Organic Process Research & Development **2008,** *12,* 540–543

Technical Notes

Development of a Mild and Robust Method for Large-Scale Palladium-Catalysed Cyanation of Aryl Bromides: Importance of the Order of Addition

Per Ryberg*

Process Chemistry, AstraZeneca PR&D So¨derta¨lje, S-151 85 So¨derta¨lje, Sweden

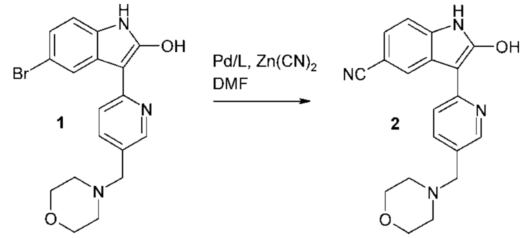
Abstract:

A mild and robust method for the large-scale palladium-catalysed cyanation of aryl bromides has been developed. The reaction is sensitive to cyanide poisoning of the catalyst, and it was found that the order of adding the reagents had a strong impact on the performance of the reaction. Addition of the cyanide source to a preheated mixture of the other reagents was critical for achieving a robust and scaleable process. This improved protocol allowed the reaction to be run to full conversion within 3 h at 50 °C on a 6.7 kg scale. Furthermore, it led to the identification of several new efficient catalysts for the reaction.

Introduction

Aromatic nitriles are structural motifs frequently occurring in such diverse compounds as pharmaceuticals, agrochemicals, and dyes. They are also important synthetic intermediates since the nitrile group can be converted to other functional groups. The traditional way of preparing aromatic nitriles involves, for example the Sandmeyer reaction,[1] or the Rosenmund–von Braun reaction[2] where an aryl halide is heated with a stoichiometric amount of copper cyanide at temperatures ≥150 °C. All these methods require harsh conditions that limit their scope. In this context the Pd-catalysed cyanation of aryl halides[3] constitutes an attractive alternative, allowing for the conversion of aryl halides or pseudohalides into the corresponding aromatic nitrile under mild conditions. Much effort has been devoted towards the development of improved conditions for the reaction, and it has been found that *N,N*-dialkylamide solvents such as DMF, DMA, and NMP in combination with zinc cyanide as the CN^- source and a Pd catalyst provides the most general protocol for the reaction.[4–9] Recent work has demonstrated the utility of potassium hexacyanoferrate as a cyanide source.[10–13] Despite these improvements the reaction still suffers from a number of problems such as lack of robustness, the requirement for long reaction times at high temperatures (typically > 100 °C), notorious difficulty to run on a scale larger than a few grams with very few examples >50 g reported in the literature.[5,14,15] In fact, most of the methods for Pd-catalysed cyanations have only been reported at subgram scale. It has been demonstrated that cyanide poisoning of the catalyst is a problem.[16–19] A study by Grushin[19] reveals that each step on the catalytic cycle may be affected by excess cyanide, and the balance between achieving sufficient cyanide in solution to promote the reaction and the level where the catalyst becomes poisoned appears to be very delicate.

Scheme 1



Recent reports have suggested slow addition of acetone cyanohydrin[20] or a slurry of $Zn(CN)_2$ and the aryl halide[18] to the reaction mixture as a solution to overcome this problem.

The manufacturing process for **2**, involves a Pd-catalysed cyanation in the final synthetic step (Scheme 1). At the outset of the development work in early 2003 a survey of the literature revealed that very few general methods for the cyanation reaction existed. The original conditions that were investigated for the reaction involved heating the starting material with $Pd(dba)_2$, DPPF, $Zn(CN)_2$, and zinc dust in DMF at 120 °C according to the method of Jin and Confalone.[8] The reaction had performed acceptably during route development work in small scale, but during scale-up to 50 g, severe problems were encountered. The reaction stopped at incomplete conversion, and both starting material and product decomposed at the temperature of the reaction to give, at best, a 50% HPLC yield

---

* Author to whom correspondence may be sent. E-mail: Per.Ryberg@astrazeneca.com.

(1) (a) Sandmeyer, T. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 2650–2653. (b) Sandmeyer, T. *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 1946–1948. (c) Sandmeyer, T. *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 1492–1496.

(2) Ellis, G. P.; Romney-Alexander, T. M. *Chem. Rev.* **1987**, *87*, 779–794.

(3) Sundermeier, M.; Zapf, A.; Beller, M. *Eur. J. Inorg. Chem.* **2003**, 3513–3526.

(4) Tschaen, D. M.; Desmond, R.; King, A. O.; Fortin, M. C.; Pipik, B.; King, S.; Verhoeven, T. R. *Synth. Commun.* **1994**, *24*, 887–890.

(5) Maligres, P. E.; Waters, M. S.; Fleiz, F.; Askin, D. *Tetrahedron Lett.* **1999**, *40*, 8193–8195.

(6) Chidambaram, R. *Tetrahedron Lett.* **2004**, *45*, 1441–1444.

(7) Ramnauth, J.; Bhardwaj, N.; Renton, P.; Rhakit, S.; Maddaford, S. P. *Synlett* **2003**, *14*, 2237–2239.

(8) Jin, F.; Confalone, P. N. *Tetrahedron Lett.* **2000**, *41*, 3271–3273.

(9) Littke, A.; Soumeillant, M.; Kaltenbach, R. F., III; Cherney, R. J.; Tarby, C. M.; Kiau, S. *Org. Lett.* **2007**, *9*, 1711–1714.

(10) Schareina, T.; Zapf, A.; Beller, M. *Chem. Commun.* **2004**, 1388–1389.

(11) Schareina, T.; Zapf, A.; Beller, M. *J. Organomet. Chem.* **2004**, *689*, 4576–4583.

10.1021/op800020r CCC: $40.75

Table 1. **Initial screen of catalysts for the cyanation reaction using method A**[a]

entry	catalyst	conversion (%)[b]
1	$Pd[P(t\text{-}Bu)_3]_2$	70
2	$Pd(dba)_2 + P(t\text{-}Bu)_3$	100
3	$[BrPdP(t\text{-}Bu)_3]_2$	100
4	$Pd(dba)_2$ + 2-$(t\text{-}Bu)_2$P-biphenyl	15
5	$Pd(dba)_2$ + 2-$(Cy)_2$P-biphenyl	15
6	$Pd(dba)_2$ + Q-phos[c]	50

[a] Aryl bromide (**1**) 1equiv, Zn 0.1 equiv, $Zn(CN)_2$ 0.55 equiv, $Pd(dba)_2$ 0.025 equiv, ligand 0.025 equiv. Reactants were dissolved in degassed DMF at 20 °C followed by 1 h of reaction at 50 °C. [b] Determined by HPLC. [c] 1,2,3,4,5-Pentaphenyl-1′-(di-*tert*)butylphosphino)ferrocene.

of the desired product **2**. The workup was difficult and ultimately required reversed phase chromatography to separate the product from the impurities.

It was obvious that in order to manage an upcoming 5-kg production, a significantly improved method for the cyanation reaction was essential. Due to the thermal instability of starting material and product under the reaction conditions, it was realized that an improved procedure for the reaction had to rely on a catalyst system that was capable of promoting the reaction at a lower temperature.

Herein we report both the development of improved conditions for the palladium-catalysed cyanation of aryl halides that are robust and allow the cyanation of **1** to **2** to be run at multikilogram scale. In addition, several new catalysts for the Pd-catalysed cyanation reaction were identified.

Results and Discussion

Initial Screen of Catalysts. An initial screen of different catalyst systems was performed at 50 °C in DMF with $Zn(CN)_2$ and zinc dust, by adding all materials to a Schlenk flask under nitrogen followed by the addition of degassed DMF and heating to 50 °C (method A, Table 1). It turned out that the $P(t\text{-}Bu)_3$-based catalysts (entries 2 and 3 in Table 1) gave fast reactions that reached full conversion in 60 min. The Q-phos-based catalyst (entry 6 in Table 1) gave an initially fast reaction, reaching 55% conversion within 10 min but then stopped. The biphenyl-based catalysts (entries 4 and 5 in Table 1) gave a very slow reaction which only reached 15% conversion after 60 min.

On the basis of these promising results the reaction using $Pd(dba)_2 + P(t\text{-}Bu)_3$ as catalyst (entry 2), was evaluated in scale-up experiments. The reaction was run by adding the aryl bromide **1**, $Zn(CN)_2$, zinc dust, and $Pd(dba)_2$ into a Schlenk flask. The Schlenk flask was evacuated and refilled with nitrogen, and degassed DMF was added. The $P(t\text{-}Bu)_3$ ligand was then added via syringe as a solution in toluene, and the mixture was heated to 50 °C. At 1-g scale the reaction worked well, but at 5-g scale it repeatedly stopped after reaching 70−80% conversion.

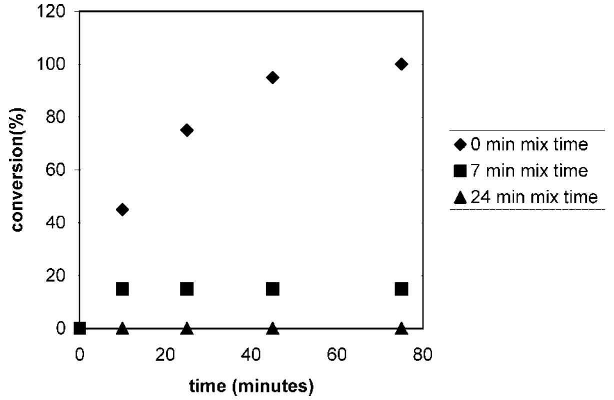


Figure 1. **Effect of contact time between $Pd(dba)_2$ and $Zn(CN)_2$ prior to addition of ligand and heating.**

Cyanide Poisoning of the Precatalyst. The failure of the reaction during scale-up led us to believe that the catalyst activation could be suffering from a competing cyanide poisoning, and a series of experiments were conducted on the $Pd(dba)_2 + P(t\text{-}Bu)_3$ system, where the mixture of **1**, $Zn(CN)_2$, zinc dust, and $Pd(dba)_2$ in DMF was stirred for 0, 7, and 24 min prior to the addition of the $P(t\text{-}Bu)_3$ ligand and following heating. As illustrated in Figure 1, the precatalyst $Pd(dba)_2$ was very sensitive to cyanide, and a delay of only 7 min between the addition of DMF and the addition of the ligand resulted in a reaction that stopped at 15% conversion.

At larger scale it would be difficult to achieve the short time delays required in order to avoid the catalyst poisoning, and so the possibility of adding the $Pd(dba)_2$ as a solution in DMF to the other components was considered.

If the mixture is heated immediately after the addition of the $Pd(dba)_2$ in DMF solution, the reaction goes to full conversion in 60 min. However, if the mixture is stirred for 5 min at 20 °C prior to the heating, no reaction occurs. Obviously at 20 °C catalyst poisoning is faster than the desired reaction, whereas at 50 °C the desired reaction is faster than catalyst poisoning.

During scale-up, heating will be slow, and the problem with catalyst poisoning is likely to be much worse.

Improved Protocol for the Reaction. In an attempt to find robust conditions for the reaction, a series of experiments were conducted where different orders of addition of the reagents were evaluated. It was found that the addition of the $Zn(CN)_2$ to a preheated mixture of the other reactants gave the most robust method. By this method the aryl bromide **1**, catalyst, and zinc dust were heated to 50 °C in degassed DMF and kept at this temperature for 5−10 min, whereafter the $Zn(CN)_2$ was added (method B). The benefit of adding the $Zn(CN)_2$ as the final component was demonstrated by re-examining the reactions in the initial screen. With this improved protocol all catalysts, even the ones that previously gave incomplete conversion, gave reactions that went to full conversion within 60 min (Table 2).

---

(12) Schareina, T.; Zapf, A.; Mägerlein, W.; Müller, N.; Beller, M. *Tetrahedron Lett.* **2007**, *48*, 1087–1090.

(13) Weissman, S. A.; Zewge, D.; Chen, C. *J. Org. Chem.* **2005**, *70*, 1508–1510.

(14) Wang, X.; Zhi, B.; Baum, J.; Chen, Y.; Crockett, R.; Huang, L.; Eisenberg, S.; Ng, J.; Larsen, R.; Martinelli, M.; Reider, P. *J. Org. Chem.* **2006**, *71*, 4021–4023.

(15) Pitts, M. R.; McCormack, P.; Whittall, J. *Tetrahedron* **2006**, *62*, 4705–4708.

(16) Takagi, K.; Okamoto, T; Sakakibara, Y.; Oka, S. *Chem. Lett.* **1973**, 471.

(17) Sundermeier, M.; Zapf, A.; Mutyala, S.; Baumann, W.; Sans, J.; Weiss, S.; Beller, M. *Chem. Eur. J.* **2003**, *9*, 1828–1836.

(18) Marcantonio, K. M.; Frey, L. F.; Liu, Y.; Chen, Y.; Strine, J.; Phenix, B.; Wallace, D. J.; Chen, C.-Y. *Org. Lett.* **2004**, *6*, 3723–3725.

(19) Dobbs, K. D.; Marshall, W. J.; Grushin, V. V. *J. Am. Chem. Soc.* **2007**, *129*, 30–31.

(20) Sundermeier, M.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1661–1664.

Table 2. **Evaluation of catalyst systems for the Pd-catalysed cyanation of 1 to 2, using method B**[a]

entry	catalyst system	conversion (%) (1 h)
1	Pd(dba)$_2$ + P(*t*-Bu)$_3$	100
2	Pd[P(*t*-Bu)$_3$]$_2$[b]	100
3	[BrPdP(*t*-Bu)$_3$]$_2$[c]	100
4	Pd(dba)$_2$ + Q-Phos	100
5	Pd(dba)$_2$ + 2-(*t*-Bu)$_2$P-biphenyl	100
6	Pd(dba)$_2$ + 2-Cy$_2$P-biphenyl	100
7	Pd(dba)$_2$ + X-Phos[d]	100
8	Pd(dba)$_2$ + P(*o*-tol)$_3$[e,f]	100
9	Pd(dba)$_2$ + DPPF[g]	10
10	Pd(dba)$_2$ + PPh$_3$	0

[a] Conditions: Arylbromide (**1**)1 equiv, Zn dust 0.1 equiv, Pd(dba)$_2$ 0.025 equiv, ligand 0.025 equiv, were heated to 50 °C in degassed DMF and kept at this temperature for 5 to 10 min, whereafter the Zn(CN)$_2$ 0.55 equiv was added. [b] 0.025 eq of the catalyst was added. [c] 0.0125 eq of the catalyst was added. [d] 2-(Dicyclohexylphosphino)-2′, 4′, 6′-tri-*i*-propyl-1,1′-biphenyl. [e] Pd(dba)$_2$ 0.05 equiv, P(*o*-tol)$_3$ 0.10 equiv. [f] Tris(2-methylphenyl)phosphine. [g] 1,1′-Bis(diphenylphosphino)ferrocene.

For the scale-up experiments the commercially available [BrPdP(*t*-Bu)$_3$]$_2$ catalyst was selected since it is reasonably air stable and it appeared to give the cleanest reaction. During scale-up experiments it was again demonstrated how important the order of addition is as the original protocol leads to reactions that stop below 80% conversion already at 5-g scale, whereas reactions according to the new protocol could repeatedly be run to full conversion at 3−7 kg scale.

The new protocol for the reaction also allowed the identification of several new catalyst systems for the Pd-catalysed cyanation reaction, that is the Q-phos-, 2-(*t*-Bu)$_2$P-biphenyl-, 2-Cy$_2$P-biphenyl-, and X-Phos-based catalysts were just as effective as the P(*t*-Bu)$_3$-based catalyst in promoting the reaction (Table 2). In addition P(*o*-tol)$_3$ (entry 8) was found to give a good catalyst for the reaction, but it required a higher catalyst loading of 5% to reach full conversion and it generated some byproducts. The original DPPF-based catalyst (entry 8) did not give any improved reaction with the new protocol, and the PPh$_3$-based catalyst (entry 9) did not give any product at all.

It is interesting to observe that, even if the investigated ligands in entries 1−8 represent a relatively large diversity with respect to steric and electronic properties, they all resulted in reactions that proceed with almost identical rates. In combination with the longer reaction times observed on larger scale it suggests that the rate of the reaction was determined by the dissolution rate of Zn(CN)$_2$. If the rate of the reaction was limited by the rate of dissolving the cyanide, the concentration of cyanide in solution would remain at a very low level since it would be consumed as soon as it had entered into solution. This again underscores the importance of adding the cyanide to the preheated mixture of the starting material and catalyst. In the preheated mixture, the catalyst will be activated, and the Zn(CN)$_2$ will, upon addition, dissolve at a rate that is slower than the potential maximum rate of the catalytic reaction. If, however, the reaction is started at room temperature and then heated, the rate of cyanide dissolution could be faster than the rate of the catalytic reaction at this temperature, and the concentration of dissolved cyanide would approach the saturation concentration, leading to catalyst poisoning.

The workup method that was found to work the best was to filter the hot reaction mixture, treat the filtrate with thiol-functionalized silica, filter the solution and then add Na$_4$-EDTA(aq) to precipitate the product which was then collected by filtration. The treatment of the reaction mixture with the thiol-functionalised silica scavenger was necessary in order to reduce the Pd content to <400 ppm and the Na$_4$-EDTA (aq) was necessary to reduce the level of Zn to <2000 ppm (exchanging the Na$_4$-EDTA to water gave Zn content of 5%).

Subsequent salt formation reduced the metal levels further to 1−2 ppm Pd and <1 ppm Zn.

Summary

Improved conditions for the Pd-catalysed cyanation have been developed. In addition, several new catalysts for the reaction have been identified. This new improved method provides a mild and robust method for the reaction that allowed the cyanation of **1** to be successfully run on a 6.7-kg scale, with full conversion to **2** within 3 h at 50 °C with an isolated yield of 90%. To the best of our knowledge this was the first time a Pd-catalysed cyanation had been reported to operate successfully on such a large scale under such mild conditions (the cyanations described in refs 5 and 14 were run on similar scale but required heating to 120 °C for 20 and 2 h, respectively).

Experimental Section

General Procedures. Commercially available materials were used as received unless otherwise noted. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brucker 400 MHz instrument. HPLC chromatography was run on a Waters instrument with a DAD detector.

2-Hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-carbonitrile, Large Scale. 5-Bromo-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indol-2-ol (**1**) (6.673 kg, 17.2 mol) and zinc-dust (98%+, <10 μm) (0.134 kg, 2.05 mol) was mixed with DMF (80 L) and the slurry stirred at room temperature. The mixture was purged with N$_2$ until the level of O$_2$ was <0.02 mg/L. Di-μ-bromobis-(tri*tert*-butylphosphine)dipalladium(I) (0.168 kg, 0.215 mol) was added to the slurry, and the vessel was inerted by evacuation and refilling with nitrogen. The mixture was heated to 40 °C, Zn(CN)$_2$ (1.109 kg, 9.45 mol) was added to the suspension in one portion, and the system was again inerted (Caution! Cyanide salts are highly toxic!). The resulting mixture was heated to an inner temperature of 50 °C and stirred for 3 h. Analyzing a sample on HPLC indicated full conversion at this point.

The reaction mixture was filtered at 50 °C, and the filter cake was washed with DMF (3 L). Thiol-functionalised silica (Silicycle, SiliaBond Thiol) (1.458 kg, 25% w/w) was added to the filtrate, and the mixture was stirred for 82 h at 50 °C. The scavenger was filtered off, and the filtrate was concentrated in vacuo. After removing 62 L (~60%) of the DMF, aqueous Na$_4$-EDTA solution (0.3 M, 142 L) was added at 40 °C, and the resulting mixture was stirred for 1 h at 40 °C. The mixture was cooled to 1 °C over 5 h, and the product was filtered off. Drying under vacuum at 50 °C gave 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-carbonitrile (**2**) (5.2

kg, 15.6 mol), 90% yield with a purity of >90% by HPLC. ^{1}H NMR (d_6-DMSO, 400 MHz) δ 14.79 (broad s, 1H), 10.86 (broad s, 1H), 8.08 (s, 1H), 7.95 (s, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.27 (dd, J = 8.0, 0.9 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 3.57 (t, J = 4.4 Hz, 4H), 3.36 (s, 2H), 2.36 (broad s, 4H); ^{13}C NMR (d_6-DMSO, 100 MHz) δ 168.8, 148.6, 141.8, 137.0, 136.1, 125.4, 123.9, 122.3, 121.1, 118.8, 118.3, 108.7, 101.3, 84.6, 66.1, 58.4, 52.8. MS (ES) m/z [M + 1] 335.

Acknowledgment

Special thanks to Dr. Silke Erbeck and Mr. Thomas Nussbaumer at Carbogen AG for executing the large-scale cyanation.

Received for review January 31, 2008.

OP800020R