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Palladium-catalyzed cyanation of aryl (pseudo)halides using a redox-active N–CN reagent†

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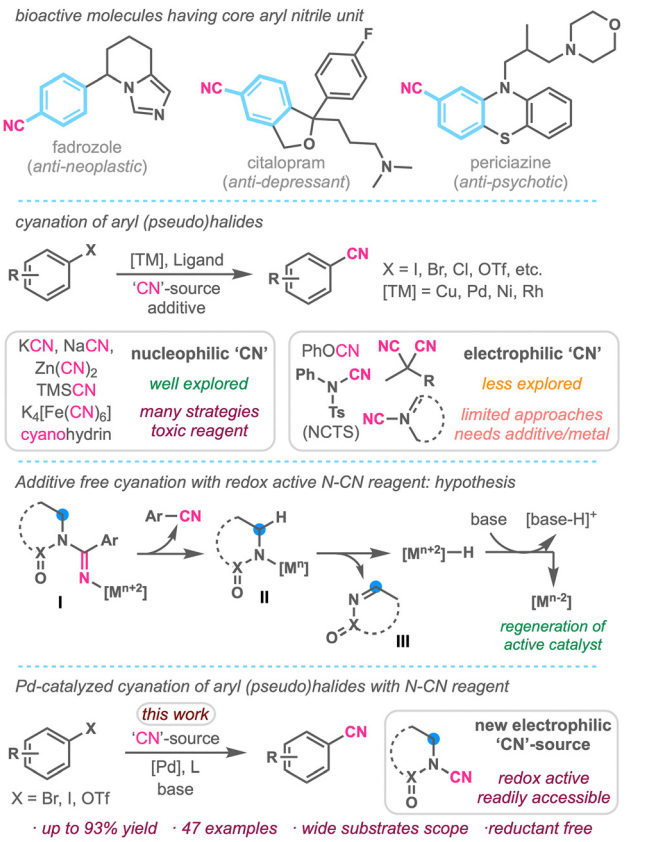
An efficient palladium-catalyzed cyanation of aryl bromides has been demonstrated using a readily accessible and redox-active electrophilic cyanating reagent. The reaction was successfully extended to the cyanation of aryl iodides, triflates, and diazonium salts. Various functionalized aryl nitriles and drug intermediates were achieved in good to excellent yields. Important features of this reaction include wide functional group tolerance, a broad substrate scope, and a reductant-free approach. The preliminary mechanistic investigation and identification of oxidized imine supported the proposed plausible reaction mechanism.

Cyanation is an essential reaction in organic synthesis that involves incorporating a cyanide group into a molecule, resulting in the formation of nitrile derivatives.[1] Particularly, aryl nitriles are highly valuable in pharmaceuticals, natural products, and industrial applications due to their wide utility.[2] Representative aryl nitrile containing bioactive molecules are shown in Scheme 1. They also serve as versatile intermediates in organic synthesis, as they can be readily transformed into various functional groups, including carboxylic acids, amides, aldehydes, amines, and heterocycles. Due to the importance of aryl nitriles, numerous methods have been established for incorporating cyano groups into aromatic rings; among them, the prominent approach is the transition-metal-catalyzed cyanation of aryl (pseudo)halides.[3]

Transition metal-catalyzed cyanation of aryl (pseudo)halides has been achieved by employing two types of cyanating reagents, which are nucleophilic and electrophilic CN sources (Scheme 1). Nucleophilic cyanating reagents have been explored well for the cyanation of aryl halides.[4] However, these cyanating reagents are intrinsically toxic, produce large super-stoichiometric amounts of metal waste, and require careful regulation of cyanide concentration to ensure efficiency and reduce the catalyst loading. These challenges in conventional cyanating reagents drive the interest in developing safer and less toxic alternatives. One of the best alternatives is electrophilic cyanating reagents,[5] which offer enhanced reactivity and selectivity, allowing cyanation to proceed under mild conditions. Although these cyanating reagents are well suited for the cyanation of aryl nucleophiles,[6] their application in the cyanation of aryl (pseudo)halides is rather limited and requires additional reductants to promote the cyanation.



Scheme 1 Transition metal-catalyzed cyanation of aryl (pseudo)halides.

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Cyanation with an electrophilic cyanating reagent, including a N–CN reagent,[5a] involves the generation of intermediate **I**, through the addition of aryl–M species to the cyano group of the reagent, followed by the elimination of aryl nitrile, which affords leaving-group bound metal **II** (Scheme 1). Species **II** generally undergo protodemetallation to afford a high-valent metal, which requires a reductant/additive to regenerate the active catalyst.[7] This highlights the need for further developments in reagent design and process optimization. To achieve the regeneration of active catalyst from intermediate **II**, in the absence of an external reductant, and to continue our interest in the cyanation,[8] we hypothesized to introduce the methylene group on the nitrogen, which can potentially undergo oxidation *via* β–H elimination to give M–H species. Next, the base-promoted reduction of M–H can regenerate the active catalyst (Scheme 1).[9] The successful development of a redox-active electrophilic cyanating reagent would offer a new way to achieve aryl nitriles from aryl (pseudo)halides under environmentally benign conditions. Thus, we herein disclose the general and efficient palladium-catalyzed cyanation of aryl (pseudo)halides using a readily accessible redox-active N–CN reagent (Scheme 1).

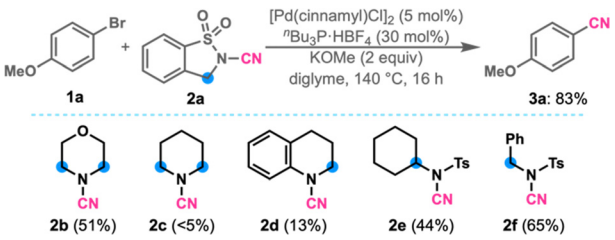
To test our hypothesis, we synthesized a series of cyanating reagents **2a**–**2f** containing methylene/methine groups and studied the palladium-catalyzed cyanation of *p*-bromoanisole **1a**. After performing a series of studies, the optimized conditions were observed with an 83% yield of **3a** when 1 equiv. of **1a** was treated with 2 equiv. of **2a** in the presence of 5 mol% of $[Pd(cinnamyl)Cl]_2$, 30 mol% of $^{n}Bu_3P{\cdot}HBF_4$ and 2 equiv. of KOMe at 140 °C (Table 1). The use of other N–CN reagents (**2b**–**2f**) in place of **2a** gave inferior results. Among them, **2b**, **2e**, and **2f** gave moderate yields.

Palladium catalysts like $Pd(OAc)_2$, $[Pd(allyl)Cl]_2$, and $Pd(CH_3CN)_4(BF4)_2$ were also examined, but all of them gave low yields compared to $[Pd(cinnamyl)Cl]_2$ (Table 1, entries 2–4). When electron-rich and bulky phosphines, such as $Cy_3P{\cdot}HBF_4$, $^{t}Bu_3P{\cdot}HBF_4$, $(o\text{-tolyl})_3P$, and X-phos were employed, the formation of **3a** was observed in most of the cases, except with bulky $^{t}Bu_3P{\cdot}HBF_4$ (Table 1, entries 5–7). Replacement of KOMe with NaOMe led to a significant decrease in the yield of **3a**, which suggests that the potassium ion is crucial for this reaction. This observation was further supported by the reaction with K_2SO_4 and K_2CO_3 (Table 1, entries 10 and 11). Employing other solvents like DMSO gave only 20% yield, and acetonitrile afforded a comparable yield (Table 1, entries 12 and 13).

Upon successfully optimizing the reaction conditions, we focused on studying the scope of (hetero)aryl bromides (Scheme 2). Initially, *para*-, *meta*-, and *ortho*-bromotoluenes were subjected to the optimized conditions, affording **3b**, **3c**, and **3d** in good yields, respectively. This observation reveals that the present conditions tolerate substitution on different positions of the aryl group. *tert*-Butyl and phenyl substituted aryl bromides gave products **3e** and **3f** in ~70% yield. A 1 mmol scale reaction of bromobiphenyl also gave **3f** in a comparable yield.

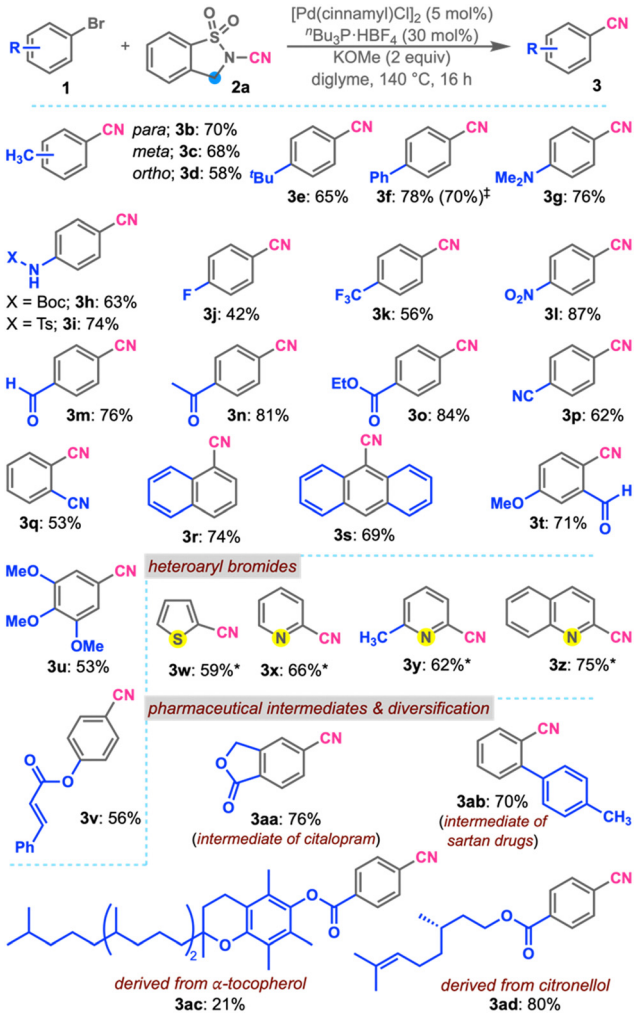
Aryl bromides substituted with strongly electron-donating (Me_2N) and moderately electron-donating (BocNH and TsNH) groups, which are relatively poor substrates for oxidative addition, underwent smooth reactions, affording **3g**, **3h**, and **3i** in ~70% yield. Besides, cyanobenzenes bearing moderately and strongly electron-withdrawing substituents like fluoro-, trifluoromethyl- and nitro-groups (**3j**, **3k**, and **3l**) were obtained in good yields. Oxidatively unstable formyl and base-sensitive acetyl and ethoxycarbonyl groups were well tolerated, affording **3m**, **3n**, and **3o** in 76, 81, and 84% yields, respectively. Interestingly, the formation of dicyanobenzenes **3p** and **3q** was observed in good yields. Sterically demanding substrates, due to the presence of peri-proton(s), 1-bromonaphthalene, and 9-bromoanthracene, were successfully converted to **3r** and **3s** in 74 and 69% yields, respectively. Formation of **3t** and **3u** having multiple substituents was also achieved in good yields. The reaction was compatible with conjugated ester and resulted in the formation of **3v** in 56% yield. Since heteroaromatic systems are well-known ligands and can coordinate with metals to quench catalytic activity, heterocyclic bromides such as 2-bromothiophene were subjected to the reaction in acetonitrile, affording **3w** in 59% yield. Similarly, strongly basic pyridine derivatives were successfully transformed into products **3x** and **3y** in good yields. Synthesis of 2-cyanoquinoline **3z** was also accomplished in 75% yield. These studies reveal that the present conditions show high compatibility with various functional groups and heterocycles. Subsequently, the synthesis of pharmaceutical intermediates and late-stage functionalization were examined. The synthesis of cyanoarene **3aa**, the key intermediate for citalopram,[10] was achieved in 76% through the palladium-catalyzed cyanation of the corresponding bromide with **2a**. Similarly, cyanation of *o*-tolylbromobenzene furnished the cyano compound **3ab**, the common intermediate

Table 1 Pd-catalyzed cyanation of **1a** with **2a**: optimization[a]

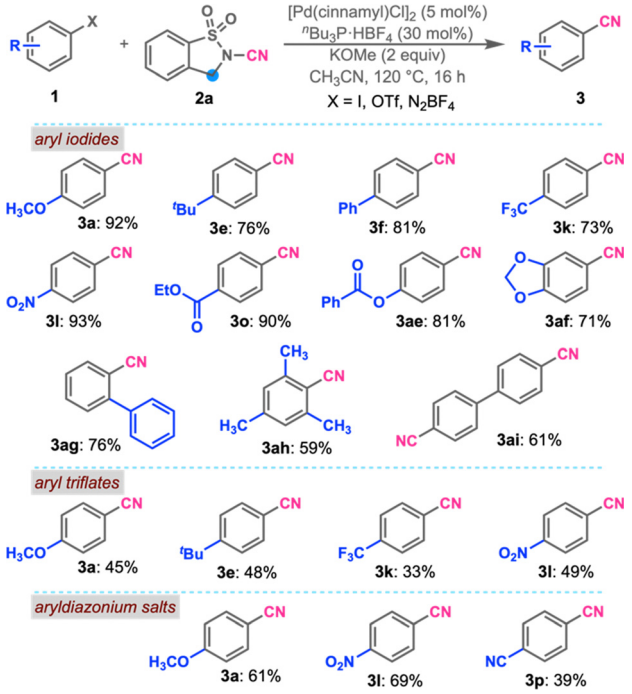


Entry	Deviation from optimized conditions	Yield[b] (%)
1	None	83
2	$Pd(OAc)_2$ instead of $[Pd(cinnamyl)Cl]_2$	23
3	$[Pd(allyl)Cl]_2$ instead of $[Pd(cinnamyl)Cl]_2$	24
4	$Pd(CH_3CN)_4(BF_4)_2$ instead of $[Pd(cinnamyl)Cl]_2$	36
5	$Cy_3P{\cdot}HBF_4$ instead of $^{n}Bu_3P{\cdot}HBF_4$	48
6	$^{t}Bu_3P{\cdot}HBF_4$ instead of $^{n}Bu_3P{\cdot}HBF_4$	—
7	$(o\text{-Tolyl})_3P$ instead of $^{n}Bu_3P{\cdot}HBF_4$	17
8	X-phos instead of $^{n}Bu_3P{\cdot}HBF_4$	30
9	NaOMe instead of KOMe	25
10	K_2SO_4 instead of KOMe	52
11	K_2CO_3 instead of KOMe	46
12	DMSO instead of diglyme	20
13	CH_3CN instead of diglyme	73

[a] Reaction conditions: **1a** (50 mg, 0.26 mmol, 1 equiv.), **2a** (104 mg, 0.53 mmol, 2 equiv.), $[Pd(cinnamyl)Cl]_2$ (6.9 mg, 5 mol%), $^{n}Bu_3P{\cdot}HBF_4$ (23 mg, 30 mol%), KOMe (55 mg, 2 equiv.), diglyme (2 mL for 0.26 mmol), 140 °C, 16 h. [b] All are isolated yields.



Scheme 2 Substrates scope. [a] Reactions were performed in acetonitrile. [b] 1 mmol scale.



Scheme 3 Scope of aryl iodides and pseudohalides.

for many sartan drugs.[11] Considering late-stage functionalization, aryl bromides derived from α-tocopherol and citronellol were successfully converted to products **3ac** and **3ad** in good yields.

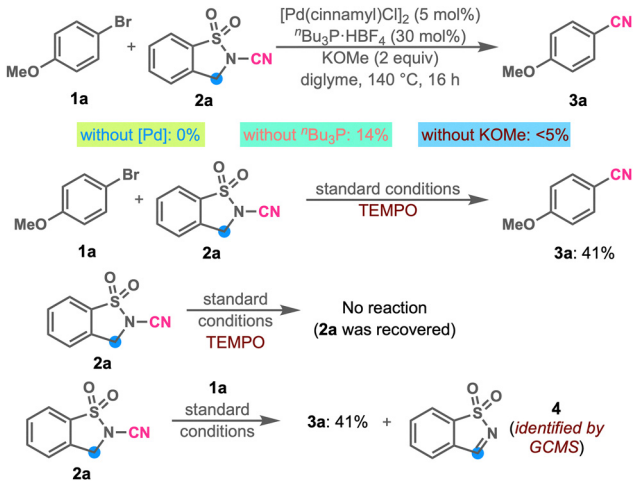
Following the successful demonstration of the cyanation of aryl bromides, we next aimed to study the cyanation of aryl iodides and pseudohalides. Interestingly, cyanation of *p*-iodoanisole under the optimized conditions at reduced temperature (120 °C) in acetonitrile furnished **3a** in 92% yield (Scheme 3). Similarly to the earlier observations, *tert*-butyl-, phenyl-, trifluoromethyl-, and nitro-substituted cyanoarenes **3e**, **3f**, **3k**, and **3l** were synthesized in excellent yields. Base-sensitive esters and Lewis acid-sensitive acetals were well tolerated under the cyanation conditions to afford **3o**, **3ae**, and **3af**. Sterically challenging substrates were also successfully transformed into the cyanated products **3ag** and **3ah**. Dicyanation of 4,4′-diiodobiphenyl was also achieved in good yield. Following aryl iodides, aryl triflates were subjected to the reaction conditions. To our delight, all the aryl triflates furnished the cyano compounds **3a**, **3e**, **3k**, and **3l** in slightly lower yields than aryl halides. Interestingly, the use of aryldiazonium salts led to a marginal improvement in the cyanation and afforded the cyanoarenes **3a**, **3l**, and **3p** in good yields.

Having successfully demonstrated the generality of the present cyanation, we next focused our attention on the control experiments. The reaction of **1a** and **2a** under the optimized conditions in the absence of a palladium catalyst did not furnish **3a**, which suggests that the present reaction is catalyzed by palladium (Scheme 4).

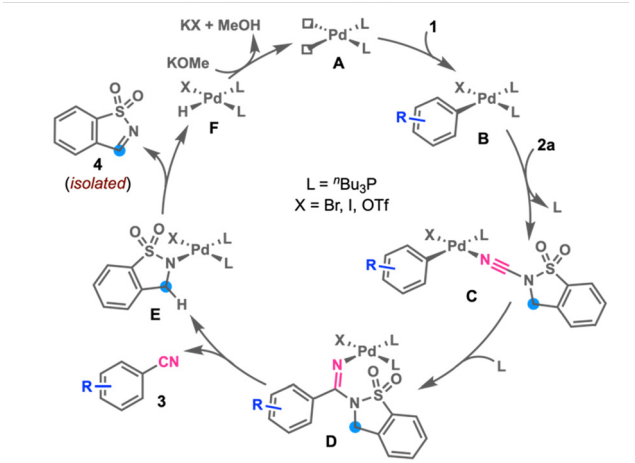
In the absence of $^{n}Bu_3P$, only a small amount of **3a** was observed, which reveals the vital role of $^{n}Bu_3P$ in stabilizing the Pd catalyst. Similar results were observed when the reaction was performed in the absence of KOMe. These studies establish the key role of [Pd(cinnamyl)Cl]$_2$, $^{n}Bu_3P$, and KOMe in the present reaction.

Next, the standard reaction was performed with TEMPO to investigate the possible involvement of radicals, which afforded **3a** in 41% yield. Besides, **2a** alone was treated with TEMPO, which did not give any product, and **2a** was fully recovered. These observations provide evidence for the non-radical mechanism. Finally, to understand the fate of **2a** after the reaction, the standard reaction was performed with K_2SO_4, which gave the imine **4** in 45% yield along with **3a**. The formation of **4** supports our hypothesis of the redox active cyanating reagent.

Based on the preliminary mechanistic investigation and literature precedent,[7a–c] the plausible reaction mechanism for the present reaction has been proposed. Catalytically active catalyst **A** could be generated from [Pd(cinnamyl)Cl]$_2$ and $^{n}Bu_3P$, which upon reaction with **1** would give intermediate **B** *via* oxidative addition. Coordination of **2a** to **B**, followed by 1,2-migratory insertion, would give intermediate **D**. Elimination of aryl nitrile **3** from **D** would generate palladium species **E**. β-Hydride elimination in **E** would form imine **4** and Pd–H



Scheme 4 Preliminary mechanistic investigation.



Scheme 5 Plausible mechanism.

species **F**, which upon base-mediated reduction would regenerate the active catalyst **A** (Scheme 5).

In conclusion, a general and efficient palladium-catalyzed cyanation of aryl bromides has been achieved by employing a new electrophilic cyanating reagent, which is readily accessible and redox-active. The optimized conditions demonstrated excellent compatibility with diverse sterically and electronically different functional groups. It was successfully extended to the cyanation of aryl iodides, triflates, and diazonium salts, which allows access to various aryl nitriles in good to excellent yields. Notably, the present reaction could be used for the synthesis of drug intermediates and their diversification, and it avoids the requirement of reductants and toxic cyanating reagents, and the generation of metal waste. The preliminary mechanistic investigation was performed, including the isolation of the imine intermediate, and also the plausible reaction mechanism was proposed.

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Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the ESI.†

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