Mechanistic insight enables practical, scalable, room temperature Chan–Lam *N*-arylation of *N*-aryl sulfonamides

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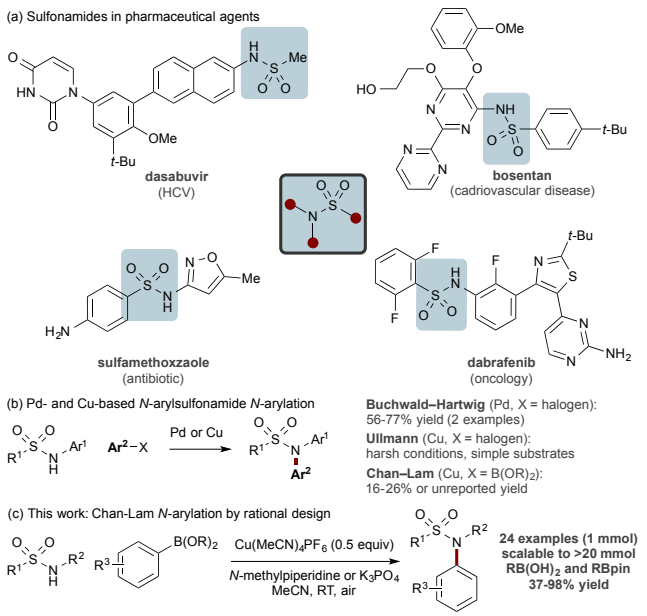
In celebration of the 20th anniversary of the Chan–Lam reaction

ABSTRACT: Sulfonamides are profoundly important in pharmaceutical design. C-N cross-coupling of sulfonamides is an effective method for fragment coupling and SAR mining. However, cross-coupling of the important *N*-arylsulfonamide pharmacophore has been notably unsuccessful. Here, we present a solution to this problem via oxidative Cu-catalysis (Chan–Lam cross-coupling). Mechanistic insight has allowed the discovery and refinement of an effective cationic Cu catalyst to facilitate the practical and scalable Chan–Lam *N*-arylation of primary and secondary *N*-arylsulfonamides at room temperature. We also demonstrate utility in the large scale synthesis of a key intermediate to a clinical HCV treatment.

KEYWORDS: boronic acid, boronic ester, catalysis, Chan–Lam, copper, sulfonamide

The *N*-aryl sulfonamide functional group is ubiquitous in medicinal chemistry, with the value of this motif demonstrated in marketed drugs for many different disease indications (Scheme 1a).[1] The broad utility of this group arises from the tetrahedral geometry, permitting control of H-bond donor/acceptor directionality to more effectively interact with a target ligand, and the imbued modulation of physicochemical properties that can be used to influence pharmacokinetics.[1]

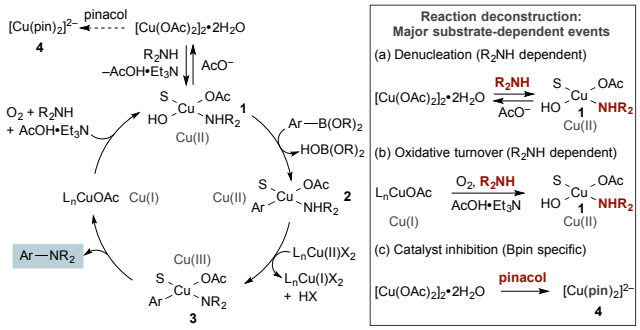
N-Arylation of *N*-arylsulfonamides is an attractive approach to target synthesis, enabling an alternative fragment coupling to *N*-sulfonylation (which is not always straightforward due to the poor nucleophilicity of diarylamines), and also providing a platform for rapid SAR analysis. Despite its appeal, this has been a challenging process to realize via transition metal catalysis.[2] To the best of our knowledge, only two examples of Pd-catalyzed arylation of *N*-arylsulfonamides have been reported (Scheme 1b),[3] with ligand development usually required for substrates of impaired Lewis basicity.[4] Ullman-based approaches are generally limited to simple substrates based on the forcing conditions required.[5] Oxidative cross-coupling using Cu-catalysis (Chan–Lam cross-coupling) offers an appealing alternative based on the generally inexpensive, ligand-free, and mild reaction conditions prevalent in this area, as well as the availability and variety of organoboron coupling partners.[6] However, Chan–Lam *N*-arylation of *N*-arylsulfonamides is particularly underdeveloped: only scattered examples are reported in the patent literature, with either low or no yields disclosed.[7,8] Perhaps more importantly, the origin of the problem is unknown. Here, we provide a mechanistically informed rationally designed system for practical and scalable Chan–Lam *N*-arylation of sulfonamides at room temperature (Scheme 1c).



Scheme 1. (a) Exemplar sulfonamides in active pharmaceutical ingredients. (b) Previous Pd- and Cu-mediated *N*-arylsulfonamide *N*-arylation. (c) A mechanistically-informed Chan–Lam *N*-arylation of *N*-arylsulfonamides.

We recently reported a functional description of Chan–Lam amination (Scheme 2).[9] The description was based on the most common reaction conditions using $Cu(OAc)_2$ and Et_3N as a base. The process is initiated by denucleation of the paddle-wheel dimer to the catalytically active monomeric Cu(II)(R_2NH) complex **1**. Transmetalation of the organoboron reagent delivers Cu(II)(Ar)(R_2NH) complex **2**, which is oxi-

dized via disproportionation to Cu(III) complex **3**.[10] Reductive elimination liberates the product and Cu(I). Completion of the catalytic cycle requires oxidation of Cu(I) to Cu(II), typically achieved by O_2.



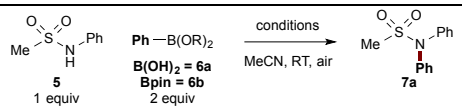
Scheme 2. Key mechanistic considerations for reaction design.

From mechanistic analysis, two *N*-substrate-dependent events were identified as critical: (1) the initial paddlewheel denucleation is highly dependent on the Lewis basicity of the *N*-substrate (Scheme 2a).[9] (2) Similarly, *N*-substrate association facilitates the oxidative turnover of the Cu catalyst (Scheme 2b).[9] Efficient Cu(I) oxidation is essential not only for turnover but also to avoid organoboron oxidation, protodeboronation, and homocoupling, which are driven by Cu(I).[9] (1) and (2) were anticipated to be the difficult steps in sulfonamide *N*-arylation based on the poor Lewis basicity of the *N*-arylsulfonamide. From the organoboron perspective, no specific issues were anticipated with arylboronic acids; however, use of BPin derivatives could lead to catalyst inhibition by pinacol (forming **4**), generated from transmetalation byproducts (Scheme 2c).[9]

Our reaction design was based on several considerations: (1) To aid paddlewheel denucleation, we selected a Cu(I) catalyst without competing ligating anions (*e.g.*, AcO^-); $Cu(MeCN)_4PF_6$.[11] This catalyst also served to reduce the quantity of uncontrolled H_2O in the system ($[Cu(OAc)_2]_2$ is usually the dihydrate), avoiding the need for rigorous drying and competing organoboron oxidation.[12] (2) Bolstering substrate ligation would aid productive catalysis, avoid organoboron homocoupling, and facilitate oxidative turnover.[9] *N*-Arylsulfonamide deprotonation was identified as a simple solution. However, base selection would be crucial: the base must deprotonate without causing competing processes – dimer-forming anionic bases would therefore be incompatible based on the points above. A second concern was inhibition of transmetallation by boron speciation, which would be a greater problem for boronic acids than BPin esters based on the propensities for hydroxy- and ternary boronate formation.[13,14] As such, we excluded anionic *O*-bases for boronic acid couplings and instead focused on amine bases. Anionic *O*-bases have shown some potential utility for Chan–Lam amination of Bpin,[9] and are anticipated to be tolerated for Bpin due to a lower propensity for boronate formation.[14] A greater base strength would help to avoid catalyst inhibition by pinacol by providing a greater solution concentration of substrate anion. Finally, adventitious desiccant effects using hygroscopic inorganic bases would lower organoboron oxidation further.[15] Based on all of these considerations, we selected K_3PO_4 for Bpin processes.

This mechanistic rationalization was successful on application (Table 1). Using sulfonamide **5** as a benchmark substrate, control reactions with $Cu(OAc)_2$ and Et_3N confirmed the arylation efficiency problem under standard conditions (entry 1). Moving to $Cu(MeCN)_4PF_6$ with Et_3N immediately improved the reaction to deliver 57% and 18% yield using **6a** and **6b**, respectively (entry 2). Use of a stronger amine base (*N*-methylpiperidine) delivered a highly effective process using **6a** (80%) and increasing base stoichiometry improved the yield further to 98% (entry 4). As expected from our previous work,[9] amine bases gave a notably poorer performance with **6b**, due to catalyst inhibition by pinacol (*ca.* 20%; entries 3 and 4). However, K_3PO_4 delivered **7a** in 50% using **6b** (entry 5) with increased stoichiometry improving to 80% (entry 6). As anticipated, K_3PO_4 was significantly detrimental to the reaction of **6a** (entries 5 and 6). All of these reaction parameters were further investigated in multivariate arrays, confirming the optimal conditions from Table 1 (see Supporting Information (SI) for full details). Several points are worth noting: (1) the use of 0.5 equiv Cu was necessary for efficiency since Cu is required as catalyst and oxidant (oxidation of Cu(II)→Cu(III) and Cu(I)→Cu(II)); (2) the organoboron was required in excess to maintain efficiency with respect to the expected competing side reactions (*i.e.*, protodeboronation, oxidation, and homocoupling); (3) selected inorganic bases were effective for reactions of **6a** when used in in conjunction with $Cu(OAc)_2$; however, these were not transferable to **6b**.

Table 1. Reaction optimization.



Entry	Conditions	**7a** from **6a** (%)[a]	**7a** from **6b** (%)[a]
1	$Cu(OAc)_2$ (0.5 equiv), Et_3N (6 equiv)	43	13
2	$Cu(MeCN)_4PF_6$ (0.5 equiv), Et_3N (6 equiv)	57	18
3	$Cu(MeCN)_4PF_6$ (0.5 equiv), *N*-methylpiperidine (6 equiv)	80	21
4	$Cu(MeCN)_4PF_6$ (0.5 equiv), *N*-methylpiperidine (8 equiv)	98	17
5	$Cu(MeCN)_4PF_6$ (0.5 equiv), K_3PO_4 (3 equiv)	40	50
6	$Cu(MeCN)_4PF_6$ (0.5 equiv), K_3PO_4 (8 equiv)	32	80

[a] Conversion to product determined by HPLC. See SI.

The origin of the efficiency gain from a mechanistic perspective was reinforced by spectroscopy (Figure 2). EPR analysis confirmed the denucleation problem (Figure 2a). Effective denucleation only takes place upon inclusion of a base capable of deprotonating **5**. *N*-Methylpiperidine and K_3PO_4 were significantly more effective than Et_3N. Similarly, UV-Vis analysis showed that Cu(I) oxidation is more effective with **5** in the presence of *N*-methylpiperidine and K_3PO_4 due to greater electron-density at Cu(I) (Scheme 2b). It is worthwhile noting that the oxidation using K_3PO_4 is slower than *N*-methylpiperidine due to the formation of some $Cu(I)PO_4$ *in situ*.[16] This further highlights the need to consider all potential substrate-catalyst and reagent-catalyst interactions in the design of these processes (Figure 2b).

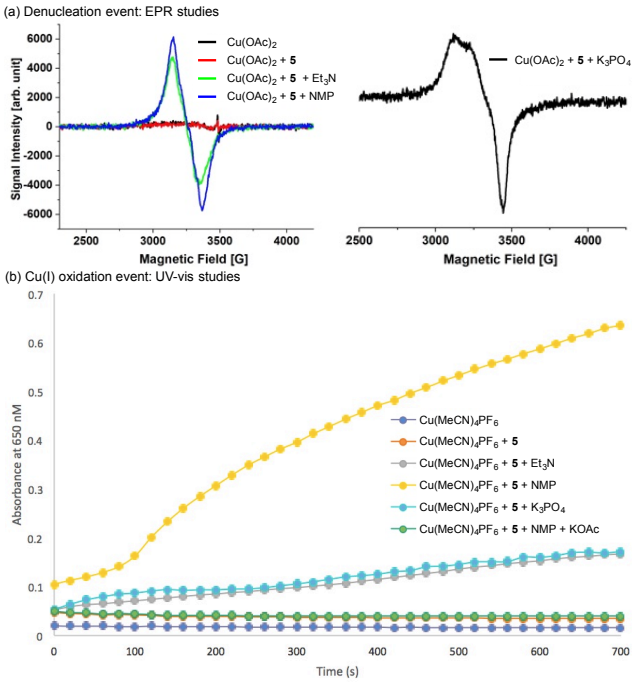
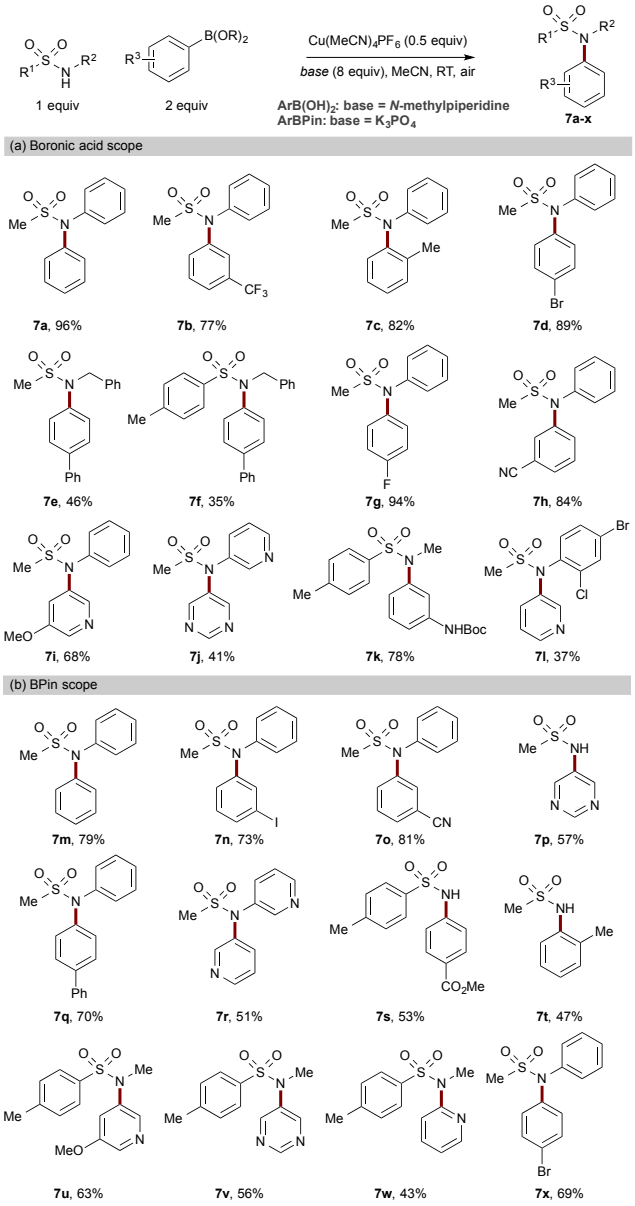


Figure 2. (a) Denucleation EPR analysis. (b) Cu(I) oxidation UV-Vis analysis. NMP = *N*-methylpiperidine.

The generality of the protocols was assessed by application to a series of substrates on 1 mmol scale (Scheme 3). Both protocols were broadly tolerant of functionality on the organoboron partner including variation of regiochemistry and electronic character, as well as the functionality on the *N*-aryl sulfonamide arene and the sulfonyl group. In particular, halide substituents (*e.g.*, **7l**, **7n**, **7x**) reinforce the orthogonality of the Chan–Lam amination with respect to redox neutral Pd and Cu methods, retaining these handles for subsequent manipulation. This key feature was important to the subsequent application of this method in target synthesis (*vide infra*). Notably, this protocol was chemoselective for the sulfonamide *N*-arylation vs. carbamate *N*-arylation (**7k**). While the focus of this study was to enable *N*-aryl sulfonamide *N*-arylation, we found the protocol amenable to arylation of both primary and *N*-alkyl sulfonamides, thereby establishing a broadly applicable method for sulfonamide arylation. Important to our focus on developing a practical methodology, the reaction operates at ambient temperature and using O_2 from air (instead of, for example, a saturated O_2 atmosphere). Yields were synthetically useful in the main, with sensitive organoborons (*e.g.*, heterocyclic examples **7j**, **7l**, **7v**, **7w**) and primary sulfonamides (**7p**, **7s**, **7t**) the most challenging.

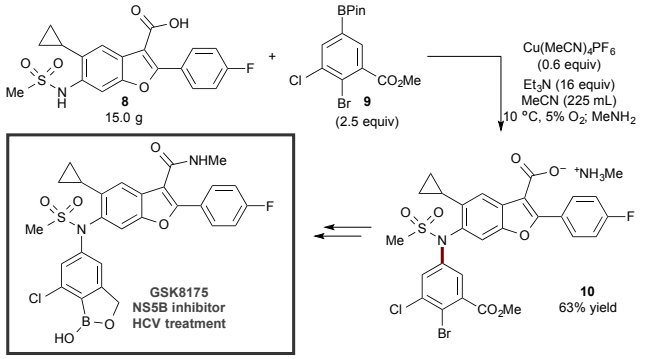


Scheme 3. *N*-Arylation scope. 1 mmol scale (sulfonamide), except for **7a** and **7q**, which are on 20 mmol scale. Isolated yields.

Similarly, our objectives required the development of a scalable process. To this end, the method was found to operate effectively on 20 mmol (3.4 g sulfonamide) scale for two examples (**7a** and **7q**, Scheme 3). The products were isolated in high purity (>98% purity), with the reaction to form **7a** requiring only a simple aqueous wash (NH_4OH, NH_4Cl) procedure. These results demonstrate the potential power of this Chan–Lam protocol not only for medicinal chemistry analogue generation and SAR, but also for eventual scale-up of potential clinical candidates.

As a final demonstration of utility, we report the use of this Chan–Lam coupling as a key transformation in the synthesis of the NS5B inhibitor GSK8175 (Scheme 4).[7c] NS5B inhibitors block the RNA polymerase activity of the NS5B viral enzyme and are an important class of hepatitis C (HCV) therapeutics.[17] HCV is a life-threatening condition with no known vaccine affecting approximately 2% of the global population,[18] with the majority of cases occurring in the developing world. Accordingly, the development of effective treatments for HCV

is a major international goal. A key structural feature of GSK8175 is the *N*,*N*-diarylsulfonamide, and the accompanying boronate ester moiety. Application of this Chan–Lam chemistry as an orthogonal coupling approach allows use of the halogenated aryl substrate **9** to access compound **10**, which can be quickly elaborated to the API.[7c] While our general conditions were found to be broadly effective on 1-20 mmol scale (Scheme 3), some optimization was necessary on this more challenging substrate. Specifically, targeted optimization led to several modifications for this specific transformation, including use of NEt_3 (to generate a soluble triethylammonium carboxylate *in situ*) and a dilute 5% O_2 stream as the terminal oxidant (to maintain a basis of safety on large scale). With these modifications to our general protocol, we have achieved 63% isolated yield of **10** on 15 g scale after crystallization of the methylammonium salt.[19]



Scheme 4. *N*-Arylsulfonamide *N*-arylation en route to GSK8175. Isolated yield.

In summary, rational methodological design enabled by mechanistic insight has allowed the development of an effective protocol for Chan–Lam arylation of a variety of primary and secondary sulfonamides. The mild reaction conditions operate effectively on small (1 mmol) scale and can be readily scaled (20 mmol and above). This methodology is facilitating the large-scale production of a clinical HCV therapy and we expect similar utility to be found in other applications in pharmaceutical development.

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All authors have given approval to the final version of the manuscript.
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Funding Sources

Engineering and Physical Sciences Research Council (EPSRC). GlaxoSmithKline.

Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data (EPR, UV), characterization data, copies of NMR spectra. The Supporting Information is available free of charge on the ACS Publications website.

ACKNOWLEDGMENT

We thank the EPSRC and GSK for a studentship (JCV). LL, KA, JAK, MGN, JLW, SX, and DCL thank all of the members of the GSK8175 team, and the members of the Global Chemical Catalysis group.

ABBREVIATIONS

EPR, electron paramagnetic resonance spectroscopy; HCV, hepatitis C virus; NMP, *N*-methylpiperidine; pin, pinacol/pinacolate; SAR, structure-activity relationahips;

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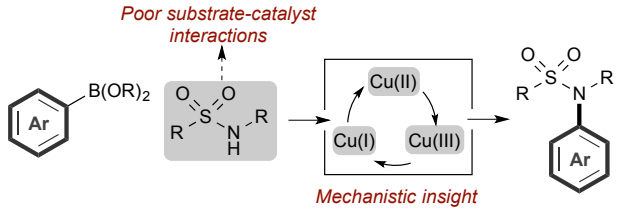

• $RB(OH)_2$ and RBpin • 24 examples •Scalable to >20 mmol