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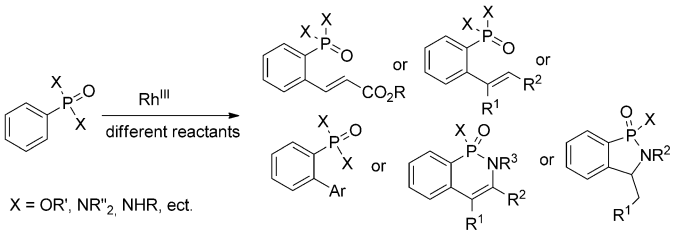
Rhodium Catalyzed *ortho*-Cyanation of Arylphosphates with *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide

Li-Jun Gu,*[a] Cheng Jin,[b] Rui Wang,[a] and Hong-Yan Ding[a]

A rhodium-catalyzed cyanation of chelation assisted C–H bonds is described. This process provided a useful method for the preparation of diverse 2-cyanated arylphosphonate and related compounds in good yields. The reaction tolerates a variety of synthetically important functional groups.

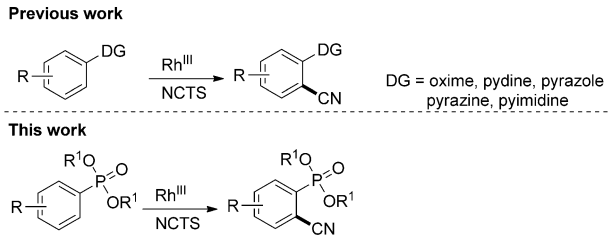
The development of novel methods for the preparation of aryl nitriles is of long-standing interest to organic chemists because of the importance of these compounds in chemistry and biology.[1] Furthermore, they can serve as synthetic scaffolds to a diverse array of building blocks such as aldehydes, ketones, amides, carboxylic acids, and amines. Consequently, the development of synthetic methods for the preparation of aryl nitriles has received considerable attention.[2–5] Traditionally, direct cyanations are achieved through the replacement approach, in which aryl nitriles are obtained by introducing a nitrile group through Sandmeyer reaction of aryldiazonium salts or by the transition-metal-mediated cyanation of aryl halides with a cyanide source.[6] However, general problems in these reactions are the use of expensive aryl halides, highly toxic cyanating reagents, high catalyst loading due to the cyanide poisoning or need for superstoichiometric amounts of additives (generally metal salts), and harsh reaction conditions.[7] Alternatively, aryl nitriles can be prepared by the dehydration approach, for example, dehydration of aryl amides or oximes,[2a,-b,3a,b] or oxidative dehydration of benzylic amines or alcohols with ammonia.[9–10] Selective cyanation of highly abundant C–H bonds with a suitable reagent is probably the most economic and benign route to the synthesis of aryl nitrile derivatives. For instance, Cu- and Pd-catalyzed 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 have been reported. In 2013, Fu and Anbarasan independently reported a Rh-catalyzed C–H cyanation reaction employing *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) as an efficient cyanating reagent.[11–13] Recently, Jiao and co-workers report a new and direct silver-catalyzed nitrogenation reaction of alkynes to nitriles through C–C bond cleavage.[14] Despite these advances, versatile and efficient methods for the direct construction of aryl–CN bonds that are compatible with various functional groups and use readily available starting materials remain highly desirable.

Organophosphorus compounds are important structural motifs frequently found in pharmaceuticals, natural products, biologically active molecules, and organic functional materials, and their functionalization has been attracting great interest in the synthetic organic chemistry community.[15] Recently, several examples on the phosphoryl-related compounds as the directing group for C–H activation have been reported (Scheme 1).[16]



Scheme 1. Phosphoryl-related directing groups in Rh^{III} catalysis.

In this context, we were interested in the use of phosphates as the directing groups for Rh-catalyzed aromatic C–H bonds (Scheme 2). Our study was inspired by the recent reports that



Scheme 2. Evolution of the rhodium-catalyzed *ortho*-selective C-H cyanation of diverse benzene derivatives.

phosphates can complement other directing groups for C–H functionalization in terms of substrate scope, and functional group compatibility.[17] In connection with our broader interest in transition-metal-catalyzed reaction,[15e,f,18] herein we describe the first example of Rh-catalyzed C–H cyanation with NCTS using arylphosphonate as the directing group.[19]

[a] *L.-J. Gu, R. Wang, H.-Y. Ding*
Key Laboratory of Chemistry in Ethnic Medicinal Resources
State Ethnic Affairs Commission & Ministry of Education
Yunnan University of Nationalities
Kunming, Yunnan, 650500 (P.R. China)
E-mail: gulijun2005@126.com

[b] *C. Jin*
New United Group Company Limited
Changzhou, Jiangsu, 213166 (P.R. China)

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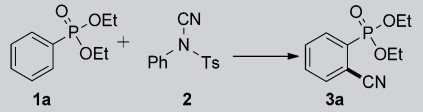
Table 1. Optimization of the reaction conditions.[a]



1a 2 3a

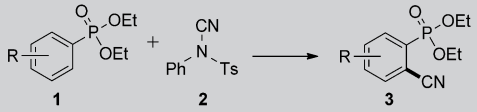
Entry	Catalyst	Additive	Solvent	Yield [%][b]
1	$[RhCp^*(CH_3CN)_3]\cdot(SbF_6)_2$	Ag_2CO_3	1,4-dioxane	31
2	$[Cp^*Rh(OAc)_2]$	Ag_2CO_3	1,4-dioxane	18
3	$[RhCp^*Cl_2]_2$	Ag_2CO_3	1,4-dioxane	51
4	$[RhCp^*Cl_2]_2$	Ag_2CO_3	toluene	43
5	$[RhCp^*Cl_2]_2$	Ag_2CO_3	DCE	62
6	$[RhCp^*Cl_2]_2$	Ag_2CO_3	MeCN	19
7	$[RhCp^*Cl_2]_2$	Ag_2CO_3	xylene	49
8	$[RhCp^*Cl_2]_2$	Ag_2CO_3	DMF	trace
9	$[RhCp^*Cl_2]_2$	Ag_2CO_3	DCE	68
10	$[RhCp^*Cl_2]_2$	HOAc	DCE	0
11	$[RhCp^*Cl_2]_2$	$AgSbF_6$	DCE	77
12	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	DCE	16
13	$[RhCp^*Cl_2]_2$	none	DCE	22
14	none	$AgSbF_6$	DCE	0

[a] Reaction conditions: **1a** (0.3 mmol), **2** (0.6 mmol), catalyst (5 mol%), additive (15 mol%), solvent (2 mL), 24 h, 110 °C under argon atmosphere. [b] Isolated yield.

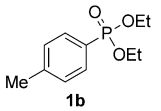
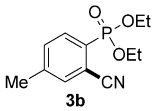
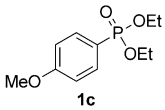
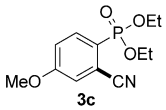
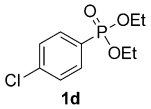
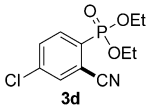
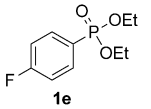
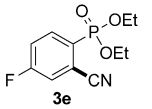
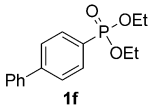
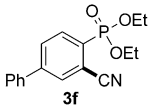
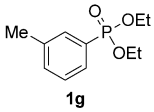
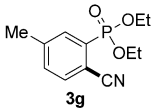
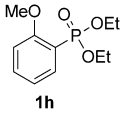
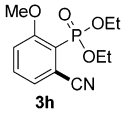
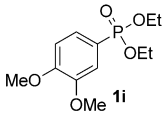
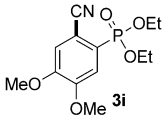
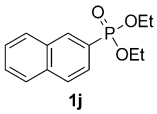
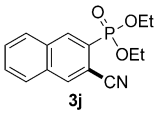
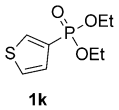
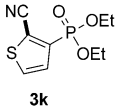
In the initial phase of this study we investigated the reaction of diethyl phenylphosphonate **1a** with NCTS **2** in the presence of $[RhCp^*Cl_2]_2$ (5% mol), Ag_2CO_3 (15% mol) in 1,4-dioxane at 115 °C with stirring for 18 h. The desired product diethyl 2-cyanophenylphosphonate **3a** was isolated with 31% yield (Table 1, entry 1). The catalyst $[RhCp^*Cl_2]_2$ provided the best results (Table 1, entries 1–3). The influence of solvent on the reaction efficiency was also significant; when 1,2-dichloroethane (DCE) was chosen as the solvent, the yield was enhanced to 62% (Table 1, entries 4–8). Increasing the reaction temperature to 125 °C further improved the efficiency of this transformation (Table 1, entry 9). Of the additives tested, $AgSbF_6$ proved particularly suitable (Table 1, entries 9–12). In the absence of $AgSbF_6$ the desired product was obtained in a low yield (Table 1, entry 13). Without the Rh catalyst, none of the desired product was obtained (Table 1, entry 14).

With the optimized reaction conditions, we next investigated the generality of the Rh-catalyzed cyanation with a variety of arylphosphonates **1**. As summarized in Table 2, a series of arylphosphonate **1** were found to participate in the reaction, affording the corresponding aryl nitriles in moderate to good yields. For example, arylphosphonate bearing electron-rich (methoxy, methyl) and electron-deficient (halogen, phenyl) substituents on the aryl ring underwent this reaction to furnish the corresponding products in generally moderate to good yields (60–78%). Substituent at the *para* position of the phenyl ring afforded the desired product smoothly and substituent at the *meta* position of the phenyl ring afforded the less sterically crowded isomer **3g** in 74% yield. However, *ortho*-substituted derivative **1h** gave a much lower yield of **3h** (Table 2, entry 7). These results indicated that the steric effects affected the efficiency of the reactions. Interestingly, the polysubstituted arylphosphonate derivative gave the desired oxidative product **2i** with a good yield. In addition, arylphosphonates with a naphthyl group (**1j**) also participated in this Rh-catalyzed cyanation, affording C3-cyanated product in 53% yield. Notably, the introduction of heterocycles into this system made this methodology more useful for the preparation of pharmaceuticals and ma-

Table 2. Scope of arylphosphonates **1**.[a]



1 2 3

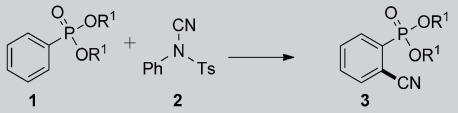
Entry	Arylphosphonates	Product	Yield [%][b]
1	 1b	 3b	78
2	 1c	 3c	69
3	 1d	 3d	71
4	 1e	 3e	62
5	 1f	 3f	60
6	 1g	 3g	74
7	 1h	 3h	44
8	 1i	 3i	71
9	 1j	 3j	53
10	 1k	 3k	56

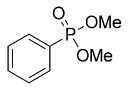
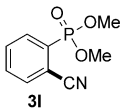
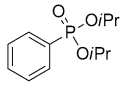
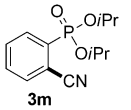
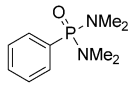
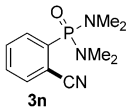
[a] Reaction conditions: **1** (0.3 mmol), **2** (0.6 mmol), $[RhCp^*Cl_2]_2$ (5 mol%), $AgSbF_6$ (15 mol%), DCE (2 mL), 24 h, 110 °C under argon atmosphere. [b] Isolated yield.

terials (Table 2, entry 10). In this case, cyanation occurred only at the 2-position and not at the 4-position.

The subsequent screening of various arylphosphonate-based chelating groups was also examined under the optimized rhodium catalyzed cyanation conditions. Dimethyl phenylphosphonate **1e** could be smoothly converted into the expected product **3e** in 54% yield. Diisopropyl phenylphosphonate **1f** could also efficiently furnish the desired product in a good yield (Table 3, entry 2). To highlight the utility of this transformation, a bulky phosphonic diethylamino group was subjected to the standard reaction conditions. The desired product was isolated in a moderate yield (Table 3, entry 3).

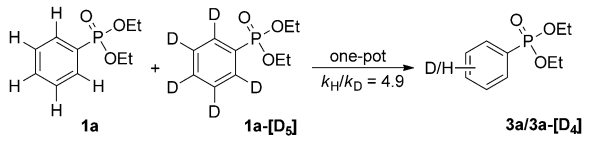
Table 3. Scope of other directing groups.[a]



Entry	Arylphosphonates	Product	Yield [%][b]
1	 1l	 3l	76
2	 1m	 3m	62
3	 1n	 3n	54

[a] Reaction conditions: **1** (0.3 mmol), **2** (0.6 mmol), catalyst (5 mol%), additive (15 mol%), DCE (2 mL), 24 h, 110 °C under argon atmosphere. [b] Isolated yield.

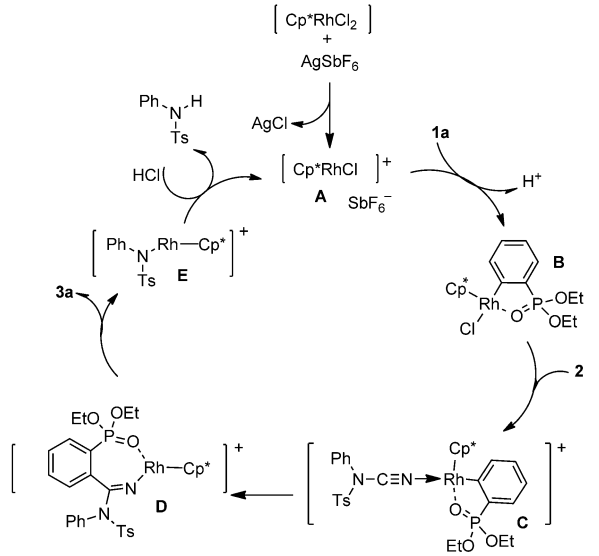
To shed more light on the reaction mechanism, a deuterium-labeling experiment was were performed (Scheme 3).[12,16a] When a 1:1 mixture of **1a** and **1a-[D_5]** was subjected to the



Scheme 3. Deuteration experiment.

Rh-catalyzed reaction conditions, we obtained the cyanation products **3a** and **3a-[D_4]** in a ratio of 4.9:1. This kinetic isotope effect (KIE) value of 4.9 is typical of Rh-catalyzed C–H activation processes.

On the basis of the above KIE experiment and previous reports on the rhodium(III)-catalyzed C–H functionalization of arylphosphonate and related compounds, a plausible mechanistic pathway is proposed (Scheme 4). Initially, treatment of a rhodium precursor with $AgSbF_6$ generates the reactive cationic rhodium(III) species **A**, which on reaction with **1a** affords the cyclic rhodium species **B** through C–H functionalization. Coordination of NCTS **2** with rhodium species **B** affords intermediate **C**, after which insertion of the CN moiety into the C–Rh^{III} bond generates **D**. Rearrangement of **D** affords the desired cyanated product along with the reactive rhodium species **E**. lastly, ligand exchange will furnish the active rhodium species **A** to complete the catalytic cycle.



Scheme 4. Plausible mechanism.

In summary, we have addressed a new strategy based on the dialkyl phosphoryl directing group to achieve the *ortho* C–H functionalization of arylphosphonate and related compounds. This tactic was used for the highly selective *ortho* C–H cyanation of easily available arylphosphonates to prepare 2-cyanated arylphosphonate and related compounds. This protocol offers several advantages including avoidance of biscyanated arylphosphonates, complete *ortho* selectivity, and relatively broad functional group tolerance. We believe that this protocol represents a practical route to 2-cyanated arylphosphonate and related compounds.

Experimental Section

Rh-catalyzed ortho*-cyanation of arylphosphates with NCTS*: General procedure: A 10 mL oven-dried Schlenk tube was charged with **1** (0.3 mmol), NCTS (0.6 mmol), $[RhCp^*Cl_2]_2$ (5 mol%), $AgSbF_6$ (15 mol%), DCE (2 mL), Then the tube was charged with argon, and was stirred at 110 °C for about 24 h. After the reaction was finished, the reaction mixture was diluted in 3 mL dichloromethane. The solution was filtered through a celite pad and washed with 10–20 mL of dichloromethane. The filtrate was concentrated and the residue was purified by silica gel column chromatography (hexane/ethyl acetate) to provide the desired products **3**.

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Keywords: arylphosphonate · C-H activation · directing groups · rhodium · synthetic methods

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