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Synthesis of *N*-arylsulfonamides through a Pd-catalyzed reduction coupling reaction of nitroarenes with sodium arylsulfinates†

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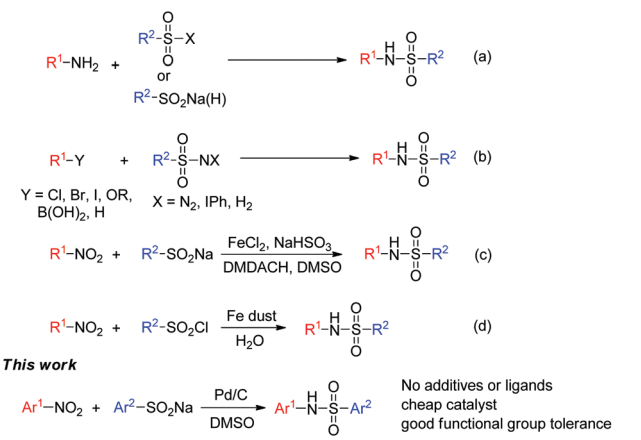
A novel one-step direct reductive coupling reaction between nitroarenes and sodium arylsulfinates was realized in the presence of an inexpensive Pd/C catalyst. In this procedure, readily available nitroarenes are employed as the nitrogen sources, and sodium arylsulfinates serve as both coupling partners and reductants. The method features high efficiency by using cheap Pd/C with low catalyst loading and good functional group tolerance in the absence of any additional reductants or ligands. This facile and mild synthetic method enables the high efficiency synthesis of functionalized *N*-arylsulfonamides from readily available substrates.

Introduction

N-Arylsulfonamides consist of a series of important functional scaffolds among biologically and medicinally active molecules.[1] Great efforts have been made to achieve their efficient preparation.[2] One of the most conventional methods to achieve the synthesis of *N*-arylsulfonamides involves the nucleophilic substitution of sodium sulfinates or sulfonyl chlorides with arylamines as the nitrogen sources (Scheme 1, path a).[3] Moreover, in the recent decades, the preparation of *N*-arylsulfonamides through transition-metal-catalyzed C–N bond formation has been established as a complementary strategy, which uses sulfonamides as nitrogen-based nucleophiles (Scheme 1, path b).[4] Notably, the oxidative S–N bond formation strategy by using thiols, disulfides and sulfonyl hydrazides as the sulfur sources has also been explored to be an alternative route to access the synthesis of *N*-arylsulfonamides.[5]

Nitroarenes, which are air-stable and readily available compounds, have been widely used as substrates in aromatic substitution, or as the precursors of arylamines and aryl halides.[6] In recent years, nitroarenes have been employed as the electrophilic coupling partner in transition metal catalyzed cross-coupling reactions.[7–11] Moreover, nitroarenes have also been explored as arylamine surrogates.[12] Considering that arylamines are generally prepared by the reduction of the corresponding nitroarenes, the employment of nitroarenes as the nitrogen source affords an atom economical and convenient strategy for assembly of *N*-containing functional molecules.

By using this strategy, Luo developed a novel Fe-catalyzed coupling reaction of sodium arylsulfinates with nitroarenes to synthesize *N*-arylsulfonamides by using $NaHSO_3$ as the reductant (Scheme 1, path c).[13] Recently, Xiang reported the reaction of sulfonyl halides with nitroarenes to form *N*-arylsulfonamides by using Fe dust which serves as the sole reductant (Scheme 1, path d).[14] These two Fe-mediated



Scheme 1 Synthetic methods for sulfonamides.

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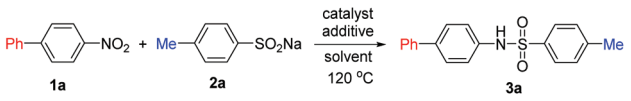
synthetic methods by using nitroarenes as the nitrogen sources require an external reductant or ligand. Thus, the concise and facile preparation of *N*-arylsulfonamides directly from nitroarenes under mild conditions is still highly desirable.[15] Considering the importance of sulfonamide scaffolds, we herein report the Pd-catalyzed direct reductive coupling reaction of nitroarenes and sodium arylsulfinates, which features the advantages of low loading of the inexpensive Pd/C catalyst and wide substrate scope, without exploring any external reductants or ligands.

Results and discussion

Initially, we treated 4-nitro-1,1′-biphenyl **1a** with sodium 4-methylbenzenesulfinate **2a** as the substrate in the Pd-catalyzed cross-coupling reaction in dimethyl sulfoxide (DMSO) at different temperatures. The corresponding *N*-arylsulfonamide **3a** was obtained in 38% isolated yield at 120 °C (entry 1), while only a trace product was observed at 80 °C. To optimize the reaction conditions, we tested various solvents including *N*-methyl-2-pyrrolidone (NMP), toluene and dioxane, and found that the reaction in DMSO gave the best result (entries 2–4). The addition of a range of external reductants, including $Na_2S_2O_3$, Na_2SO_3, NaHS, PPh_3 and $NaHSO_3$, could not increase the yield apparently (entries 5–9). To our delight, in terms of substrates, on increasing the loading of **2a** from 1.5 to 4.0 equiv., the yield of **3a** increased to 72% (entries 10–12). Subsequently, a series of palladium catalysts were examined in this coupling reaction. This reaction gave the highest yield by using the inexpensive Pd/C catalyst without the addition of any ligand (entry 14). Moreover, other common transition-metal catalysts were also tested in this transformation (entries 15–19). As a result, only copper(II) chloride served as an efficient catalyst and afforded **3a** in a moderate yield (entry 17). The control experiment indicated that the palladium catalyst was essential in this direct reductive coupling reaction (entry 20). The reaction was conducted under air or oxygen atmosphere, affording **3a** in 48% (entry 21) and 18% (entry 22) yields, respectively. This result demonstrates that an inert atmosphere is necessary for this coupling reaction. Besides, increasing of the **2a**/**1a** molar ratio could not enhance the yield of **3a** (entries 23 and 24).

With the optimized reaction conditions (Table 1, entry 14) in hand, we first evaluated the scope of the reactions of 4-nitro-1,1′-biphenyl **1a** or nitrobenzene **1b** with various substituted sodium arylsulfinates (Scheme 2, **3a–3j**). In most cases, these reductive coupling reactions by using 4-nitro-1,1′-biphenyl **1a** or nitrobenzene **1b** as the nitrogen source demonstrate good functional group tolerance. The sodium arylsulfinates bearing electron-donating and electron-withdrawing substituents on the aromatic rings successfully afford the corresponding *N*-arylsulfonamides in good to excellent yields, such as methyl (**3a**, **3h**, **3i**, and **3k**), halogen (**3c**, **3d**, **3j**, **3m**, and **3n**), methoxy (**3e**), cyano (**3f**), trifluoromethoxy (**3g**), and ethoxycarbonyl groups (**3o**). In the case of **3h**, the relatively low yield is

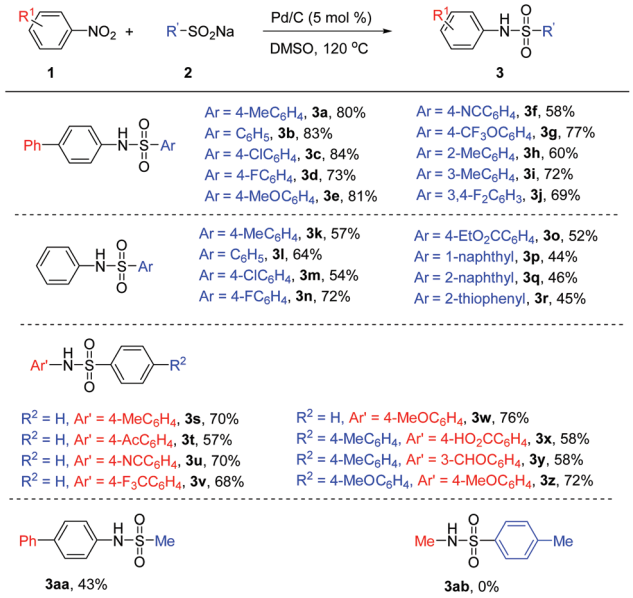
Table 1 Optimization of reaction conditions[a]



1a 2a 3a

Entry	Solvent	Ratio (**1a** : **2a**)	Catalyst (mol %)	Additive (equiv.)	Yield[b] (%)
1	DMSO	1 : 1.5	$PdCl_2$ (5)		38
2	NMP	1 : 1.5	$PdCl_2$ (5)		7
3	1,4-Dioxane	1 : 1.5	$PdCl_2$ (5)		15
4	Toluene	1 : 1.5	$PdCl_2$ (5)		Trace
5	DMSO	1 : 1.5	$PdCl_2$ (5)	$Na_2S_2O_3$ (0.5)	Trace
6	DMSO	1 : 1.5	$PdCl_2$ (5)	Na_2SO_3 (0.5)	34
7	DMSO	1 : 1.5	$PdCl_2$ (5)	NaHS (0.5)	0
8	DMSO	1 : 1.5	$PdCl_2$ (5)	PPh_3 (0.5)	18
9	DMSO	1 : 1.5	$PdCl_2$ (5)	$NaHSO_3$ (3.0)	41
10	DMSO	1 : 3	$PdCl_2$ (5)		59
11	DMSO	1 : 3.5	$PdCl_2$ (5)		68
12	DMSO	1 : 4	$PdCl_2$ (5)		72
13	DMSO	1 : 4	$Pd(PPh_3)_4$ (5)		Trace
14[c]	**DMSO**	**1 : 4**	**Pd/C (5)**		**80**
15	DMSO	1 : 4	$NiCl_2$ (10)		0
16	DMSO	1 : 4	$FeCl_2$ (20)		10
17	DMSO	1 : 4	$CuCl_2$ (10)		44
18	DMSO	1 : 4	$FeCl_3$ (10)		0
19	DMSO	1 : 4	$CoCl_2$ (10)		0
20	DMSO	1 : 4	—		0
21	DMSO	1 : 4	Pd/C (5)		48[d]
22	DMSO	1 : 4	Pd/C (5)		18[e]
23	DMSO	1 : 5	Pd/C (5)		72
24	DMSO	1 : 6	Pd/C (5)		68

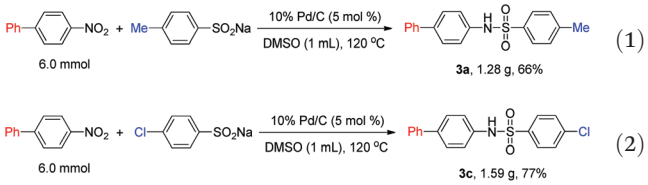
[a] Reaction conditions: 4-Nitro-1,1′-biphenyl **1a** (0.3 mmol, 1.0 equiv.), sodium 4-methylbenzenesulfinate **2a** (1.5 to 4.0 equiv.), solvent (1 mL), 120 °C, 12 h. [b] Isolated yields. [c] Pd/C (0.015 mmol, 5 mol%, [Pd/C] 10 wt%). [d] The reaction was conducted under air atmosphere. [e] The reaction was conducted under an oxygen atmosphere.



Scheme 2 Scope of substrates. Reaction conditions: nitroarenes (0.3 mmol, 1.0 equiv.), sodium aryl sulfinate (1.2 mmol, 4.0 equiv.), Pd/C (5 mol%, 10 wt%), DMSO (1 mL), 120 °C, 12 h.

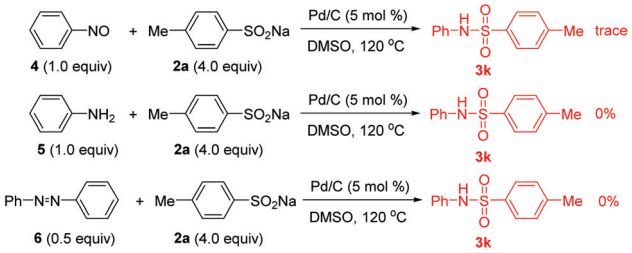
probably due to the steric hindrance. The major by-products during these transformations are the biaryl compounds, diaryl thioethers, and diaryl disulfides through the side reactions of sodium arylsulfinates **2**.[16] Moreover, the reactions of nitrobenzene with naphthyl and thiophenyl sulfinates are also implemented, smoothly affording the desired products (**3p**, **3q**, **3r**) in moderate yields. Subsequently, a series of substituted nitroarenes are subjected to this coupling reaction with sodium arylsulfinates. All in all, this transformation with sodium benzenesulfinate (**2b**) is tolerant to either electron-rich or -deficient substituents on the ring of the nitrobenzene moiety, affording methyl (**3s**), acyl (**3t**), cyano (**3u**), trifluoromethyl (**3v**), and methoxy group (**3w**) substituted sulfonamides in good yields. Furthermore, the carboxylate, formyl and methoxy derived nitrobenzenes are also employed as the substrates in this transformation with substituted sodium arylsulfinates, giving rise to highly functionalized *N*-arylsulfonamides in moderate to good yields (**3x–3z**). Notably, when sodium methanesulfinate was used as the substrate, the corresponding alkyl sulfonamide **3aa** was obtained in 43% yield. However, when nitromethane was used under standard conditions, no desired product (**3ab**) was observed.

To demonstrate the practical application of this method, this reductive coupling reaction was carried out on a gram scale for two sodium aryl sulfinate substrates with 4-nitro-1,1′-biphenyl **1a**. As shown in eqn (1) and (2), the corresponding *N*-arylsulfonamide derivatives (**3a**, **3c**) were successfully obtained in comparable good yields on about one gram scale.

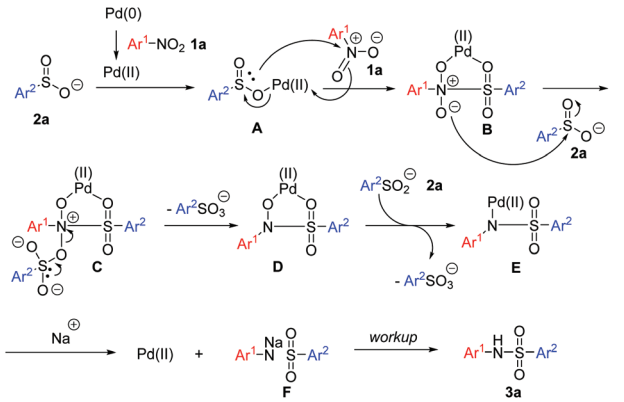


Subsequently, some control reactions were examined to obtain a better understanding of the details of the mechanism. In the reaction condition optimization, we found that the palladium catalyst exhibits higher efficiency than other transition metal catalysts, including iron, copper, nickel or cobalt complexes. In addition, nitrosobenzene (**4**), aniline (**5**) and azobenzene (**6**) were respectively subjected to this reductive coupling reaction under standard conditions within 12 hours. However, the reaction of nitrosobenzene (**4**) with **2a** only gave a trace amount of the desired product **3k**. We could not observe **3k** during the coupling reaction of aniline (**5**) or azobenzene (**6**) with **2a**. These results indicated that nitrosobenzene (**4**), aniline (**5**) or azobenzene (**6**) was not involved as the key intermediate in this reductive coupling reaction (Scheme 3).

Based on the above experimental investigation and the literature reported before,[13] a proposed mechanism was illustrated to account for this Pd-catalyzed reductive cross-coupling reaction. As shown in Scheme 4, we hypothesize that the Pd(0) species is oxidized to the Pd(II) species at first, which coordinated with sodium arylsulfinate **2a** to form palladium(II) arylsulfinic acid salt **A**. Then, Pd(II) facilitates the nucleophilic



Scheme 3 Control experiments.



Scheme 4 Possible reaction mechanism.

addition of the lone pair of the sulfur moiety to the nitro group of **1a**, generating a metallocyclic five-membered intermediate **B**. Next, **B** is reduced by the second molecule of **2a** to form intermediate **C**, followed by the release of the aryl sulfonate to afford intermediate **D**. Subsequently, **D** is reduced by the third molecule of **2a** to form palladium *N*-arylsulfonamide salt **E** along with the generation of the aryl sulfonate. Finally, the transmetallation and protonation afford *N*-arylsulfonamide **3a** and regenerate the Pd(II) active species. Although the effect of the palladium catalyst and the mechanistic details are still not clear, this plausible mechanism can rationalize the reaction pathway of this Pd-catalyzed direct coupling of nitroarenes with sodium arylsulfinates.

Experimental

General procedure for Pd-catalyzed reductive coupling reactions

Under a nitrogen atmosphere, sodium 4-methylbenzenesulfinate **2a** (1.2 mmol, 4.0 equiv., 214 mg), 4-nitro-1,1′-biphenyl **1a** (0.3 mmol, 1.0 equiv., 60 mg), and Pd/C (0.015 mmol, 5 mol%, 16 mg, [Pd/C] 10 wt%) were weighed in a 10 mL reaction tube. DMSO (1 mL) was then added in succession. The resulting reaction solution was stirred for 12 h at 120 °C. After cooling to room temperature, the reaction system was diluted with 5.0 mL of ethyl acetate, and washed with water (3 × 5.0 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude product, which was further purified by silica gel column chromato-

graphy (petroleum ether/ethyl acetate = 10 : 1 to 3 : 1) to obtain *N*-([1,1′-biphenyl]-4-yl)-4-methylbenzenesulfonamide (**3a**) in 80% isolated yield (78 mg) as a white solid.

Conclusions

In summary, we have developed a novel and concise synthetic method towards N–S bond construction through a Pd-catalyzed reductive cross-coupling reaction of sodium aryl sulfinates with nitroarenes. From two readily available substrates, the highly functionalized *N*-arylsulfonamides are facilely and directly obtained in one-step in good yields. The method features high efficiency by using cheap Pd/C with low catalyst loading, good functional group tolerance, and no participation of any additional reductants or ligands.

Conflicts of interest

There are no conflicts to declare.

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