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A highly catalytic robust palladium catalyzed cyanation of aryl bromides

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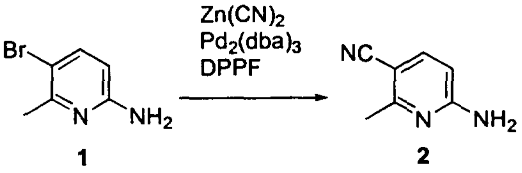
Abstract

A dependable high yielding palladium catalyzed aryl bromide cyanation procedure has been developed. The optimized cyanation features extremely low levels of palladium and DPPF ligand. © 1999 Elsevier Science Ltd. All rights reserved.

The most direct and versatile method for the preparation of aryl nitriles is the transition metal catalyzed cyanation of aryl halides.[1] Unfortunately the classic copper mediated cyanations often involve the use of stoichiometric quantities of copper cyanide at high temperatures (>150°C) followed by an often difficult workup to remove the copper salts from the product. The palladium catalyzed cyanation of aryl halides has been reported as a more convenient alternative.[2] Despite this, palladium catalyzed cyanations have been known to be notoriously unreliable.[3]

We required a convenient preparation of 2-amino-5-cyano-6-picoline (**2**) from the commercially available 2-amino-5-bromo-6-picoline (**1**) (Scheme 1). Reaction of **1** with 1.2 equiv. of CuCN in 1-methyl-2-pyrrolidinone (NMP) or DMF at 150–250°C gave **2** in 60–80% HPLC assay yield only after laborious extractive workup. Performing the reaction in the presence of lithium halides, *n*-Bu_4NBr or $Zn(CN)_2$ required complex workups due to gummy precipitates and often the reaction mixture itself was a difficult to stir slurry at best. Attempted cyanation of **1** with $Ni(CN)_2$ or $Co(CN)_2$ in NMP resulted in no reaction, while in the presence of zinc dust and PPh_3 complete conversion of **1** to **2** was realized, although workup was again difficult.



Scheme 1.

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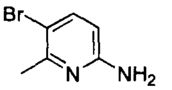
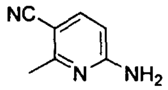
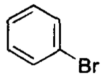
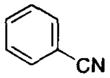
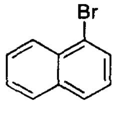
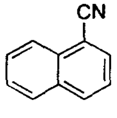
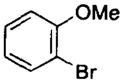
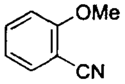
Table 1
Effect of ligand on cyanation

Entry	Ligand (mole%)	% conversion at 22 h	% conversion at 48 h
1	PPh_3 (8)	50-100	50-100
2	DPPE (4)	0	0
3	DPPP (4)	10	20
4	DPPB (4)	50	90
5	DPPF (4)	100	100
6	BINAP (4)	50	90

Table 2
Cyanation of aryl bromides

Entry	Substrate	Product	Yield %
1			94
2			95
3			91
4			87

In order to avoid the aforementioned problems, palladium catalyzed cyanations were explored. Cyanation of **1** with $Zn(CN)_2$ in the presence of 2–4 mol% $Pd(PPh_3)_4$ in NMP at 150°C gave 80–85% isolated yield of **2**.[4] The use of <2 mol% of $Pd(PPh_3)_4$ as well as the use of other sources of palladium[5] alone or in the presence of PPh_3 gave extremely unreliable results. A variety of phosphine ligands were explored (Table 1) in the palladium catalyzed cyanation with $Zn(CN)_2$ employing 1 mol% tris(dibenzylideneacetone)dipalladium (Pd_2dba_3) in NMP at 120°C with and without additives.[6] Variable results were obtained with PPh_3 (entry 1). In contrast, the use of DPPF (entry 5) consistently resulted in complete reactions.[7] In addition, employing DPPF as the ligand resulted in a dramatically cleaner and more robust reaction even at lower catalyst levels. A further screen of solvents showed wet DMF to give optimal results.[8]

Thus, reaction of **1** with 0.6 equiv. $Zn(CN)_2$ in the presence of 0.05 mol% Pd_2dba_3 and 0.12 mol% DPPF in wet DMF for 20 h at 120°C resulted in complete conversion (>99.5%) of **1** to **2**. Addition of aq. NH_4Cl and NH_4OH resulted in direct crystallization of **2** (>99.9 HPLC area %purity) from the reaction mixture in 94% yield.[9] Washing of the dried product with toluene was found to remove last traces of catalyst/color with 97% recovery; thus 91% yield of **2** was obtained on a 4 kg scale. Cyanation of several aryl bromides was performed under the above conditions resulting in >98% conversions (Table 2).[10] Bromobenzene was converted to benzonitrile and the more sterically hindered and electron rich 1-bromonaphthalene and 2-bromoanisole were converted to the corresponding nitriles. To summarize, an efficient and reliable aryl bromide cyanation highly catalytic in palladium and DPPF has been developed and demonstrated on a multikilogram scale.

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4. Unpublished results, Zhao, M. Department of Process Research, Merck Research Laboratories, Merck & Co. Inc., P O Box 2000, Rahway, New Jersey 07065.
5. Other sources of palladium include allylpalladium chloride dimer, $PdCl_2$, $Pd(PPh_3)_2Cl_2$, $Pd(OAc)_2$ and $Pd(Acac)_2$.
6. Each experiment was run on a 2 mmol scale employing 0.75 mol% of Pd_2dba_3 and 3 mL of degassed solvent. Ligands: DPPE=1,2-bis(diphenylphosphino)ethane, DPPP=1,3-bis(diphenylphosphino)propane, DPPB=1,4-bis(diphenylphosphino)butane, DPPF=1,1′-bis(diphenylphosphino)ferrocene, BINAP=2,2′-bis(diphenylphosphino)-1,1′-binaphthyl. The addition of LiCl (10 equiv.), LiI (5 equiv.), *n*-Bu_4NBr (1 equiv.), CuCN (0.15 equiv.) or CuI (0.04 equiv.) to reaction systems using PPh_3 as the ligand employing the conditions in Table 1, entry 1 resulted in no improvement in the reaction rate. The addition of CuI (0.04 mol%) to reaction systems using DPPE, DPPP, DPPF or BINAP as ligands resulted in no improvement. Other ligands such as tri-*o*-tolylphosphine, tri-*m*-tolylphosphine, tri-*o*-anisylphosphine, tri-2-furylphospine, $AsPh_3$, 1,1′-bis(di-*o*-tolylphosphino)ferrocene, and 2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl (Tol–BINAP) gave less satisfactory results.
7. The ligand DPPF has been exploited by Hartwig in a variety of palladium coupling reactions: Hartwig, J. F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2046–2067. In our case variation of the ratio of DPPF to Pd_2dba_3 showed the optimum ratio was 2.4:1. Takagi has shown that DPPF is superior to PPh_3 as a ligand employing KCN as the cyanide source for the palladium catalyzed cyanation of aryl iodides and triflates: Takagi, K.; Sasaki, K.; Sakakibara, Y. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1118–1121. Employing NaCN or KCN in the presence of Pd_2dba_3 and PPh_3 or DPPF as ligands resulted in either sluggish reactions or no reaction at all. Addition of salts or a copper(I) cocatalyst offered no advantage.
8. A screen for reaction solvents revealed that only some of the more polar aprotic solvents such as: DMF, dimethylacetamide, NMP, 2-pyrrolidinone and 1,3-dimethyl-3,4,5,6-tetrahydro-2(*H*)-pyrimidininone gave complete reactions. The addition of water appeared to improve the reaction workup by eliminating most of the gummy colored byproducts. The use of wet DMF showed the cleanest reaction and further optimization with smaller quantities of catalyst showed that the reaction proceeded most dependably with 0.5–2.0% added water while higher percentages of water slowed the reaction down. The following solvents gave <20% conversion after 48 h: *m*-xylene, PhCl, anisole, *n*-hexanol, phenol, cyclohexanone, methyl benzoate, butyrolactone, valeronitrile, benzonitrile, *p*-tolunitrile, formamide and sulfolane. Interestingly the use of $(n\text{-BuO})_3PO$ as a solvent gave 90% conversion after 48 h, while tetramethylurea gave <50% conversion.
9. A degassed mixture of DMF (10.3 kg), water (100 mL), **1** (6.24 kg, 33.3 mol), $Zn(CN)_2$ (2.35 kg, 20.0 mol), DPPF (22.2 g, 0.040 mol) and Pd_2dba_3 (15.3 g, 0.017 mol) was heated to 120°C for 20 h under nitrogen. TLC and HPLC (Waters Spherisorb S5 OD/CN column) analysis indicated complete consumption of **1** (<0.5%) after 20 h and the mixture was cooled to 80°C. The mixture was gradually diluted with 4:1:4 v/v/v saturated aq. NH_4Cl-concd NH_4OH–water solution (33.3 L) over 1 h. The slurry was cooled to –9°C over 1.5 h and filtered. The tan crystalline solid was washed with 4:1:5 v/v/v saturated aq. NH_4Cl-concd NH_4OH–water solution (33.3 L) and water (40 L) at 5°C. The solid was dried under a stream of nitrogen, washed with toluene (33.3 L) and dried under a stream of nitrogen to provide cyanopicoline **2** (4.05 kg, 91.3%). **2**: mp=168–170°C; R_f=0.33 (9:1 MTBE–hexane); ^{1}H NMR (250.1 MHz, CD_3OD) δ 7.52 (d, J=8.7, 1H), 6.33 (d, J=8.7, 1H), 2.44 (s, 3H); ^{13}C NMR (62.9 MHz, CD_3OD) δ 163.1, 162.5, 141.8, 119.7, 107.1, 96.1, 23.2; FTIR (nujol mull) ν_{max} 3392, 3323, 3151, 1653, 1594, 1554 cm^{-1}; Anal. calcd for $C_7H_7N_3$: C, 63.14; H, 5.30; N, 31.56. Found: C, 63.09; H, 5.19; N, 31.62.
10. Reactions were performed on 20 mmol scale in sealed ampules employing the conditions in Ref. 9 with a 72 h age. The corresponding nitriles were isolated via flash column chromatography using silica gel (Merck 70–230 mesh, ASTM).