (3 mL), 12 h, isolated yield.

[b] Reaction carried out on a gram scale (5.56 mmol scale).

well to provide the corresponding products in acceptable yields (**3cm–cp**, **4dm–dp**).

To further demonstrate the synthetic utility of our protocol, we first scaled up the reaction to a gram scale, whereby the (2,2-difluoroethyl)arene and (2,2,2-trifluoroethyl)arene **3ci** and **3di** were furnished with yields of 82% and 74%, respectively. Then, some late-stage direct 2,2-difluoroethylation and 2,2,2-trifluoroethylation reactions of biologically active compounds were explored. On treatment of the flavanone-derived and the estrone-derived arylboronic acids[10,16] with $ICH_2CF_2H$ and $ICH_2CF_3$, the reactions gave the desired products in quite good yields (Scheme 2), thus significantly highlighting the importance of this method.



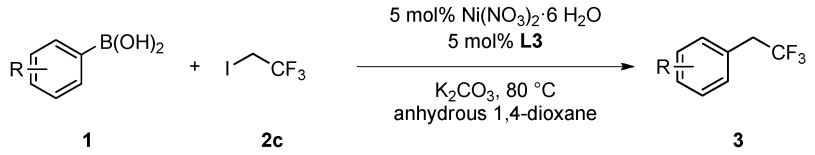

**Scheme 2.** 2,2-Difluoroethylation and 2,2,2-trifluoroethylation of the flavanone-derived and the estrone-derived arylboronic acids.

## Conclusions

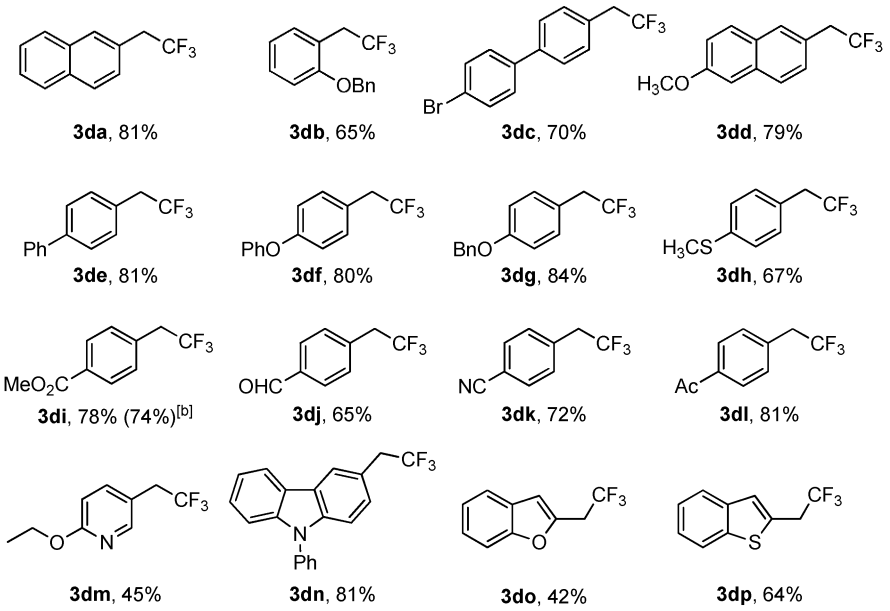
In conclusion, a facile and mild method for nickel-catalyzed C($sp^3$)–C($sp^2$) Suzuki cross-couplings of alkyl halides with aryl- and heteroarylboronic acids has been developed. Due to the low cost of the nickel catalyst and the mild conditions, this protocol provides a general, efficient and practical synthesis for the construction of C($sp^3$)–C($sp^2$) bonds. Moreover, this is

**Table 5.** Nickel-catalyzed cross-couplings of $ICH_2CF_3$ (**2c**) with various aryl- and heteroarylboronic acids[a]




1 2c 3




[a] *Reaction conditions (unless stated otherwise):* **1** (0.5 mmol, 1.0 equiv.), **2a** (1.5 mmol, 3.0 equiv.), $K_2CO_3$ (2.0 mmol, 4.0 equiv.), anhydrous 1,4-dioxane (3 mL), 12 h, isolated yield.

[b] Reaction carried out on a gram scale (5.56 mmol scale).

the first nickel-catalyzed 2,2,2-trifluoroethylation of aryl- and heteroarylboronic acids with $ICH_2CF_3$ and the first example of direct 2,2-difluoroethylation by $ICH_2CF_2H$. As well as the broad scope of substrates and excellent compatibility of functional groups, this synthetic method will have many promising applications in drug discovery and development.

## Experimental Section

### General Procedure

A sealed tube of 15 mL equipped with a magnetic stirrer was charged with 4-(methoxycarbony)benzeneboronic acid **1a** (90 mg, 0.5 mmol), iodoocyclohexane **2a** (210 mg, 1.0 mmol), $K_2CO_3$ (207 mg, 1.5 mmol), $Ni(NO_3)_2{\cdot}6H_2O$ (7 mg, 0.025 mmol), 4,4′-di-*t*-Bubpy **L3** (7 mg, 0.025 mmol) and 3 mL anhydrous 1,4-dioxane (0.5 equiv. NaI was added if necessary). This tube was purged with argon and the mixture stirred at room temperature for 10 min. After the tube had been sealed under an argon atmosphere and the content stirred at 80 °C for 12 h, the mixture was cooled to room temperature. The reaction mixture was diluted with 30 mL of water, and then extracted with EtOAc (10 mL × 3). The combined extracts were successively washed with brine, dried over $Na_2SO_4$ and evaporated to dryness. The crude product was purified by silica gel chromatography eluted with PE: EtOAc = 30: 1 to give the product as a colorless oil: yield: 88 mg (81%). For further details of the synthesis and characterization, see the Supporting Information.

## Acknowledgements

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