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Rhodium-Catalyzed Directed C−H Cyanation of Arenes with *N*-Cyano-*N*-phenyl-*p*-toluenesulfonamide

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Supporting Information

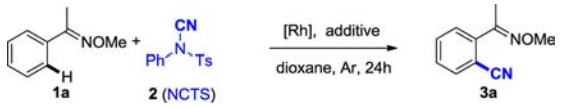
ABSTRACT: A Rh-catalyzed directed C−H cyanation reaction was developed for the first time as a practical method for the synthesis of aromatic nitriles. *N*-Cyano-*N*-phenyl-*p*-toluenesulfonamide, a user-friendly cyanation reagent, was used in the transformation. Many different directing groups can be used in this C−H cyanation process, and the reaction tolerates a variety of synthetically important functional groups.

The introduction of a CN group onto the aromatic rings of biologically active compounds or other functional molecules may dramatically modify their properties.[1] As a result, the development of new methods to build aryl−CN bonds has been intensively studied in synthetic organic chemistry.[2] While earlier studies in this field usually relied on the use of very toxic reagents such as KCN, $Zn(CN)_2$, and CuCN,[3] recent attention has been turned to more benign and user-friendly cyanation reagents such as $K_3Fe(CN)_6$ and *N*,*N*-dimethylformamide (DMF).[4] At present, an interesting challenge is to employ these new cyanation reagents in catalytic arene C−H functionalization reactions.[5] For instance, Cu-[6] and Pd-catalyzed[7] C−H cyanation reactions of 2-arylpyridines with CH_3NO_2 and DMF/NH_3, respectively, as the CN source and a Pd-catalyzed 3-cyanation reaction of indoles using DMF as the CN source[8] have been reported. However, further development of user-friendly C−H cyanation reactions [particularly ones using other transition-metal (TM) catalysts] is needed to expand the scope and utility of this category of synthetically valuable transformations.

In this context, we were interested in the use of Rh catalysts for directed cyanation of aromatic C−H bonds. Our study was inspired by the recent reports that Rh catalysts can complement other transition metals for C−H functionalization in terms of selectivity, substrate scope, and functional group compatibility.[9] After several attempts, we found that *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS),[10] a less toxic, easily handled, and bench-stable crystalline salt, is a practical reagent for Rh-catalyzed C−H cyanation.[11] It can be readily synthesized with a low cost via treatment of phenylurea with *p*-toluenesulfonyl chloride.[12] Very recently, Beller and co-workers reported cyanation reactions of arylboronic acids and Grignard reagents with NCTS.[13] Here we describe the first example of Rh-catalyzed C−H cyanation with NCTS. Significantly, many different directing groups (e.g., oxime, pyridine, pyrazole) can be employed in this new C−H cyanation reaction, and the C−H activation process tolerates a variety of synthetically important functional groups (e.g., sulfane, unprotected phenol, Ar−I, epoxide) that would be challenging with other TM catalysts.

We chose the C−H cyanation of acetophenone *O*-methyl oxime (**1a**) with NCTS as a model reaction. When **1a** was treated with $[RhCp^*Cl_2]_2$, $AgSbF_6$, and NCTS (**2**) in dioxane at 110 °C for 24 h, the desired ortho-cyanated product **3a** was obtained in 35% yield (Table 1, entry 1). The catalysts $[RhCp^*(CH_3CN)_3](SbF_6)_2$ and $Cp^*Rh(OAc)_2$ gave higher yields (48 and 37%, respectively) even in the absence of $AgSbF_6$ (entries 2 and 3). Changing the additive to $Cu(OAc)_2$, AgOAc, KOAc, or HOAc diminished the reactivity (entries 4−7), whereas the use of Ag_2CO_3 increased the yield to 56% (entry 8). Increasing the reaction temperature to 120 °C further improved the yield to

Table 1. Optimization of the Reaction Conditions[a]



1a 2 (NCTS) 3a

entry	[Rh] (5 mol %)	additive (20 mol %)	*T* (°C)	yield (%)[b]
1	$[RhCp^*Cl_2]_2$	$AgSbF_6$	110	35
2	$[RhCp^*(CH_3CN)_3](SbF_6)_2$	–	110	48
3	$Cp^*Rh(OAc)_2$	–	110	37
4	$[RhCp^*(CH_3CN)_3](SbF_6)_2$	$Cu(OAc)_2$	110	0
5	$[RhCp^*(CH_3CN)_3](SbF_6)_2$	AgOAc	110	42
6	$[RhCp^*(CH_3CN)_3](SbF_6)_2$	KOAc	110	0
7	$[RhCp^*(CH_3CN)_3](SbF_6)_2$	HOAc	110	19
8	$[RhCp^*(CH_3CN)_3](SbF_6)_2$	Ag_2CO_3	110	56
9	$\mathbf{[RhCp^*(CH_3CN)_3](SbF_6)_2}$	$\mathbf{Ag_2CO_3}$	**120**	**86**
10	$[RhCp^*(CH_3CN)_3](SbF_6)_2$	Ag_2CO_3	100	21
11	$[RhCp^*(CH_3CN)_3](SbF_6)_2$	–	120	81
12	–	$BF_3{\cdot}OEt_2$	120	0
13	–	–	120	0

[a]All of the reactions were carried out with 0.2 mmol of **1a** and 0.4 mmol of **2** in 1 mL of dioxane. [b]Isolated yields.

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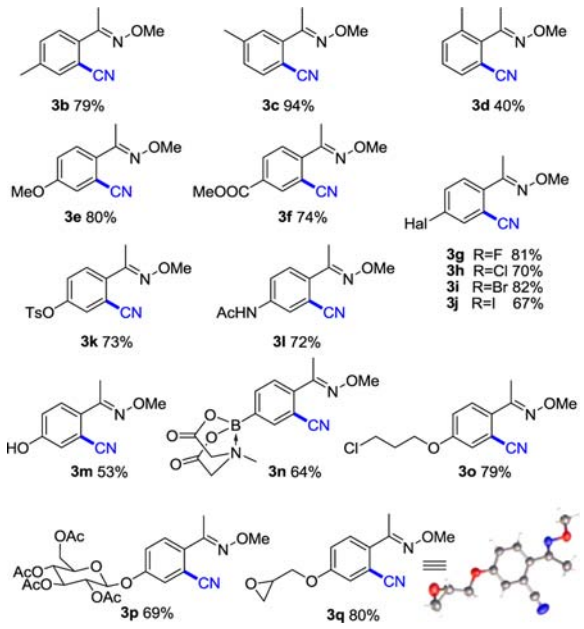
86% (entry 9). Without Ag_2CO_3, the yield was slightly lower (81%; entry 11). In view of a recent report that $BF_3{\cdot}OEt_2$ can catalyze the direct cyanation of indoles and pyrroles,[11] we carried out a control experiment showing that the present reaction does not proceed through a Lewis acid-promoted electrophilic aromatic substitution process (entry 12). Furthermore, without adding Rh catalyst we obtained no product (entry 13).

With the optimized reaction conditions in hand, we examined the effect of substrate substitution on the reaction (Table 2).

Table 2. Scope of Aryl Ketone Oximes[a]



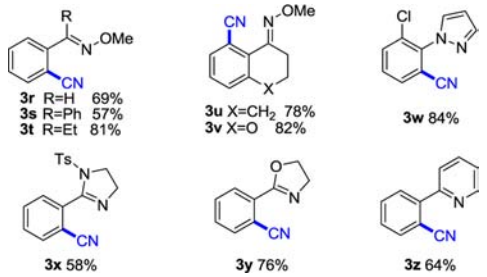
[a]Reactions were carried out at 120 °C for 24 h on a 0.2 mmol scale. Isolated yields are shown.

First, for the *O*-methyl oximes of methylated acetophenones, the 4-Me derivative gave a 79% isolated yield of **3b** and the 3-Me derivative afforded the less sterically crowded isomer **3c** in 94% yield. In contrast, the 2-Me derivative gave a much lower yield of **3d** (40%), possibly because the 2-Me group interfered with the formation of the five-membered rhodacycle intermediate.[14] As to the electronic effect of the substituents, both electron-donating (**3e**) and -withdrawing (**3f**) groups could be tolerated. Moreover, the halogen and OTs substituents were well-compatible with the Rh-catalyzed process (**3g**–**k**), enabling additional functionalization at these positions. Thus, the present reaction is complementary to previous cyanation methods involving TM-catalyzed cross-coupling.[4g,6−8]

Interestingly, when an acetamide group was present in the substrate, the C−H cyanation reaction occurred only at the position ortho to the oxime residue (**3l**). Furthermore, the reaction tolerated an unprotected phenol group (**3m**). A recent study described the Rh-catalyzed cyanation of arylboronic acids with NCTS.[13] Here we found that an *N*-methyliminodiacetic acid (MIDA)-protected boronic acid[15] easily survived the C−H cyanation process to afford **3n**, a MIDA boronate building block ready for further transformations. In the case of a substrate containing an alkyl−Cl moiety, the present cyanation reaction selectively introduced a CN group without affecting the C−Cl bond (**3o**). Such selectivity would be rather difficult to achieve using the conventional nucleophilic cyanation reagents. We also found that the C−H cyanation process could be applied to a glycoconjugate (**3p**). Finally, we were surprised to find that an epoxide group smoothly survived the cyanation process, as confirmed by X-ray analysis of the product (**3q**). This finding is synthetically interesting because epoxides are useful groups for additional functionalization and very few TM-catalyzed C−H activation reactions are compatible with epoxides.

To explore the scope of other directing groups in this Rh-catalyzed C−H cyanation process, we first tested several different *O*-methyl oximes (Table 3). Both acyclic and cyclic *O*-methyl

Table 3. Scope of Other Directing Groups[a]

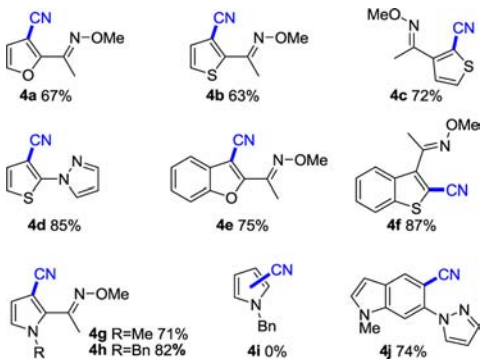


[a]The reactions were carried with substrate (0.2 mmol), **2** (0.4 mmol), $[RhCp^*(CH_3CN)_3](SbF_6)_2$ (5 mol %), and Ag_2CO_3 (20 mol %). See the Supporting Information (SI) for details.

oximes can be used in the reaction to generate the desired ortho-cyanated products in modest to good yields (**3r**–**v**). This finding is synthetically valuable because *O*-methyl oximes are derived from ketones. More gratifyingly, other N-based directing groups were also found to be useful in the transformation. For instance, using pyrazole as the directing group gave the C−H cyanation product **3w** in 84% yield despite the presence of a potentially reactive Cl in the substrate. In addition, using dihydroimidazole, dihydrooxazole, or pyridine as the directing group also afforded the desired products (**3x**–**z**). Our data indicate that the present Rh-catalyzed C−H cyanation process is a rather general reaction that can be extended to many more directing groups.

Heteroaromatic compounds are highly interesting as building blocks in drug design. Accordingly, we were interested to see whether the Rh-catalyzed C−H cyanation reaction could be used to synthesize cyanated aromatic heterocycles (Table 4). We were delighted to find that furan (**4a**, **4e**), thiophene (**4b**–**d**, **4f**), pyrrole (**4g**, **4h**), and indole (**4j**) derivatives were successfully cyanated when a directing group (either an oxime version of the acyl group or an N-heterocycle) was available. In the case of **4c**, cyanation occurred only at the 2-position and not at the 4-

Table 4. Cyanation of Aromatic Heterocycles[a]



[a]See the SI for details.

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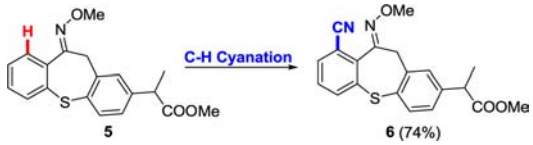
position. Furthermore, when no directing group was present, the C−H cyanation reaction did not take place (**4i**).

To test the application of the new C−H cyanation reaction to complex bioactive molecules, we converted zaltoprofen (a nonsteroidal anti-inflammatory drug) to its *O*-methyl oxime methyl ester derivative **5**. When **5** was subjected to the Rh-catalyzed C−H cyanation process, we successfully obtained **6** in 74% isolated yield (Scheme 1). Significantly, although thioethers

Scheme 1. Cyanation of Zaltoprofen Derivative 5[a]

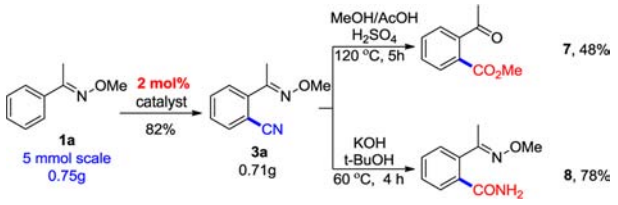


[a]The optimized conditions (see Table 1, entry 9) were used.

impede many TM-catalyzed reactions, the thioether moiety in **5** was well-tolerated in the Rh-catalyzed C−H cyanation process. This result indicates that the new C−H cyanation process may be useful for the rapid generation of derivatives of bioactive compounds.

In a scaled-up experiment (5 mmol scale, Scheme 2), we found that the catalyst loading could be lowered to 2 mol % while

Scheme 2. A Larger-Scale C−H Cyanation Reaction



maintaining a satisfactory yield (82%). The CN group in the product **3a** was converted to the ester and amide groups in **7** and **8** through acid and base treatments, respectively. Moreover, product **9** obtained by C−H cyanation of 1-phenylpyrazole (Scheme 3) was readily reduced to benzylamine **10**, which was

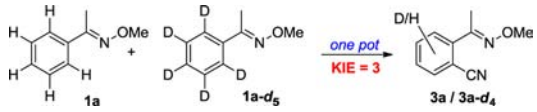
Scheme 3. Introduction of an Aminomethyl Group

previously used as a key intermediate for the development of thrombin inhibitors.[16] Thus, the Rh-catalyzed C−H cyanation reaction is synthetically useful because CN can be readily converted to various functional groups.

To comprehend the mechanism of the reaction, we carried out a kinetic isotope effect (KIE) experiment.[17] When a 1:1 mixture of **1a** and **1a**-d_5 was subjected to the Rh-catalyzed reaction conditions, we obtained the cyanation products **3a** and **3a**-d_4 in a ratio of 3:1 (Scheme 4). This KIE value of 3 is typical of Rh-catalyzed C−H activation processes.

On the basis of the above KIE experiment, we propose the mechanism shown in Figure 1. First, the Rh(III) catalyst reacts with the substrate (**1a**) through a C−H activation step (mostly likely via a concerted metalation−deprotonation process) to

Scheme 4. Measurement of the Kinetic Isotope Effect



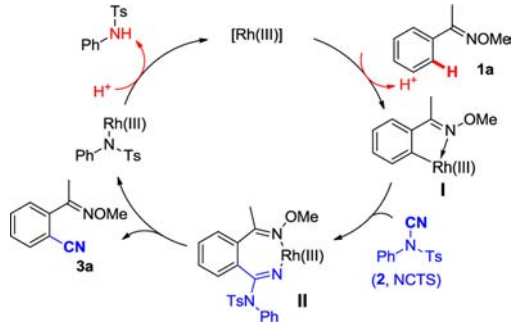


Figure 1. Proposed mechanism.

generate five-membered rhodacycle intermediate **I**.[18] NCTS then coordinates to Rh(III) in **I**, after which insertion of the C≡N moiety into the C−Rh(III) bond produces **II**. Finally, elimination of a tosylaniline-coordinated Rh(III) complex from **II** generates the product (**3a**), and the Rh(III) complex is returned to the catalytic cycle.

To summarize, we have developed an unprecedented Rh-catalyzed C−H cyanation reaction that uses less toxic and readily available *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) as the cyanation reagent. This transformation extends the concept and scope of the recently popularized Rh-catalyzed C−H functionalization reactions. Many different directing groups (e.g., oxime, pyridine, pyrazole) can be used in this C−H cyanation process. The reaction also tolerates a variety of synthetically important functional groups (e.g., unprotected phenol, Ar−I, epoxide) that are challenging with other TM catalysts (e.g., Pd). A number of aromatic and heteroaromatic nitriles were successfully synthesized using the new method. Because CN can be readily converted to many other synthetically useful groups, the present reaction may provide a practical tool for rapid derivatization of functional molecules.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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