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Novel *N*-Aryl and *N*-Heteroaryl Sulfamide Synthesis via Palladium Cross Coupling

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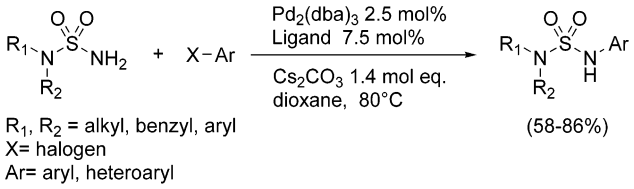
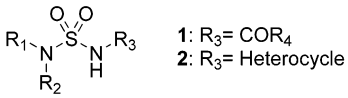
ABSTRACT



A novel and efficient synthesis of *N*-aryl and *N*-heteroaryl sulfamides via an intermolecular palladium-catalyzed coupling process has been developed. The reactions proceeded with good to excellent yields and were tolerant of a wide range of functional groups.

In the area of combinatorial library synthesis for medicinal agents there is a constant need for new methodologies. The sulfamide moiety is a ubiquitous entity in many therapeutic agents in medicinal chemistry.[1,2] Acyclic sulfamides bearing an electron-withdrawing group such as carbonyl **1** or aromatic heterocycles **2** can produce weakly acidic compounds capable of acting as bioisosteres, for example, of carboxylic acids and phenols.[3]



Wider use of **2** in this context has been largely impeded by their relatively difficult synthetic accessibility. Indeed, to date, the only available methods for the preparation of **2** are the thermal displacement of activated heterocyclic halides with the alkaline salt of the dersired *N*-mono- or *N*,*N*-disubstituted sulfamide[2,4] and the sulfonylation of the heterocyclic aniline with a suitable sulfamoyl chloride derivative.[5] In our hands, these reactions have usually been low yielding and have not involved readily accessible reagents. In addition, they were relatively unstable under the required reaction conditions.

The transition metal-catalyzed formation of C−N bonds between an amine/amide and an aryl/heteroaryl halide has been the topic of much research over the past few years, resulting in the development of mild conditions accom-

(1) For selected examples from recent literature, see: (a) Zhong, J.; Gan, X. *Bioorg. Med. Chem.* **2004**, *12*, 589−593. (b) Collins, I. J.; Cooper, L. C. WO-2003093264, 2003; *Chem. Abstr.* **2003**, *139*, 381492. (c) Kadow, J. F.; Regueiro-Ren, A.; Xue, Q. M. WO-2004000210, 2003; *Chem. Abstr.* **2003**, *140*, 59662. (d) Cherney, R. J.; King, B. W. WO-2002028846, 2002; *Chem. Abstr.* **2002**, *136*, 309923. (e) Schaal, W.; Karlsson, A.; Ahlsén, G.; Lindberg, J.; Andersson, H. O.; Danielson, U. H.; Classon, B.; Unge, T.; Samuelsson, B.; Hultén, J.; Hallberg, A.; Karlén, A. *J. Med. Chem.* **2001**, *44*, 155−169. (f) Groutas, W. C.; He, S.; Kuang, R.; Ruan, S.; Tu, J.; Chan, H.-K. *Bioorg. Med. Chem.* **2001**, *9*, 1543−1548. (g) Shih, N.-Y.; Shue, H.-J.; Reichard, G. A.; Paliwal, S.; Blynthin, D. J.; Piwinski, J. J.; Xiao, D.; Chen, X. WO-2001044200, 2001; *Chem. Abstr.* **2001**, 135, 61331. (h) Kuang, R.; Epp, J. B.; Ruan, S.; Chong, L. S.; Venkataraman, R.; Tu, J.; He, S.; Truong, T. M.; Groutas, W. C. *Bioorg. Med. Chem.* **2000**, *8*, 1005−1016. (i) He, S.; Kuang, R.; Venkataraman, R.; Tu, J.; Truong, T. M.; Chan, H.-K.; Groutas, W. C. *Bioorg. Med. Chem.* **2000**, *8*, 1713−11717. (j) Martinez, A.; Gil, C.; Perez, C.; Castro, A.; Prieto, C.; Otero, J.; Andrei, G.; Snoeck, R.; Balazarini, J.; De Clerk, E. *J. Med. Chem.* **2000**, *43*, 3267−3273. (k) Benson, G. M.; Rutledge, M. C.; Widdowson, K. L. WO-2000076501, 2000; *Chem. Abstr.* **2001**, *134*, 56675. (l) Lee, C. H.; Kohn, H. *J. Pharm. Sci.* **1990**, *79*, 716−718.

(2) Bolli, M.; Boss, C.; Fischli, W.; Clozel, M.; Weller, T. WO-2002053557, 2002; *Chem. Abstr.* **2002**, *137*, 93766.

(3) (a) *The Practice of Medicinal Chemistry*, 2nd ed; Wermuth, C. G., Ed.; Academic Press: London, 2003. (b) Albright, J. D.; DeVries, V. G.; Du, M. T.; Largis, E. E.; Miner, T. G.; Reich, M. F.; Shepherd, R. G. *J. Med. Chem.* **1983**, *26*, 1393−1411.

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modating a wide range of functional groups.[6,7] Most recently the emergence of new phosphine ligands has led to the incorporation of sulfonamides into these processes.[8] Buchwald and co-workers were first to report a palladium-catalyzed coupling of aryl bromides with primary and secondary sulfonamides.[9] Wu et al. have also described *N*-aryl sulfonamide formation via a copper(I)-catalyzed process through the use of microwave irradiation,[10] and Cao et al. have reported a related palladium-catalyzed process employing several sulfonamides and aryl/heteroaryl chlorides.[11]

To the best of our knowledge, the formation of *N*-aryl sulfamides by transition metal-catalyzed processes is unprecedented in the literature. We hereby report the first palladium-catalyzed process for the formation of these potentially biologically interesting molecules.

N,*N*-Disubstituted sulfamides are readily available by reaction of amines with sulfamide[12] or alternatively by stepwise addition of an alcohol (e.g., *tert*-butyl alcohol or benzyl alcohol) and an amine to chlorosulfonyl isocyanate, followed by deprotection of the carbamate moiety.[13] More recently, Montero et al. have reported a procedure related to the latter using a stable DMAP complex.[14]

To establish the optimum reaction conditions, a limited screen was undertaken focusing on seven phosphine-based ligands (Figure 1) commonly used in palladium-catalyzed

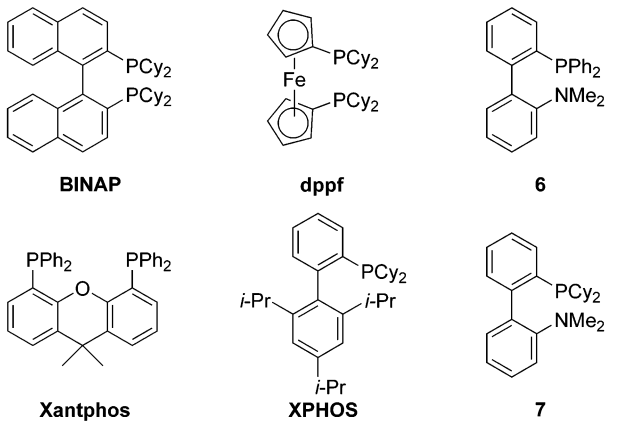
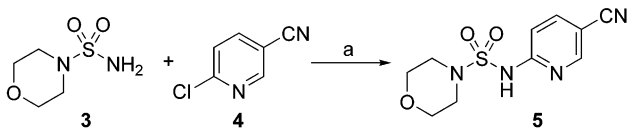


Figure 1. Ligands assessed for the Pd-catalyzed *N*-heteroarylation of 6-chloronicotinonitrile **4**.

C−N bond-forming processes. The standard reaction conditions subjected sulfamide **3** and 6-chloronicotinonitrile **4** to $Pd_2(dba)_3$ (2.5 mol %), the ligand (7.5 mol %, Figure 1),

Scheme 1. Pd-Catalyzed *N*-Heteroarylation of *N*,*N*-Disubstituted Sulfamide[15]



[a] Conditions: 2.5 mol % $Pd_2(dba)_3$, 7.5 mol % ligand, 1.4 mol equiv of Cs_2CO_3, dioxane, 80 °C, 18 h.

and Cs_2CO_3 (1.4 equiv) in dioxane heated to 80 °C for 18 h (Scheme 1).[15] The results of this study are summarized in Table 1.

Table 1. Ligand Effect on the Pd-Catalyzed *N*-Heteroarylation of 6-Chloronicotinonitrile **4**

entry	ligand	conversion (%)[a]
1	BINAP	0
2	dppf	0
3	**6**	0
4	$(t\text{-Bu})_3P$	65
5	Xantphos	90
6	XPHOS	95
7	**7**	95

[a] Conversion determined by crude ^1H NMR.

A control experiment showed that omission of palladium catalyst leads to no reaction. Reactions employing BINAP, dppf, and ligand **6** also failed to catalyze any reaction (Table 1, entries 1−3). Electron-rich sterically crowded monophosphine $(t\text{-Bu})_3P$ only led to moderate conversion (Table 1, entry 4), whereas Xantphos, XPHOS, and N,P ligand **7** all gave near complete conversion to the *N*-heteroaryl sulfamide

(5) (a) Esteve, C.; Vidal, B. *Tetrahedron Lett.* **2002**, *43*, 1019−1021. (b) Hogberg, M.; Engelhart, P.; Vrang, L.; Zhang, H. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 265−268. (c) Goya, P.; Lissavetzky, J.; Rozas, I. *Synthesis* **1989**, 280−282. (d) Wheeler, W. K.; Degering, F. *J. Am. Chem. Soc.* **1944**, *66*, 1242−1243 and references cited herein.

(6) For a recent review on copper-catalyzed C−N bond formation, see: Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400−5449.

(7) For recent reviews on palladium-catalyzed C−N bond formation, see: (a) Muci, A. B.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. (b) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; p 1051.

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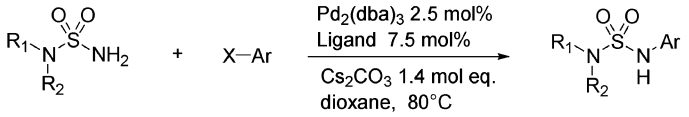
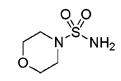
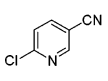
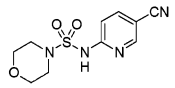
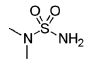
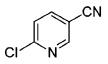
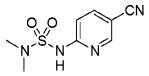
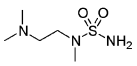
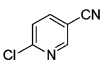
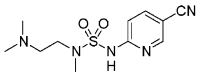
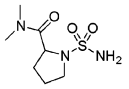
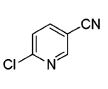
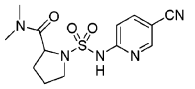
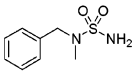
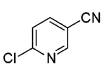
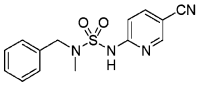
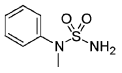
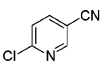
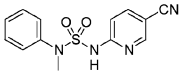
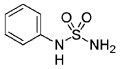
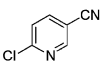
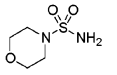
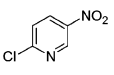
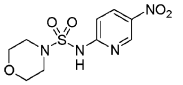
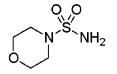
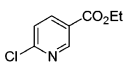
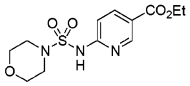
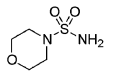
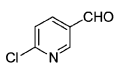
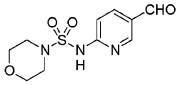
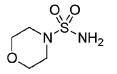
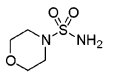
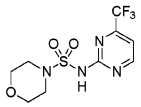
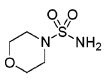
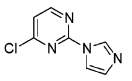
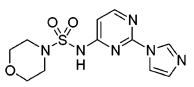
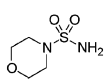
(14) Winum, J.-Y.; Toupet, L.; Barragan, V.; Dewynter, G.; Montero, J.-L. *Org. Lett.* **2001**, *3*, 2241−2243.

(15) **General Procedure.** A 25 mL round-bottom flask was charged with sulfamide **3** (166 mg, 1 mmol), 6-chloronicotinonitrile **4** (138 mg, 1 mmol), Cs_2CO_3 (456 mg, 1.4 mmol), N,P ligand **7** (30 mg, 75 μmol), and $Pd_2(dba)_3$ (23 mg, 25 μmol). The flask was flushed with N_2 for 30 s and charged with anhydrous dioxane (2.5 mL). The flask was heated at 80 °C for 18 h under a nitrogen atmosphere. The reaction mixture was then allowed to cool to room temperature and diluted with dichloromethane (5 mL), and acetic acid was added (500 μL). After filtration through a cotton wool plug, the crude mixture was concentrated under vacuum and purified by reverse-phase HPLC to afford the product **5** in 74% yield.

Table 2. Pd-Catalyzed *N*-Aryl/Heteroarylation of *N*,*N*-Disubstituted Sulfamides[15]



entry	sulfamide	aryl/heteroaryl halide	product	yield%[a]
1				74[d, e]
2				50[b,e] 60[c, e]
3				70[b, e]
4				79[c, f]
5				66[b, g]
6				70[c, g]
7			-	0[d]
8				75[b, e]
9				18[b, g] 76[c, g] 86[d, g]
10				62[b, e]
11			-	0[b or d]
12				78[b, e]

entry	sulfamide	aryl/heteroaryl halide	product	yield%[a]
13				80[b, g]
14				75[b, e]
15				81[d, f]
16				76[b, e]
17				58[b, f] 66[d, f]
18				80[b, f]
19				30[b, f] 79[c, f]
20				84[b, f]
21				15[b, f] 30[c, f] 72[d, f]
22				R=CO_2Et:33[d, h] R=CN: 48[d, h] R=NO_2: 42[d, h]
23				0[b, h] 5[c, h] 30[d, h]

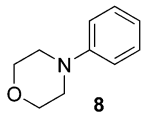
[a] Isolated yields. [b] Xantphos. [c] X-PHOS. [d] N,P **7**. [e] Purified by reverse-phase HPLC. [f] Purified by flash chromatography. [g] Purified by crystallization (DCM/Et_2O). [h] Conversion determined by LC/MS.

5 (Table 1, entries 5−7). Further exploration of the reaction conditions showed toluene to be an alternative solvent, while more polar solvents such as DMF, NMP, MeCN, and *t*-BuOH gave poor conversions or complex product mixtures. This was also the case when employing KO*t*-Bu[16] or tertiary amines as bases.

With the optimum conditions identified (Table 1, entries 6 and 7), the reaction scope was investigated by variation of the sulfamide and halide components (Table 2).

In most cases, conversions were greater than 90% when employing one of the three catalytically active ligands (Xantphos, XPHOS, and N,P ligand **7**). A range of sulfa-

mides were first coupled with 6-chloronicotinonitrile **4**. *N*-Alkyl, benzyl, and phenyl sulfamides all coupled well in the process (Table 2, entries 1−6). However, a monosubstituted sulfamide failed to afford any product (Table 2, entry 7). Other pyridines activated in the 3-position were also found to be good substrates for this reaction. Nitro, ester, and aldehyde functional groups were all tolerant to the reaction conditions, although only 70% conversion was achieved in the aldehyde case (Table 2, entries 8−10). In contrast, unactivated 2-bromopyridine undergoes no reaction when employing our best conditions (Table 2, entry 11). Substituted chloro-pyrimidines and 1,4-pyrazines also coupled well to afford the required sulfamides in acceptable yields (Table 2, entries 12−17). Finally, aryl bromides activated by electron-withdrawing groups in the *para* position also proved to be good substrates in this reaction. Complete, or near complete, conversion was observed for ester-, aldehyde-, nitrile-, and nitro-substituted phenyl bromides (Table 2, entries 18−21). However, the corresponding *ortho* isomers were more sluggish under the reaction conditions and represent a limitation of this methodology (Table 2, entry 22). Furthermore, the importance of the activation was underlined when attempting to couple bromobenzene with **3**. Poor conversion resulted along with the isolation of byproduct **8**[17] (Table 2, entry 23).



8

In summary, we have reported an efficient Pd-catalyzed synthesis of *N*-aryl/heteroaryl sulfamides that tolerates a range of secondary sulfamides and functionalized heterocycles. Application of this reaction toward the synthesis of sulfamides libraries is currently underway.

Acknowledgment. We are grateful to Hema Pancholi for her expert assistance with MS studies.

Supporting Information Available: ^{1}H and ^{13}C NMR and HRMS data for the products illustrated in Table 2. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049091L

(16) This is consistent with previous reports of the limited functional group compatibility of KO*t*-Bu when used as a stoichiometric base in a palladium coupling reaction: Wolfe, J. P.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6359−6362,

(17) During the course of our work with N,N-disubstituted sulfamides, we have observed that they can undergo base-catalyzed thermal decomposition to release the corresponding amine. This has previously been reported in the literature: Kavalek, J.; Kralikova, U.; Machacek, V.; Seldlak, M.; Sterba, V. *Collec. Czech. Chem. Commun.* **1990**, *55*, 202−222. We thus suspect that **8** is the result of a palladium-catalyzed coupling between morpholine and bromobenzene.