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Palladium-catalyzed desulfitative arylation of azoles with arylsulfonyl hydrazides†

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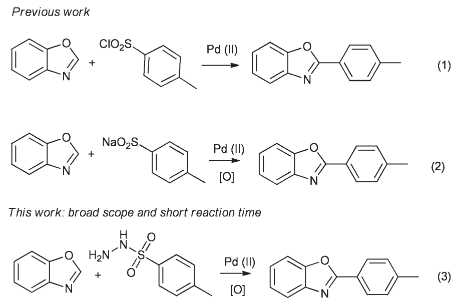
Palladium-catalyzed desulfitative and denitrogenative arylation of azoles with arylsulfonyl hydrazides has been achieved. A broad scope of azoles and arylsulfonyl hydrazides has been used to produce arylated azoles in high yields.

Transition metal-catalyzed direct arylation of heteroaromatics *via* C–H activation has recently emerged as an efficient and straightforward process to construct C_{aryl}–C_{aryl} bonds, which have been widely found in pharmaceuticals and natural products.[1] In the past several years, various arylating reagents have been explored for this type of reaction, including aryl halides,[2] arylsilanes,[3] aryl boronic acids,[4] arylaryltrifluoroborates,[5] diaryliodonium salts,[6] and ArC(O)OH.[7] $ArSO_2Cl$ has been applied as a convenient source of sulfonyl group during the formation of S–C, S–N, and S–O bonds.[8] Furthermore, in some cases desulfitation could occur,[9] where this substrate provides the source of an aryl group. Despite these successes, limitations of this reagent have been noted such as moisture sensitivity and long reaction time. Thus it is necessary to explore alternatives. In fact, the past two years have witnessed the applications of several closely related $ArSO_2X$ (X = H, Na, and $NHNH_2$) compounds as a source of aryl group in oxidative C–C coupling reactions where substrates such as aldehydes,[10] and olefins,[11] have been oxidatively arylated using $ArSO_2X$. In 2011, Deng and co-workers[11a] and Wang and Miao[11b] independently reported the palladium-catalyzed arylation of olefins such as styrenes and acrylates using $ArSO_2H$ and $ArSO_2Na$, respectively. In late 2011, Loh and co-workers achieved a type of oxidative coupling chemistry using $ArNHNH_2$ as a new arylating reagent *via* a denitrogenative process.[12] While our work was conducted in 2012, Tian combined the features of these two processes and achieved the desulfitative–denitrogenative coupling of olefins with $ArSO_2NHNH_2$.[13] Owing to the high activity of azoles in palladium-catalyzed C–H functionalization reactions,[14] You, Deng, Wang, and Cheng have recently reported the arylation of azoles, and indoles[16b] using $ArSO_2Na$[15–17] and $ArSO_2Cl$[18] (Scheme 1). Despite these extensive studies, the previously reported systems have limitations. In all cases, a long reaction time is necessary



Scheme 1 Palladium-catalyzed desulfitative arylation of benzoxazole.

(typically 24–48 h). In addition, the substrate scope is somewhat limited. For example, a lower yield was obtained for thiazole substrates or for sterically hindered arylating reagents.[17] To further address issues of substrate scope, activity, and catalytic efficiency and to continue our interest in palladium-catalyzed oxidative coupling reactions, we now report the efficient coupling of azoles with $ArSO_2NHNH_2$, which has been rarely used as an arylating reagent.[19]

We initiated our studies with the screening of the conditions for the coupling of benzoxazole (**1a**) and $TsNHNH_2$ (**2a**) under palladium catalysis. Initially, when $Pd(OAc)_2$ (10 mol%) was selected as the catalyst and $Cu(OAc)_2$ (5 equiv) was used as an oxidant in 1,4-dioxane in the presence of phenanthroline hydrate (Phen·H_2O), the coupled product was obtained in 52% HPLC yield, together with two homo-coupling byproducts (Table 1, entry 1). Under these conditions, other protic and aprotic solvents examined proved less favorable. The efficiency was further affected by a base additive. The HPLC yield was improved to 75% when Na_2CO_3 was applied (Table 1, entry 2). In contrast, other bases such as CsOAc or K_2CO_3 proved less effective (Table 1, entries 3–4). Gratifyingly, by switching to $Pd(MeCN)_2Cl_2$ as a catalyst, an HPLC yield of 75% was obtained when both Phen·H_2O (6 mol%) and Na_2CO_3 (1.5 equiv) were introduced, and a slightly higher yield was obtained when a mixed solvent of dioxane and DMSO (Table 1, entry 6) was used. Further optimization indicated that when two equivalents of $TsNHNH_2$ were used, the yield of product **3a** was increased to 90% even with a lower catalyst loading (5 mol%, Table 1, entry 7).

We noted that TBAB has been previously used to stabilize active palladium species in oxidative C–C coupling

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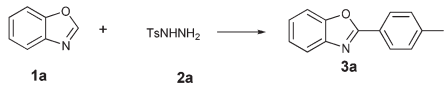
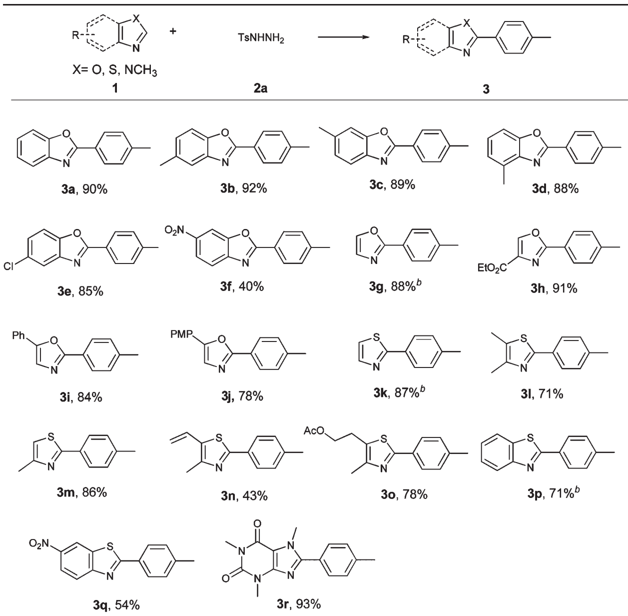
Table 1 Optimization of reaction conditions[a]



Entry	Catalyst	Oxidant	Additive	Solvent	Yield[b]
1	$Pd(OAc)_2$	$Cu(OAc)_2$		Dioxane	52
2	$Pd(OAc)_2$	$Cu(OAc)_2$	Na_2CO_3	Dioxane	75
3	$Pd(OAc)_2$	$Cu(OAc)_2$	CsOAc	Dioxane	66
4	$Pd(OAc)_2$	$Cu(OAc)_2$	K_2CO_3	Dioxane	62
5	$Pd(MeCN)_2Cl_2$	$Cu(OAc)_2$	Na_2CO_3	Dioxane	75
6	$Pd(MeCN)_2Cl_2$	$Cu(OAc)_2$	Na_2CO_3	Dioxane : DMSO (9 : 1)	79
7[c,d]	$Pd(MeCN)_2Cl_2$	$Cu(OAc)_2$	Na_2CO_3	Dioxane : DMSO (9 : 1)	90
8[d,e]	$Pd(MeCN)_2Cl_2$	$Cu(OAc)_2$	Na_2CO_3	Dioxane : DMSO (9 : 1)	92
9[d,e]	$Pd(MeCN)_2Cl_2$	$Cu(OAc)_2$	Na_2CO_3	Dioxane : DMSO (9 : 1)	81[f]

[a] Conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), Pd catalyst (10 mol%), Phen·H_2O (12 mol%), $Cu(OAc)_2$ (6 equiv.), additive (1.5 equiv.), solvent (5 mL), 100 °C, 4.5 h, under Ar. [b] HPLC yields based on **1a**. [c] 2 equiv. of **2a** was introduced. [d] Pd catalyst (5 mol%) and Phen·H_2O (6 mol%) were used. [e] TBAB (20 mol%) was added. [f] 0.6 mmol of **2a** was introduced.

Table 2 Arylation of oxazoles with *p*-tolysulfonyl hydrazides[a]



[a]Conditions: **1** (0.5 mmol), **2a** (0.75 mmol), $Pd(CH_3CN)_2Cl_2$ (5 mol%), Phen·H_2O (6 mol%), $Cu(OAc)_2$ (3 mmol), Na_2CO_3 (0.75 mmol), TBAB (0.1 mmol), 1,4-dioxane–DMSO (9 : 1, 6 mL), 100 °C, under N_2 for 4.5 h. The yields are of the isolated products. [b]Without TBAB.

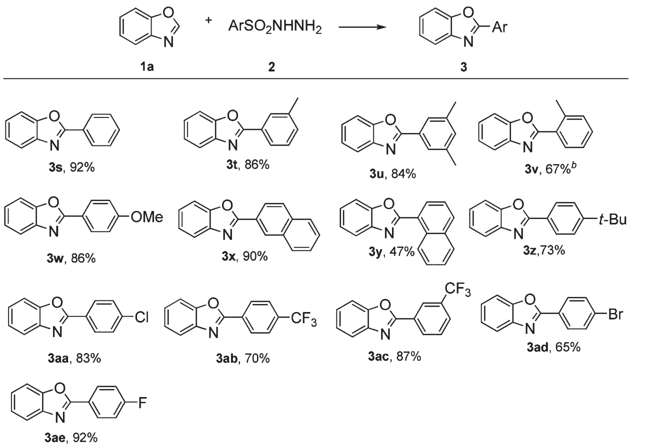
reactions.[20–21] Thus when TBAB (20 mol%) was introduced, the product was eventually obtained in 92% HPLC and 90% isolated yield after 4.5 h with 1.5 equivalent of **2a** introduced (Table 1, entry 8). Under these optimized conditions, the amount of $TsNHNH_2$ can be reduced to 1.2 equiv with 81% HPLC yield (Table 1, entry 9).

With the optimized conditions in hand, we then explored the scope of the azole substrate in the coupling with $TsNHNH_2$ under our standard conditions (Table 2). Simple benzoxazole and benzoxazoles bearing electron-donating and halogen groups at the 5 and 6 positions all reacted smoothly to give the corresponding products in high yield. In contrast, a low-yielding coupling was obtained for 6-nitrobenzoxazole with or without the TBAB additive, indicating the limitation of this system, and previous reports indicated that low yields were consistently obtained for nitro-substituted azoles.[15–18] Similarly, simple oxazole and oxazoles bearing 3-ester and 4-phenyl groups are efficient coupling partners and comparably high isolated yields were obtained (84–91%). In addition, benzothiazoles and thiazoles, including thiazoles bearing vinyl, methyl, nitro, and $AcOCH_2CH_2$ substituents in the backbone, are viable substrates, and the coupled products were isolated in moderate to high yield. Here a 6-nitro substituted benzothiazole coupled with $TsNHNH_2$ in moderate yield (54%). A vinyl-substituted thiazole substrate gave only moderate yield (**3n**), likely due to a competitive oxidative olefination reaction. Indeed, under the current conditions, the coupling of (*E*)-ethyl but-2-enoate with $TsNHNH_2$ proceeded smoothly to afford the olefination product in nearly quantitative yield.[19] Consistent with previous reports, high reactivity of caffeine was also observed (Table 2) (**3r**).

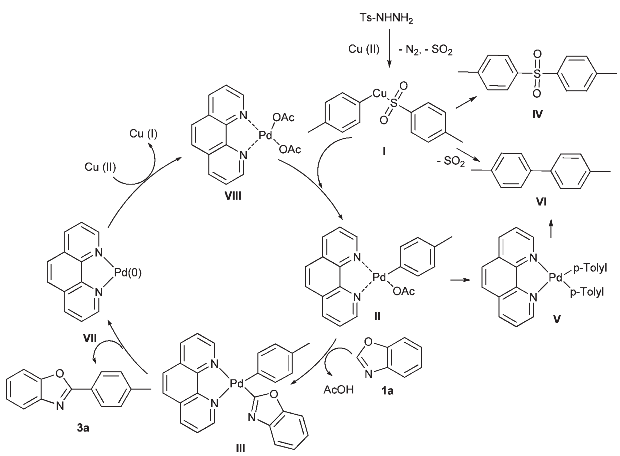
The scope of the sulfonyl hydrazide was explored for the coupling with **1a** (Table 3). Simple benzenesulfonyl hydrazide and those bearing electron-donating, -withdrawing, and halogen groups at the 3- and 4-positions all undergo smooth coupling and the products were isolated in 47–92% yield. Wang reported that a diminished yield (49%) was obtained when sodium *ortho*-tolylsulfinate was allowed to couple with **1a** as a result of steric effects of this arylating reagent.[17] In our system, *o*-$TsNHNH_2$ coupled smoothly with **1a** to give product **3u** in 67% yield, although the efficiency of the reaction is still affected by a steric effect. In addition to a substituted phenyl group, 1- and 2-naphthylsulfonyl hydrazides reacted with high efficiency, although a slightly lower yield was obtained for 2-naphthylsulfonyl hydrazide, also due to steric reasons.

Several experiments have been performed to explore the mechanism of this reaction. When radical inhibitors such as BHT and TEMPO were introduced into the reaction system of **1a** and $TsNHNH_2$, essentially no decrease of the yield of product **3a** was detected, indicating that no organic radical species is involved.[22] In addition, when the reaction of **2a** was carried out

Table 3 Arylation of benzoxazoles with arylsulfonyl hydrazides[a]



[a]Conditions: **1a** (0.5 mmol), **2** (0.75 mmol), $Pd(CH_3CN)_2Cl_2$ (5 mol%), Phen·H_2O (6 mol%), $Cu(OAc)_2$ (3 mmol), Na_2CO_3 (0.75 mmol), TBAB (0.1 mmol), in 1,4-dioxane–DMSO (9 : 1, 6 mL), 100°C, under N_2, 4.5 h. The yields refer to isolated products. [b]Without TBAB.



Scheme 2 Proposed mechanism.

in the absence of azole but in the presence of $Pd(MeCN)_2Cl_2$ (10 mol%), Phen·H_2O (12 mol%) and $Cu(OAc)_2$ (4 equiv), 4,4′-dimethylbiphenyl (**VI**) was isolated as the major product in 65% yield, suggesting that a Pd(*p*-tolyl)$_2$ species (**V**) is involved. In contrast, when the palladium catalyst was omitted, the reaction of **2a** and $Cu(OAc)_2$ afforded a mixture of 4,4′-dimethylbiphenyl (**VI**) (yield: 13%) and SO_2(*p*-tolyl)$_2$ (**IV**) (yield: 25%).[22] On the basis of these results, a mechanism is proposed (Scheme 2). Copper-mediated denitrogenative and desulfitative oxidation of $TsNHNH_2$ affords a copper(II) aryl sulfonyl species (**I**), which undergoes transmetalation to afford a palladium *p*-tolyl intermediate (**II**), which can subsequently lead to the 4,4′-dimethylbiphenyl byproduct (**III**). This palladium *p*-toyl is proposed to interact with benzoxazole **1a**, leading to C–H activation and formation of a palladium(II) aryl heteroaryl intermediate (**III**), C–C reductive elimination of which furnishes product **3a**. The catalytic cycle is completed when the Pd(0) species is oxidized to Pd(II) by $Cu(OAc)_2$.

In summary, we have developed palladium-catalyzed desulfitative–denitrogenative arylation of azoles with arylsulfonyl hydrazides. Various oxazoles and arylsulfonylhydrazides can be tolerated in this reaction to afford the desired products in good to high yields. This method expands the utility of arylsulfonyl hydrazides as arylating reagent in C–H activation of heteroaromatics.

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