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Direct Copper-Catalyzed Three-Component Synthesis of Sulfonamides

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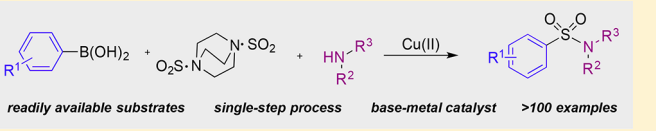
Supporting Information

ABSTRACT: First introduced into medicines in the 1930s, the sulfonamide functional group continues to be present in a wide range of contemporary pharmaceuticals and agrochemicals. Despite their popularity in the design of modern bioactive molecules, the underpinning methods for sulfonamide synthesis are essentially unchanged since their introduction, and rely on the use of starting materials with preinstalled sulfur-functionality. Herein we report a direct single-step synthesis of sulfonamides that combines two of the largest monomer sets available in discovery chemistry, (hetero)aryl boronic acids and amines, along with sulfur dioxide, using a Cu(II) catalyst, to deliver a broad range of sulfonamides. Sulfur dioxide is provided by the surrogate reagent DABSO. The reaction tolerates broad variation in both coupling partners, including aryl, heteroaryl and alkenyl boronic acids, as well as cyclic and acyclic alkyl secondary amines, and primary anilines. We validate the method by showing that a variety of drugs, and drug-fragments, can be incorporated into the process.



INTRODUCTION

For a functional group with negligible presence in nature, the widespread occurrence of sulfonamides in medicinal and agrochemical agents is remarkable.[1] The favorable physiochemical profile, chemical and metabolic stability, three-dimensional topology, heteroatom-rich nature, and often crystalline form, combine to propel sulfonamides to the forefront of functional groups employed in the design of modern bioactive molecules.[2] The resulting molecules are used in myriad applications, ranging from antibiotics, treatments for migraines and HIV, to herbicides (Scheme 1a).[1] Despite the advances made in their application, the most common method of sulfonamide synthesis[3] remains unchanged from that used for the preparation of the first "sulfa drug", Prontosil, in the 1930s.[4] The key reaction combines an amine with a corresponding activated sulfonyl derivative, most commonly a sulfonyl chloride, and although this is robust methodology, it is limited by the stability and availability of specific sulfonyl chlorides.[5] These sulfonyl chlorides are most usually prepared by the electrophilic chlorosulfonylation of the parent arene,[6] or by oxidative chlorination of an aryl organosulfur compound.[7] Electrophilic aromatic substitution processes often require harsh acidic conditions, limiting functional group compatibility, and are only effective for the preparation of specific substitution patterns as determined by the electronic characteristics of the starting arene. Similarly, oxidative chlorination procedures place strict limits on tolerable functionality, and frequently require the use of odorous thiol substrates. These issues could be avoided if a direct route to sulfonamides was possible from readily available starting materials that did not require preinstalled sulfur-functionality. Employing starting materials of increased diversity would have the added benefit of allowing the exploration of new chemical space,[8] which is an important consideration in discovery chemistry.[9]

A conceptually attractive route to sulfonamides, which avoids the use of sulfur-containing starting materials, involves the insertion of a molecule of sulfur dioxide between appropriate carbon and nitrogen fragments. To be synthetically useful, particularly for discovery chemistry, these two fragments would ideally be simple organic feedstocks, preferably with wide commercial availability. The last eight years has seen the use of sulfur dioxide in catalysis become an established technology for introducing sulfonyl-derived functional groups, with the 2010 report from our laboratory of the Pd-catalyzed synthesis of *N*-aminosulfonamides from the combination of aryl iodides, sulfur dioxide and hydrazines, providing the key advance (Scheme 1b).[10] This report was the first to show that cross-coupling type reactions with sulfur dioxide incorporation were possible, and that the use of a sulfur dioxide surrogate,[11] in this case the double adduct of sulfur dioxide with the amine DABCO, offered significant advantages over the use of sulfur dioxide gas.[12] Several closely related procedures in which the starting substrate,[13] catalyst[13c] or the SO_2-source[14] were changed have been subsequently reported; however, all of these intermolecular processes maintain the restriction to the use of hydrazine nucleophiles, thus providing esoteric *N*-aminosulfonamide products, which have few applications in medicinal chemistry. Simple amine coupling partners, which are required for the preparation of the parent sulfonamides, cannot be used in these reactions, although an intramolecular process which is specific for the formation of 5-membered

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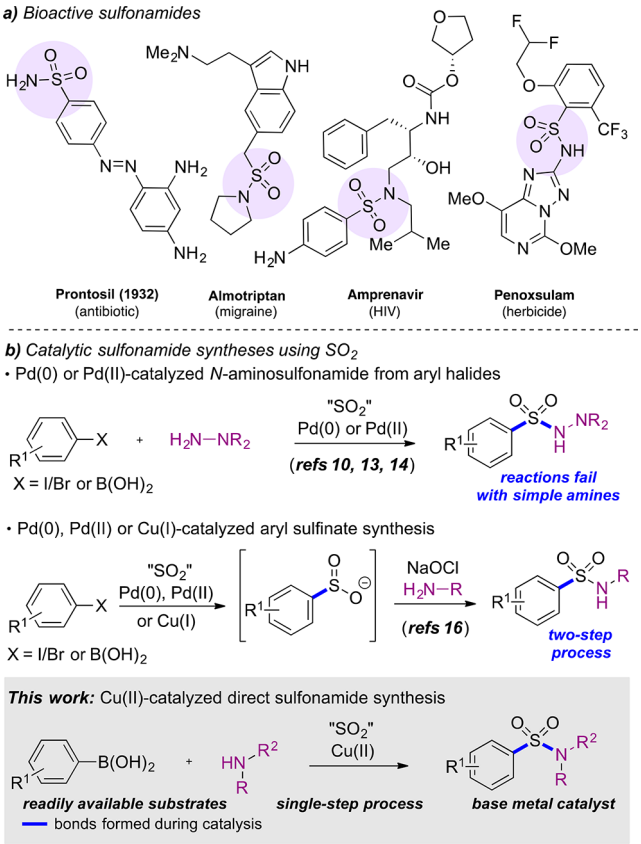
Scheme 1. (a) Examples of Biologically Relevant Sulfonamides; (b) Catalytic Syntheses of Sulfonamides Using Sulfur Dioxide, and the Target Transformation

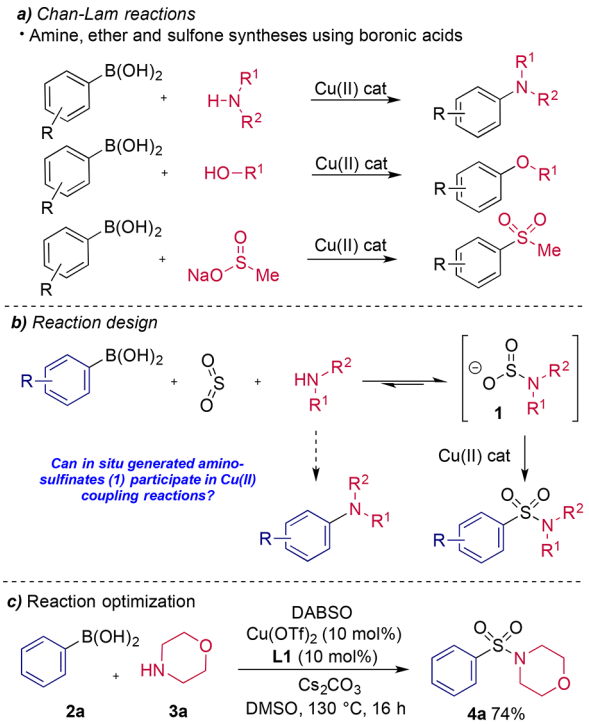


sulfonamides has demonstrated the use of amine nucleophiles.[15] A number of intermolecular Pd-catalyzed sulfinate syntheses have been developed, and these have been applied to sulfonamide preparation in the form of two-step procedures using in situ derivatization of the sulfinates (Scheme 1b).[16] The Buchwald group have reported a related strategy, and employed Pd-catalysis to convert aryl boronic acids into sulfonyl chlorides using phenyl chlorosulfate as the coupling partner.[17] A small number of direct sulfonamide syntheses based on sulfur dioxide insertion are known, but these employ activated, or noncommercial substrates; for example, the Cu(I)-catalyzed combination of aryl hydrazines, DABSO and amines,[18] the Cu(II)-catalyzed union of aryl diazonium salts, DABSO and *N*-chloro amines,[19] and the catalyst-free combination of *N*-tosylhydrazones, DABSO and amines,[20] all deliver sulfonamides. Despite these advances, and others,[21] a catalytic single-step sulfonamide synthesis which employs amines, a readily available arene substrate class, and sulfur dioxide or an equivalent, remains elusive. In this study, we provide a solution to this challenge, and show that by using a Cu(II) catalyst it is possible to achieve the efficient union of aryl boronic acids, sulfur dioxide (from DABSO), and amines, to deliver sulfonamides in a direct single step process (Scheme 1b).

RESULTS AND DISCUSSION

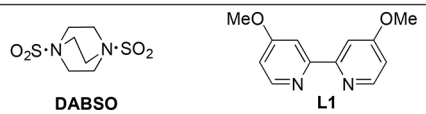
Given the failure to achieve a direct and general sulfonamide synthesis using palladium-catalysis, we considered alternative mechanistic scenarios and catalysts to achieve a single-step synthesis of these valuable molecules. In particular, we wished to avoid the requirement for a final S–N bond-forming reductive elimination from a Pd-center. Copper(II) catalysts have been used to promote coupling between aryl boronic acids and a broad range of heteroatom nucleophiles, including amines,[22] phenols[23] and sulfinates,[24] and this chemistry, initially developed by Chan, Lam and Evans, has now been applied in a multitude of settings (Scheme 2a).[25] Inspired by

Scheme 2. (a) Cu(II)-Catalyzed Chan–Lam Reactions; (b) Reaction Design; (c) Optimized Conditions for the Formation of Sulfonamide 4a



c) Reaction optimization

Entry	Variation from above conditions	Yield
1	$Cu(OAc)_2$ instead of $Cu(OTf)_2$	62%
2	$Cu(MeCN)_4BF_4$ instead of $Cu(OTf)_2$	49%
3	no ligand	34%
4	no Cs_2CO_3	58%
5	AcOH (1 equiv)	49%
6	100 °C	43%
7	$K_2S_2O_5$ in place of DABSO	0%
8	$PhBF_3K$ in place of $PhB(OH)_2$	9%
9	DMF in place of DMSO	0%
10	benzoquinone as an additive, in DMF	0%



the success and scope of these reactions, in particular the sulfone syntheses using sulfinate nucleophiles, we postulated that a three-component system, comprising an aryl boronic acid, sulfur dioxide and an amine, could, in the presence of a copper(II) catalyst, lead to sulfonamide formation (Scheme 2b). The direct coupling of the boronic acid and amine would be a competing process, although we speculated that rapid formation of "amino-sulfinate" (sulfuramidite) intermediates

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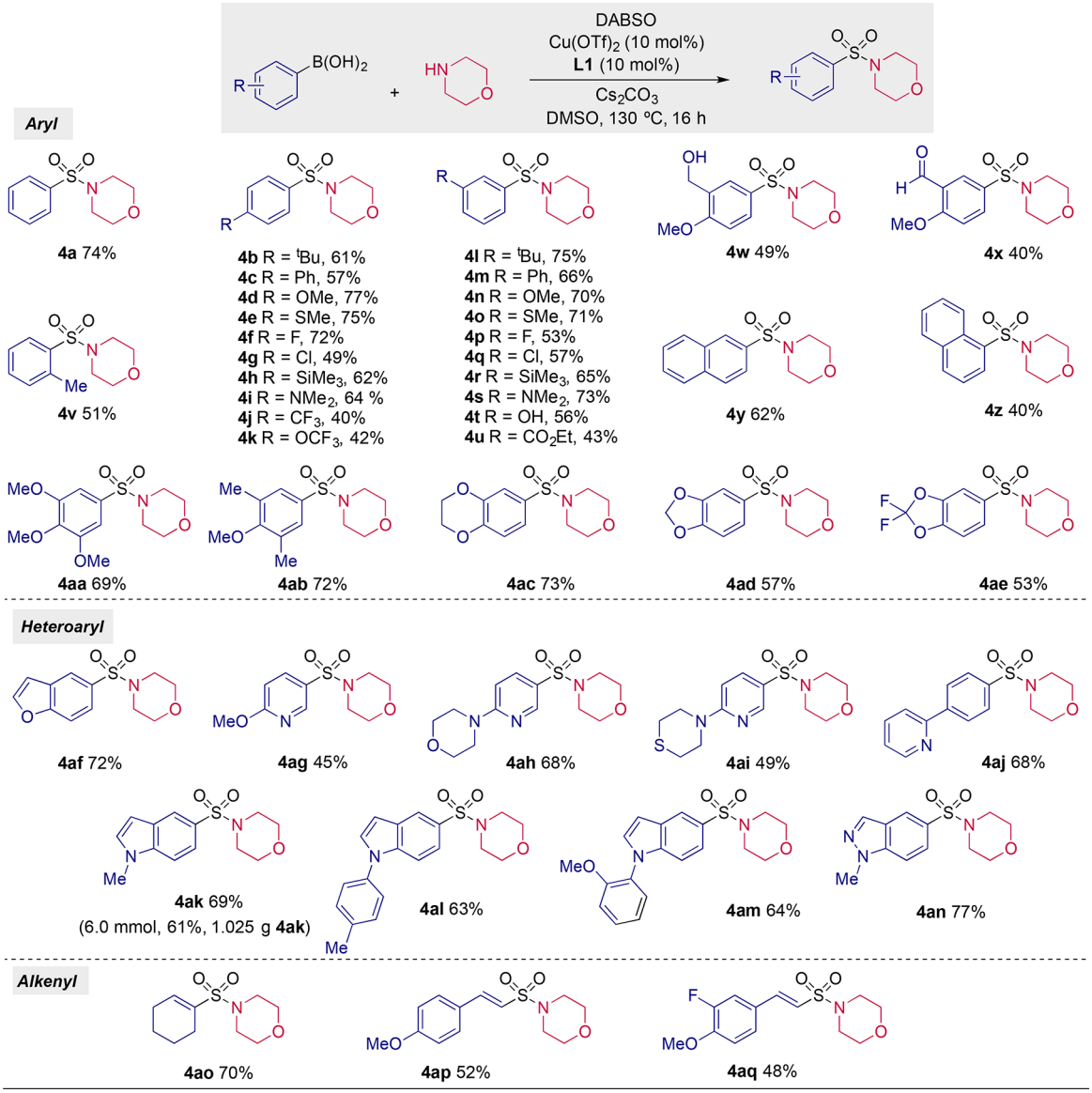
Table 1. Scope of the Boronic Acid Coupling Partner[a]



[a]Reaction conditions: morpholine (1.0 equiv), aryl boronic acid (2.0 equiv), copper(II) triflate (10 mol %), **L1** (10 mol %), DABSO (2.0 equiv), cesium carbonate (1.0 equiv), DMSO, 130 °C, 16 h. Isolated yields.

(**1**)[26] should limit this pathway. The challenge would be to engage amino-sulfinates **1** in cross-coupling.

To explore this concept we chose the coupling of phenyl boronic acid (**2a**), morpholine (**3a**), and sulfur dioxide. We selected the Lewis adduct formed between DABCO and sulfur dioxide, DABSO, as our sulfur dioxide source,[12] as it is an easy to handle solid reagent that has been shown to be effective in a number of catalytic processes (Scheme 2c).[10,16a,c,f,18,19] Pleasingly, initial results employing $Cu(OAc)_2$, the catalyst used in the majority of Chan–Lam reactions,[25a] delivered a 17% yield of sulfonamide **4a**. An extensive optimization study was then undertaken and delivered reaction conditions based on the use of $Cu(OTf)_2$ in combination with a supporting bipyridine ligand in DMSO as solvent (see Supporting Information for full details). Specific variations from these optimized conditions, and their effect on reaction efficiency, are also provided. Key observations were that DABSO was the optimal SO_2 source, the use of base was advantageous (but not essential), boronic acids were the boron reagent of choice, and that the use of alternative oxidants (to DMSO)[27] was not successful.[28]

With optimal conditions for the preparation of sulfonamide **4a** in hand, a full substrate scope was explored with respect to the boronic acid, using morpholine as the amine coupling partner (Table 1). A broad range of *para*-substituted aromatics could be tolerated, delivering the expected sulfonamides in good yields (**4b–k**), as could *meta*-substituted substrates (**4l–u**). These examples showed that both electron-donating and electron-withdrawing groups could be employed, although substrates bearing electron-withdrawing substituents provided reduced yields in some cases, with the mass balance comprising unreacted amine and protodeborylated arene. These examples also demonstrate the excellent functional group tolerance of the process, with reactive groups such as alcohols, amines, esters and halides all being unaffected by the reaction conditions. It is notable that oxidation-sensitive sulfides are compatible with the reaction (**4e,o**). A variety of more complex di- (**4w,x**) and trisubstituted aryl boronic acids

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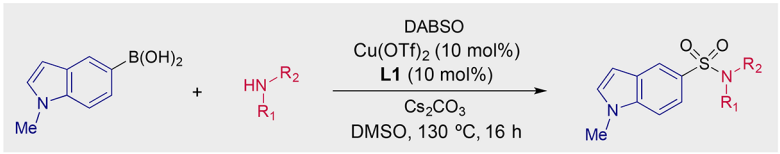
Table 2. Scope of the Amine Coupling Partner[a]



[a]Reaction conditions: amine (1.0 equiv), aryl boronic acid (2.0 equiv), copper(II) triflate (10 mol %), **L1** (10 mol %), DABSO (2.0 equiv), cesium carbonate (1.0 equiv), DMSO, 130 °C, 16 h. Isolated yields.

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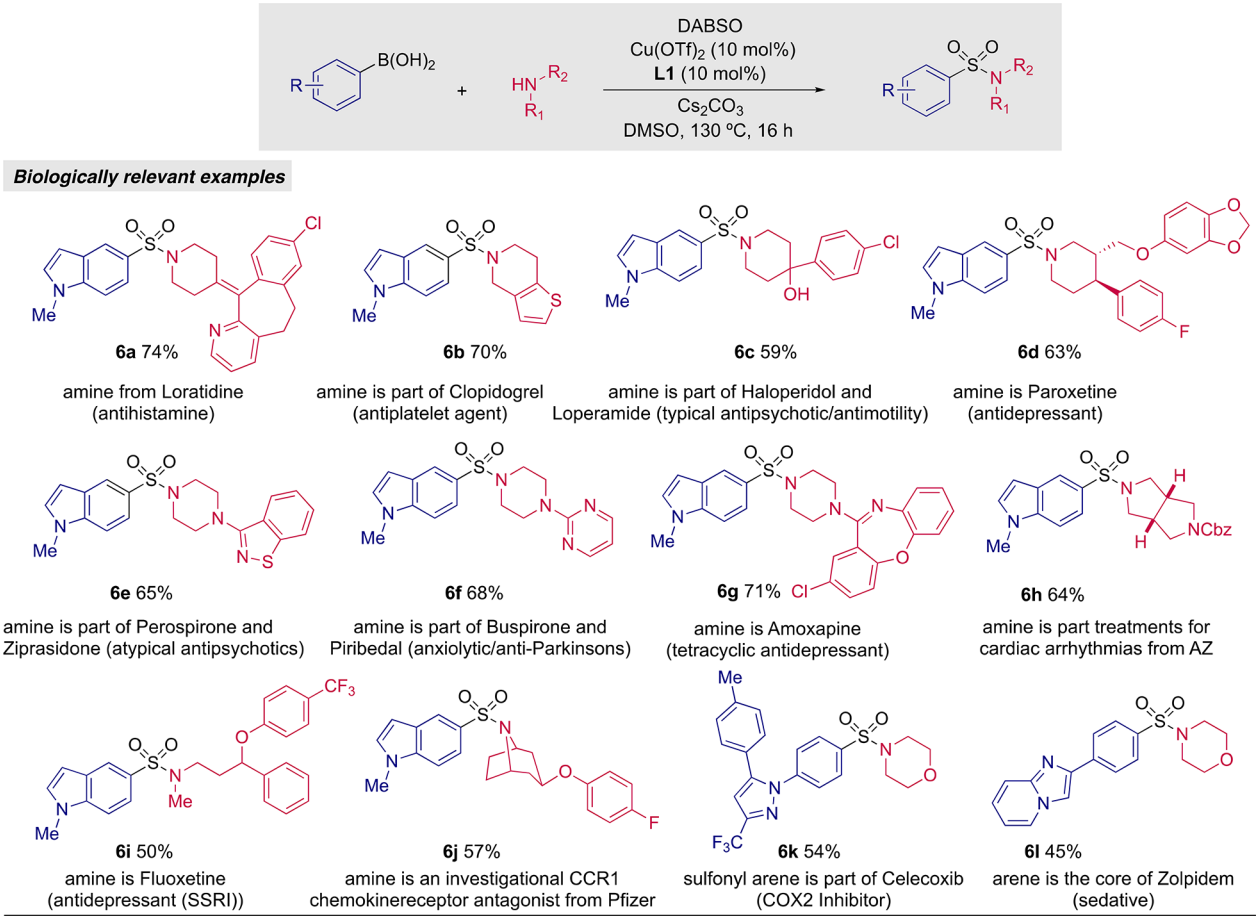
Table 3. Incorporation of Pharmaceutical APIs, and Related Fragments, into a Single-Step Sulfonamide Synthesis[a]



[a]Reaction conditions: amine (1.0 equiv), aryl boronic acid (2.0 equiv), copper(II) triflate (10 mol %), **L1** (10 mol %), DABSO (2.0 equiv), cesium carbonate (1.0 equiv), DMSO, 130 °C, 16 h. Isolated yields.

(**4aa,ab**), as well as naphthyls (**4y,z**), and examples fused with saturated heterocycles (**4ac−ae**), were also shown to work well. Importantly, a selection of heteroaromatic boronic acids were successfully converted into sulfonamides, including benzofuran (**4af**), pyridines (**4ag−aj**), indoles (**4ak−am**) and indazole (**4an**). The indole example **4ak** was scaled to deliver >1.0 g of product without issue. Finally, a group of alkenyl boronic acids were also shown to be effective substrates (**4ao−aq**).

Variation of the amine fragment was evaluated next, using *N*-methylindole-5-boronic acid as the coupling partner (Table 2). Disubstituted acyclic amines, exemplified by a series of *N*-methyl amines, performed well in the reactions, providing the corresponding sulfonamides in good yields (**5a−e**). Disubstituted acyclic amines that were more sterically demanding provided the sulfonamides in significantly reduced yields (poor yielding substrates are documented in the Supporting Information). Amines based on the piperidine ring-system were excellent substrates (**5f−v**), and this scaffold was consequently used to probe the functional group tolerance of the transformation with respect to the amine. Pleasingly, a broad range of reactive functional groups, including alcohols, amines, esters, ketones, sulfides, and nitriles, were readily tolerated. Tertiary alcohol (**5s**), spirocyclic ketal (**5t**) and spirocyclic azetidine (**5v**) examples further validate the high tolerance of the reaction to potentially sensitive functionality. In addition, the tetrahydroisoquinoline example (**5u**) demonstrates that oxidation-sensitive functionality is also tolerated under the oxidative conditions that are employed. Piperazine rings are common motifs in medicinal agents, and pleasingly a range of these cyclic amines substituted with carbamate (**5w**), aryl (**5x**) and heteroaryl (**5y−aa**) groups were converted into sulfonamides in an efficient manner. Cyclic amines of different ring-sizes and composition, including azetidines, were also effective substrates (**5ab−ae**). Although simple primary alkyl amines were not effective substrates (see Supporting Information), the less nucleophilic aniline class of amines were well tolerated, and examples featuring a variety of substituents (**5af−ak**), including saturated heterocycles (**5al−ao**), were effective. Indole (**5ap**) and pyridine-derived (**5aq**) aromatic amines were also successfully used. A set of representative amine nucleophiles, comprising a piperadine, a piperazine and an aniline, were also combined successfully with the less reactive arene components benzene boronic acid and 4-fluoro-benzene boronic acid (**5ar−aw**).

We anticipate that this chemistry will find wide application in discovery medicinal and agrochemistry, and accordingly wanted to demonstrate that coupling-fragments of established value in these communities could be incorporated. The examples presented in Table 3 show that a variety of amines that are either actual active pharmaceutical ingredients (APIs), or closely related derivatives, can be effectively converted into sulfonamides. For example, a series of complex substituted piperidine derivatives performed well, and allowed the

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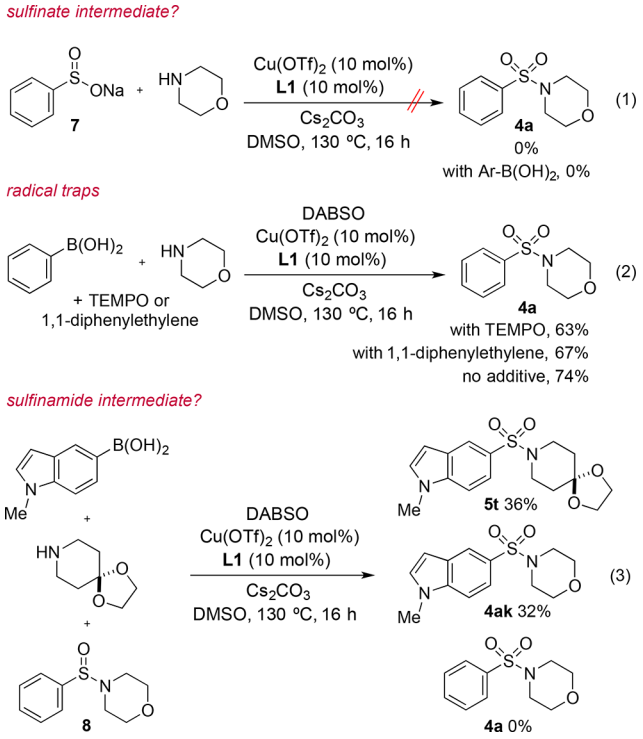
incorporation of amine fragments from antihistamine (Loratidine, **6a**), antiplatelet (Clopidogrel, **6b**) and antipsychotic (Haloperidol, **6c**) agents, as well as the actual API of the antidepressant Paroxetine (**6d**). Piperazines that feature in the atypical antipsychotics Perospirone and Ziprasidone (**6e**), and the anti-Parkinson's compound Piribedal (**6f**), all performed well, in addition to the piperazine moiety that is the API in the antidepressant Amoxapine (**6g**). A pyrrolo-pyrrole fused heterocycle that is part of reported treatments for cardiac arrhythmias (**6h**),[29] the acyclic *N*-methylamine that is the API in the antidepressant Fluoxetine (**6i**), and a tropane used as a CCR1 antagonist (**6j**)[30] complete the bioactive amines that were used. We were also able to employ appropriate boronic acids to allow the formation of sulfonamides featuring the sulfonylarene fragment from the COX2 inhibitor Celecoxib (**6k**), and the arene core of the sedative Zolpidem (**6l**). Importantly, modification of our optimized reaction conditions was not needed for any of these more complex examples.

When considering the potential mechanism of our developed single-step sulfonamide synthesis, we were aware of a report from Jiang and co-workers,[31] who had shown that aryl sodium sulfinates could be converted into the corresponding aryl sulfonamides by treatment with an amine and a copper-catalyst under oxidative conditions, raising the potential of the involvement a sulfinate intermediate in our system. Reaction of isolated sodium benzenesulfinate (**7**) with morpholine, under our reaction conditions delivered no sulfonamide product (Scheme 3, eq 1). Similarly, the inclusion

Scheme 3. Preliminary Mechanistic Control Experiments



of two equivalents of 4-F-phenylboronic acid to this system failed to deliver any sulfonamide product. The Jiang chemistry is susceptible to radical trapping;[31] however, this is not the case for the transformations reported here, as reactions carried out in the presence of two different radical scavengers, (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO) and 1,1-diphenylethylene, respectively, delivered good yields of sulfonamides (eq 2). We have similarly considered the possible formation of a sulfinamide intermediate that then undergoes oxidation to the desired sulfonamide product.[15] However, a coupling reaction doped with sulfinamide **8** resulted in the formation an approximate 1:1 mixture of sulfonamides **5t** and **4ak** (eq 3). Sulfonamide **4a**, the oxidation product of sulfinamide **8**, was not observed. Sulfonamides **5t** and **4ak** are presumed to arise from amine exchange with sulfinamide **8**. The requirement to use DMSO as solvent is key in our process, and is consistent with this simple sulfoxide acting as an oxidant and allowing substoichiometric amounts of a Cu(II) complex to be used as a catalyst.[32] Direct coupling of the amines and aryl boronic acids, to give anilines, was not observed. These mechanistic investigations are only preliminary in nature, and a detailed mechanistic investigation is underway.

CONCLUSIONS

The examples collected in Tables 1−3 demonstrate the broad scope and high functional group tolerance of the developed single-step sulfonamide synthesis. They also establish the ability of the method to process established bioactive fragments. Amines and boronic acids are both popular and widely available monomer sets used extensively by chemists in the pharmaceutical and agrochemical industries; DABSO is a commercially available and convenient to use sulfur dioxide surrogate, and copper(II) triflate and bipyridine ligand **L1** are also items of commerce, are widely used in other catalytic reactions, and are readily encountered in many synthetic chemistry laboratories. Given the availability of these substrates and reagents, and the widespread use of sulfonamides in discovery chemistry, we anticipate the rapid take-up and application of the methodology disclosed in this report.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b04532.

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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