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Insights Into Palladium-Catalyzed Cyanation of Bromobenzene: Additive Effects on the Rate-Limiting Step

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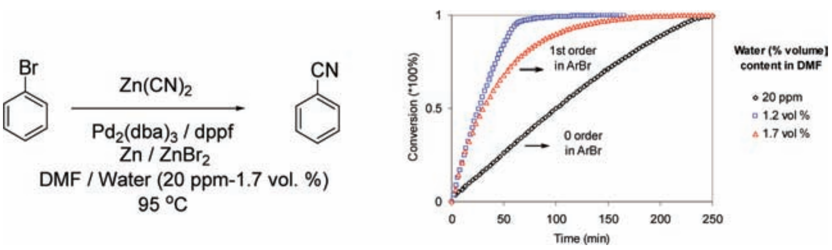
ABSTRACT



Kinetic studies using reaction calorimetry were conducted under synthetically relevant conditions to study the effect of additives in the cyanation of bromobenzene catalyzed by palladium complexes. This work demonstrates that the addition of a catalytic amount of ZnBr$_2$ facilitates the reaction with an elimination of the induction period observed without additive. This study afforded a qualitative assessment of the effect of water on the rate-limiting step and the apparent reaction order in bromobenzene.

Over the past few years, the metal-catalyzed cyanation of aryl halides has received much attention as a broad synthetic method for the preparation of substituted benzonitriles.[1] Benzonitriles are important building blocks of natural products, agrochemicals, and pharmaceutical products with interesting biological properties.[2] Prior studies of palladium-catalyzed cyanation reactions revealed that catalyst deactivation was dependent on the concentration of dissolved cyanide species, which can form unreactive complexes.[3] Intensive efforts to prevent catalyst deactivation and to improve the reaction have been undertaken. This has usually consisted of efforts to reduce the solubility of cyanide ions, such as the use of nonpolar solvents[4] or less soluble cyanide reagents (zinc cyanide[5] and potassium ferrocyanide(II)[6]). Other approaches to improve the reaction rate include the combination of various additives (e.g., Bu$_3$SnCl,[7] Zn(OAc)$_2$[8] or Zn dust, Br$_2$[9]) and/or the addition of a catalytic amount of water to

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the catalytic system.[10] Despite this progress, only a few mechanistic and kinetic studies have been reported to understand the effect of these additives for the cyanation process.[11] We report herein the kinetic analysis of the cyanation of bromobenzene with zinc cyanide catalyzed by palladium complexes in the presence of additives such as water and/or $ZnBr_2$ (see Scheme 1) using reaction calorimetry[12] as an in situ monitoring technique under practical synthetic conditions. These studies provide a basis for discussion of proposed reaction mechanisms and the efficient optimization of the cyanation process.

Scheme 1. Cyanation Reaction

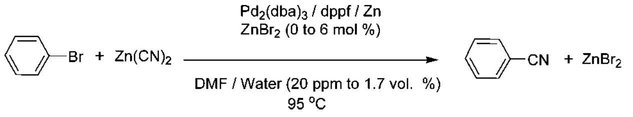

Figure 1 shows a typical reaction heat flow profile as a function of time for the reaction initiated by addition of bromobenzene ($[ArBr]_0 = 1.1$ M) to a reaction vial, equilibrated thermally for 45 min in a reaction calorimeter (Omnical, Super CRC) at 95 °C, containing a heterogeneous mixture of $Zn(CN)_2$ (0.7 equiv or 0.77 $mmol_{(s)}$/mL solvent)[13] and a preformed catalyst mixture of $Pd_2(dba)_3$ (0.5 mol %), dppf (1.4 mol %), and Zn dust[14] (8 mol %) in DMF (5 mL) containing 1.7 vol % of water (equivalent to $[H_2O] = 0.8$ M).[10b] Comparison of fraction conversion determined by reaction calorimetry and from HPLC analysis of samples extracted over time confirmed that the heat flow profile provides an accurate measure of the reaction rate.[15] The reaction heat flow versus time reveals that a key feature of this reaction is an induction period during which the rate increased for more than 30 min as the substrate concentration decreased, which would suggest that more active or more soluble species were formed over the reaction conversion.

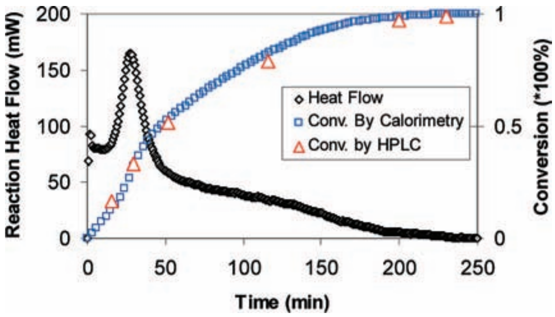

Figure 1. (◇) Reaction heat flow versus time for the cyanation of bromobenzene (1.1 M) with $Zn(CN)_2$ (0.7 $mmol_{(s)}$/mL), Zn (8 mol %), $Pd_2(dba)_3$ (0.5 mol %), and dppf (1.4 mol %) in DMF (5 mL) with 1.7 vol % water at 95 °C. Comparison of conversion measured by heat flow calorimetry (□) to the conversion measured by HPLC (△).

To obtain more information about the reaction kinetics over time, an experimental protocol involving a series of three consecutive injections of bromobenzene aliquots to a single vessel containing all other reagents with an excess of $Zn(CN)_2$ sufficient to provide full conversion of bromobenzene was carried out at 95 °C (Figure 2). As expected, the first injection exhibited the sudden exotherm observed in the previous experiment and the subsequent two injections exhibited a well-behaved positive order rate profile. The difference of the reaction rates observed between the second and third injection could be due to a deactivation of catalyst over time in the presence of a large excess of zinc cyanide. It was hypothesized that the zinc(II) bromide side product of the reaction could be the species responsible for the acceleration of rate observed in the initial phase of the reaction.[16]

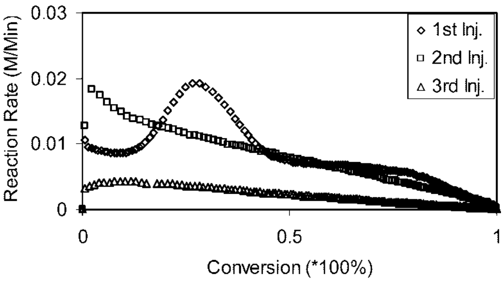

Figure 2. Consecutive reactions with three added aliquots of bromobenzene (5.9 mmol) to a solution of $Zn(CN)_2$ (11.8 mmol), Zn (8 mol %), $Pd_2(dba)_3$ (0.5 mol %), and dppf (1.4 mol %) in 5.9 mL of DMF/water (1.7 vol %) at 95 °C.

Figure 3 shows that with a catalytic amount of $ZnBr_2$ (6 mol %) added initially, the reaction kinetics directly afforded

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(12) For significant examples of kinetic studies using reaction calorimetry, see: (a) Mathew, J. S.; Klussmann, M.; Iwamura, H.; Valera, F.; Futran, A.; Emmanuelsson, E. A. C.; Blackmond, D. G. *J. Org. Chem.* **2006**, *71*, 4711–4722. (b) Blackmond, D. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4302–4320.

(13) $Zn(CN)_2$ is poorly soluble in DMF. The amount of $Zn(CN)_2$ introduced is noted as mmol of solid $Zn(CN)_2$/mL solvent ($mmol_{(s)}$/mL).

(14) In the absence of Zn powder, the reaction stalled at low conversion as observed in refs 8 and 10a. We believe that the zinc dust should play a role to maintain palladium(0) complexes, avoiding inhibition processes of the catalyst system.

(15) Reproducibility of the reaction heat flow profile versus time has been checked, and the heat of reaction was in average 26.8 (±1.5) kcal/mol.

(16) A significant induction period could be attributed to the slow activation of the catalytic precursors. A solution of $Pd_2(dba)_3$/dppf/Zn was stirred for 20 min at rt before addition of $Zn(CN)_2$ and the reaction solution was equilibrated at 95°C for 45 min; no significant difference in the heat flow profile was observed with longer equilibration time (1 h). For palladium complexes activation, see: Shekhar, S.; Ryberg, P.; Hartwig, J. F.; Mathew, J. S.; Blackmond, D. G.; Strieter, E. R.; Buchwald, S. *J. Am. Chem. Soc.* **2006**, *128*, 3584–3591.

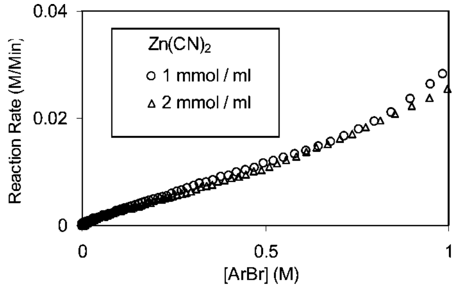

Figure 3. Reaction rate versus [ArBr]. Standard conditions: $[ArBr]_0$ = 1.0 M with $Zn(CN)_2$ ((◊) (1 $mmol_{(s)}$/mL), (Δ) (2 $mmol_{(s)}$/mL) and Zn (8 mol %), $ZnBr_2$ (6 mol %), $Pd_2(dba)_3$ (0.5 mol %), and dppf (1.4 mol %) in DMF with 1.7 vol % water at 95 °C.

a kinetic profile without the sudden exotherm. The methodology of reaction progress kinetic analysis was employed to establish the kinetic profile.[12] With different zinc cyanide loadings, the curves of reaction rate versus bromobenzene concentration overlay, showing that the reaction rate is not dependent on the amount of zinc cyanide introduced in the reaction, and exhibit a straight line, indicating that the reaction rate is dependent on bromobenzene concentration.

Figure 4 shows the reaction rate versus palladium concentration. It appears that the reaction is first order in palladium at low catalyst concentration and negative order at high catalyst concentration.[17] Finally, these experiments reveal that the reaction rate is first order in bromobenzene and in palladium (at low catalyst concentration) and zero order in zinc cyanide and is in alignment with the effects of Zn dust/Br_2 observed in ref 9, which indicates that zinc bromide formed during the initial phase of the reaction plays a role in the formation of the more active or more soluble species.[18] Determination of the solubility of cyanide confirmed that the addition of $ZnBr_2$ (10 wt %) to a solution of $Zn(CN)_2$ in wet DMF at 95 °C increased the amount of dissolved cyanide species by up to 5-fold.[19]

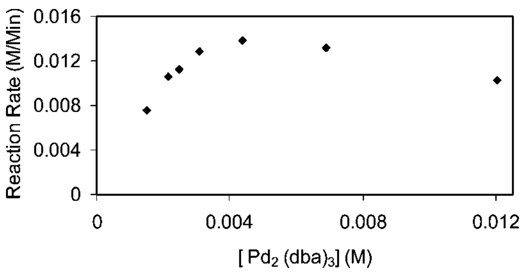

Figure 4. Reaction rate at 50% conversion versus $[Pd_2(dba)_3]$. $[ArBr]_0$ = 1.1 M, $Zn(CN)_2$ (0.77 $mmol_{(s)}$/mL), Zn (6 mol %), $ZnBr_2$ (6 mol %), $Pd_2(dba)_3$ (0.1−1.0 mol %), and dppf (0.3−3.0 mol %) in DMF/water (1.7 vol %) at 95 °C.

To further evaluate the effect of water, experiments were conducted with varying concentrations of zinc bromide and zinc cyanide under anhydrous conditions (20 ppm water). Addition of $ZnBr_2$ (6 mol %) was again observed to eliminate the induction period of the reaction (Figure 5b). Interestingly, under these conditions, the reaction showed a different kinetic profile, with the reaction rate constant over the course of the reaction. No effect of palladium catalyst concentration on the rate of reaction was observed (Figure 5c), while the reaction rate was found to be dependent on the amount of $Zn(CN)_2$ introduced at the beginning of the reaction (Figure 5d). This would suggest that the reaction rate is zero order in bromobenzene concentration and is limited by the dissolution of $Zn(CN)_2$ under anhydrous conditions.

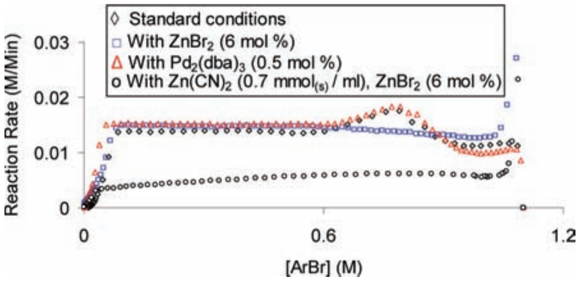

Figure 5. Reaction rate versus [ArBr] in *dry* DMF (20 ppm water) at 95 °C. (5a, ◊) Standard conditions: $[ArBr]_0$ = 1.1 M, $Zn(CN)_2$ (2.1 $mmol_{(s)}$/mL), Zn (8 mol %), $Pd_2(dba)_3$ (0.3 mol %), and dppf (0.8 mol %). (5b, □) Standard conditions with $ZnBr_2$ (6 mol %); (5c, Δ) with $Pd_2(dba)_3$ (0.5 mol %), dppf (1.4 mol %); (5d, ○) with $ZnBr_2$ (6 mol %) and $Zn(CN)_2$ (0.7 $mmol_{(s)}$/mL).

Figure 6 shows the role of water on the rate-limiting step by varying amounts of water (20 ppm to 1.7 vol %). With 0.2 vol % water, the reaction rate appears to be zero order and significantly increased compared to the 20 ppm experiment. With 1.2 vol % water, the reaction rate has a complex order of [ArBr] between zero and first order where the time to achieve high conversion is approximately 4-fold faster than under anhydrous conditions (see Supporting Information). Further addition of water (1.7 vol %) slowed down the reaction rate, which appears to be first order in bromobenzene. Overall these studies demonstrate a significant impact of water on reaction order and on the rate-limiting step of the reaction.

Scheme 2 shows a simplified mechanism of Pd-catalyzed cyanation with successive steps: (a) oxidative addition of aryl halide to the Pd(0) catalyst,[20] (b) dissolution of $Zn(CN)_2$, (c) transmetalation to form ArPdCN, (d) reductive elimination and regeneration of catalyst. The mechanistic points

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(17) The order observed at high palladium concentration would support the presence of an inactive palladium dimer. The authors would like to acknowledge one of the referees for their comments and suggestions on the interpretation of the catalyst order.

(18) Another possible role of zinc bromide, mentioned by one of the referees, is that it could presumably act as Lewis acid, facilitating halide abstraction from an oxidative addition intermediate.

(19) Solubility of $Zn(CN)_2$ in DMF/water (1 vol %) at 95 °C was determined by ionic chromatography: 0.654 mg/mL, equivalent to $[CN^-]$ = 0.025 M if all cyanide species in solution are free cyanide ions. With added $ZnBr_2$ (10 wt %) solubility is 3.491 mg/mL equivalent to $[CN^-]$ = 0.13 M. In ref 10a, $Zn(CN)_2$ solubility in dry DMF at 80°C was 0.180 mg/mL ($[CN^-]$ = 0.007 M).

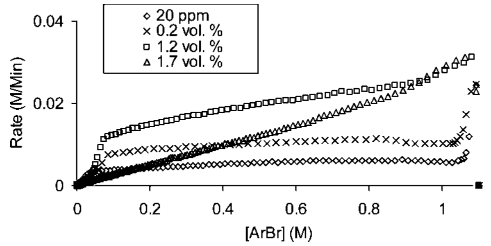
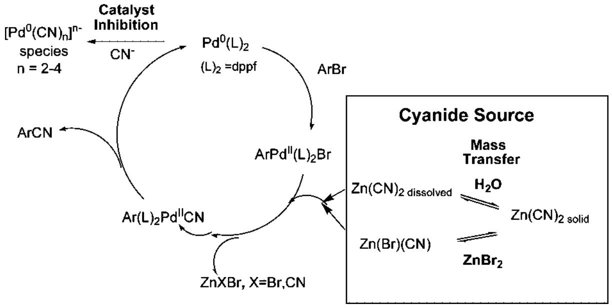


Figure 6. Influence of water on the reaction rate at 95 °C. $[ArBr]_0 = 1.1$ M, $Zn(CN)_2$ (0.77 $mmol_{(s)}$/mL), Zn (8 mol %), $ZnBr_2$ (6 mol %), $Pd_2(dba)_3$ (0.3 mol %), dppf (0.8 mol %) in DMF containing water (◇) 20 ppm ($[H_2O] = 0.01$ M), (×) 0.2 vol % ($[H_2O] = 0.10$ M), (□) 1.2 vol % ($[H_2O] = 0.55$ M), (Δ) 1.7 vol % ($[H_2O] = 0.80$ M).

revealed by our kinetic studies are that the initial charge of a catalytic amount of $ZnBr_2$ may have a dual effect by increasing the concentrated of dissolved cyanide ion[13] and/or forming some other active zinc species such as Zn(CN)(Br).[9,21] Addition of water has a *dramatic* effect on the apparent order of the reaction and has implications on the catalytic cycle. This different reaction order may be explained by a change of the rate-limiting step from a mass transfer step (dissolution of $Zn(CN)_2$ solid) to a step that could be the oxidative addition (first order in bromobenzene and palladium). This change of the rate-limiting step is likely a consequence of an increase in the solubility of zinc cyanide[22] in the presence of water and an inactivation of catalyst due to the increased concentration of dissolved cyanide ions.[3] Optimization of the water amount was considered a good means to identify conditions with an optimum rate, which struck a compromise between an increase in the mass transfer rate while simultaneously minimizing catalyst deactivation.

Scheme 2. Proposed Reaction Mechanism



In summary, this work affords some mechanistic insights into the effect of additives[8−10] in the cyanation reaction of bromobenzene catalyzed by palladium complexes. The addition of $ZnBr_2$ may facilitate the reaction initially by increasing the concentration of dissolved cyanide ions, likely by formation of a more active, more soluble, noninhibitory mixed zinc species. This kinetics study highlights the complex and opposing role that water could play in the kinetic regime of this heterogeneous palladium-catalyzed reaction. Deconvoluting these effects will aid in obtaining true mechanistic understanding in these reactions. Further studies to establish the overall kinetics and modeling are underway and will be reported in due course.

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Supporting Information Available: Experimental procedures and kinetic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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