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A General Palladium-Catalyzed Sonogashira Coupling of Aryl and Heteroaryl Tosylates

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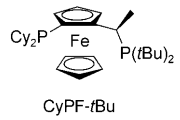
Aryl alkynes are important synthetic precursors for a wide variety of target compounds.[1] The most straightforward and reliable method for the regioselective construction of these intermediates is the palladium-catalyzed Sonogashira coupling.[2] Considerable efforts have been made to enhance the efficiency and generality of this reaction. Several palladium catalyst systems have been developed that enable the reaction to proceed at room temperature,[3] without requiring copper(I) as a cocatalyst,[4] and expanding the substrate range to aryl triflates and aryl chlorides.[5] However, the use of tosylates as coupling partners for the C_{sp^2}–C_{sp} bond formation has remained almost unexplored until recently.[6] The use of aryl tosylates as electrophiles is attractive, since they can be prepared from the large number of readily available phenols with less expensive reagents than the corresponding triflates. Furthermore, aryl tosylates are more convenient to use because they are highly crystalline solids with a significantly higher hydrolytic stability than triflates.[7] These properties allow aryl tosylates to be used as inert protecting groups during a multistep synthesis, permitting several orthogonal transformations and then their transformation through Sonogashira coupling at an appropriate stage in the synthetic sequence.[8] Conversely, the greater stability of aryl tosylates makes this functionality less reactive towards palladium-catalyzed processes. Recently, the Sonogashira coupling of strongly activated, electron-deficient *para*- and *meta*-substituted aryl tosylates was reported using the monodentate X-Phos (2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl) ligand.[9] This catalyst system was only successful when the alkyne was added slowly over the course of the reaction, presumably due to the competing oligomerization of the alkyne at higher concentration. Thus, slow addition of the alkyne substrate over 8 h and high purity of the tosylate were prerequisites for a successful transformation. To the best of our knowledge, no general procedure for the Sonogashira coupling of nonactivated or *ortho*-substituted aryl tosylates or heteroaryl tosylates has been reported so far. Herein, we report a general, efficient, and robust catalyst system for the Sonogashira coupling of diverse aryl and heteroaryl tosylates.[10]

We initiated our investigation by searching for conditions under which the coupling reaction of *ortho*-(acetamidophenyl) tosylate and alkyl alkynes proceeded efficiently. This was attractive because it gives access to the extremely useful alkyne precursors of the Larock indole synthesis,[11] yet the substrate is also a challenging one because there it contains a potentially interfering acetamido group in close proximity to the reacting tosylate moiety.[12]

A screening of phosphine ligands, including $P(t\text{Bu})_3$, $P(Cy)_3$, and X-Phos, revealed that 1-dicyclohexylphosphino-2-(di-*tert*-butylphosphinoethyl)ferrocene (CyPF-*t*Bu)[13] in combination with $Pd(TFA)_2$ and K_3PO_4 effectively catalyzed this reaction in *t*BuOH at 85 °C to form alkyne **3** (Table 1, entries 1 and 2; see also Table S-1 in the Supporting Information).



CyPF-*t*Bu

Furthermore, it was also found that neither slow addition nor a significant excess of alkyne was required to obtain selective and almost quantitative conversion.

The optimized reaction conditions accept a broad substrate scope in both aryl tosylate and alkyne coupling partners (Table 1).[14] Several diversely and, in particular, *ortho*-substituted aryl tosylates (Table 1, entries 7 and 8) are tolerated and react with comparable efficiency. Importantly, nonactivated substrates, such as phenyl tosylate, or even deactivated aryl tosylates, such as *para*-tolyl- or *ortho*-methoxyphenyl tosylates, were found to be reactive under these conditions (Table 1, entries 9–12).

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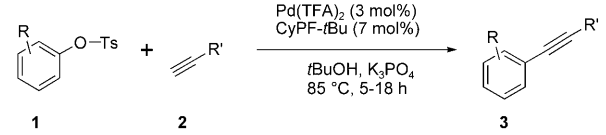
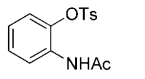
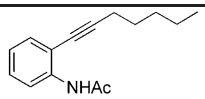
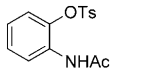
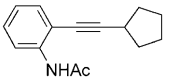
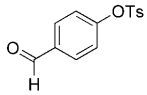
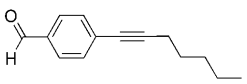
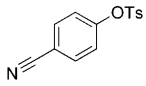
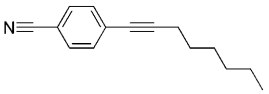
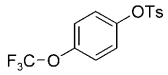
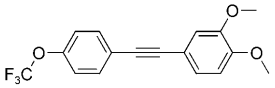
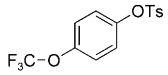
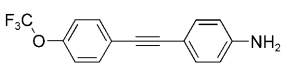
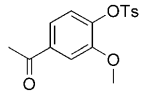
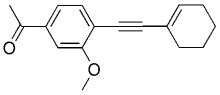
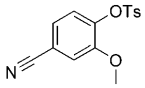
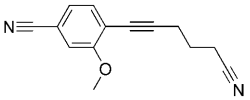
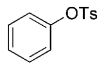
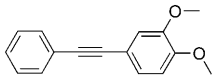
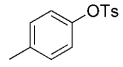
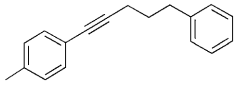
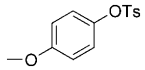
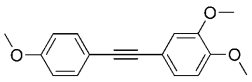
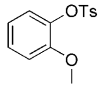
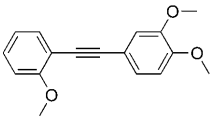
Table 1. Scope of the Sonogashira coupling with aryl tosylates.[a]

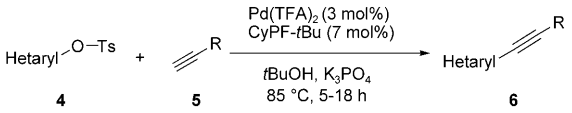


1 2 3

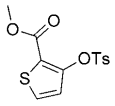
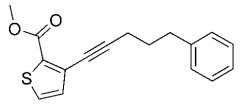
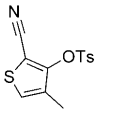
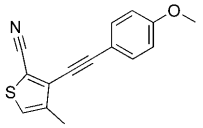
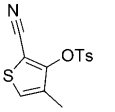
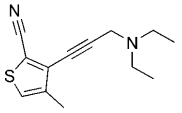
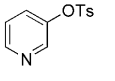
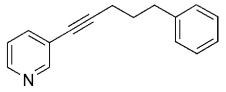
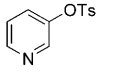
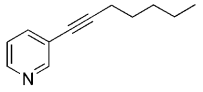
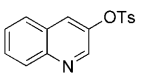
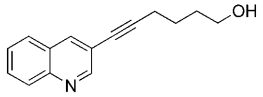
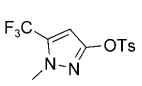
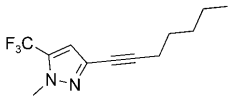
Entry	Tosylate	Product		Yield [%][b]
1[c]			**3a**	80
2[c]			**3b**	71
3			**3c**	72
4			**3d**	74
5			**3e**	80
6			**3f**	60
7[c]			**3g**	90
8			**3h**	62
9			**3i**	73
10			**3j**	85
11			**3k**	97
12			**3l**	81

[a] All reactions were performed with **1** (1.6 mmol), **2** (1.8 mmol), Pd catalyst (3 mol%), CyPF-*t*Bu (7 mol%) in *t*BuOH, and K_3PO_4 (1.4 equiv based on tosylate **1**) at 85°C for 5–18 h. Ts = tosyl. [b] Isolated yields. [c] Performed by using 2 equiv of **2** (3.2 mmol) and 3.0 equiv K_3PO_4 (based on tosylate **1**).

Table 2. Scope of the Sonogashira coupling with heteroaryl (Hetaryl) tosylates.[a]



4 5 6

Entry	Tosylate	Product		Yield [%][b]
1[c]			**6a**	60
2			**6b**	73
3			**6c**	65
4			**6d**	73
5			**6e**	67
6[c]			**6f**	88
7			**6g**	65
8[c]			**6h**	84
9			**6i**	73
10			**6j**	63

[a] All reactions were performed with **4** (1.6 mmol), **5** (1.8 mmol), Pd catalyst (3 mol%), CyPF-*t*Bu (7 mol%) in *t*BuOH, and K_3PO_4 (1.4 equiv based on tosylate **4**) at 85°C for 5–18 h. [b] Isolated yields. [c] Performed by using 2 equiv of **5** (3.2 mmol) and 3.0 equiv K_3PO_4 (based on tosylate **4**).

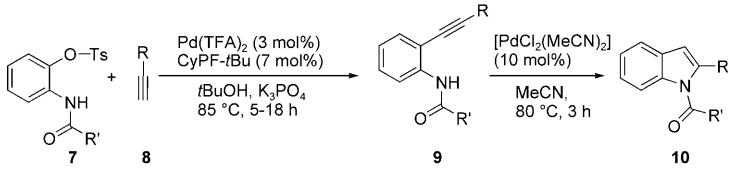
A number of potentially reactive functionalities, such as ketones, aldehydes, hydroxy groups, nitriles, methyl esters, and even a free primary amine, are compatible and remain unaffected, which illustrates the robustness of the catalyst system (Tables 1 and 2).

An important aspect of the reaction is the applicability of the reaction to heterocycles, which are frequently precursors of pharmacologically relevant scaffolds. In this context, we observed that besides functionalized aryl tosylates, heteroaryl tosylates, such as thienyl and pyridyl tosylates, react with good efficiency (Table 2, entries 1–6). Moreover, the corresponding tosylates of pyra- and indazolones are suitable substrates under these conditions and afford the desired alkynes in good to high yields (Table 2, entries 7–10).

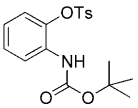
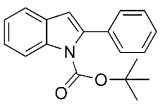
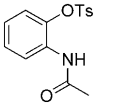
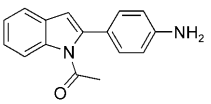
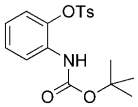
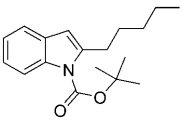
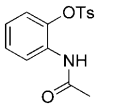
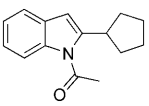
The tosylate Sonogashira approach also provided facile access to various indoles and isoquinoline heterocyles by using *N*-boc- (Boc = *tert*-butyloxycarbonyl) or *N*-acetamide-protected *ortho*-(aminophenyl) tosylates **7** and the *ortho*-(formylphenyl) tosylate **11**, respectively, as starting materials. Notably, to the best of our knowledge, this is the first example of accessing indoles and isoquinolines by using a tosylate activation (Tables 3 and 4). Interestingly, for the synthesis of indoles **10**, no in situ cyclization of the precursor **9** was observed during the coupling reaction; this required a subsequent hydroamination step through known cyclization procedures[15] (Table 3, entries 1–4).

In conclusion, we have developed a novel, mild, and efficient protocol for the palladium-catalyzed coupling of aryl and heteroaryl tosylates. This simple procedure is easy to carry out and does not require slow addition of the alkyne substrate and thus provides facile access to a variety of functionalized aryl and heteroaryl alkynes in good to very good yields. The high tolerance towards many functional groups and heterocycles combined with the high stability of the tosylate precursors considerably extends the scope of aromatic and heteroaromatic hydroxy compounds as potential precursors for the Sonogashira coupling and its applicability in multistep syntheses. Furthermore, we have demonstrated that the Sonogashira adducts were easily transformed into indoles and isoquinolines in high yields.[17]

Table 3. Accessing indoles via a Sonogashira coupling cyclization sequence with aryl tosylates.[a]

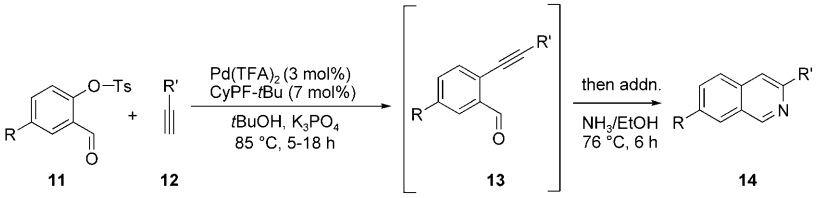


7 8 9 10

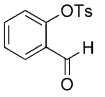
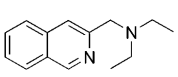
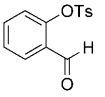
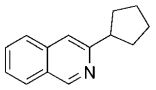
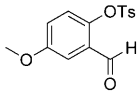
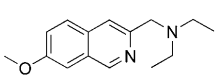
Entry	Tosylate	Product		Yield [%][b]
1			**10a**	67
2			**10b**	78
3[c]			**10c**	72
4[c]			**10d**	60

[a] All reactions were performed with **7** (1.6 mmol), **8** (1.8 mmol), Pd catalyst (3 mol%), CyPF-*t*Bu (7 mol%) in *t*BuOH, and K_3PO_4 (1.4 equiv based on tosylate **7**) at 85°C for 5–18 h. [b] Isolated yields, two steps. [c] Performed by using 2 equiv of **8** (3.2 mmol) and 3.0 equiv K_3PO_4 (based on tosylate **7**).

Table 4. Accessing isoquinolines through a Sonogashira coupling cyclization sequence with aryl tosylates.[a]



11 12 13 14

Entry	Tosylate	Product		Yield [%][b]
1			**14a**	62
2			**14b**	76
3			**14c**	73

[a] All reactions were performed with **11** (1.8 mmol), **12** (2.2 mmol), Pd catalyst (3 mol%), CyPF-*t*Bu (7 mol%) in *t*BuOH, and K_3PO_4 (1.4 equiv based on tosylate **11**) at 85°C for 5–18 h. [b] Isolated yields over two steps.

Experimental Section

General: A Schlenk tube was charged under an atmosphere of argon with the aryl tosylate or heteroaryl tosylate (1.6 mmol), palladium trifluoroacetate (0.048 mmol, 3 mol%), Cy-PF-*t*Bu (0.112 mmol, 7 mol%), K_3PO_4 (2.2 mmol), and a magnetic stirring bar. Then, *t*BuOH (7 mL) and the alkyne (1.8 mmol) were added and the mixture was again purged with argon, sealed with a serum cap, and heated to 85°C for 5–18 h. After cooling, the reaction mixture was diluted with EtOAc and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the crude product was purified either by chromatography on silica gel (using heptane/EtOAc or CH_2Cl_2/EtOAc as eluent) or by

preparative HPLC (C18 reverse phase column, elution with a water/MeCN gradient).

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Keywords: alkynes · aryl tosylates · cross-coupling · palladium · Sonogashira coupling

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