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Application of polymer-supported triphenyl phosphine in the palladium-catalyzed cyanation reaction under microwave conditions

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Abstract—A variety of aryl nitriles were prepared in excellent yields from the palladium acetate catalyzed coupling of aryl halides with $Zn(CN)_2$ using polymer-supported triphenyl phosphine as the ligand and dimethylformamide as solvent under microwave irradiation conditions.

Substituted benzonitriles are an integral part of dyes, natural products, herbicides, agrochemicals, and pharmaceuticals.[1] In organic synthesis, nitriles play a crucial role as they can be easily converted into a variety of functional groups[2] such as acids, esters, and amides, etc. In medicinal chemistry, nitriles are very useful as they can be transformed into a variety of biologically important structures such as tetrazoles, triazoles, oxazoles, thiazoles, oxazolidinones, to name just a few. For example, tetrazoles are very often used as the metabolically stable bioisosteres of the carboxylic groups.[3]

In general, aryl nitriles are synthesized from aryl halides and stoichiometric amounts of copper(I) cyanide (Rosenmund–von Braun reaction),[4] on an industrial scale via amoxidation of the corresponding toluenes,[5a] or from aniline[5b] via diazotization and a subsequent Sandmeyer reaction. Nickel-[6] and palladium-catalyzed[7] methods have been developed as milder alternatives to the classical Rosenmund–von Braun nitrile synthesis, but these transition metal catalyzed reactions take several hours. Microwave-induced reaction rate enhancement has become a powerful tool in organic synthesis because of milder reaction conditions, better selectivity, and associated ease of manipulation. Automated and focused microwave flash heating continues to find greater applications in parallel synthesis and in drug discovery processes. Recently microwave heating has been proven to be very effective in accelerating the cyanation reactions.[8] Leadbeater and co-workers[8b,c] have shown that classical Rosenmund–von Braun cyanation reaction could be completed in minutes (as compared to hours under traditional heating) under microwave condition. Similarly the reaction times for nickel[8d] and palladium[8e,f] mediated cyanation reactions have also been greatly improved under microwave heating.

Rapid development of combinatorial chemistry and robotic parallel synthesis has led to a growing demand for fast reactions and efficient purification procedures. The major problems associated with the broad application of currently known transition metal catalyzed cyanation reactions in high throughput synthesis is the removal of homogeneous palladium catalyst and dissociated ligand by-products that add purification steps in the synthesis. Another disadvantage with the current palladium-catalyzed cyanation reaction is catalyst poisoning. Mechanistic studies have revealed that cyanides form very stable complexes with transition metal catalysts[9] and thus relatively high quantities of catalysts are needed to compensate for the poisoned catalyst.

Because of the need for more environmentally benign chemistry and the desire to develop simplified protocols for rapid screening methods, there is a need for heterogeneous catalysis systems to address the bottleneck

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Keywords: Aryl halides; Nitriles; Palladium; Heterogeneous catalyst; Microwave irradiation.

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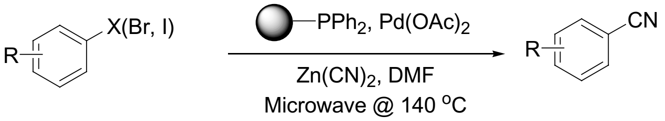
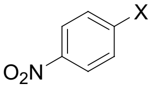
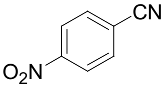
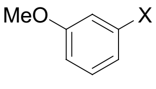
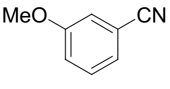
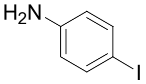
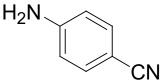
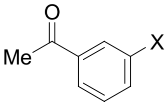
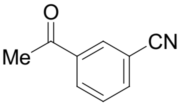
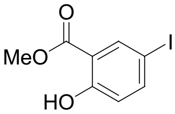
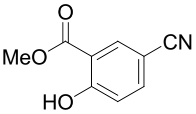
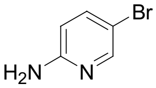
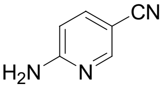
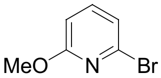
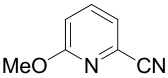
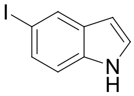
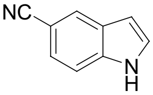
issues of purification associated with soluble ligands and catalyst removal (recovery). Although adoption of microwave conditions[8] have improved on the reaction time for the palladium-catalyzed cyanation reaction, use of soluble catalysts and ligands require purification steps to remove the ligands. Also, recovery of catalyst remains a major challenge when reactions are performed on large scales. We envisioned that a heterogeneous catalyst system in combination with microwave heating would be ideally suited for the synthesis of aryl nitriles in combinatorial chemistry applications. Various systems of solid-supported catalysts[10] have been prepared and applied successfully in organic synthesis, but to the best of our knowledge, there is no report of heterogeneous palladium-catalyzed cyanation reaction. In the present study we focused our studies on polymer-supported palladium catalysts for cyanation reactions.

Several solid-supported palladium catalysts are known in the literature and have been widely used in organic synthesis.[10] Some of these heterogeneous palladium catalysts (or corresponding ligands) are commercially available although at high cost. For the present study we choose to utilize readily available polymer-supported triphenyl phosphine resin. This inexpensive heterogeneous ligand is available through a variety of commercial sources. The desired heterogeneous catalyst was prepared by mixing the resin supported triphenyl phosphine and $Pd(OAc)_2$ in dimethylformamide solvent. Initial studies revealed that premixing of the catalyst and ligand was essential for the optimal catalytic activity. In a typical experiment polymer-supported triphenylphosphine resin (50 mg, 0.15 mmol, 3 mmol of triphenylphosphine per gram of resin, Aldrich) was taken up into dimethylformamide (3 mL) along with $Pd(OAc)_2$

Table 1. Polymer-supported Pd-catalyzed cyanation of aryl halides



1 a-k **2 a-h**

Entry	Aryl halides (1)		Products[a] (2)		Microwave heating	
					Time[b] (min)	Yield[c,d] (%)
1		**a** X = I		**a**	30	99
2		**b** X = Br			30	95
3		**c** X = I		**b**	30	92
4		**d** X = Br			30	98
5		**e**		**c**	50	92
6		**f** X = I		**d**	30	96
7		**g** X = Br			30	89
8		**h**		**e**	30	91
9		**i**		**f**	50	93
10		**j**		**g**	30	84[e]
11		**k**		**h**	50	96

[a] Confirmed by ^1H NMR and MS.

[b] Reaction times not optimized.

[c] Isolated yield.

[d] Aryl halides were completely consumed in the reaction as determined by TLC.

[e] Product tends to sublime under high vacuum.

(15 mg, 0.07 mmol) in a 5 mL glass microwave reactor tube. The solution was purged with nitrogen and then tube was closed with a septum. The mixture was stirred for 2 h. During this time the yellow color of $Pd(OAc)_2$ solution was transferred to the beads leaving behind a colorless solution. This is an indication of formation of a palladium–phosphine complex (that such a complex is formed on the resin and acts as catalyst is further supported by control experiments).[11] The septum was removed from the tube and aryl halide (1 mmol) along with $Zn(CN)_2$ (1.0 mmol) was added and once again the solution was purged with nitrogen and tube was closed with the septum. The reaction mixture was exposed to microwave irradiation[12] at 140 °C for 30–50 min (Table 1). After the reaction was judged to be complete (TLC analysis), the solution was cooled to room temperature and the liquid was filtered through a glass frit to remove the resin and the resin was washed with ether (3×10 mL). The combined organic fractions were washed with water (3×5 mL), brine (1×10 mL), and dried ($MgSO_4$). The solvent was then concentrated on a rotary evaporator to obtain the desired nitriles in excellent yield and in high purity (>90%) as determined by ^1H NMR and HPLC (monitored at 254 nm) analysis.

In summary, we have successfully demonstrated the use of commercially available polymer-supported triphenyl phosphine in the palladium-catalyzed synthesis of aryl nitriles. Microwave irradiation was used as the energy source. A variety of electron rich and electron deficient aryl iodides and bromides were efficiently converted into their corresponding nitriles. Products were obtained in high yields and in excellent purity without the need of any purification. This methodology has a potential application in parallel synthesis. More detailed study is under way to study the scope and limitations of this methodology.

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11. Control experiments: (a) reaction was performed with $Pd(OAc)_2$ (15 mol%), $Zn(CN)_2$ (1.0 equiv) in DMF at 140 °C for 30 min without polymer-supported triphenylphosphine. Under this condition **1b** yielded only trace amounts of **2a**. (b) In another control experiment, removal of the solution from the resin (after premixing with $Pd(OAc)_2$) followed by addition of fresh solvent, **1b**, and $Zn(CN)_2$ gave the desired nitrile, **2b**, in quantitative yield.
12. Reactions were run in Emrys^{TM} Optimizer from Personal Chemistry (now Biotage) in a 5 mL glass tube.