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Note

Reservoir catalysis: Rationalization of anomalous reaction orders in Pd-catalyzed amination of aryl halides

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ABSTRACT

Reversible partitioning of a portion of the catalyst away from the active cycle provides a mechanistic rationalization of the anomalous reaction orders observed in the presence of additives. The concept of stable reservoir species leads to a practical protocol for maintaining a robust catalyst system that may be particularly useful for development of reactions under harsh conditions likely to lead to catalyst deactivation and incomplete turnover. Probing Pd-catalyzed amination reactions in the presence of competitive binding events reveals the key role that reservoir species connected reversibly to the catalytic cycle can play.

1. Introduction

The Pd catalyzed amination of aryl halides has rapidly become one of the most viable methods to synthesize substituted arylamines [1], important molecules for pharmaceuticals and agrochemicals. Mechanistic studies have revealed much about the rich chemistry of the catalytic cycle [2], but a challenge remains to develop systems that can operate to high turnover for less reactive substrates under demanding conditions. Competitive amination reactions have helped to rationalize the origin of selectivity in terms of amine binding strengths and nucleophilicity [3]. We recently reported investigations of the reactions of Scheme 1 carried out with amines **2a** and **2b** both in separate reactions and in competition to gain insight into the relative importance of the stability and the reactivity of intermediate species [4]. This work led us to probe the effects of competitive binding of non-reacting additives. Here we report how these studies help to rationalize anomalous reaction orders, understand catalyst stability, and design effective reaction protocols for robust processes.

2. Results and discussion

The currently accepted mechanism for this reaction involves oxidative addition of the aryl halide to Pd^0 followed by reaction with amine, deprotonation by base, and reductive elimination of the product to complete the catalytic cycle. For reaction of primary aliphatic amines such as **2a**, oxidative addition is rate-determining and the reaction has been shown to give first- and zero-order kinetics in [**1**] and [**2a**], respectively [2,4]. Intriguingly, Fig. 1 shows that when the reaction of Scheme 1 is carried out in the presence of hydrazone **3b**, the steady-state rate of reaction of **1** + **2a** is *first order* in amine concentration [**2a**], not zero order as expected, and *zero order* in aryl halide concentration [**1**], not first order as expected.

To understand how the presence of **3b** affects the reaction, we compared conversion profiles of the reaction of aryl halide **1** with amine **2a** in the presence and absence of amine **3b** obtained by reaction calorimetry.[1] Fig. 2a shows that rate is suppressed in the presence of **3b**; however, the overlay of rate curves in "same excess" [5] reactions of **1** + **2a** shown in Fig. 2b confirms steady-state catalytic behavior, indicating that no irreversible loss of Pd from the cycle occurs over the course of the reaction in the presence of **3b**.

While the secondary amine **3b** is not reactive under the conditions of the experiments of Figs. 1 and 2, in the absence of primary amine **2a** arylation of **3b** with **1** can occur to form **3c** at a rate nearly tenfold slower than arylation of **2a** (Scheme 2). If this reaction proceeds mechanistically as a typical Pd-catalyzed amination, amine **3b** adds to the oxidative addition complex of **1** to form a Pd species containing both **1** and **3b**, which we term **6b**, that is a competent intermediate for transmetallation and reductive elimination of the biarylated product.

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[1] Arylation of **3b** with **1** occurs only under large excess of **1** and at a rate ca. tenfold slower than arylation of **2a**.

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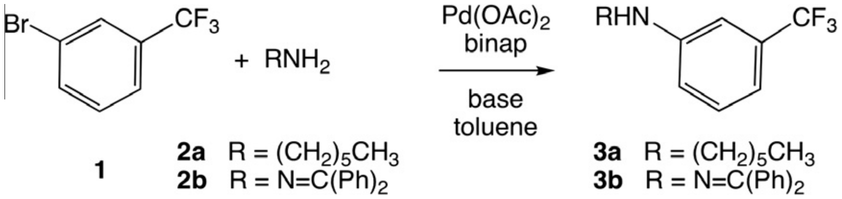

Scheme 1. Amination of aryl halides catalyzed by Pd(binap).

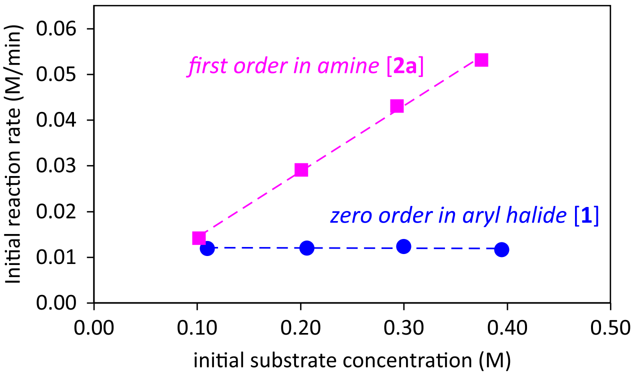

Fig. 1. Initial rate as a function of initial substrate concentration for reactions of **1** and **2a** at 90 °C carried out in the presence of 0.2 M **3b**. Magenta squares: dependence on amine [**2a**] with $[\mathbf{1}]_0 = 0.4$ M; blue circles: dependence on aryl halide [**1**] with $[\mathbf{2a}]_0 = 0.1$ M. $Pd(OAc)_2$ (0.0045 M); binap (0.006 M); *t*-BuONa (0.4 M). See Supporting Information for full reaction calorimetry profiles. (For interpretation of the references in color in this figure legend, the reader is referred to the web version of this article.)

Our previous studies have shown that the resting state in the amination of **1** with the hydrazone **2b** is a Pd complex containing both substrates and that this species monopolizes a large fraction of the catalyst in competitive reactions between **2a** and **2b**. By analogy, a Pd complex containing **1** and **3b** is likely to form a species that is more stable under catalytic conditions than any of the on-cycle species, all of which are revealed by the kinetic data to be fleeting in concentration during amination of primary amines such as **2a**.

Scheme 3 shows how the presence of an off-cycle species such as **6b** reversibly linked to the catalytic cycle helps to rationalize the anomalous kinetics as shown in Scheme 3. **3b** binds strongly and reversibly to the oxidative addition species **5** to form **6b**. This off-cycle species occupies a significant portion of active Pd such that **6b** becomes the resting state as a "dead-end" reservoir in equilibrium with catalytic cycle. The rate-determining step of the cycle therefore shifts to the addition of **2a** to the oxidative addition product **5** in equilibrium with **6b** (Eq. 1).

$$r_{rds} = \boldsymbol{k}[\mathbf{5}]\cdot[\mathbf{2a}] = \frac{\boldsymbol{k}}{\boldsymbol{K}_{\mathbf{eq}}}\cdot\frac{[\mathbf{6b}]}{[\mathbf{3b}]}\cdot[\mathbf{2a}] \qquad (1)$$

Eq. (1) confirms that the cycle presented in Scheme 3 renders the reaction zero-order in aryl halide [1], which appears prior to the resting state **6b**, first order in [**2a**], which reacts with **5** in the rate-determining step, and negative order in [**3b**], which acts to remove species **5** from the productive catalytic cycle. Scheme 3 thus rationalizes all of the kinetic observations of Figs. 1 and 2.[2]

^{31}P NMR spectroscopic studies of reactions at 90 °C in the presence **3b** identified a single Pd(binap) species (see Supporting Information) that lends further support to the proposal of a species such as **6b**. This species is not isolable but reverts to $Pd(binap)_2$ **4a** upon cooling to ambient temperature, suggesting that the relative stability of the two species switches with reaction temperature. The higher stability of **6b** compared to **4a** at high temperature was confirmed by the results of reactions using increased concentrations of binap: arylation of **2a** at 90 °C, which in the absence of **3b** gave the expected inverse relationship between rate and [binap], was unaffected by increasing [binap] in the presence of **3b** (Fig. 3).

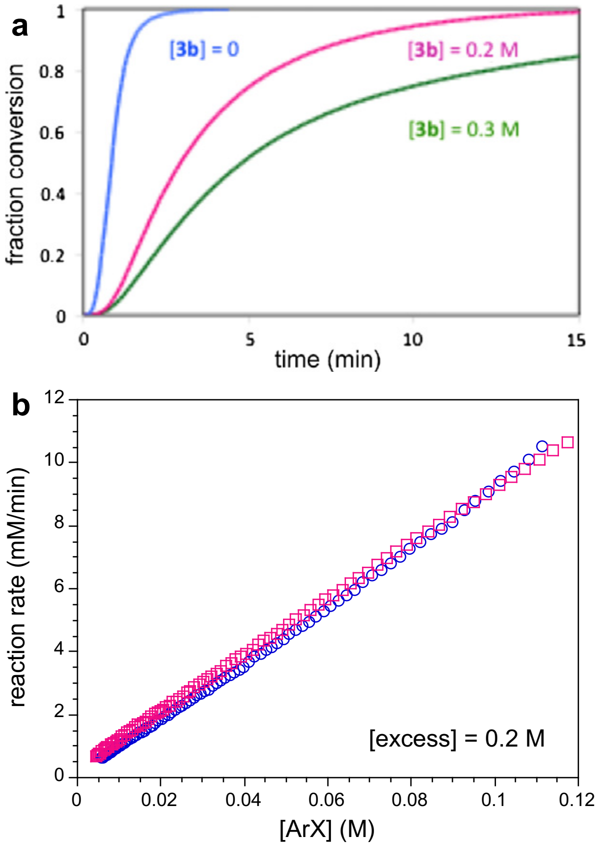

Fig. 2. (a) Conversion profiles as a function of time for the amination of **1** and **2a** at 90 °C with added **3b** as shown. $[\mathbf{1}]_0 = [\mathbf{2a}]_0 = 0.2$ M; 0.0045 M $Pd(OAc)_2$; 0.006 M binap; 0.4 M $[t\text{-BuONa}]_0$; (b) two same excess experiments (excess = 0.02 M) in the presence of 0.2 M **3b** and $Pd(OAc)_2$, binap, and base concentrations as above; $[\mathbf{1}] = 0.2$ M, $[\mathbf{2a}]_0 = 0.22$ M (open blue circles); $[\mathbf{1}] = 0.14$ M, $[\mathbf{2a}] = 0.16$ M (open magenta squares). (For interpretation of the references in color in this figure legend, the reader is referred to the web version of this article.)

Both **4a** and **6b** serve as spectators to the catalytic cycle, acting as "dead-end" reservoir species connected reversibly to a catalytic cycle [6,7]. Such a reservoir may be used to advantage during reactions carried out under harsh conditions where irreversible deactivation may occur, by channeling Pd into the cycle and thereby ensuring a constant concentration of catalyst within the cycle [7–9].

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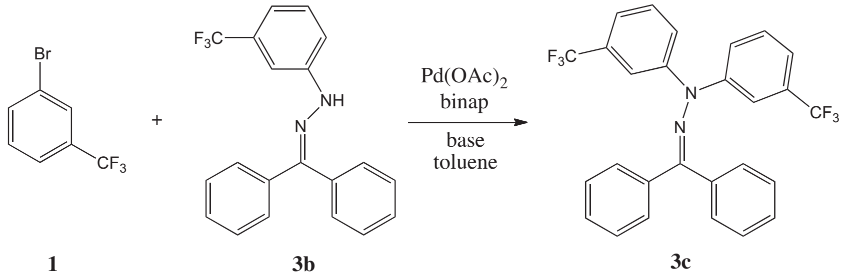
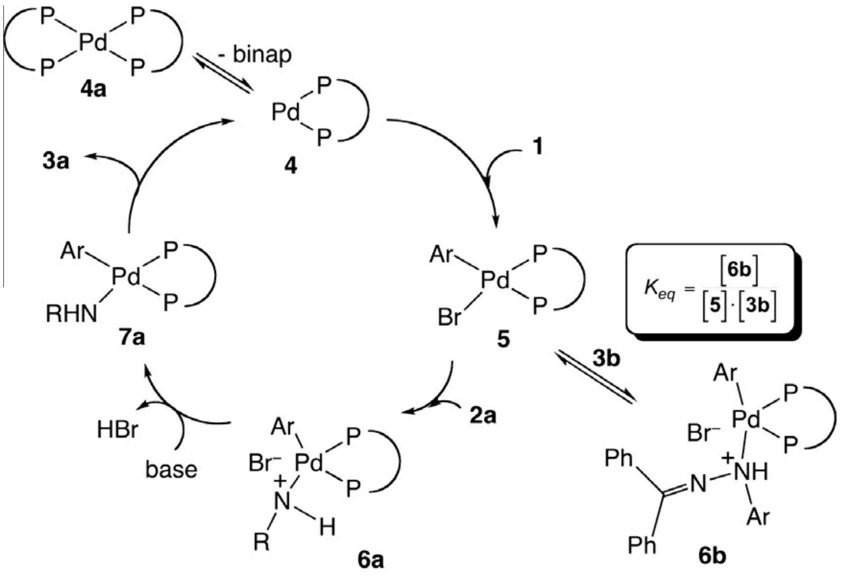
[2] Addition of **2a** directly to **6b** directly displacing **3b** is ruled out because this step as rate-determining cannot account for the observed negative order in [**3b**].



Scheme 2. Arylation of **3b**.



Scheme 3. Proposed catalytic network.

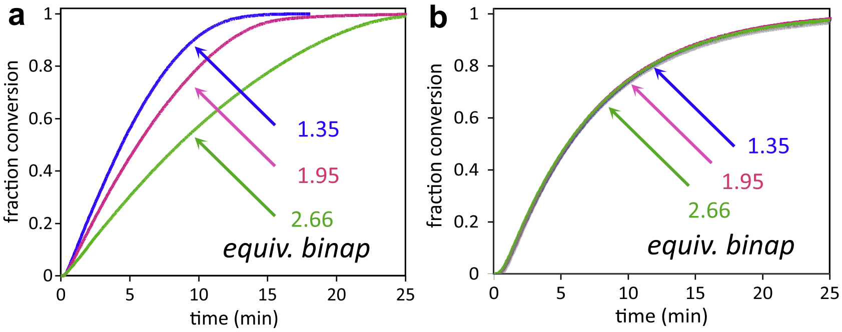


Fig. 3. Conversion profiles for the reaction of Scheme 1 in the presence of increasing amounts of binap as shown. Reaction conditions **2a** (0.1 M) and **1** (0.2 M), *t*-BuONa (0.5 M), $Pd(OAc)_2$ 0.0045 M, in toluene; (a) no added **3b**, 70 °C; (b) 0.2 M added **3b**, 90 °C.

We have previously employed a multiple sequential reaction protocol to probe the stability of catalysts over many turnovers [10]. Such experiments were carried out here to compare the effectiveness of added binap vs. **3b** in stabilizing the active catalyst concentration. Fig. 4 shows the results of multiple injections of equal aliquots of substrates **1** and **2a** into a reaction vial containing all of the other components. Each injection represents 11 turnovers under identical conditions; a decrease in the peak height over consecutive injections thus indicates catalyst deactivation. The initial activity of the system employing 1.2 equivalents of binap is significantly higher than either that employing added equivalents of binap or added **3b**; however, the system rapidly deactivates under these conditions. By contrast, both added ligand and **3b** give lower initial rates but steady activity over multiple injections, ultimately completing more turnovers in total. Added **3b** appears to stabilize the catalyst slightly better than 4 equivalents of binap (see inset to Fig. 4).

One explanation for an advantage of species **6b** over **4a** as a reservoir is that Pd^{2+} species may be inherently more stable against precipitation of Pd black, a common form of deactivation, especially at higher temperatures. Off-cycle Pd^{2+} species based on dimeric Pd complexes or Pd clusters have been reported in Heck coupling reactions that permit high turnover numbers at high temperatures [8,9].

These experiments suggest a protocol for robust catalytic processes by utilizing reservoir species that may serve as an

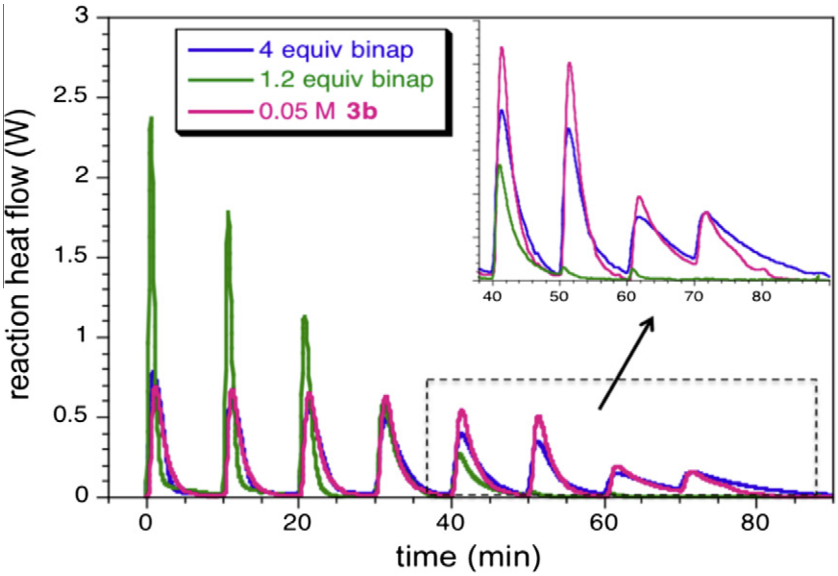


Fig. 4. Reaction profile for consecutive reactions at 90 °C of **2a** (0.1 M) and **1** (0.1 M) to a solution containing *t*-BuONa (1 M), 1 (0.05 M), $Pd(OAc)_2$ 0.0045 M, binap (0.006 M, blue and magenta curves; 0.018 M, green curve). Magenta curve: reaction mixture also contains 0.05 M **3b**. (For interpretation of the references in color in this figure legend, the reader is referred to the web version of this article.)

alternative to extra equivalents of costly ligands or precious metals for the purpose of stabilizing the active catalyst concentration and ensuring high turnover. Reaction progress kinetic methodology may be readily employed for rapid screening to discover additives that produce reservoir species of appropriate stability and reactivity for the development of robust catalytic processes.

3. Summary

Probing Pd-catalyzed amination reactions in the presence of competitive binding events reveals the key role that reservoir species connected reversibly to the catalytic cycle can play. Mechanistic rationalization of the anomalous reaction orders observed in the presence of additives leads to a practical protocol for maintaining a robust catalyst system that may be particularly useful for development of reactions under harsh conditions likely to lead to catalyst deactivation and incomplete turnover. Further studies of the role of competitive binding in these systems are underway.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ica.2011.01.018.

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