

Nickel-Catalyzed Amination of Aryl Sulfamates**

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Carbon–nitrogen bonds are ubiquitous in medicinal agents and natural products.^[1] Transition metal-catalyzed amination reactions, pioneered by Buchwald and Hartwig, are amongst the most powerful methods available for accessing these motifs.^[1] Copper- and palladium-mediated aminations of aryl halides and triflates are now well-established,^[1] and examples of mesylate^[2] and tosylate^[3] aminations have been reported. Most recent efforts have focused on the amination of classically “inert” phenolic derivatives (i.e., arylmethyl ethers^[4] and aryl pivalate esters^[5]), which could potentially be used in multistep synthesis.^[6,7] With the aim of assembling polysubstituted aryl amines, motifs commonly encountered in drug scaffolds, naturally occurring small molecules, pesticides, ligands for catalysis, and materials chemistry, we sought to uncover a versatile class of phenol-derived substrates that could undergo transition metal-catalyzed amination.

Although relatively unexplored, *N,N*-dialkylaryl *O*-sulfamates (e.g., **1**, Scheme 1) are highly attractive electrophiles for cross-coupling reactions. They are easy to prepare,^[8] stable to a variety of reaction conditions, and exhibit low reactivity

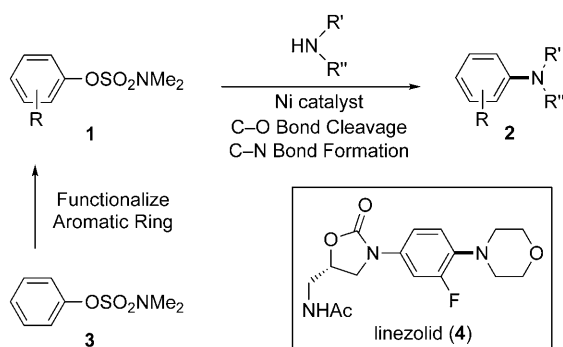
toward Pd⁰.^[9,10] Moreover, the sulfamate moiety can be used to functionalize an arene at both the *ortho* or *para* positions,^[9a,10,11] prior to carrying out a cross-coupling event. Despite that aryl *O*-sulfamates have been employed in carbon–carbon bond forming reactions,^[9,10] their use in carbon–nitrogen bond construction has remained undiscovered.^[12] Herein, we report the first amination of aryl *O*-sulfamates (**1**→**2**) and the application of this methodology to a concise synthesis of the antibacterial drug linezolid (**4**).^[13]

Initial studies were aimed at promoting the amination of dimethylsulfamate derivatives of phenol and 1-naphthol. Although catalytic systems based on nickel and PCy₃ have been the cornerstone of several recent nickel-catalyzed cross-coupling reactions involving carbon–oxygen bonds,^[14] including the Suzuki–Miyaura coupling of aryl *O*-sulfamates,^[10] this metal/ligand combination was ineffective in our amination studies.^[12] After conducting an extensive survey of reaction parameters (e.g., nickel catalysts, ligands, solvents, bases, temperature, etc.) it was observed that *N*-heterocyclic carbene (NHC) ligands uniquely facilitated the desired amination. Under optimal conditions, treatment of sulfamate **3** with morpholine in the presence of catalytic [Ni(cod)₂] (cod = cyclooctadiene), SIPr·HCl (**5**), and NaOtBu, in dioxane at 80 °C for 3 h afforded the aminated product in 95 % yield (Table 1, entry 1).^[15]

A variety of sulfamate substrates were examined in the nickel-catalyzed amination process (Table 1). Methyl substituents at the *para* and *meta* positions were tolerated (entries 2 and 3), in addition to the electron-withdrawing trifluoromethyl group and the electron-donating methoxy group (entries 4 and 5, respectively). Given the utility of the sulfamate in directed metalation chemistry,^[9a,10] we examined the amination of several *ortho*-substituted substrates bearing a methyl, trimethylsilyl (TMS), phenyl, or methoxy substituent. In all cases, amination proceeded smoothly (entries 6–9). Naphthyl-based substrates were found to be excellent amination substrates (entries 10 and 11). Furthermore, heterocycles, such as indole and pyridine, were tolerated in this methodology (entries 12 and 13).

As shown in Table 2, the scope of aryl *O*-sulfamate amination is also broad with respect to the amine coupling partner. Both cyclic and acyclic secondary amines were found to be suitable substrates (entries 1–3). In addition, anilines could be employed (entries 4–6), including 2,6-dimethylaniline (entry 6). The methodology also allows for the coupling of amines with appended heterocycles, as demonstrated by the coupling of pyridine- and carbazole-containing substrates (entries 7 and 8).

To further probe the scope and utility of the sulfamate amination methodology, a concise synthesis of the antibacterial drug linezolid (**4**) was performed (Scheme 2).^[13] Beginning from phenol (**6**), fluorosulfamate **7** was readily prepared



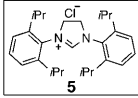
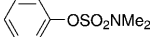
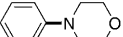
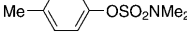
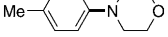
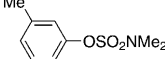
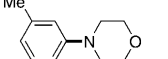
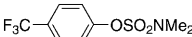
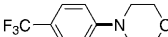
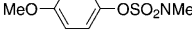
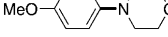
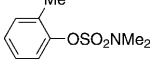
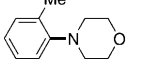
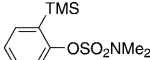
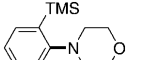
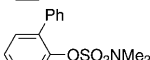
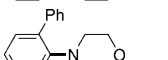
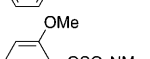
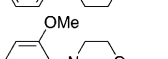
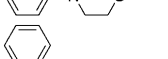
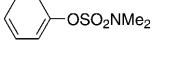
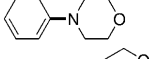
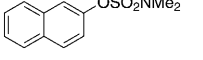
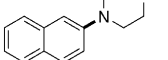
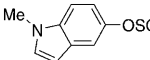
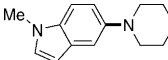
Scheme 1. Amination of aryl sulfamates and linezolid (**4**).

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Table 1: Cross-coupling of aryl sulfamates with morpholine.^[a]

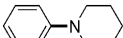
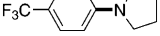
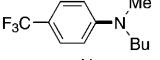
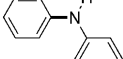
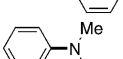
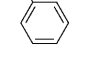
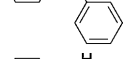
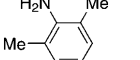
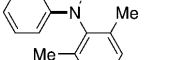
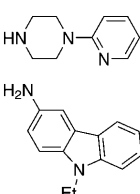
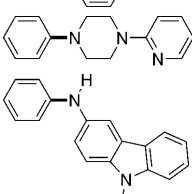
$\text{Ar-OSO}_2\text{NMe}_2 + \text{HN} \begin{array}{c} \diagup \diagdown \\ \text{O} \end{array} \xrightarrow[\text{NaOtBu, dioxane, 80 }^\circ\text{C}]{[\text{Ni}(\text{cod})_2], \text{SiPr-HCl (5)}} \text{Ar-N} \begin{array}{c} \diagup \diagdown \\ \text{O} \end{array}$ 			
Entry	Ar-OSO ₂ NMe ₂	Product	Yield [%] ^[b]
1			95
2			76
3			77
4			91
5 ^[c]			80
6 ^[d]			80
7 ^[e]			50
8 ^[f]			64
9 ^[f]			74
10			96
11			86
12 ^[d]			72
13			86

[a] Conditions unless otherwise stated: [Ni(cod)₂] (5 mol%), **5** (10 mol%), sulfamate substrate (1 equiv), morpholine (1.2 equiv), NaOtBu (1.4 equiv), dioxane (0.2 M), 80 °C for 3 h. [b] Yields of isolated product. [c] [Ni(cod)₂] (10 mol%), **5** (20 mol%), NaOtBu (1.5 equiv). [d] [Ni(cod)₂] (15 mol%), **5** (30 mol%), morpholine (1.8 equiv), NaOtBu (2.2 equiv). [e] [Ni(cod)₂] (20 mol%), **5** (40 mol%), NaOtBu (1.7 equiv), 60 °C. [f] [Ni(cod)₂] (15 mol%), **5** (30 mol%), NaOtBu (1.6 equiv).

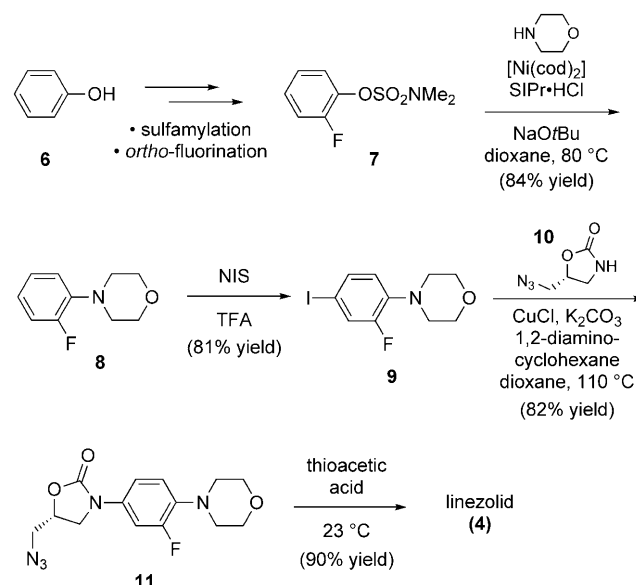
using our previously reported sequence.^[10] This conversion proceeds by sulfamylation, followed by *ortho*-fluorination (two steps), and showcases the sulfamate's directing ability. Nickel-catalyzed sulfamate amination proceeded smoothly to deliver intermediate **8**, without interference from the fluoro substituent.^[16] Subsequent iodination furnished trisubstituted arene **9**, which in turn, underwent copper-catalyzed coupling with oxazolidinone **10** to afford arylated oxazolidinone **11** in good yield. In the final step, reductive acetylation of azide **11** furnished linezolid (**4**). Overall, our synthesis illustrates the merits of sulfamate-directed arene functionalization and coupling methodology in a complex setting.

In summary, we have discovered the first amination reactions of aryl *O*-sulfamates, which are attractive cross-coupling partners, particularly for use in multistep synthesis.

Table 2: Cross-coupling of aryl sulfamates with amines.^[a]

$\text{X-C}_6\text{H}_4\text{-OSO}_2\text{NMe}_2 + \text{HN} \begin{array}{c} \diagup \diagdown \\ \text{R}' \\ \text{R}'' \end{array} \xrightarrow[\text{NaOtBu, dioxane, 80 }^\circ\text{C}]{[\text{Ni}(\text{cod})_2], \text{SiPr-HCl (5)}} \text{X-C}_6\text{H}_4\text{-N} \begin{array}{c} \diagup \diagdown \\ \text{R}' \\ \text{R}'' \end{array}$			
Entry	Amine	Product	Yield [%] ^[b]
1 ^[c]			88
2			93
3			84
4 ^[d]			77
5 ^[d]			64
6 ^[e]			91
7 ^[c]			90
8 ^[c]			92

[a] Conditions unless otherwise stated: [Ni(cod)₂] (5 mol%), **5** (10 mol%), sulfamate substrate (1 equiv), amine (1.2 equiv), NaOtBu (1.4 equiv), dioxane (0.2 M), 80 °C for 3 h. [b] Yields of isolated product. [c] [Ni(cod)₂] (10 mol%), **5** (20 mol%), NaOtBu (1.5 equiv). [d] [Ni(cod)₂] (15 mol%), **5** (30 mol%), amine (1.8 equiv), NaOtBu (2.2 equiv). [e] [Ni(cod)₂] (15 mol%), **5** (30 mol%), amine (2.4 equiv), NaOtBu (2.2 equiv).



Scheme 2. Synthesis of linezolid (**4**) using Ni-catalyzed amination. SiPr-HCl = 1,3-bis-(2,6-diisopropylphenyl)imidazolium chloride, [Ni(cod)₂] = bis(1,5-cyclooctadiene)nickel(0), NIS = *N*-iodosuccinimide, TFA = trifluoroacetic acid.

The amination is broad in scope with respect to both the sulfamate and amine coupling partners. The methodology presented herein provides an effective means for accessing polysubstituted aryl amines, as demonstrated by a concise synthesis of the antibacterial drug linezolid.

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