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Palladium-Catalyzed Desulfitative C–H Arylation of Heteroarenes with Sodium Sulfinates

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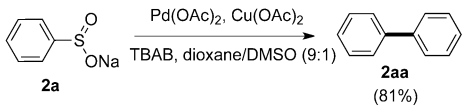
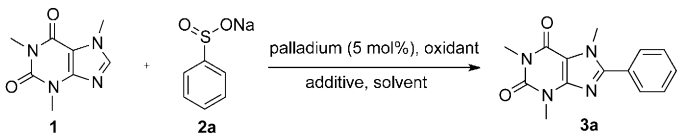
The structural motif with aryl–heteroaryl bonds is a predominant substructure of many biologically active compounds, natural products, pharmaceuticals, and functional materials. Transition-metal-catalyzed direct C–H arylation of heteroaromatics has recently received a great deal of attention as an efficient approach for the straightforward synthesis of aryl–heteroaryl units.[1] Over the past several years, the scope of the arylating reagents has been extended from aryl halides[2] to various surrogates such as arenesulfonates,[3] arylsilanes,[4] aryl boronic acids,[5] aryltrifluoroborates,[6] diaryl iodonium salts,[7] and aromatic carboxylic acids.[8] Despite remarkable advances in these types of transformations, the search for new reliable alternative arylating reagents is still critically important from both scientific and practical standpoints.

Arylsulfonyl chlorides ($ArSO_2Cl$) have been widely used as sulfonylating agents for formation of S–O, S–N and S–C bonds,[9] and have recently been demonstrated as electrophilic partners in transition-metal-catalyzed desulfitative C–C cross-coupling reactions.[10] Despite readily availability, inexpensiveness, and high versatility, the active arylsulfonyl chlorides generally suffer from moisture sensitivity with the release of the acidic HCl gas. Thus, the air stable and easy to handle arylsulfinic acids (or salts) would serve as the ideal arylating reagent for the C–C bond-forming reactions through the liberation of sulphur dioxide gas. Nevertheless, to date, sulfinic acids (or salts) are rarely used as the aryl source in transition-metal-catalyzed desulfinative reactions,[11] whereas current research is mainly focused on sulfonylation reagents.[12] The presently known desulfitative C–C bond formation reactions include Heck-type coupling,[13] and coupling between aldehydes or nitriles and arenesulfinic acid salts to aryl ketones;[14] however, the extension of the reaction to the direct C–H arylation of heteroaromatics remains unresolved. In line with our continuous efforts to forge aryl–heteroaryl bonds, we herein wish to develop an efficient desulfitative C–H arylation of a wide range of heteroarenes with arenesulfinic acid sodium salts to enrich the current synthetic methodologies. However, we may face a series of hindrances: 1) In comparison with alkenes, it is well known that N-heteroarenes themselves are susceptible to oxidative homocoupling and decomposition with transition-metal-catalyzed oxidative conditions; and 2) aromatic sulfinic acid sodium salts were observed to easily encounter desulfitative self-coupling in the presence of a Pd^{II} species and an oxidant (Scheme 1). Thus, to achieve the heterocoupling process, both of the unwanted homocouplings of substrates must be suppressed to some extent. In this work, we describe the discovery, development, and solution of reactions that meet these challenges.



Scheme 1. Palladium-catalyzed desulfitative homocoupling of sodium benzenesulfinate. Reaction conditions: $Pd(OAc)_2$ (5 mol%), $Cu(OAc)_2$ (2.0 equiv), TBAB (20 mol%), and sodium benzenesulfinate (0.5 mmol) in a 0.5 M dioxane/DMSO (9:1) solution at 110 °C for 24 h under N_2. TBAB = tetra-*n*-butylammonium bromide.

Xanthines (for example, caffeine, theophylline, theobromine, etc.) are important biologically active alkaloids with an imidazole skeleton. 8- (Hetero)aryl-substituted xanthines are highly potent and selective antagonists at human A_{2B} adenosine receptors.[15] Following our continuing interest in the direct C-arylation of xanthines,[16] we initially focused on the heterocoupling of caffeine **1** with sodium benzenesulfinate **2a** (Scheme 2). The initial reaction screening led to disappointing results in the absence of an oxidant or a Pd^{II} salt (Table 1, entries 1–2). In this model reaction, we screened several parameters (for example, oxidant, solvent, additive, and palladium source, etc.) shown in Table 1. Among the ox-



Scheme 2. Direct C–H arylation of caffeine with sodium benzenesulfinate.

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Table 1. Optimization of the coupling of caffeine with sodium benzenesulfinate.[a]

Entry	Palladium source	Oxidant	Additive	Solvent	Solvent ratio	Yield [%][b]
1	–	$Cu(OAc)_2$	–	dioxane/DMSO	9:1	n.r.
2	$Pd(OAc)_2$	–	–	dioxane/DMSO	9:1	n.r.
3	$Pd(OAc)_2$	O_2	–	dioxane/DMSO	9:1	trace
4	$Pd(OAc)_2$	BQ	–	dioxane/DMSO	9:1	n.r.
5	$Pd(OAc)_2$	$K_2S_2O_8$	–	dioxane/DMSO	9:1	n.r.
6	$Pd(OAc)_2$	Ag_2CO_3	–	dioxane/DMSO	9:1	trace
7	$Pd(OAc)_2$	AgOAc	–	dioxane/DMSO	9:1	trace
8	$Pd(OAc)_2$	$Cu(OAc)_2$	–	dioxane/DMSO	9:1	68
9[c]	$Pd(OAc)_2$	$Cu(OAc)_2$	–	dioxane/DMSO	9:1	44
10[d]	$Pd(OAc)_2$	$Cu(OAc)_2$	–	dioxane/DMSO	9:1	25
11	$Pd(OAc)_2$	$Cu(OAc)_2$	–	dioxane	–	55
12	$Pd(OAc)_2$	$Cu(OAc)_2$	–	dioxane/DMSO	1:1	trace
13	$Pd(OAc)_2$	$Cu(OAc)_2$	–	DMSO	–	trace
14	$Pd(OAc)_2$	$Cu(OAc)_2$	–	DMF	–	28
15	$Pd(OAc)_2$	$Cu(OAc)_2$	–	NMP	–	18
16	$Pd(OAc)_2$	$Cu(OAc)_2$	–	DMA	–	28
17	$Pd(OAc)_2$	$Cu(OAc)_2$	–	toluene	–	trace
18	$Pd(OAc)_2$	$Cu(OAc)_2$	TBAB	dioxane/DMSO	9:1	72
19	$Pd(OAc)_2$	$Cu(OAc)_2$	BQ	dioxane/DMSO	9:1	35
20	$Pd(OAc)_2$	$Cu(OAc)_2$	CuBr	dioxane/DMSO	9:1	77
21	$Pd(OAc)_2$	$Cu(OAc)_2$	PivOH	dioxane/DMSO	9:1	82
22	$PdCl_2$	$Cu(OAc)_2$	–	dioxane/DMSO	9:1	90
23	$Pd_2(dba)_3$	$Cu(OAc)_2$	–	dioxane/DMSO	9:1	84
24	$Pd(PhCN)_2Cl_2$	$Cu(OAc)_2$	–	dioxane/DMSO	9:1	93
25	$Pd(dppf)Cl_2$	$Cu(OAc)_2$	–	dioxane/DMSO	9:1	72

[a] Reactions were carried out using a palladium source (5 mol%), $Cu(OAc)_2$ (2.0 equiv), additive (20 mol%), caffeine (0.25 mmol), and sodium benzenesulfinate (0.5 mmol) in a 0.25 M solution at 110 °C for 24 h. [b] Isolated product yields. [c] 1.5 equiv of $Cu(OAc)_2$ was used. [d] 1.0 equiv of $Cu(OAc)_2$ was used. DMSO = dimethyl sulfoxide, DMF = *N*,*N*-dimethylformamide, NMP = *N*-methyl-2-pyrrolidone, DMA = *N*,*N*-dimethyl acetamide, n.r. = no reaction, BQ = benzoquinone, dba = dibenzylideneacetone, dppf = 1,1′-bis(diphenylphosphino)ferrocene, PivOH = pivalic acid, NMP = *N*-methyl-2-pyrrolidone, DMA = dimethylacetamide.

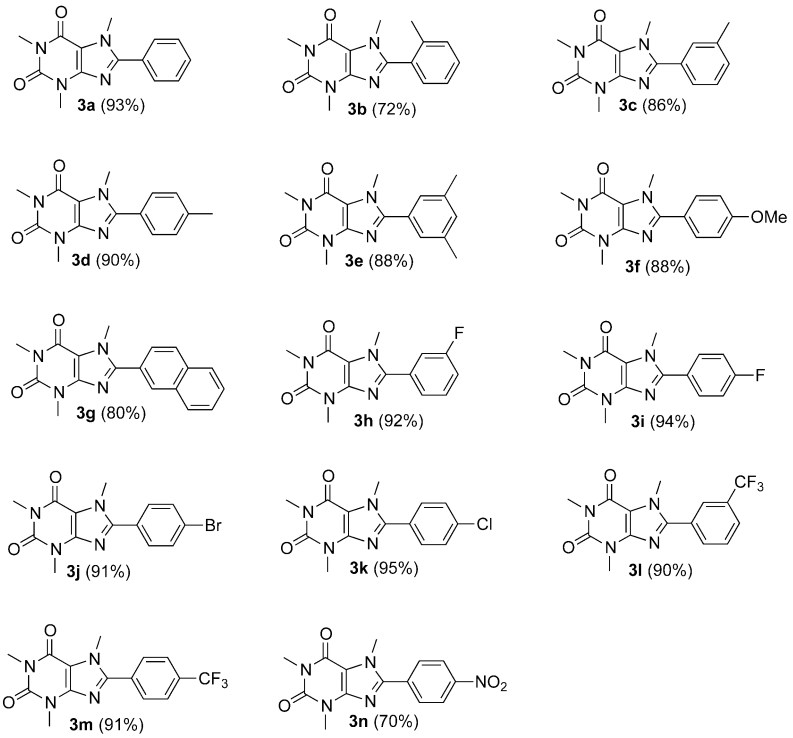
idants investigated, $Cu(OAc)_2$ proved to be an ideal choice (Table 1, entries 3–8). An attempt to lower the amount of $Cu(OAc)_2$ to one equivalent resulted in a low consumption of caffeine (Table 1, entries 8–10). After examining a variety of solvents (e.g., dioxane, DMSO, DMF, NMP, DMA, and toluene, etc.), dioxane/DMSO (9:1) was clearly the best solvent system (Table 1, entries 8 and 11–17). Remarkably, the use of $Pd(PhCN)_2Cl_2$ as the palladium source significantly improved the catalytic efficiency (Table 1, entries 8, 22–25). Thus, the best results were obtained in the presence of $Pd(PhCN)_2Cl_2$ (5 mol%) in combination with two equivalents of $Cu(OAc)_2$ as the oxidant in dioxane/DMSO (9:1) at 110 °C for 24 h.

With the optimized conditions in hand, we explored the scope of this process with respect to sodium sulfinate structures summarized in Scheme 3. It was gratifying to find that our catalyst system accelerated the C–H arylation of caffeine with a variety of sodium sulfinates. Whether sodium sulfinates were electron rich, electron poor, or having substituents at a different position on the aromatic ring, all of them afforded good to excellent yields (Scheme 3, **3a**–**n**). It is known that aryl bromides can go through the direct C–H arylation with N-heteroarenes in the presence of palladium catalyst. It is important to stress that bromo-substituted aromatic sulfinic acid sodium salts highly selectively underwent the desulfitative C–H arylation, which may be subject to further synthetic transformations (Scheme 3, **3j**).

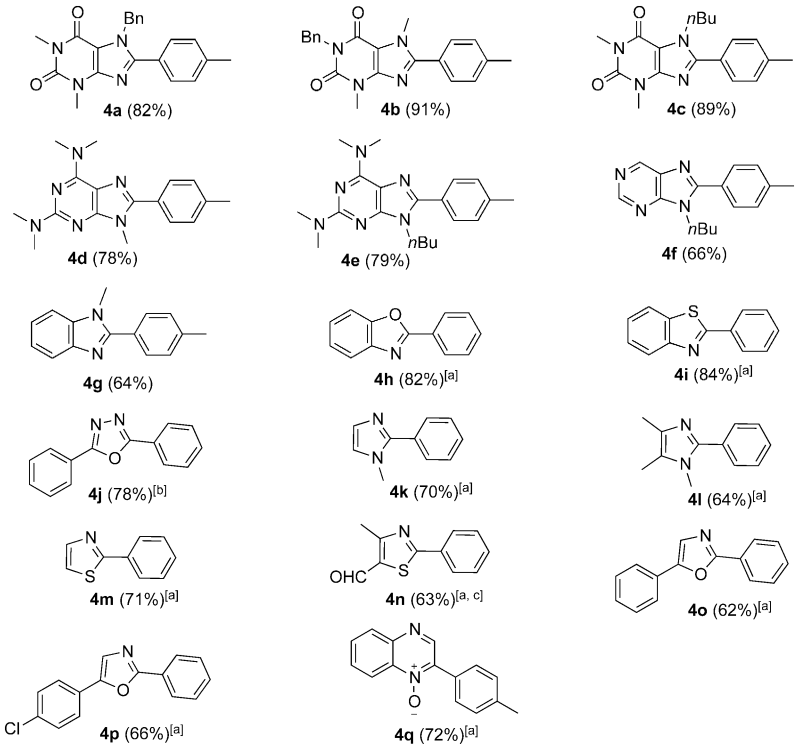
We subsequently applied this protocol to other xanthines (for example, benzylic theobromine, benzylic theophylline, and *n*-butyl theophylline, etc.) to synthesize 8-arylated xanthines in good to excellent yields (Scheme 4, **4a**–**c**). Our methodology could also be suitable for the synthesis of various 8-arylated purines (Scheme 4, **4d**–**f**). In addition to these important alkaloids, we next determined that a wide range of azoles were amenable to the coupling reactions at the C2 site. However, azoles (for example, benzoxazoles, benzothiazoles, 1,3,4-oxadiazoles, imidazoles, thiazoles, and oxazoles, etc.) sluggishly carried out the arylation under the standard conditions. To our delight, as shown in Scheme 4, the replacement of $Pd(PhCN)_2Cl_2$ with $Pd(OAc)_2$ in combination with tetra-*n*-butylammonium bromide (TBAB, 20 mol%) could significantly advance the catalytic efficiency (Scheme 4, **4h**–**q**). Worthy of note was that the 2,5-unsubstituted azoles would usually go through the arylation at both the C2 and C5 positions with various arylating reagents. In this current catalytic system, the 2,4,5-unsubstituted azoles selectively underwent the C2 arylation, and the C5-substituted azoles were not observed at all (Scheme 4, **4k** and **4m**). Besides the abovementioned azoles, quinoxaline *N*-oxide also smoothly furnished the desired product **4q** in 72% yield (Scheme 4, **4q**).

It is well known that Cu^I salts have been used as catalyst or activator in direct C–H functionalization of N-heteroarenes.[17] As demonstrated in Table 1, other oxidants including inorganic oxidants, organic oxidants, and dioxygen except $Cu(OAc)_2$ were completely incapable of fulfilling the catalytic cycle, suggesting that an (even catalytic) amount of copper(I) formed from $Cu(OAc)_2$ might promote the generation of the azole–copper species **IM2**, which could take part in the catalytic cycle.[18] In addition, an addition of extra CuBr (20 mol%) could result in an improvement of the yield of the heterocoupling product, hinting that the copper(I) salt played an important role (Table 1, entries 8 and 20). Although the mechanism was not well understood at this stage, on the basis of the above observations, we proposed that a plausible catalytic route could consist of 1) desulfitation of sodium sulfinate to form the arylpalladium species **IM1**, and 2) subsequent transmetalation with the azole–copper species **IM2** to give the key heterocoupling intermediate **IM3**, followed by reductive elimination to produce the desired product. Pd^0 could be reoxidized by $Cu(OAc)_2$ to realize the catalytic cycle (Scheme 5).

In conclusion, we have disclosed for the first time that inexpensive and easily available, air stable and easy to handle sodium sulfinates can be used as the coupling partners in the transition-metal-catalyzed C–H arylation of a wide



Scheme 3. Catalytic C-arylation of caffeine with a variety of aromatic sulfinic acid sodium salts. Reactions were carried out using $Pd(PhCN)_2Cl_2$ (5 mol%), $Cu(OAc)_2$ (2.0 equiv), caffeine (0.25 mmol), and aromatic sulfinic acid sodium salt (0.5 mmol) in a 0.25 M dioxane/DMSO (9: 1) solution at 110 °C for 24 h. The yields of the isolated products are in parentheses.



Scheme 4. Catalytic C-arylation of heteroarenes with aromatic sulfinic acid sodium salts. Reactions were carried out using $Pd(PhCN)_2Cl_2$ (5 mol%), $Cu(OAc)_2$ (2.0 equiv), heteroarene (0.25 mmol), and aromatic sulfinic acid sodium salt (0.5 mmol) in a 0.25 M dioxane/DMSO (9: 1) solution at 110 °C for 24 h. The yields of the isolated products are in parentheses. [a] $Pd(OAc)_2$ (5 mol%) in combination with TBAB (20 mol%). [b] $Pd(OAc)_2$ (5 mol%), and free TBAB. [c] Reaction time = 6 h.

range of N-heteroarenes to construct aryl–heteroaryl bonds without the need for any extra ligands. We believe that this methodology would provide a valuable complement to synthetic and medicinal chemistry both in industry and in academia. Additionally studies aimed at extending sodium sulfinates to other cross-coupling reactions are underway.

Experimental Section

General Procedure: $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol) or $Pd(PhCN)_2Cl_2$ (4.8 mg, 0.0125 mmol), N-heterocycle (0.25 mmol), aromatic sulfinic acid sodium salt (0.5 mmol), $Cu(OAc)_2$ (0.5 mmol) and dioxane/DMSO (9: 1) (1.0 mL) in presence or absence of TBAB (20 mol%) was added to a flame-dried Schlenk test tube with a magnetic stirring bar under N_2. A rubber septum was replaced with a glass stopper, and the system was then evacuated twice and back filled with N_2. The reaction mixture was stirred for 5 min at room temperature, and then heated at 110 °C for 24 h. The reaction mixture was then cooled to ambient temperature, diluted with 20 mL of CH_2Cl_2, filtered through a Celite pad, and washed with 10–20 mL of CH_2Cl_2. The combined organic extracts were concentrated, and the resulting residue was purified by column chromatography on silica gel to provide the desired product.

Acknowledgements

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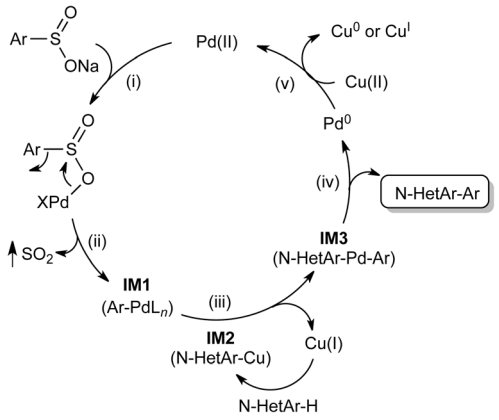
Keywords: C–H activation · cross-coupling · heterocycles · palladium · sodium sulfinates



Scheme 5. Plausible catalytic cycle of desulfitative C–H arylation of heteroarenes with aromatic sulfinic acid sodium salts.

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