Photochemically-mediated nickel-catalyzed synthesis of *N*-(hetero)aryl sulfamides

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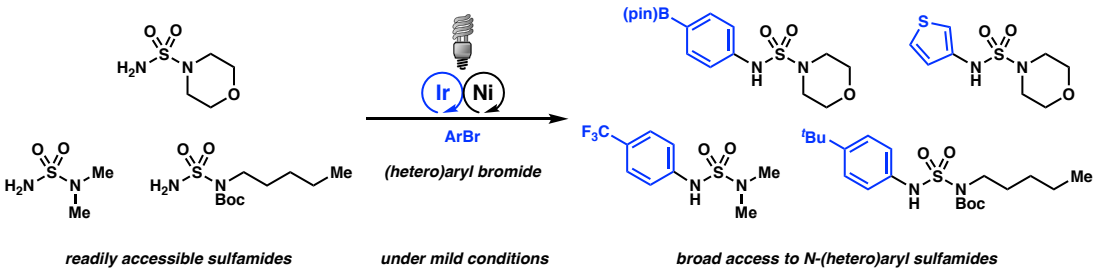


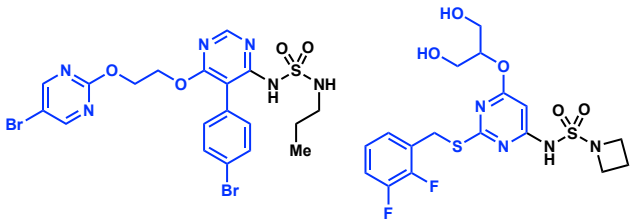
ABSTRACT: A general method for the *N*-arylation of sulfamides with aryl bromides is described. The protocol leverages a dual-catalytic system of nickel and a photoexcitable iridium complex and proceeds at room temperature under visible light irradiation. Using these tactics, aryl boronic esters and aryl chlorides can be carried through the reaction untouched. Thereby, this method complements known Buchwald-Hartwig coupling methods for *N*-arylation of sulfamides.

INTRODUCTION

N-Aryl sulfamides are critical components of active pharmaceutical[1] and agrochemical[2] agents (Figure 1).[3,4] In drug discovery, sulfamides can be valuable analogues of sulfamate, sulfonamide, urea, carbamate, and amide functional groups.[1a] In reactions, *N*,*N*'-disubstituted sulfamides are useful as chiral auxiliaries,[5] as organocatalysts,[6] as reagents to promote dehydration,[7] as precursors to sterically encumbered carbon–carbon bonds[8] and as directing groups for C–H functionalization processes.[9] Despite the potential of this valuable functional group,

sulfamides may be underutilized due to limitations in practical methods for their preparation.[10, 11, 12]

Figure 1. *N*-heteroaryl sulfamides are important FDA-approved drugs and therapeutic targets

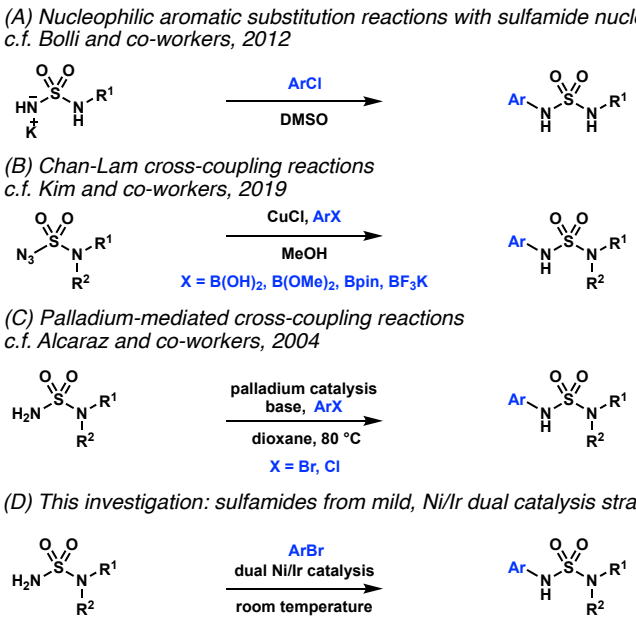


macitentan (brand name: Opsumit)
FDA approved treatment for pulmonary arterial hypertention

azetidine derivative
patented as a potential chemokine receptor modulator

To date, approaches to prepare *N*-(hetero)aryl sulfamides rely on N–S bond-forming reactions that involve the nucleophilic addition of amines to SO_2 sources (not depicted),[12, 13] or on C–N bond-forming strategies (Scheme 1). These direct methods for C–N bond formation have been primarily limited to nucleophilic substitution reactions (Scheme 1A), copper-mediated Chan-Lam coupling processes that transform sulfamoyl azides (Scheme 1B),[14] and Buchwald-Hartwig amination conditions that are palladium-mediated (Scheme 1C).[15, 16, 17]

Recently, room temperature Buchwald-Hartwig reaction protocols have emerged that are photochemically-driven and nickel-catalyzed.[18, 19] These mild conditions are complementary to palladium-mediated protocols, representing one of the most general platforms in terms of the breadth of arenes tolerated in *N*-arylation processes.[18a] Additionally, nickel-catalyzed photochemically-driven conditions engage a broader range of nucleophilic coupling partners in efficient C–N bond-forming reactions.[19] Accordingly, we anticipated that these photo-driven, nickel-catalyzed processes would afford an efficient, robust, and complementary strategy to access valuable *N*-(hetero)aryl sulfamides. Herein disclosed is the first photochemically-mediated, nickel-catalyzed method to access *N*-(hetero)aryl sulfamides.



Scheme 1. Recent advances allow for diverse and complementary strategies for the synthesis of *N*-(hetero)aryl sulfamides

Results and Discussion

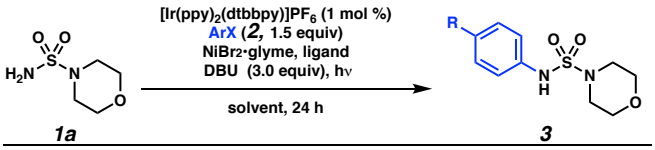
We[13] and others[18d] have observed that, relative to electron-deficient arylbromides, electron-rich arylbromides can be more challenging electrophiles when employing nickel-mediated cross-coupling technologies. Accordingly, we optimized the reactions of sulfamide **1a** with electron-deficient 4-(trifluoromethyl)bromobenzene and electron-rich 4-(*tert*-butyl)bromobenzene concurrently (Table 1).

Relying on previously established conditions for the arylation of sulfamate esters,[13] sulfamide **1a** reacts with 4-(trifluoromethyl)bromobenzene to afford *N*-aryl sulfamide **3a** in quantitative yield (Table 1, entry 1). This synthetic protocol can transform aryl chloride and iodide electrophiles, albeit in slightly diminished yields (entries 2–3). Unsurprisingly, sulfamide **1a** reacts with 4-(*tert*-butyl)bromobenzene *inefficiently* (entries 4–5). Consistent with previous

observations,[13, 18d] higher turnover numbers can be achieved when 4,4'-di-*tert*-butyl-2,2'-dipyridyl (dtbbpy) is employed as a ligand for nickel (entry 6).

To our surprise, the efficiency of this reaction improves substantially when it is run in absolute ethanol, or with ethanol as a co-solvent (entries 7–8). Importantly, the solvent and the aryl bromide do not engage in undesirable C–O coupling processes, as the predicted products of these processes are not detected. Unfortunately, the reaction efficiency drops in the presence of 100 equiv of water (entry 9). When we assessed a single solvent from each of seven solubility clusters,[20] the reaction was less efficient in these other solvents (entries 10–15). The advantages of ethanol were isolated to reactions engaging this more electron-rich aryl bromide, and did not translate to the reaction of 4-(trifluoromethyl)bromobenzene (entries 16–17). This synthetic protocol can be used to transform aryl iodide electrophiles but does not transform electron-rich aryl chlorides in synthetically useful efficiencies (entries 18–19). Control experiments confirm that nickel, photocatalyst, and light are critical to the success of both of the optimized cross-coupling protocols (see supporting information for details).

Table 1. Optimization informs distinct conditions for electron-deficient and electron-rich aryl bromides



entry	R	X	[Ni] (mol %)	ligand	solvent	yield (%)[b]
1	CF_3	Br	5	–	MeCN	>98[c]
2	CF_3	I	5	–	MeCN	79
3	CF_3	Cl	5	–	MeCN	43
4	^{t}Bu	Br	5	–	MeCN	32
5	^{t}Bu	Br	10	–	MeCN	33
6	^{t}Bu	Br	10	dtbbpy	MeCN	47
7	^{t}Bu	Br	10	dtbbpy	EtOH	89[c]
8	^{t}Bu	Br	10	dtbbpy	9:1 MeCN: EtOH	90

9	^{t}Bu	Br	10	dtbbpy	EtOH with H_2O (100 equiv)	6
10	^{t}Bu	Br	10	dtbbpy	MeOH	76
11	^{t}Bu	Br	10	dtbbpy	^{i}PrOAc	7
12	^{t}Bu	Br	10	dtbbpy	CH_2Cl_2	0
13	^{t}Bu	Br	10	dtbbpy	DMSO	32
14	^{t}Bu	Br	10	dtbbpy	acetone	35
15	^{t}Bu	Br	10	dtbbpy	2-methyl tetrahydrofuran	23
16	CF_3	Br	5	–	EtOH	70
17	CF_3	Br	5	–	MeOH	81[c]
18	^{t}Bu	I	10	dtbbpy	EtOH	81
19	^{t}Bu	Cl	10	dtbbpy	EtOH	7

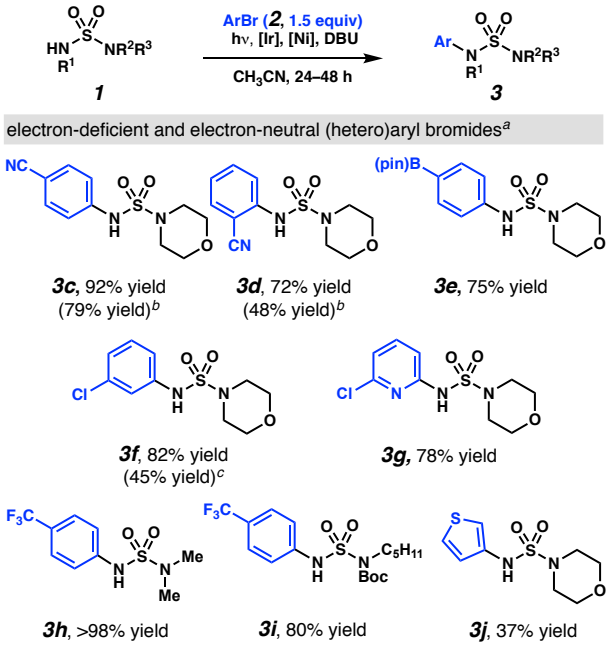
[a] General reaction conditions: sulfamide **1a** (1.0 equiv), aryl halide **2** (1.5 equiv), $NiBr_2$•glyme, $[Ir(ppy)_2(dtbbpy)]PF_6$ (1 mol %), DBU (3.0 equiv), and ligand (4 mol %) in indicated solvent (0.25 M) with stirring and irradiation between two 34 W blue Kessil lamps for 24 h. [b] NMR yield using an internal standard of 2,3,5,6–tetrachloronitrobenzene. [c] Isolated yield.

These dual catalyzed processes offer complementary reactivity profiles to those available through palladium-mediated Buchwald-Hartwig reactions. We have employed the developed ligand-free conditions to recapitulate palladium-mediated C–N bond-forming reactions to access arylated **3c** and **3d**.[16a] The developed nickel-mediated transformations furnish these products with increased yields, relative to those documented using a known palladium-mediated protocol,[16a] suggesting that this nickel-mediated approach is worthy of concurrent investigation in the course of synthetic campaigns. Given our interest in functionalized pyridines,[21] we were pleased to find that bromopyridines were effective arylating agents using the disclosed protocol. Furthermore, this dual catalytic reaction manifold can transform aryl bromides, without engaging either $C(sp^2)$–B (**3e**) and $C(sp^2)$–Cl (**3f-g**) bonds to afford products with useful synthetic handles for further functionalization.

The reaction arylates *N*,*N*-disubstituted sulfamides in synthetically useful yields, with examples including *N*-morpholino **1a**, *N*,*N*-dimethylated **1b**, and *N*-carbonyl-*N*-alkylated **1c**

sulfamides. In this arylation reaction, *N*-carbonyl-*N*-alkylated sulfamides, such as **1c**, are appropriate surrogates for sterically deshielded *N*-monosubstituted sulfamides, which are not prone solely to monoarylation reactions under the developed protocols.

Scheme 2. Photochemically-mediated nickel-catalyzed conditions engage a variety of electron-deficient aryl bromides and sulfamides



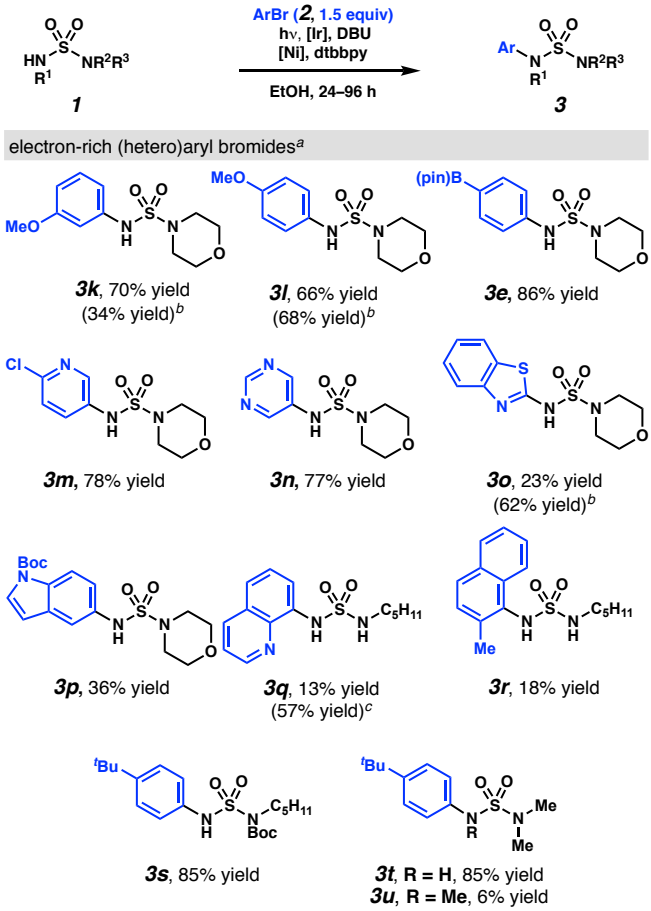
[a] General conditions: sulfamide **1** (1.0 equiv), (hetero)aryl bromide (1.5 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (1 mol %), $NiBr_2$•glyme (5 mol %), and DBU (3.0 equiv) in MeCN (0.25 M) with stirring between two 34W blue Kessil lamps for 24–48 h. [b] Isolated yield through a palladium-mediated cross-coupling reaction.[16a] [c] Isolated yield when prepared from subjecting morpholinyl sulfamoyl chloride[22] following literature conditions.[23]

In general, electron-deficient aryl bromides *N*-arylate sulfamides in good to excellent yields (**3c–3i**). By contrast, in acetonitrile, some electron-rich aryl bromides react with modest efficiency (c.f. Table 1, entry 4; Scheme 2, **2j**). In spite of this limitation, a thiophene (**2j**) can be installed onto a sulfamide in modest yield. This result suggests that this protocol overcomes the common tendency of nickel catalysts to engage in C–S bond activation,[24] or to be deactivated upon reaction with sulfur.

Fortunately, with the use of EtOH as a solvent and inclusion of a ligand, the protocol can transform a similar range of sulfamide substrates and allows the efficient cross-coupling of electronically-varied (hetero)aryl bromides. Specifically, electron-rich *para*- and *meta*-substituted *N*-aryl sulfamides **3k, 3l** were synthesized with similar or improved yields relative to those reportedly isolated upon reaction of morpholinyl sulfamyl chloride with anilines. As anticipated, under these conditions, aryl bromides can react, without engaging either C(sp^2)–B (**3e**) and C(sp^2)–Cl (**3m**) bonds to afford products with useful synthetic handles for further functionalization. Furthermore, these conditions can be used to install heteroaryl groups including a pyrimidine (**3n**). Unfortunately, the installation of more conjugated benzothiazole, *tert*-butyl indole-1-carboxylate, quinoline, and 2-methylnaphthalene moieties has proven less efficient (c.f. **3o**–**3r**). By comparison, while 13% yield of the quinoline analogue **3q** can be isolated under the developed nickel/iridium-mediated conditions, its preparation has proven more efficient by way of nucleophilic substitution on sulfur(VI), which proceed in 57% yield.[13b]

In EtOH, some variations in sulfamide substitution are well tolerated. The reaction engages *N*,*N*-disubstituted sulfamides in synthetically useful yields, with examples including *N*-morpholino **1a**, *N*-carbonyl-*N*-alkylated **1c**, and *N*,*N*-dimethylated **1b** sulfamides. In this arylation reaction, *N*-carbonyl-*N*-alkylated sulfamides, such as **1c**, are appropriate surrogates for sterically deshielded *N*-monosubstituted sulfamides, which can be forced to engage in monoarylation reactions when larger aryl bromide electrophiles are employed, albeit in low efficiency. Notably, this protocol does not provide efficient access to a tetrasubstituted sulfamide **3u**.

Scheme 3. Photochemically-mediated nickel-catalyzed conditions engage a variety of sulfamides and electron-rich aryl bromides



[a] General conditions: sulfamide **1** (1.0 equiv), (hetero)aryl bromide (1.5 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (1 mol %), $NiBr_2$•glyme (10 mol %), dtbbpy (4 mol %) and DBU (3.0 equiv) in EtOH (0.25 M) with stirring between two 34 W blue Kessil lamps for 24–96 h. [b] Isolated yield when prepared from *N*,*N*-dichlorosulfamide.[25] [c] Isolated yield when prepared from sulfamic acid.[13b]

Conclusion

We have developed a new catalytic method for sulfamide *N*-(hetero)arylation. This protocol offers several attributes, as it proceeds under mild conditions, and employs a variety of readily available substrates and reagents that complements the range that may be used under palladium-mediated Buchwald-Hartwig reaction conditions. The developed photo-driven nickel-mediated tactics can be employed with (hetero)aryl bromide, iodide, and chloride electrophiles.

Fortunately, owing to the higher reaction efficiency with (hetero)aryl bromides, aryl boronic esters and aryl chlorides can be carried through the reaction untouched, so these useful synthetic handles can be retained for further synthetic manipulation. Owing to these attributes, this method extends chemists' ability to use a sulfamide in the most versatile step a medicinal chemistry campaign, the "production step."[26] Moreover, it broadens the synthetic access to *N*-(hetero)aryl sulfamides, which are of increasing pharmacological interest.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

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Supplementary Data

Supplementary data to this article can be found online at insert hyperlink to SI here.

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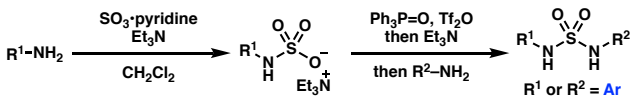

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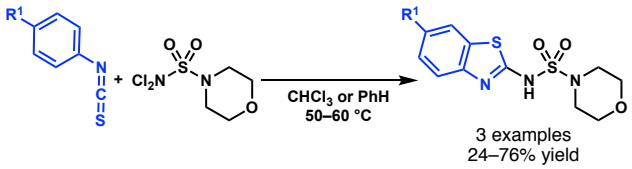

[26] By definition, the "production step" is a transformation that allows for ready installation of related but varied molecular components, such as aryl groups, on a single functional group handle, such as a sulfamide, to generate a focused yet diverse small molecule library.

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