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Palladium-Catalyzed C−H Bond Functionalization with Arylsulfonyl Chlorides

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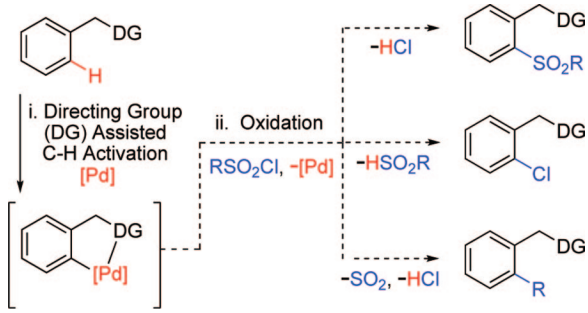
Selective functionalization of C−H bonds is a longstanding goal that continues to drive discovery in organic synthesis.[1] Combination of transition metals and directing groups has been prolific, affording valuable transformations of sp^2-hybridized C−H bonds to C−O,[2] C−X,[3] C−C,[4] and C−N bonds.[5] However, the power and scope of this chelation-assisted strategy is ultimately limited by the oxidants and coupling partners possible. It occurred to us that sulfonyl chlorides could serve as readily available, inexpensive, and highly versatile reagents for catalytic C−H bond functionalization (Scheme 1). Herein, we disclose a Pd-catalyzed C−H bond activation/cross-coupling with arylsulfonyl chlorides to produce sulfones, a structural motif considered to be both a useful synthetic intermediate[6] and a privileged medicinal target.[7] In addition to C−S bond formation, this communication reveals the potential of arylsulfonyl chlorides as convenient oxidants for formation of C−Cl and C−C bonds.

Scheme 1. Proposed Pd-Catalyzed C−H Bond Activation and Functionalization with Arylsulfonyl Chlorides

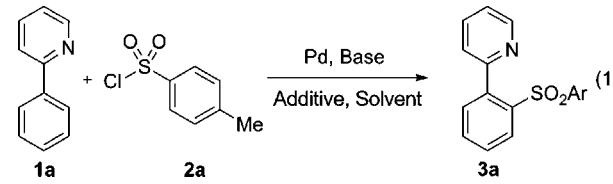


In accordance with previous reports,[8] we expected that Pd would undergo substrate-directed C−H bond activation to generate a metallacycle, as shown in Scheme 1. We envisioned that this palladacycle could be oxidized with sulfonyl chlorides to generate arylsulfones, arylchlorides, or biaryl compounds, depending on the reaction conditions. Because of the prevalence of pyridine-containing structures in medicinal chemistry[9] and the well-known coordinating ability of pyridine moieties,[10] we chose 2-phenylpyridine (**1a**) as the substrate for investigation.

Our initial aim was to develop a regioselective sulfone synthesis that did not require a prefunctionalized organometallic reagent.[7,11] With **1a** and *p*-tolylsulfonyl chloride (**2a**) as reactants, the reaction parameters (i.e., catalyst, solvent, temperature, base, and additives) were varied to achieve this goal. Key results are shown in Table 1. The control experiment in the absence of metal catalyst resulted in recovery of **1a** (entry 1). The use of $Pd_2(dba)_3$ and $Pd(OAc)_2$ as catalyst precursors resulted in trace formation of the sulfone **3a** (entries 2 and 3). Using $Pd(CH_3CN)_2Cl_2$ as the catalyst (with K_2CO_3 in 1,4-dioxane at 120 °C for 6 h) led to the isolation of **3a** in 82% yield with excellent regioselectivity (entry 4).[12] To our knowledge, this transformation represents the first intermolecular transition-metal-catalyzed C−H bond activation to form a C−S bond.[13]

With a selective sulfonylation protocol in hand, we investigated the effect of electronic and structural variations of the phenylpyridine component (Table 2). Substrates bearing para and meta substituents were

Table 1. Pd-Catalyzed C−H Bond Sulfonylation with Phenylpyridine **1a** and Sulfonyl Chloride **2a**[a]

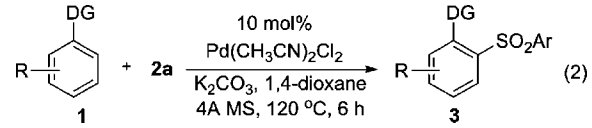


1a **2a** **3a**

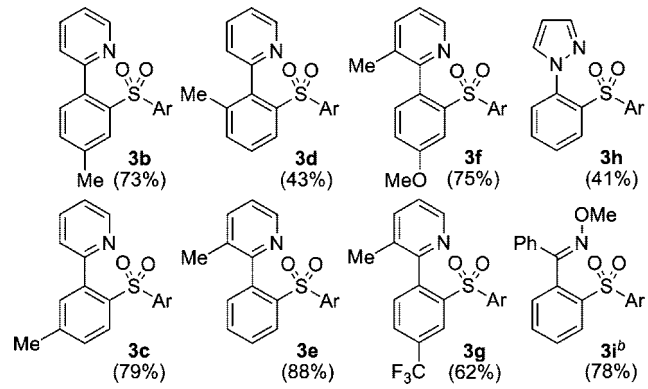
entry	catalyst	conversion (%)[b]
1	none	no reaction
2[c]	$Pd_2(dba)_3$	11
3	$Pd(OAc)_2$	14
4	$Pd(CH_3CN)_2Cl_2$	94 (82)[d]

[a] Reaction conditions: **1a**, 0.2 mmol; **2a**, 3 equiv; Pd, 10 mol %; K_2CO_3, 2 equiv; 4A MS; 1,4-dioxane, 1 mL; 120 °C, 6 h. Ar = *p*-MeC_6H_4. [b] Conversion of **1a** determined by GC−MS. [c] Using 5 mol % catalyst. [d] Isolated yield in parentheses.

Table 2. Structural Variation of the Phenylpyridine Component **1**[a]



1 **3**



[a] Reaction conditions: **1**, 0.2 mmol; **2a**, 3 equiv; $Pd(CH_3CN)_2Cl_2$, 10 mol %; K_2CO_3, 2 equiv; 4A MS; 1,4-dioxane, 1 mL; 120 °C, 6 h. Isolated yields are indicated. Ar = *p*-MeC_6H_4. [b] Using 2 equiv of Na_2CO_3 instead of K_2CO_3; 10 h.

successfully coupled to the arylsulfonyl chloride to produce the corresponding products **3b** (73% yield) and **3c** (79% yield). The more sterically hindered *o*-methyl-substituted substrate was transformed into **3d** in a lower yield of 43%. The use of 3-methyl-2-phenylpyridine (**1b**) proved to be most effective (precluding competing difunctionalization), thereby resulting in the formation of **3e** in 88% yield. An electron-donating group such as *p*-methoxy was well-tolerated, affording **3f** in 75% yield. An electron-deficient substrate bearing a CF_3 group proceeded to produce **3g** with relatively diminished efficiency (62% yield). Although these reaction conditions were optimized for a pyridine-directed C−H bond sulfonylation,

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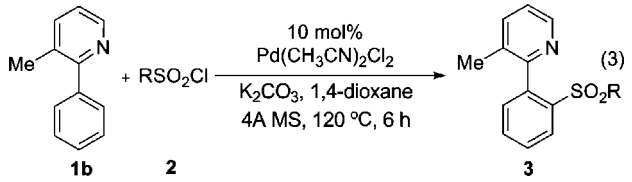
substrates bearing pyrazole- and oxime-directing groups underwent sulfonylation to produce the corresponding sulfones **3h** and **3i** in promising yields (41% and 78%, respectively).

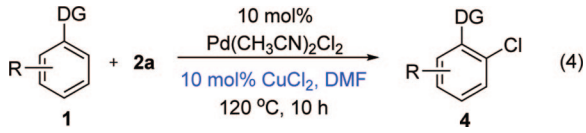
Table 3. Structural Variation of the Sulfonyl Chloride Partner[a]

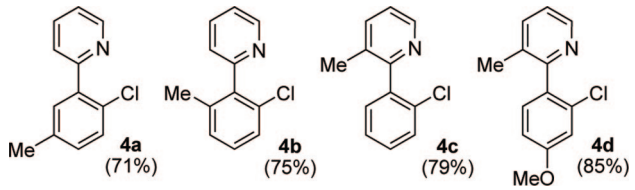


entry	2	R	product	yield (%)[b]
1	**2b**	C_6H_5	**3j**	87
2	**2c**	*m*-MeC_6H_4	**3k**	85
3	**2d**	*o*-MeC_6H_4	**3l**	57
4	**2e**	*p*-$MeOC_6H_4$	**3m**	83
5	**2f**	*p*-FC_6H_4	**3n**	83
6	**2g**	*p*-$NO_2C_6H_4$	**3o**	68
7[c]	**2h**	2-naphthyl	**3p**	76
8	**2i**	*n*-butyl	**3q**	0

[a] Reaction conditions: **1b**, 0.2 mmol; **2**, 3 equiv; $Pd(CH_3CN)_2Cl_2$, 10 mol %; K_2CO_3, 2 equiv; 4A MS; 1,4-dioxane, 1 mL; 120 °C, 6 h. [b] Isolated yield. [c] Using 2 equiv of Na_2CO_3 instead of K_2CO_3; 10 h.

Table 4. Pd-Catalyzed C−H Bond Chlorination with Phenylpyridine **1a** and Sulfonyl Chloride **2a**[a]

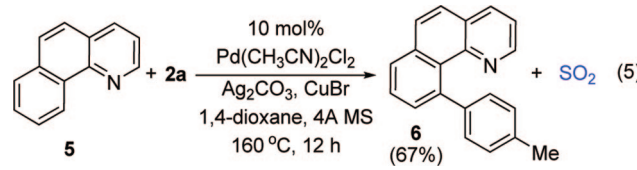




[a] Reaction conditions: **1**, 0.2 mmol; **2a**, 3 equiv; $Pd(CH_3CN)_2Cl_2$, 10 mol %; $CuCl_2$, 10 mol %; DMF, 1 mL; 120 °C, 10 h. Reactions were performed in air.

Next, we examined the scope of the sulfonyl chloride (Table 3). Meta substitution was tolerated, as sulfone **3k** was furnished in 85% yield (entry 2). Ortho substitution resulted in a lower yield (presumably as a result of steric hindrance); sulfone **3l** was obtained in 57% yield (entry 3). The electronics of the aromatic ring were varied, and substrates bearing *p*-methoxy and *p*-fluoro substituents underwent sulfonylation to give **3m** and **3n**, respectively, each in 83% yield (entries 4 and 5). The highly electron-deficient nitroaromatic sulfonyl chloride was an effective coupling partner (**3o**, 68% yield, entry 6). C−H bond functionalization with naphthylsulfonyl chloride produced sulfone **3h** in 76% yield (entry 7). However, attempts to use aliphatic sulfonyl chlorides resulted in their thermal decomposition under these conditions (entry 8).

During the course of these studies, we discovered that the reactivity of arylsulfonyl chlorides could be dramatically altered. When DMF was used as the solvent and $CuCl_2$ as a cocatalyst,[14] a highly selective Pd-catalyzed C−H bond chlorination was achieved. Four examples are shown that highlight the use of arylsulfonyl chlorides as chlorinating agents (71−85% yield, Table 4).[15] While either sulfonylation or chlorination is possible, the alternative desulfitative cross-coupling was observed only in trace amounts from model substrate **1b**. Intriguingly, at elevated temperatures, we found that quinoline **5** participated in a selective desulfitative cross-coupling with sulfonyl chloride **2a** to generate **6** in 67% isolated yield, as shown in eq. 5.[16] Importantly, this observation demonstrates the potential utility of sulfonyl chlorides as oxidants for C−H to C−C bond elaboration.



In conclusion, this communication highlights the use of arylsulfonyl chlorides as remarkably flexible reagents for Pd-catalyzed C−H bond functionalization. The indicated C−S, C−Cl, and C−C bond-forming processes presumably occur via C−H bond activation and involve either $Pd^{0/II}$ or $Pd^{II/IV}$ intermediates. Further studies are underway to provide insight into the scope and mechanism of these arylsulfonyl chloride C−H bond functionalizations, and these results will be reported in due course.

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Supporting Information Available: Experimental procedures, spectroscopic data, and X-ray crystallographic data for **3a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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