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Palladium-Catalyzed C(sp^2)–H Cyanation Using Tertiary Amine Derived Isocyanide as a Cyano Source

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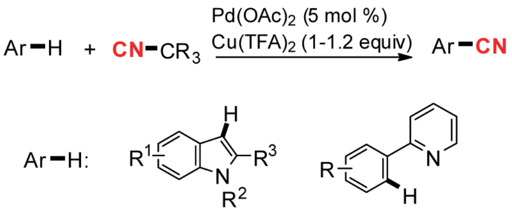
ABSTRACT



An unprecedented palladium-catalyzed cyanation of aromatic C–H bonds by using tertiary amine derived isocyanide as a novel cyano source was developed. Cu(TFA)$_2$ was used as a requisite stoichiometric oxidant. Mechanistic studies suggest that a tertiary carbon cation-based intermediate is involved following the C–N bond breakage.

The great versatility of aromatic nitriles in chemical transformations[1] and their frequent appearance in pharmaceuticals, biologically active products, and functional materials have motivated substantial efforts toward their preparation.[2] Classical methods of introducing a cyano group into aromatic rings require prefunctionalized arenes as precursors, such as diazonium salts (Sandmeyer reaction),[3] aryl halides (Rosenmund–von Braun reaction and transition-metal-catalyzed cross-couplings),[4] aldehydes (Schmidt reaction),[5] primary carboxyamides and aldoximes (by dehydration),[6] and many others.[7] However, these approaches suffer from multiple synthetic steps, a lack of atom economy, and/or the indispensable use of toxic cyano sources. Transition-metal-catalyzed direct functionalization of aromatic C–H bonds, with or without a directing group, has now been recognized as an atom- and step-efficient alternative for C–C and C–heteroatom bond formation.[8] Compared with other types of C–H functionalization reactions, straight cyanation of aromatic C–H bonds is relatively underdeveloped (Scheme 1). In 2006, Yu's group disclosed the first example of a Cu-catalyzed C–H cyanation of 2-arylpyridine using TMSCN as a CN source.[9] Later on, C–H cyanation by using other "normal" cyano sources, such as CuCN,[10] K$_4$[Fe(CN)$_6$], and TsN(Ph)CN,[11] were reported. Recently, Jiao et al.

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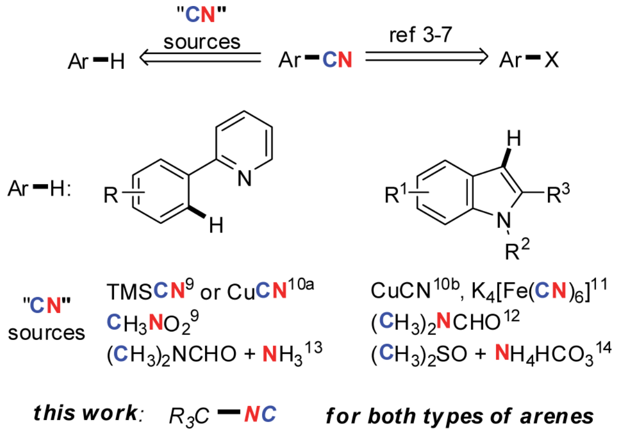
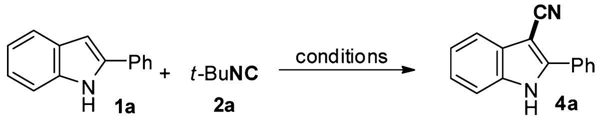
communicated a novel cyanation of indoles by employing DMF as the sole source of CN.[12] An unprecedented combined source (DMF and NH_3) of CN in the cyanation of 2-arylpyridines was first discovered by Chang's group.[13] A combination of DMSO and an ammonium ion was also found to be effective in the cyanation of indoles described by Cheng.[14] These methods take advantage of not only obviating the prefunctionalization of arenes but also applying novel nontoxic single or combined CN sources. Nevertheless, alternative approaches for the direct cyanation of arenes applicable to a broader substrate scope being performed under milder conditions are still desirable. Herein, we report a novel palladium-catalyzed $C(sp^2)$–H cyanation of free (NH)-indoles as well as 2-arylpyridines by using tertiary amine derived isocyanide as an unprecedented cyano source via C–N bond cleavage.

Scheme 1. Cyano Sources for C–H Cyanation



The distinctive reactivity of isocyanides makes them well-known in Lewis or Brønsted acid promoted Passerini and Ugi mutlicomponent reactions and others.[15] They also serve as isoelectronic equivalents of CO in transition-metal-catalyzed imination, carboxyamidation, and amidination reactions of prefunctionalized aryl halides[16] or aromatic C–H bonds in the presence of directing groups.[17] Recently, we reported an acid-controlled carboxyamidation of 2-unsubstituted indoles via palladium-catalyzed C–H activation followed by isocyanide insertion.[18] When 2-phenylindole **1a** was used as a substrate, the desired product *N-tert*-butyl-2-phenyl-1*H*-indole-3-carboxamide **3a** was obtained in less than 10% yield. In an effort to improve the yield of **3a** by changing the solvent from THF to HOAc, **3a** was isolated in 65% yield together with an unexpected side product, 2-phenyl-1*H*-indole-3-carbonitrile **4a** (5%). The intriguing mechanism prompted us to investigate this unique transformation in detail.

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst (10 mol %)	oxidant (1.0 equiv)	solvent	time (h)	yield (%)[b]
1	$Pd(TFA)_2$	$Cu(TFA)_2$	THF	3	34[c]
2	$Pd(TFA)_2$	$Cu(TFA)_2$	$ClCH_2CH_2Cl$	3	84
3	$Pd(OAc)_2$	$Cu(TFA)_2$	$ClCH_2CH_2Cl$	1	82
4	$Pd(TFA)_2$	$Cu(OAc)_2$	$ClCH_2CH_2Cl$	3	0[d]
5[e]	**$Pd(OAc)_2$**	**$Cu(TFA)_2$**	**$ClCH_2CH_2Cl$**	**1**	**80**
6[f]	$Pd(TFA)_2$	–	$ClCH_2CH_2Cl$	1	82
7[g]	–	$Cu(TFA)_2$	$ClCH_2CH_2Cl$	1	n.d.
8[h]	$Pd(OAc)_2$	–	$ClCH_2CH_2Cl$	1	0

[a] Conditions: **1a** (0.20 mmol), **2a** (0.24 mmol), catalyst (10 mol %), oxidant (1.0 equiv), solvent (1.0 mL), air, sealed tube, 70 °C. [b] Yield of isolated **4a**. [c] 46% of **3a** was also isolated. [d] *N*-Acetyl-*N*-*tert*-butyl-2-phenyl-1*H*-indole-3-carboxamide **3b** was obtained in 36% yield. [e] 5 mol % of $Pd(OAc)_2$ was used. [f] 1.0 equiv of $Pd(TFA)_2$ was used. [g] Homocoupling of **1a** at C3 occurred. [h] 1.0 equiv of $Pd(OAc)_2$ was used. 21 mg (36%) of **3a** and 34 mg (51%) of **3b** were isolated.

We started to optimize the reaction conditions by using 2-phenylindole **1a** and *tert*-butylisocyanide **2a** as substrates in the presence of 10 mol % of $Pd(TFA)_2$ as a catalyst and 1 equiv of $Cu(TFA)_2$ as an oxidant. When the reaction was performed in THF at 70 °C, the isolated yield of **4a** was improved to 34%, together with a significant amount of **3a** (46%, entry 1, Table 1). To our delight, the formation of **3a** was completely suppressed when the solvent was changed to $ClCH_2CH_2Cl$, and the yield of **4a** was increased dramatically to 84%. $Pd(OAc)_2$ was also effective in catalyzing this reaction, producing **4a** in a compatible yield (82%, entry 3). It was intriguing that when the oxidant was switched from $Cu(TFA)_2$ to $Cu(OAc)_2$, *N*-acetyl-*N*-*tert*-butyl-2-phenyl-1*H*-indole-3-carboxamide **3b** was observed to be the only isolatable product,[19] indicating the vital role played by the counteranion in cyanation (entry 4). Reactions with other oxidants led to either unidentified reaction mixtures or recovery of **1a** (see Supporting Information). The loading of $Pd(OAc)_2$ can be reduced to 5 mol %, and the yield of **4a** was almost maintained (entry 5). A control reaction with a stoichiometric amount of $Pd(TFA)_2$ in the absence of any copper

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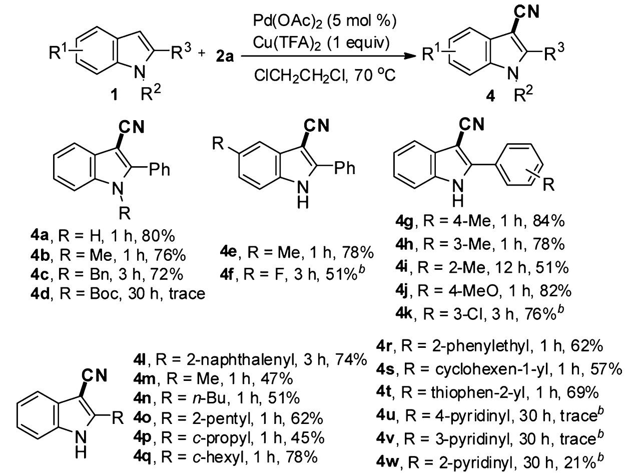
salt provided **4a** in an equal yield of 82%. However, a reaction with only 1 equiv of $Cu(TFA)_2$ resulted in no desired product formation, indicating that a palladium catalyst was indispensable. Finally, a reaction with a stoichiometric amount of $Pd(OAc)_2$ was performed. Interestingly, secondary and tertiary carboxyamidated indole derivatives **3a** and **3b** were isolated in 36% and 51% yields, respectively. This result further proved that the counteranion trifluoroacetate (CF_3COO^-) was necessary in the desired cyanation product formation (entry 8).

Next, the scope of indole derivatives was investigated under the optimal reaction conditions involving $Pd(OAc)_2$ (5 mol %) and $Cu(TFA)_2$ (1 equiv), in $ClCH_2CH_2Cl$ at 70 °C. 2-Phenyl substituted indoles with *N*-methyl and *N*-benzyl groups were cyanated smoothly in 76% and 72% yields, respectively (**4b** and **4c**, Scheme 2). However, *N*-Boc protected 2-phenylindole furnished only a trace amount of the product even when the reaction time was extended to 30 h (**4d**), suggesting that the electron density on indole was crucial. 5-Methyl-2-phenylindole was cyanated in 78% yield (**4e**) under the standard conditions. In contrast, for an electron-deficient 5-fluoro substituted analogue, addition of PivOH (1.0 equiv) was necessary to drive the reaction to completion at 80 °C (**4f**, 51%). To some extent, the reaction was sensitive to methyl substitution on the ortho position of the 2-phenyl ring, delivering **4i** in a much lower yield (51%) than a meta (**4h**, 78%) or para (**4g**, 84%) counterpart. Other functional groups on the 2-phenyl ring, including Cl and OMe, also survived the reaction conditions, giving corresponding indole-3-carbonitriles **4j** and **4k** in 82% and 76% yields, respectively. Moreover, 2-alkyl-substituted indoles were also suitable substrates in the current C3 cyanation protocol, albeit in lower yields. Various acyclic and cyclic 2-alkyl-1*H*-indole-3-carbonitriles (**4m**–**s**) were produced in moderate to good yields. 2-(Thiophen-2-yl)-1*H*-indole was cyanated to its corresponding indole-3-carbonitrile **4t** in 69% yield. However, in the case of electron-deficient pyridine substitued indoles, only 2-(pyridin-2-yl)-1*H*-indole was able to be cyanated in 21% yield (**4w**), probably due to coordination of the pyridine nitrogen with the palladium catalyst.

To explore the feasibility of the current protocol in the cyanation of electron-deficient arenes, 2-phenylpyridine **5a** was first used as a model substrate. Harsher reaction conditions employing the same palladium catalyst and a copper oxidant in the presence of 0.5 equiv of TsOH in toluene at 120 °C were identified, furnishing a monocyanated product **6a** in a moderate yield (41%, Scheme 3). Substituents with varied electronic properties, such as methyl (**6b**), acetyl (**6c**), chloro (**6d**), and phenyl (**6e**), on the meta and para positions of the phenyl ring were tolerable under the reaction conditions, albeit in low to acceptable yields. Quinoline could act as a directing group as well, delivering the corresponding aryl nitrile **6g** in 45% yield. In addition, benzo[*h*]quinoline demonstrated the highest efficiency in the current cyanation reaction (66%, **6h**).

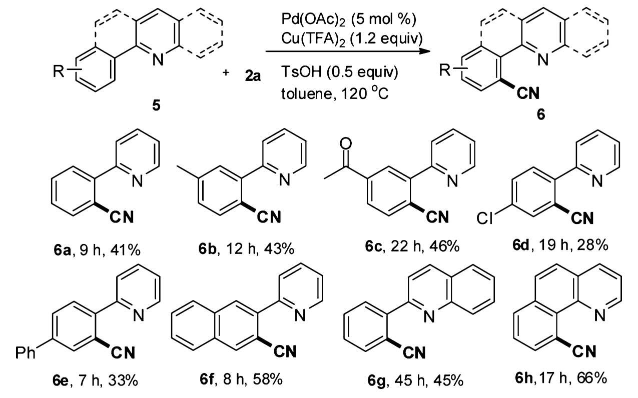
To confirm the origin of the carbon in the cyano group, ^{13}C-labeled 1-adamantanylisocyanide **2b** (see Supporting Information) was synthesized and subjected to the standard reaction conditions in place of **2a**. As anticipated, **4a** with complete ^{13}C incorporation was formed in 86% yield, indicating that the CN in the product was derived from isocyanide. Another tertiary amine derived isocyanide **2c** was also a suitable substrate to deliver a CN group to C3 of **1a** (eq 1, Scheme 4). The rest of **2c** was detected as an inseparable mixture of 1-(4-fluorophenyl)-2-methyl-propene **7** and 3-(4-fluorophenyl)-2-methyl-propene **8** in a 2:1 ratio as indicated by ^1H NMR, indicating a tertiary carbon cation might be an intermediate. In contrast, when secondary amine and aniline derived isocyanides were used as substrates, only the corresponding carboxyamidated products were obtained (see Supporting Information).

Scheme 2. Scope of Indole Substrates[a]



[a] Reaction conditions: **1** (0.4 mmol), **2a** (0.48 mmol), $Pd(OAc)_2$ (5 mol %), $Cu(TFA)_2$ (1.0 equiv), $ClCH_2CH_2Cl$ (2.0 mL), air, sealed tube, 70 °C. [b] PivOH (1.0 equiv) was added, 80 °C.

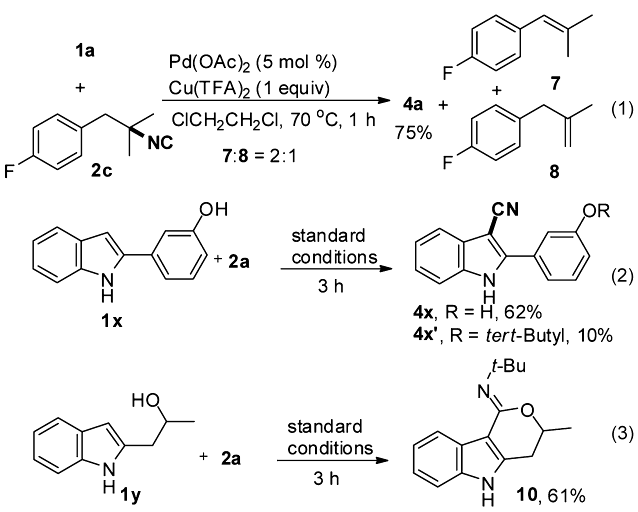
Scheme 3. Scope of Electron-Deficient Arenes[a]



[a] Reaction conditions: **5** (0.4 mmol), **2a** (0.60 mmol, 1.5 equiv), $Pd(OAc)_2$ (5 mol %), $Cu(TFA)_2$ (1.2 equiv), TsOH (0.5 equiv), toluene (2.0 mL), air, sealed tube, 120 °C, isolated yields of **6**.

Substrate **1x** bearing a phenolic hydroxy group on the meta position of the 2-phenyl ring was employed as a substrate under the standard conditions (eq 2). Surprisingly,

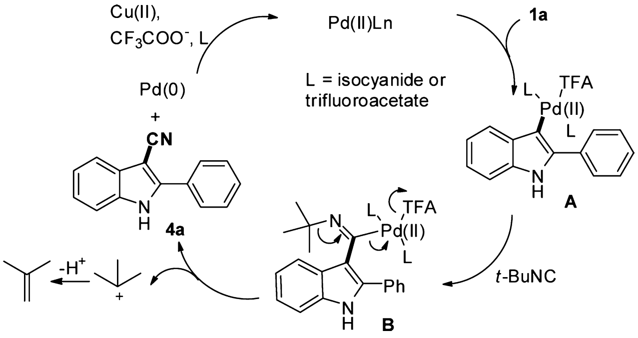
Scheme 4. Mechanistic Studies



together with the normal cyanated product **4x**, another cyanated product **4x′** with a *tert*-butyl group attached to the phenol oxygen was also isolated in 10% yield, most likely, resulting from the *tert*-butyl carbon cation being trapped by the free phenol. In addition, substrate **1y** containing a secondary alcohol was initially designed to trap the carbon cation intermediate. Instead of cyanation product formation, cyclic imidic ester **10** was isolated in 61% yield, suggesting that a cyclic imidoyl palladium(II) intermediate was formed rather than the in situ generation of a cyanide anion (eq 3).

Based on the results of mechanistic studies, a plausible reaction mechanism is proposed in Scheme 5. Initially, electrophilic palladation of Pd(II) on C3 of the indole gives the σ-indolylpalladium(II) intermediate **A**. The following migratory insertion of isocyanide generates the key imidoyl palladium(II) intermediate **B**, in which the loosely coordinated trifluoroacetate makes the palladium center more electrophilic. The high electrophilicity of Pd(II) and the stability of the tertiary carbon cation are the driving forces to break the C−N bond, leading to the cyanation product, palladium(0) species, and 2-methylpropene by proton elimination via a *tert*-butyl carbon cation intermediate. The lack of any one of the “driving forces” will lead the reaction pathway to direct reductive elimination from an intermediate similar to **B**, giving a secondary and/or tertiary carboxyamide. Oxidation of Pd(0) by Cu(II) regenerates the active Pd(II) catalyst.

Scheme 5. Proposed Reaction Mechanism



In summary, we have developed an unprecedented palladium-catalyzed cyanation of aromatic C−H bonds by using tertiary amine derived isocyanide as a novel cyano source. Cu(TFA)$_2$ was used as a requisite stoichiometric oxidant, in which the trifluoroacetate counteranion plays a vital role in promoting cyanation product formation. Both electron-rich 2-alkyl(aryl)indoles and electron-deficient 2-arylpyridine derivatives/analogues can be cyanated. Mechanistic studies suggest that a key electrophilic imidoyl palladium(II) intermediate is involved followed by the C−N bond breakage to give the cyanation product and a tertiary carbon cation-based fragment. The carbon cation intermediate can be partially trapped by an inbuilt phenolic nucleophile.

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Supporting Information Available. Experimental procedure, and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.