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Palladium-Catalyzed Norbornene-Mediated Tandem Amination/Cyanation Reaction: A Method for the Synthesis of *ortho*-Aminated Benzonitriles

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Supporting Information

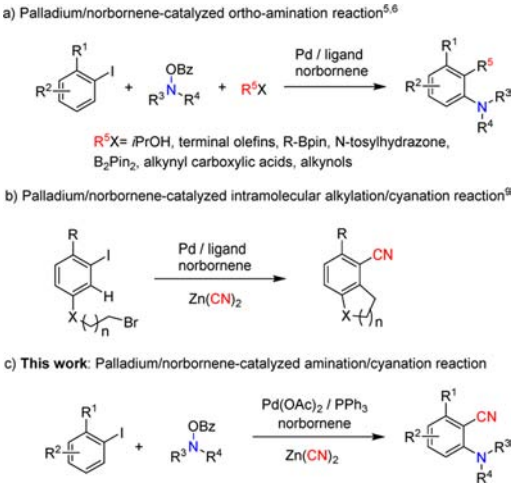
ABSTRACT: A palladium-catalyzed, norbornene-mediated tandem amination/cyanation reaction via Catellani-type C−H functionalization was developed using *N*-benzoyloxyamines as the amination reagent and $Zn(CN)_2$ as the terminating agent. This transformation, in which one C−N bond and one C−C bond are formed, provides an efficient approach for the synthesis of *ortho*-aminated benzonitriles in one pot from easily accessible starting materials.

Transition-metal-catalyzed C−C and C−heteroatom bond forming reactions are among the most widely used catalytic reactions in synthetic organic chemistry.[1] Among them, special attention has been paid to palladium-catalyzed reactions due to their broad functional group tolerance and diverse reaction pathways. The Catellani reaction, which was first discovered by Catellani[2] and further developed by us and others,[3,4] is a powerful method for the synthesis of highly substituted aromatic compounds and fused aromatic rings due to the capability of functionalizing both the *ortho*- and *ispo*-position of aryl iodides in a single transformation. Although the scope of terminating reagents for *ispo*-C−I functionalization has been broadened considerably since its discovery, *ortho*-C−H functionalization is largely limited to alkylation and arylation. Recently, the palladium-catalyzed, norbornene-mediated *ortho*-C−H amination of aryl iodides was reported by Dong,[5] who used ^{i}PrOH as the hydride source to terminate the reaction. This synthetic strategy has been extended to a wide variety of terminating reagents, such as terminal olefins,[6a] aromatic pinacol boronates,[6b] *N*-tosylhydrazone,[6c] bis(pinacolato) diboron,[6d] alkynyl carboxylic acids,[6e] and alkynols[6f] (Scheme 1a), for the synthesis of polysubstituted aniline derivatives. However, it was not known if this type of *ortho*-amination reaction could tolerate cyanide as the nucleophile. Herein, we report such a palladium-catalyzed, norbornene-mediated amination/cyanation reaction using cyanide as the terminating reagent to afford *ortho*-aminated benzonitriles, which are of great significance as starting materials for the synthesis of many biologically active agents, such as quinazolines, 1*H*-indazoles, quinazolinamines, etc.[7] Moreover, the nitrile group can be transformed into a variety of functional groups, such as carboxyl, carbonyl, carbamoyl, aminomethyl, and heterocycles.[8]

The first example of terminating the Catellani reaction with $Zn(CN)_2$ was reported by our group in 2006, affording polycyclic benzonitriles via tandem intramolecular *ortho*-alkylation/cyanation reaction (Scheme 1b).[9] We found intermolecular alkylation/cyanation could also occur between aryl iodides and alkyl halides using $[K_4Fe(CN)_6{\cdot}3H_2O]$ as the terminating reagent.[10] Most recently, Chen reported the synthesis of 2-cyanoarylketones through palladium-catalyzed, norbornene-mediated tandem C−H amination and C−I cyanation, employing CuCN as the terminating reagent.[11]

Based on these previous reports, we envisioned that the protocol could also work for the synthesis of *ortho*-aminated benzonitriles through a palladium-catalyzed tandem C−N bond and C−CN bond formation process, provided that suitable conditions could be identified (Scheme 1c). Gratifyingly, after

Scheme 1. Previous Work and This Work



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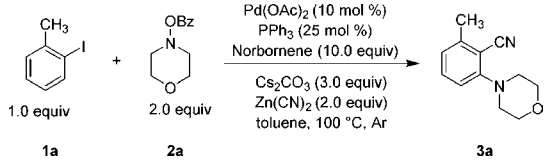
some optimization, we found that when the reaction was carried out with $Pd(OAc)_2$ (10 mol %), PPh_3 (25 mol %), and $Zn(CN)_2$ (2 equiv) in toluene at 100 °C for 24 h, the desired product **3a** could be isolated in 82% yield (Table 1, entry 1). The yield

Table 1. Optimization of the Reaction Conditions



1a **2a** **3a**

entry	variation from "standard" condition	yield (%)[a]
1	none	83(82)
2	$[K_4Fe(CN)_6{\cdot}3H_2O]$ instead of $Zn(CN)_2$	15
3	CH_3CN instead of toluene	5
4	DME instead of toluene	58
5	DCE instead of toluene	68
6	dioxane instead of toluene	80(76)
7	$(2\text{-furyl})_3P$ instead of PPh_3	72
8	$(3\text{-tolyl})_3P$ instead of PPh_3	83(79)
9	3.0 equiv of norbornene instead of 10.0 equiv	60
10	120 °C instead of 100 °C	92(89)

[a]Determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. Isolated yield after column chromatography are given in parentheses.

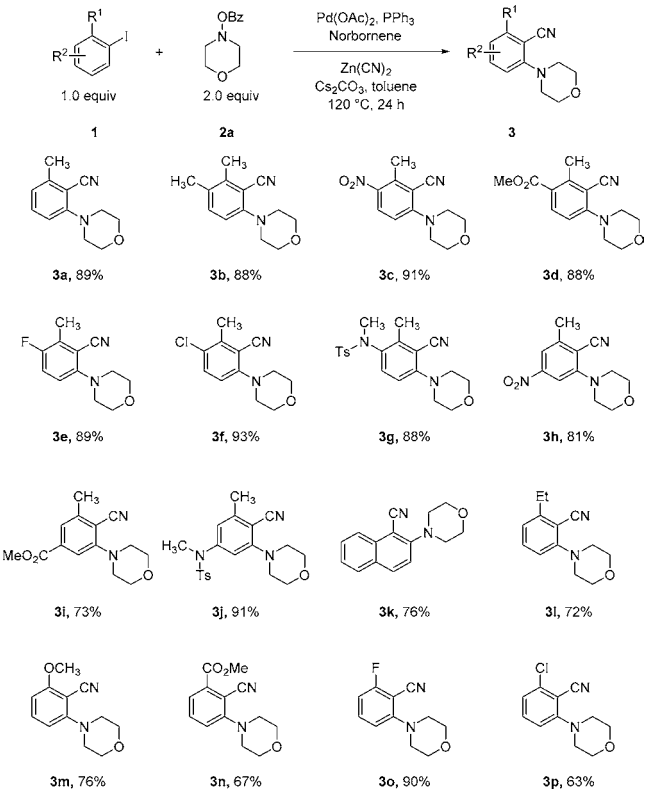
decreased significantly to 15% when 2.0 equiv of $[K_4Fe(CN)_6{\cdot}3H_2O]$ was used as the CN source (entry 2). Further investigation of various solvents revealed that toluene was the best (entries 3–6). The effect of the monodentate phosphine ligand was also examined. While $(2\text{-furyl})_3P$ and $(3\text{-tolyl})_3P$ were effective for the reaction, the yields are slightly lower (entries 7 and 8). The yield decreased to 60% when 3.0 equiv of norbornene was used (entry 9), which indicates the amount of norbornene affects this reaction significantly. The isolated yield of **3a** could be further increased to 89% when the reaction was conducted at 120 °C in a sealed tube (entry 10), which was defined as the optimal conditions for further study.

Under the optimized reaction conditions, a range of aryl iodides were examined. Generally, aryl iodides containing electron-donating and electron-withdrawing groups were well-tolerated, providing the corresponding *ortho*-aminated benzonitriles **3a–3p** in moderate to excellent yields (Scheme 2). More specifically, *ortho*-methyl-substituted aryl iodides with a variety of functional groups (i.e., nitro, ester, fluoro, chloro, amine) at the *meta*- or *para*-position all reacted smoothly with **2a** and $Zn(CN)_2$, affording **3b–j** in good to excellent yields (73–93%). The structure of **3a** was confirmed by X-ray analysis (see Supporting Information). 1-Iodonaphthalene was also employed, providing the product **3k** in good yield (76%). Other *ortho*-substituted aryl iodides were also competent in the reaction, delivering **3l–p** in moderate to good yields (63–90%).

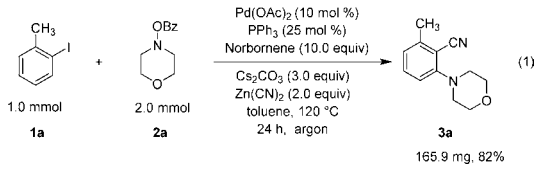
To demonstrate the practical utility of the protocol, we scaled up the reaction with 1.0 mmol **1a**, 2.0 mmol **2a**, and 2.0 mmol $Zn(CN)_2$. No significant changes were noted, and the desired product **3a** was obtained in 82% yield (eq 1).

In the case of aryl iodides **4** lacking an *ortho*-substituent, 2,6-diaminated benzonitriles **5** can be obtained (Scheme 3). Moderate to excellent yields of products **5a–i** (54–88%) were observed when 2.5 equiv of **2a** and 5.0 equiv of Cs_2CO_3 were employed in the reaction. The structure of **5b** was confirmed by

Scheme 2. Scope of *ortho*-Substituted Aryl Iodides[a]



[a]Reaction conditions: **1** (0.2 mmol, 1.0 equiv), **2a** (2.0 equiv), $Zn(CN)_2$ (2.0 equiv), $Pd(OAc)_2$ (10 mol %), PPh_3 (25 mol %), norbornene (10.0 equiv), Cs_2CO_3 (3.0 equiv), toluene (3.0 mL), 120 °C, 24 h, argon.



X-ray analysis (see Supporting Information). It is noteworthy that chloro, cyano, aldehyde, trifluoromethyl, and ester groups were all compatible with the reaction, suggesting that the protocol might be useful for the synthesis of more complex molecules.

To further explore the generality of this reaction, different substituted *N*-benzoyloxyamines were tested (Scheme 4). It was found that the reaction proceeds smoothly for secondary, cyclic *N*-benzoyloxyamines, giving the corresponding amination products **3q–s** in good to excellent yields (79–90%). However, pyrrolidine gave the desired product **3t** in low yield (38%). An acyclic *N*-benzoyloxyamine was equally compatible with this multicomponent reaction, giving product **3u** in good yield (66%). Removal of the benzyl group would lead to the secondary arylamine product.[12] Unfortunately, only a trace amount of product **3v** was isolated when the dibenzyl-protected *N*-benzoyloxyamine was employed. However, *O*-benzoyl-*N*,*N*-diethyloxylamine could react with **1a** and $Zn(CN)_2$ to afford product **3w**, albeit in low yield (29%).

Based on the above experimental results and previous reports,[5,6] a plausible mechanism is proposed in Scheme 5. The first step involves oxidative addition of iodoarene **1** or **4** with

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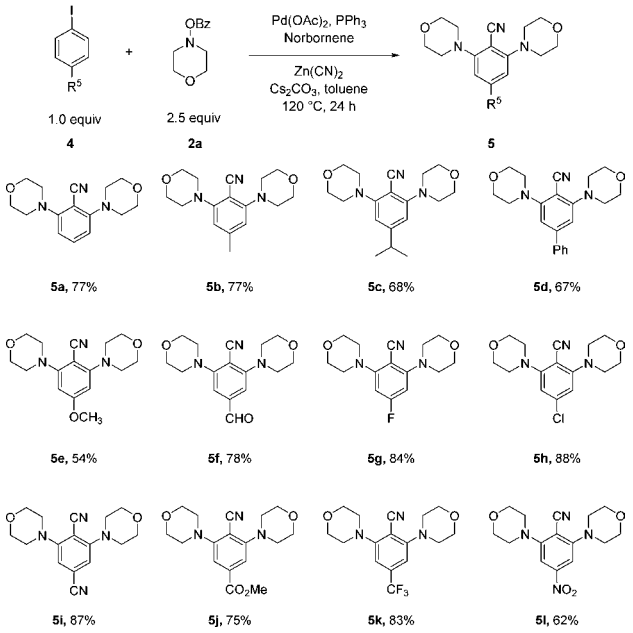
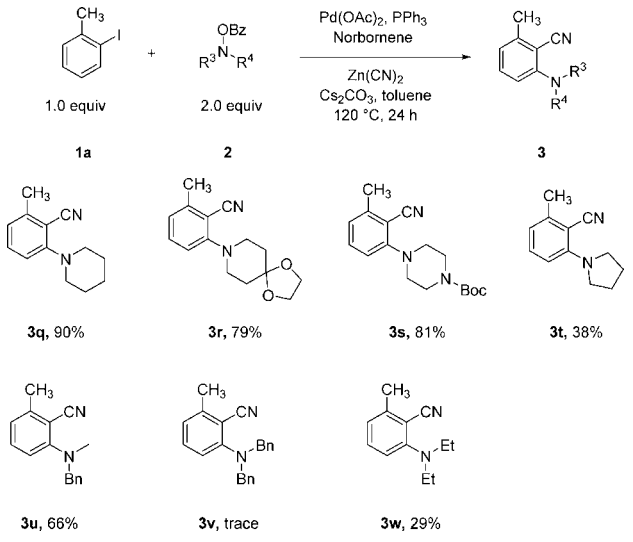
Scheme 3. Scope of Aryl Iodides without an *ortho*-Substituent[a]



[a]Reaction conditions: **4** (0.2 mmol, 1.0 equiv), **2a** (2.5 equiv), $Zn(CN)_2$ (2.0 equiv), $Pd(OAc)_2$ (10 mol %), PPh_3 (25 mol %), norbornene (10.0 equiv), Cs_2CO_3 (5.0 equiv), toluene (3.0 mL), 120 °C, 24 h, argon.

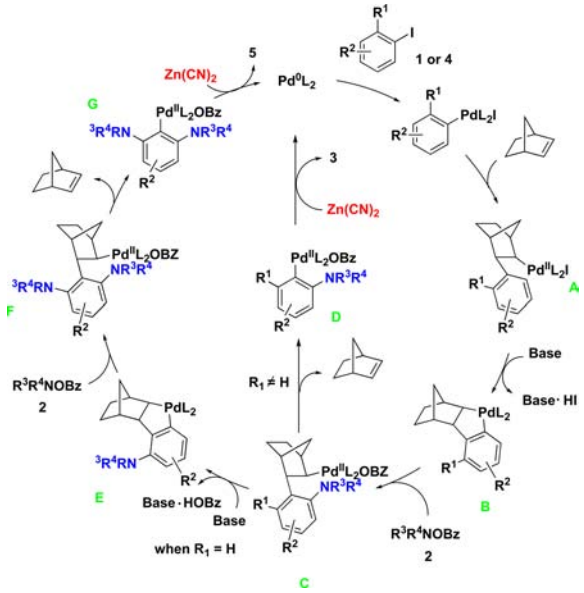
Scheme 4. Scope of *N*-Benzoyloxyamines[a]



[a]Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2** (2.0 equiv), $Zn(CN)_2$ (2.0 equiv), $Pd(OAc)_2$ (10 mol %), PPh_3 (25 mol %), norbornene (10.0 equiv), Cs_2CO_3 (3.0 equiv), toluene (3.0 mL), 120 °C, 24 h, argon.

Pd(0), followed by carbopalladation of norbornene, forming species **A**. Subsequent *ortho*-C−H activation and elimination of HI with the aid of base gives a five-membered palladacycle **B**. The oxidative addition of *N*-benzoyloxyamines (R^3R^4N-OBz) to palladacyale **B** is proposed to form a Pd(IV) species, which undergoes reductive elimination, leading to the *ortho*-aminated arene **C**. Alternatively, the direct electrophilic amination of R^3R^4N-OBz with palladacycle **B** followed by N−O bond cleavage may also form amination complex **C**.[5,6] Next, in the case of *ortho*-blocked substrates ($R^1 \neq H$), retro-carbopalladation with concomitant expulsion of norbornene gives an aminated ArPd-OBz intermediate **D**, which reacts with $Zn(CN)_2$ to give the final product **3**, along with the regeneration of Pd(0) to complete the catalytic cycle. With species **C**, without *ortho*-substituent (R^1 = H), the C−H activation process can be repeated at the second *ortho*-position, leading to a new five-membered palladacycle **E** and the amination complex **F**, which following a similar pathway would afford the diaminated product **5**.

Scheme 5. Possible Catalytic Cycle



In conclusion, we have developed a palladium-catalyzed, norbornene-mediated tandem amination/cyanation reaction to synthesize *ortho*-aminated benzonitriles in moderate to excellent yields and with good functional group tolerance. This approach involves the formation of a C−N bond and a C−CN bond by using electron-deficient *N*-benzoyloxyamines as the electrophilic nitrogen source and $Zn(CN)_2$ as the nucleophilic coupling partner. This method is complementary to the reported protocols for the Catellani-type reaction and demonstrates that cyanide can act as a terminating reagent in the *ortho*-C−H amination reactions of aryl iodides. Moreover, it should stimulate the design of new synthetic methods to access valuable arylamine and benzonitrile derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02249.

All characterization data; ^1H and ^{13}C spectra (PDF)
Crystallographic data for **3a** (CIF)
Crystallographic data for **5b** (CIF)

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Notes

The authors declare no competing financial interest.

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