Palladium-Catalyzed Cyanation under Mild Conditions: A Case Study to Discover Appropriate Substrates among Halides and Pseudohalides

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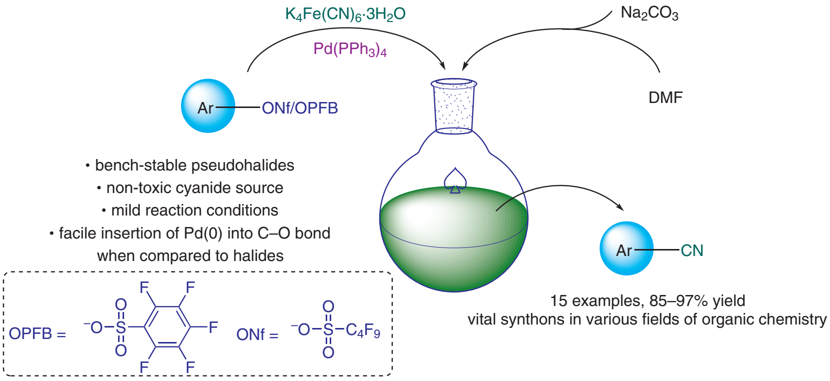

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Abstract A case study has been effectively carried out to identify a suitable substrate among halides and pseudohalides for the palladium-catalyzed cyanation reactions under mild conditions. Among the various substrates considered for evaluation, aryl pentafluorobenzenesulfonates and nonaflates were identified to be the best substrates when compared to corresponding halides and pseudohalides. The substoichiometric use of nontoxic, environmentally benign potassium hexacyanoferrate as a cyanide source and exceptionally milder conditions further highlights the significance of the protocol developed. A wide range of electronically biased and sterically challenging substrates provided the corresponding the nitriles in good to excellent yields.

Key words palladium, pentafluorobenzenesulfonates, nonaflates, potassium hexacyanoferrate, cyanation

Aromatic nitriles are of significant importance in synthetic organic chemistry as they are essential building blocks in many drugs, pesticides, herbicides, natural products, dyes, and pigments. The possibility of converting the nitriles into other useful functionalities like amines, acids, amides, ester, imine, amidine, heterocyclic compounds, etc. also emphasizes the necessity of synthesizing various substituted benzonitriles under mild conditions.[1] Additionally, they serve as vital synthons in the synthesis of many important pharmacophores like tetrazoles, oxadiazoles, etc., which are known to improve the biological profiles of lead compounds in any drug discovery program. The general method for the synthesis of cyanoarenes in industrial scale include the diazotization of amines followed by Sandmeyer reaction and Rosenmund–von Braun reaction[2] of aryl halides using stoichiometric amount of copper(I) cyanide at high temperature. The ammoxidation reaction of toluene is also widely used in industries, but its scope is limited to only a few benzonitriles and requires very high temperature (350–500 °C).[3] An alternative methodology include the transition-metal-catalyzed (Ni, Pt, Pd, Cu, etc.) reactions by employing various cyanide sources like zinc cyanide, potassium/sodium cyanide, trimethyl silyl cyanide, and tributyl tin cyanide. Among the transition-metal-catalyzed reactions, the palladium-catalyzed cross-coupling reactions between aromatic halides or triflates and different cyanide sources are more widely used for procuring the corresponding benzonitriles owing to its good functional group tolerance, less sensitivity, and high reactivity.[4] However, the major limitations associated with this technology are the need for toxic cyanide source and harsh conditions like high temperature and long reaction times. Furthermore, the dissolution of excess cyanide ions in the reaction medium is expected to inhibit the catalytic cycle thereby decreasing the rate of formation of the desired product significantly.[5] Recently, potassium hexacyanoferrate ($K_4FeCN_6{\cdot}3H_2O$) was introduced as a nontoxic cyanide source in order to circumvent the aforementioned concerns.[6] Nevertheless, the need for high temperature and extended reaction times prevailed to be indispensable for the success of those protocols (Scheme 1). These observations highlight the need for de-

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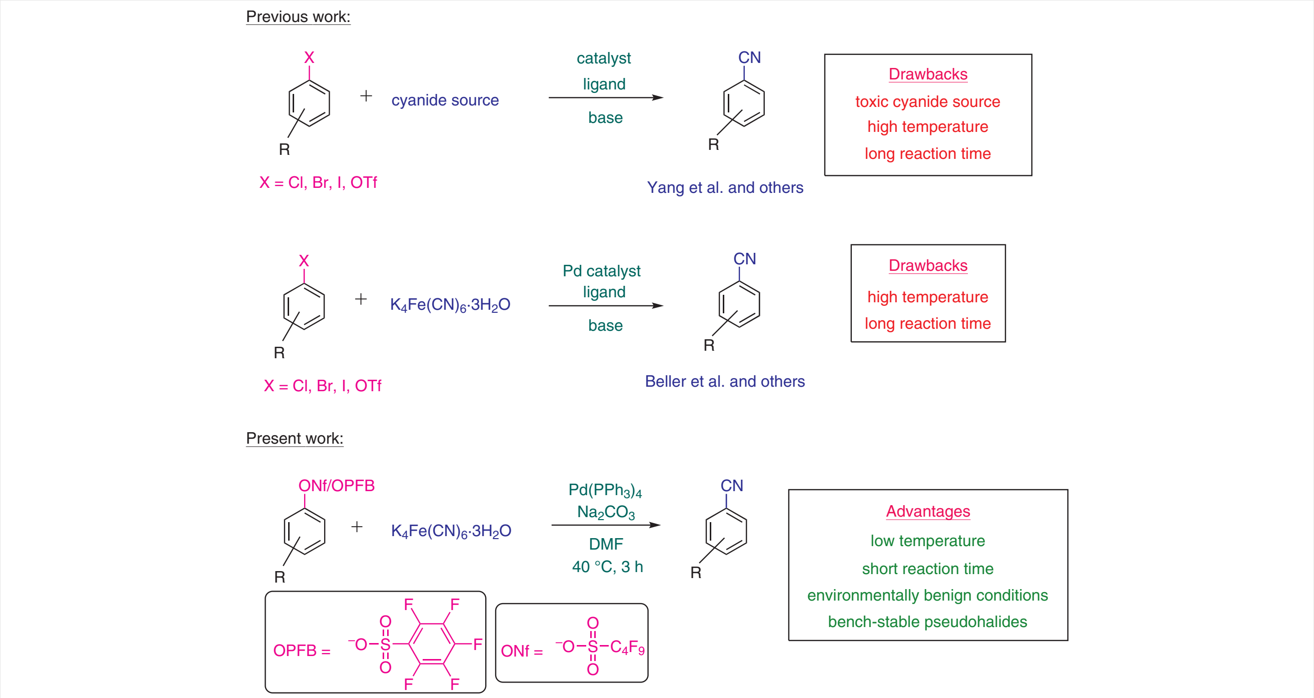


Scheme 1 Previous works on cyanation and present work

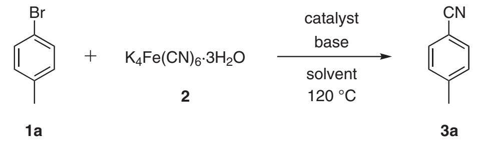
veloping a milder and efficient protocol for synthesizing aromatic nitriles of significant industrial and pharmacological relevance.

The presence of nitrile functionality in many FDA approved drugs and also in many bioactive lead molecules highlights its significance in the area of organic synthesis. This has led to the development of facile and scalable synthetic protocols for introducing the nitrile group in a molecule from halide or pseudohalide counterparts. Although the introduction of nitrile functionality into an organic molecule is well reported, most of the protocols require either the use of hazardous cyanide source, high temperature, or the use of palladium-based precatalytic systems. The use of these precatalytic systems has been reported on halides and pseudohalides using zinc cyanide as the cyanide source which facilitated milder reaction conditions.[7] As a part of our research efforts,[8] we were focused on developing an efficient and milder synthetic protocol for accessing the cyano functionality from bench-stable aryl pentafluorobenzenesulfonates (ArOPFB) and aryl nonaflates (ArONf) employing traditional catalytic systems. Furthermore, a case study to identify the superior reactivity of these bench-stable pseudohalides over their corresponding halides has also been explored.

As a starting point, we took 4-bromo toluene as a model substrate and subjected for the palladium-catalyzed cyanation reaction by using 0.2 equiv of $K_4FeCN_6{\cdot}3H_2O$ as cyanide source as reported by Weissmann et al.[9] The reaction was carried out at 120 ℃ by using 0.1 mol% $Pd(OAc)_2$ as the catalyst and Na_2CO_3 as base in DMA for 5 h. Unsurprisingly, we could obtain only 10% of the desired product **3a** as reported by them (Table 1, entry 1). Increasing the catalyst loading to 5 mol% and changing the solvent from DMA to DMF slightly improved the yield (entries 2 and 3). The addition of extra ligands to the catalyst was found to be ineffective in significantly improving the yield of the desired product (entries 4 and 5). However, we could see the formation of the desired cyanoarene in 50% yield when tetrakis was used as a catalyst instead of $Pd(OAc)_2$ at 120 ℃ for 24 h (entry 7). Further increasing the time of the reaction or temperature did not give any considerable improvement in the yield (entries 8 and 9). Changing the base from Na_2CO_3 to other inorganic and organic bases decreased the formation of desired product (entries 10–12). Although the yield of the desired product obtained from our best conditions (entry 7) was found to be satisfactory (50%), the requirement of harsh reaction conditions and prolonged reaction time insisted us to continue our quest for developing a milder and efficient protocol for cyanation.

These observations encouraged us to screen other halides and pseudohalides as substrates for the palladium-catalyzed cyanation reaction. Initially, we took *p*-cresol and synthesized its corresponding pseudohalides like tosylate, mesylate, triflate, nonaflate (ONf), and pentafluorobenzene sulfonate (OPFB) (see the Supporting Information). The corresponding halides (chloro, bromo, and iodo) were also arranged for our control experiments. All these substrates

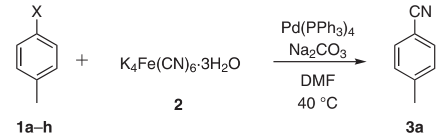
Table 1 Reaction Optimization for the Cyanation of 4-Bromotoluene[a]



Entry	Catalyst	Ligand	Base	Solvent	Yield (%)[b]
1	$Pd(OAc)_2$	–	Na_2CO_3	DMA	10[c]
2	$Pd(OAc)_2$	–	Na_2CO_3	DMA	20
3	$Pd(OAc)_2$	–	Na_2CO_3	DMF	24
4	$Pd(OAc)_2$	PPh_3	Na_2CO_3	DMF	18
5	$Pd(OAc)_2$	Xantphos	Na_2CO_3	DMF	15
6	$Pd(PPh_3)_4$	–	Na_2CO_3	DMF	30
7	$Pd(PPh_3)_4$	–	Na_2CO_3	DMF	50[d]
8	$Pd(PPh_3)_4$	–	Na_2CO_3	DMF	48[e]
9	$Pd(PPh_3)_4$	–	Na_2CO_3	DMF	45[f]
10	$Pd(PPh_3)_4$	–	K_2CO_3	DMF	20[d]
11	$Pd(PPh_3)_4$	–	Cs_2CO_3	DMF	12[d]
12	$Pd(PPh_3)_4$	–	TEA	DMF	trace[d]

[a] Reaction conditions: 4-bromotoluene (1 equiv), $K_4Fe(CN)_6·3H_2O$ (0.2 equiv), catalyst (5 mol%), ligand (10 mol%), base (1 equiv) in dry DMF, heated for 5 h at 120 ℃.
[b] Isolated yield after column chromatography.
[c] 0.1 mol% of catalyst used.
[d] Reaction carried out for 24 h.
[e] Reaction carried out for 36 h.
[f] Reaction carried out at 150 ℃.

Table 2 Screening of Different Substrates for Reaction Optimization[a]



X = Br, Cl, I, OTs, OMs, OTf, ONf, OPFB

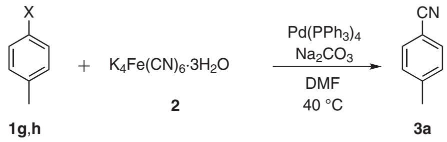
Entry	Substrate	Halide/pseudohalide	Yield (%)[b]
1	**1a**	bromo	10
2	**1b**	chloro	nil
3	**1c**	iodo	15
4	**1d**	tosylate	nil
5	**1e**	mesylate	nil
6	**1f**	triflate	12
7	**1g**	nonaflate	72
8	**1h**	pentafluorobenzenesulfonate	75

[a] Reaction conditions: toluene derivative (1 equiv), $K_4Fe(CN)_6·3H_2O$ (0.2 equiv), $Pd(PPh_3)_4$ (5 mol%), Na_2CO_3 (1 equiv) in dry DMF, heated for 5 h at 40 ℃.
[b] Isolated yield after column chromatography.

were subsequently screened under our previously best reaction conditions (Table 1, entry 7) at 40 ℃ for 5 h (Table 2). To our disappointment, we could obtain only a negligible amount of the desired product with 4-bromotoluene as the substrate, and the unreacted starting material was found to be major (Table 2, entry 1). From this point, we decided to carry out a case study by examining the same reaction conditions with other halides and pseudohalides. Among the halides, the chloro substrate was unreactive whereas the corresponding iodo gave 15% of the desired product (entries 2 and 3). Amongst the pseudohalides, tosylates and mesylates were found to be unreactive (entries 4 and 5). The triflates reacted almost similar to that of the bromo counterpart but showed the presence hydrolyzed product (4-hydroxytoluene) as a competing side product (entry 6). Gratifyingly, we could obtain the desired product in reasonable yield when OPFB (75%) and ONf (70%) were used as substrates (entries 7 and 8).

Based on these results, we decided to further optimize the cyanation reaction conditions with more reactive and bench-stable pseudohalides (OPFB and ONf) as the substrates (Table 3). We altered the stoichiometric ratio of $K_4FeCN_6·3H_2O$, temperature, and reaction time so as to improve the yield of the desired cyanoarene **3a**. The yield of the required product was dramatically increased when 0.33 equiv of $K_4FeCN_6·3H_2O$ were used (entry 2). To our delight, we obtained the desired product in excellent yield when the reaction was carried out at 40 ℃ for 3 h (entry 3). Further reduction in temperature and time led to incomplete conversions (entries 4 and 5).

Table 3 Reaction Optimization with Nonaflates and Pentafluorobenzenesulfonates[a]

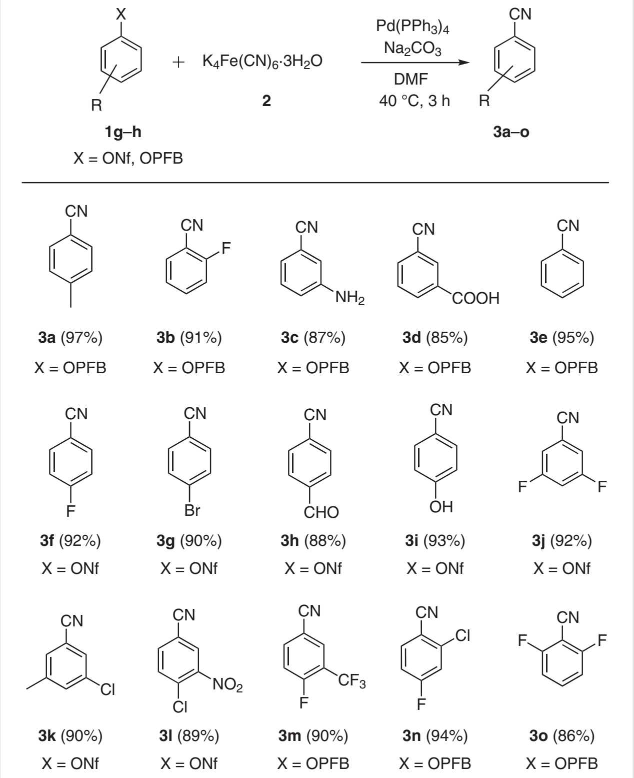


X = ONf, OPFB

Entry	$K_4Fe(CN)_6·3H_2O$ (equiv)	Time (h)	Yield of **3a** (%)[b]	
			X = ONf	X = OPFB
1	0.2	5	72	75
2	0.33	5	90	92
3	0.33	3	96	97
4	0.33	2	85	84
5	0.33	3	80[c]	82[c]

[a] Toluene derivative (1 equiv), $K_4FeCN_6·3H_2O$, $Pd(PPh_3)_4$ (5 mol%), Na_2CO_3 (1 equiv) in dry DMF, heated for 3–5 h at 40 ℃.
[b] Isolated yield after column chromatography.
[c] Reaction carried out at 30 ℃.

After getting a mild and greener protocol for cyanation reaction, our next attention was to evaluate the generality of the developed protocol. We synthesized a series of diverse nonaflates and pentafluorobenzene sulfonates and propagated the synthesis of corresponding nitriles (Scheme 2). All the ONfs and OPFBs, irrespective of their electronic properties, reacted well enough to furnish the desired nitriles in good to excellent yield.[10]



Scheme 2 Substrate scope of the developed protocol. *Reagents and conditions*: Aryl nonaflate/pentafluorobenzenesulfonate (1 equiv), $K_4FeCN_6·3H_2O$ (0.33 equiv), $Pd(PPh_3)_4$ (5 mol%), Na_2CO_3 (1 equiv) in dry DMF, heated for 3 h at 40 ℃. Isolated yields after column chromatography are given in parentheses.

The diversity in the availability of phenols and its facile conversion into the corresponding nonaflates or OPFBs emphasize the applicability of utilizing aryl OPFBs or nonaflates as an alternative substrate in the palladium-catalyzed cyanation reaction for obtaining aryl nitriles. The stability of nonaflates and pentafluorobenzenesulfonates in the reaction medium for palladium-catalyzed reactions has already been reported previously.[11] The nonaflates are known to suppress the O–S bond cleavage in the reaction medium and thereby prevent its hydrolysis to the corresponding phenols. The OPFBs are highly stable and more reactive towards traditional palladium-catalyzed cross-coupling reactions owing to its superior reactivity and stability. In our successful trials, we have figured out that the use of bench-stable and reactive ArOPFBs and ArONfs as electrophiles resulted in good to excellent conversions under exceptionally milder conditions. This could be probably attributed to the facile oxidative addition of these electrophiles using conventional palladium-catalyst systems like $Pd(PPh_3)_4$ under very milder conditions as observed with previous palladium-mediated reactions involving these pseudohalides.[11e,12]

We have successfully performed a case study for finding a suitable substrate for the palladium-catalyzed cyanation reaction under mild conditions. The key findings of our study paved the way for developing aryl nonaflates and pentafluorobenzenesulfonates as effective substrates for the proposed reaction. As a result, we developed an exceptionally mild protocol for the palladium-catalyzed cyanation reaction to generate a series of cyanoarenes in good to excellent yields. The developed protocol can be extended for the synthesis of other complex nitriles in future.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707218.

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(10) **Typical Experimental Procedure for the Synthesis of 3a**
To a pre-dried 10 mL screw cap equipped reaction vial, aryl pentafluorobenzenesulfonate (**1h**, 1 mmol), $K_4Fe(CN)_6{\cdot}3H_2O$ (**2**, 0.33 mmol, 0.33 equiv) and Na_2CO_3 (1 mmol, 1 equiv) were added, dissolved in dry DMF (3 mL), and degassed for 5 min. $Pd(PPh_3)_4$ (5 mol%) was then added, and the reaction mixture was heated in a pre-heated metal block at 40 °C for 3 h under continuous stirring. After the completion of the reaction, the reaction mixture was filtered through a short column using diethyl ether. The filtrate was distilled under reduced pressure, and the crude mixture was purified by column chromatography to afford the **3a** (114 mg, 97%) as colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.40 (s, 3 H, CH_3), 7.25 (d, *J* = 8 Hz, 2 H, ArH), 7.51 (d, *J* = 8 Hz, 2 H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.7, 111.2, 121.0, 131.7, 133.9, 145.6.

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