COMMUNICATION

Discovery, scope, and limitations of an *N*-dealkylation/*N*-arylation of secondary sulfonamides under Chan–Lam conditions

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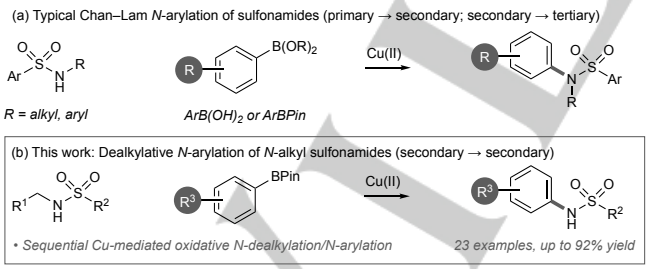
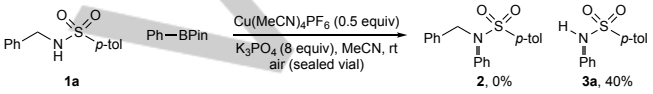
Abstract: We report the discovery, scope, and limitations of a Cu-mediated sulfonamide *N*-dealkylation/*N*-arylation reaction. Specific secondary *N*-alkyl sulfonamides undergo Cu-mediated oxidative dealkylation followed by *N*-arylation under Chan–Lam conditions. The reaction is relatively general, allowing the synthesis of a range of *N*-aryl secondary sulfonamides in good yield. Mechanistic investigations determined the sequence of reaction events as well as the efficiency-limiting events. Limitations in the methodology are also presented.

The Chan–Lam reaction is a versatile methodology capable of forming an array of C–X bonds under usually mild conditions.[1] C–N bond formation is arguably the most broadly used application, of this reaction, with extensive investigation in methodological development as well as utility in medicinal chemistry.[1a] Chan–Lam *N*-arylation of sulfonamides delivers *N*-arylsulfonamides – an important chemotype in drug design.[2] Usually, *N*-arylation of a primary or secondary sulfonamide will deliver the corresponding secondary or tertiary sulfonamide, respectively (Scheme 1a).[2,3] Here we report the serendipitous discovery, scope, and limitations of a process where specific secondary *N*-alkyl sulfonamides undergo dealkylation/*N*-arylation to give secondary *N*-aryl sulfonamides (Scheme 1b).



Scheme 1. (a) General Chan–Lam arylation of sulfonamides and (b) dealkylative Chan–Lam arylation of sulfonamides.

We recently reported the development of general reaction conditions that allowed the efficient *N*-arylation of *N*-aryl sulfonamides as part of a wider campaign to enable the scalable production of an HCV API.[2] During these studies, exploration of selected *N*-alkyl sulfonamides led to some unexpected results. Specifically, use of *N*-benzyl sulfonamide **1a** as a substrate under the optimized reaction conditions led to product **3a** instead of the expected product **2** (Scheme 2).



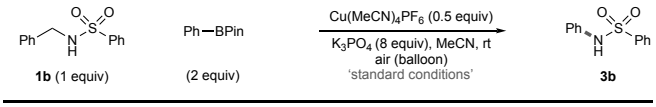
Scheme 2. Initial discovery of the dealkylation/*N*-arylation process.

This observation was potentially useful from a synthetic standpoint since, unusually, it afforded the corresponding secondary *N*-aryl sulfonamide products, despite using a secondary sulfonamide starting material. The discovery was also interesting from a mechanistic standpoint, since this may imply the presence of specific copper species in Chan–Lam reactions and provide additional insight into the reaction mechanism.

To establish the potential of the reaction as a synthetic methodology, optimization was undertaken using an exemplar system (Table 1; see Electronic Supporting Information (ESI) for full details). Optimized conditions were established (entry 1), with 1:2 stoichiometry of sulfonamide **1b**:PhBPin, in the presence of 0.5 equiv of $Cu(MeCN)_4PF_6$, with the requirement of excess base (K_3PO_4) and a balloon of air. Stirring at room temperature for 18 h delivered the product **3b** in good yield. Several data points were notable from this optimization: using a sealed vial (air atmosphere, no balloon) or having an open vial led to significantly lower yield (entries 2 and 3). Increasing the quantity of $Cu(MeCN)_4PF_6$ was detrimental (entry 4), and alternative Cu sources were less effective (*e.g.*, $Cu(OTf)_2$; entries 5 and 6; see ESI). Increasing the reaction temperature, which was effective in previous investigations for sulfonamide arylation,[2] was curiously less effective in this system (entry 7). Similarly, while protodeboronation and organoboron oxidation products were observed, increasing the quantity of organoboron was detrimental (entry 8) and use of the equivalent boronic acid (to preclude Cu inhibition by pinacol[4]) was also less effective (entry 9). Finally, the choice of base was crucial to reaction efficiency, with use of Et_3N, the most common base for Chan–Lam reactions, completely inhibiting the process (entry 10; see ESI).

The generality of the method was assessed by application to a range of substrates (Scheme 3). The reaction accommodated a selection of aryl boronic acid pinacol esters (BPin; Scheme 3a), including the general classes of electron-neutral (**3b**, **3c**), electron-rich (**3d**–**3i**), and electron-poor (**3j**–**3o**) substrates.

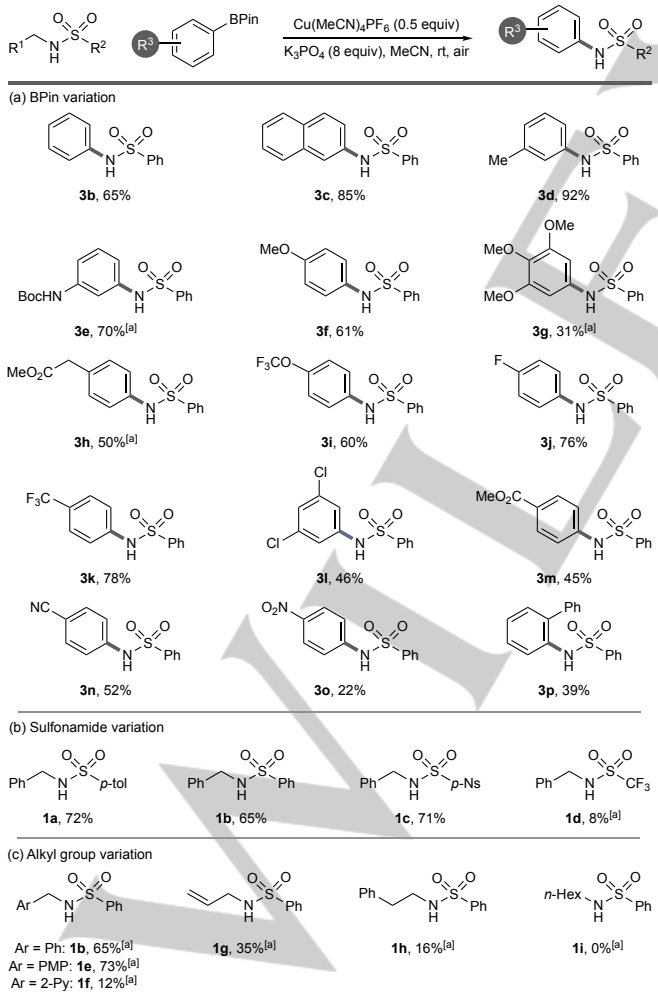
Table 1. Reaction optimization.[a]



1b (1 equiv) (2 equiv) **3b**

Entry	Deviation from 'Standard Conditions'	**3b** (%)[b]
1	None	70
2	Sealed vial (no balloon)	40
3	Open to air	27
4	$Cu(MeCN)_4PF_6$ (2 equiv)	55
5	$Cu(OTf)_2$ (0.5 equiv)	65
6	$Cu(OTf)_2$ (2 equiv)	55
7	80 ºC	7
8	PhBPin (5 equiv)	24
9	$PhB(OH)_2$ instead of ArBPin	39
10	Et_3N instead of K_3PO_4	0

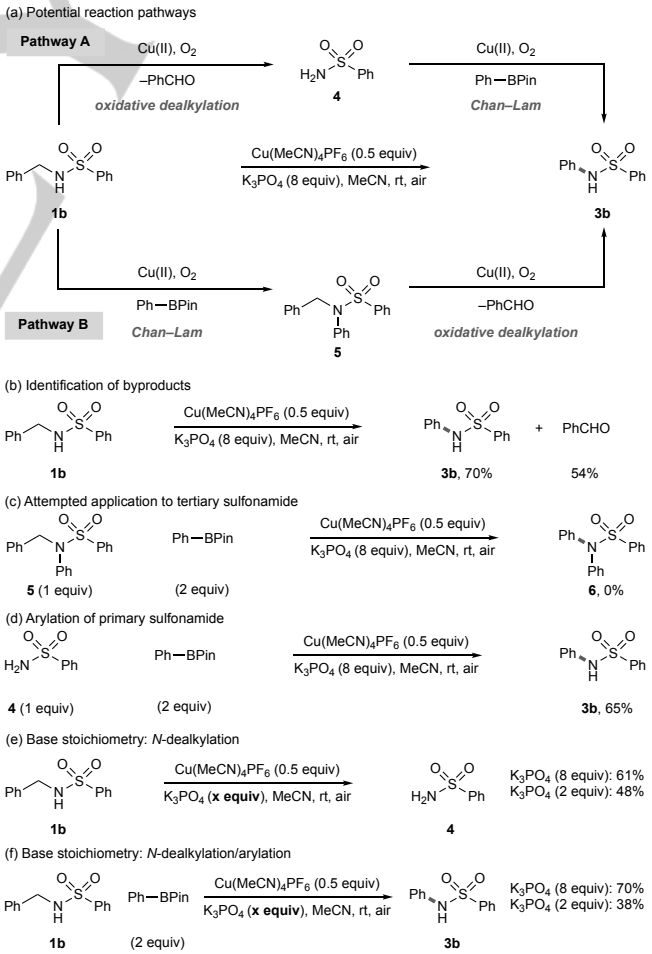
[a] 'Standard conditions' (entry 1): **1b** (0.25 mmol, 1 equiv), PhBPin (0.5 mmol, 2 equiv), $Cu(MeCN)_4PF_6$ (0.125 mmol, 0.5 equiv), K_3PO_4 (2 mmol, 8 equiv), MeCN (1 mL, 0.25 M). [b] Determined by ^{1}H NMR using an internal standard.



Scheme 3. Scope of the oxidative *N*-dealkylation/arylation. Isolated yields unless noted. [a] Determined by ^{1}H NMR using an internal standard.

Yields were typically good; however, strongly electron-rich or -poor substrates were notably lower (*e.g.*, **3g**, **3o**), as were substrates with an *ortho*-substituent (**3p**) – a common issue in the Chan–Lam reaction.[1a] Heteroaryl and allyl BPin were not tolerated (see ESI). Variation of the aryl group on the sulfonamide was similarly tolerated; however, triflamide **1d** was notably less effective (Scheme 3b). Finally, variation of the *N*-alkyl group was informative (Scheme 3c). Consistent with suspected radical pathway enabling C–H oxidation (*vide infra*), PMB substrate **1e** offered a slight improvement in reaction efficiency as compared to standard benzyl substrate **1b**, while 2-pyridyl derivative **1f** was significantly less effective; however, the lower yield for **1f** could not be directly attributed to electronic contribution or potential Cu-ligation or a combination of both. Consistent with a perceived requirement for an activated C–H position, *N*-allyl sulfonamide **1g** delivered the expected product but in a considerably lower yield as compared to the analogous benzyl species **1b**. Based on a mechanism anticipated to proceed via oxidation of a labile C–H, homobenzylic substrate **1h** was expected to be inert; however, this substrate delivered 16% of the coupled product suggesting activation of a relatively unactivated alkyl C–H. Probing this further with the simple *n*-hexyl sulfonamide substrate **1i** failed to deliver any product, implying some activation is required. These latter two substrates (**1h** and **1i**) raised significant questions regarding the specific mechanism of this process.

From a mechanistic standpoint, the reaction appeared to be a two-fold sequence (Scheme 4a).

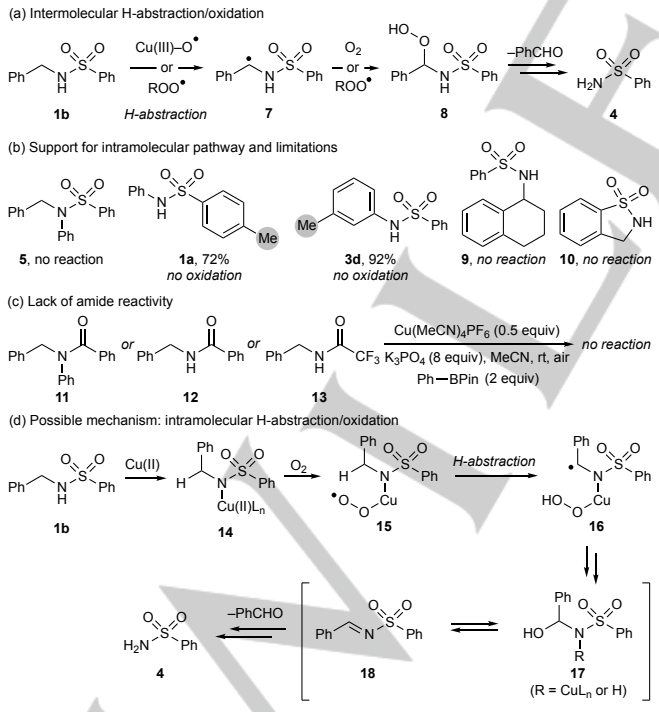


Scheme 4. Possible reaction pathways and control experiments. Determined by ^{1}H NMR using an internal standard.

Using substrate **1b** as the benchmark, the reaction either comprised a dealkylation event followed by Chan–Lam arylation of the resulting primary sulfonamide **4** to give **3b** (Pathway A) or Chan–Lam arylation of **1b** to deliver tertiary sulfonamide **5** followed by dealkylation to give **3b** (Pathway B). Firstly, benzaldehyde was readily detected as a reaction byproduct, supporting an oxidative dealkylation (Scheme 4b).

Several control experiments established Pathway A to be most likely: (i) Synthesis of tertiary sulfonamide **5** and exposure to the reaction conditions did not deliver **3b** – no dealkylation was detected (Scheme 4c); (ii) exposure of primary sulfonamide **4** to the standard reaction conditions delivered **3b** in the same yield as found in the two-stage process, supporting Pathway A also suggesting that the dealkylation may be significantly more efficient than the subsequent Chan–Lam event. However, examination of the dealkylation event suggested the overall process is more complicated. The dealkylation is indeed more efficient when using 8 equiv K_3PO_4 and the subsequent *N*-arylation is also more efficient consistent with previous observations (Scheme 4e).[2]

The oxidation of benzylic (and other labile) positions by Cu in the presence of O_2 is well known, and has been proposed to be related to enzymatic processes.[5-8] The mechanism(s) of these processes remain elusive but have been attributed to Cu species such as Cu(III)O• or biscopper species (*e.g.*, $[Cu_2(\mu\text{-}O)_2]^{2+}$) or though peroxy radicals generated by Cu-mediated reduction of O_2.[9] In the present system, intermolecular H-abstraction may lead to the expected benzylic radical that may be intercepted by O_2 or peroxy radicals (Scheme 5a).



Scheme 5. Possible mechanistic pathways.

Subsequent peroxide cleavage and hydrolysis (with loss of PhCHO) would generate primary sulfonamide **4**. However, several data suggest this is unlikely. Specifically, (i) the lack of reactivity of tertiary sulfonamide **5** (bearing an oxidizable benzylic position), (ii) the lack of any observed oxidation of the tolyl groups of **1a** and **3d**, and (iii) the lack of reactivity of sulfonamides **9** and **10**, both of which seemingly fulfill the criteria for reaction but are inert in the process (Scheme 5b). Moreover, attempting the reaction on amide substrates **11**, **12**, and **13** was similarly unsuccessful, regardless of NH pK_a (Scheme 5c). In addition, that sulfonamide **1h** (Scheme 3c) delivers the expected product (albeit in low yield) implies that H-abstraction does not proceed via direct intermolecular H-abstraction.

Accordingly, a more plausible pathway may be via intramolecular H-abstraction (Scheme 5d). Base may promote the formation of Cu(II)sulfonamide complexes, such as **14**; a series of similar complexes are known.[10] Engagement of **14** with O_2 could lead to Cu(peroxy) complex **15**, primed for intramolecular H-abstraction to deliver the required benzylic radical **16**.[9,11] Oxidation to the aminal would deliver **17**, in equilibrium with sulfonyl imine **18**, with hydrolysis finally liberating **4**. Dealkylation of *N*-benzylamines has been shown to be effective with discrete Cu(II)peroxy complexes, suggesting this is a more likely scenario.[9] In addition, the reverse process, *N*-alkylation (benzylation) of sulfonamides takes place using a variety of Cu sources under air with the requirement of elevated temperatures (150 ºC).[12] This may explain why elevated temperatures delivered poor yields of product (**3b)** in the dealkylation/*N*-arylation process (Table 1, entry 1 *vs.* entry 7): elevated temperatures may disfavor dealkylation by promoting formation of **1b**. However, since similar Cu•amide complexes are also known,[13] a similar pathway could be assumed to allow access to *N*-alkyl amide dealkylation/arylation, yet this was not successful under any of the conditions employed (Scheme 5c). Accordingly, there may be additional factors involved with the seemingly selective reaction of the sulfonamides investigated here.

In summary, a novel Cu-mediated sulfonamide *N*-dealkylation/*N*-arylation reaction of *N*-alkyl sulfonamides has been discovered and investigated. The reaction is general and delivers secondary *N*-aryl sulfonamides from selected secondary *N*-alkyl sulfonamides offering an expansion in Chan–Lam amination methodology. Control experiments determined the order of events and unexpected observations regarding substrate compatibility have suggested C–H oxidation in the α-position to the sulfonamide nitrogen as the likely pathway. We believe this reactivity is likely to be driven by Cu(peroxo) species; however, elucidation of the true structure of the Cu species and mechanism of the oxidation requires additional insight.[14]

Experimental

Experimental Section

Representative experimental procedure. For example, synthesis of compound **3b**. To an oven-dried 20 mL microwave vial was added *N*-benzylbenzenesulfonamide (**1b**; 61.8 mg, 0.25 mmol, 1 equiv), 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (PhBPin; 102.1 mg, 0.5 mmol, 2

equiv), $Cu(MeCN)_4PF_6$ (46.6 mg, 0.125 mmol, 0.5 equiv), and K_3PO_4 (424 mg, 2.00 mmol, 8 equiv). The vial was capped, MeCN (1 mL, 0.25 M) was added via syringe, and the septum was pierced with a needle attached to a balloon filled with air. The reaction mixture was stirred at rt for 18 h. The vial was then decapped and the reaction mixture was diluted with EtOAc (10 mL), washed with aq. NH_3OH solution (5 mL, 10% w/w) and brine (10 mL). The aqueous phase was back extracted with EtOAc (3 x 10 mL), and the combined organics were dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude residue was purified by column chromatography (silica gel, 5-15% EtOAc in petroleum ether 40-60°) to afford the desired product as a white solid (38.1 mg, 65 %).

Acknowledgements

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Keywords: arylation • boron • copper • cross-coupling • oxidation

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[14] The research data underpinning this publication can be accessed at https://doi.org/10.17630/32bd65fd-d283-40a8-9eac-505959982984

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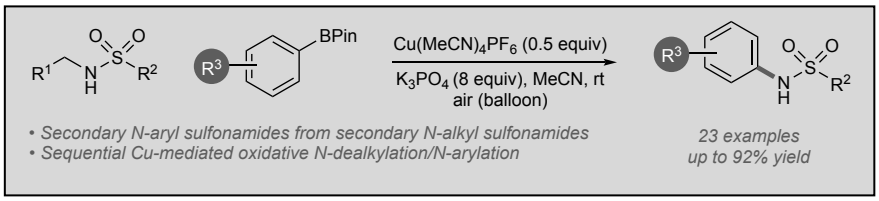

Chan–Lam *N*-arylation of specific *N*-alkyl secondary sulfonamides delivers *N*-aryl secondary sulfonamides via Cu-mediated oxidative *N*-dealkylation followed by *N*-arylation. The reaction is general, delivering a range of secondary *N*-aryl sulfonamides in good yield. Starting material compatibility, the limitations of the process, and the likely reaction mechanism are discussed.

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