The Room-Temperature Palladium-Catalyzed Cyanation of Aryl Bromides and Iodides with Tri-*t*-butylphosphine as Ligand

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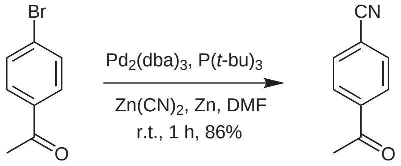
Abstract: The palladium-catalyzed cyanation of aryl bromides and iodides to the corresponding nitriles occurs at room temperature when tri-*t*-butylphosphine is used as ligand, $Zn(CN)_2$ as the cyanide source and Zn dust as a co-catalyst in DMF as solvent. A variety of aromatic halides, including electron-withdrawing and electron-donating, can be efficiently cyanated under these conditions. The reactions are completed in less than 1 hour and products are produced in good to excellent yield.

Key words: palladium-catalyzed, cyanation, aryl iodide, aryl bromide, tri-*t*-butylphosphine.

Aryl nitriles are important synthetic intermediates in the pharmaceutical industry because they serve as building blocks for a number of different functionalities with interesting biological properties.[1] The most direct method for the synthesis of aryl nitriles is the transition metal-catalyzed cyanation of aryl halides.[2] Although a number of elegant methods have been developed, the general procedure calls for elevated temperatures and in many cases long reaction times. In the course of our work, we needed a mild method for the preparation of aryl cyanide from an aryl bromide and thus explored other reaction conditions. We focused on the possibility of using a palladium(0) catalyzed process since palladium catalysts can be fine-tuned to perform a number of reactions at lower temperature. For example, during the past few years, the use of tri-*t*-butylphosphine as ligand in a variety of palladium-catalyzed processes, including Suzuki,[3] Heck,[4] Negishi,[5] Sonogashira,[6] amination of aryl halides[7] and Stille[8] couplings have been reported to occur under very mild conditions. Encouraged by these reports, we explored conditions for the cyanation of aryl halides using a Pd–$P(t\text{-}Bu)_3$ catalyst system.

The use of $Zn(CN)_2$ as the cyanide source in the palladium-catalyzed cyanation of aryl halides in DMF has been shown to be general and reliable, albeit at elevated temperatures.[2a,2c–e] Using this protocol, with 4′-bromoacetophenone as a model substrate, we explored a number of room temperature reaction conditions (Table 1). To our delight, with 2.5 mol% $Pd_2(dba)_3$, 5 mol% tri-*t*-butylphosphine and zinc as a co-catalyst, the reaction was complete in 1 hour and we obtained an excellent isolated yield of 4′-cyanoacetophenone (Scheme 1) (Table 1, entry 1). A lower catalyst loading greatly affected the yield. When 1.25 mol% $Pd_2(dba)_3$, and 2.5 mol% tri-*t*-butylphosphine were used, an isolated yield of 60% was obtained after one hour (Table 1, entry 2). Increasing the reaction time to two hours gave an improved yield of 75%. However when 0.62 mol% $Pd_2(dba)_3$ and 1.25 mol% tri-*t*-butylphosphine were used no product was obtained (Table 1, entry 3).



Scheme 1

The reaction was also highly dependent on the ligand. A number of ligands which have been reported to be effective at higher temperatures for palladium-catalyzed cyanation reactions, were used in place of tri-*t*-butylphosphine. Replacement of tri-*t*-butylphosphine with PPh_3, Dppf, Xantphos, or 2′-dicyclohexylphosphinobiphenyl in the general procedure yielded no product after 1 hour at room temperature (Table 1, entries 4–7). This demonstrated that tri-*t*-butylphosphine is a superior ligand for this transformation.

Table 1 Pd-Catalyzed Cyanation of 4′-Bromoacetophenone

Entry	Pd	Ligand (mol%)	Isolated Yield (%)
1	5%	$P(t\text{-}Bu)_3$ (5)	86
2	2.5%	$P(t\text{-}Bu)_3$ (2.5)	60
3	1.25%	$P(t\text{-}Bu)_3$ (1.25)	0
4	5%	PPh_3	0
5	5%	Dppf[a]	0
6	5%	Xantphos[b]	0
7	5%	DCPB[c]	0

General conditions: Substrate (1.0 equiv), $Zn(CN)_2$ (1.8 equiv), Zn (0.12 equiv), 1 h at r.t.

[a] 1,1′-Bis(diphenylphosphino)ferrocene.

[b] 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene.

[c] 2′-Dicyclohexylphosphinobiphenyl.

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The effect of the stoichiometry of the tri-*t*-butylphophine ligand was also examined in the palladium-catalyzed cyanation of 4′-bromoacetophenone. With 5 mol% of palladium, we found that the reaction was not as efficient when the ratio of Pd–ligand was 1:4 as compared to a 1:1 Pd–ligand ratio. In fact, the reaction was only about 50% complete after 1 hour and did not proceed further after longer reaction times. This phenomenon has been observed in other transition metal-catalyzed reactions involving tri-*t*-butylphosphine.[7,9]

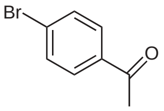
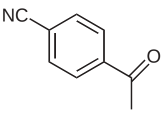
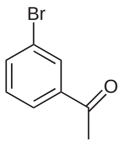
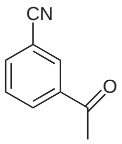
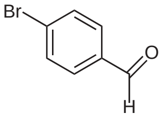
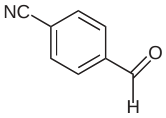
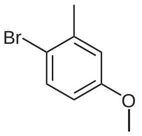
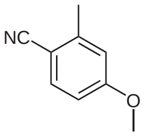
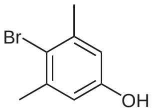
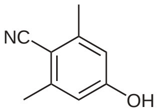
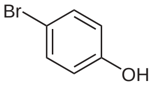
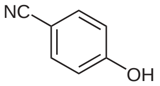
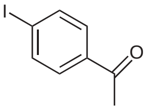
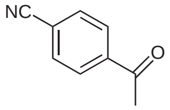
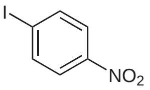
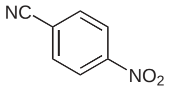
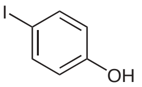
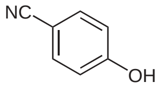
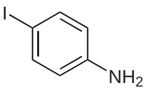
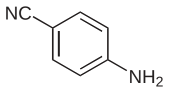
When the cyanide source was changed from $Zn(CN)_2$ to KCN no reaction was observed. A similar result has been reported for the cyanation of aryl chlorides at elevated temperature and is rationalized on the basis of cyanide poisoning of the catalyst.[2c] We also found that the use of zinc dust as a co-catalyst facilitates the reaction with complete conversion after 1 hour.[10] Without zinc, the reaction was sluggish and went to about 70% completion with an isolated yield of 66% for the nitrile.

In addition to this, it appears that the polarity of the solvent also plays a key role. The reaction proceeded rapidly in DMF as solvent, however no product was obtained when toluene or dioxane were used as solvents.

Having optimized the conditions for the cyanation of 4′-bromoacetophenone, we were interested in the scope of this methodology.[11] The results are presented in Table 2. As can be seen, both electron-withdrawing and electron-donating aryl bromides and iodides are cyanated in good to excellent yields. The yields are modest for sterically congested aryl bromides (Table 2, entries 4 and 5). It should be noted that phenols (Table 2, entries 5, 6 and 9) and in one case an aniline (Table 2, entry 10) can be cyanated under these conditions in good yields. This shows that the cyanation is very fast under these conditions and side reactions do not occur at a significant rate.

In summary, although a number of methods exist for the synthesis of aryl nitriles via transition metal catalyzed cyanation of aryl halides, they require elevated temperatures and long reaction times. In contrast, we have reported a practical, efficient and mild, room temperature method for the palladium-catalyzed cyanation of aryl bromides and iodides to the corresponding nitriles using tri-*t*-butylphosphine. We are currently exploring conditions to extend this methodology to aryl chlorides.

Table 2 Room Temperature Cyanation Reactions of Aryl Bromides and Iodides Catalyzed by Pd(0)–P(*t*-Bu)$_3$[a]

Entry	Aryl Halide	Product	Yield (%)
1			86
2			71
3			80
4			58
5			61
6			83
7			84
8			93
9			84
10			81

[a] General conditions: Substrate (1 equiv), $Pd_2(dba)_3$ (0.025 equiv), $Zn(CN)_2$ (1.8 equiv), $P(t\text{-}Bu)_3$ (0.05 equiv), Zn (0.12 equiv), 1 h at r.t.

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(11) General Procedure: An oven-dried, Ar-purged, round bottom flask was charged with the aryl halide (0.5 mmol), $Zn(CN)_2$ (0.9 mmol), $Pd_2(dba)_3$ (0.013 mmol), and Zn dust (0.06 mmol) followed by DMF (5 mL). The ligand (10 wt% in hexane, 0.025 mmol) was added and the reaction mixture was rapidly stirred at r.t. for 1 h. After this time, the mixture was partitioned between 20 mL EtOAc and 10 mL H_2O. The EtOAc layer was separated, washed with brine (10 mL) and dried over $MgSO_4$. After concentration, the residue was subjected to silica gel column chromatography using a hexane–EtOAC solvent system to furnish the aryl nitrile. Spectroscopic data and melting points were consistent with known values.