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Palladium-catalyzed *N*-arylsulfonamide formation from arylsulfonyl hydrazides and nitroarenes†

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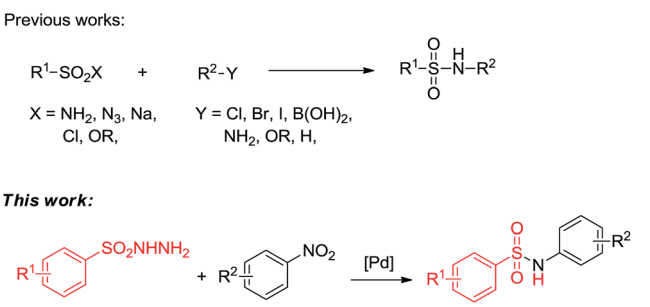
A palladium-catalyzed construction for *N*-arylsulfonamide from nitroarenes and arylsulfonyl hydrazides is developed. In this protocol, abundant and stable nitroarenes serve as the nitrogen sources by *in situ* reduction reaction of hydrogen released from arylsulfonyl hydrazides. No external oxidants or reductants are needed for this kind of transformation.

It is well-known that *N*-arylsulfonamides are a class of crucial building blocks that are ubiquitous in many biologically active compounds and pharmaceutical intermediates, and these structures have important roles in organic synthesis and biological and medicinal study.[1] Therefore, the exploration of efficient and green methods for the synthesis of sulfonamides under mild conditions is an attractive area for organic and pharmaceutical chemists. During the past years, various efforts have been made for the construction of sulfonamides.[2] The conventional route mainly relies on the reaction of sulfonyl chlorides[3] or sodium sulfinates[4] with amino compounds due to the simplicity and practicability. The transition-metal-catalyzed couplings of sulfonamides with aryl halides,[5] aryl boronic acids,[6] cyclohexanones,[7] alcohols[8] and hydrocarbons[9] provide alternative methods to synthesize *N*-arylsulfonamides. However, there are still many shortcomings existing in the current research, such as harsh reaction conditions, unstable starting materials, poor functional group tolerance, requirements of additional ligand and/or base. Some of approaches suffer from the utility of amino groups as nitrogen sources, which are potentially toxic, volatile and thus leading to limitations and tedious procedures. To overcome these drawbacks, it is highly desirable to develop a method for the synthesis of *N*-arylsulfonamides from cheap and stable nitrogen sources.

As we known, aromatic nitro compounds can undergo reductive reactions for the preparation of the corresponding arylamines. In recent years, there have been significant attractions to transition-metal-catalyzed C–N bond formations by utilizing nitroarenes as starting materials. The nitroarenes were reduced *in situ via* borrowing hydrogen strategy (hydrogen transfer)[10,11] or by adding external reducing agent.[12] We envisioned that it might be rational using nitroarenes instead of aromatic amines as abundant and stable nitrogen sources for the selective construction of S–N bond. Previously, our group demonstrated a series of protocols by harnessing alcohols and nitroarenes to form second amines,[13] tertiary amines,[14] amides[15] and N-containing heterocycles.[16] We also reported a palladium-catalyzed one-pot synthesis of diarylamines from nitroarenes and cyclohexanones.[17] In these methods, nitroarenes successfully acted as the hydrogen acceptors and were reduced to amines *in situ* through hydrogen transfer methodology, and no external reductants were needed to the reactions. As part of our continuing efforts in using nitroarenes as the coupling partners to construct C–N and N-hetero bonds, herein, we report a palladium-catalyzed formation of *N*-arylsulfonamides from nitroarenes and arylsulfonyl hydrazides using the hydrogen transfer strategy (Scheme 1).



Scheme 1 Different pathways for the synthesis of sulphonamides.

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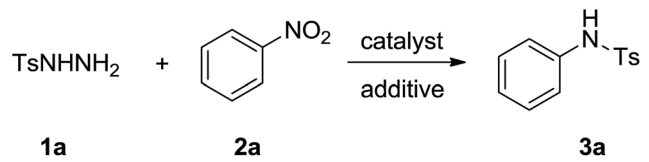
We begin our research by investigating the reaction of *p*-toluenesulfonyl hydrazides (**1a**) with nitrobenzene (**2a**) in DMF by using $Pd(OAc)_2$ as catalyst and the desired product was obtained in 19% yield as detected by GC and NMR methods (Table 1, entry 1). Afterwards, a variety of palladium catalysts were examined for this reaction. Similar results were achieved when employing $PdCl_2$, $PdBr_2$, $Pd(COD)Cl_2$ as the catalyst (Table 1, entries 2–4). $Pd(acac)_2$ and $Pd(TFA)_2$ improved the reaction yield to 36% and 35%, respectively (entries 5 and 6). Among the catalysts screened, $Pd(OH)_2$ showed the most effective and afford **3a** in 42% yield (entry 7). Solvents also played an important role and the effect of solvents on this transformation was also examined. DMA, NMP and pyridine gave a similar result (entries 8–10). A lower yield was obtained when DMSO was employed as the solvent (entry 11). Unfortunately, when the reaction was conducted in weak polar solvent such as dioxane and toluene, only a trace amount of desired product was acquired under the similar reaction conditions (entries 12 and 13). In order to improve the reaction yield, we attempted to investigate some additives. Encouraged by the result of entry 10, we used 1 equiv. of pyridine as the additive in DMF. To our delight, the yield of **3a** was increased to 58% (entry 14). We tested some external reductants such as hydrazine hydrate and isopropanol to enhance the reaction yield, however both of them were not efficient (entries 15 and 16). We proposed that the role of pyridine was acted as a base so we tried organic base triethylamine and inorganic base potassium carbonate, but the results were also unsatisfactory (entries 16–17). Notably, a desired yield could be obtained when the reaction was performed under an argon atmosphere and molecular sieve was added to the reaction system (entries 18–20).

With the optimized reaction conditions in hand, we explored the scope of this transformation. As presented in Table 2, a variety of arylsulfonyl hydrazides were successfully reacted with nitrobenzene (**2a**) to produce corresponding *N*-arylsulfonamides in moderate to good yields. Generally, alkyl substituents at the *para* position of sulfonyl hydrazide slightly affected the reaction yield (**3a–3d**). Functional groups such as halogens and trifluoromethoxy were well tolerated under the optimal reaction conditions (**3e–3h**). It should be noted that cleavage of C-halogen bond was not observed during the reaction process. When *ortho*-substituted arylsulfonyl hydrazides reacted with nitrobenzene, relatively lower yields were obtained probably due to the steric effect of the substituents (**3i-3j**).

Subsequently, a number of substituted nitroarenes were employed to react with *p*-toluenesulfonyl hydrazide and the results are shown in Table 3. Methyl and methoxy nitrobenzenes reacted smoothly with **1a** to give the corresponding products in reasonable yields (**3k–3m**). Halogen substituents

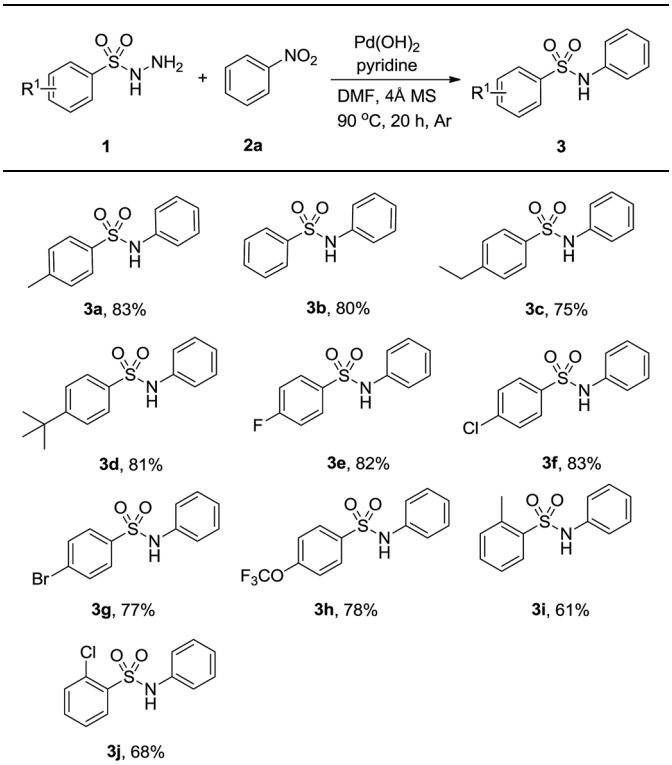
Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst	Additive	Solvent	Yield[b] (%)
1	$Pd(OAc)_2$		DMF	19
2	$PdCl_2$		DMF	25
3	$PdBr_2$		DMF	24
4	$Pd(COD)Cl_2$		DMF	42
5	$Pd(acac)_2$		DMF	36
6	$Pd(TFA)_2$		DMF	35
7	$Pd(OH)_2$		DMF	42
8	$Pd(OH)_2$		DMF	36
9	$Pd(OH)_2$		NMP	34
10	$Pd(OH)_2$		Pyridine	37
11	$Pd(OH)_2$		DMSO	23
12	$Pd(OH)_2$		Toluene	Trace
13	$Pd(OH)_2$		Dioxane	Trace
14	$Pd(OH)_2$	Pyridine	DMF	58
15	$Pd(OH)_2$	$N_2H_4 \cdot H_2O$	DMF	Trace
16	$Pd(OH)_2$	i-PrOH	DMF	19
17	$Pd(OH)_2$	Et_3N	DMF	21
18	$Pd(OH)_2$	K_2CO_3	DMF	Trace
19[c]	$Pd(OH)_2$	Pyridine	DMF	66
20[d]	$Pd(OH)_2$	Pyridine	DMF	72
21[c,d]	$Pd(OH)_2$	Pyridine	DMF	84

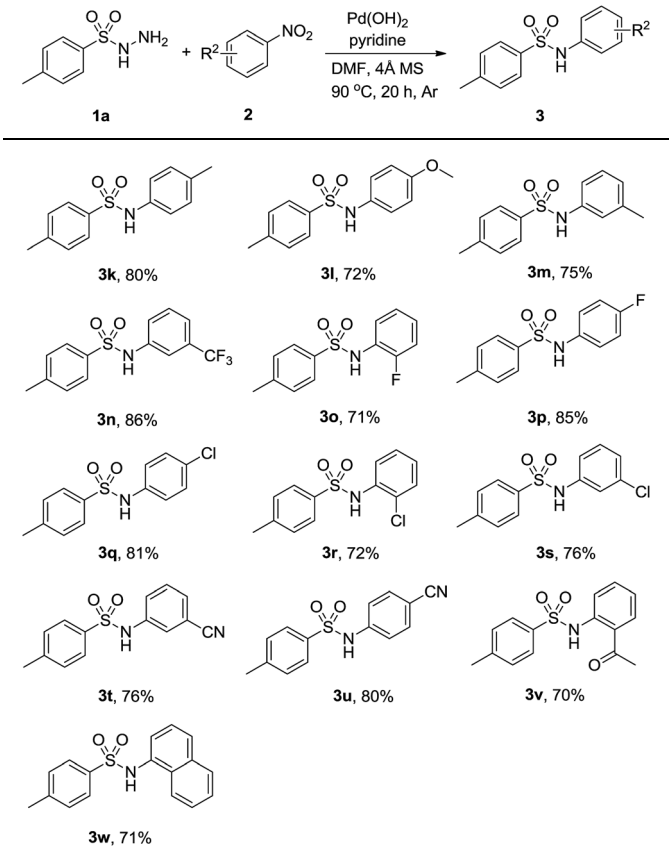
[a] Conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), catalyst (5 mol%), additive (0.2 mmol), solvent (0.8 mL), 90 °C, 20 h under air unless otherwise noted. [b] GC yield based on **2a**. [c] 100 mg 4 Å molecular sieves was added. [d] Under argon.

Table 2 Reaction of **2a** with various sulfonyl hydrazides (**1**)[a]



[a] Conditions: **1** (0.4 mmol), **2a** (0.2 mmol), $Pd(OH)_2$ (5 mol%), pyridine (0.2 mmol), DMF (0.8 mL), 4 Å MS (100 mg), 90 °C, 20 h, under argon; isolated yield based on **2a**.

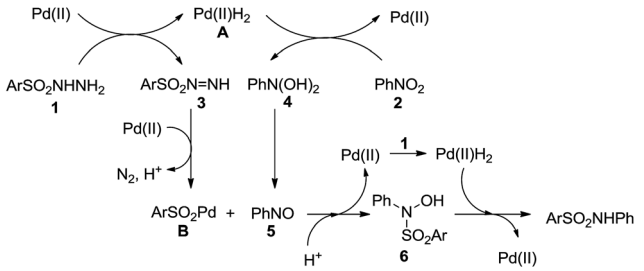
Table 3 Reaction of **1a** with various nitroarenes (**2**)[a]



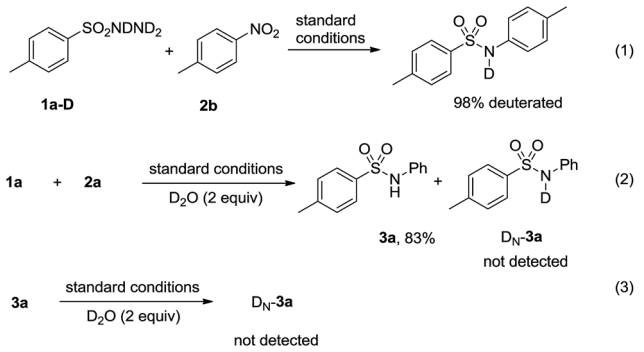
[a] Conditions: **1a** (0.4 mmol), **2** (0.2 mmol), $Pd(OH)_2$ (5 mol%), pyridine (0.2 mmol), DMF (0.8 mL), 4 Å MS (100 mg), 90 °C, 20 h, under argon; isolated yield based on **2**.

such as trifluoromethyl, fluoro and chloro were well tolerated under the optimized reaction conditions, and the target products were obtained in good yields (**3n–3s**). Other substrates bearing electron-withdrawing group such as cyano remained effective and gave the corresponding arylsulfonamides in good yields (**3t–3u**). Notably, when 1-(2-nitrophenyl)ethanone was subjected to this reaction system, the desired product could be achieved in 70% yield (**3v**). Finally, a more steric bulky substrate such as 1-nitronaphthelene also successfully afforded the product in 71% yield (**3w**).

For the mechanism of this transformation, we proposed a catalytic process that includes the following steps (Scheme 2). The reaction of arylsulfonyl hydrazide with a Pd catalyst results in a Pd complex **A** and sulfonyl diazene **3**, which is formed through successive hydrogen transferring and β-hydride elimination. In the presence of a Pd catalyst, liberation of N_2 and H^+ from **3** leads to the formation of arylsulfonylpalladium **B**.[18] On the other hand, nitrobenzene is reduced to nitrosobenzene with the help of complex **A**.[17,19] Then, the reaction of complex **B** with nitrosobenzene gives *N*-arylsulfonyl-*N*-phenylhydroxyamine **6**. At last, hydrogenation of **6** affords the desired product and regenerates the Pd catalyst.



Scheme 2 Proposed reaction mechanism.



Scheme 3 Deuterium labelling experiments.

To gain a mechanistic insight, deuterium labelling experiments were conducted and the results were summarized in Scheme 3. When $TsNDND_2$ (ref. 20) (**1a–D**) reacted with **2a** under the standard reaction conditions, *N*-deuterated product was obtained (Scheme 3, eqn (1)). When **1a** reacted with **2a** in the presence of D_2O, no deuterated product **3a** was observed (Scheme 3, eqn (2)). Treatment of **3a** with D_2O led to **3a** recovered and no deuterated **3a** was obtained (Scheme 3, eqn (3)). These results indicated that the hydrogen transfer process very likely proceeded according to the proposed mechanism.

Conclusions

In summary, we have developed a novel approach for the synthesis of *N*-arylsulfonamides from nitroarenes and arylsulfonyl hydrazides under palladium-catalysis conditions. Nitroarenes were reduced *in situ* by hydrogen released from arylsulfonyl hydrazides and no external reducing agent is necessary. The reaction showed good substrate scope and various functional groups such as halogens, acetyl, trifluoromethyl and cyano were well tolerated under the optimized reaction conditions. This method affords an efficient approach using readily available and stable nitroarenes for facile construction of *N*-arylsulfonamides under mild reaction conditions with good selectivity. Further investigations of the scope and mechanism for this transformation are undergoing in our laboratory.

Acknowledgements

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