

# An Investigation into Causes and Effects of High Cyanide Levels in the Palladium-Catalyzed Cyanation Reaction

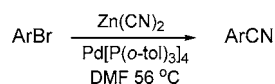
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## ABSTRACT



The palladium-catalyzed cyanation reaction is known to be sensitive to dissolved cyanide. Investigation into some causes of high levels of dissolved cyanide is presented here, along with a robust solution to this problem.

Due to the versatility of the cyano group in synthesis and its prevalence in pharmaceutical agents, palladium- and copper-catalyzed cyanations of aryl halides are widely used,<sup>1</sup> and there are almost as many variations in reaction conditions as there are substrates.<sup>2</sup> From nearly as early as the discovery of the reaction it was known that palladium-catalyzed cyanation reactions are sensitive to cyanide.<sup>3</sup> While cyanide is necessary for reaction, it has been proposed that an excess can sequester the catalyst, rendering it inactive. This is one of the reasons for the widespread use of Zn(CN)<sub>2</sub> in these reactions, as it is less soluble in DMF and NMP than KCN or NaCN.<sup>4</sup> However, even reactions using Zn(CN)<sub>2</sub> can be unreliable, suggesting that they may also suffer from the problem of high levels of cyanide in solution sequestering the catalyst.<sup>5</sup>

To our knowledge there has been no thorough documentation of elements in a reaction that cause high levels of cyanide in solution. With the goal of developing a robust and reproducible cyanation reaction that was amenable to scale-up, we set out to identify common chemicals (reagents, impurities, or byproducts) that could lead to high soluble cyanide in reaction mixtures. In particular, we were interested in looking at chemicals that may be carried over from previous steps or from manipulations of a cyanation substrate and how these materials may adversely affect a downstream cyanation.

Our investigation into causes of high soluble cyanide led us to look into common laboratory procedures that could affect the quality of a substrate to be cyanated. For example, many workup sequences involve base washes and some finish with a brine wash. Additionally, MgSO<sub>4</sub> is often used to dry solutions, and many compounds are purified with silica gel. All these operations have the potential to leave residual materials behind with the substrate. The commonly employed cyanation solvent DMF is known to decompose thermally to dimethylamine (DMA), which consequently could be present in the reaction. Therefore, we chose to investigate

(1) (a) Excellent recent review: Sundermeier, M.; Zapf, A.; Beller, M. *Eur. J. Inorg. Chem.* **2003**, 3513–3526 and references therein. (b) Ellis, G. P.; Romney-Alexander, T. M. *Chem. Rev.* **1987**, *87*, 779–794.

(2) Some different examples: (a) Tschaen, D. M.; Desmond, R.; King, A. O.; Fortin, M. C.; Pipik, B.; King, S.; Verhoeven, T. R. *Synth. Commun.* **1994**, *24*, 887–890. (b) Malignes, P. E.; Waters, M. S.; Flietz, F.; Askin, D. *Tetrahedron Lett.* **1999**, *40*, 8193–8195. (c) Anderson, B. A.; Bell, E. C.; Ginah, F. O.; Harn, N. K.; Pagh, L. M.; Wepsiec, J. P. *J. Org. Chem.* **1998**, *63*, 8224–8228. (d) Sundermeier, M.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1661–1664. (e) Okano, T.; Kiji, J.; Toyooka, Y. *Chem. Lett.* **1998**, 425–426. (f) Chidambaram, R. *Tetrahedron Lett.* **2004**, *45*, 1441–1444.

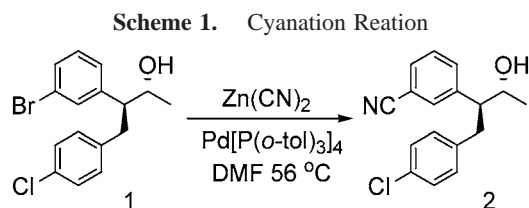
(3) (a) Takagi, K.; Okamoto, T.; Sakakibara, Y.; Ohno, A.; Oka, S.; Hayama, N. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3298–3301. (b) Takagi, K.; Okamoto, T.; Sakakibara, Y.; Oka, S. *Chem. Lett.* **1973**, 471–473.

(4) (a) See refs 4 and 5 in ref 2a. (b) Sakakibara, Y.; Okuda, F.; Shimobayashi, A.; Kirino, K.; Sakai, M.; Uchino, N.; Takagi, K. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1985–1990.

(5) Very recently, there has been publication of K<sub>4</sub>[Fe(CN)<sub>6</sub>] as a cyanation source which eliminates the release of free cyanide: Schareina, T.; Zapf, A.; Beller, M. *Chem. Commun.* **2004**, 1388–1389.

whether low levels of the following compounds—NaOH, NaCl, MgSO<sub>4</sub>, silica gel, and DMA—had an effect on the amount of soluble cyanide generated in the reaction mixture and how this in turn might affect the outcome of the catalytic reaction.

To investigate the effect of these additives on cyanide solubility we studied each of them under cyanation conditions being developed in our laboratory. Each additive was aged in a DMF solution of aryl bromide **1** (Scheme 1) containing



Zn(CN)<sub>2</sub> at 56 °C for 16 h. A sample of each was then filtered to remove undissolved Zn(CN)<sub>2</sub>, and the solution was assayed for soluble cyanide using ion chromatography (IC), Table 1.<sup>6</sup>

**Table 1.** Spiking Experiments with Common Laboratory Substances<sup>a</sup>

entry	additive	CN (ppm)
1	none, control	121
2	10 wt % MgSO <sub>4</sub>	130
3	10 wt % silica gel	135
4	10 mol % NaCl	2269
5	20 mol % NaCl	3825
6	30 mol % NaCl	5065
7	10 mol % NaOH	2978
8	20 mol % NaOH	6252
9	30 mol % NaOH	10520
10	10 mol % DMA	576
11	20 mol % DMA	989
12	30 mol % DMA	1641

<sup>a</sup> All experiments conducted at 56 °C for 16 h in a 5 mL/g DMF solution of bromide **1** containing 0.6 equiv of Zn(CN)<sub>2</sub>; additive amounts are based on the amount of Zn(CN)<sub>2</sub>.

As depicted in Table 1, with no additive the amount of soluble cyanide was low. The addition of MgSO<sub>4</sub> or silica gel did not raise this number. However, the presence of even 10 mol % NaCl, NaOH or DMA relative to Zn(CN)<sub>2</sub> significantly elevated the amount of cyanide in solution.<sup>7</sup> These trends were also observed in the absence of substrate **1**.

Having established that NaCl, DMA, and NaOH have an elevating effect on soluble cyanide levels in DMF slurries

(6) The samples for IC were diluted with 1:1 MeOH/0.25 M NaOH, and the base liberated dissolved Zn(CN)<sub>2</sub> to free cyanide ions. The IC was therefore a measure of all cyanide in solution including dissolved Zn(CN)<sub>2</sub>, not necessarily of free cyanide ions present when the sample was taken. The column used was a Dionex IonPac AS7; the generic method used can be found in the Dionex IC/HPLC Column Selection Guide.

of Zn(CN)<sub>2</sub>, we wanted to determine the effect of these additives on the actual cyanation reaction. A procedure that had previously given reliable reactions was chosen for this study, i.e., the cyanation of bromide **1**, using Zn(CN)<sub>2</sub> and Pd[P(*o*-tol)<sub>3</sub>]<sub>4</sub> as catalyst,<sup>8</sup> Scheme 1.

To determine the effect of residual NaCl on this reaction, a toluene solution of bromide **1** was washed with 5% aq NaCl, leaving behind noticeable salt with the organic layer. This solution was directly switched into DMF, slurried with Zn(CN)<sub>2</sub>, and degassed. The catalyst (1 mol % Pd[P(*o*-tol)<sub>3</sub>]<sub>4</sub>) was prepared separately and added. This reaction gave no conversion to cyano product **2**. To mimic DMF decomposition, gaseous DMA was bubbled briefly through a Zn(CN)<sub>2</sub> slurry of bromide **1** in DMF before the catalyst was added. Again, no reaction was observed. Clearly these materials have a detrimental effect on the cyanation reaction.<sup>9</sup>

Further investigation into the failed reactions involved taking samples for IC analysis of cyanide in solution before and after addition of catalyst. The samples taken within minutes after catalyst addition show a significant decrease in soluble cyanide,<sup>10</sup> implying that the cyanide sequesters the catalyst before the reaction can start. It has been proposed<sup>11</sup> that 2 equiv or more of cyanide to palladium will inactivate the palladium, forming a stable palladium cyanate complex.<sup>3a</sup> On the basis of this assertion, there should be a balance between the amount of catalyst used in the reaction and the allowable amount of cyanide in solution. Evidence of this relationship was obtained in two sets of experiments. One set involved reactions using different amounts of catalyst on a substrate with the same amount of cyanide in solution. The second set involved reactions using the same catalyst loading on solutions with different cyanide levels. In the first

(7) Base is known to liberate cyanide; no previous data are available for NaCl or DMA.

(8) Bromide **1** (20 g, 58.88 mmol) was dissolved in DMF (100 mL). Zn(CN)<sub>2</sub> (4.15 g, 35.33 mmol) was added, and the resulting slurry was degassed with a subsurface nitrogen sparge for 20 min. The slurry was then heated to 56 °C. In a separate flask, Pd(OAc)<sub>2</sub> (264 mg, 1.18 mmol) and P(*o*-tol)<sub>3</sub> (1.44 g, 4.72 mmol) were dissolved in DMF (40 mL). The solution was degassed with subsurface nitrogen sparge and then heated to 56 °C and held for 30 min. ZnEt<sub>2</sub> (1.61 mL, 1.77 mmol, 1.1 M in toluene) was then added, forming a yellow-green slurry over 15 min. This slurry was aged at 56 °C for 45 min and then transferred via cannula to the reaction. The reaction was aged at 56 °C for 4–12 h, until complete conversion was attained. The reaction was then cooled in an ice bath and concd NH<sub>4</sub>OH (20 mL) was added. The slurry was aged an additional 30 min and then filtered. To the filtrate were added toluene (200 mL), NH<sub>4</sub>OH (28 mL), and water (112 mL) followed by vigorous stirring for 30 min. The aqueous layer was cut away, and the toluene layer was washed with 15% aq NaCl (140 mL) and then water (140 mL). The toluene layer assayed for 15.48 g of cyano **2** (54.17 mmol, 92% yield based on chromatographed standard). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 7.67 (s, 1H), 7.59 (d, 1H, *J* = 7.63 Hz), 7.52 (d, 1H, *J* = 7.63 Hz), 7.40 (app t, 1H, *J* = 7.63 Hz), 7.21 (d, 2H, *J* = 8.03 Hz), 7.11 (d, 2H, *J* = 8.03 Hz), 4.72 (d, 1H, *J* = 4.02 Hz), 3.90–3.81 (m, 1H), 3.11–3.06 (m, 1H), 3.03–2.89 (m, 2H), 0.92, (d, 3H, *J* = 6.42 Hz). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>): δ 143.5, 139.8, 135.0, 133.2, 131.2, 130.7, 130.3, 129.2, 128.4, 119.6, 111.0, 68.1, 53.6, 37.2, 22.0. HRMS [(M + Li)<sup>+</sup>] calcd 291.1072, found 291.1071.

(9) Water is often used as a cosolvent in cyanation reactions, cf. ref 2b. Therefore, water could be ruled out as the cause of reaction failure in the brine wash study.

(10) For example, in a reaction using 1 mol % catalyst, the cyanide in solution decreased from 840 to 300 ppm; a reaction with 0.5 mol % catalyst decreased from 192 to 37 ppm. Note: the IC method does not detect cyanide complexed to palladium.

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

**Table 2.** Cyanation Reactions of Substrate **1** in Relation to Cyanide Assay

	CN (ppm)	catalyst (mol %)	method of addition <sup>a</sup>	conversion <sup>b</sup> (%)
1	505	2	A	100
2	505	1	A	0
3	167	0.5	A	0
4	80	0.5	A	99
5	617	1	A	0
6	617	0.5	B	100
7	617	1	B	100
8	617	0.5	B, fast	0
9	696	1	A	0
10	777	1	B	100
11	1146	1.5	A	0
12	1146	1.5	B	100
13	2000	1	B	0
14	2070	3	B	99

<sup>a</sup> Method A: catalyst added to Zn(CN)<sub>2</sub> slurry over 2 min. Method B: Zn(CN)<sub>2</sub> slurry added to catalyst over 30 min, except where noted. <sup>b</sup> As determined by HPLC.

case, a higher catalyst loading worked where a lower loading failed (Table 2, entry 1 vs 2). Likewise, when the catalyst loading was held constant, the higher amount of soluble cyanide prevented reaction while the lower amount allowed for complete conversion to product (Table 2, entry 3 vs 4).

To overcome the problem of high soluble cyanide, one must ensure that the catalytic cycle initiates before the cyanide has a chance to deactivate catalyst. One way to do this is to add the Zn(CN)<sub>2</sub> slurry to the catalyst over 20–30 min,<sup>12</sup> ensuring the catalyst is only exposed to a small amount of cyanide and is not overwhelmed. Table 2 illustrates several examples in which a batch of bromide **1** and Zn(CN)<sub>2</sub> in DMF assayed for high soluble cyanide and then gave no conversion to product when catalyst was added to the batch. Conversely, when the slurry of bromide **1** and Zn(CN)<sub>2</sub> was added to the same amount of catalyst or less, complete conversion was achieved (Table 2, entry 5 vs 6 and 7; entry 9 vs 10; entry 11 vs 12).

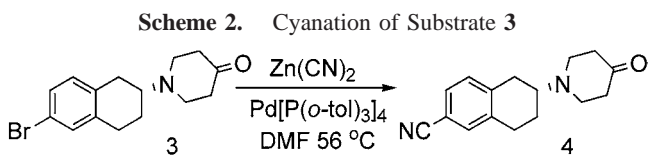
Unfortunately, there is an upper limit even with this inverse method of addition, where there is just too much cyanide in solution for reaction to take place. For example, in a reaction

(12) Pd(OAc)<sub>2</sub> (131 mg, 0.599 mmol) and P(*o*-tol)<sub>3</sub> (712 mg, 2.40 mmol) were dissolved in DMF (30 mL). The solution was degassed with subsurface nitrogen sparge and then heated to 56 °C and held for 30 min. ZnEt<sub>2</sub> (0.81 mL, 0.89 mmol, 1.1 M in toluene) was then added, forming a yellow-green slurry over 15 min. This slurry was aged at 56 °C for 45 min. In a separate flask, bromide **1** (10 g, 29.94 mmol) was dissolved in DMF (40 mL). Zn(CN)<sub>2</sub> (2.06 g, 17.54 mmol) was added, and the resulting slurry was degassed with a subsurface nitrogen sparge for 20 min. The slurry was heated to 56 °C and then transferred over 30 min via cannula to the catalyst. The reaction was aged at 56 °C for 4–12 h, until complete conversion was attained. Workup as in ref 8.

with 2000 ppm of cyanide there was no reaction when the batch was added slowly to the catalyst (Table 2, entry 13). However, this detrimentally high level of cyanide was overcome by using a larger loading of catalyst (Table 2, entry 14).

The rate of addition is also important in this method. When a batch was added to the catalyst over 30 min the reaction worked, but when the batch was added quickly the reaction failed (Table 2, entry 6 vs 8). In this example, the rapid addition of batch to catalyst had the same effect as adding catalyst to the batch—the catalyst was overwhelmed by cyanide.

To ensure that the effect of high cyanide was not specific to our substrate, we investigated this effect with another compound,<sup>13</sup> Scheme 2. Under our initial cyanation condi-



tions, substrate **3** underwent complete conversion to cyano product **4**. To test our hypothesis, 20 mol % DMA was added to a slurry of compound **3** and Zn(CN)<sub>2</sub> producing a soluble cyanide level of 1927 ppm. The batch was split into two portions; to one portion was added 2 mol % catalyst and the reaction failed. The other portion was added to 2 mol % catalyst over 30 min, and the reaction reached complete conversion. Clearly, the effect of materials causing high levels of cyanide in solution is not specific to our substrate.

In summary, we have discovered that a few common laboratory operations can detrimentally affect a subsequent cyanation reaction by leaving behind residual amounts of materials that increase cyanide solubility. NaCl, NaOH, and DMA were shown to increase cyanide in solution when aged with Zn(CN)<sub>2</sub> slurries in DMF. The problem of high levels of cyanide in solution was demonstrated to be overcome by using a higher catalyst loading. More practically, a method to overcome this problem was developed which entailed adding the reaction slowly to the catalyst to prevent swamping of the catalyst with cyanide. The robustness of this method was demonstrated with a variety of catalyst loadings and levels of cyanide in solution and on two substrates.

**Acknowledgment.** We thank Bob Waters for introducing us to ion chromatography and Shane Krska for helpful catalyst-related suggestions.

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(13) Tschäen, D. M.; Abramson, L.; Cai, D.; Desmond, R.; Dolling, U.-H.; Frey, L.; Karady, S.; Shi, Y.-J.; Verhoeven, T. R. *J. Org. Chem.* **1995**, *60*, 4324–4330.