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Rhodium-catalyzed *ortho*-cyanation of symmetrical azobenzenes with *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide†

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A rhodium-catalyzed *ortho*-cyanation of symmetrical azobenzenes is described employing *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide as an environmentally friendly cyanide source. The present protocol allows the synthesis of various benzonitrile derivatives in moderate to good yields and tolerates many useful functional groups.

The synthesis of aryl nitriles has attracted a great deal of attention because of the importance of cyano-containing compounds in chemistry and biology. The installation of the CN group into biologically active molecules may dramatically modify their properties. The nitrile moiety has also served as a valuable intermediate and an effective precursor for the synthesis of various functional group compounds such as aldehydes, ketones, amines, amidines, amides, carboxylic acids, and heterocycles.[1] Traditionally the synthesis of aryl nitriles was achieved by the Rosenmund–von Braun reaction,[2] the Sandmeyer reaction,[3] and catalytic cyanation of aryl halides.[4] Recently, considerable attention has been paid to direct cyanation of C–H bonds with metallic cyano-group sources[5] and "nonmetallic" organic cyano-group sources.[6] Representative examples of "nonmetallic" cyano-group sources include palladium catalyzed and copper mediated direct cyanation of aromatic compounds with nitromethane,[7] DMF/NH_3,[8] DMF,[9] TMSCN,[10] CH_3CN,[11] isonitrile,[12] azobisisobutyronitrile[13] and tosyl cyanide[14].

The $BF_3{\cdot}OEt_2$-catalyzed C–H cyanation of heteroarenes such as pyrroles and indoles was first reported by Wang using *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) as a new "nonmetallic" cyanating reagent.[15] It is noteworthy that NCTS could be readily and efficiently prepared *via* treatment of inexpensive phenylurea with *p*-toluenesulfonyl chloride.[16] However, the potential of NCTS as an electrophilic cyanating reagent in the C–H activation process was not evaluated until very recently.[17–20] In 2013, a rhodium-catalyzed cyanation reaction of arenes employing NCTS as an efficient cyanating reagent was developed by Fu[18] and Anbarasan[19] independently. Gu and co-workers also documented *ortho*-cyanation of arylphosphates with NCTS in the presence of rhodium catalyst and $AgSbF_6$ in 2014.[20] Although many significant advances have been achieved in this area, there are still few reports on rhodium-catalyzed cyanation of the C–H bond.

On the other hand, significant developments on azo-group-directed C–H functionalization of aromatic azo compounds, such as acylation, alkoxylation, halogenation and amidation, have been achieved.[21] However, the direct *ortho*-cyanation of azobenzene was not reported before. Based on the effectiveness of rhodium catalysis on C–H bond activation[22] and our continuing interest in the C–H functionalization of aromatic azo compounds,[23] we herein describe a rhodium-catalyzed C–H cyanation of symmetrical azobenzenes with NCTS as the cyanide source by the chelation effect of the azo group.

Initially, the cyanation of azobenzene (**1a**) with NCTS (**2**) was chosen as a model reaction to screen the reaction conditions. The results are summarized in Table 1. The reaction of azobenzene (**1a**) with NCTS (**2**) was first investigated in the presence of $[RhCp^*Cl_2]_2$, $AgSbF_6$ and $Cu(OAc)_2$ in 1,4-dioxane (entry 1). To our delight, the corresponding product **3a** was isolated in 26% yield. After surveying a series of solvents, such as DCE, toluene, DMSO and THF, DCE was found to be a good choice of solvent (entries 2–5). The yield of product **3a** could be obviously improved by changing the base to Ag_2CO_3, AgOAc and NaOAc. NaOAc was proved to be more efficient for this transformation. The effects of different additives were also evaluated. We found that altering the additive to $AgBF_4$ diminished the reactivity, whereas the use of $AgNTf_2$ increased the yield of product **3a** (entries 9 and 10). The *ortho*-cyanation reaction of **1a** with NCTS (**2**) was carried out at 120 °C, leading to the product **3a** in 69% yield using the ratio of **1a**/**2** (1 : 2) and 50 mol% of $AgNTf_2$ (entry 11). Finally, the effect of reaction

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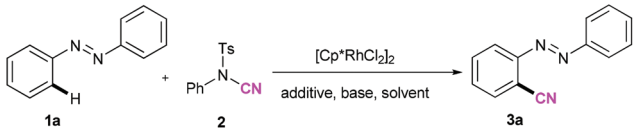
Table 1 Screening for optimal reaction conditions[a]



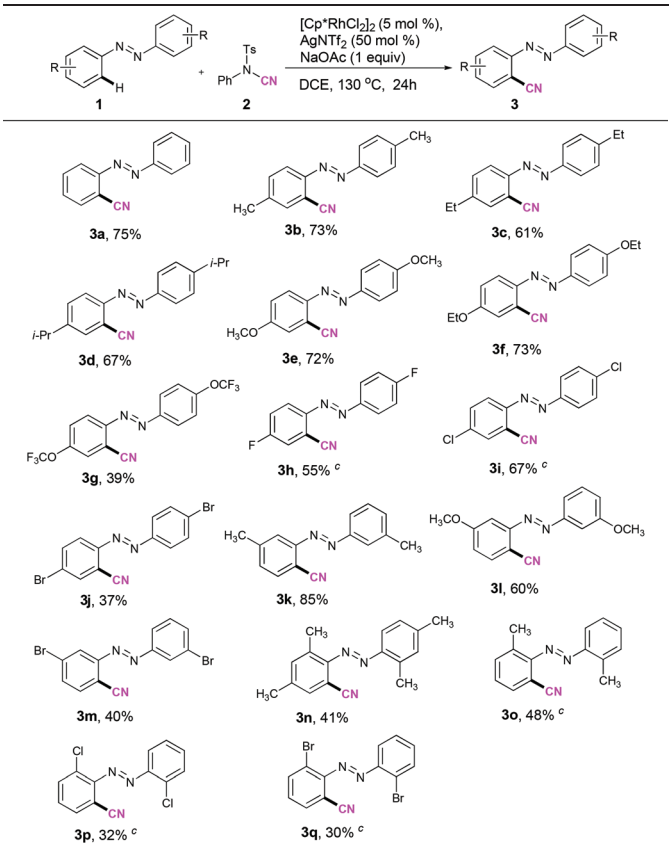
Entry	Additive	Base	Solvent	T (°C)	Yield[c] (%)
1	$AgSbF_6$	$Cu(OAc)_2$	1,4-Dioxane	120	26
2	$AgSbF_6$	$Cu(OAc)_2$	DCE	120	31
3	$AgSbF_6$	$Cu(OAc)_2$	Toluene	120	0
4	$AgSbF_6$	$Cu(OAc)_2$	DMSO	120	0
5	$AgSbF_6$	$Cu(OAc)_2$	THF	120	0
6	$AgSbF_6$	Ag_2CO_3	DCE	120	38
7	$AgSbF_6$	AgOAc	DCE	120	46
8	$AgSbF_6$	NaOAc	DCE	120	55
9	$AgBF_4$	NaOAc	DCE	120	0
10	$AgNTf_2$	NaOAc	DCE	120	60
11[b]	$AgNTf_2$	NaOAc	DCE	120	69
12[b]	**$AgNTf_2$**	**NaOAc**	**DCE**	**130**	**75 (68)**[d]
13[b]	$AgNTf_2$	NaOAc	DCE	110	60

[a] Reaction conditions: **1a** (0.15 mmol), **2** (1 equiv.), $[Cp^*RhCl_2]_2$ (5 mol%), base (1 equiv.) and additive (20 mol%) in solvent (1.0 mL) at 120 °C for 24 h. [b] Reaction conditions: **1a** (0.15 mmol), **2** (2 equiv.), $[Cp^*RhCl_2]_2$ (5 mol%), $AgNTf_2$ (50 mol%) and NaOAc (1 equiv.) in DCE at indicated temperature for 24 h. [c] Isolated yield. [d] The cyanation reaction was performed on a 1 mmol scale.

temperature on the reaction was investigated. Higher reaction temperature could further improve the efficiency of this transformation, but a lower yield of product **3a** was obtained when the reaction proceeded at 110 °C (entries 12 and 13). It should be noted that the cyanation reaction of **1a** with NCTS (**2**) could be carried out to give **3a** in 68% yield on a 1 mmol scale without the lack of activity.

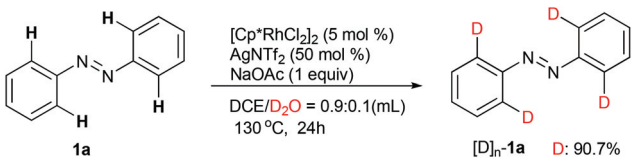
Having established the optimal conditions for rhodium-catalyzed *ortho*-cyanation of azobenzene, we then extended the reaction with a variety of substrates to evaluate the scope of this protocol. As shown in Table 2, a series of azobenzene derivatives **1** were found to participate in the reaction, affording the corresponding aryl nitriles **3** in a satisfactory yield. For example, the *para*-substituted substrates with methyl, ethyl or isopropyl underwent this reaction to furnish the corresponding products (73% for **3b**; 61% for **3c**; 67% for **3d**, respectively). Azobenzene with a methoxy or ethoxy group gave the cyanated products **3e** and **3f** in 72% and 73% yields, respectively, but the substrate with a trifluoromethoxy group afforded the product **3g** in 39% yield. Further studies showed the presence of a halogen atom such as fluoro, chloro or bromo was unfavorable to this cyanation reaction. Only when 100 mol% $AgNTf_2$ was used under optimized conditions, could the cyanated products **3h** and **3i** be isolated in moderate yield (55% for **3h** and 67% for **3i**). In these cases, the starting materials were recovered after the reaction finished. These results indicated that the direct cyanation of aromatic azo compounds possessing electron-donating groups was more effective than those with electron-withdrawing groups. The electronic effect of substituents on this cyanation reaction was

Table 2 Substrate scope for direct C–H cyanation of substituted azo compounds with NCTS[a,b,c]

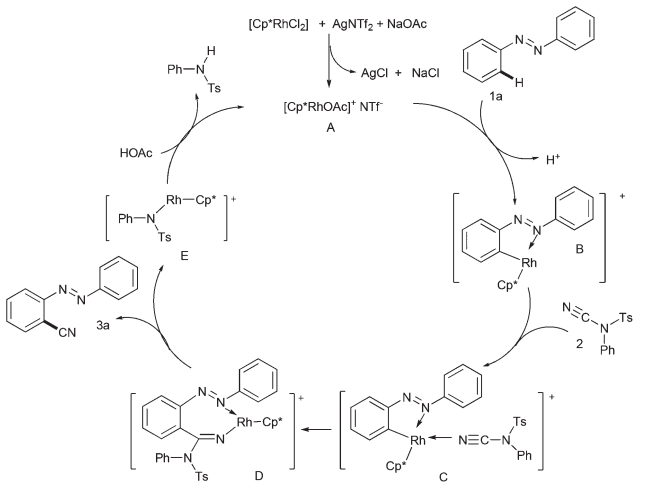


[a] Reaction conditions: **1** (0.15 mmol), **2** (1.5 equiv.), $[Cp^*RhCl_2]_2$ (5 mol%), $AgNTf_2$ (50 mol%) and NaOAc (1 equiv.) in DCE (1 mL) at 130 °C for 24 h. [b] Isolated yield. [c] $AgNTf_2$ (100 mol%) was used.

further extended to other substrates. The *meta*-substituted (Me, OMe) azobenzene reacted with NCTS (**2**) smoothly to give cyanated products **3k** and **3l** in 85% and 60% yields, while the *meta*-bromo-substituted azobenzene provided the corresponding product **3m** in 40% yield. Compared with *p*-methyl-substituted azobenzene **1b**, 2,4-dimethyl-substituted azobenzene **1n** was treated with NCTS (**2**) to provide the corresponding product **3n** in 41% yield, which was due to the steric hindrance effect from methyl at the *ortho* position of azobenzene. The *ortho*-substituted substrates could also be cyanated in our cyanation methodology and led to the desired products **3o–q** in lower yields (48% for **3o**; 32% for **3p**; 30% for **3q**, respectively), albeit with the use of 100 mol% $AgNTf_2$.



Scheme 1 The H/D exchange experiment of **1a**.



Scheme 2 Proposed mechanism.

To obtain some insight into this cyanation reaction mechanism, the H/D exchange experiment was performed (Scheme 1). When D_2O was subjected to the reaction mixture, a remarkable H/D exchange of the recovering substrate $[D]_n$-**1a** was observed. This demonstrated that the cyanation reaction was typical of the rhodium-catalyzed C–H bond activation process.

On the basis of the above result and previous related studies,[18–20] a possible mechanism for the newly developed cyanation protocol is proposed, as shown in Scheme 2. First, treatment of a rhodium precursor with $AgNTf_2$ and NaOAc generates the reactive cationic rhodium(III) species **A**, which reacted with azobenzene (**1a**) to obtain the cyclic rhodium species **B** with a vacant coordination site. Then coordination of NCTS (**2**) with rhodium species **B** provides intermediate **C**, followed by insertion of the CN group into the C–Rh^{III} bond generating **D**. Subsequent rearrangement of **D** leads to the cyanated product (**3a**) and reactive rhodium species **E**. Finally, active rhodium species **A** participates in the next catalytic cycle after the ligand exchange.

In conclusion, we have developed a useful synthetic method of aryl nitriles *via* rhodium-catalyzed *ortho*-cyanation of symmetrical azobenzenes with NCTS as the "nonmetallic" cyanide source by azo-group-directed C(sp^2)–H bond activation. The reaction exhibited functional group tolerance because azobenzene with either electron-donating or electron-withdrawing groups could be directly cyanated to provide important aromatic azo compounds with a cyano-group, which have a broad utility in organic synthesis.

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