



# Synthesis of bromodifluoromethyl(arylsulfonyl) compounds and microwave-assisted nickel catalyzed cross coupling with arylboronic acids



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## ABSTRACT

A nickel catalyzed Suzuki coupling of arylboronic acids and novel bromodifluoromethyl(arylsulfonyl) compounds is described, providing an example of direct C<sub>sp2</sub>-CF<sub>2</sub>SO<sub>2</sub>Ar bond formation. High-throughput experimentation (HTE) was utilized for identifying the catalyst and reaction conditions.

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## Introduction

Synthetic methods for introducing fluorinated fragments into organic molecules which are mediated or catalyzed by a transition metal are highly desirable, as fluorine is known to impart significant changes to biologically relevant parameters [1]. Methods to introduce the difluoromethylene fragments CF<sub>2</sub>R (R = H, alkyl, alkene, alkyne, aryl) [2] or CF<sub>2</sub>X (X = halide, ester, phosphonate, acetamide) [3] are attractive as these groups can be bioisosteric to either hydroxyl, carbinol, or thiol groups, show enhanced metabolic stability, and improve pharmacokinetic properties [4]. In particular, the CF<sub>2</sub>SO<sub>2</sub>Ar (Ar = aryl or heteroaryl) moiety has shown promise for biological applications, such as activity against HIV (Fig. 1a) [5a], and analgesic activity through selective CB<sub>2</sub>-receptor agonism (Fig. 1b, c) [5b,c].

These studies utilize various multi-step, stoichiometric synthetic strategies for constructing the CF<sub>2</sub>SO<sub>2</sub>Ar group [5]. In fact, there are a limited number of reported examples of metal-mediated methods to introduce a CF<sub>2</sub>SO<sub>2</sub>Ar group to organic substrates, which are shown in Scheme 1 [6–8]. Reutrakul and coworkers reported a Pd mediated Heck-type coupling of PhSO<sub>2</sub>CF<sub>2</sub>Br with styrene derivatives [6], and Wang and coworkers reported a Ru based photocatalytic process for coupling PhSO<sub>2</sub>CF<sub>2</sub>I with elec-

tron-rich heteroarenes including functionalized indoles [7]. Hu and coworkers used stoichiometric Cu to couple PhSO<sub>2</sub>CF<sub>2</sub>H with aryl boronic acids in a two-step, low-temperature method [8].

In these studies, the CF<sub>2</sub>SO<sub>2</sub>Ph group is used exclusively, with the idea that SO<sub>2</sub>Ph can be readily cleaved *via* reductive desulfonation to furnish a CF<sub>2</sub>H group in the final product. However, a catalytic C–C coupling reaction tolerating CF<sub>2</sub>SO<sub>2</sub>Ar groups (Ar = functionalized arene) has yet to be developed. Importantly, the prepared CF<sub>2</sub>SO<sub>2</sub>Ar containing compounds could constitute a novel series of functionalized bioactive molecules [9]. Herein, we utilize high-throughput experimentation to investigate the feasibility of a catalytic variant of the coupling reaction between novel ArSO<sub>2</sub>CF<sub>2</sub>Br compounds and widely available arylboronic acids. Despite identifying significant challenges associated with this transformation, we report a successful microwave-assisted nickel catalyzed method.

## Results and Discussion

We prepared two novel bromodifluoromethyl(arylsulfonyl) compounds, **2a–b**, derived from 2-naphthalenethiol and 7-mercapto-4-methylcoumarin, respectively, and CF<sub>2</sub>Br<sub>2</sub> (Scheme 2). The thiol starting materials are first treated with NaH and CF<sub>2</sub>Br<sub>2</sub> in NMP to form bromodifluoromethylsulfanyl compounds **1a–b** [10]. The sulfide linkage was then oxidized with an excess of mCPBA in CH<sub>2</sub>Cl<sub>2</sub> to afford sulfone compounds **2a–b**. The <sup>19</sup>F

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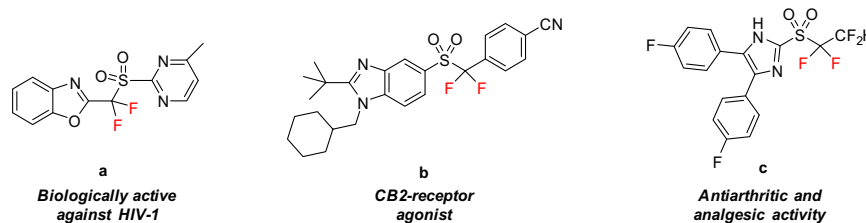
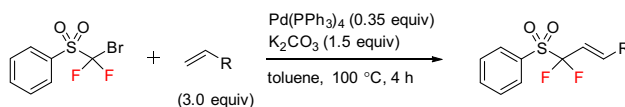
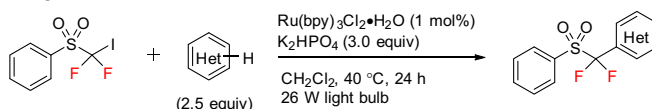


Fig. 1. Examples of bioactive molecules containing  $\text{CF}_2\text{SO}_2\text{Ar}$  groups.

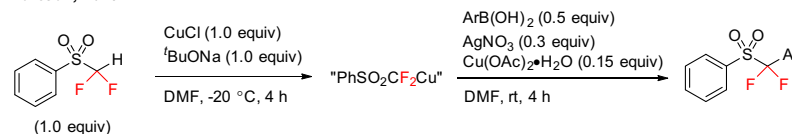
Previous work:  
Reutrakul et al., 2012



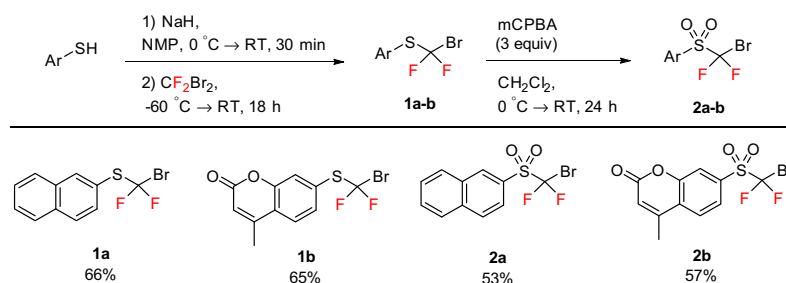
Wang et al., 2014



Hu et al., 2016



Scheme 1. Metal mediated difluoromethyl(phenylsulfonyl) coupling reactions.



Scheme 2. Synthesis of bromodifluoromethyl(arylsulfonyl) compounds.

NMR spectra of compounds **1** and **2** are highly characteristic. Sulfonyl compounds **1a** and **1b** feature  $^{19}\text{F}$  NMR resonances at  $\delta = -21.3$  ppm and  $\delta = -21.5$  ppm, respectively, and there is a significant upfield shift upon oxidation to sulfonyl derivatives **2a** and **2b**, with resonances at  $\delta = -56.9$  ppm and  $\delta = -57.3$  ppm.

With bromodifluoromethyl(arylsulfonyl) compounds **2a-b** in hand, we sought to screen catalysts and conditions for a Suzuki type coupling reaction with arylboronic acids, using a high-throughput experimentation (HTE) platform to rapidly evaluate various combinations of metal precursors, ligands, bases, and solvents in small-scale reactions (*ca.* 5–10 mg substrate, 0.8–2.0 mL solvent). After multiple unsuccessful screens (details in supporting information), we observed conditions which enabled the cross coupling of **2a** with benzenboronic acid (Table 1). The combination of  $\text{Ni}(\text{acac})_2$ , phosphine ligand, and  $\text{K}_2\text{CO}_3$  in 1,2-dichloroethane (DCE) at  $120^\circ\text{C}$  (MW) gave the desired phenylated difluoromethyl-sulfone product **3a**, as detected using GC-MS analysis. These conditions share similarities to the optimized conditions reported by Wang and coworkers for the Suzuki coupling of  $\text{PhSO}_2\text{CFHI}$  [11]. As in their study, we found the use of chlorinated solvent to be

essential. Importantly, high temperatures and pressures provided by a microwave reactor were critical to the success of the reaction, and it was found that higher temperatures were necessary for coupling  $\text{ArSO}_2\text{CF}_2$  ( $120$ – $160^\circ\text{C}$ , MW) compared to  $\text{PhSO}_2\text{CFH}$  ( $100^\circ\text{C}$ , conventional heating). This could be due to the increased M-C bond strength for  $\text{CF}_2\text{X}$  fragments compared to  $\text{CFHX}$  in intermediate species, a known trend for late transition metal complexes [12]. It is also noteworthy that extensive screening of sulfonyl compounds **1a-b** for the Suzuki coupling were unsuccessful (details in supporting information), consistent with the work of Reutrakul [6].

We further examined selected reactions from Table 1 on a larger scale to determine more accurately the reaction yield (Table 2). The combination of simple  $\text{PPh}_3$  and  $\text{Cs}_2\text{CO}_3$  gave the best results with formation of product **3a** in 31% yield while mitigating the formation of significant quantities of the major side-product, hydrode-brominated starting material **2a-H**. Control experiments determined that in the absence of either catalyst or base, no product was observed. The discrepancy between the percent conversion of **2a** and formation of **3a/2a-H** could not be accounted for

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