Synthetic Methods

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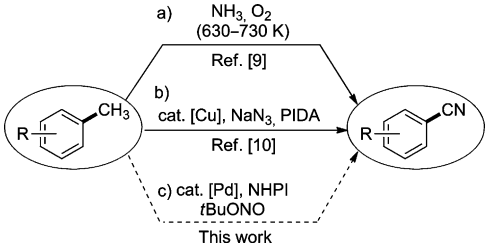
Palladium(II)-Catalyzed Direct Conversion of Methyl Arenes into Aromatic Nitriles**

Zhibin Shu, Yuxuan Ye, Yifan Deng, Yan Zhang, and Jianbo Wang**

The nitrile group is a prevalent functional group in organic synthesis and can be easily used for functional group transformations, including the formation of amines, amides, acids, aldehydes, and heterocycles.[1] In particular, aromatic nitriles have found wide application in the synthesis of natural products, materials, pharmaceuticals, agricultural chemicals, and dyes.[2] However, the methods to introduce a cyano group onto an aromatic ring are still limited. The Sandmeyer reaction[3] and the Rosenmund–von Braun reaction[4] are the traditional methods for the synthesis of aromatic nitriles. However, in both cases, highly toxic copper(I) cyanide is used as the cyanating agent. More recently, transition-metal-catalyzed cyanation of aromatic halides has emerged as an attractive method to access aromatic nitriles.[5] In particular, aromatic cyanation using non-metallic cyano-group sources has attracted great attention.[6,7] The dehydration of aryl amides or oximes, and the oxidative dehydration of benzylic amines or alcohols with ammonia are alternative approaches toward aromatic nitriles.[8]

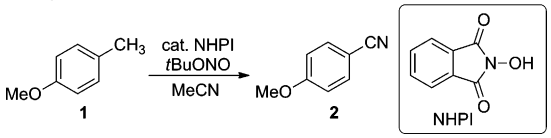
The conversion of methyl arenes into aromatic nitriles through ammoxidation has attracted significant attention and was further developed for large scale industrial applications.[9] This type of cyanation is important because methyl arenes are abundant starting materials. However, such a transformation usually requires very harsh conditions (Scheme 1 a). More recently, Jiao and co-workers developed a Cu-catalyzed transformation of *para*-substituted toluenes into the corresponding aromatic nitriles, with NaN_3 as the nitrogen source and an excess amount of phenyliodonium diacetate (PIDA) as the oxidant (Scheme 1 b).[10] This novel transformation achieved ammoxidation under mild conditions; however, its substrate scope is limited to toluene derivatives bearing electron-rich substituents at the *para* position. Herein, we report a palladium-catalyzed ammoxidation of methyl arenes with *tert*-butyl nitrite (TBN) as both the nitrogen source and the oxidant. The reaction proceeds under mild conditions and shows a much wider substrate scope.



Scheme 1. Direct transformation of methyl arenes into aromatic nitriles.

Our investigation began with evaluation of the direct ammoxidation of *para*-methylanisole (**1**) under oxidative conditions (Table 1). Interestingly, when we chose *tert*-butyl nitrite (TBN) as the nitrogen source, the reaction provided 4-methoxybenzonitrile (**2**) in 80% yield in the presence of catalytic $Pd(OAc)_2$ and *N*-hydroxyphthalimide (NHPI) in

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



Entry	Catalyst (mol%)	TBN [equiv]	NHPI [mol%]	*T* [°C]	*t* [h]	Yield [%][b]
1	$Pd(OAc)_2$ (10)	3	20	60	24	80
2	$Pd(OTFA)_2$ (10)	3	20	60	24	73
3	$[Pd(dba)_2]$ (10)	3	20	60	24	75
4	LA[c] (10)	3	20	60	24	–[d]
5	None	3	20	60	24	–
6	$Pd(OAc)_2$ (10)	0	20	60	24	–
7	$Pd(OAc)_2$ (10)	3	0	60	24	–
8	$Pd(OAc)_2$ (10)	5	20	60	24	70
9	$Pd(OAc)_2$ (10)	3	10	60	24	68
10	$Pd(OAc)_2$ (10)	3	20	60	48	85
11[e]	$Pd(OAc)_2$ (5)	3	30	80	18	54
12[f]	$Pd(OAc)_2$ (5)	2	30	80	8	89
13[e]	$Pd(OAc)_2$ (5)	2	30	70	16	83

[a] If not otherwise noted, the reaction conditions are as follows: **1** (0.3 mmol), catalyst, NHPI, TBN in acetonitrile (1.5 mL) under N_2. [b] Yields of isolated products. [c] LA = Lewis acids, which include $BF_3{\cdot}Et_2O$, $AlCl_3$, $GaCl_3$, $AuCl_3$, $Bi(OTf)_3$, $Sc(OTf)_3$, AgOTf, $Zn(OTf)_2$, $Sm(OTf)_3$, $Y(OTf)_3$, CuI, $CuCl_2$, $CuBr_2$, $Fe(OAc)_2$, $FeCl_3$, $Co(OAc)_2$, and $CoCl_2$. [d] The major product is the aldehyde. [e] Acetonitrile (0.6 mL). [f] Acetonitrile (0.3 mL). dba = dibenzylideneacetone, TBN = *t*BuONO, TFA = trifluoroacetyl.

[*] Z. Shu, Y. Ye, Y. Deng, Dr. Y. Zhang, Prof. Dr. J. Wang
Beijing National Laboratory of Molecular Sciences (BNLMS) and Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, Peking University
Beijing 100871 (China)
E-mail: yan_zhang@pku.edu.cn
wangjb@pku.edu.cn
Prof. Dr. J. Wang
The State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences
354 Fenglin Lu, Shanghai 200032 (China)

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acetonitrile (Table 1, entry 1). Other palladium catalysts, such as $Pd(OTFA)_2$ and $[Pd(dba)_2]$, also worked for this reaction (entries 2 and 3). However, product **2** was not detected when the salts of other metals, including Cu, Fe, Co, Au, Zn, Sc, and Al, were employed as the catalysts (entry 4). Control experiments also showed that no cyanation product is formed in the absence of a metal catalyst (entry 5). In addition, when the reaction was carried out in the absence of either TBN or NHPI, product **2** was also not observed (entries 6 and 7). We found that the yield of product **2** diminished slightly as the loading of TBN increased, or when a smaller amount of NHPI was used (entries 8 and 9). We then carried out further optimization of the reaction conditions. To our delight, we found that the loading of $Pd(OAc)_2$ could be reduced to 5 mol%, when adjusments were made to the reaction temperature and concentration (entries 11–13).

With the optimized reaction conditions, we proceeded to explore the substrate scope of this transformation. As the reaction conditions are mild, we expected that various functional groups would be tolerated. To our delight, we could indeed show that a wide range of functional groups are tolerated under the reaction conditions (Scheme 2). Reactions with toluene derivatives bearing electron-donating groups such as MeO and Me proceeded efficiently in good to excellent yields (**2**, **4**–**7**, **22**–**25**; Scheme 2). Substrates substituted with weakly electron-withdrawing groups, such as F, Cl, Br, and I, also worked well and afforded the desired products (**8**–**15**), which could be used in further coupling reactions. When there are two methyl substituents, only one methyl group is converted into a cyano group. However, with a high loading of NHPI at 80 °C, the second methyl group can also be converted into a cyano group (**32**).

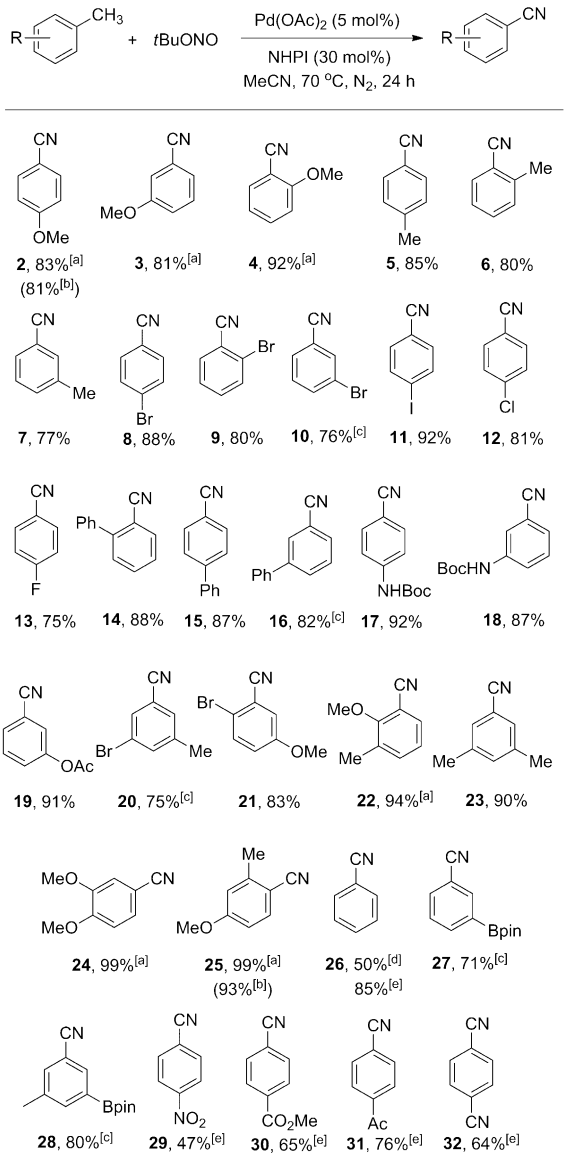
The reaction also works with toluene derivatives bearing strongly election-withdrawing substituents, such as NO_2, CO_2Me, Ac, and CN (**29**–**32**). However, in these cases, the reaction needs to be carried out with a high loading of NHPI (100 mol%) and at slightly elevated temperatures (80 °C). Notably, this cyanation method also works for toluene derivatives bearing more than one substitutent or an oxidation-sensitive group, such as Bpin (**27** and **28**; Bpin = pinacolborane).

Next, we extended this transformation to polycyclic aromatic hydrocarbons and heteroaromatic compounds (Scheme 3). Polycyclic aromatics are highly reactive substrates and gave the expected cyanation products in excellent yields (**33**–**35**; Scheme 3). For indole derivatives, the reaction also worked well (**36**–**38**). For heteroaromatic compounds containing electron-deficient pyridine rings, the reactions gave diminished yields (**39** and **40**).

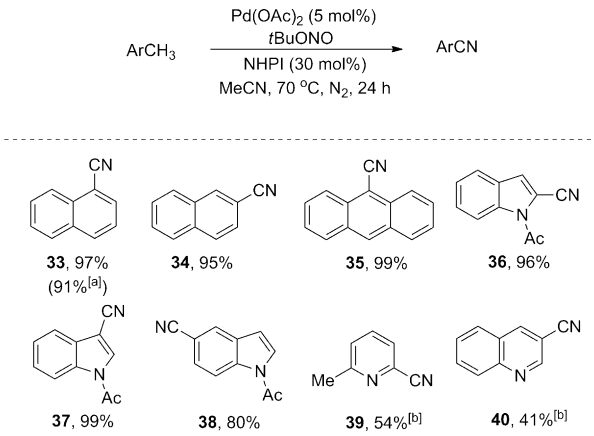
To gain insight into the mechanism, several control experiments were carried out. First, when the reaction was conducted in the presence of stoichiometric amounts of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO), the transformation of **1** was almost completely inhibited and only trace amounts of product could be detected by GC analysis (Scheme 4a). This result indicates that the transformation may proceed through a radical intermediate.

Second, when diphenyl methane **41** was employed as the substrate, the reaction produced benzophenone **42** in 80% yield (Scheme 4b). Hence, we hypothesized that an aldehyde might be an intermediate of the cyanation reaction. However, when benzaldehyde (**43**) was submitted to the reaction conditions, it was recovered unchanged (Scheme 4c).

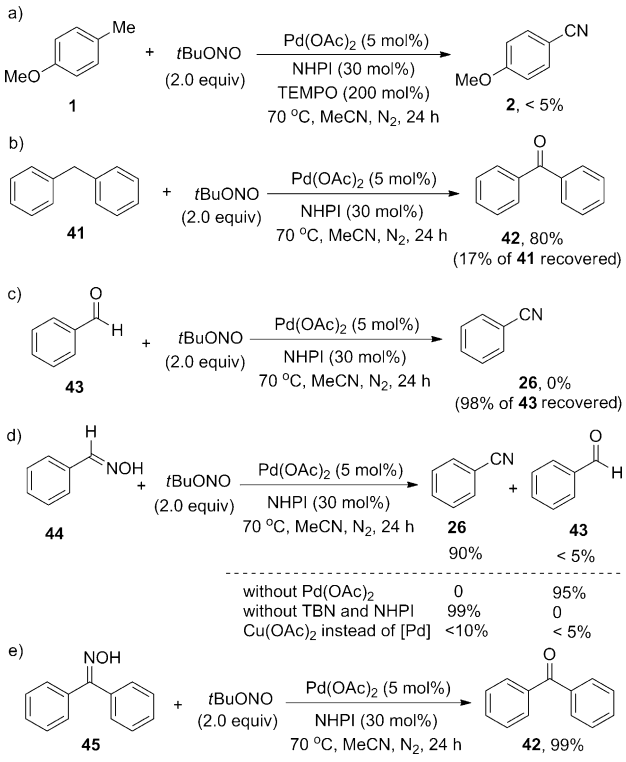
Subsequently, we hypothesized that an aldoxime might be the key intermediate of this transformation. To verify this hypothesis, several experiments were carried out. At first, we found that aldoxime **44** could be effectively transformed into the nitrile **26** in 90% yield under the optimized reaction conditions, with minor formation of benzaldehyde (**43**,



Scheme 2. Direct conversion of methyl arenes into aromatic nitriles. If not otherwise noted, the reaction conditions are as follows: methyl arene (0.5 mmol), TBN (1.5 mmol), $[Pd(OAc)_2]$ (0.025 mmol), and NHPI (0.15 mmol) in MeCN (0.5 mL) at 70 °C under N_2 for 24 h. Yields of isolated products are given. [a] TBN (2.0 equiv) was used. [b] The isolated yield for a reaction performed on a 1.0 gram scale is shown in parentheses. [c] NHPI (50 mol%) was used. [d] The yield is based on GC analysis. [e] These reactions were carried out with an increased loading of NHPI (100 mol%) in MeCN (0.5 mL) at 80 °C for 24 h. Ac = acetyl, Boc = *tert*-butoxycarbonyl, pin = pinacolato.



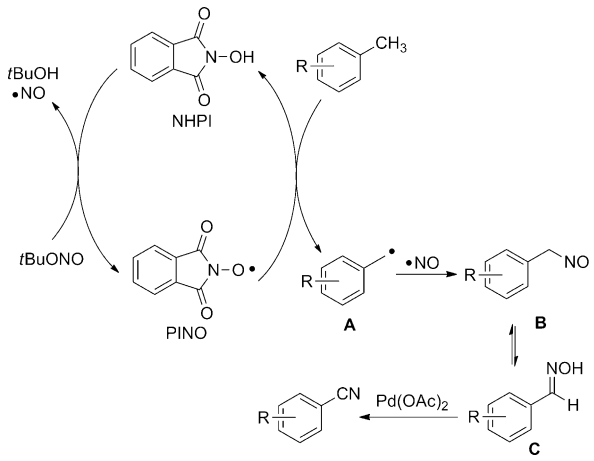
Scheme 3. Substrate scope with polycyclic aromatics and heteroaromatics. If not otherwise noted, the reaction conditions are as follows: methyl arene (0.5 mmol), TBN (1.5 mmol), $Pd(OAc)_2$ (0.025 mmol), and NHPI (0.15 mmol) in MeCN (1.0 mL) at 70 °C under N_2 for 24 h. Yields of isolated products are given. [a] The isolated yield for a reaction performed on a 1.0 gram scale is shown in parentheses. [b] These reactions were carried out with an increased loading of NHPI (100 mol%) in MeCN (0.5 mL) at 80 °C for 24 h.



Scheme 4. Control experiments for mechanistic studies.

Scheme 4d). In contrast, in the absence of $Pd(OAc)_2$, the reaction gave **43** as the only product, and the nitrile was not obtained. However, **44** can be efficiently transformed into nitrile **26** in the absence of both TBN and NHPI. It has been reported that both $Pd(OAc)_2$[11] and $Cu(OAc)_2$[12] can catalyze the conversion of aldoximes into nitriles.[8] However, under the same reaction conditions, when $Pd(OAc)_2$ was replaced with $Cu(OAc)_2$, the aldoxime **44** remained essentially unchanged (Scheme 4d). This was shown to be due to the incompatibility of $Cu(OAc)_2$ with TBN. Finally, oxime **45** was converted into benzophenone **42** under the standard reaction conditions (Scheme 4e). Collectively, these results indicate that an aldoxime is the key intermediate in this transformation.

A possible reaction mechanism is proposed in Scheme 5. First, NHPI is converted into the active phthalimide *N*-oxyl (PINO) radical by TBN, which decomposes into an NO



Scheme 5. Proposed reaction mechanism.

radical and 2-methyl-2-propanol.[13] Benzylic radical **A** is then generated upon hydrogen abstraction by PINO. The reaction of **A** with the NO radical leads to the formation of intermediate **B**, which isomerizes to aldoxime **C**. Finally, **C** is converted into the corresponding nitrile by $Pd(OAc)_2$ catalysis.[11] Although various transition metals can catalyze the conversion of aldoximes into nitriles,[12] it is likely that the incompatibility of these metal salts with the presence of TBN resulted in the failure of these metal salts as catalysts for this transformation.

In summary, we have developed a novel method for the direct synthesis of aromatic nitriles from the corresponding methyl arenes under palladium-catalyzed conditions using TBN as the nitrogen source. This direct conversion of a methyl group into a cyano group proceeds under mild conditions, with high efficiency for a wide range of substrates.

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