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Palladium-catalyzed regio- and chemoselective direct desulfitative arylation of anilides with arylsulfonyl chlorides

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ABSTRACT

A straightforward and practical palladium-catalyzed regioselective arylation of anilides is described. This method provides a new approach to prepare 2-aminobiaryls, which are valuable precursors for the synthesis of various *N*-containing heterocycles, using arylsulfonyl chlorides as readily available arylating agents.

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1. Introduction

The prevalence of biaryl moiety in natural and biologically active compounds as well as advanced organic materials is motive for finding efficient methods for the construction of this structural motif.[1] Direct transition metal-catalyzed functionalization of unreactive C–H bonds serves as a powerful tool in organic synthesis.[2] Direct C–H bond arylation through transition metal-catalyzed reactions using various coupling reagents such as arylboronic acids,[3] organometallic reagents,[4] aryl halides, aryl tosylates,[5] (di)aryliodonium salts,[6] benzoic acids[7] and arenes[8] have been reported. In most cases, the presence of a directing group to activate the target C–H bond selectively is crucial and choosing the most beneficial directing group is still the challenging part of a synthetic approach.[9] Among the enormous number of directing groups introduced in the last decades, carbonyl containing groups have received special consideration. For example, acylamino groups are beneficial directing groups to activate *ortho* C–H bonds of arenes and are easily removed to attain anilines which are omnipresent structural motifs found in many bioactive compounds.[9a]

2-Aminobiaryls have received particular attention due to their applications in organic synthesis. They can be used as precursors for synthetically important heterocycles such as carbazoles.[10] In addition to well-known coupling reactions such as Suzuki-Miyaura,[11a,b] Kumada[11c-e] and Negishi reactions,[11f] the direct regioselective coupling of anilides with various coupling partners have been reported for the synthesis of this structural motif.[12] As shown in Scheme 1, in 2007, Shi and co-workers described direct palladium catalyzed arylation of acetanilides with silyl reagents (eq (1).).[12a] Palladium-catalyzed decarboxylative arylation of anilides with acylperoxides was reported by Wang and co-workers in 2014 (eq (2).).[12b] *Ortho*-arylation of pivanilide derivatives with aryl iodides as coupling reagents was reported by Cheng et al. in 2015 (eq. (3)).[12c] A ruthenium catalyzed arylation of acetanilides using bronic acid derivatives as coupling partners was reported independently by Jeganmohan's and Ackermann's groups in 2014 and 2015, respectively (eq (4).).[12d,e]

Direct arylation of anilides with arenes has also been reported.[12f-i] Yu and coworkers described Pd-catalyzed arylation of pivanilides using arenes as both solvent and coupling reagent (eq (5).).[12h,i] As part of our ongoing research program on the development of efficient methods for direct functionalization of C–H bonds, we turned our attention to the synthesis of 2-arylanilides via a palladium catalyzed C–H bond activation reaction. In comparison with the above-mentioned methods, an appropriate economically favorable coupling partner is obviously required. Among the coupling candidates, arylsulfonyl chlorides could be the best choice because of their indisputable advantages.

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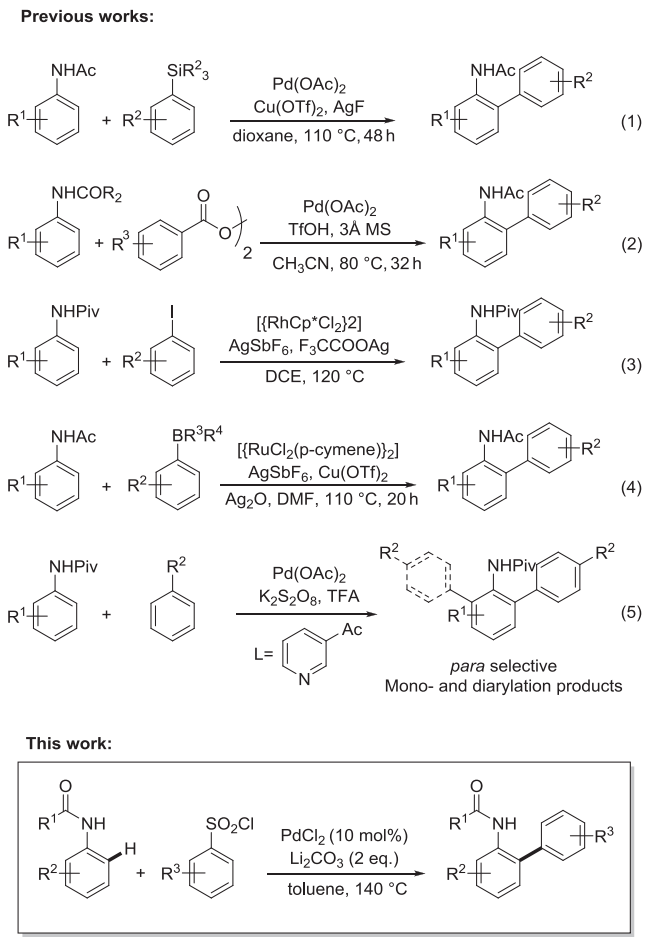


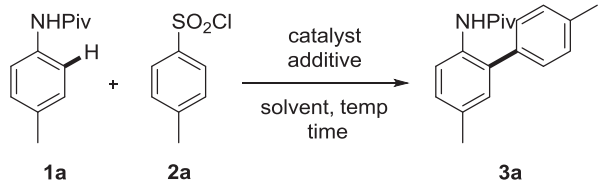
Scheme 1. Examples of anilide arylation.

Palladium-catalyzed C–H bond functionalization with arylsulfonyl chlorides has been reported, recently.[13] To the best of our knowledge palladium-catalyzed desulfitative direct arylation of arenes using arylsulfonyl chlorides as the coupling partners has not received more attention. Towards addressing these reports and in continuation of our interest in this area,[14] we wish to report the palladium-catalyzed regioselective direct arylation of anilides with arylsulfonyl chlorides as the arylation agent through C–H bond activation for the first time (Scheme 1).

2. Results and discussion

Our initial attempt toward this aim was started by an investigation of the reaction between 4-methyl pivanilide (**1a**) and *p*-toluenesulfonyl chloride (**2a**) as the model reaction (Table 1). To optimize the reaction parameters, the effects of different catalysts, additives, solvents and temperature were examined. To begin our initial trial the reaction between **1a** and **2a** in the present of 10 mol % of $PdCl_2$ as catalyst and 2 equivalents of Li_2CO_3 as additive in 1,4-dioxane was considered and to our delight, the desired product **3a** was formed in 51% yield (Table 1, entry 1). Various solvents were screened to optimize the reaction conditions (Table 1, entries 2–7, see also Table S1, entries 8–10 in the Supporting Information). When the reaction was carried out in DCE the yield slightly increased but the best result was obtained in toluene with 81% yield (Table 1, entry 7). The reaction was performed in the presence of different additives and it was revealed that the role of the additive

Table 1
Optimization of the reaction conditions.[a]



Entry	Catalyst (mol %)	Additive (equiv)	Solvent	Yield[a] (%)
1	$PdCl_2$ (10)	Li_2CO_3 (2)	1,4-dioxane	51
2	$PdCl_2$ (10)	Li_2CO_3 (2)	DCE	59[b]
3	$PdCl_2$ (10)	Li_2CO_3 (2)	DME	43
4	$PdCl_2$ (10)	Li_2CO_3 (2)	DMF	–
5	$PdCl_2$ (10)	Li_2CO_3 (2)	CH_3CN	–
6	$PdCl_2$ (10)	Li_2CO_3 (2)	PhCl	63
7	**$PdCl_2$ (10)**	**Li_2CO_3 (2)**	**toluene**	**81**
8	$PdCl_2$ (10)	Na_2CO_3(2)	toluene	35
9	$PdCl_2$ (10)	K_2CO_3 (2)	toluene	trace
10	$PdCl_2$ (10)	Cs_2CO_3 (2)	toluene	trace
11	$PdCl_2$ (10)	LiCl (2)	toluene	80
12	$PdCl_2$ (10)	–	toluene	–
13	–	Li_2CO_3 (2)	toluene	–
14	$PdCl_2(MeCN)_2$ (10)	LiCl (2)	toluene	43
15	$Pd(OAc)_2$ (10)	LiCl (2)	toluene	47
16	$PdCl_2$(COD) (10)	LiCl (2)	toluene	54
17	$PdCl_2(PPh_3)_2$(10)	LiCl (2)	toluene	31
18	$PdCl_2$ (5)	LiCl (2)	toluene	69
19	$PdCl_2$ (10)	LiCl (2)	toluene	36[c]

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 eq), additive (2 eq.) in solvent (2.0 mL) were stirred at 140 °C for 48 h.
[b] The *ortho* chlorinated pivanilide was detected in 29% yield as the side product.
[c] The reaction was carried out at 120 °C.

is crucial for this transformation, and the formation of the desired product **3** is strongly depended on the presence of lithium salts. As shown in Table 1, the best results were obtained with Li_2CO_3 and LiCl whereas Na_2CO_3, K_2CO_3 and Cs_2CO_3 were found to be inferior (entries 7–11, see also Table S1, entries 6 and 7 in the Supporting Information), and finally, no desired product was obtained in the absence of additive (Table 1, entry 12). Other common palladium catalysts such as $Pd(OAc)_2$, $PdCl_2(CH_3CN)_2$, $PdCl_2(COD)_2$ and $PdCl_2(PPh_3)_2$ were examined and no improvement in yields was observed (Table 1, entries 13–17). Decreasing the amount of catalyst from 10 to 5 mol% led to insufficient outcomes (Table 1, entry 18) and control experiments showed that no reaction occurred in the absence of catalyst (Table 1, entry 13). The effect of ligand was also investigated and no improvement in yields was observed in the presence of Ph_3P, bipyridine, phenanthroline or Et_3N (Table S1, entries 1–4). Finally, upon decreasing the reaction temperature from 140 to 120 °C, the yield of the reaction decreased from 81 to 36% (Table 1, entry 19).

Once the optimized conditions for the desired arylation reaction were established, the scope of the reaction was investigated (Scheme 2). Anilides with halo substituents (F, Cl, Br) smoothly led to the corresponding arylated products in good yields.

Given that these halogen substituents remained intact during the reaction, they can enable additional functionalization at these positions (**3e**, **3f**, **3g**). No remarkable electronic effect of substituents at *para* or *meta* position of pivanilides was observed but in general the presence of alkyl groups slightly enhanced the yields. The presence of CF_3 group on *meta* or *para* position of anilide ring resulted in lower yields (**3h** and **3m**). It is worth noting that with pivanalides bearing strong electron-donating groups, such as OMe, the corresponding chlorinated products were obtained as the side

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