Cross-Coupling

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A General, Practical Palladium-Catalyzed Cyanation of (Hetero)Aryl Chlorides and Bromides**

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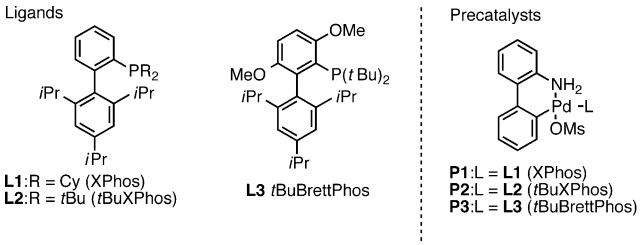
Aromatic nitriles have application in a variety of fields as both synthetic intermediates and final targets.[1] For example, the antineoplastic Letrozole, antidepressant Citalopram, and anti-HIV drug Etravirine all possess an aryl nitrile moiety. Traditionally, benzonitriles are synthesized by diazotization of anilines followed by a Sandmeyer reaction with superstoichiometric amounts of copper(I) cyanide.[2] Another common route to benzonitriles is the Rosenmund–von Braun reaction, which typically entails heating superstoichiometric amounts of copper(I) cyanide with an aryl iodide at elevated temperature.[3] Recent advances have allowed for the use of catalytic quantities of copper; however, these approaches still have limitations.[4]

The palladium-catalyzed coupling of cyanide with aryl (pseudo)halides proceeds under milder conditions and displays increased functional-group tolerance. The first Pd-catalyzed cyanation method was reported by Takagi et al. 40 years ago.[5] Despite great advances,[1,6] cross-coupling procedures to form aryl nitriles have obtained a reputation as being highly irreproducible.[7] Mechanistic studies by Grushin and co-workers have shown this is due, in part, to catalyst deactivation by cyanide, which is able to poison all of the intermediates in the catalytic cycle.[8] Common methods to avoid catalyst poisoning include the addition of reducing agents[9] or exploiting the low solubility of NaCN, KCN, and $Zn(CN)_2$ in organic solvents. The NaCN method by Ushkov and Grushin,[7] while of high industrial relevance, requires the use of rigorously anhydrous conditions (glovebox setup), which renders this chemistry inconvenient or inaccessible to many synthetic chemists. Furthermore, MCN salts (M = Na or K) are often milled prior to their use to guarantee solubility and reproducibility in their application. Milling is problematic considering the high toxicity in conjunction with the possibility of aerosolizing fine cyanide salts. Zinc cyanide finds the widest use in Pd-catalyzed cyanations of functionalized substrates.[10] With a toxicity of approximately 10% that of its sodium or potassium congeners, $Zn(CN)_2$ is less hazardous, but still poses a significant risk.

To address safety concerns, several Pd-catalyzed methods involving alternative cyanide sources have been described.[11] The research groups of Beller[12] and Weissman[13] discovered that $K_4[Fe(CN)_6]$, a nontoxic food additive, could serve as a cyanide source for Pd-catalyzed coupling reactions. Aqueous systems of $K_4[Fe(CN)_6]\cdot 3H_2O$ with a phase-transfer catalyst have been reported, but these still require temperatures greater than 140 °C.[14] Significant advances were reported by the research groups of Huang[15] and Kwong,[16] who employed a 1:1 organic/aqueous solvent mixture to enable cyanide transfer from $K_4[Fe(CN)_6]\cdot 3H_2O$ under milder conditions. However, the scope is narrow, with examples of five-membered heterocycles being rare. Thus, while progress has been made towards a practical benzonitrile synthesis using nontoxic cyanide sources, a general, efficient method for the cyanation of (hetero)aryl halides is still needed. Herein, we disclose a Pd-catalyzed cyanation system that: 1) is applicable to aryl chlorides at low to modest catalyst loadings; 2) works well with a wide range of heterocyclic halides, including in many cases five-membered heterocycles bearing free NH groups; and 3) is complete in one hour at ≤ 100 °C.

Our initial experiments focused on identifying conditions to prepare benzonitrile **1a** from the corresponding aryl chloride. Using our third generation palladacycle precatalysts (**P1**–**P3**; Scheme 1),[17] a preliminary survey of ligands revealed that use of a catalyst based on XPhos (**L1**) provided superior yields of benzonitrile **1a**, outperforming *t*BuXPhos (**L2**) and *t*BuBrettPhos (**L3**), as well as other phosphines commonly used for aryl cyanation reactions, such as tri-*tert*-butylphosphine [$(P(tBu)_3$] and 1,1′-bis(diphenylphosphino)-ferrocene (dppf; see Supporting Information for details). Next, we examined the effect of base, temperature, and



Scheme 1. Ligands and precatalysts used in this study. Ms = mesyl.

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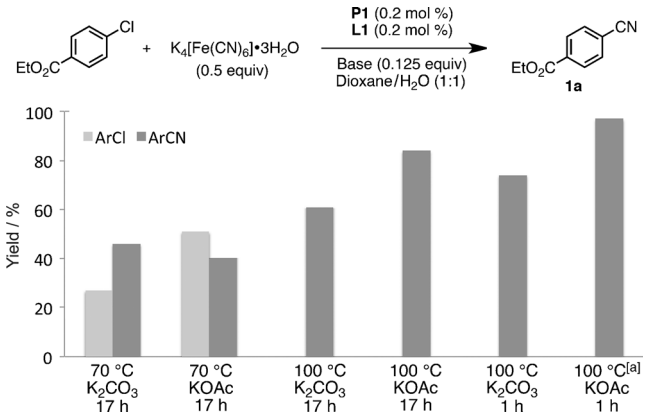


Figure 1. Optimization of base, temperature, and time. Reaction conditions: ethyl 4-chlorobenzoate (1 mmol), $K_4[Fe(CN)_6]\cdot 3H_2O$ (0.5 equiv), **P1** (0.2 mol%), **L1** (0.2 mol%), base (0.125 equiv), dioxane (2.5 mL), H_2O (2.5 mL). Yields determined by GC analysis of the crude reaction mixture. [a] Yield of isolated product, average of 2 independent runs.

reaction time on the overall yield, utilizing 0.2 mol% **P1** and **L1** in a 1:1 mixture of dioxane and water (Figure 1). Although carbonate bases are most often used to promote cyanide dissociation from $K_4[Fe(CN)_6]\cdot 3H_2O$, we observed significant substrate and/or product decomposition in experiments with K_2CO_3. However, we obtained excellent results using a weaker base, KOAc, and by conducting the reactions at 100 °C for 1 h.[18,19]

As shown in Figure 2, palladacycle precatalyst **P1** proved to be the most effective palladium precursor when compared

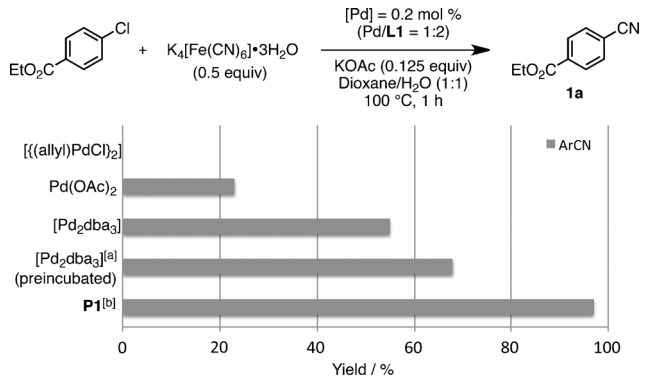
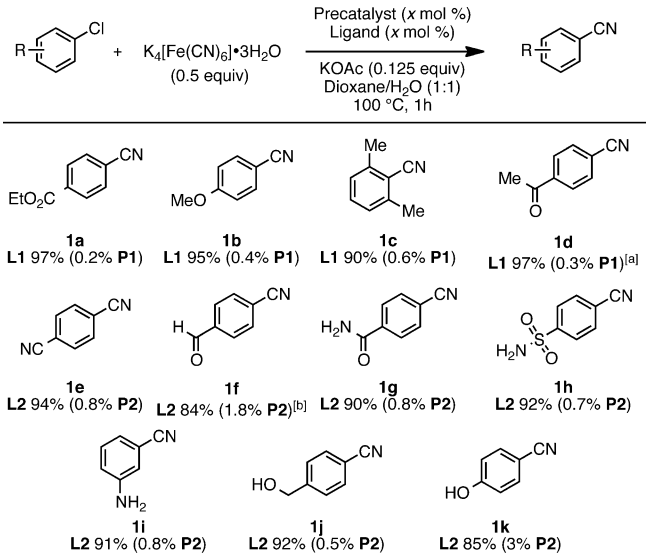


Figure 2. Comparison of palladium sources. Reaction conditions: ethyl 4-chlorobenzoate (1 mmol), $K_4[Fe(CN)_6]\cdot 3H_2O$ (0.5 equiv), [Pd] (0.2 mol%), **L1** (Pd/L 1:2), KOAc (0.125 equiv), dioxane (2.5 mL), H_2O (2.5 mL). Yields determined by GC analysis of the crude reaction mixture. [a] $[Pd_2dba_3]$ and ligand were preincubated in dioxane at 120 °C for 3 min before addition to other reagents. [b] Yield of isolated product, average of 2 independent runs.

to commonly used Pd complexes. The commonly used Pd sources $Pd(OAc)_2$ and $[\{(allyl)PdCl\}_2]$ require reduction and ligand complexation to form the active catalyst, and poisoning by cyanide likely occurs when activation is performed under the reaction conditions.[20] Another palladium source, $[Pd_2dba_3]$, has been shown to engender higher catalytic activity in C–N coupling processes when preincubated with a phosphine ligand at 120 °C.[21] However, implementing this protocol delivered only a moderate improvement in yield over that obtained from the direct use of $[Pd_2dba_3]$ without preincubation.[22,23] In contrast, the use of **P1** afforded **1a** in excellent yield (97%) and was operationally simple, as the active catalyst is generated efficiently in situ upon exposure to base. Other precatalysts have been applied to Pd-catalyzed cyanations,[24] but this system is the only one known that is capable of converting aryl chlorides into benzonitriles at low catalyst loading with a nontoxic cyanide source.

We next explored the substrate scope of our protocol (Scheme 2). Electron-rich (**1b**), electron-poor (**1a**, **1d**), and

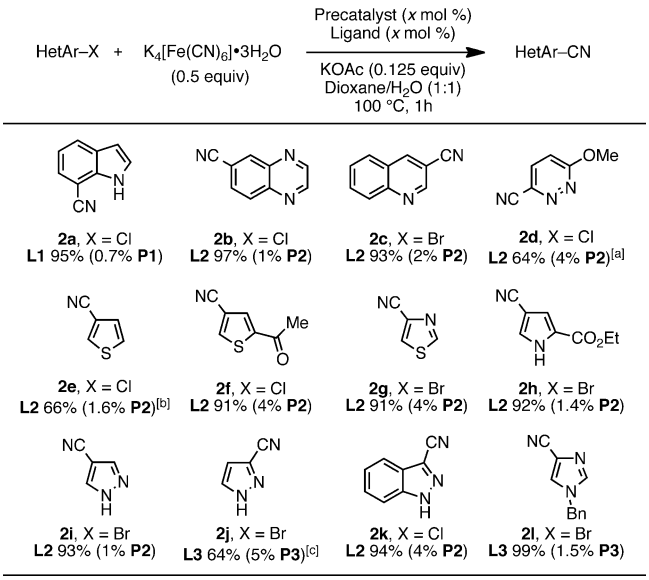


Scheme 2. Cyanation of aryl chlorides. Reaction conditions: aryl chloride (1 mmol), $K_4[Fe(CN)6]\cdot 3H_2O$ (0.5 equiv), precatalyst (*x* mol%), ligand (*x* mol%) KOAc (0.125 equiv), dioxane (2.5 mL), H_2O (2.5 mL). The yields of isolated products are given, average of 2 independent runs. [a] 10 mmol scale: 96% yield. [b] 70 °C, 12 h.

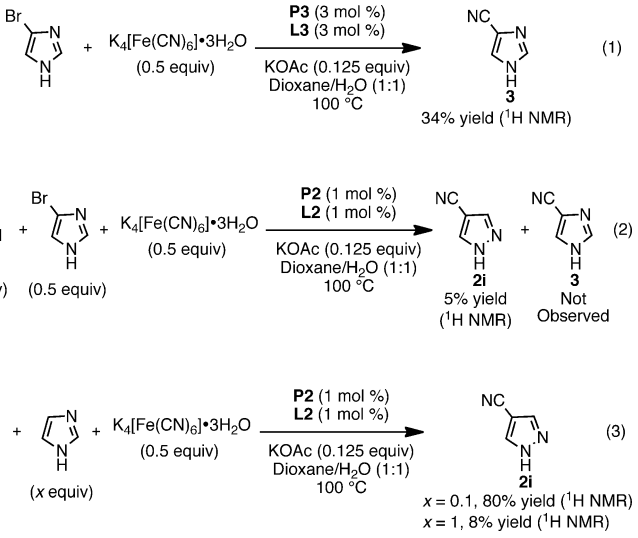
di-*ortho*-substituted (**1c**) aryl chlorides can efficiently be converted into benzonitriles by using a catalyst based on **L1**. Interestingly, more electron-deficient aryl chlorides (such as **1e**) required the use of the di-*tert*-butylphosphino analogue **L2**. Recently, Klinkenberg and Hartwig showed that reductive elimination to form ArCN is slower for electron-deficient aryl groups.[25] That a catalyst based on the larger ligand **L2** allows for more facile reductive elimination for electron-deficient substrates is in accord with this view. This method exhibits high tolerance for substrates bearing free NH or OH groups, such as primary amides (**1g**), sulfonamides (**1h**), anilines (**1j**), and benzylic alcohols (**1j**), all of which could be converted into the corresponding benzonitrile by using less than 1 mol% Pd. In general, aryl chlorides with coordinating functional groups afforded higher yields when **L2** was employed. Coupling an aryl chloride containing a phenol (**1k**) proved more challenging, yet could be accomplished in 85% yield by using of 3 mol% **P2**. In contrast, cyanation of the less acidic benzylic alcohol (**1j**) proceeded using only

0.5 mol% **P2**. Additionally, reactive substituents such as aldehydes (**1f**) are also tolerated. Treatment of aldehydes with cyanide and base typically results in benzoin condensation, which occurred under standard conditions at 100 °C. At 70 °C, no benzoin condensation was observed and the benzonitrile product could be isolated in high yield, albeit using slightly higher catalyst loadings.

Five-membered heterocycles are extremely important in the fields of pharmaceutical, agrochemical, and materials science; however, general procedures for their cyanation by cross-coupling are lacking. We have found that our method accommodates a wide range of heteroaryl halides (Scheme 3). For example, unprotected indole **2a**, bearing an *ortho*-NH group, afforded 95% of the product when only 0.7 mol% **P1** is used. Sulfur-containing heterocycles, such as thiophenes (**2e, 2f**) and thiazole (**2g**), also afforded product, although the use of higher catalyst loading was required. Furthermore, pyrroles (**2h**), pyrazoles (**2i**, **2j**), and indazoles (**2k**) are all well-tolerated. These last examples represent, to the best of our knowledge, the first Pd-catalyzed cyanations of 4-bromopyrazole (**2i**),[26] 3-bromopyrazole (**2j**), and 3-chloroindazole (**2k**).[27]



Scheme 3. Cyanation of heteroaryl halides. Reaction conditions: heteroaryl halide (1 mmol), $K_4[Fe(CN)_6]\cdot 3H_2O$ (0.5 equiv), precatalyst (*x* mol%), ligand (*x* mol%) KOAc (0.125 equiv), dioxane (2.5 mL), H_2O (2.5 mL). The yields of isolated products are given, average of 2 independent runs. [a] 0.5 equiv KOAc. [b] Low yield because of product volatility. [c] Isolated as HCl salt, 95:5 mixture of HetArCN/HetArBr.

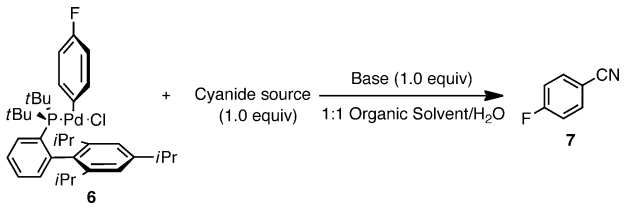


Increasing the catalyst loading did not aid in driving the reaction to full conversion or increasing the yield in an appreciable manner. A competition experiment showed that the cyanation of 4-bromopyrazole in the presence of 4-bromoimidazole yielded only a small amount of product **2i** [Eq. (2)]. Imidazole appears to have an inhibitory effect on catalysis, but only when present in a stoichiometric quantity [Eq. (3)]. We hypothesized N-protection of 4-bromoimidazole would prevent inhibition. Indeed, subjecting 4-bromo-*N*-benzylimidazole[28] to our protocol yielded **2l** in 99% yield at 1.5 mol% Pd loading.

Application of this method to the preparation of a pharmaceutical intermediate was also investigated. 4-Cyano-7-azaindole (**5**) was used as an intermediate for the preparation of 2-[(1*H*-pyrrolo[2,3-b]pyridine-4-yl)methylamino]-5-fluoronicotinic acid.[29] $Zn(CN)_2$ with 3.2 mol% [Pd(dppf)] were used in the reported synthesis [Eq. (4)]. By using our procedure, **5** was obtained in similar yield by using half the catalyst loading, in half the time, at lower temperature, and using $K_4[Fe(CN)_6]\cdot 3H_2O$ in lieu of $Zn(CN)_2$.[30]

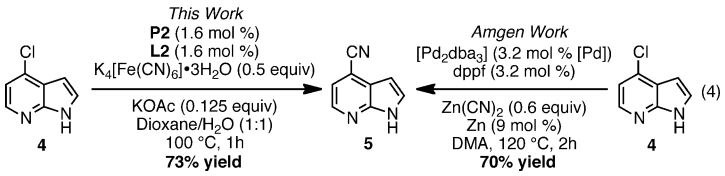
Finally, the transmetalation of cyanide with oxidative addition complex **6** was examined (Table 1). Grushin and coworkers have reported that $[(PPh_3)_2Pd(Ph)(I)]$ reacts with $[Bu_4N]^+[CN]^-$ to afford PhCN;[8a] similarly, we observed rapid transmetalation of KCN with **6** and reductive elimination to form **7** at room temperature. Allowing **6** to react with

Table 1: Transmetalation studies.



Entry	Cyanide source	Base	*T*	*t* [min]	Yield [%] (**7**)[a]
1[b]	KCN	KOAc	RT	5	56
2[b]	KCN	KOH	RT	5	69
3[b]	$[K_4Fe(CN)_6]\cdot 3H_2O$	KOAc	RT	30	0
4[c]	$[K_4Fe(CN)_6]\cdot 3H_2O$	KOAc	100 °C	5	66

[a] ^{19}F NMR spectroscopic yield. [b] Solvent = THF. [c] Solvent = dioxane.



$K_4[Fe(CN)_6]\cdot 3H_2O$ at room temperature for 30 min afforded no Pd-CN complex or **7** (by ^{19}F NMR spectroscopy), thus suggesting that dissociation of cyanide from the iron center requires higher temperatures. In accord with this, when the reaction was conducted at 100 °C, cyanide transfer from $K_4[Fe(CN)_6]\cdot 3H_2O$ and reductive elimination to form **7** proceeded at a rate and efficiency comparable to the use of KCN at room temperature. Future efforts will focus on promoting more facile transfer of cyanide from $K_4[Fe(CN)_6]\cdot 3H_2O$ to enable room-temperature cyanation.

In conclusion, we have disclosed a general method for the cyanation of (hetero)aryl halides. The use of a nontoxic cyanide source in conjunction with wide functional-group tolerance and fast reaction times make this method particularly convenient to synthetic chemists.

Experimental Section

General procedure for the Pd-catalyzed cyanation of (hetero)aryl chlorides and bromides: Precatalyst, ligand, $K_4[Fe(CN)_6]\cdot 3H_2O$ (211 mg, 0.5 equiv), and (if solid) (hetero)aryl halide (1 mmol) were added to a screw-top test tube equipped with a magnetic stir bar. After sealing the vessel with a teflon-lined screw-cap septum, it was evacuated and backfilled with nitrogen (this process was repeated for a total of three cycles). (Hetero)Aryl halide (if liquid; 1 mmol), dioxane (2.5 mL), and 0.05 M KOAc in degassed water (2.5 mL, see the Supporting Information for degassing procedure) were then added to the reaction tube by syringe. The test tube was placed in an oil bath preheated to 100 °C and stirred for 1 h. A clear, yellow solution was observed upon initial stirring. During the course of the reaction, a yellow or green precipitate formed on the walls of the reaction vessel. After stirring the reaction mixture at 100 °C for 1 h, it was then cooled to room temperature. The contents of the test tube were transferred to a separatory funnel using EtOAc (15 mL) and brine (15 mL), and the organic layer was separated from the aqueous layer. If the reaction was successful, during the extraction process the color of the aqueous layer turned dark blue. This is a colloidal suspension of insoluble fine particles. Isolation and PXRD analysis revealed this solid to be Prussian Blue. The aqueous layer was further extracted with EtOAc (total 2×15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting mixture was adsorbed onto silica gel, dried in vacuo, and purified by column chromatography to yield the product. Notes: Efficient stirring is absolutely essential for this procedure to be successful for the cyanation of (hetero)aryl halides. All reactions in Figures 1 and 2 and Schemes 2 and 3 were conducted on a 1 mmol scale, except for entry **1d** which was also carried out using 10 mmol of aryl chloride. All 1 mmol scale reactions were performed using a stir plate set to 900 rpm. Deviations in reaction vessel size, stir bar size, and reaction scale may require optimization of the stirring efficiency to guarantee the best results. Additionally, deviation from a 1:1 organic/water solvent mixture can result in incomplete conversion. It is important to make sure no solvent can escape the vessel or be absorbed by the septum to ensure optimal yields. See the Supporting Information for more details.

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