



Cross coupling of 3-bromopyridine and sulfonamides ($R^1\text{NHSO}_2R^2$, $R^1 = \text{H, Me, alkyl}$; $R^2 = \text{alkyl and aryl}$) catalyzed by $\text{CuI}/1,3\text{-di}(\text{pyridin-2-yl})\text{propane-1,3-dione}$

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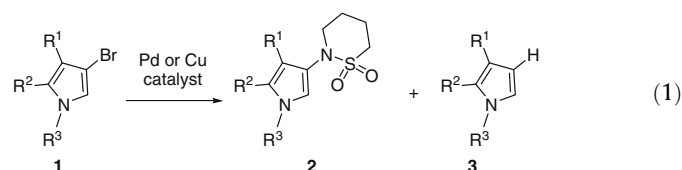
ABSTRACT

N-(3-Pyridinyl)-substituted secondary and tertiary sulfonamides have been synthesized in good to excellent yields by the reaction of 3-bromopyridine with primary and secondary alkyl and aryl sulfonamides (MeSO_2NH_2 , MeSO_2NHMe , $\text{ToISO}_2\text{NH}_2$, $\text{ToISO}_2\text{NHMe}$, 1,3-propanesultam, and 1,4-butanessultam), catalyzed by CuI (20 mol %) and 1,3-di(pyridin-2-yl)propane-1,3-dione (20 mol %) with K_2CO_3 (200 mol %) in DMF (0.17 M for ArBr) at 110–120 °C over 36–40 h. 2-Bromopyridine, 4-bromopyridine, and a wide variety of substituted phenyl bromides can also be successfully coupled with sulfonamides under these reaction conditions.

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N-Arylated sulfonamides have been of interest to medicinal chemists in recent years as β -secretase inhibitors for Alzheimer's disease,^{1a,b} dipeptidyl peptidase IV inhibitors for diabetes,^{1c} insulin-like growth factor receptor (IGF-IR) inhibitors for cancer,^{1d} HCV NS5B polymerase inhibitors for acute hepatitis and chronic liver disease,^{1e} and as antibacterial agents.^{1f} One of the most direct ways of preparing them is the coupling of (hetero)aryl halides with primary or secondary sulfonamides, generally using palladium or copper catalysis. In the Pd-catalyzed reactions, Pd/Xantphos combination² has been employed most frequently. However, other Pd/ligand combinations have also been reported.³ CuI has been used as a catalyst without any ligand,⁴ or in the following combinations: $\text{Cu}_2\text{O}/2,2\text{-bipyridine}$,^{2c} $\text{CuI}/\text{trans-}N,N'\text{-dimethyl-1,2-cyclohexanediamine}$,^{5a} and $\text{CuI}/N,N'\text{-dimethylglycine}$.^{5b} Very recently, newer ligands have also been coupled with Cu(I) salts for the preparation of *N*-arylated heterocycles and amides. These include the use of $\text{CuBr}/\beta\text{-ketoester}$,^{6a} $\text{CuI}/(S)\text{-pyrrolidinylmethylimidazole}$,^{6b} $\text{CuI}/\text{oxazolidin-2-one}$,^{6c} and $\text{CuI}/1,3\text{-di}(\text{pyridin-2-yl})\text{propane-1,3-dione}$.^{6d}

During the course of a medicinal chemistry effort, we desired an efficient method to access compound **2** in order to study the SAR and to modulate the pharmacokinetic properties of these heteroarylated sulfonamides in comparison with the corresponding amides. In our hands, Pd/Xantphos² gave only reduced product **3**. After screening a number of the above-mentioned Cu(I) /ligand combinations, we were delighted to find that compound **2** was formed in 35% yield along with 35% of reduced product **3** using the $\text{CuI}/1,3\text{-di}(\text{pyridin-2-yl})\text{propane-1,3-dione}$ combination (Eq. 1).^{6d}



Having successfully applied these conditions to a molecule with the complexity of compound **1** (polycyclic with a molecular weight of 350–400, containing two amide-like NH groups), we were prompted to explore the application of these conditions to the coupling of sulfonamides with bromopyridines. The resulting pyridines would not only be more drug-like than the corresponding electron-rich pyrroles, but reaction conditions developed for these more challenging substrates would also be more likely to accommodate other medicinally relevant heteroaryl halides. Although 2-bromopyridine^{2c,f,8} has been reported to be a good substrate for this type of coupling reaction, 3-bromo^{3a,9} and 4-bromopyridine¹⁰ are not. For example, 2-bromopyridine was reacted with SES-NH_2 under Pd/Xantphos conditions to afford the coupled product in 85% yield.^{2f} It was also coupled with 1,4-butanessultam under $\text{Cu}_2\text{O}/\text{bipyridine}$ conditions (93% yield)^{2c} and under Pd/Xantphos conditions (62% yield).^{2c} However, when 3-chloropyridine was reacted with phenylmethanesulfonamide under Pd catalysis, only 8% of coupled product was formed.^{3a} When pre-complexed to Et_3B , 4-bromopyridine reacts smoothly with 4-methylbenzenesulfonamide under Pd/Xantphos conditions to afford the *N*-arylated product in 91% yield. However, without pre-complexation the same product was formed in only 41% yield.¹⁰

Reaction of 2-, 3-, or 4-bromopyridine with 1,4-butanessultam or 1,3-propanesultam at 110 °C for 40 h in the presence of 20 mol % of CuI , 20 mol % of 1,3-di(pyridin-2-yl)propane-1,3-dione, and 200 mol % of K_2CO_3 afforded the corresponding pyridinyl-substi-

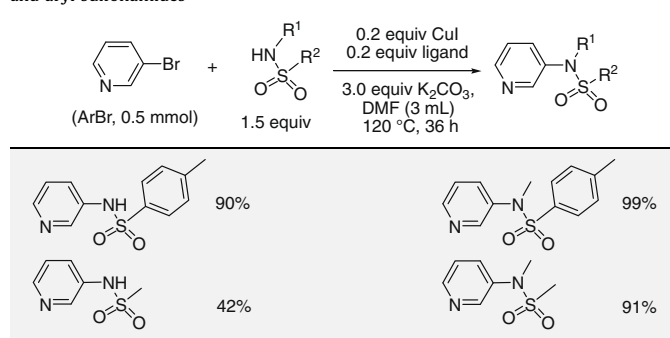
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tuted sulfonamides in good to excellent yields (60–86%, Table 1). Among the three halopyridine regioisomers, 3-halopyridines are the most challenging substrates toward transition metal-catalyzed C–N coupling reactions.^{2,3,8–10} Therefore, to further explore the scope of these conditions, 3-bromopyridine was reacted with a number of primary and secondary alkyl and aryl sulfonamides under similar reaction conditions (120 °C for 36 h vs 110 °C for 40 h). Although the product obtained using methanesulfonamide was formed in only modest yield (42%), the other three sulfonamides afforded excellent yields of the N-arylated products (90–99%, Table 2). We hypothesized that this catalytic system works well with 3- and 4-bromopyridines because of the very stable complex that forms between CuI and 1,3-di(pyridin-2-yl)propane-1,3-dione.¹¹ Therefore, the unproductive coordination of the nitrogen atom of the halopyridine and Cu⁺ is prevented, allowing the catalytic reaction to proceed smoothly to product.¹⁰

These reaction conditions were also applied to the reaction of substituted phenyl bromides with 1,4-butanediol and 1,3-propanediol (Table 3). Methyl 4-bromobenzoate underwent clean conversion to afford **4** in 85% yield, while methyl 3-bromobenzoate produced **5** in 60% yield and methyl 2-bromobenzoate gave none of the desired product **6** (even upon complete consumption of the bromide starting material). This failure was likely due to intramolecular interaction of the ester functionality with C–Cu bond of the formed intermediates after oxidative addition but before reductive elimination. Both 4- and 3-methoxyphenyl bromides afforded the desired product in modest yields (**7–8**, 43%). Yields were higher when based on recovered starting material (brsm), improving the yields to 60% and 65%, respectively. 2-Methoxyphenyl bromide afforded **9** in poor yield (10% isolated; 40% brsm). Although the yields of **7–9** were low to moderate, the reaction of 4-methoxyphenyl bromide with SES-NH₂ did not afford any of the desired coupling product using the Pd/Xantphos conditions.^{2f} When the phenylbromide contained both an electron-donating group (EDG) at the *para* position and an electron-withdrawing group (EWG), the substrate reacted well (**10**, 64%). 2-Bromotoluene afforded **11** in low yield (14% isolated; 38% brsm), and there was no desired product formed from the very hindered 2,6-dimethyl phenyl bromide (**12**). These bromides were also reacted with 1,3-propanediol under the same reaction conditions. These reactions showed trends similar to the aforementioned results (i.e., **4** vs **13**, **7** vs **14**, **10** vs **15**). These findings are in good agreement with the well-established notion that Cu-catalyzed carbon–nitrogen bond-forming reactions of aryl halides are particularly sensitive to steric

Table 2
CuI-catalyzed cross coupling of 3-bromopyridine with primary and secondary alkyl and aryl sulfonamides



hindrance at the electrophile, and that EWG-substituted phenyl bromides are better substrates than EDG-substituted bromides in these types of reactions.^{2,3,12}

Substituted phenyl bromides also performed well in reactions with primary and secondary alkyl and aryl sulfonamides. For example, methyl 4-bromobenzoate underwent reaction with 4-methylbenzenesulfonamide, *N*,4-dimethylbenzenesulfonamide, methanesulfonamide, and *N*-methylmethanesulfonamide to afford the coupling products in modest to good yields (51–78%) (see Table 4).

To study the electronic effects of sulfonamides on CuI/1,3-di(pyridin-2-yl)propane-1,3-dione-catalyzed coupling reactions, 3-bromopyridine and 4-nitrobenzenesulfonamide were reacted and the coupling product was formed in 33% yield. In comparison, there was no coupling product formed between 4-chloroquinoline and 4-nitrobenzenesulfonamide under palladium catalysis, although other sulfonamides worked fine.^{3a} 4-Chloro- and 4-methoxybenzenesulfonamide were also coupled with 3-bromopyridine to afford desired coupling products in modest yields (Eq. 2).¹³

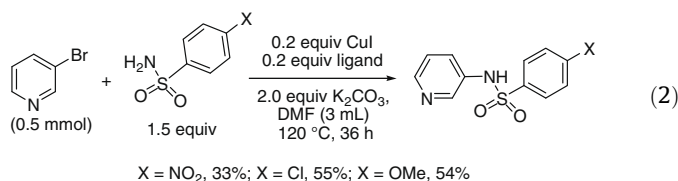
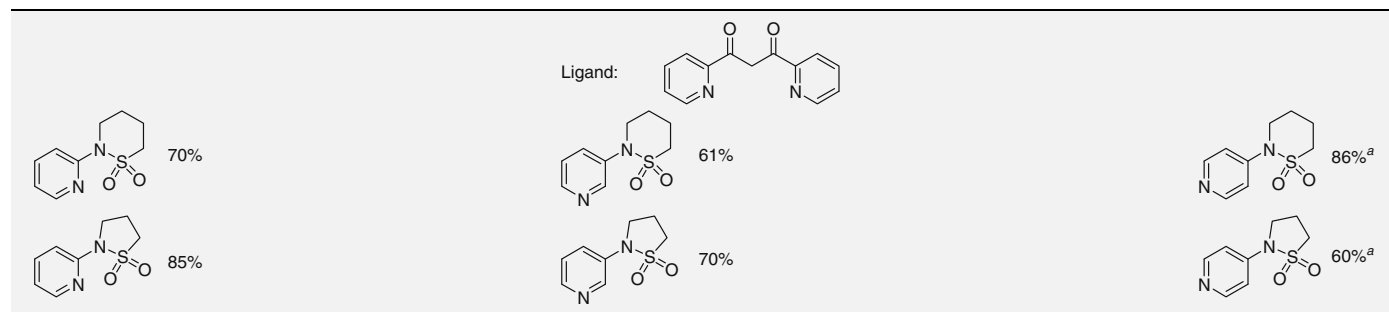
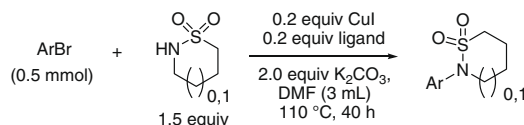


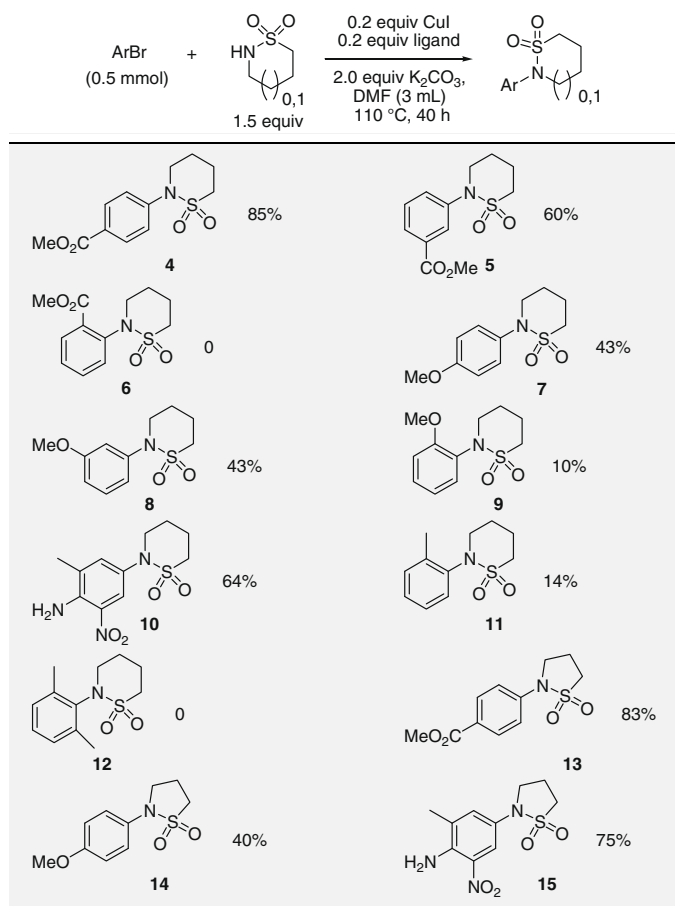
Table 1
N-Arylation of 1,4-butanediol by aryl bromides catalyzed by copper



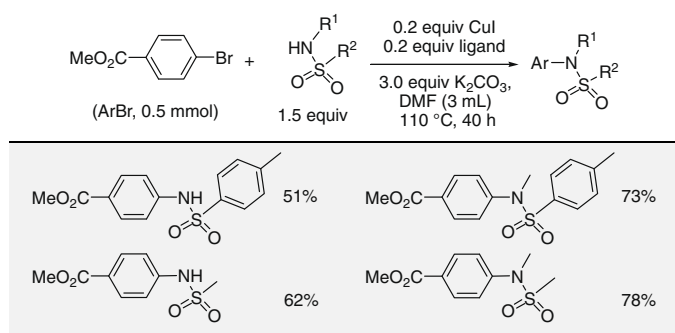
^a 4-Bromopyridine hydrochloride salt was used, and 3 equiv of K₂CO₃ was used.

Table 3

N-Arylation of 1,3-propanesultam and 1,4-butanedisultam by aryl bromides catalyzed by copper

**Table 4**

CuI-catalyzed cross coupling of aryl bromides with primary and secondary alkyl and aryl sulfonamides



In conclusion, we have found that CuI/1,3-di(pyridin-2-yl)propane-1,3-dione, first developed by Chen,^{6d} successfully catalyzed the coupling of primary and secondary alkyl and aryl sulfonamides with 2-, 3-, and 4-bromopyridines and other substituted phenyl bromides.¹⁴ This is the first catalytic system to afford modest to excellent yields of coupling products between 3-bromopyridine and various primary and secondary sulfonamides. We anticipate that this catalytic system will find wide application in the medicinal chemistry community for the coupling of nitrogen-containing heteroaromatic bromides and varied primary and secondary sulfonamides.

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Supplementary data

Supplementary data (¹H, ¹³C NMR spectra for all synthesized compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.11.037.

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- Shen, Q.; Ogata, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 6586–6596. In our reactions, when the reaction mixtures were extracted with EtOAc and 6 N NH₄OH, the aqueous layer was almost colorless, lacking the blue color indicative of no complexation of ammonia with copper. This further supports the hypothesis that a stable complex was formed between CuI and 1,3-di(pyridin-2-yl)propane-1,3-dione.
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- I acknowledge that one of the referees suggested these three experiments to study electronic effects of sulfonamides on the coupling reactions.
- General reaction procedure is as follows: A 10 mL microwave vial was charged with aryl bromide (0.50 mmol), substituted sulfonamide (0.75 mmol), 1,3-di(pyridin-2-yl)propane-1,3-dione (0.023 g, 0.10 mmol), copper(I) iodide (0.019 g, 0.10 mmol), and potassium carbonate (0.138 g, 1.0 mmol). After the reaction vessel was degassed under a flow of N₂ for 5 min, DMF (3 mL, degassed by a flow of N₂ for 30 min) was added. The resulting mixture was further degassed by a flow of N₂ for 5 min and heated at 120 °C for 36 h. All volatiles were removed and the resulting residue was extracted with EtOAc (twice) and washed with brine. The combined organic layers were dried over Na₂SO₄, filtered, concentrated, and purified by flash chromatography (EtOAc/hexanes or 2 M NH₃-MeOH/CH₂Cl₂).