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Palladium-Catalyzed Intermolecular Coupling of Aryl Chlorides and Sulfonamides under Microwave Irradiation

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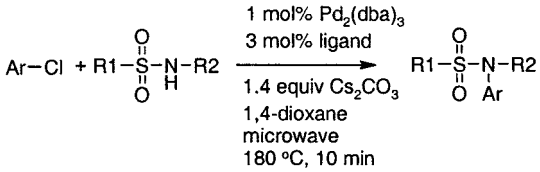
ABSTRACT



An efficient intermolecular *N*-arylation of sulfonamides with aryl chlorides is realized using palladium catalysis. The reaction proceeds under microwave irradiation at 180–200 °C for 10 min with 2–10 mol % of Pd catalyst in 32–85% isolated yields.

N-Arylsulfonamides constitute an important class of therapeutic agents in medicinal chemistry.[1] Over 30 drugs containing this moiety are in clinical use in the areas of antibacterials,[2] non-nucleotide reverse transcriptase inhibitors,[3] antitumor agents,[4] and HIV-1 protease inhibitors.[5]

Traditional preparation of sulfonamides involves reaction of sulfonyl chlorides with amines, but the sulfonylation of weakly nucleophilic amines (e.g., 4-aminoquinoline) is difficult. Transition-metal-catalyzed C−N bond-forming reactions are extensively utilized in industrial chemistry and academic laboratories.[6] Transition-metal-catalyzed *N*-arylation of sulfonamides offers a straightforward method for the preparation of *N*-arylsulfonamides. Despite significant advances in the palladium-catalyzed *N*-arylation of amines and amides, there are very few reports describing the use of sulfonamides as the nitrogen nucleophile. To our knowledge, the first report of the synthesis of *N*-arylsulfonamides by C−N bond formation was through the copper-catalyzed coupling of sulfonamides with arylboronic acids.[7] More recently, Buchwald and co-workers[8,9] reported the palladium-catalyzed coupling of aryl bromides with several sulfonamides. During the preparation of this manuscript, Wu et al.[10] described the copper-catalyzed *N*-arylation of a sulfona-

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mide with aryl bromides and iodides under microwave irradiation. However, it required a prolonged reaction time (2−4 h of microwave irradiation at 195 °C), and aryl chlorides were inert under their conditions.

Recent advances in microwave instrumentation have increased the accessibility of this technique for organic synthesis[11] including more elegant applications such as transition-metal-catalyzed transformations.[12] Despite these advances, very few microwave-assisted metal-catalyzed *N*-arylations of sulfonamides have been reported.

Herein, we wish to report an efficient microwave-promoted palladium-catalyzed coupling of aryl chlorides with sulfonamides.[13]

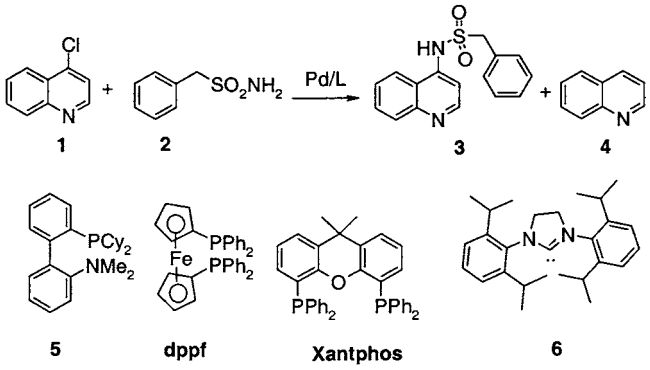
To optimize conditions for the sulfonamide coupling, we undertook an intensive screening of a variety of ligands and reaction variables using 4-chloroquinoline **1** and α-toluenesulfonamide **2** as well as benzenesulfonamide as representative substrates. In a typical experiment, a mixture of 1 equiv of **1** and 1.5 equiv of **2** in 1,4-dioxane was microwaved for 10 min at 180 °C in the presence of 2 equiv of Cs_2CO_3 and 2 mol % of palladium catalyst (1mol % $Pd_2(dba)_3$). Reactions were monitored by LC/MS, and the results are summarized in Table 1. Ten commonly used Pd−phosphine catalysts were screened, and we found that the catalysts employing the hemilabile N,P ligand **5**, discovered by the Buchwald group for amination of aryl chlorides,[14] provide the most consistent results. The less electron-rich chelating ligands DPPF, Xantphos,[8] and monodentate dihydroimidazoline carbene ligand **6**[15] could also be used for the transformation (Scheme 1). A high concentration of reactants in 1,4-dioxane (1.0 M) was desired for efficient microwave heating. In addition to Cs_2CO_3, NaO-*t*-Bu was identified as an alternative base providing similar results for the C−N bond formation. In a few reactions, the reduction product **4** was detected (Table 1, entry 5).

Table 1. Palladium-Catalyzed Amination of 4-Chloroquinoline

entry	Pd catalyst[a]	conv, %[b]	byproduct **4**%
1	$Pd_2(dba)_3$ + **5**	100	0
2	$Pd_2(dba)_3$ + dppf	100	0
3	$Pd_2(dba)_3$ + Xantphos	86	0
4	$Pd_2(dba)_3$ + **6**	100	0
5	$Pd_2(dba)_3$ + **7**[17]	60	10
6	$Pd_2(dba)_3$ + BINAP	0	N/A
8	$Pd_2(dba)_3$ + **8**[17]	50	0
9	$Pd_2(dba)_3$ + **9**[17]	50	0
10	$Pd_2(dba)_3$ + **10**[17]	40	0

[a] The palladium catalysts were generated in situ from $Pd_2(dba)_3$ at room temperature for 30 min. [b] The conversion was detected by LC/MS.

Scheme 1. Pd-catalyzed *N*-Arylation of Sulfonamide



For comparison, the reaction in Scheme 1 was also conducted using a preheated oil bath under otherwise identical conditions as for the microwave reaction, i.e., Pd-DPPF, 100 °C, 17 h. As expected, lower conversion (78%) was observed under the thermal conditions as compared to the microwave irradiation (100%). Without the Pd catalyst no reaction occurs under microwave irradiation.

The microwave conditions from entry 1 in Table 1 were identified as the preferred reaction conditons[16] and were utilized for the synthesis of a diverse set of *N*-aryl sulfonamides. Analysis of the crude reaction mixtures by LC/MS showed complete conversion in most cases. Following preparative HPLC purification, satisfactory isolated yields were obtained (Table 2). The coupling of 4-chloroquinoline with various aryl sulfonamides is fairly general with a variety of electronic and steric factors (e.g., 2-trifluoromethoxy (Table 2, entry 5) and 2,4,6-triisopropyl (Table 2, entry 7) well tolerated. In addition to arylsulfonamides, aliphatic sulfonamides (Table 2, entries 12−17), the six-membered

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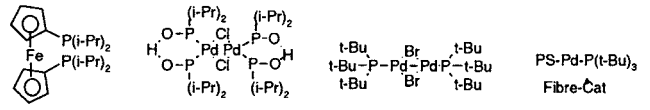
(16) **Typical Experimental Procedure.** A Smith process vial (0.5−2 mL) was charged with 1 mol % $Pd_2(dba)_3$ (4.6 mg, 5 μmol), 3 mol % ligand (6.0 mg, 15 μmol), and Cs_2CO_3(228 mg, 0.7 mmol). After sealing the cap and twice purging with N_2, the vial was charged with 100 μL of anhydrous 1,4-dioxane and stirred at room temperature for 10 min. A solution of 0.5 mmol of aryl chloride (4-chloroquinoline, 81 mg, 0.5 mmol) and 0.6 mmol of sulfonamide (α-toluenesulfonamide, 103 mg, 0.6 mmol) in 400 μL of anhydrous 1,4-dioxane was introduced via syringe. The resulting mixture was stirred at room temperature for 30 min and then was irradiated at 180 °C for 10 min in the Smith Synthesizer. After irradiation, the sample was cooled and purified by reversed-phase HPLC to afford 123 mg (60%) of 1-phenyl-*N*-quinolin-4-ylmethanesulfonamide (Table 1, entry 1) TFA salt as a solid.

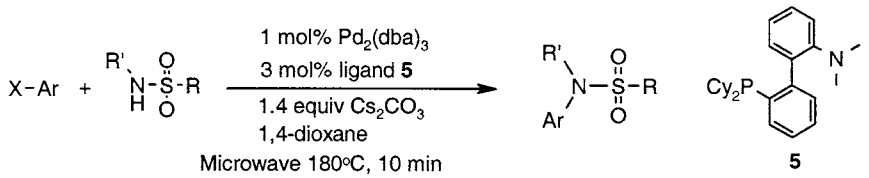
(17) Phosphine ligands used in Table 1: (a) Strem, www.strem.com; (b) Combi-phos, www.combiphos.com; (c) Johnson Matthey, www.chemicals.matthey.com.

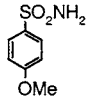
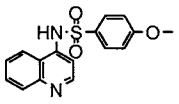
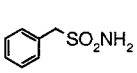
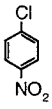
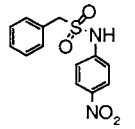
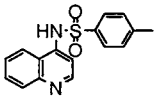
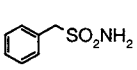
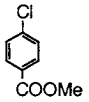
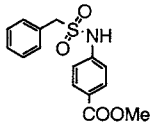
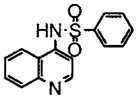
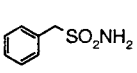
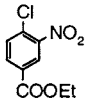
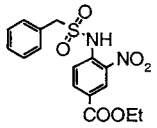
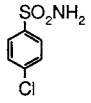
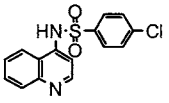
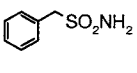
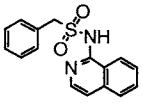
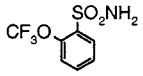
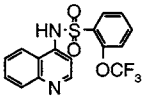
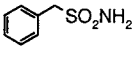
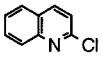
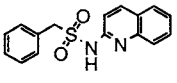
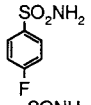
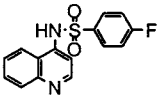
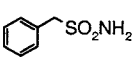
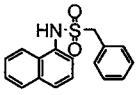
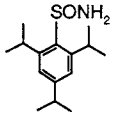
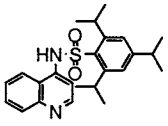


Strem[a] | CombiPhos[b] | Johnson Matthey[c] | Johnson Matthey[c]

7 | 8 | 9 | 10

Table 2. Palladium Catalyzed *N*-Arylation of Aryl Chlorides with Sulfonamides[a]



entry	sulfonamide	aryl chlorides	product	yield%[b]	entry	sulfonamide	aryl chlorides	product	yield%[b]
1				41	12				60
2				69	13				52
3				70	14				53[c]
4				37[c]	15				61
5				74	16				54
6				62	17				62[c]
7				64	18				48[c]
8				61	19				33[c,d]
9				82	20				N.R.[c]
10				68	21				N.R.[c]
11				N.R.[c]	22				8%[c]

[a] Reaction conditions: 1.0 equiv of aryl chloride, 1.2 equiv of sulfonamide, **5**/$Pd_2(dba)_3$ = 3/1 (L/Pd = 1.5/1), 2 mol % Pd refers to 1 mol % $Pd_2(dba)_3$ 1.4 equiv of Cs_2CO_3, 1,4-dioxane, 180 °C, 10 min. Personal Chemistry Smith Synthesizer. [b] Purified yield after reversed-phase HPLC. [c] 5 mol % $Pd_2(dba)_3$, 15 mol % ligand **5**, 200 °C, 20 min. [d] Small amount of halide reduction product (10−15%) also formed.

ring sultam (Table 2, entry 9), and secondary aryl sulfonamides (Table 2, entry 10) are also effective nucleophiles. Arylsulfonamides with a strong electron-withdrawing group at the para-position (Table 2, entry 11) were unreactive even when using 10 mol % Pd-catalyst. α-Toluenesulfonamide **2** reacted efficiently with a variety of aryl chlorides with electron-withdrawing groups (Table 2, entries 12−16) under typical reaction conditions. For less reactive aryl chlorides, e.g., 1-chloronaphthalene (Table 2, entries 17−19), satisfactory coupling with α-toluenesulfonamide **2**, 4-methoxy-

benzenesulfonamide, and benzenesulfonamide was achieved with the higher catalyst loading, 10 mol %. The *N*-arylation of electron-rich aryl chlorides (e.g., 4-chloroanisole, Table 2, entry 21) did not proceed under similar conditions. Surprisingly, in contrast to the results obtained with 2-chloroquinoline and 1-chloroisoquinoline (Table 2, entries 16 and 15, respectively), 2-chloropyridine and 3-chloropyridine (Table 2, entries 20 and 22) provided little or no desired product.

In conclusion, the use of N,P phosphine **5** as the ligand, 1,4-dioxane as solvent, Cs_2CO_3 as the base with microwave irradiation as heating source allows for an efficient intermolecular C−N bond-forming reaction between aryl halides and sulfonamides. This *N*-arylation proceeds efficiently at 180−200 °C with 2−10 mol % of Pd catalyst to form *N*-aryl sulfonamides in good to excellent yields. The results presented in this paper represent a significant improvement in the scope of the aryl halides over the previous reports by the application of microwave heating. Further study to expand the reaction scope and application to parallel library synthesis is under investigation.

Acknowledgment. We thank Victoria Magaard, Walter Johnson, Bing Wang, and Stone Shi for analytical support.

Supporting Information Available: Experimental procedures and characterization data for *N*-arylation products. This material is available free of charge via the Internet at http://pubs.acs.org.

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