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Palladium-Catalyzed Three-Component Arylcyanation of Internal Alkynes with Aryl Bromides and $K_4[Fe(CN)_6]$

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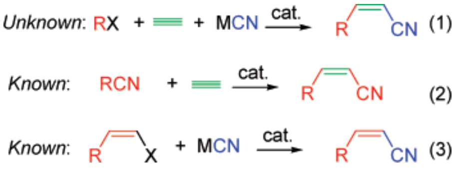
ABSTRACT

The one-pot, palladium-catalyzed, three-component coupling of aryl bromides, internal alkynes, and environmentally friendly $K_4[Fe(CN)_6]$ provides an efficient and direct method for the preparation of β-arylalkenylnitriles.

Transition-metal-catalyzed domino coupling of aryl halides, alkynes, and various functional groups has become a simple and convenient method in organic synthesis. These reactions proceed via a key vinylpalladium intermediate, which reacts with various terminators to give aromatic derivatives or multisubstituted olefins.[1] However, this method has not been applied to the synthesis of alkenylnitrile (eq 1), as the resulting products contain important structural motifs of numerous biologically active compounds.[2] In addition, the cyanide group has broad synthetic applications in organic and material chemistry.[3]

Several transition-metal-catalyzed or -mediated alkenylnitrile formations from two-component reactions have been reported, such as additions of cyanide-containing σ bonds to alkynes (eq 2),[4] and cyanation of alkenyl halides (eq 3).[5] Despite the significant progress made in this area, there is still a need for new methods that involve readily available starting material and environmentally friendly cyanation reagent.



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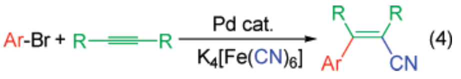
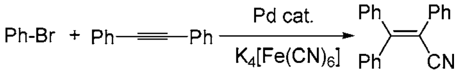
Herein, we describe the first example of Pd-catalyzed, sequential three-component arylcyanation of internal alkynes with aryl bromides and environmentally friendly $K_4[Fe(CN)_6]$,[6] which provided an efficient route for the synthesis of highly substituted β-arylalkenylnitriles from simple starting materials (eq 4).



In an initial research, we found that the reaction of bromobenzene (1 equiv), diphenylacetylene (1.5 equiv), and $K_4[Fe(CN)_6]$ (0.3 equiv) in the presence of $Pd(OAc)_2$ (2 mol %) and Na_2CO_3 (1 equiv) in *N*,*N*-dimethylacetamide (DMAc)-at 120 °C for 5 h, provided the desired product **3a** in a low but promising yield (Table 1, entry 1, 41%) along with 38% yield of tetraphenylnaphthalene.[7] Further research revealed that the formation of tetraphenylnaphthalene could be suppressed significantly by changing the molar ratio of **1a**:**2a** from 1:1.5 to 1.5:1; the isolated yield of **3a** was increased to 76% (entry 2). The base played an important role in this reaction. Only trace amount of the desired product **3a** was obtained when NEt_3 was used (entry 3). No satisfied results were obtained with K_2CO_3 and NaOAc (entries 4, 5). Na_2CO_3 was observed to furnish the highest yield (entry 2). The reaction in DMAc (entry 2) is better than the reaction in DMF or NMP (entries 7, 8).

Table 1. Pd-Catalyzed Arylcyanation of Diphenylacetylene[a]



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

entry	base	cat.	solvent	yield(%)[b]
1	Na_2CO_3	$Pd(OAc)_2$	DMAc	41[c]
2	Na_2CO_3	$Pd(OAc)_2$	DMAc	76
3	NEt_3	$Pd(OAc)_2$	DMAc	trace
4	K_2CO_3	$Pd(OAc)_2$	DMAc	20
5	NaOAc	$Pd(OAc)_2$	DMAc	46
6	$NaHCO_3$	$Pd(OAc)_2$	DMAc	68[d]
7	Na_2CO_3	$Pd(OAc)_2$	DMF	53
8	Na_2CO_3	$Pd(OAc)_2$	NMP	38
9	Na_2CO_3	$PdCl_2$	DMAc	45
10	Na_2CO_3	$Pd(PPh_3)_4$	DMAc	40
11	Na_2CO_3	$Pd(OAc)_2 + PPh_3$(4 mol %)	DMAc	43
12	Na_2CO_3	$Pd(OAc)_2 + PCy_3$(4 mol %)	DMAc	41

[a] All reactions were carried out with 0.75 mmol of **1a,** 0.5 mmol of **2a**, 0.15 mmol of $K_4[Fe(CN)_6]$, 1 equiv of base and 2 mol % of catalyst in 1 mL of DMAc under nitrogen atmosphere at 120 °C for 5 h. [b] Isolated yield of **3a**. [c] 0.5 mmol of **1a**, 0.75 mmol of **2a**. [d] 2 equiv of $NaHCO_3$ were used.

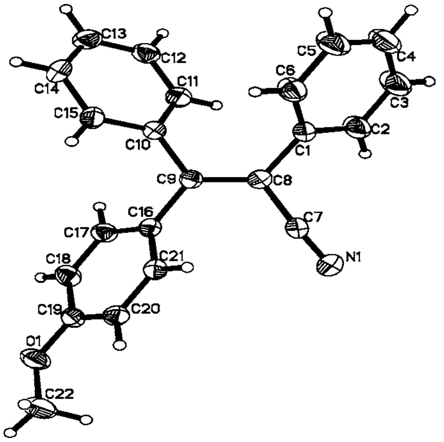


Figure 1. Crystal structure of **3f**.

When $PdCl_2$ or $Pd(PPh_3)_4$ was used as catalyst, **3a** was isolated in a low yield (entries 9, 10). The side reaction was found to be enhanced significantly by adding phosphine ligands, and tetraphenylnaphthalene was isolated in more than 40% yield (entries 11, 12). Although $Pd(OAc)_2$-catalyzed cyanation of aryl bromides with $K_4[Fe(CN)_6]$ has been developed efficiently,[6c] to our delight, this three-component reaction proceeded with high selectivity, and only a very small amount of benzonitrile was observed by GC.

As indicated in Table 1, the reaction conditions of entry 2 were used for the further examination of the scope of this reaction with various aryl bromides and internal alkynes. The typical results are summarized in Table 2. As shown in Table 2, all of electron-neutral (entries 1, 9, 11, 12, 13), electron-rich (entries 2, 3), and electron-poor (entries 7, 8) aryl bromides could afford the fully substituted α,β-unsaturated nitriles in good yields. Even substrates with stronger electron-donating groups, such as 4-dimethylaminobromobenzene and 4-bromoanisole, could work well when $NaHCO_3$ was used as base (entries 5, 6). Dialkyl-substituted alkynes also could be used in this reaction. For example, 5-decyne and 4-octyne provided the corresponding alkyl-substituted acrylonitriles **3l** and **3m** in 66% and 61% yields, respectively (entries 12, 13).

Ortho substituents hampered the reaction and led to the formation of the product in low yields (entry 4, 39%). The starting materials were recovered when the reaction was carried out with 2,6-dimethylbromobenzene. The reaction with more reactive iodobenzene provided **3a** only in 46% yield, and tetraphenylnaphthalene was isolated in 50% yield. Unfortunately, under the standard conditions, heteroaryl

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(6) For application of $K_4[Fe(CN)_6]$ as cyanation reagent, see: (a) Schareina, T.; Zapf, A.; Beller, M. *Chem. Commun.* **2004**, *12*, 1388. (b) Schareina, T.; Zapf, A.; Beller, M. *J. Organomet. Chem.* **2004**, *689*, 4576. (c) Weissman, S. A.; Zewge, D.; Chen, C. *J. Org. Chem.* **2005**, *70*, 1508. (d) Schareina, T.; Zapf, A.; Beller, M. *Tetrahedron Lett.* **2005**, *46*, 2585. (e) Grossman, O.; Gelman, D. *Org. Lett.* **2006**, *8*, 1189. (f) Li, L. H.; Pan, Z. L.; Duan, X. H.; Liang, Y. M. *Synlett* **2006**, *13*, 2094. (g) Cheng, Y. N.; Duan, Z.; Li, T.; Wu, Y. J. *Synlett* **2007**, *4*, 543. (h) Cheng, Y. N.; Duan, Z.; Li, T.; Wu, Y. J. *Lett. Org. Chem.* **2007**, *4*, 352. (i) Pinto, A.; Jia, Y. X.; Neuville, L.; Zhu, J. P. *Chem. Eur. J.* **2007**, *13*, 961. (j) Schareina, T.; Zapf, A.; Mägerlein, W.; Müller, N.; Beller, M. *Chem. Eur. J.* **2007**, *13*, 6249. (k) Mariampillai, B.; Alliot, J.; Li, M. Z.; Lautens, M. *J. Am. Chem. Soc.* **2007**, *129*, 15372.

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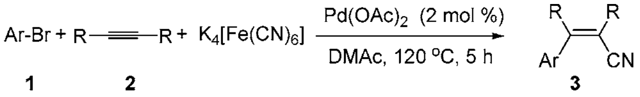
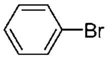
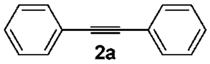
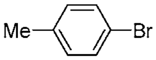
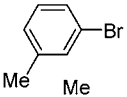
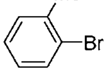
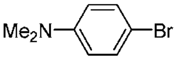
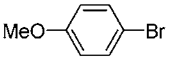
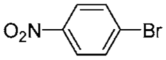
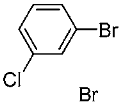
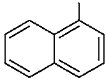
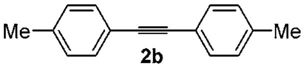
Table 2. Palladium-Catalyzed Arylcyanation of Internal Alkyne with Aryl Bromides and $K_4[Fe(CN)_6]$[a]



entry	Ar-Br		R—≡—R	products	yield(%)[b]
1		**1a**	 **2a**	**3a**	76
2		**1b**	**2a**	**3b**	73
3		**1c**	**2a**	**3c**	65
4		**1d**	**2a**	**3d**	39
5		**1e**	**2a**	**3e**	65[c]
6		**1f**	**2a**	**3f**	63[c]
7		**1g**	**2a**	**3g**	65
8		**1h**	**2a**	**3h**	68
9		**1i**	**2a**	**3i**	85
10	**1b**		 **2b**	**3j**	70
11	**1i**		**2b**	**3k**	80
12	**1i**		Bu—≡—Bu **2c**	**3l**	66
13	**1i**		Pr—≡—Pr **2d**	**3m**	61

[a] All reactions were carried out with 0.75 mmol of aryl bromide, 0.5 mmol of internal alkyne, 0.15 mmol of $K_4[Fe(CN)_6]$, 1 equiv of Na_2CO_3, and 2 mol % of $Pd(OAc)_2$ in 1 mL of DMAc under N_2 atmosphere at 120 °C for 5 h. [b] Isolated yield. [c] 2 equiv of $NaHCO_3$ were used.

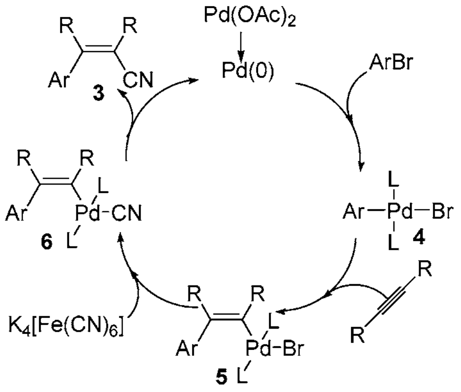
bromides and aryl chlorides exhibited very low reactivity, and no desired product was obtained.

It is worth noting that the reaction proceeded with high stereoselectivity and gave the *cis*-addition product. The structure of **3f** was confirmed by X-ray analysis (Figure 1).

We proposed the following reaction mechanism (Scheme 1): (1) oxidative addition of the aryl bromide to Pd(0) giving an arylpalladium(II) intermediate **4**; (2) *cis*-carbopalladation of the internal alkyne, giving a vinylic palladium intermediate **5**; (3) ligand exchange with cyanide ion[6b] of $K_4[Fe(CN)_6]$ to form a new intermediate **6**; (4) reductive elimination, producing acrylonitrile **3** with simultaneous regeneration of the Pd(0) catalyst.

In summary, we developed an efficient three-component coupling procedure for stereoselective synthesis of fully substituted α,*β*-unsaturated nitriles. The use of readily accessible internal alkynes, aryl bromides, and an environmentally friendly cyanation reagent made this Pd-catalyzed arylcyanation attractive. This reaction also provides a simple

Scheme 1. Proposed Reaction Mechanism



and direct method to β-arylalkenylnitriles, potential intermediates of biologically active compounds as well as organic materials.[4f] Efforts for expansion of the scope, especially with heteroaryl halides, and further utilization of the reaction products are currently underway in our laboratories.

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Supporting Information Available: General reaction procedures, copy of ^{1}H and ^{13}C NMR spectra of products and crystallographic data of **3f** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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