# Uncovering the Mechanism of the Ag(I)/Persulfate Reaction of Arylboronic Acids and Heteroarenes

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Introduction:

Catalytic oxidations that proceed through single-electron transfer are arguably one of the most important approaches for the formation of C-C bonds in synthetic molecules of pharmaceutical and biological importance.[1] A recently developed reaction involving the Ag(I)-persulfate cross-coupling of arylboronic acids with electron deficient pyridines provides access to a variety of substituted heteroarenes (Eq 1).[2] A mechanistic analysis of the individual components in the reaction reveal a great degree of complexity.[3]

$$ (1) $$
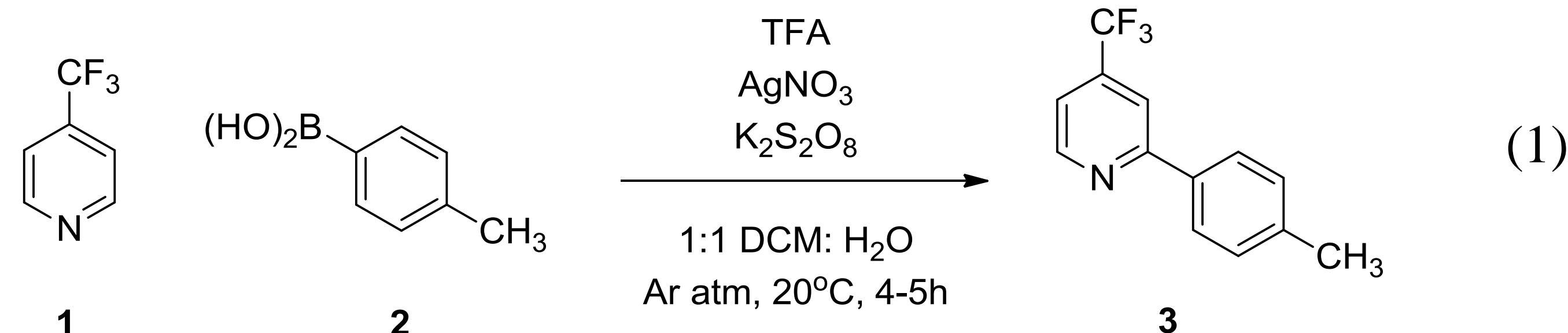
Kinetic Study:

Kinetic studies were performed using reaction progress kinetic analysis (RPKA),[4] in which either the loss of starting material or growth of product was followed over time via gas chromatography (GC). A same excess experiment was performed to determine the stability of the catalyst during the course of the reaction (Table 1). The lack of overlay of Runs 1 and 2 suggests that the catalyst is being deactivated during the course of the reaction (Figure 1).

Table 1. Same excess experiment reaction conditions

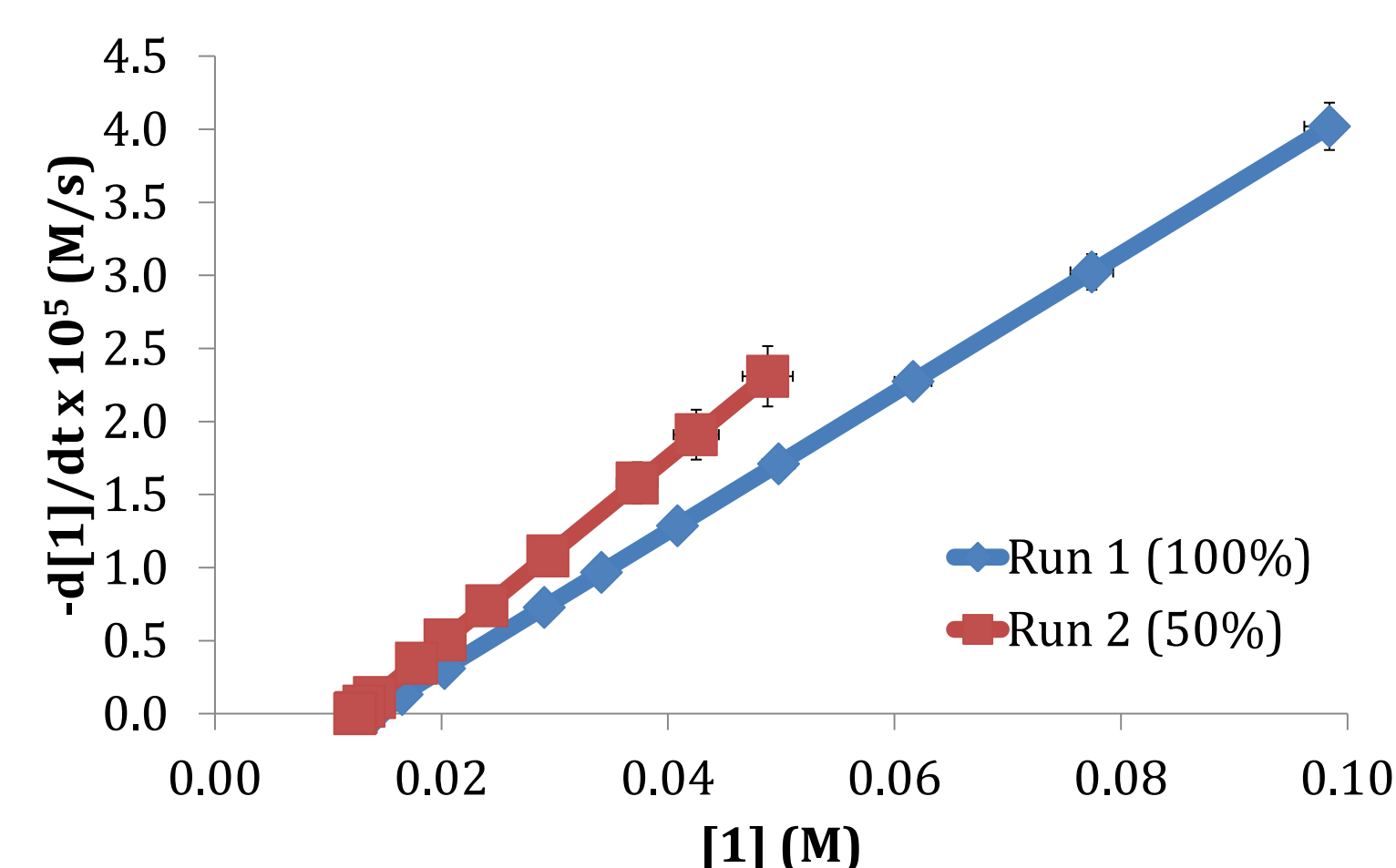| Run	[1] (M)	[2] (M)	[excess] (M)	[K$_2$S$_2$O$_8$] (M)	[excess] (M)	[AgNO$_3$] (M)
1 – 100%	0.10	0.15	0.05	0.30	0.20	0.02
2 – 50%	0.05	0.10	0.05	0.25	0.20	0.02

Figure 1. Rate vs. [1] for same excess experiments

Different excess experiments were performed to determine the rate orders of each of the substrates in the reaction (Table 2). To find the rate order of **2**, kinetic runs (Run 2 and 3) were performed, in which the initial concentration of **2** was increased and the concentrations of the other reactants remained unchanged (Table 3). The order of **2** was found by normalizing the rate plots to obtain overlay (Figure 2).

Table 2. Rate orders of substrates in reaction

	Rate Order		
1[a]	**2**[b]	**K$_2$S$_2$O$_8$**[c]	**AgNO$_3$**[d]
1	-0.5	0*	1

[a] [1]= 0.10 M [2]=0.15M [K$_2$S$_2$O$_8$]= 0.30 M [AgNO$_3$]= 0.02M (100% run) [b] [1]= 0.10 M [2]= 0.3M [K$_2$S$_2$O$_8$] = 0.30 M [AgNO$_3$]= 0.02M [c] [1]= 0.10 M [2]= 0.15M [K$_2$S$_2$O$_8$]= 0.60 M [AgNO$_3$]= 0.02M [d] [1]= 0.10 M [2]= 0.15M [K$_2$S$_2$O$_8$]= 0.30 M [AgNO$_3$]= 0.04M *Due to low solubility of K$_2$S$_2$O$_8$ (5.29 g/100 ml at 20°C); when using Na$_2$S$_2$O$_8$ (55.6g/100mL), rate order shown to be positive.

Table 3. Different excess experiment reaction conditions for reaction order of **2**

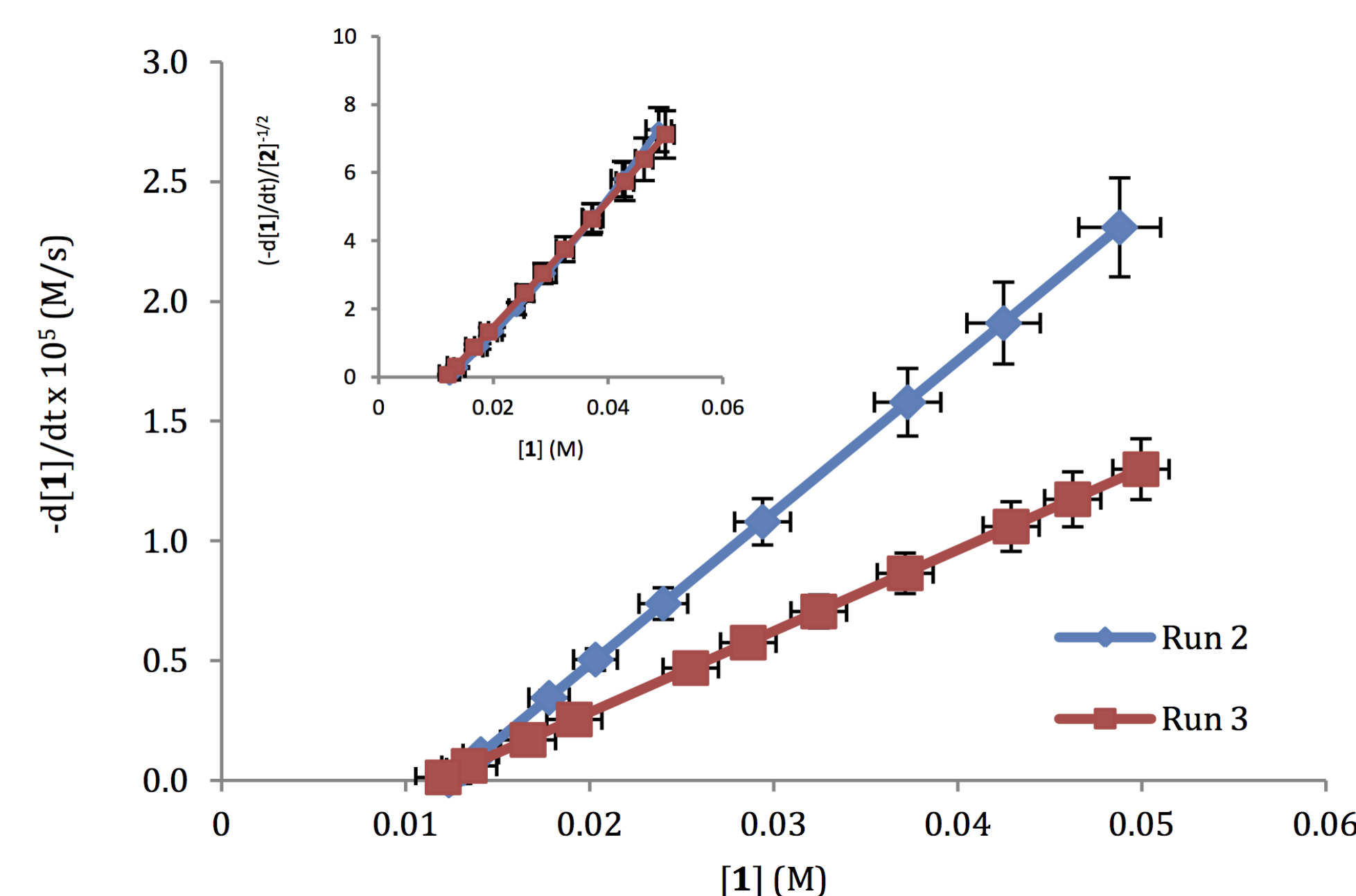| Run	[1] (M)	[2] (M)	[excess] (M)	[K$_2$S$_2$O$_8$] (M)	[AgNO$_3$] (M)
2	0.05	0.10	0.05	0.25	0.02
3	0.05	0.30	0.25	0.25	0.02

Figure 2. Rate vs. [1] for different excess experiments for **2**

NMR experiments:

To investigate the possible interaction between **1** and AgNO$_3$, ^{1}H NMR studies were carried out in D$_2$O to mimic reaction conditions. Upon addition of TFA and AgNO$_3$ to **1**, a slight upfield shift of aromatic protons is seen compared to the mixture of **1** and TFA. The lack of overlay of the spectra suggests the formation of a complex between **1** and AgNO$_3$.
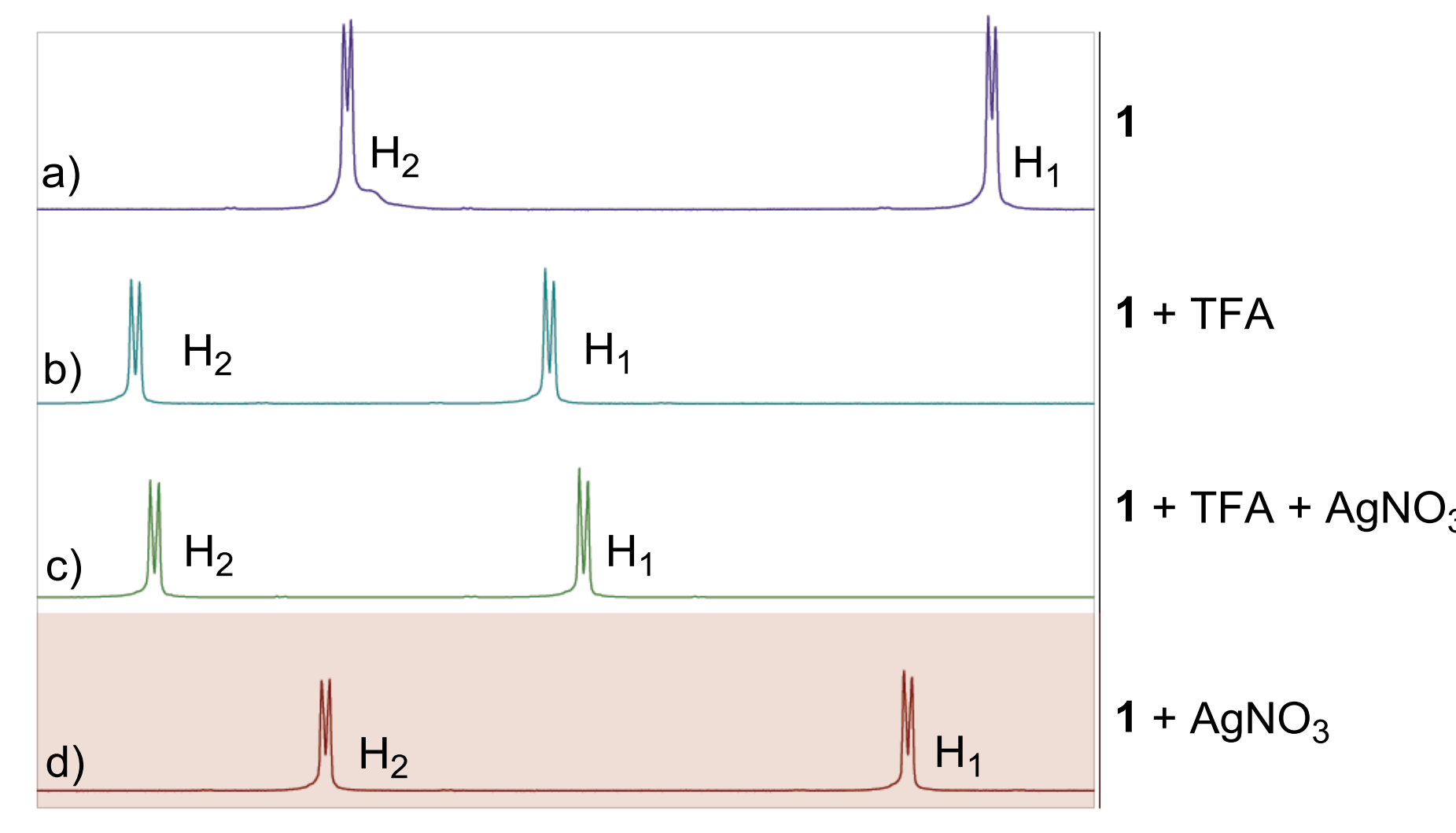
Figure 3. ^{1}H NMR spectra of **1** with additives

Additional studies:

Ammoniacal AgNO$_3$ solutions and arylboronic acids are known to form insoluble salts, which upon heating lead to hydrolytic cleavage products.[5] Similarly, in the presence of **1** more toluene was formed, a finding consistent with inhibition of AgNO$_3$ and consumption of **2** outside of the desired reaction pathway (Figure 4).
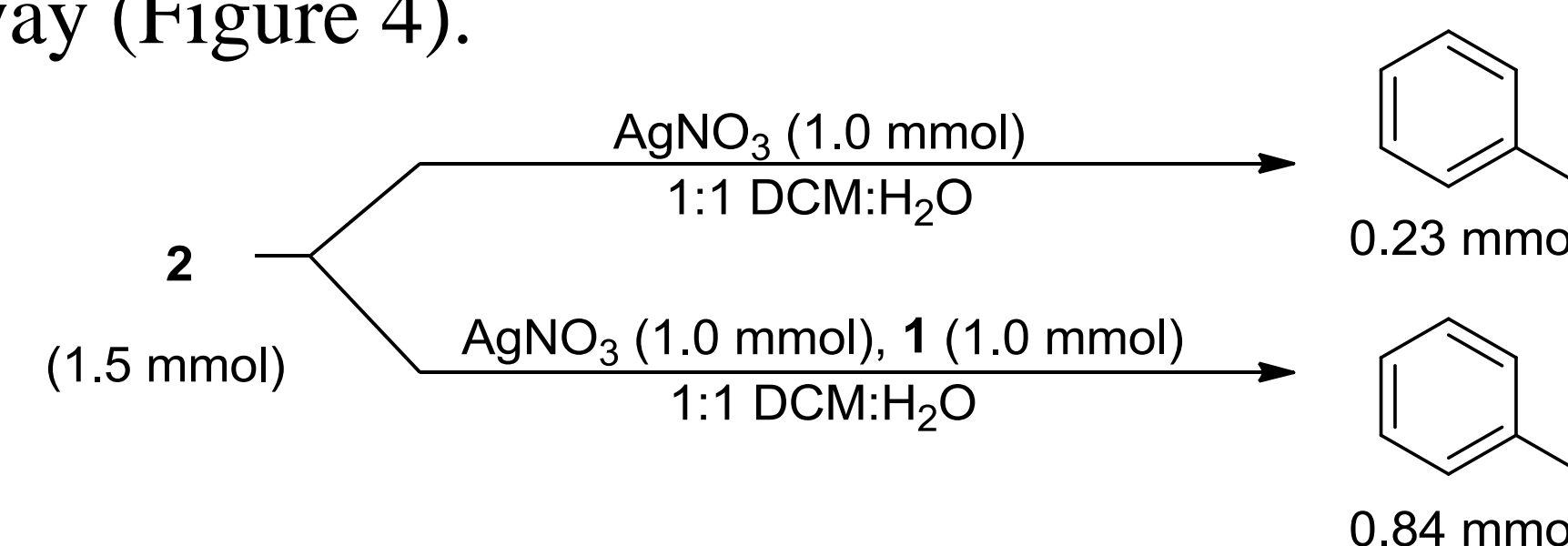
Figure 4. Off-cycle step involving arylboronic acid

Proposed Mechanism:

Based on the observed kinetic and spectroscopic data, a reaction mechanism is proposed that involves: i) a pre-equilibrium step in which **1** and Ag(I) form a complex, ii) the reduction of S$_2$O$_8^{2-}$ by the Ag(I)-**1** complex in the rate-determining step, and iii) an off-cycle step involving the protodeboronation of **2** by the Ag(I)-**1** complex (Scheme 1).
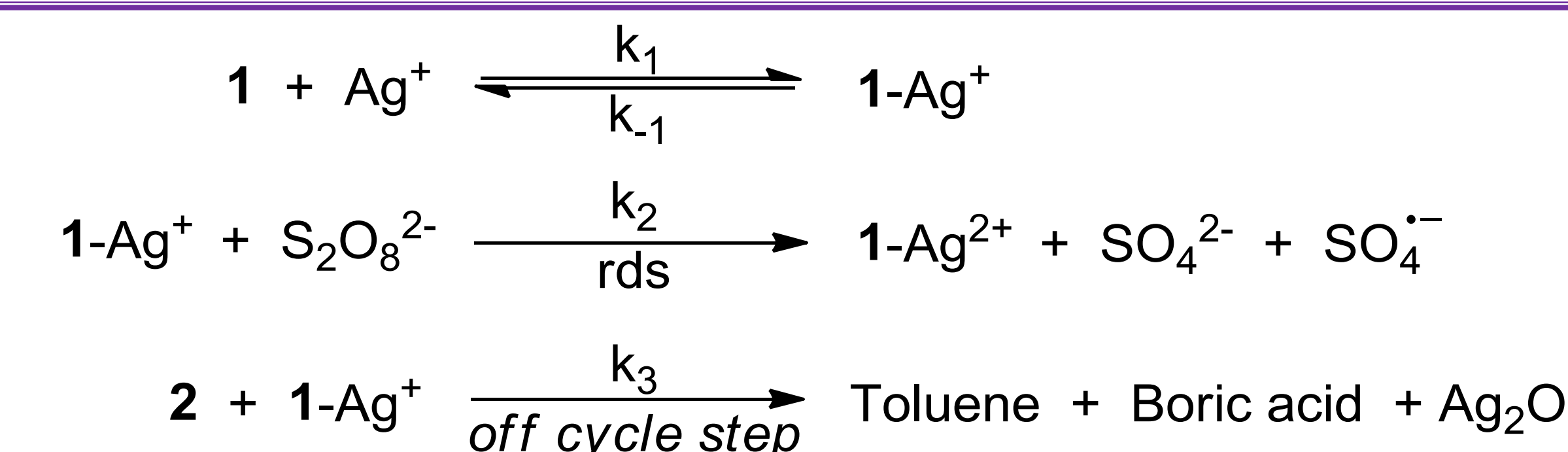
Scheme 1. Mechanism of Ag(I)/Persulfate-Catalysis in Coupling of Arylboronic acid and Electron-deficient Pyridine

Assuming steady state for the Ag(I)-**1** complex, and accounting for all states of Ag(I), a derived rate law can be expressed as Equation 2, which can be compared to the empirical rate law.

$$ -\frac{d[1]}{dt} = k_1 k_2 [1][S_2O_8^{2-}][Ag^I]_{tot} \left(\frac{k_{-1}+k_2[S_2O_8^{2-}]+k_3[2]}{k_{-1}^2+2k_{-1}k_3[2]+k_3^2[2]^2} \right) \approx k_{obs} \frac{[1][S_2O_8^{2-}][Ag^I]_{tot}}{[2]^{0.5}} \quad (2) $$

Addition of a reagent capable of preventing formation of catalytically inactive Ag(I) should be beneficial to reaction progress. A reaction was initiated using 0.5 M HNO$_3$ to prevent the formation of catalytically inactive Ag(I). Employing these modified conditions enabled the reduction of AgNO$_3$ to 10 mol% and persulfate to 2 equivalents.

To explore the oxidation of the arylboronic acid after the rate-determining step, a reaction was performed with allyl acetate, a good radical trap for SO$_4^{·-}$. Interestingly, the rate of reaction increased upon addition of allyl acetate suggesting the reagent oxidizing the arylboronic acid is Ag(II), and not SO$_4^{·-}$ in this reaction.

An overall reaction mechanism is proposed for the cross-coupling of arylboronic acid and electron-deficient pyridine in a Ag(I)/persulfate-catalyzed reaction (Figure 5).
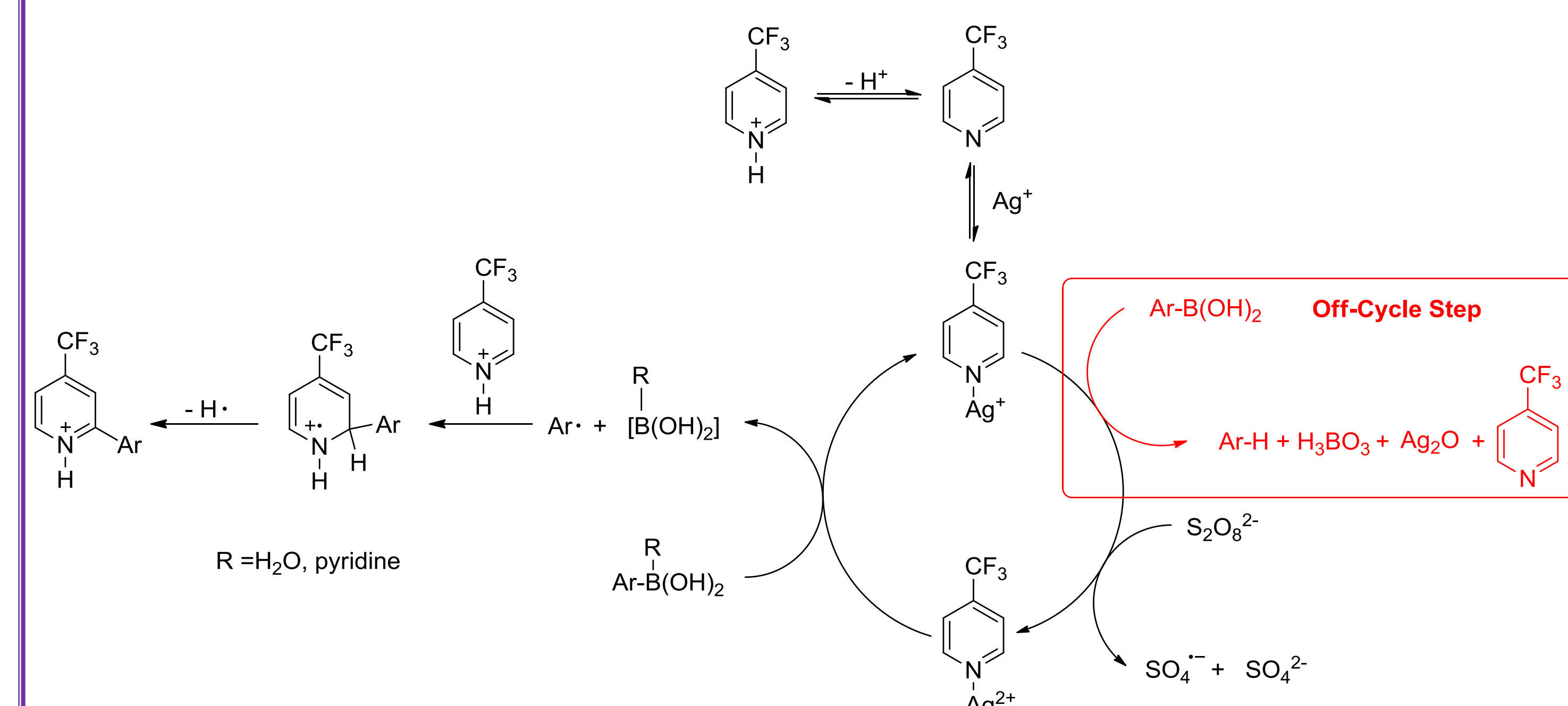
Figure 5. Proposed Mechanism of the Ag(I)/Persulfate-Catalyzed Arylation of Electron-deficient Pyridine

Conclusion:

A reaction mechanism was proposed involving the formation of a Ag(I)-pyridine complex, as well as an off-cycle pathway which involves the protodeboronation of the arylboronic acid by Ag(I)-pyridine, contributing to the deactivation of catalyst. Evidence demonstrates that Ag(II) is the likely oxidant responsible for the formation of aryl radicals. These studies provide key mechanistic insights that enable control of the off-cycle process, thus providing higher efficiency and yield.

References: (1) (a) Jahn, U. *Top. Curr. Chem.* **2012**, 320, 121-190. (b) Jahn, U. *Top. Curr. Chem.* **2012**, 320, 191-322. (c) Jahn, U. *Top. Curr. Chem.* **2012**, 320, 323-452. (2) Seiple, I. B., Su, S., Rodriguez, R. A., Gianatassio, R., Fujiwara, Y., Sobel, A. L., Baran, P. S. *J. Am. Chem. Soc.* **2010**, 132, 13194-13196. (3) Patel, N. R., Flowers, R. A., II. *J. Am. Chem Soc.* **2013**, *ASAP.* (4) (a) Blackmond, D. G. et. al. *J. Org. Chem.* **2006**, 71, 4711-4722. (b) Blackmond, D. G. *Angew. Chem. Int. Ed.* **2005**, 44, 4302-4320. (5) (a) Michaelis and Becker. *Chem. Ber.* **1882**, 15, 181. (b) Johnson, J. R.; Van Campen, M. G.; Grummitt, O. *J. Am. Chem. Soc.* **1938**, 60, 111-115. (c) Seaman, W.; Johnson, J. R. *J. Am. Chem. Soc.* **1931**, 53, 711-723.