

Uncovering the Mechanism of the Silver(I)/Persulfate-Catalyzed Cross-Coupling of Arylboronic Acids with Heteroarenes

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Instrumentation

GC analyzes were done using a Shimadzu Gas Chromatograph GC-14B. Proton, carbon, and boron NMR were recorded on a Bruker 500 MHz spectrometer. GC-MS analyses were done with an HP 5890 Series II Gas Chromatograph with an HP Mass Selector Detector. Column chromatography was performed using the automated CombiFlash® Rf system from Teledyne Isco, Inc. Products were separated using prepacked silica gel columns with a gradient elution of ethyl acetate and hexanes.

Materials for synthetic and kinetic studies

AgNO_3 , $\text{K}_2\text{S}_2\text{O}_8$, $\text{Na}_2\text{S}_2\text{O}_8$ were purchased from Acros Organics. **1** was purchased from Oakwood Products, Inc. **2** was purchased from TCI Fine Chemicals. TFA and **4** was purchased from Alfa Aesar. All chemicals were used without further purification.

Procedure for degassing solvents

CH_2Cl_2 was purified by a Solvent Purification system (Innovative Technology Inc.; MA). H_2O was degassed by bubbling through with argon overnight.

Procedure for synthesis of 3

In a 25 mL round bottom flask with a magnetic stirring bar, **1**, TFA, and **2** were dissolved in 10 mL CH_2Cl_2 . To the flask, 5 mL degassed H_2O was added. AgNO_3 was dissolved in 5 mL degassed water and added to the reaction. $\text{K}_2\text{S}_2\text{O}_8$ was added to the reaction as a solid. The flask was then evacuated of air, a septum was attached, and was back-filled with Ar. The reaction was allowed to stir overnight. Reaction workup involved diluting the reaction with 10 mL CH_2Cl_2 and quenching with 10 mL saturated bicarbonate solution. The organic layer was separated and run through a plug of neutral alumina. The alumina was washed with ethyl acetate. Product formation was confirmed by GC-MS. The organic layer was rotary evaporated to dryness. Crude

product formation was observed by ^1H NMR in CDCl_3 . Product was purified via automated flash chromatography and characterized by ^1H NMR and ^{13}C NMR.

Procedure for Reaction Progress Kinetic Analysis¹ Studies

In a 100 mL round bottom flask with a magnetic stirring bar, **1**, TFA, and **2** were dissolved in 30 mL CH_2Cl_2 . To the flask, 15 mL degassed H_2O was added. AgNO_3 was dissolved in 15 mL degassed water and added to the reaction. $\text{K}_2\text{S}_2\text{O}_8$ was added to the reaction as a solid. The flask was then evacuated of air, a septum was attached, and was back-filled with Ar. The reaction was stopped and 0.5 mL aliquots were taken from the organic layer during the course of the reaction. Aliquots taken were quenched with 1.0 mL saturated bicarbonate solution, and 0.5 mL of biphenyl in ethyl acetate solution was added as an internal standard. The organic layer was extracted and analyzed by GC.

Procedure for pyridine ^1H NMR studies

^1H NMR spectra were obtained for four solutions: 1) In a vial, 28.75 μL (0.25 mmol) of **1** was dissolved in 1.0 mL CDCl_3 . 2) In a vial, 28.75 μL (0.25 mmol) of **1** and 18.575 μL (0.25 mmol) of TFA was dissolved in 1.0 mL CDCl_3 . 3) In a vial, 28.75 μL (0.25 mmol) of **1**, 18.575 μL (0.25 mmol) of TFA, and 42.475 mg (0.25 mmol) of AgNO_3 were dissolved in 1.0 mL CDCl_3 . 4) In a vial, 28.75 μL (0.25 mmol) of **1** and 42.475 mg (0.25 mmol) of AgNO_3 were dissolved in 1.0 mL CDCl_3 .

Procedure for ^{11}B NMR studies

^{11}B NMR studies were done using quartz NMR tubes. Spectra were obtained for the following solutions: 1) **2** dissolved in D_2O . 2) In a vial, 0.15 mmol of **4**, 0.1 mmol of **1**, 0.1 mmol of TFA, and 0.02 mmol of AgNO_3 was dissolved in 1 mL D_2O . The solution was then transferred

¹ (a) Mathew, J S.; Klussman, M.; Iwamura, H.; Valera, F.; Futran, A.; Emanuelsson, 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. (c) Devery, J. J., III.; Conrad, J. C.; MacMillan, D. W. C.; Flowers, R. A., II. *Angew. Chem. Int. Ed.* 2010, 49, 6106-6110. (d) Choquette, K. A.; Sadasivam, D. V.; Flowers, R. A., II. *J. Am. Chem. Soc.* 2011, 133, 10655-10661. (reference 7 in paper)

to a quartz NMR tube. A ^{11}B NMR spectrum was immediately obtained. After letting the previous sample sit for 4h, a ^{11}B NMR spectrum was obtained again, showing some hydrolysis of **4** to **2**. 3) In a vial, 0.15 mmol of **4**, 0.1 mmol of TFA, and 0.02mmol of AgNO_3 was dissolved in 1mL D_2O . The solution was then transferred to a quartz NMR tube. A ^{11}B NMR spectrum was immediately obtained. After letting the previous sample sit for 4h, a ^{11}B NMR spectrum was obtained again, showing some hydrolysis of **4** to **2**.

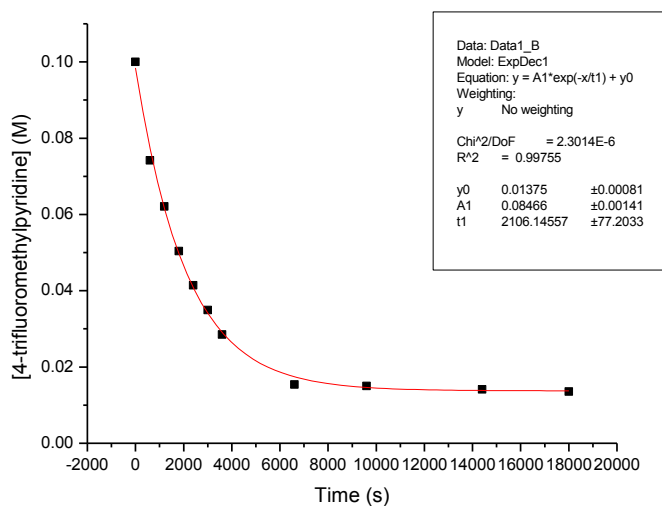
Spectroscopic data for **3**

^1H NMR (500 MHz, CDCl_3) δ (ppm): 8.85 (1H, d), 7.93 (3H), 7.42 (1H, d), 7.32 (2H, d), 2.43 (3H, s); ^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 158.85, 150.54, 140.04, 139.08, 135.32, 129.69, 126.92, 121.95, 117.13, 115.63, 21.31; GC/MS m/z (rel. abundance) 237 (100), 91 (13).

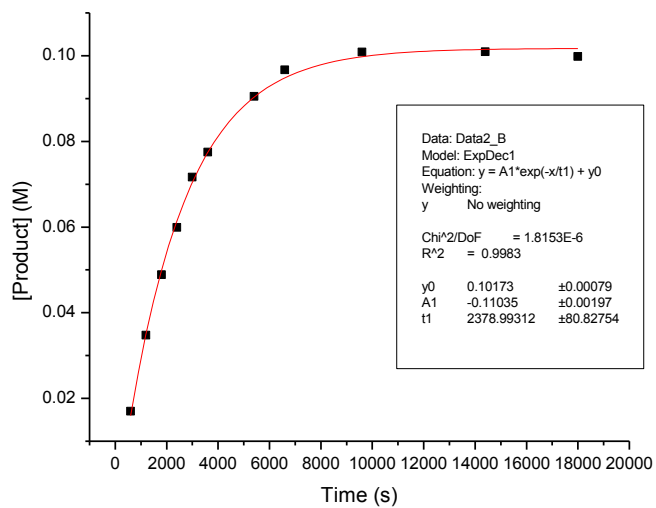
Conditions for same excess experiments (Run 1 and 2)

Run	[1] (M)	[2] (M)	[e] (M)	$\text{K}_2\text{S}_2\text{O}_8$ (M)	[e] (M)	AgNO_3 (M)
1-100%	0.1	0.15	0.05	0.3	0.2	0.02
2-50%	0.05	0.1	0.05	0.25	0.2	0.02

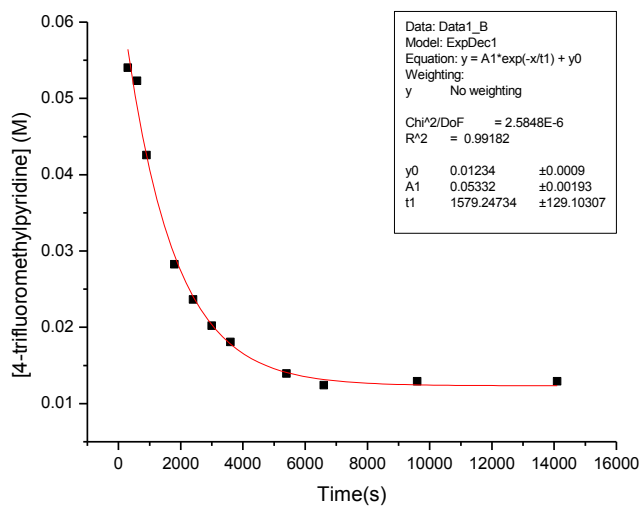
Decay data for Run 1



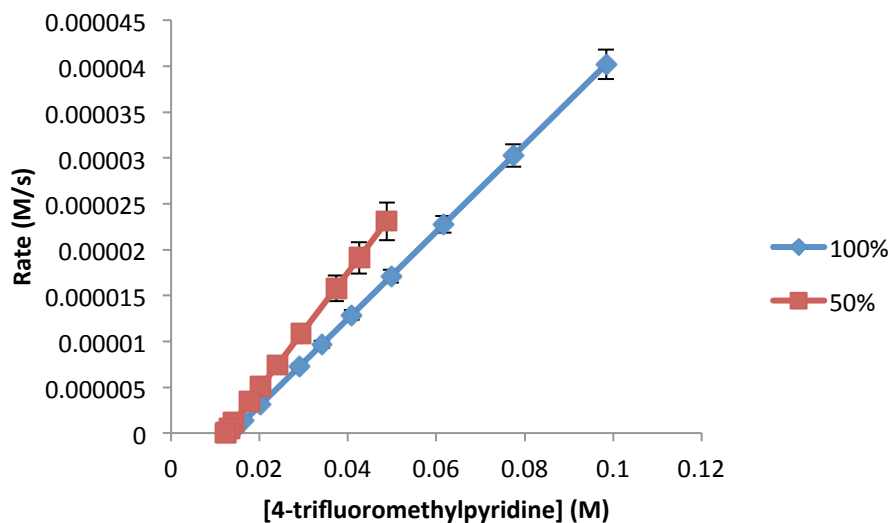
Growth data for Run 1



Decay data for Run 2



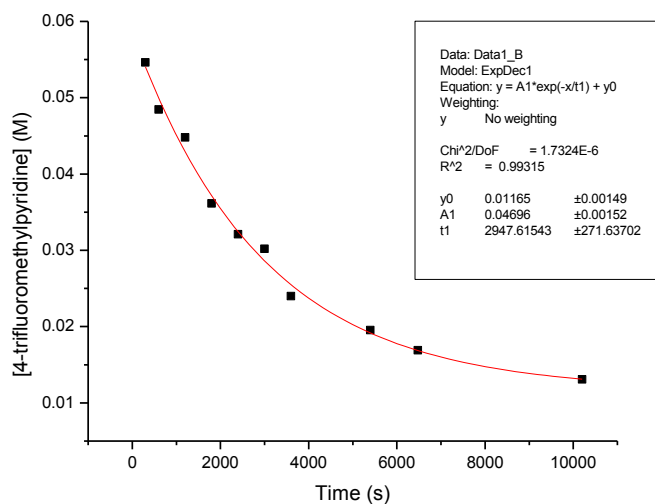
Plot of rate vs. [1] for catalyst stability



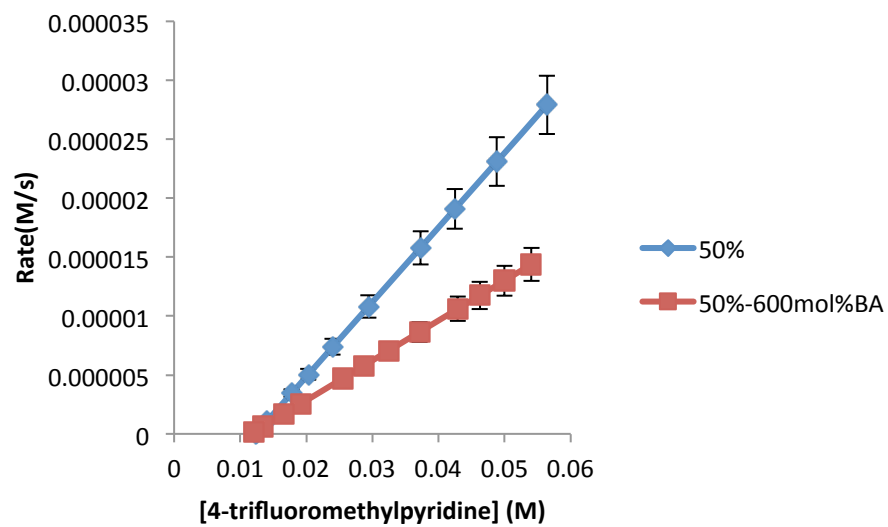
Conditions for different excess experiments for rate order for 2

Run	[1] (M)	[2] (M)	[e] (M)	K ₂ S ₂ O ₈ (M)	AgNO ₃ (M)
2-50%	0.05	0.1	0.05	0.25	0.02
3-Diff xs	0.05	0.3	0.25	0.25	0.02

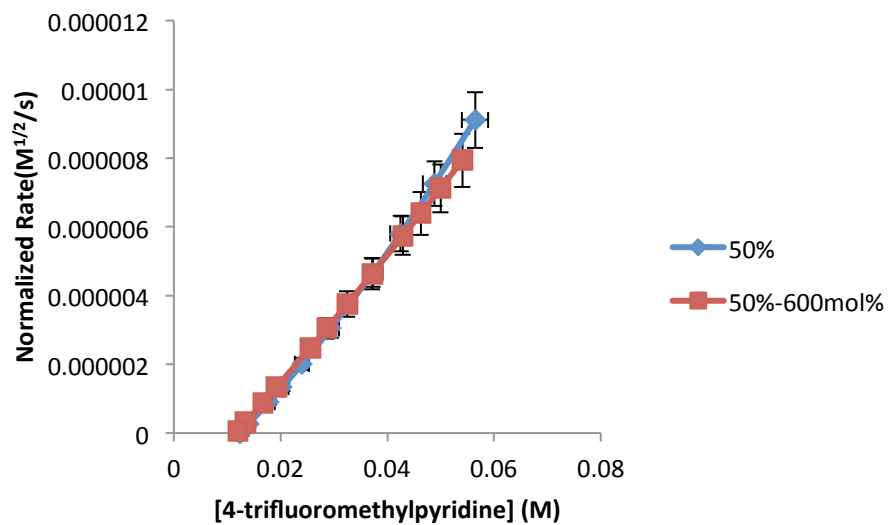
Decay data for Run 3



Plot of rate vs. [1] for rate order for 2 – Run 3



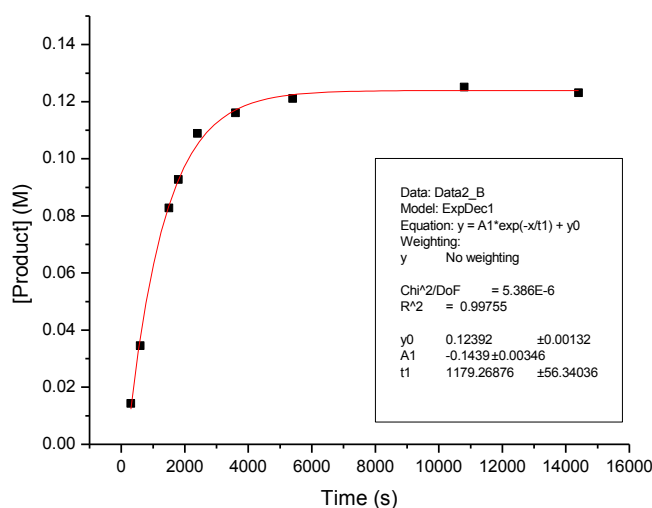
Plot of normalized rate vs. [1] for rate order for 2 – Run 3



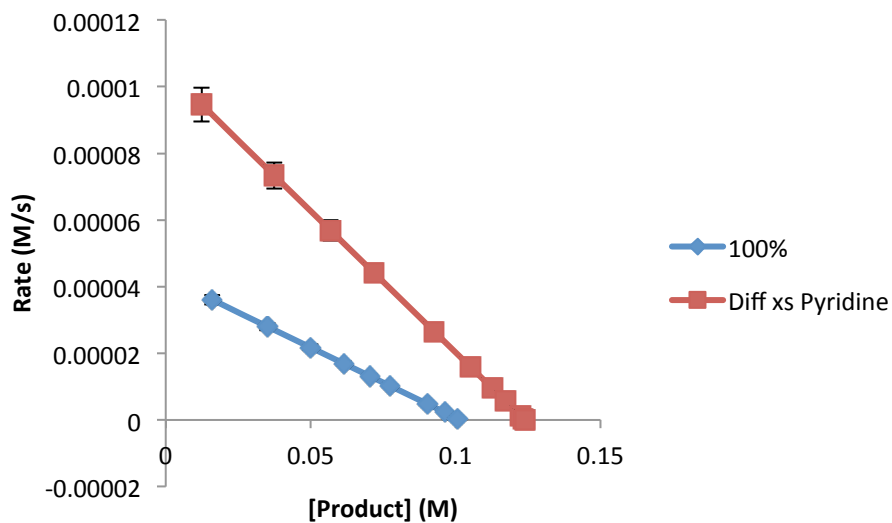
Conditions for different excess experiments for rate order for 1

Run	[1] (M)	[2] (M)	K ₂ S ₂ O ₈ (M)	AgNO ₃ (M)
1-100%	0.1	0.15	0.3	0.02
4-Diff xs	0.2	0.15	0.3	0.02

Growth data for Run 4



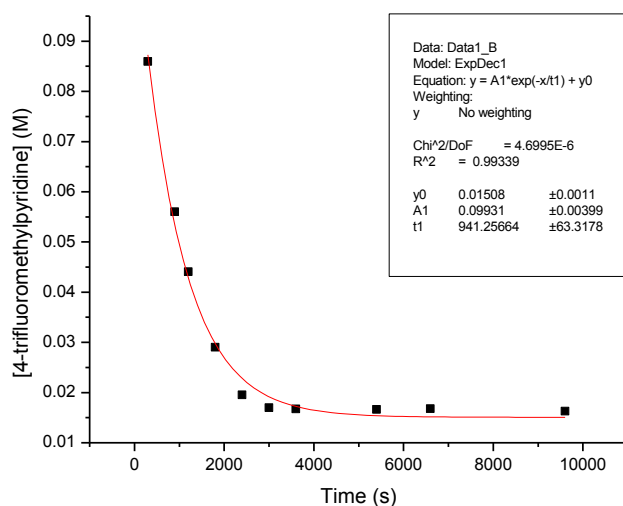
Plot of rate vs. [3] for rate order of 1



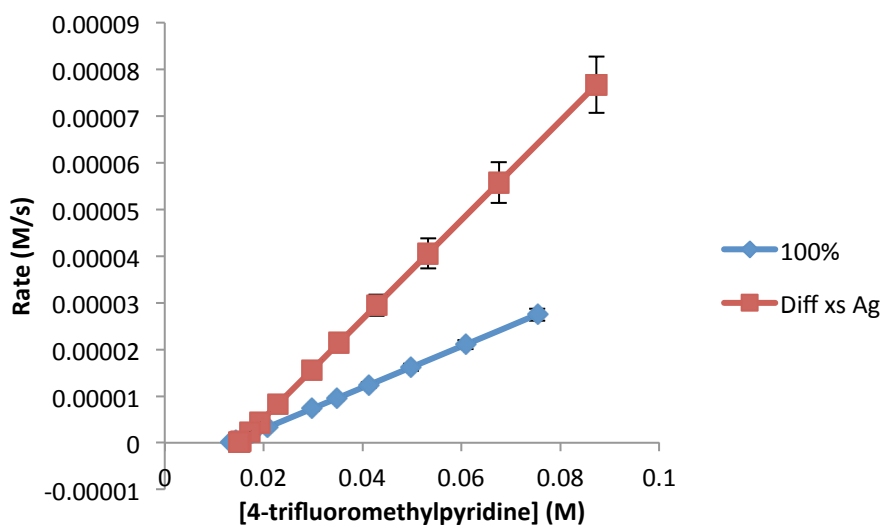
Conditions for different excess experiments for rate order for AgNO₃

Run	[1] (M)	[2] (M)	K ₂ S ₂ O ₈ (M)	AgNO ₃ (M)	[e] (M)
1-100%	0.1	0.15	0.3	0.02	0.08
5-Diff xs	0.1	0.15	0.3	0.04	0.06

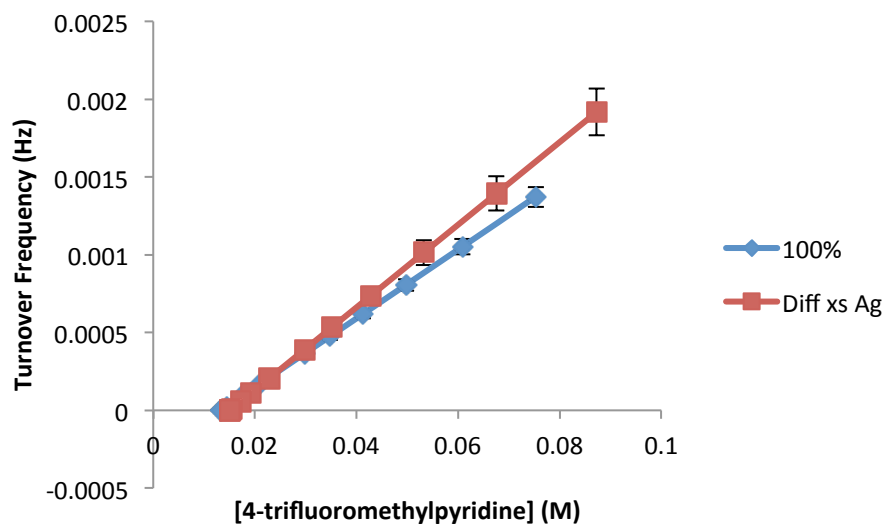
Decay data for Run 5



Plot of rate vs. [1] for rate order for AgNO₃



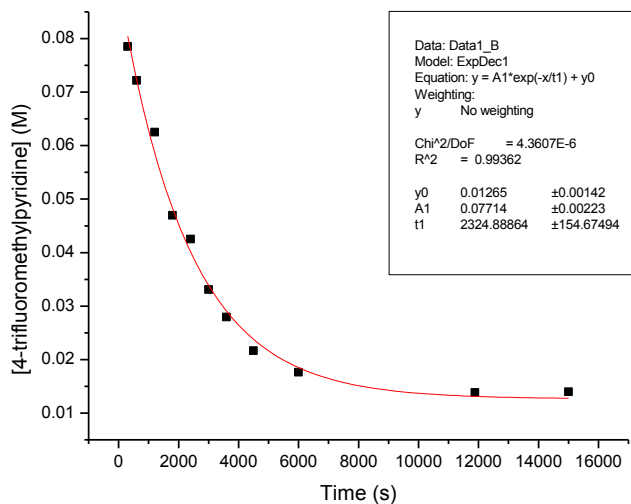
Plot of normalized rate vs. [1] for rate order of AgNO_3



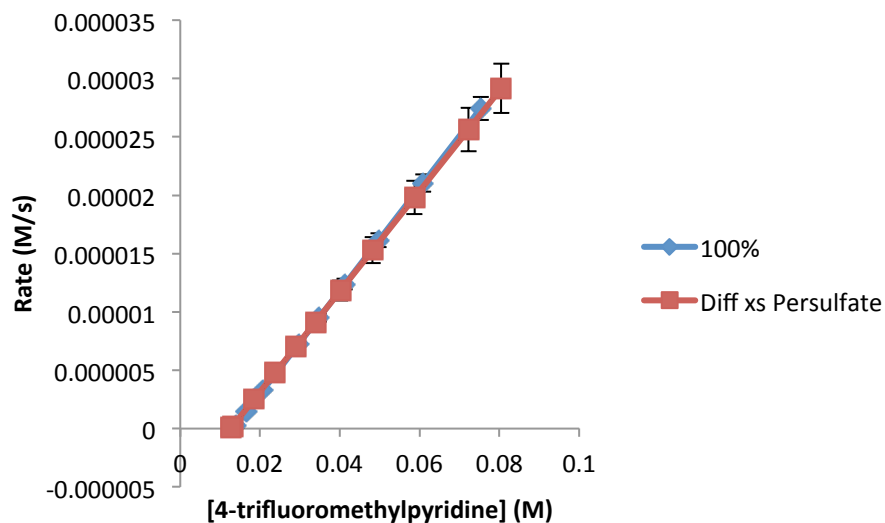
Conditions for different excess experiments for rate order for $\text{K}_2\text{S}_2\text{O}_8$

Run	[1] (M)	[2] (M)	$\text{K}_2\text{S}_2\text{O}_8$ (M)	[e] (M)	AgNO_3 (M)
1-100%	0.1	0.15	0.3	0.2	0.02
6-Diff xs	0.1	0.15	0.6	0.5	0.02

Decay data for Run 6



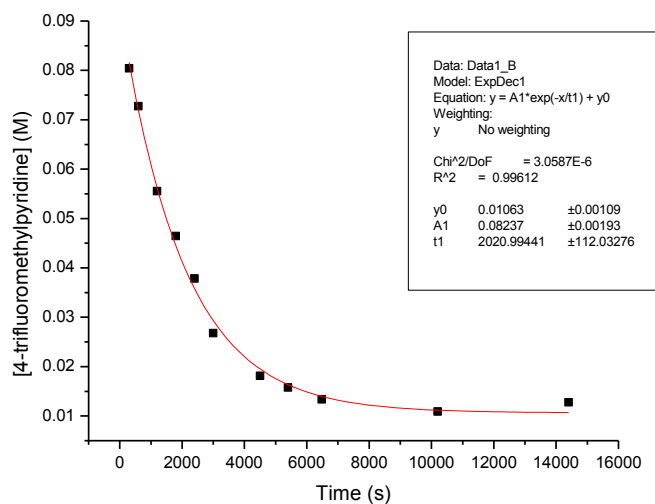
Plot of rate vs. [1] for rate order for $K_2S_2O_8$



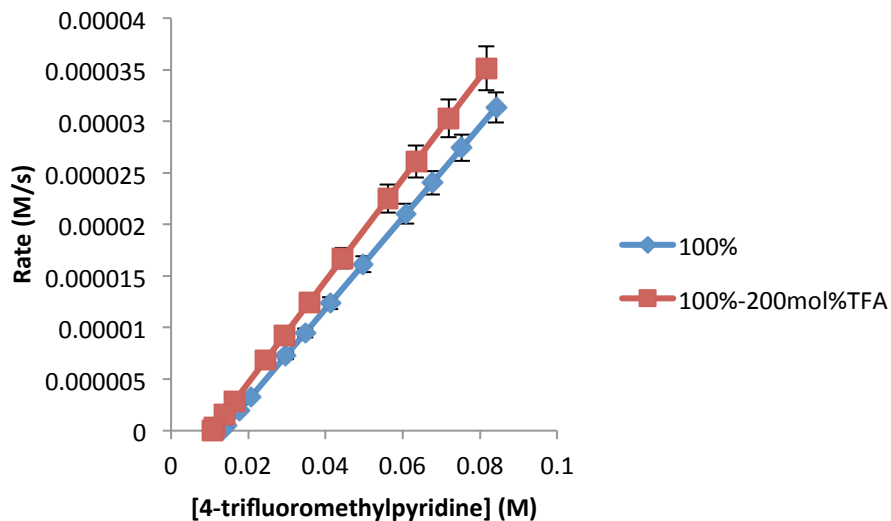
Conditions for different excess experiments for rate order for TFA

Run	[1] (M)	[2] (M)	$K_2S_2O_8$ (M)	$AgNO_3$ (M)	TFA (M)
1-100%	0.1	0.15	0.3	0.02	0.1
7-Diff xs	0.1	0.15	0.3	0.02	0.2

Decay data for Run 7



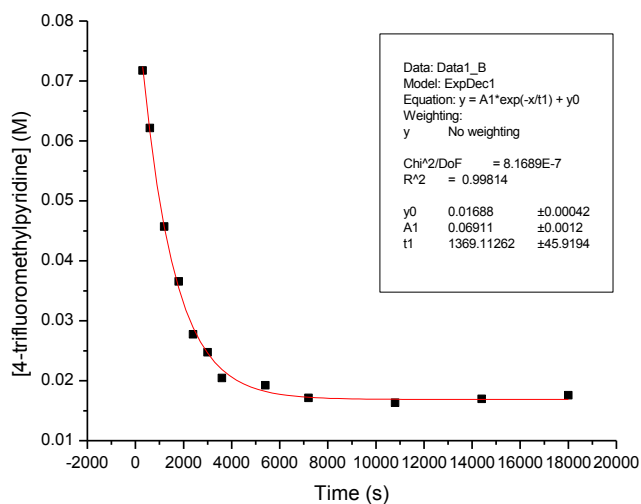
Plot of rate vs. [1] for rate order for TFA



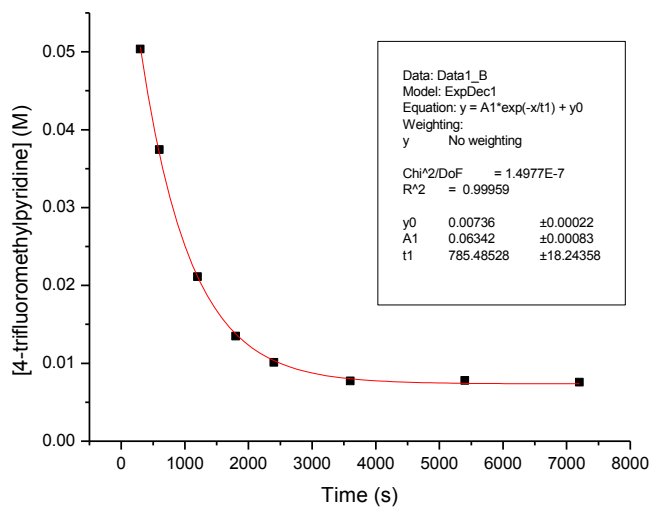
Conditions for different excess experiments for rate order for Na₂S₂O₈

Run	[1] (M)	[2] (M)	Na ₂ S ₂ O ₈ (M)	[e] (M)	AgNO ₃ (M)
8-100%	0.1	0.15	0.3	0.2	0.02
9-Diff xs	0.1	0.15	0.6	0.5	0.02

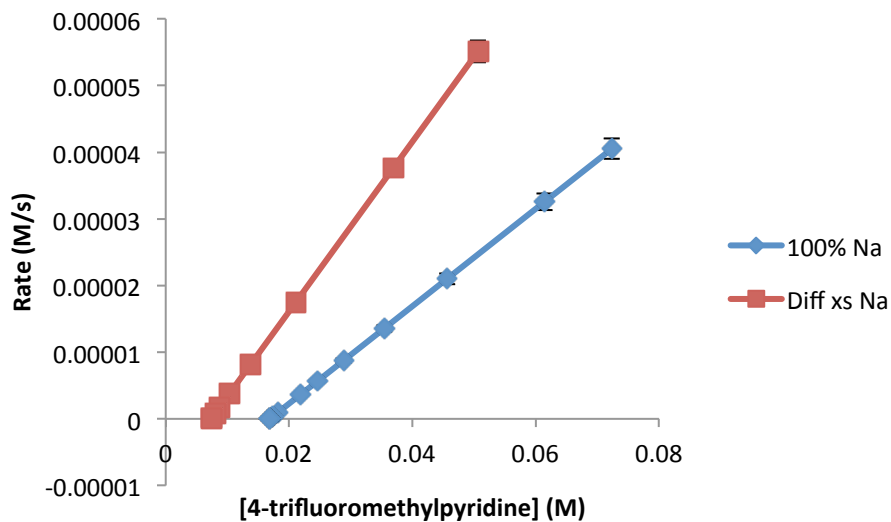
Decay data for Run 8



Decay data for Run 9



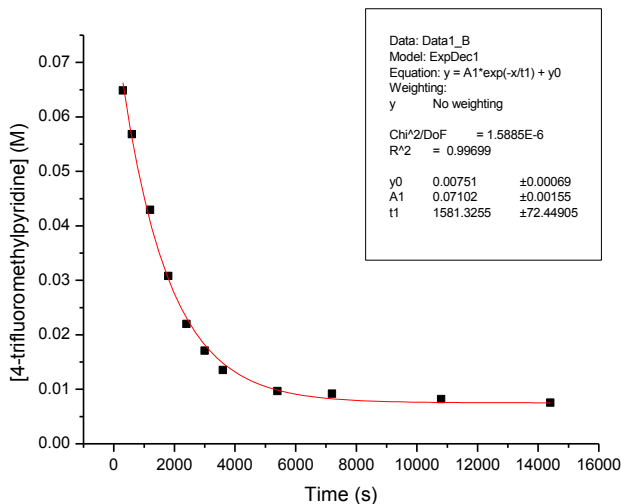
Plot of rate vs. [1] for rate order for Na₂S₂O₈



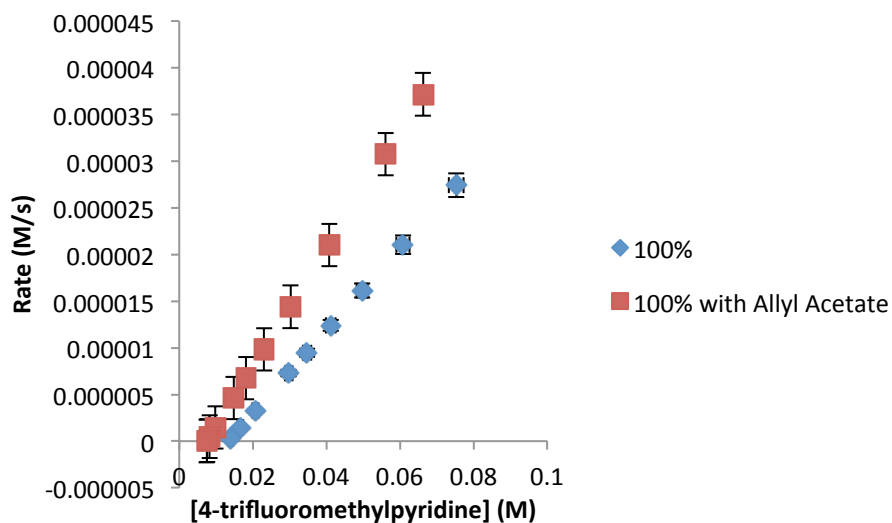
Conditions for experiments using allyl acetate as sulfate radical anion trap

Run	[1] (M)	[2] (M)	Na ₂ S ₂ O ₈ (M)	AgNO ₃ (M)	Allyl Acetate (M)
1-100%	0.1	0.15	0.3	0.02	0.0
10-AllylAc	0.1	0.15	0.3	0.02	0.6

Decay plot for Run 10



Plot of rate vs. [1] comparing Run 1 (100% run) to Run 10 (100% run with Allyl Acetate)



Calculation of conversion of rate data and error

Concentration samples at specific time points are plotted as [1] (M) vs. time (s). The data are then fit to a first order exponential decay using Equation 1.

$$[1] = y_0 + Ae^{-\frac{time}{t}} \quad (1)$$

The standard deviation of the [1] resulting from curve fitting is determined using Equation 2.

$$\sigma_{[1]} = Ae^{-\frac{time}{t}} \sqrt{\left(\frac{-e^{-\frac{time}{t}}}{t}\right)^2 + \left(\frac{\sigma_A}{A}\right)^2} + \sigma_{y_0} \quad (2)$$

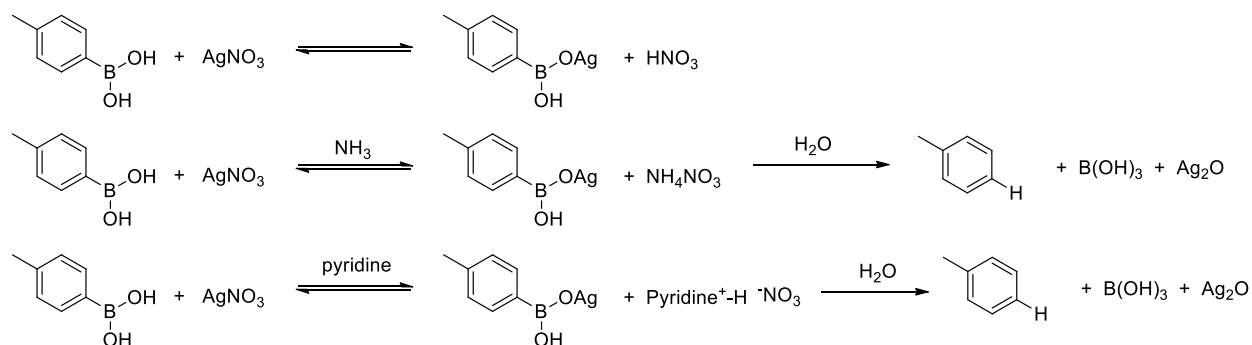
The derivative of Equation 1 provides the equation for the rate of change in [1] and is given in Equation 3.

$$-\frac{d[1]}{dt} = \frac{Ae^{-\frac{time}{t}}}{-t} \quad (3)$$

The standard deviation of $-d[1]/dt$ resulting from Equation 3 is determined using Equation 4.

$$\sigma_{\frac{d[1]}{dt}} = \frac{Ae^{-\frac{time}{t}}}{-t} \sqrt{\left(\frac{-e^{-\frac{time}{t}}}{t} \frac{time}{\sigma_t}\right)^2 + \left(\frac{\sigma_A}{A}\right)^2 + \left(\frac{\sigma_t}{t}\right)^2} \quad (4)$$

Reactions of boronic acid with silver nitrate



Derivation of rate law

Rate Equation:

$$-\frac{d[CF_3C_5H_4N]}{dt} = k_2[CF_3C_5H_4N - Ag^I][S_2O_8]$$

The interaction between silver(I) and pyridine was assumed to be at steady state:

$$[CF_3C_5H_4N - Ag^I] = \frac{k_1[CF_3C_5H_4N][Ag^I]}{k_{-1} + k_2[S_2O_8^{2-}] + k_3[Ar-B(OH)_2]}$$

$$-\frac{d[CF_3C_5H_4N]}{dt} = \frac{k_1 k_2 [CF_3C_5H_4N][Ag^I][S_2O_8]}{k_{-1} + k_2[S_2O_8^{2-}] + k_3[Ar-B(OH)_2]}$$

A mass balance was written for the silver complexes in the system:

$$[Ag^I]_{tot} = [Ag^I] + [CF_3C_5H_4N - Ag^I]$$

$[Ag^I]$ was solved for and inserted into the rate law:

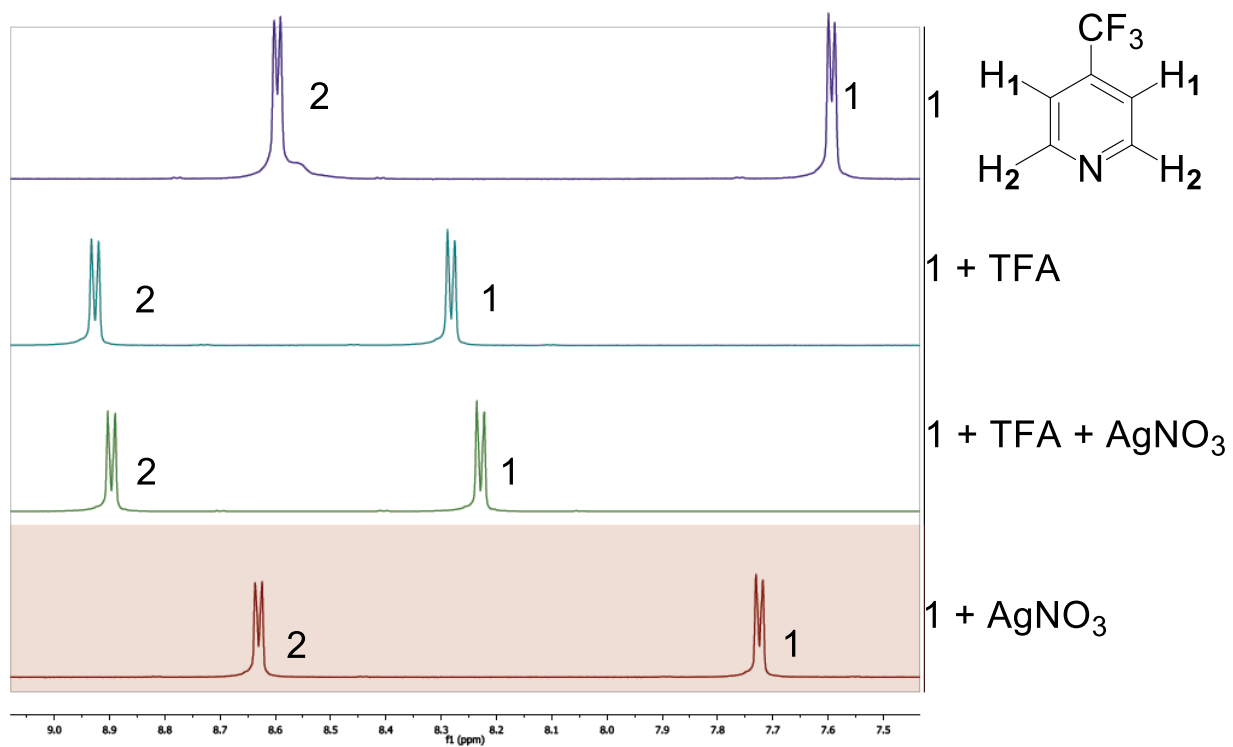
$$-\frac{d[CF_3C_5H_4N]}{dt} = \left(\frac{k_1 k_2 [CF_3C_5H_4N][S_2O_8]}{k_{-1} + k_2[S_2O_8^{2-}] + k_3[Ar-B(OH)_2]} \right) \left(\frac{k_{-1}[Ag^I]_{tot} + k_2[S_2O_8^{2-}][Ag^I]_{tot} + k_3[Ar-B(OH)_2][Ag^I]_{tot}}{k_{-1} + k_2[S_2O_8^{2-}] + k_3[Ar-B(OH)_2] + k_1[CF_3C_5H_4N]} \right)$$

Assuming $k_2 \ll k_{-1}$, $k_2 \ll k_3$, $k_2 \ll k_1$, and that Ag^I is the resting state of the catalyst:

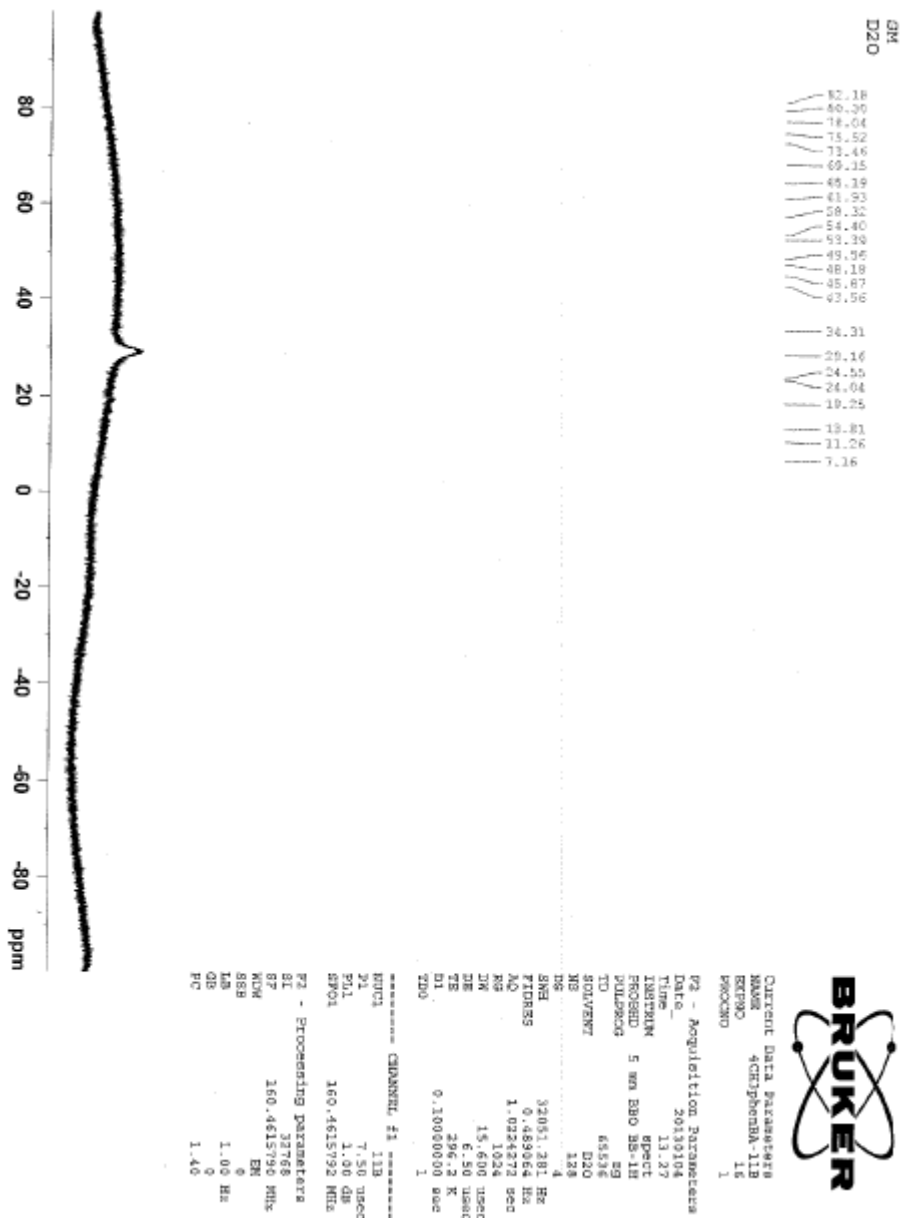
$$-\frac{d[CF_3C_5H_4N]}{dt} = k_1 k_2 [CF_3C_5H_4N][S_2O_8^{2-}][Ag^I]_{tot} \left(\frac{k_{-1} + k_2[S_2O_8^{2-}] + k_3[Ar-B(OH)_2]}{k_{-1}^2 + 2k_{-1}k_3[Ar-B(OH)_2] + k_3^2[Ar-B(OH)_2]^2} \right)$$

$$\approx k_{obs} \frac{[CF_3C_5H_4N][S_2O_8^{2-}][Ag^I]_{tot}}{[Ar-B(OH)_2]^{0.5}}$$

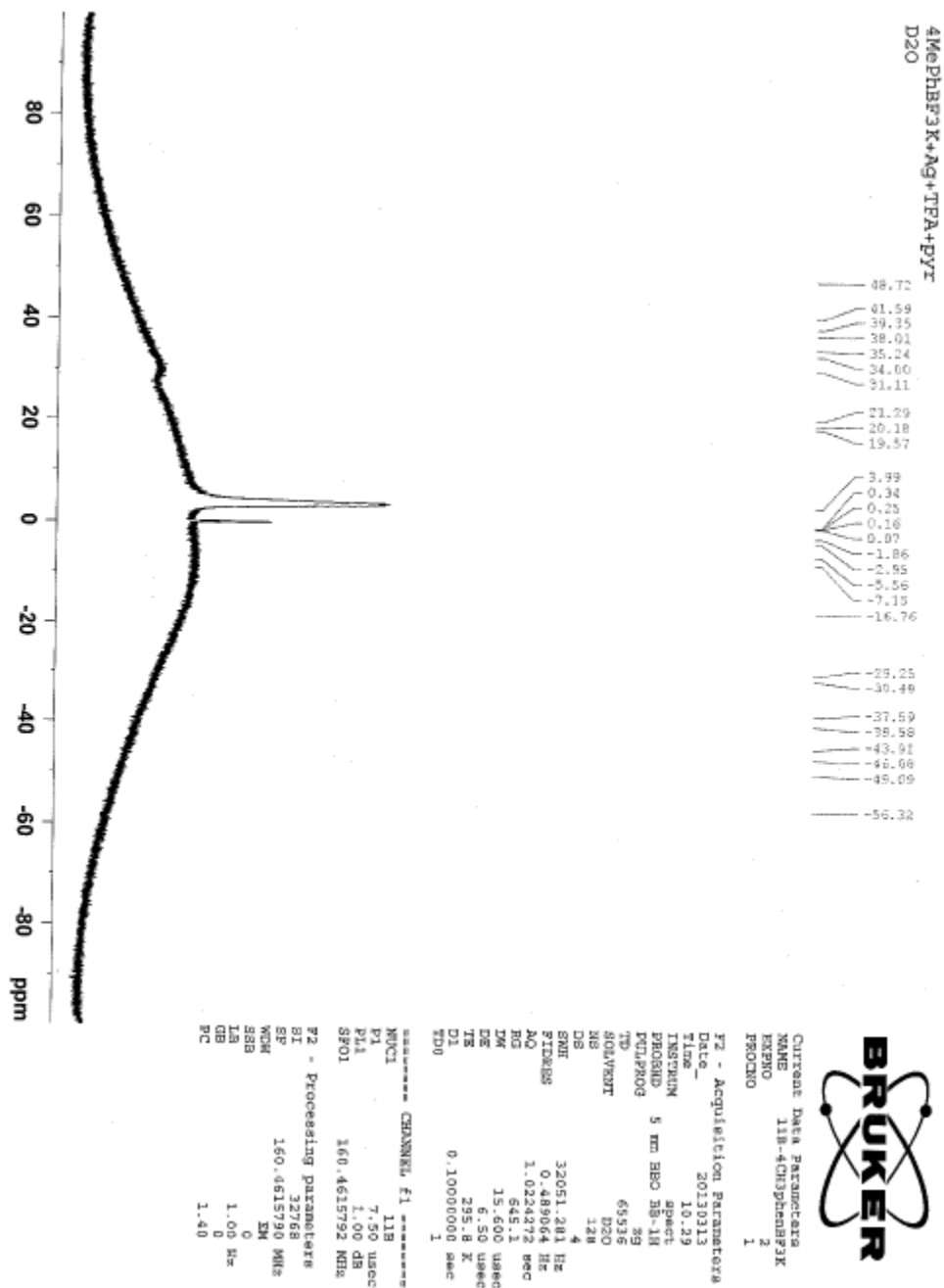
Spectral data for pyridine ^1H NMR studies



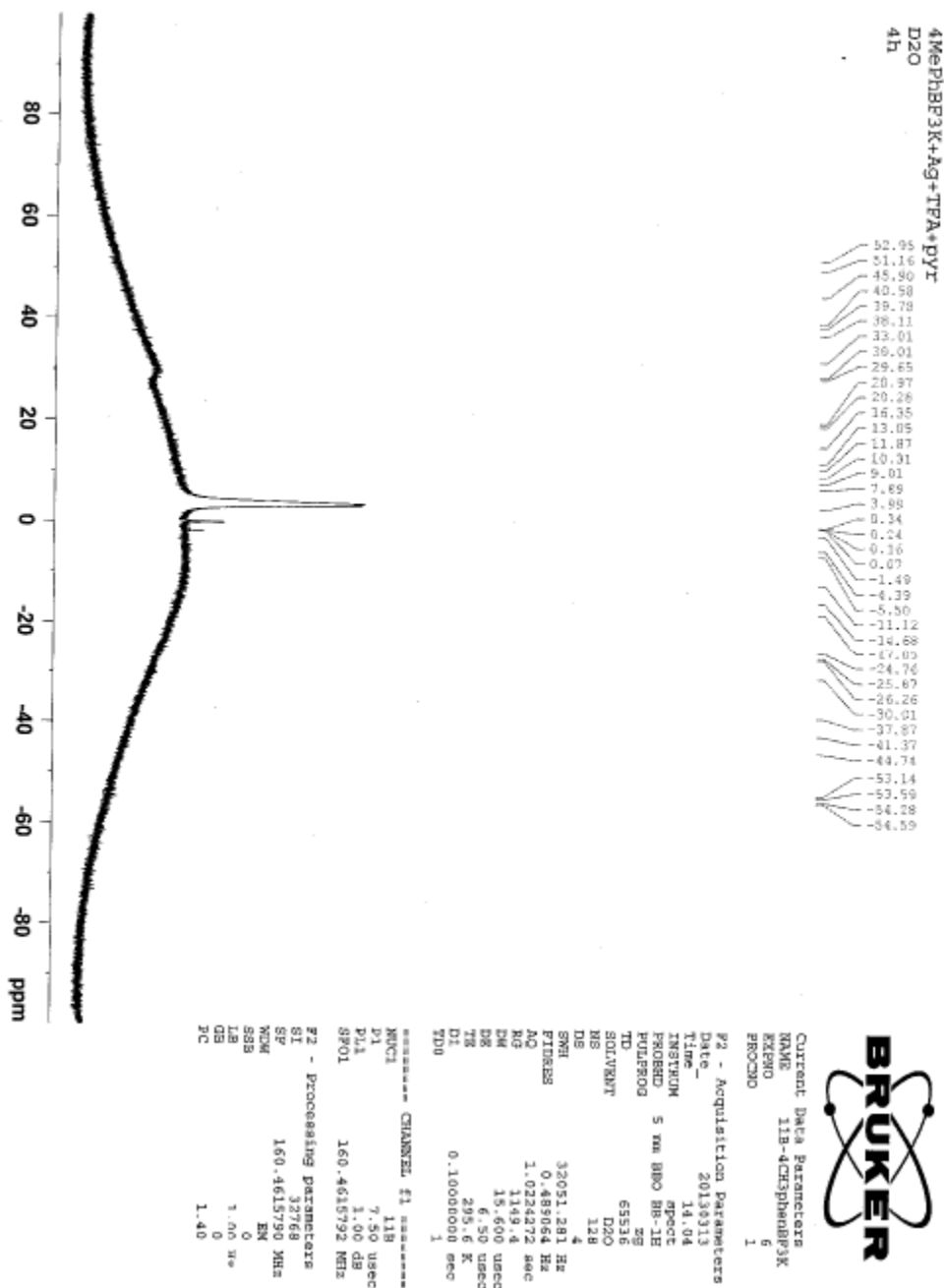
¹¹B NMR spectrum of 2



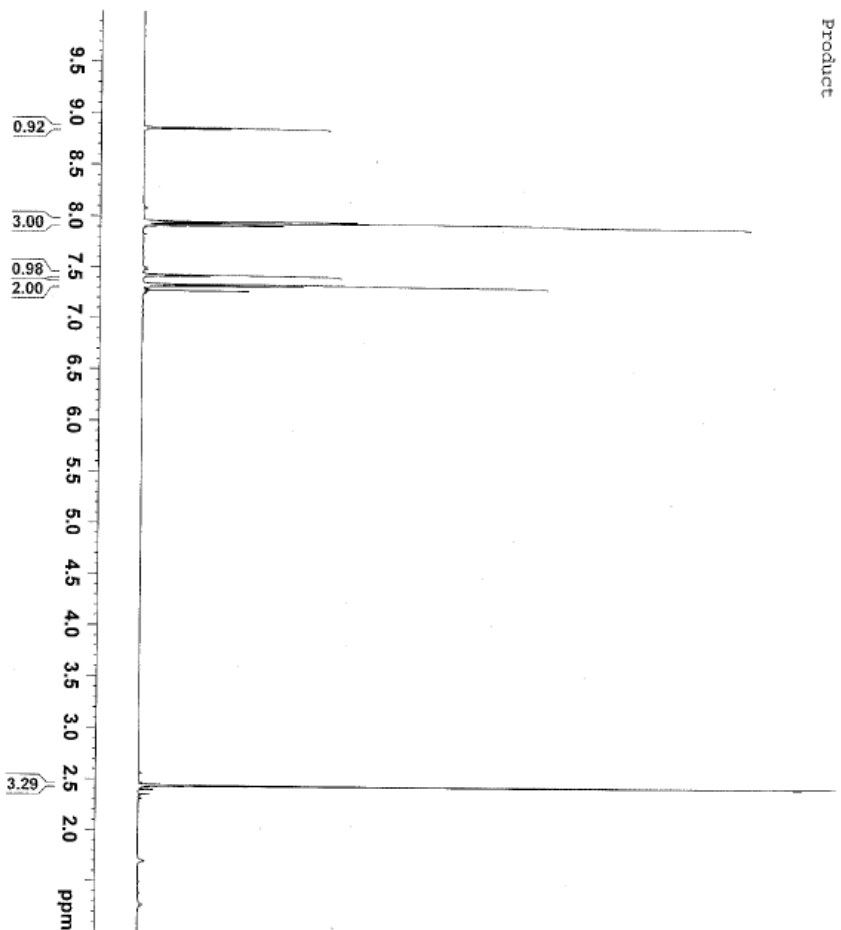
^{11}B NMR spectrum of **4** under reaction conditions at $t = 0$ mins



¹¹B NMR spectrum of **4** under reaction conditions at t = 4h



¹H and ¹³C NMR spectra for cross-coupled product 3



Product



```

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PROCNO   1

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DE         254.100 usec
TE         294.2 K
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TD0        1

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 97D: 0
 98D: 0
 99D: 0
 100D: 0
 F2P1RES: 0
 AQ: 0.480000 sec
 RG: 1.000000 sec
 IN: 1.000000 sec
 DE: 1.000000 sec
 15: 7.00 usec
 16: 7.00 usec
 17: 298.2 K
 18: 1.000000 sec
 19: 0.000000 sec
 20: 0.000000 sec
 21: 0.000000 sec
 22: 0.000000 sec
 23: 0.000000 sec
 24: 0.000000 sec
 25: 0.000000 sec
 26: 0.000000 sec
 27: 0.000000 sec
 28: 0.000000 sec
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 83: 0.000000 sec
 84: 0.000000 sec
 85: 0.000000 sec
 86: 0.000000 sec
 87: 0.000000 sec
 88: 0.000000 sec
 89: 0.000000 sec
 90: 0.000000 sec
 91: 0.000000 sec
 92: 0.000000 sec
 93: 0.000000 sec
 94: 0.000000 sec
 95: 0.000000 sec
 96: 0.000000 sec
 97: 0.000000 sec
 98: 0.000000 sec
 99: 0.000000 sec
 100: 0.000000 sec
 ===== CHANNEL f1 =====
 NUC1: 13C
 P1: 14.00 usec
 PL1: 0.00 dB
 FREQ1: 125.7615440 MHz
 SFO1: 125.7615440 MHz
 ===== CHANNEL f2 =====
 CDETRM2: walters
 NUC2: 1H
 P2: 9.00 usec
 PL2: 0.00 dB
 FREQ2: 500.1371250 MHz
 SFO2: 500.1371250 MHz
 F2 - Processing parameters
 SI: 32768
 SF: 125.7615440 MHz
 WDM: 0 Hz
 SSB: 0 Hz
 GB: 1.00 Hz
 PC: 1.40

160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm