

A mechanistic investigation of the Pd-catalyzed cross-coupling between *N*-tosylhydrazones and aryl halides

Supporting Information

Gilian T. Thomas*, Kiera Ronda, J. Scott McIndoe*

Department of Chemistry, University of Victoria, PO Box 1700 STN CSC, Victoria, BC V8W 2Y2, Canada.

Fax: +1 (250) 721-7147; Tel: +1 (250) 721-7181; E-mail: gilian.t.thomas@gmail.com,
mcindoe@uvic.ca

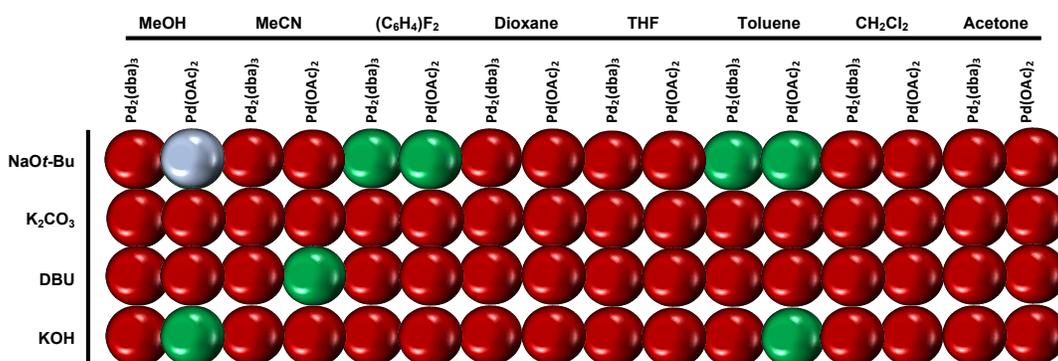


Figure S1. Reaction screen results for the cross-coupling between acetophenone tosylhydrazone and bromotoluene, reaction shown above. Red = no product generation; green = product generation and heterogeneous mixture; blue = product generation and homogeneous mixture. Conditions: bromotoluene, acetophenone tosylhydrazone, 1% [Pd], 2% SPhos, 70-110°C, 4 hrs. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, (C₆H₄)F₂ = 1,2-difluorobenzene.

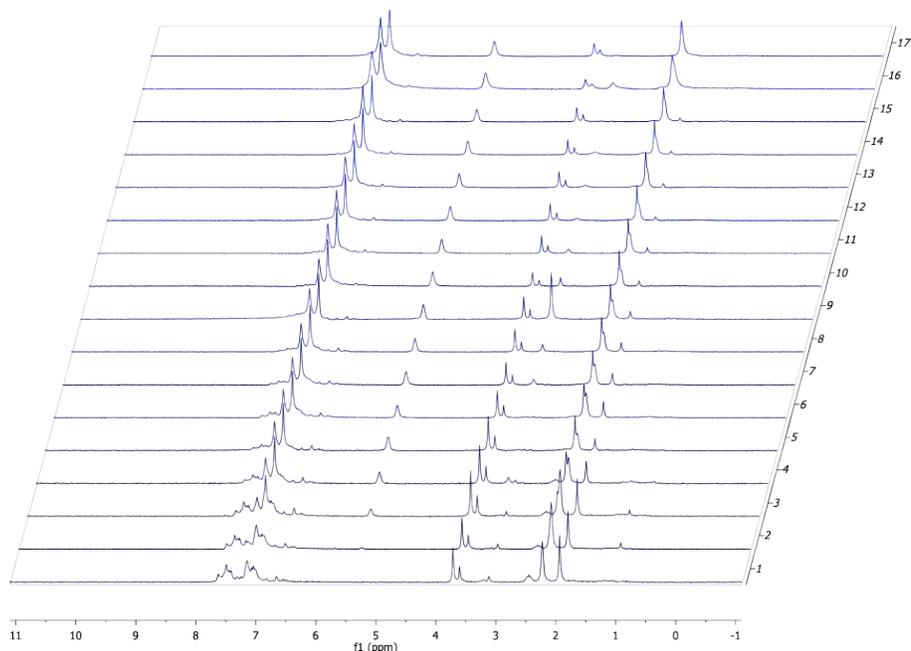


Figure S2. Example reaction monitoring spectra on the 60 MHz NMR spectrometer. Bottom = $t_{0\text{hr}}$, top = $t_{48\text{hr}}$. Product was quantified using the alkene peak at 5.40ppm and 1,2,3-trimethoxybenzene as internal standard.

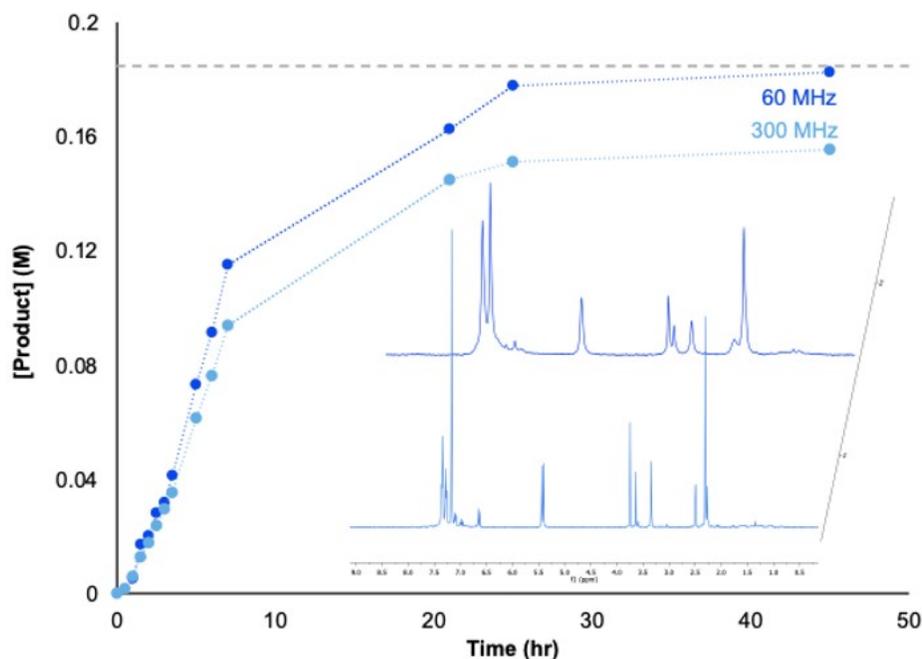


Figure S3. ^1H -NMR reaction monitoring trace over 48 hours on a 60 MHz NMR spectrometer, and a 300 MHz NMR spectrometer. Inset: representative spectrum after 14 hours on a 60MHz NMR spectrometer (dark blue), and a 300 MHz NMR spectrometer (light blue). Dashed grey line indicates theoretical yield of product. Conditions: 1% [Pd], 2% SPhos, 0.003 mol acetophenone tosylhydrazone, 0.003 mol bromotoluene, 0.0067 mol NaOt-Bu, 70°C.

The 60 MHz spectrometer provided concentration values that were consistently 15% lower due to the difference in acquisition time between the two spectrometers. The 60 MHz spectrometer had a total acquisition time of 4.65 seconds per scan, compared to a 3 second acquisition time on the 300 MHz spectrometer. The shorter acquisition time on the 300 MHz spectrometer means the nuclei are not allowed as much time to relax, leading to varying quantitative results. In the 60 MHz spectrum the aromatic region is amalgamated into two signals (Figure S3 inset, dark blue), however several other signals are observed in this region on the 300 MHz spectrum (Figure S3 inset, light blue).

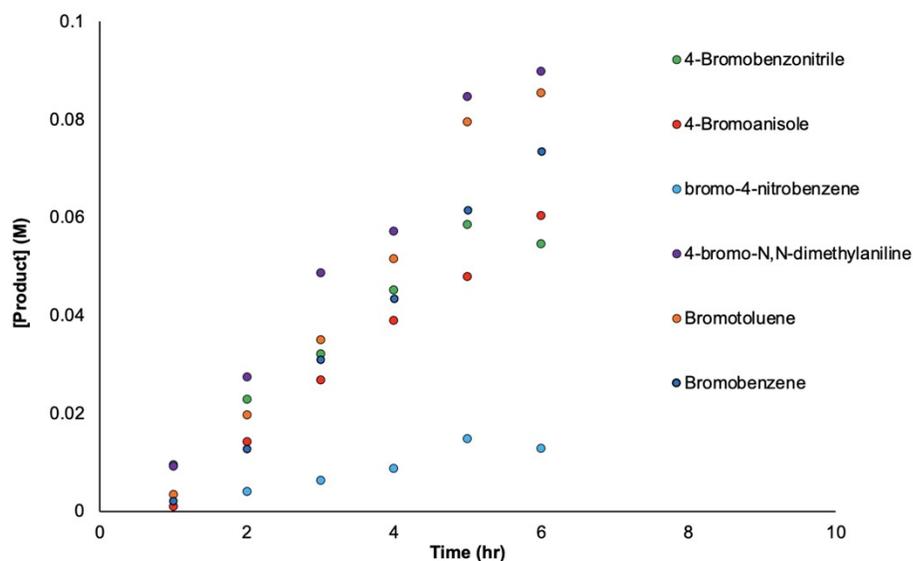


Figure S4. Summary of aryl bromide substrate variation. These initial rates were used in the Hammett analysis

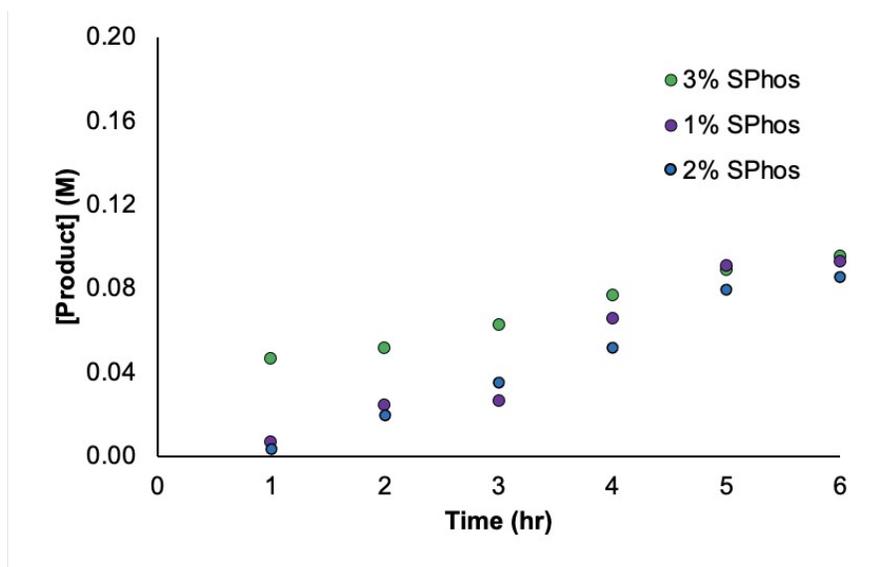


Figure S5. Comparison of % Sphos (L) used under standard NMR reaction monitoring conditions.

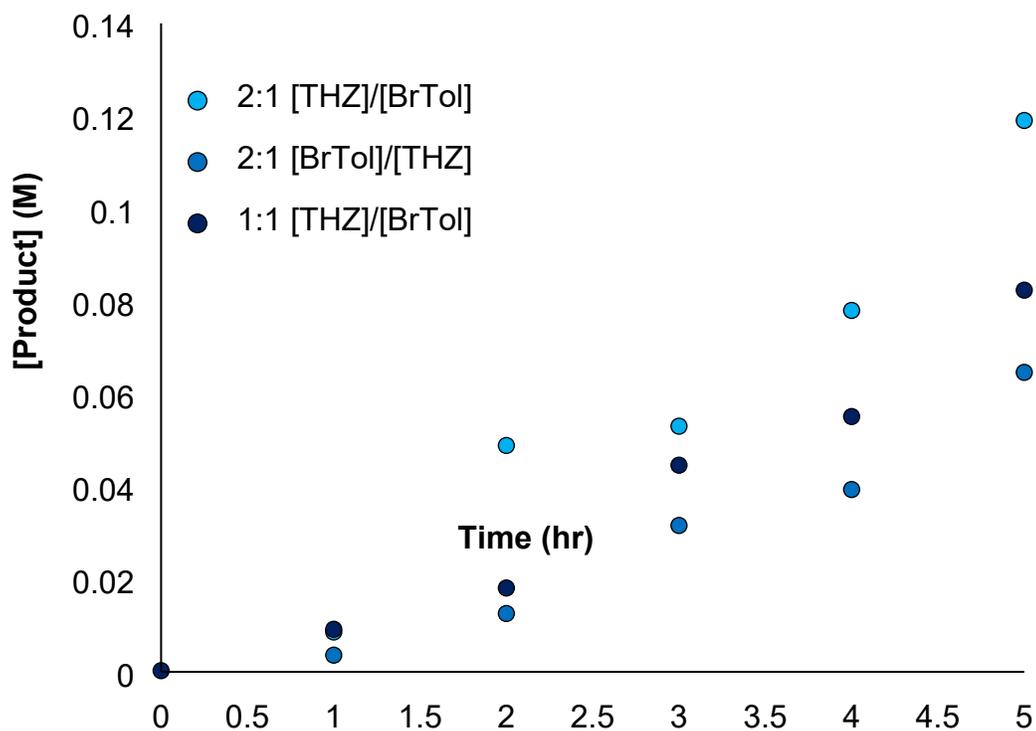


Figure S6. Comparison of concentration ratios – 2:1 bromotoluene (0.34 M)/tosylhydrazone (0.17 M), vs 2:1 tosylhydrazone (0.34 M)/bromotoluene (0.17 M) vs 1:1 (0.17 M).

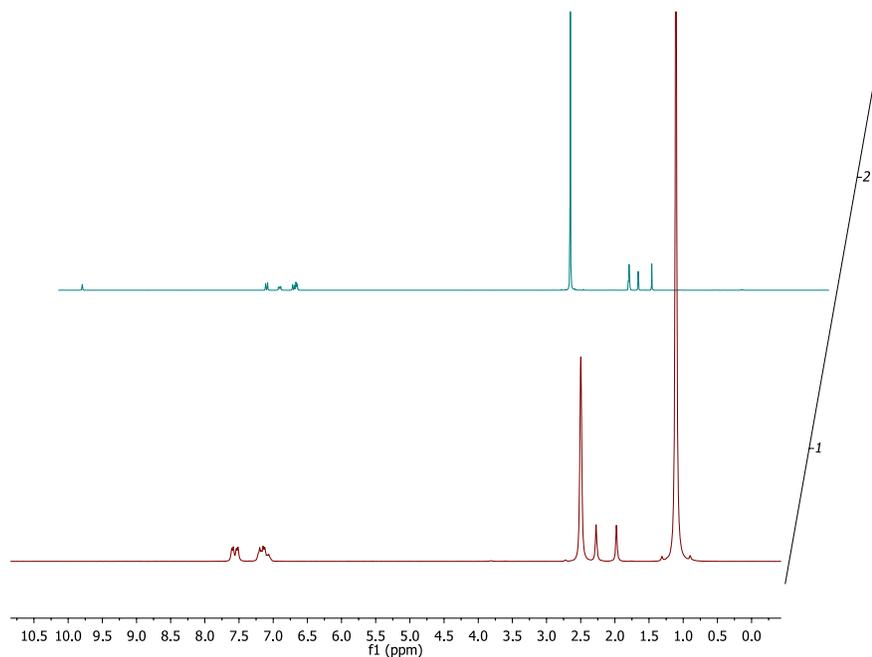


Figure S7. NMR spectra comparison of acetophenone tosylhydrazone (top) and acetophenone tosylhydrazone in the presence of sodium *tert*-butoxide (bottom). Acetophenone tosylhydrazone assignments: 2.16 ppm (s, 3H), 3.26 ppm (s, 3H), 7.34-7.42 ppm (m, 5H), 7.58-7.63 ppm (m, 2H), 7.78-7.82 ppm (m, 2H), 10.5 ppm (s, 1H). Acetophenone tosylhydrazone + sodium *tert*-butoxide assignments: 1.11 ppm (s, 9H), 1.98 ppm (s, 3H), 2.27 ppm (s, 3H), 7.04-7.22 ppm (m, 5H), 7.51-7.61 ppm (m, 4H). 300 MHz, DMSO- d_6 .

Nanalysis NMReady-60PRO Tests

Error bars on the concentration of product do not suggest significant deviation from the mean, and further testing on the Nanalysis NMReady-60PRO instrument demonstrated its reproducibility in measurements.

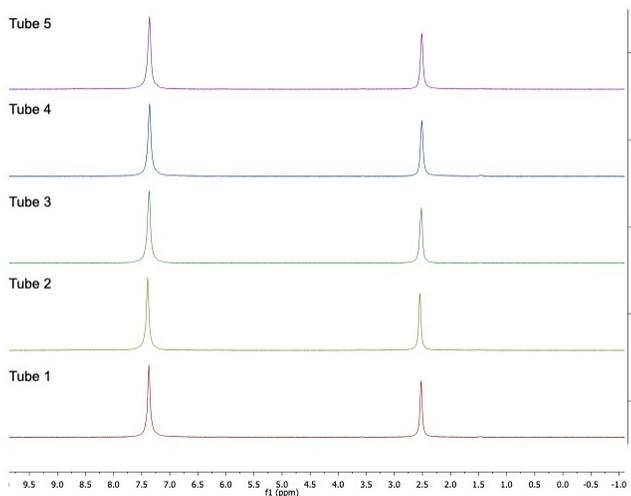


Figure S8. Five different NMR tubes, all containing 100 μL toluene, 500 μL CDCl_3 .

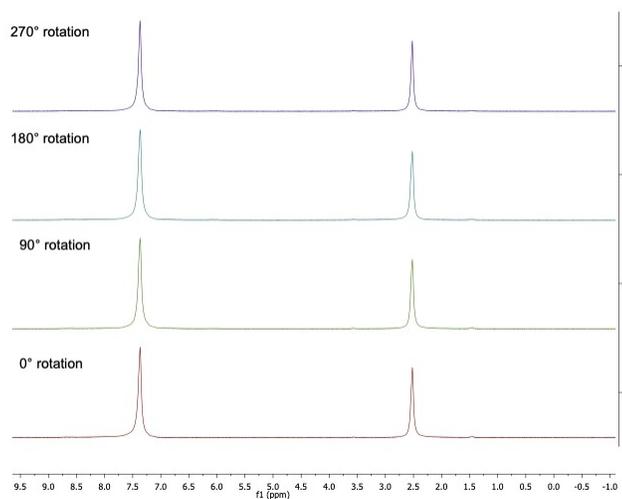


Figure S9. Rotation of a single NMR tube within the sample holder inside the spectrometer, containing 100 μL toluene, 500 μL CDCl_3 .

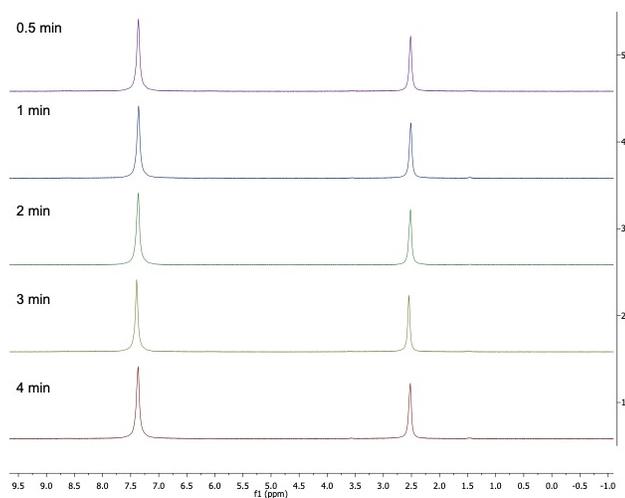


Figure S10. Variation of time spent inside the accompanying sample warmer from 0.5 minutes to 4 minutes of incubation time prior to acquisition of the spectra.

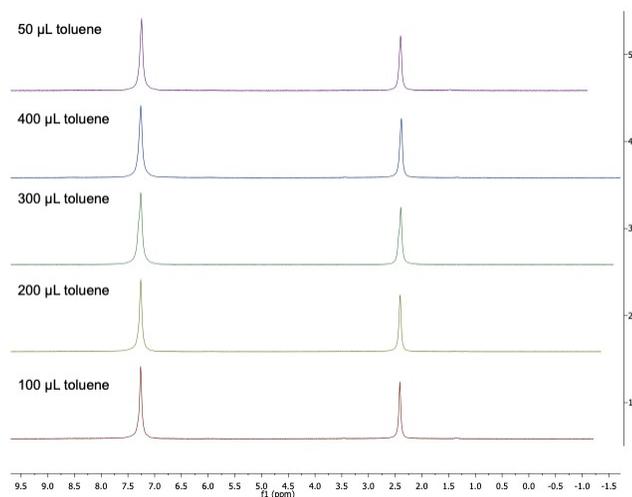


Figure S11. Variation of concentration of analyte from 50-400 µL of toluene and remaining volume composed of CDCl_3 , maintaining a total volume of 700 µL inside the NMR tube.

Experimental

General Information

Acetophenone tosylhydrazone was synthesized from acetophenone and *p*-toluenesulfonyl hydrazide according to literature procedure.^{1,2} SPhos, sSPhos, Pd₂(dba)₃, and Pd(OAc)₂ were weighed in a N₂-filled glovebox. NMR spectra were analyzed using Mestrenova (12.0.0) software. All substrates were used without purification and purchased from Sigma-Aldrich. All solvents were used without purification and purchased from Fischer Chemical.

Reaction Screen

Stock solutions of acetophenone tosylhydrazone, NaO-*t*Bu, KOH, Pd₂(dba)₃, Pd(OAc)₂, K₂CO₃, and SPhos were prepared in solvent being screened (i.e. methanol, THF, dioxane, acetonitrile, 1,2-difluorobenzene, toluene, dichloromethane, acetone). These reactions were conducted at 0.167 M with respect to acetophenone tosylhydrazone (1 mL solvent), with 2.2 equivalents of base, 1% [Pd], 2% SPhos. The reaction was heated at 50°C-110°C for 4 hours, and subsequently taken up into pentanes and filtered through celite. After drying *in vacuo*, the contents were dissolved in DMSO-*d*₆ and transferred to an NMR tube. Each reaction was analyzed on a Nanalysis NMReady 60PRO spectrometer, 64 ¹H scans.

NMR Reaction Monitoring

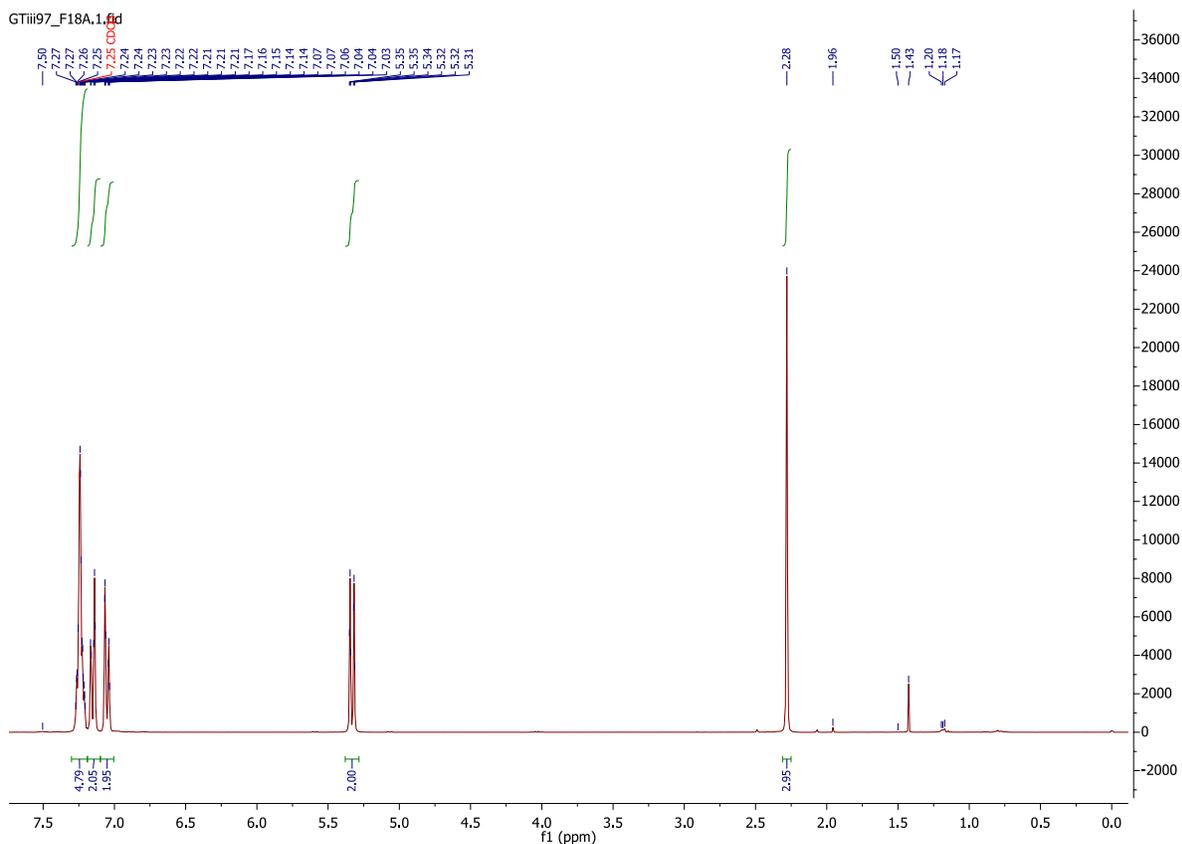
A Schlenk flask was equipped with 0.0172 g of Pd₂(dba)₃ and 0.0283 g SPhos inside the glovebox. Acetophenone tosylhydrazone (0.883 g) and NaO-*t*Bu (0.633 g) were weighed on the bench and added to the flask on a Schlenk line in the fumehood. 1,3,5-trimethoxybenzene was used as the internal standard (0.084 g). THF, toluene and methanol (6 mL each) were then added to the flask and the contents were allowed to stir at 70°C for approximately 1 minute prior to the addition of bromotoluene (369 μL).

Every hour a 1 mL aliquot was taken into 2 mL of pentane. This solution was then filtered through celite, and dried down. The contents were then re-suspended in DMSO-*d*₆ and analyzed on a Nanalysis NMReady 60PRO spectrometer, 64 ¹H scans and/or a Bruker AV III 300 MHz NMR spectrometer.

MS Reaction Monitoring

A PSI flask³ was equipped with SPhos (0.0019 g)/sSPhos (0.0023 g), and Pd₂(dba)₃ (0.0011 g) in 18 mL of 1:1:1 methanol/THF/toluene and stirred at 70°C. A pressure of 6 psi was applied to the flask to initiate pressurized sample infusion⁴ into a Waters Acquity triple quadrupole mass spectrometer. Bromotoluene (21 μL) was added upon completion of catalyst activation. After the oxidative addition was complete, acetophenone tosylhydrazone (0.059 g) and NaO-*t*Bu (0.043 g) were added to the reaction flask. THF was dried over CaH₂ and distilled prior to use for MS analysis to remove BHT additives.

1,1-diphenylethylene (DMSO-d₆, 300 MHz):



References

- 1 X. Zhao, J. Jing, K. Lu, Y. Zhang and J. Wang, *Chem. Commun.*, 2010, **46**, 1724–1726.
- 2 V. P. Miller, D. Y. Yang, T. M. Weigel, O. Han and H. W. Liu, *J. Org. Chem.*, 2002, **54**, 4175–4188.
- 3 G. T. Thomas, L. MacGillivray, N. L. Dean, R. L. Stoddard, L. P. E. Yunker and J. S. McIndoe, *Int. J. Mass Spectrom.*, 2019, **441**, 14–18.
- 4 K. L. Vikse, M. P. Woods and J. S. McIndoe, *Organometallics*, 2010, **29**, 6615.