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Nickel(II)-Catalyzed Synthesis of Sulfinates from Aryl and Heteroaryl Boronic Acids and the Sulfur Dioxide Surrogate DABSO

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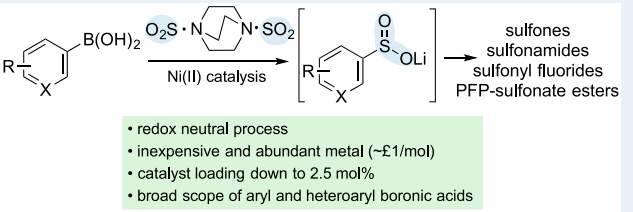
Supporting Information

ABSTRACT: We report a redox-neutral Ni(II)-catalyzed sulfination of readily available aryl and heteroaryl boronic acids. Using the combination of commercially available, air-stable $NiBr_2$·(glyme), a commercially available phenanthroline ligand, and DABSO, boronic acids are efficiently converted to the corresponding sulfinate salts, which can be further elaborated to valuable sulfonyl-containing groups, including sulfones, sulfonamides, sulfonyl fluorides, and sulfonate esters. The catalyst loading can be reduced to 2.5 mol % on a gram scale. This practically simple protocol tolerates an unprecedented range of pharmaceutically relevant and electron-poor (hetero)aryl boronic acids, allowing the direct synthesis of active pharmaceutical ingredients.



KEYWORDS: *nickel, catalysis, sulfinates, boronic acids, sulfones, sulfonamides, sulfonyl fluorides, sulfur dioxide*

Sulfonyl-containing ($-SO_2-$) compounds such as sulfones and sulfonamides have broad applications in fields ranging from synthetic chemistry,[1] pharmaceuticals, and agrochemicals, to materials science (see Figures 1a−c).[2] Conventional approaches to synthesize these valuable functional groups can often require multistep sequences. For example, sulfones are usually synthesized by oxidation of the corresponding sulfides, which, in turn, are commonly prepared from alkylation of thiols.[3] The use of thiols is a limitation because of their often unpleasant odor, and their relatively limited availability from commercial vendors. Aryl sulfonamides, meanwhile, are most usually available from the combination of sulfonyl chlorides and amines.[4] However, the preparation of the former via the electrophilic aromatic substitution (S_EAr) of arenes requires harsh acidic reaction conditions, which limits functional group tolerance.[5] In addition, the high levels of regiocontrol often observed in S_EAr processes makes access to all isomers of these products challenging.

Catalytic methods for the sulfination of abundant feedstocks, such as aryl halides and boronic acids, have had a tremdous impact of the synthesis of sulfonyl-containing molecules.[6] In 2010, our laboratory reported the use of DABCO·$(SO_2)_2$ (DABSO) as a convenient sulfur dioxide surrogate.[7] This air-stable, easy-to-handle, and now commercially available solid has been employed by us,[8] and others,[9] to access a wide range of sulfonyl-containing products using metal catalysis. Inorganic sulfur dioxide surrogates such as $K_2S_2O_5$ and $Na_2S_2O_5$ have also been used,[10] as have noncatalytic methods.[11]

The direct palladium-catalyzed synthesis of sulfinate salts from aryl halides represented a signficant advance,[8a,12] as these versatile intermediates could be readily transformed to a variety of valuable functional group, such as sulfones,[13] sulfonamides,[8,14] sulfonyl fluorides,[8e,15] and sulfonate esters.[8f] Sulfinates can also be employed as reaction partners in desulfinylative cross-coupling processes,[16] and as radical precursors.[17] Later, aryl boronic acids were also employed in place of aryl halides, and these substrates have also been used in combination with Au(I),[18] Pd(II),[8c,10b,19] and Cu(I)[8d] catalysts (see Figure 1d). Despite these advances in sulfinate synthesis, signficant challenges remain unsolved. For example, the scope of these processes is generally limited to electron-rich or neutral aryl systems. Electron-poor aryl and heteroaryl boronic acids commonly provide only low yields of products, or fail completely.[8c,d,f,g,18−20] An exception to this is the palladium-catalyzed system reported by Chen and Tu, in which a bespoke *N*-heterocyclic carbene ligand enables some success with these substrates for the synthesis of simple sulfone products. However, a general catalytic system that employs commerical reaction components and is able to tolerate a broad range of electronically varied boronic acids is as yet unknown.

In recent years, a focus of both academic and industrial communities has been the use of abundant base-metal catalysts in synthetic chemistry. In particular, the replacement of precious metal catalysts with these lower-cost, more-sustainable metals that are less susceptible to risk of supply, has attracted significant attention.[21] Nickel catalysis features prominently in this field, not only because of its significantly lower cost, relative to palladium, but also because it frequently provides alternative, often complementary, reactivity.[22] For

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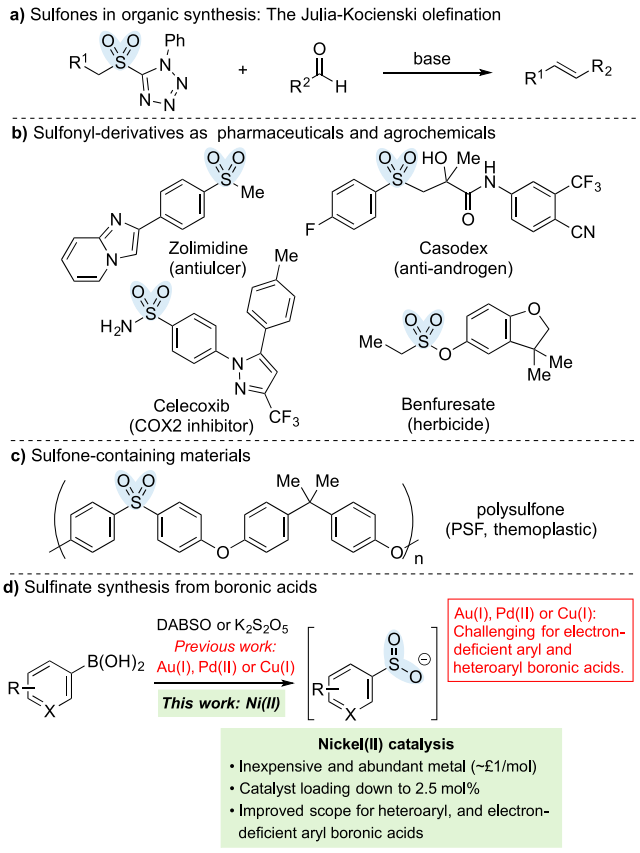
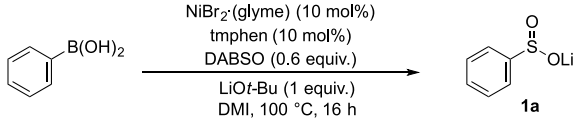


Figure 1. (a–c) Applications of sulfones and sulfonamides; and (d) catalytic synthesis of sulfinates from boronic acids.

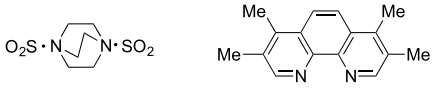
example, nickel undergoes ready oxidative addition with less-reactive and more-abundant electrophiles such as aryl chlorides, ethers, and carbamates.[22a−c] In addition, it can be used, in combination with photoredox catalysts, to deliver modes of reactivity[23] that are challenging to achieve with palladium systems. Given these advantages, we speculated that nickel catalysis could deliver new reactivities in sulfination chemistry and address the limitations of earlier catalytic methods (see Figure 1d).

We selected the addition of phenylboronic acid to DABSO as a test platform and evaluated a range of Ni(II) catalysts (see Table 1). We were pleased to find that using 10 mol % of commercially available and air-stable $NiBr_2$·(glyme), in combination with 10 mol % of 3,4,7,8-tetramethyl-1,10-phenanthroline (tmphen) as ligand, was sufficient to promote the reaction, providing the targeted sulfinate in 91% yield. The reaction used DMI as a solvent at 100 °C and required only 0.6 equiv of DABSO and 1 equiv of LiO*t*-Bu (Table 1, entry 1). A lower reaction temperature (90 °C), higher loading of ligand, or base, or increasing the concentration, all provided less-efficient reactions (Table 1, entries 2−6). We also found that using a strong base was crucial in this transformation, with LiO*t*-Bu being optimal; using a weaker base or KO*t*-Bu resulted in diminished yields (Table 1, entries 7 and 8). Substituting DABSO for an inorganic source of sulfur dioxide ($K_2S_2O_5$), or replacing phenylboronic acid with potassium phenyltrifluoroborate was unproductive (Table 1, entries 9 and 10). Full details of the reaction optimization are provided in the Supporting Information.

Table 1. Optimization of Reaction Conditions for the Formation of Sulfinate 1a from Phenylboronic Acid[a]



Entry	Variation	Yield of 1a (%)
1	as above	91
2	90 °C	31
3	20 mol% ligand	28
4	1.0 equiv. DABSO	90
5	2.0 equiv. LiO*t*-Bu	68
6	0.4 M DMI	78
7	0.4 M DMI, Li_2CO_3 instead of LiO*t*-Bu	33
8	0.4 M DMI, KO*t*-Bu instead of LiO*t*-Bu	64
9	1.0 equiv. $K_2S_2O_5$ instead of DABSO	0
10	$PhBF_3K$ instead of phenylboronic acid	0



[a]Reaction conditions: phenylboronic acid (0.2 mmol, 1.0 equiv), $NiBr_2$·(glyme) (10 mol %), tmphen (10 mol %), DABSO (0.12 mmol, 0.6 equiv), LiO*t*-Bu (0.2 mmol, 1.0 equiv), DMI (1.0 mL, 0.2 M). Yields were calculated from HPLC analysis using acetophenone as an internal standard.

With the optimized conditions in hand, we examined the scope, with respect to boronic acids, by reacting the in situ formed sulfinates with *tert*-butyl bromoacetate as the electrophile, to prepare the corresponding sulfones in a one-pot two-step sequence (see Table 2). Generally, a wide range of aryl boronic acids could be effectively converted to sulfinates and then to sulfones. Boronic acids bearing different electronic substitutions were well-tolerated, with electronically neutral phenyl (**2a**) and *p*-trimethylsilyl (**2b**), and electron-rich *p*-methoxy (**2c**) and *p*-thiomethyl (**2d**) substituents delivering excellent isolated yields. Previously challenging substrates with electron-withdrawing groups could also be incorporated in the arene unit, including sensitive functional groups such as nitrile (**2g**), ketone (**2i**), and ester (**2j**), as well as the first example of a trifluoromethylated aryl boronic acid being used in catalytic sulfination chemistry (**2f**). Boronic acids substituted with all four halogens (**2k−2o**) were well-tolerated under the reaction conditions, with the caveat that using NiI_2 as the catalyst was necessary when *p*-iodophenyl boronic acid (**2o**) was the substrate. For this example, using the original $NiBr_2$·(glyme) catalyst resulted in a degree of bromo/iodo substitution in the product. The catalyst loading could be lowered to 2.5 mol %, delivering 70% isolated yield of sulfone (**2m**) on a 0.2 mmol scale, and a 71% yield when performed on a gram scale (7 mmol) at a slightly elevated temperature (110 °C). Further reducing the catalyst loading to 1 mol % resulted in diminished yields. Methylthio (**2d**)- and methanesulfonyl (**2h**)-substituted examples showcase the potential utility of this reaction, demonstrating how it is possible to access mixed-oxidation-state S-centers, as well as disparate sulfonyl functional groups.

Meta-substituted boronic acids were also reacted well, giving identical yields compared to the para-substituted counterpart (**2g** and **2q**). However, *ortho*-substituted (**2r**) and alkenyl boronic acid (**2s**) were less successful, with only poor to modest product yields isolated even at elevated temperature.

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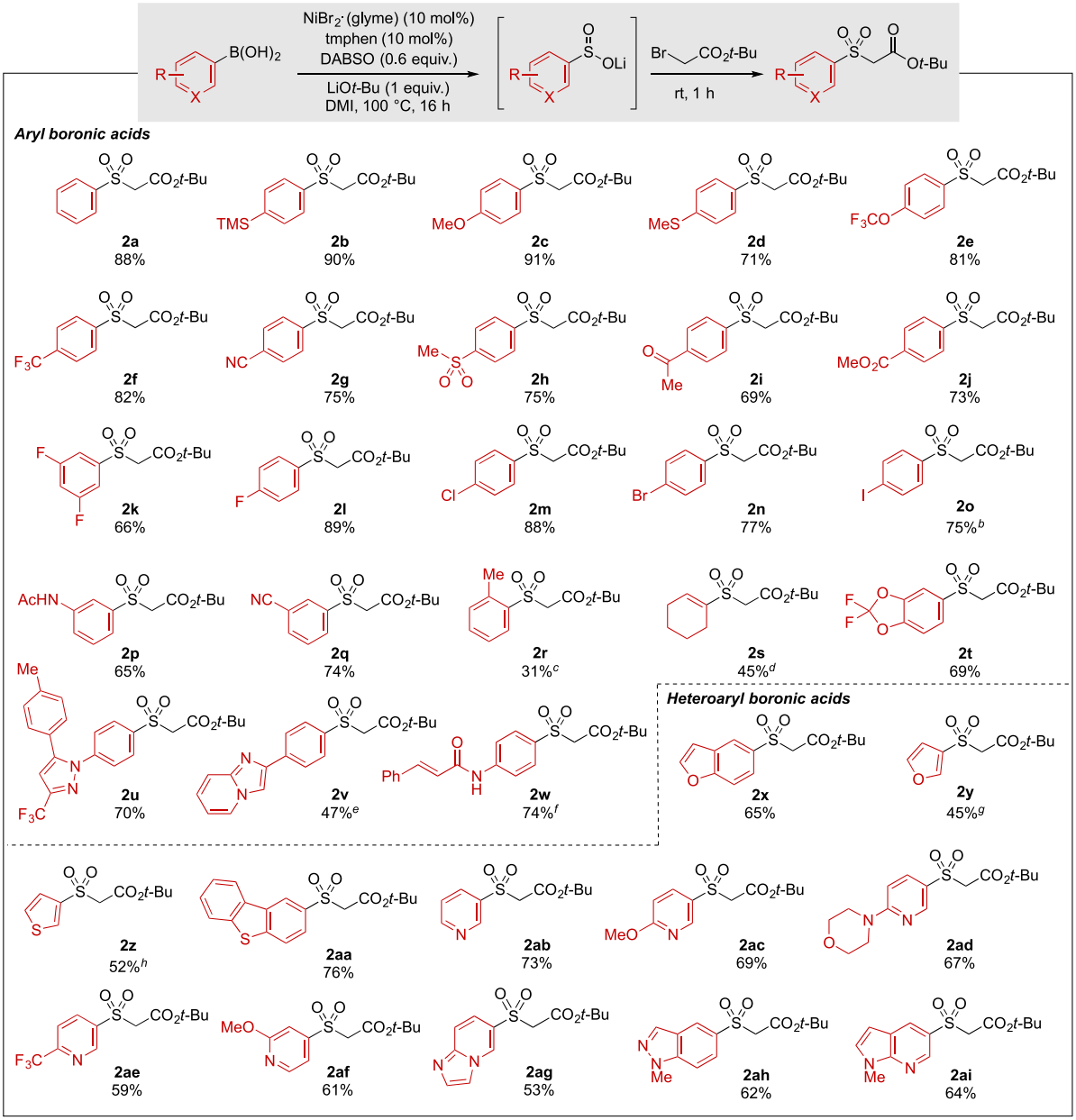
Table 2. Scope of the Boronic Acid Reaction Component[a]



[a]Reaction conditions: (hetero)aryl boronic acid (0.2 mmol, 1.0 equiv), $NiBr_2$·(glyme) (10 mol %), tmphen (10 mol %), DABSO (0.12 mmol, 0.6 equiv), LiO*t*-Bu (0.2 mmol, 1.0 equiv), DMI (1.0 mL, 0.2 M), 100 °C, 16 h, then *tert*-butyl bromoacetate (2.0 equiv), rt, 1 h. [b]NiI_2 used as catalyst. [c]120 °C. [d]110 °C. [e]6 h for second step. [f]2 h for second step. [g]1 h for first step. [h]2 h for first step.

We were pleased to find that several pharmaceutically relevant boronic acids reacted smoothly under the optimized conditions, delivering the sulfonylarene core of the COX2 inhibitor Celecoxib (**2u**), antiulcer drug Zolimidine (**2v**) and CrtN inhibitor NP16 (**2w**).[2b] A range of heteroaryl boronic acids were also suitable substrates, including *O*- (**2x**, **2y**) and *S*-heterocycles (**2z**, **2aa**), as well as a variety of challenging substituted pyridyl groups (**2ab**−**2af**). Imidazopyridine (**2ag**), indazole (**2ah**), and azaindole (**2ai**) groups were also included, delivering the desired sulfones in good yields. It is also worth noting that, in previous reported sulfinations of aryl boronic acids using Au(I),[18] Pd(II),[8c,19,20] or Cu(I)[8d] catalytic systems, electron-deficient aryl (e.g., nitrile, trifluoromethyl) and pyridine-derived boronic acids generally reacted poorly or failed completely. However, these substrates reacted smoothly under the Ni(II) catalytic systems reported here, highlighting the utility of the present chemistry.

We then explored alternative derivatization processes for the sulfinate intermediates. *p*-Chlorophenylboronic acid was selected as the model substrate. Table 3a outlines the sulfones prepared by combining the sulfinates with a variety of carbon-based electrophiles, including alkyl halides (**3a**), heteroaryl halides (**3b**), diaryliodonium salts (**3c**), and epoxides. The antiulcer drug Zolimidine (**3d**) was prepared conveniently using methyl iodide as the alkylating agent. In situ alkylation of the sulfinate intermediates with allyl bromide afforded allyl sulfones (**3e**−**3h**), which are a class of sulfone with established utility in desulfinative cross-coupling and aromatic sulfonyla-

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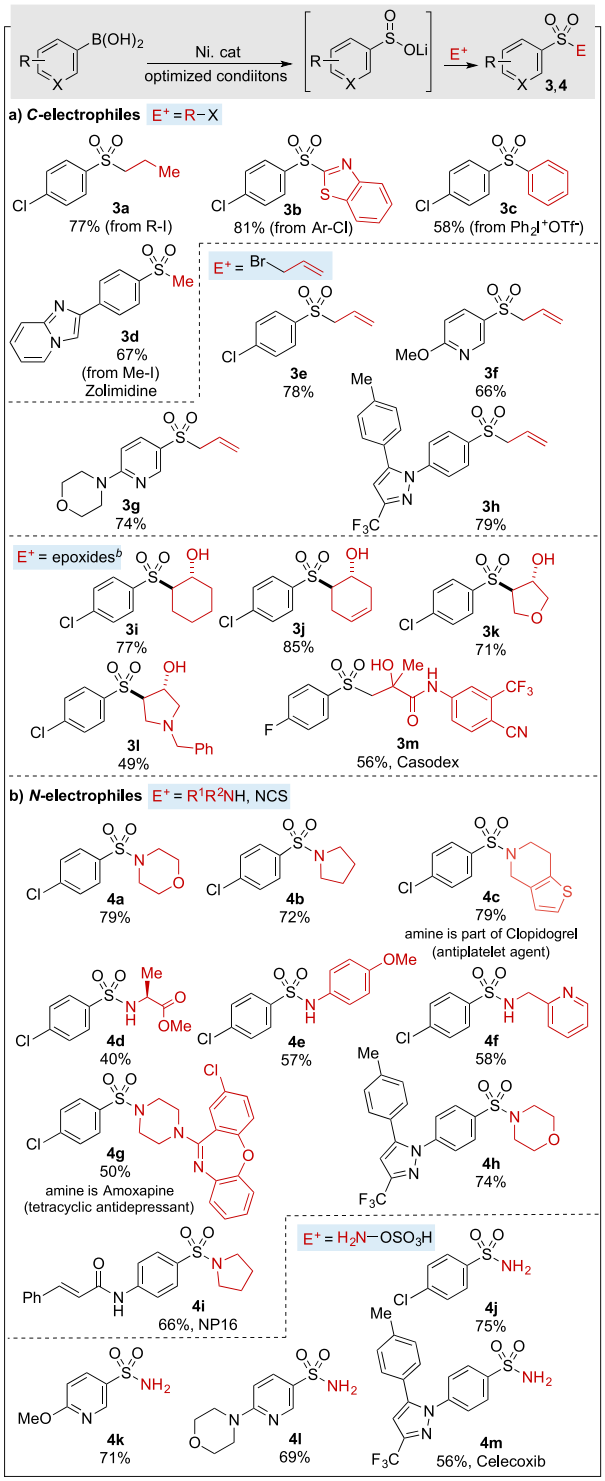
Table 3. Scope of Carbon- and Nitrogen-Based Electrophiles To Form Sulfones and Sulfonamides[a]

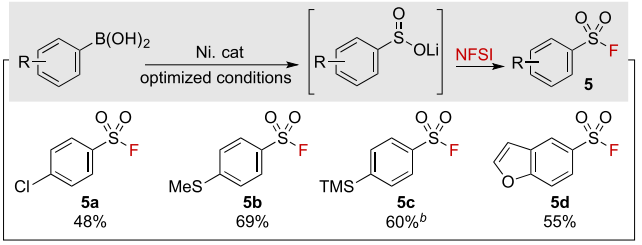


[a]Reaction conditions for sulfinate derivatization step: E^+ (2 equiv), rt or 100 °C, 1 h. For epoxides: aqueous workup, DIPEA (3 equiv), epoxide (5 equiv), H_2O, 100 °C, 48 h. For sulfonamides: R^1R^2NH (1.5 equiv), NCS (1.5 equiv), 0 °C to rt, 1 h; H_2N-OSO_3H (2 equiv), rt, H_2O, 24 h. For individual variations, see the Supporting Information. [b]For products **3i**−**3l**, dr >20:1.

tion processes.[16d,24] Notably, pyridine- (**3f**, **3g**) and Celecoxib-derived (**3h**) allyl sulfones were prepared in good yields. Epoxide ring opening delivered the corresponding *β*-hydroxy sulfones in good yields (**3i**−**3m**) and allowed the direct synthesis of the antiandrogen pharmaceutical Casodex (**3m**). The examples in Table 3b show that sulfonamides are accessible if *N*-electrophiles are used. Secondary and tertiary sulfonamides are available using an electrophile generated from the combination of an appropriate amine and *N*-chlorosuccinimide (NCS).[14b] The conditions can tolerate both secondary (**4a**−**4c**) and primary (**4f**) amines, including amino acids (**4d**) and anilines (**4e**), as well as other biologically relevant amines (**4c**, **4g**). Different boronic acid reaction partners were also employed, allowing the preparation of an analogue of Celecoxib (**4h**) and the CrtN inhibitor NP16 (**4i**). Primary sulfonamides were available by combining the in-situ-generated sulfinates with hydroxylamine-*O*-sulfonic acid (H_2NOSO_3H).[25] Several pyridyl (**4k**, **4l**) examples were prepared in good yield, as was the primary sulfonamide Celecoxib (**4m**).

Sulfonyl fluorides have recently received increased recognition in the field of chemical biology, because of their unconventional balance between reactivity and stability under physiological conditions.[26] Table 4 shows that, by using *N*-fluorobenzenesulfonimide (NFSI) as the electrophilic component, we are able to prepare a selection of sulfonyl fluorides in good to modest yields.

Table 4. Preparation of Sulfonyl Fluorides, Using NFSI as the Electrophilic Reagent[a]

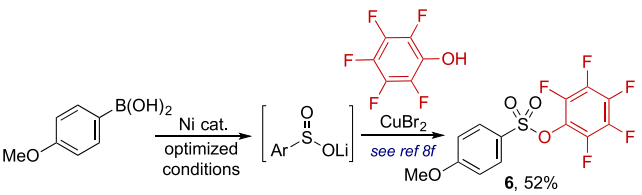


[a]Reaction conditions for sulfinate derivatization step: aqueous workup, then DIPEA (3 equiv), NFSI (1.5 equiv), rt, 1 h. [b]NFSI (1 equiv) used.

Pentafluorophenyl (PFP) sulfonate esters are often crystalline and bench-stable replacements for sulfonyl chlorides.[8f,27] Our laboratory has recently reported the preparation of PFP sulfonate esters using copper-catalyzed oxidative coupling of sulfinates and pentafluorophenol.[8f] Here, we show that the copper-catalyzed PFP sulfonate ester synthesis can be combined with nickel-catalyzed sulfinate formation. Accordingly, PFP-ester **6** was prepared in 52% yield from the corresponding boronic acid (see Scheme 1).

In conclusion, we have developed the first examples of nickel-catalyzed sulfination. The developed chemistry is redox-neutral and combines (hetero)aryl boronic acids and DABSO

Scheme 1. Synthesis of a PFP Sulfonate Ester



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as the source of sulfur dioxide. A broad range of boronic acids was tolerated, including electron-deficient and heterocyclic, including pyridyl, systems. Significantly, these types of boronic acids delivered only low yields or failed completely with prior methods, which were based predominantly on precious-metal catalysts, and often required custom ligands. The developed protocol can be scaled up to a preparative gram scale using 2.5 mol % catalyst. The in-situ-formed sulfinates were elaborated efficiently to sulfones, sulfonamides, sulfonyl fluoride, and PFP sulfonate esters. The procedure was applicable to the direct synthesis of several active pharmaceutical ingredients, providing a good demonstration of the functional group compatibility of the system. Given the increasing attention on nickel as a sustainable and inexpensive base-metal catalyst, and the importance of sulfonyl-containing compounds in both pharmaceuticals and agrochemicals, we anticipate wide uptake of the reported methods.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.9b04363.

Experimental procedures and supporting characterization data and spectra (PDF)

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Notes

The authors declare no competing financial interest.

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