J|A|C|S
COMMUNICATIONS

Published on Web 12/14/2006

Why Excess Cyanide Can Be Detrimental to Pd-Catalyzed Cyanation of Haloarenes. Facile Formation and Characterization of $[Pd(CN)_3(H)]^{2-}$ and $[Pd(CN)_3(Ph)]^{2-}$

Kerwin D. Dobbs, William J. Marshall, and Vladimir V. Grushin*
Central Research & Development, E. I. DuPont de Nemours and Company, Inc., Experimental Station, Wilmington, Delaware 19880-0328

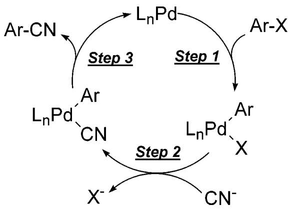
Received September 26, 2006; E-mail: vlad.grushin-1@usa.dupont.com

Palladium-catalyzed cyanation of haloarenes (eq 1) is one of the most important modern methods for the introduction of the cyano group into the aromatic ring.[1] This reaction is extensively used in the synthesis of pharmaceuticals, agrochemicals, dyes, and various intermediates.[1]

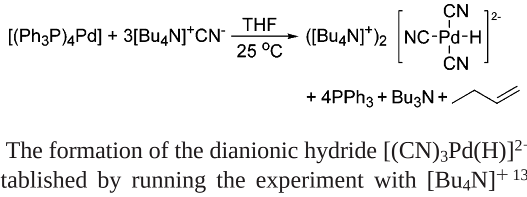
$$\mathrm{Ar{-}X} + \mathrm{CN^-} \xrightarrow{\text{Pd catalyst}} \mathrm{Ar{-}CN} + \mathrm{X^-} \qquad (1)$$

Since the discovery[2] of Pd- and Ni-catalyzed aromatic cyanation, it has been widely recognized that the amount of free cyanide *in solution* during the reaction must be carefully controlled. While being one of the two reagents (eq 1), the cyanide ion in excess can deactivate the catalyst, which leads to process termination.[1] This has been recently re-confirmed in a special study.[3] Furthermore, $Zn(CN)_2$[4] and $K_4[Fe(CN)_6]$[5] with weakly ionizable M−CN bonds have been found advantageous for use in reaction 1, as compared to the conventional ionic cyanide sources, KCN and NaCN. Surprisingly, the origin of the detrimental effect of the CN^- in excess remains unclear, except it has been shown[6] that $[Bu_4N]^+ CN^-$ retards the ability of $[(Ph_3P)_4Pd]$ to oxidatively add an aryl halide. In this communication, we report that each key step of the catalytic loop for the cyanation process (Scheme 1) can be affected by excess cyanide in a startling manner.

Scheme 1. Accepted Simplified Mechanism for Reaction 1



We found that adding anhydrous $[Bu_4N]^+ CN^-$ to $[(Ph_3P)_4Pd]$ in dry THF resulted in immediate color change from yellow to tan, after which the solution gradually faded to colorless. Analysis of the reaction products revealed a remarkably selective, unexpected transformation, as shown in eq 2.



$$[(Ph_3P)_4Pd] + 3[Bu_4N]^+CN^- \xrightarrow[25\ ^\circ C]{THF} ([Bu_4N]^+)_2 \left[NC{-}\overset{CN}{\underset{CN}{Pd}}{-}H \right]^{2-} + 4PPh_3 + Bu_3N + \text{1-butene} \qquad (2)$$

The formation of the dianionic hydride $[(CN)_3Pd(H)]^{2-}$ (**1**)[7] was established by running the experiment with $[Bu_4N]^{+}\,{}^{13}CN^-$ and observing the hydrido resonance as a doublet of triplets at −10.85 ppm (^1H NMR, Figure 1). In the $^1H\{^{13}C\}$ NMR spectrum, this resonance appeared as a singlet. The ^{13}C NMR spectrum of **1**-^{13}C displayed two signals, a doublet at 144.6 ppm (2C, mutually trans-CN ligands) and a triplet at 148.0 ppm (1C, CN trans to H) with the same coupling constant $J_{C-C} = 6.8$ Hz. The formation of Bu_3N and 1-butene was confirmed by ^1H and ^{13}C NMR data. A *sharp* singlet at −5.5 ppm was observed in the ^{31}P NMR spectrum of the reaction solution, pointing to full release of all of the PPh_3 originally bound to the starting Pd(0). While $[Bu_4N]^+{}_2{\cdot}\mathbf{1}$ is an oil at room temperature, $[PPN]^+{}_2{\cdot}\mathbf{1}$ obtained from $[Bu_4N]^+{}_2{\cdot}\mathbf{1}$ and $[PPN]^+ CN^-$ (PPN = Ph_3PNPPh_3) by metathesis is a solid and was isolated (see below).[8]

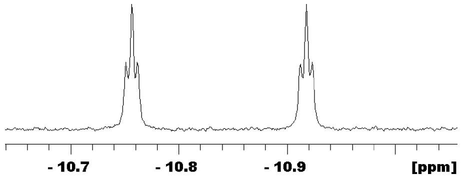


Figure 1. ^1H NMR signal from $[(^{13}CN)_3Pd(H)]^{2-}$ (*trans*-$J_{C-H} = 64.0$ Hz; *cis*-$J_{C-H} = 2.3$ Hz).

Extra PPh_3 strongly inhibited reaction 2. When run with [Pd] = 1.7×10^{-2} M and $[^{13}CN^-] = 6.9 \times 10^{-2}$ M in THF-d_8 at 25 °C, reaction 2 proceeded to ca. 80 and 20% conversion (^{13}C NMR) after 6 h without and with extra PPh_3 (6 equiv per Pd), respectively. Full conversion was achieved faster for more dilute solutions, certainly of relevance to the catalytic process (eq 1) that employs low concentrations of Pd catalysts. Thus, the above-described reaction without extra PPh_3 reached full conversion (complete discoloration) after 1 day. Under identical, rigorously dry conditions but with twice the concentration of the reagents, full color loss was observed only after 1 week. Added water (2 equiv per Pd) neither had a dramatic effect on reaction 2 nor decomposed **1**.[9]

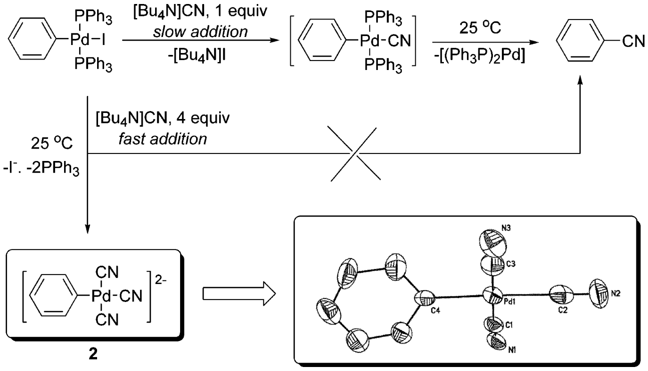
No reaction between $[Bu_4N]^+ X^-$ (X = I, Cl) and $[(Ph_3P)_4Pd]$ was observed under similar conditions. It is clear, however, that the use of $R_4N^+ X^-$ as phase-transfer catalysts for reaction 1[1] might easily damage the active Pd catalyst, as shown in eq 2. The uncommon reactivity (eq 2) apparently originates from mixed cyano−phosphine Pd(0) species. Our preliminary low-temperature NMR (^{13}C and ^{31}P) and computational DFT studies indicated that both $[(Ph_3P)_3Pd(CN)]^-$ and $[(Ph_3P)_2Pd(CN)_2]^{2-}$ may be formed upon treatment of $[(Ph_3P)_4Pd]$[10] with the CN^- (see Supporting Information).[11] Such anionic Pd(0) complexes are fully expected to exhibit enhanced reactivity toward oxidative addition, especially upon loss of one more phosphine ligand.[12] It is conceivable[12,13] that a C−N bond of the $[Bu_4N]^+$ oxidatively adds to a mixed phosphine−cyanide Pd(0) species, followed by β-elimination and ligand exchange to produce **1**. Our computations, however, point to significant localization of a negative charge on the N atom(s) of $[(Ph_3P)_nPd(CN)_m]^{m-}$ (see Supporting Information). Therefore, classical Hofmann elimination involving deprotonation at a β-position of $[Bu_4N]^+$ should not be ruled out at this point. Both N-protonation of coordinated cyanide[14] and H-transfer from L_nMCNH to form

10.1021/ja066931d CCC: $37.00 © 2007 American Chemical Society

$L_nM(H)CN$[14b] are well documented. A detailed mechanistic study of reaction 2 is currently underway.

Regardless of whether the cyanation (eq 1) is run with or without $[R_4N]^+$ as a phase-transfer agent, excess CN^- can poison the Pd catalyst at Step 2 of the catalytic loop (Scheme 1). When an *equimolar* amount of $[Bu_4N]^+ CN^-$ was slowly added to $[(Ph_3P)_2Pd(I)Ph]$ in THF at 25 °C, an instantaneous reaction occurred to produce PhCN and Pd(0). In sharp contrast, quick mixing of $[(Ph_3P)_2Pd(I)Ph]$ with a 4-fold *excess* of $[Bu_4N]^+ CN^-$ in THF resulted in no PhCN formation but rather led selectively to stable $[(CN)_3PdPh]^{2-}$ (**2**); see Scheme 2.[15] Similarly, the reaction of $[(Ph_3P)_2Pd(I)Ph]$ with 4−6 equiv of $K^{13}CN$ in a biphasic D_2O/benzene system cleanly afforded $K_2[(^{13}CN)_3PdPh]$ (aqueous phase; ^1H and ^{13}C NMR) and free PPh_3 (organic phase; ^{31}P NMR).[16] Assuming the NMR detection limit at ca. 1%, the exclusive formation of either PhCN or **2** (Scheme 2) indicates that rate constants for the I^-/CN^- exchange, Ph_3P/CN^- exchange, and Ph−CN reductive elimination decrease in the order $k_{I/CN} > k_{P/CN} \geq k_{RE} \times 10^2$.

Scheme 2. Reactions of $[(Ph_3P)_2Pd(I)Ph]$ with 1 Equivalent of $[Bu_4N]^+ CN^-$ and with 4 Equivalents of $[Bu_4N]^+ CN^-$ in THF



Like $[Bu_4N]^+{}_2\cdot$**1**, $[Bu_4N]^+{}_2\cdot$**2** is an oil at room temperature but $[PPN]^+{}_2\cdot$**2** is a solid that was isolated and structurally characterized (Scheme 2). Although cyanide is known to displace R_3P in Pd complexes,[17] this remarkably facile, apparently irreversible R_3P/CN^- ligand exchange has not received sufficient investigation in previous studies of Pd-catalyzed aromatic cyanation (eq 1). We found that not only PPh_3 but even more strongly binding PCy_3 is easily and fully released from Pd in the presence of the CN^-. Treatment of $[(Cy_3P)_2Pd(Cl)Ph]$ with excess of $[Bu_4N]^+ CN^-$ in THF cleanly produced free PCy_3 and **2** in quantitative yield.

Both dianions **1** and **2** were found to be stable in solution in the presence of extra cyanide. However, freshly isolated well-shaped white crystals of $[PPN]^+{}_2\cdot$**1** turned grayish on the surface upon drying under vacuum for only a few minutes.[18] When this salt was redissolved in MeCN-d_3, the originally solid-free, colorless solution turned cloudy and yellowish-gray within a minute. After 10 min, the formation of a dark-brown precipitate and HCN (^1H NMR: 4.2 ppm, s) was observed, pointing to reductive elimination of HCN from **1**. Similarly, **2** was found to be stable in aqueous or organic (THF, MeCN) solutions containing extra cyanide even in small amounts (ca. 10%) but readily underwent reductive elimination of PhCN at room temperature when the solution was CN^--free.[19] Reductive elimination from Pd(II) is often promoted by ligand dissociation, commonly proceeding from three- rather than four-coordinate Pd(II) complexes.[20] It is likely therefore that predissociation of one cyanide ligand from **1** and **2** is required for the reductive elimination to occur. Extra CN^- shifts the equilibria toward nondissociated, four-coordinate **1** and **2** which are not prone to reductive elimination under these conditions.

In conclusion, unexpected side reactions at the Pd center have been identified for Pd-catalyzed cyanation of haloarenes (eq 1). In the presence of excess cyanide, these reactions can proceed with ease, interfering with the key steps of the catalytic loop (Scheme 1) and thereby disrupting the process.

Acknowledgment. This is DuPont CR&D Contribution No. 8745. We thank Ms. Laurie A. Howe and Dr. D. Christopher Roe for selected NMR experiments, and Drs. Albert L. Casalnuovo, Jörg Brüning, and Stuart A. Macgregor for discussions.

Supporting Information Available: Experimental and computational details, NMR data (PDF), and X-ray analysis data (CIF) for $[PPN]^+{}_2\cdot$**2**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For a recent review, see: Sundermeier, M.; Zapf, A.; Beller, M. *Eur. J. Inorg. Chem.* **2003**, 3513.

(2) (a) Pd: Takagi, K.; Okamoto, T.; Sakakibara, Y.; Oka, S. *Chem. Lett.* **1973**, 471. (b) Ni: Cassar, L. *J. Organomet. Chem.* **1973**, *54*, C57.

(3) 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.

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

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

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

(7) (a) A material has been formulated as a *neutral, four-coordinate Pd(IV)* complex $[HPd(CN)_3]$, based on C,H-analysis data: Nozaki, K. U.S. Patent 3835123, 1974. (b) $[HPt(CN)_3]^{2-}$ has been reported: Almeida, J. F.; Pidcock, A. *J. Organomet. Chem.* **1981**, *208*, 273.

(8) X-ray analysis of $[PPN]^+{}_2\cdot$**1** was inconclusive because of disorder.

(9) This stability of **1** is uncommon in the chemistry of palladium hydrides: Grushin, V. V. *Chem. Rev.* **1996**, *96*, 2011.

(10) $[(Ph_3P)_4Pd]$ undergoes full dissociation of one PPh_3 in solution: Mann, B. E.; Musco, A. *J. Chem. Soc., Dalton Trans.* **1975**, 1673.

(11) The ΔG values (298 K) for the sequential stepwise PPh_3 displacement reactions of $[(Ph_3P)_4Pd]$ with cyanide to $[(Ph_3P)_3Pd(CN)]^-$, $[(Ph_3P)_2Pd(CN)_2]^{2-}$, $[(Ph_3P)Pd(CN)_3]^{3-}$, and finally $[Pd(CN)_4]^{4-}$ were computed at −52, +23, +112, and +194 kcal mol^{-1}, respectively.

(12) For detailed accounts of the pioneering work of Amatore, Jutand, and co-workers in the field, see: Amatore, C.; Jutand, A. *J. Organomet. Chem.* **1999**, *576*, 254 and *Acc. Chem. Res.* **2000**, *33*, 314.

(13) For example, Suzuki coupling has been reported with $[ArNMe_3]^+$ as the arylating electrophile: Blakey, S. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 6046.

(14) For reviews, see: (a) Fehlhammer, W. P.; Fritz, M. *Chem. Rev.* **1993**, *93*, 1243. (b) Pombeiro, A. J. L. *Inorg. Chem. Commun.* **2001**, *4*, 585.

(15) The anion $[(CN)_3PdPh]^{2-}$ has been reported to form from the redox reaction of $K_2[Pd(CN)_2]\cdot xNH_3$ with KCN and $[Ph_4P]^+$: Nast, R.; Buelck, J.; Kramolowsky, R. *Chem. Ber.* **1975**, *108*, 3461.

(16) ^{31}P NMR (C_6H_6, 25 °C, δ): −5.5 ppm (s, PPh_3). NMR for $K_2[(^{13}CN)_3PdPh]$ in the D_2O phase (25 °C, δ): ^1H: 7.1 (t, 1H, *p*-Ph); 7.2 (t, 2H, *m*-Ph); 7.5 (d, 2H, *o*-Ph). ^{13}C: 145.4 (d, J_{C-C} = 7.3 Hz, 2C, mutually trans-CN); 146.7 (t, J_{C-C} = 7.3 Hz, 1C, CN trans to Ph).

(17) For instance, cyanide has been used to displace BINAP mono-oxide from its Pd complex: Gladiali, S.; Pulacchini, S.; Fabbri, D.; Manassero, M; Sansoni, M. *Tetrahedron: Asymmetry* **1998**, *9*, 391.

(18) For this reason, no combustion analysis of $[PPN]^+{}_2\cdot$**1** was attempted.

(19) Stirring $[(Ph_3P)_2Pd(I)Ph]$ in benzene with D_2O containing a substoichiometric amount (2.9 equiv; see Scheme 2) of $K^{13}CN$ led to extra cyanide-free $K_2[(^{13}CN)_3PdPh]$ in the aqueous phase (^{13}C NMR). The separated clear D_2O solution turned cloudy in ca. 30 min, and after 12 h, the formation of an amorphous-looking, brown−black precipitate was observed. The mixture was extracted with CD_2Cl_2 to detect $Ph^{13}CN$ in the extract (^{13}C NMR, δ: 119.0 (s) and GC−MS).

(20) See, for example: (a) Yamashita, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 5344. (b) Marshall, W. J.; Grushin, V. V. *Organometallics* **2003**, 22, 1591. (c) Grushin, V. V. *Organometallics* **2000**, *19*, 1888.

JA066931D