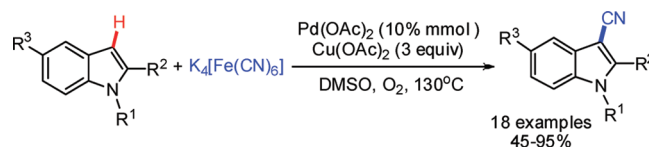


Palladium-Catalyzed Direct Cyanation of
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Received January 8, 2010

ABSTRACT

Direct cyanation of indole derivatives has been achieved with nontoxic $K_4[Fe(CN)_6]$ as cyanating agent through Pd-catalyzed C–H bond activation.

Aromatic nitriles have found wide applications as pharmaceuticals, agrochemicals, dyes, and so on.¹ They are also important intermediates in organic synthesis.² Traditional methods for introducing a cyano group into the aromatic ring are Sandmeyer reaction³ and Rosenmund–von Braun reaction.⁴ In both cases, copper(I) cyanide is used as cyanating source. More recently, transition-metal-catalyzed cyanation of aromatic halide has emerged as a more attractive method to synthesize aromatic nitriles.⁵ In contrast to these reactions, in which either aromatic halides or amines are used as starting materials, direct cyanation through transition-metal-catalyzed C–H bond activation is obviously more attractive. Although transition-metal-catalyzed aromatic C–H bond activation has witnessed explosive development in recent

years,⁶ there are only a few reports on cyanation through direct C–H bond activation. Yu and co-workers in 2006 reported a chelation-assisted Cu-catalyzed cyanation of the C–H bond using Me_3SiCN and $MeNO_2$ as cyanide sources.⁷ Subsequently, Cheng and co-workers disclosed their study on Pd-catalyzed direct cyanation with copper(I) cyanide as cyanating agent.⁸ The same group recently reported a cyanation with safe and nontoxic potassium hexacyanoferrate(III) ($K_3[Fe(CN)_6]$) in a Pd-catalyzed cascade bromination/cyanation reaction.⁹ However, to our knowledge, transition-metal-catalyzed direct cyanation of the aromatic C–H

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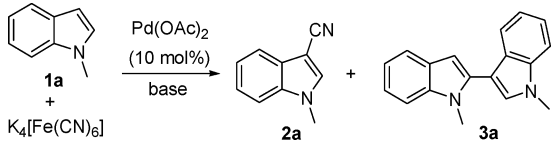
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bond without chelation assistance is not known in the literature.¹⁰ On the other hand, indoles represent an important class of aromatic compounds frequently encountered in natural products and pharmaceuticals.¹¹ Transition-metal-catalyzed selective and controllable C–H functionalization of indoles has been extensively studied in recent years.^{12,13} Herein we report a Pd-catalyzed cyanation of indoles through C–H bond activation. The reaction uses safe and nontoxic $K_4[Fe(CN)_6]$ as cyanating agent¹⁴ and selectively introduces a cyano group into the 3-position of indoles with high efficiency.

On the outset of this investigation, we used *N*-methylindole **1a** as model substrate with $K_4[Fe(CN)_6]$ to screen suitable reaction conditions. In order to ensure sufficient solubility of $K_4[Fe(CN)_6]$, dipolar aprotic solvents such as DMF, DMSO, *N,N*-dimethyl acetamide (DMA), and 1-methyl-2-pyrrolidinone (NMP) were examined. C3 cyanation took place in the presence of $Pd(OAc)_2$ (10%) with $Cu(OAc)_2$ (3 equiv) and O_2 (1 atm) as oxidant in DMSO at 130 °C. However, the homocoupling of **1a** predominated under such conditions, giving product **3a** (Table 1, entry 1).¹⁵ To our delight, we found that addition of potassium acetate (KOAc) in above system could dramatically suppress the homocoupling (entry 2). Further optimization showed that reactions in the other three solvents (DMF, DMA, NMP) gave almost exclusively C3 cyanation product **2a**, but the reactions took

Table 1. Optimization of Pd-Catalyzed Cyanation of **1a** with $K_4[Fe(CN)_6]$ ^a



entry	solvent	base	additive	time (h)	yield (%) ^b	2a/3a ^c
1	DMSO	–	–	5	78	1:3
2	DMSO	KOAc	–	3	85	3:1
3	DMF	KOAc	–	24	66	21:1
4	DMA	KOAc	–	36	51	21:1
5	NMP	KOAc	–	48	44	20:1
6	DMF/DMSO (10:1)	KOAc	–	3	78	3:1
7	DMF	CsOAc	–	4	71	11:1
8	DMF	NaOAc	–	36	50	32:1
9	DMF	KOAc	<i>n</i> Bu ₄ NCl	12	76	11:1
10	DMF	KOAc	<i>n</i> Bu ₄ NBr	36	56	8:1
11	DMF	KOAc	BnEt ₃ NCl	36	38	11:1
12	DMF	KOAc	3-NO ₂ Py	36	30	8:1
13^d	DMF	KOAc	–	24	73	18:1
14 ^e	DMF	KOAc	–	24	0	–

^a Unless otherwise noted, the reaction conditions are as follows: *N*-methylindole **1a** (0.45 mmol), $K_4[Fe(CN)_6]$ (0.5 equiv), $Pd(OAc)_2$ (0.1 equiv), $Cu(OAc)_2$ (3.0 equiv), base (2.0 equiv), additive (1.0 equiv) in anhydrous solvent (5 mL), 130 °C, with O_2 balloon. ^b Isolated yield. ^c Ratio determined by ¹H NMR. ^d The reaction was carried out at 150 °C. ^e The reaction was carried out in the absence of $Pd(OAc)_2$.

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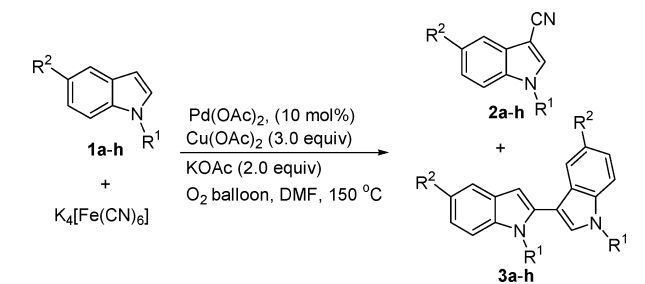
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longer with slightly decreased yields (entries 3–5). Reaction with a mixed solvent of DMSO and DMF improved the yield, but the ratio of **2a** to **3a** dropped significantly (entry 6). Switch of KOAc to NaOAc or CsOAc could not significantly increase the yields (entries 7 and 8). Adding additional additives such as *n*-Bu₄NCl, *n*-Bu₄NBr, BnEt₃NCl, or 3-nitropyridine also failed to improve the reaction (entries 8–12). The yield of the reaction and the ratio of **2a** to **3a** were slightly improved by increasing reaction temperature (entry 13). Finally, a control experiment demonstrated that no product **2a** could be detected when the reaction was carried out in the absence of $Pd(OAc)_2$.

Under the optimized conditions, the substrate scope of this reaction was investigated (Table 2).¹⁶ It was observed that the reaction was significantly affected by electronic effects of the substituents on the indole substrates. The reaction of *N*-methylindole with electron-donating substituent on the benzene ring of indole substrates proceeded efficiently (entries 2 and 3). On the contrary, for 5-nitro-*N*-methylindole,

(16) Typical procedure for cyanation of indoles. Under O_2 balloon or open air, a reaction tube was charged with indoles (0.45 mmol), $K_4[Fe(CN)_6]$ (0.5 equiv), $Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2$ (3 equiv), and dry DMF or DMSO (5 mL). In the reaction with **1a–h**, KOAc (2.0 equiv) was added. The mixture was kept stirring at 130 or 150 °C for 2–36 h. After completion of the reaction, the solution was extracted with ethyl acetate (3 × 10 mL), then combined solution washed with H_2O and brine, and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a crude product which was purified on silica gel (petroleum ether/EtOAc) to afford the products.

Table 2. Pd-Catalyzed Direct C–H Bond Cyanation of Indoles **1a–h** with $K_4[Fe(CN)_6]^a$ 

entry	indole 1a–h	time (h)	yield (2 , %) ^b	2/3 ^c
1	$R^1 = Me, R^2 = H$	24	73	18:1
2	$R^1 = Me, R^2 = Me$	12	74	>19:1
3	$R^1 = Me, R^2 = OMe$	12	81	>19:1
4	$R^1 = Me, R^2 = NO_2$	48	trace	–
5	$R^1 = Ph, R^2 = H$	24	48	>19:1
6	$R^1 = p\text{-MeOC}_6\text{H}_4, R^2 = H$	24	50	10:1
7	$R^1 = Bn, R^2 = H$	24	56	15:1
8	$R^1 = H, R^2 = Me$	24	trace	–

^a Reaction conditions: indoles **1a–h** (0.45 mmol), $K_4[Fe(CN)_6]$ (0.5 equiv), $Pd(OAc)_2$ (0.1 equiv), $Cu(OAc)_2$ (3.0 equiv), KOAc (2.0 equiv), dry DMF (5 mL), 150 °C, under O_2 balloon. ^b Isolated yield. ^c Ratio determined by 1H NMR.

only a trace amount of the desired product could be detected (entry 4). The substituent on the nitrogen showed marginal effect on the reaction (entries 5–7), but reaction with an indole substrate bearing no N-substituent provided trace desired cyanation product (entry 8).

Since the only byproduct in this Pd-catalyzed cyanation is homocoupling of indole at the C2 and C3 positions, we then decided to examine the indole substrates with a substituent at the C2 position. Thus, 1,2-dimethyl-1*H*-indole **4a** was employed as a model substrate to screen suitable reaction conditions for this type of indole substrate (Table 3). The cyanation product **5a** was isolated in moderate to good yields in the presence of 10% $Pd(OAc)_2$ as catalyst and $Cu(OAc)_2$ (3.0 equiv)/ O_2 as oxidant in three different solvents (DMF, DMA, and DMSO) at 130 °C (Table 3, entries 1–3). The results indicated that DMSO was a better reaction media than DMF and DMA, and in contrast to the reaction of **1a**, KOAc was not required for reaction of **4a**. We then attempted to reduce the catalyst and oxidant loading, but under such conditions the yields decreased and the reaction took longer (entries 4–7). We also found that reaction temperature significantly affected the reaction. Only trace quantities of the desired product could be detected at 80 °C, and the main byproduct was 1,2-dimethyl-1*H*-indol-3-yl acetate (entry 10). We speculate that this may be attributed to the difficulty of cyanide transfer from $K_4[Fe(CN)_6]$ when reaction temperature was below 120 °C. Interestingly, comparable yield could be obtained by carrying out the reaction under air instead of O_2 (entry 11). However, when the reaction was carried out under N_2 , only 67% of the desired product was isolated and the reaction took much longer. Finally, as in the case of cyanation of aryl halides,⁵

Table 3. Optimization of Pd-Catalyzed Cyanation of **4a** with $K_4[Fe(CN)_6]^a$

Reaction scheme showing the optimization of Pd-catalyzed cyanation of **4a** with $K_4[Fe(CN)_6]$. The reaction conditions are: $Pd(OAc)_2$, $Cu(OAc)_2$, solvent, temp.

entry	solvent	$Pd(OAc)_2$ (mol %)	$Cu(OAc)_2$ (equiv)	T (°C)	t (h)	yield (%) ^b
1	DMF	10	3	130	24	76
2	DMA	10	3	130	24	58
3	DMSO	10	3	130	5	95
4	DMSO	10	2	130	6	81
5	DMSO	10	1	130	24	51
6	DMSO	10	0	130	48	18
7	DMSO	5	3	130	6	69
8	DMSO	0	3	130	24	0
9	DMSO	10	3	110	36	67
10	DMSO	10	3	80	72	trace
11 ^c	DMSO	10	3	130	5	92
12 ^d	DMSO	10	3	130	36	67
13 ^{c,e}	DMSO	10	3	130	5	86
14 ^{c,f}	DMSO	10	3	130	5	78

^a Unless otherwise noted, the reaction conditions are as follows: solvent (5 mL), **4a** (0.3 mmol), $K_4[Fe(CN)_6]$ (0.5 equiv), under oxygen. ^b Isolated yield. ^c Reaction was carried out under open air. ^d Reaction was carried out under nitrogen. ^e $K_4[Fe(CN)_6]$ (0.4 equiv). ^f $K_4[Fe(CN)_6]$ (0.3 equiv).

it would be desirable that all six cyanide anions in $K_4[Fe(CN)_6]$ were transferred into the product. This was indeed possible, but the yields decreased gradually with the decrease of $K_4[Fe(CN)_6]$ (entries 13 and 14).

A series of 2-substituted indoles **4a–q** were then subjected to the optimized reaction conditions, and the results are summarized in Figure 1.¹⁶ We observed that the reaction was sensitive to the electronic nature of N-substituents of the indole substrates. Both *N*-alkyl- and *N*-arylindoles were smoothly converted to the 3-cyanoindoles under the standard conditions (**5a,d,g–n**). The reaction also worked with indoles without N-substituent (**5b,c,e,f**), whereas the indoles with *N*-acetyl, *N*-phenylsulfonyl, or *N*-Boc substituents were inactive under the same conditions (**5o–q**). The substituents on the C2 position of indoles also affect the reaction (**5f–j**). Electron-withdrawing groups, such as an ester group, completely deactivated the indole substrate (**5h**). However, the electronic nature of substituents on the benzene ring of the indoles had relatively less effect on the cyanation (**5c–e**).

A plausible mechanism for the cyanation of indoles is proposed in Scheme 1. First, the cyanide anion is transmetalated from $K_4[Fe(CN)_6]$ to palladium to form Pd(II) species **A**, which undergoes electrophilic palladation at the C3 position of the indole to afford intermediate **B**. Reductive elimination occurs from intermediate **B** to give the product along with a Pd(0) species, which was oxidized to Pd(II) by Cu(II) and/or air to complete the catalytic cycle. A general problem of metal-catalyzed cyanation is the deactivation of the metal catalyst due to the formation of stable cyanide complexes. Thus, controlling of the concentration of cyanide ion is crucial for this type of reaction.^{5c,14} We attribute the

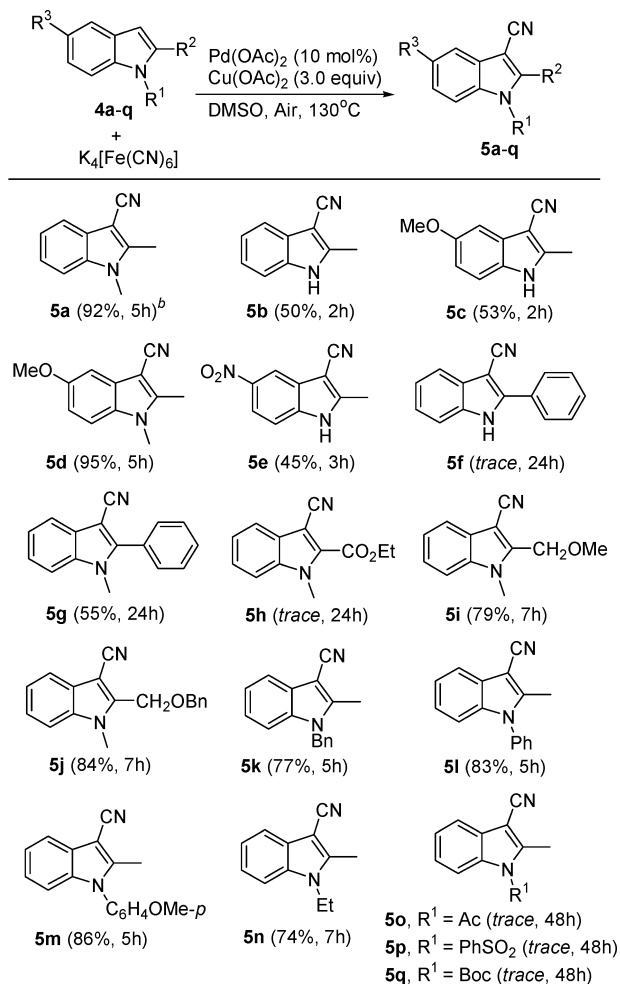
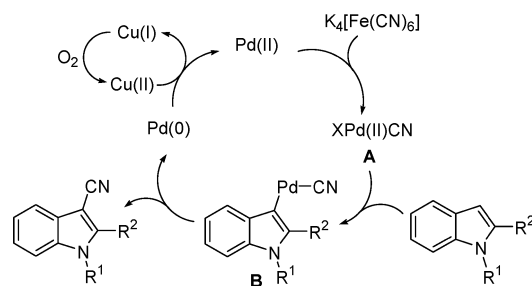


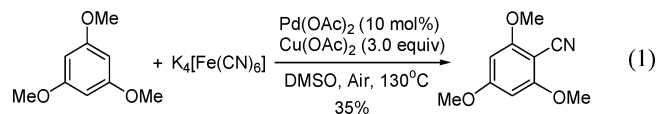
Figure 1. Pd-catalyzed direct C–H bond cyanation of indole **4a–q** with $\text{K}_4[\text{Fe}(\text{CN})_6]$. Reaction conditions: indoles **4a–q** (0.45 mmol), $\text{K}_4[\text{Fe}(\text{CN})_6]$ (0.5 equiv), $\text{Pd}(\text{OAc})_2$ (10 mol %), $\text{Cu}(\text{OAc})_2$ (3 equiv), DMSO (5 mL), 130 °C, under air. ^bIsolated yield and reaction time in parentheses.

success of this Pd-catalyzed cyanation to the slow liberation of cyanide anion from $\text{K}_4[\text{Fe}(\text{CN})_6]$. As a comparison, we also carried out the cyanation with Me_3SiCN or $\text{Zn}(\text{CN})_2$ as cyanide sources under otherwise identical conditions. Only trace amount of cyanation product could be obtained in both cases.

Scheme 1. Mechanistic Rationale



Encouraged by the success of direct cyanation of indoles, we next attempted to explore the cyanation of other aromatic systems under the same reaction conditions. Thus, electron-rich arenes, including pyrrole, benzofuran, benzo[*b*]thiophene, benzo[*d*]thiazole, and benzo[*d*]oxazole, were subjected to identical reaction conditions, but only a trace amount of the cyanation products could be identified in all cases. However, the reaction with electron-rich 1,3,5-trimethoxybenzene afforded the expected product in 35% yield (eq 1).



In summary, we have reported the first selective cyanation of indoles through a Pd-catalyzed direct C–H bond functionalization reaction. Current efforts are directed toward the extension of the Pd-catalyzed cyanation to other electron-rich arenes.

Acknowledgment. The project is supported by NSFC and 973 Program (No. 2009CB825300).

Supporting Information Available: Experiment procedure, characterization data, ¹H and ¹³C NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL1000439