C–H Bond Functionalization

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Palladium-Catalyzed Direct Arylations of Heteroarenes with Tosylates and Mesylates**

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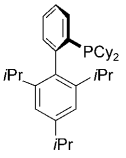
Palladium-catalyzed cross-coupling reactions between organic halides or triflates and organometallic reagents are among the most important tools for regioselective $C(sp^2)$–$C(sp^2)$ bond formations.[1–3] Particularly, their applications to heteroaromatic substrates sets the stage for novel routes to substituted heterocycles, which are valuable substructures of compounds having activities that are relevant to material or biological sciences.[4] The corresponding organometallic nucleophilic starting materials are often not commercially available and lead to the formation of undesired side products. Therefore the research focus has shifted in recent years to the direct arylation[5] of heteroarenes[6] by C–H bond functionalizations as ecologically and economically friendly alternatives.

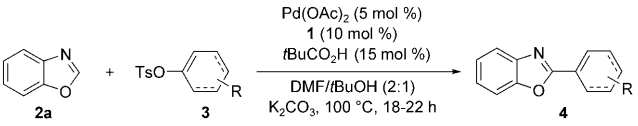
The use of tosylates or mesylates as electrophiles in cross-coupling chemistry is highly desirable because they can be prepared from readily available, inexpensive starting materials. Furthermore, these sulfonates are easy to handle because they are stable towards hydrolysis and are highly crystalline. Infortunately, their improved stabilities translate into significantly reduced reactivities in transition-metal-catalyzed cross-coupling reactions. Generally applicable methodologies for the palladium-catalyzed cross-coupling reactions of these sulfonates with organometallic nucleophiles have been developed only recently.[7] Despite this remarkable progress, more sustainable palladium-catalyzed[8] direct arylations through C–H bond functionalizations with tosylates as electrophiles have not been reported previously. Herein, we disclose a protocol for the first palladium-catalyzed direct arylation using tosylates as arylating reagents. Notably, these findings represent unprecedented direct arylation of heteroarenes with tosylates, as well as the first atom-economical[9] direct arylation using mesylates as electrophiles.

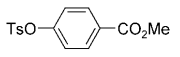
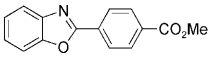
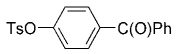
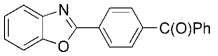
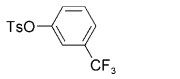
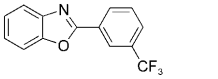
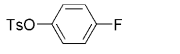
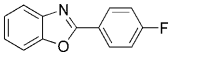
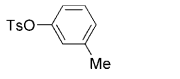
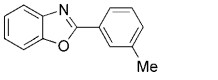
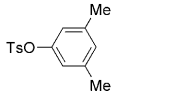
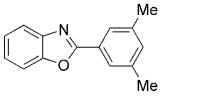
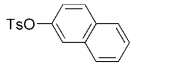
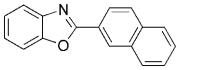
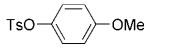
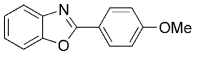
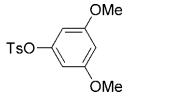
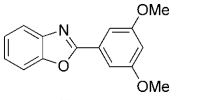
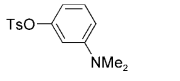
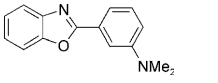
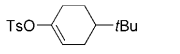
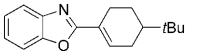
As part of our program directed towards the development of metal-catalyzed C–H bond functionalizations,[10] we probed different metal catalysts for the challenging direct arylation of heteroarenes with electron-rich, thereby electronically deactivated, aryl tosylates (see Tables S-1 and S-2 in the Supporting Information). Interestingly, a catalytic system comprising $Pd(OAc)_2$ and the monophosphine biphenyl ligand X-Phos (**1**),[11] as well as K_2CO_3 as the base, and DMF/*t*BuOH or 1,4-dioxane/*t*BuOH solvent mixtures, gave optimal results. Whereas the use of alcoholic solvents is rather uncommon in direct arylation reactions, *t*BuOH is often the (co)solvent of choice for traditional cross-coupling reactions of aryl tosylates.[7] Notably, the addition of $tBuCO_2H$[12] in catalytic amounts was beneficial for the direct arylation of heteroarene **2a** (Table 1).



1

Table 1: Direct arylations of benzoxazole (**2a**) with tosylates **3**.[a]



Entry	3	Product		Yield [%]
1			**4a**	89
2			**4b**	85[b]
3			**4c**	82
4			**4d**	78
5			**4e**	97
6				91[c]
7			**4f**	95
8			**4g**	82
9			**4h**	86
10			**4i**	92
11			**4j**	88
12			**4k**	52[b]

[a] Reaction conditions: **2a** (0.50 mmol), **3** (0.60 mmol), $Pd(OAc)_2$ (5 mol%), **1** (10 mol%), K_2CO_3 (0.75 mmol), $tBuCO_2H$ (15 mol%), DMF (2 mL), *t*BuOH (1 mL) 100°C, 18–22 h. Yield of isolated product reported. [b] 1,4-dioxane (2 mL), *t*BuOH (1 mL). [c] $PdCl_2$ (5 mol%).

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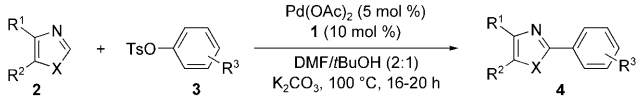
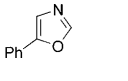
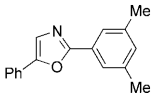
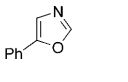
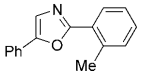
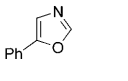
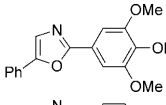
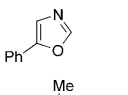
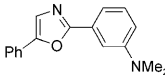
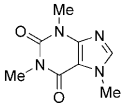
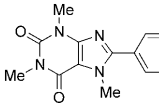
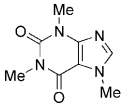
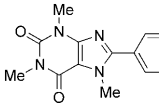
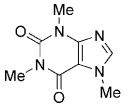
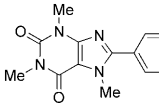
Under the optimized reaction conditions, electron-deficient aryl tosylates displaying important functional groups were efficiently converted into the desired products (Table 1, entries 1–4). A variety of more demanding electron-rich tosylates were found to be viable substrates for the direct arylation of heteroarene **2a** as well (Table 1, entries 5–11). Remarkably, catalytic amounts of the less expensive $PdCl_2$ led to product **4e**, which was isolated in a yield comparable to the one obtained when using $Pd(OAc)_2$ (Table 1, entries 5 and 6). The methodology was not restricted to aryl-substituted electrophiles, but also allowed C–H bond functionalizations using an alkenyl tosylate (Table 1, entry 12).

With an effective palladium catalyst for direct functionalization of benzoxazole (**2a**) in hand, we probed the scope of the arylation of various pronucleophilic heteroarenes, focusing particularly on the use of electron-rich tosylates. Heterocycles, such as an oxazole (Table 2, entries 1–5) or caffeine (Table 2, entries 6–9), were regioselectively functionalized in high yields. Here, the catalytic performance was not significantly affected by the addition of $tBuCO_2H$ (Table 2, entries 1 and 8 versus entries 2 and 9, respectively).

Given their recent practical impact on numerous research areas,[13] we became interested in evaluating 1,2,3-triazoles **5** as pronucleophiles in the palladium-catalyzed[14,15] direct arylation using tosylates (Table 3). The palladium complex derived from X-Phos (**1**) enabled direct arylation of 1,2,3-triazoles **5** with tosylates **3**, which proceeded with excellent regioselectivities through C–H bond functionalization on the

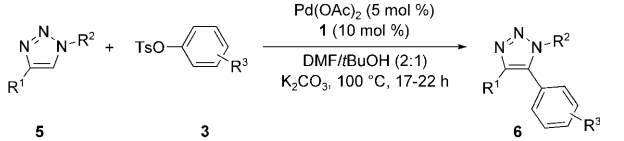
Table 2: Direct arylation of heteroarenes **2** using tosylates **3**.[a]



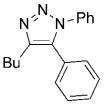
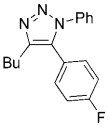
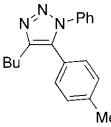
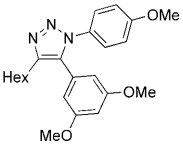
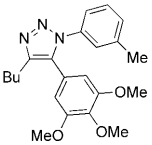
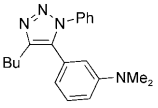
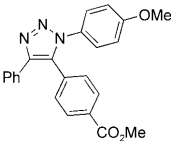
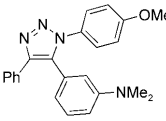
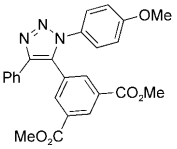
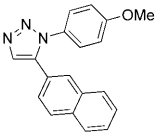
Entry	2	R^3	Product		Yield [%]
1		3,5-Me_2		**4l**	74
2					72[b]
3		2-Me		**4m**	65
4		3,4,5-$(OMe)_3$		**4n**	68
5		3-NMe_2		**4o**	72
6		H		**4p**	58
7		4-Me		**4q**	76
8		3,5-Me_2		**4r**	80
9					79[b]

[a] Reaction conditions: **2** (0.50 mmol), **3** (0.60 mmol), $Pd(OAc)_2$ (5 mol%), **1** (10 mol%), K_2CO_3 (0.75 mmol), DMF (2 mL), *t*BuOH (1 mL), 100°C, 16–20 h. Yields for isolated product reported. [b] $tBuCO_2H$ (15 mol%).

Table 3: Direct arylation of 1,2,3-triazoles **5**with tosylates **3**.[a]



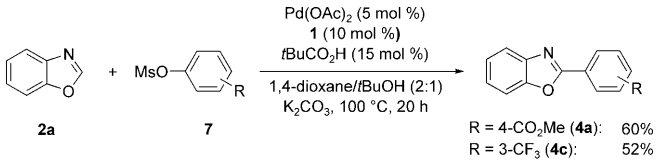
5 **3** **6**

Entry	R^1	R^2	R^3	Product		Yield [%]
1	Bu	Ph	H		**6a**	72
2	Bu	Ph	4-F		**6b**	62
3	Bu	Ph	4-Me		**6c**	90
4	Hex	4-MeO-C_6H_4	3,5-$(OMe)_2$		**6d**	99
5	Bu	3-Me-C_6H_4	3,4,5-$(OMe)_3$		**6e**	87
6	Bu	Ph	3-NMe_2		**6f**	98
7	Ph	4-MeO-C_6H_4	4-CO_2Me		**6g**	72
8	Ph	4-MeO-C_6H_4	3-NMe_2		**6h**	97
9						79[b]
10	Ph	4-MeO-C_6H_4	3,5-$(CO_2Me)_2$		**6i**	81
11	H	4-MeO-C_6H_4	2-naphthyl		**6j**	90

[a] Reaction conditions: **5** (0.50 mmol), **3** (0.60 mmol), $Pd(OAc)_2$ (5 mol%), **1** (10 mol%), K_2CO_3 (0.75 mmol), DMF (2 mL), *t*BuOH (1 mL), 100°C, 17–22 h. Yield for isolated product reported. [b] 80°C.

heterocyclic moieties. Notably, reactions could be performed with a comparable efficacy at a significantly reduced temperature of 80 °C (Table 3, entry 9). A monosubstituted 1,2,3-triazole regioselectively gave rise to the 1,5-disubstituted product **6j** (Table 3, entry 11), which can be rationalized with a electrophilic aromatic substitution-type mechanism.

Because of the significantly lower molecular weights of the aryl mesylates, processes utilizing these electrophiles are more atom-economical than those employing tosylates. However, metal-catalyzed direct arylations with mesylates as electrophilic substrates have thus far not been reported. Consequently, we probed our optimized catalytic system for the functionalization of benzoxazole (**2a**) with these sulfonates. Importantly, direct arylation with the aryl mesylates **7** was accomplished in the presence of substoichiometric amounts of tBuCO$_2$H, regioselectively yielding the heterocycles **4** (Scheme 1).



Scheme 1. Palladium-catalyzed direct arylations with mesylates **7**.

In summary, we have reported the first palladium-catalyzed direct arylations using tosylates as electrophiles. A catalyst derived from X-Phos (**1**) enabled a broadly applicable C–H bond functionalization of various heterocycles using aryl tosylates, and also proved applicable to the unprecedented direct arylations using mesylates.

Experimental Section

Representative procedure for palladium-catalyzed direct arylations. Synthesis of **4e** (Table 1, entry 5): A solution of $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5 mol %), **1** (23.8 mg, 0.050 mmol, 10 mol %), K_2CO_3 (104 mg, 0.75 mmol), **2a** (60 mg, 0.50 mmol), and 3-methylphenyl tosylate (157 mg, 0.60 mmol) in DMF (2 mL) and tBuOH (1 mL) was stirred for 21 h at 100 °C under N_2. At ambient temperature, Et_2O (25 mL) and H_2O (50 mL) were added to the reaction mixture. The separated aqueous phase was extracted with Et_2O (2 × 75 mL). The combined organic layers were washed with H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo. The remaining residue was purified by column chromatography on silica gel (n-pentane/Et_2O 50:1 → 30:1) to yield **4e** (101 mg, 97 %) as a colorless solid (m.p. 97–98 °C).

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