Revisiting the mechanism of the Fujiwara-Moritani reaction

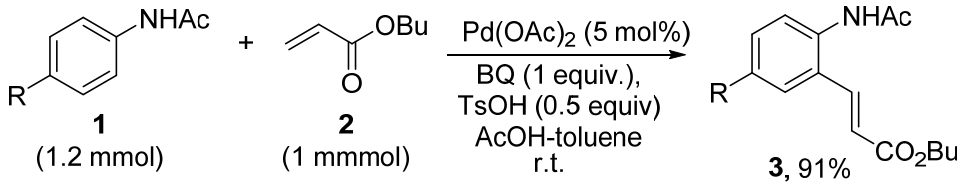
Christopher J. Mulligan, Jeremy S. Parker and King Kuok (Mimi) Hii

Supporting Information

1 General Remarks

Unless otherwise stated, materials were purchased from commercial sources and used as received. Palladium(II) acetate was donated by Johnson-Matthey PLC and AstraZeneca. Benzoquinone was purified by sublimation prior to use. Column chromatography was performed on silica gel (60 Å, 230-240 mesh).

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV400 spectrometer. ^{1}H and ^{13}C NMR chemical shifts are reported relative to residual solvent peaks ($CDCl_3$: $\delta_H = 7.26$ ppm and $\delta_C = 77$ ppm). Multiplicity is denoted as follows: s = singlet, b = broad, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet and *J* values are given in Hz. Infrared spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer fitted with an ATR accessory. Melting points were recorded using a Gallenkamp melting point apparatus. All mass spectra were recorded by Lisa Haigh at Imperial College London: Electrospray ionisation mass spectroscopy (ESI-MS) was recorded on a Waters LCT premier spectrometer. HPLC analysis was performed using an Agilent 1100 instrument, fitted with a C18 column and a diode array UV-Vis Detector. Absorbance at 215, 254 and 280 nm were used for quantification. Calorimetry experiments were performed using an Omnical Super CRC reaction calorimeter. Unless otherwise stated, volumes less than 1 mL were measured using Gilson pipettes.



Fujiwara-Moritani coupling reaction: 4-Methylacetanilide (178.8 mg, 1.2 mmol), benzoquinone (108.1 mg, 1 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 5 mol%) and 4-TsOH·H_2O (95.1 mg, 0.5 mmol) were dissolved in acetic acid (12 mL) at room temperature. *n*-Butyl acrylate (144.4 µL, 1 mmol) was added, and the reaction mixture was stirred at 30 °C for 18 h. The volume was then reduced under vacuum and purified by column chromatography (SiO_2, ethyl acetate/ petroleum ether (3/1), furnishing the product **3** as a white solid, 250.6 mg, 91%, Mp 92-95 °C (lit[1] 93-94 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, 1H, *J* = 15.8), 7.51 (d, 1H, *J* = 8.0), 7.42 (bs, 1H), 7.35 (s, 1H), 7.17 (d, 1H, *J* = 7.9), 6.37 (d, 1H, *J* = 15.8), 4.18 (t, 2H, *J* = 6.5), 2.32 (s, 3H), 2.19 (s, 3H), 1.66 (p, 2H, *J* = 6.7), 1.46-1.37 (m, 2H), 0.95 (t, 3H, *J* = 7.3); ^{13}C (101 MHz, $CDCl_3$) δ 169.15, 166.92, 139.57, 135.74, 133.48, 131.60, 127.89, 127.33, 125.78, 119.81, 64.56, 30.63, 23.90, 21.10, 19.13, 13.68; HRMS (ESI^+ TOF): *m/z* Calc. for $C_{16}H_{22}NO_3$ $[M+H]^+$ 276.1600, found 276.1610.

2 Kinetic experiments

Kinetic analyses were conducted by using both the initial rates method and reaction progress kinetic analysis (RPKA). The initial rates method is frequently used for interrogating concentration dependencies.[2] As its name implies, only the initial portion of a reaction profile is considered, so that linearity can be forced allowing for the rate to be extracted. However, as this method only considers the initial portion of the reaction, any changes in rate dependencies at a later stage in the reaction (such as catalyst deactivation and product inhibition) would not be observed. In contrast, 'Reaction Progress Kinetic Analysis' (RPKA), was developed by Blackmond,[3, 4] is a set of techniques used to analyse and present data collected over the full course of the reaction. By plotting a function of the rate vs. a function of a reactant concentration, simple visual interpretation of the data can be made. Plotting the data in this way has been termed a 'graphical rate equation'.

2.1 Kinetics experiments (HPLC Sampling)

The appropriate quantities of 4-methylacetanilide (**1**), benzoquinone (BQ), $TsOH \cdot H_2O$ and $Pd(OAc)_2$ were dissolved in acetic acid (3 mL) at 30 °C. The reaction was initiated by the addition of *n*-butyl acrylate (**2**). 50 µL aliquots of the reaction mixture were taken at appropriate time intervals and diluted with a combined quench (56 mM $FeCl_2$ solution, 450 µL) and internal standard (benzyloxy phenol, 1.0 mg/mL) in methanol. Yields were determined by HPLC analysis.

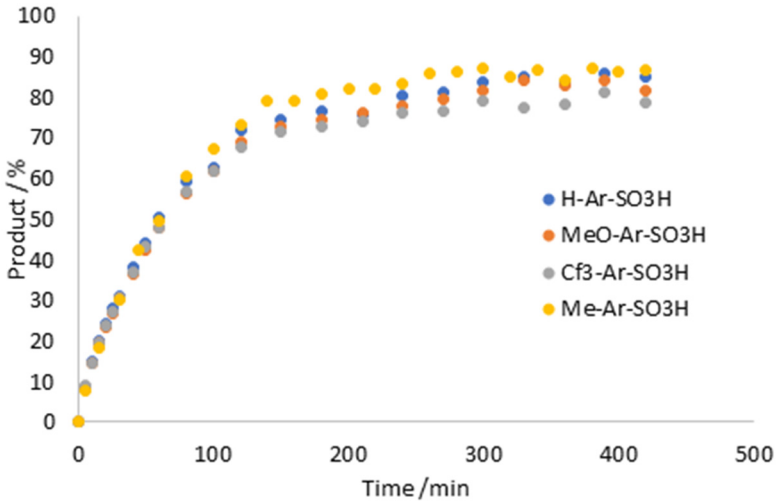


Figure S1. Reaction profiles using different *para*-substituted aryl sulfonic acids, *p*-Z-$C_6H_4SO_3H$ (monitored by HPLC). Reaction conditions: 4-methylacetanilide (0.75 mmol), n-butyl acrylate (0.75 mmol), $Pd(OAc)_2$ (5 mol%, 0.0375 mmol), aryl sulfonic acid (0.75 mmol, 1 equivalent), AcOH (3 mL), BQ (0.75 mmol), 30 °C.

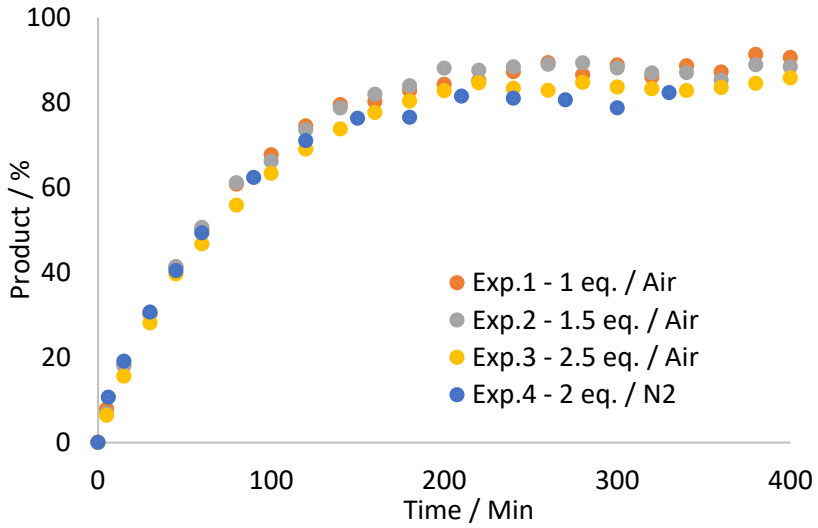


Figure S2. Reaction profiles using different amounts of BQ (1-2.5 equivalents) under air or an inert atmosphere: 4-Methylacetanilide (0.75 mmol), n-butyl acrylate (0.75 mmol), $Pd(OAc)_2$

(5 mol%, 0.0375 mmol), aryl sulfonic acid (0.75 mmol, 1 equivalent), AcOH (3 mL), 30 °C. The results show that: i) the reaction rate is independent of [BQ]; and ii) air does not compete with BQ as an oxidant under these conditions.

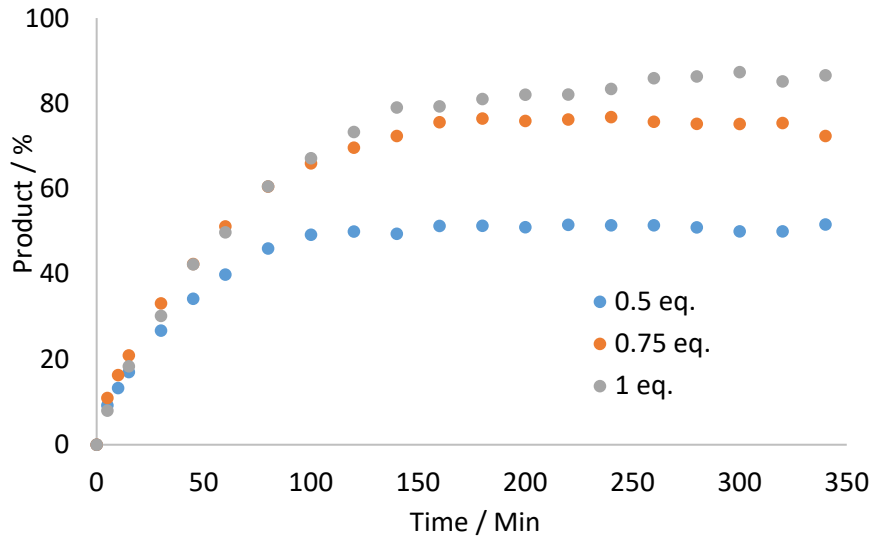


Figure S3. Reaction profiles using different amounts of acrylate (0.5-1 equivalents): 4-methylacetanilide (0.75 mmol), $Pd(OAc)_2$ (5 mol%, 0.0375 mmol), aryl sulfonic acid (0.75 mmol, 1 equivalent), AcOH (3 mL), BQ (0.75 mmol), 30 °C. The initial rates show that the reaction is zero order in acrylate. Note: these experiments were conducted using sub-stoichiometric amount of the alkene to prevent formation of di-substituted compound.

The overlap of the reaction profiles in Figure S1 and S2 showed that the rate of the catalytic reaction is unaffected by the para-substituent of the aryl sulfonic acid, or the amount of BQ between 1-2.5 equivalents. In Figure S3, the initial rate of the reaction (between 0-50 min) was also unaffected by the amount of methyl acrylate employed.

2.2 Kinetics experiments (Calorimetry)

The appropriate quantities of 4-methylacetanilide, *n*-butyl acrylate and benzoquinone were added to the reaction vessel along with acetic acid (0.9 mL). A solution of $Pd(OAc)_2$ dissolved in acetic acid (2 mL) was then added. The vessel was placed in a SuperCRC reaction calorimeter and stirred at 30°C until thermal equilibrium had been reached (approximately 2 h). The reaction was initiated by the addition of p-TsOH·H_2O dissolved in acetic acid (0.1 mL) by micro syringe and the heat flow was monitored. The final concentrations were determined by HPLC analysis.

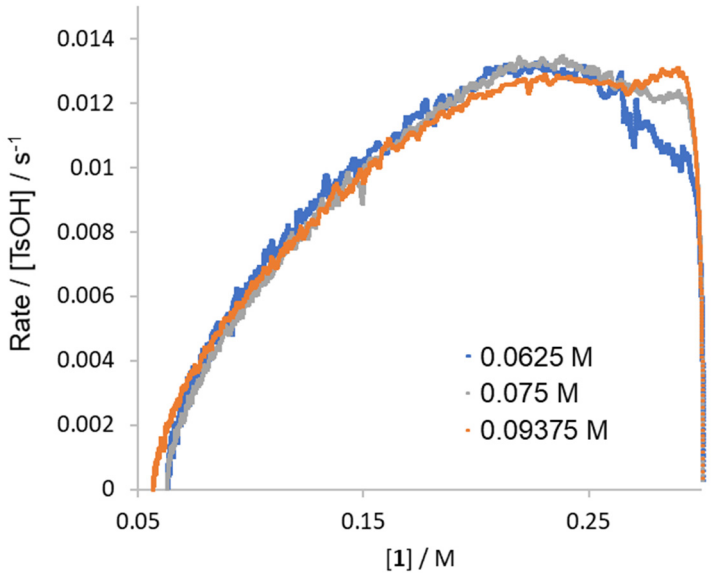


Figure S4. Plot of reaction rate/[TsOH] vs [**1**], between 2.5-37.5 mol% (0.0625-0.09375 M) of TsOH.

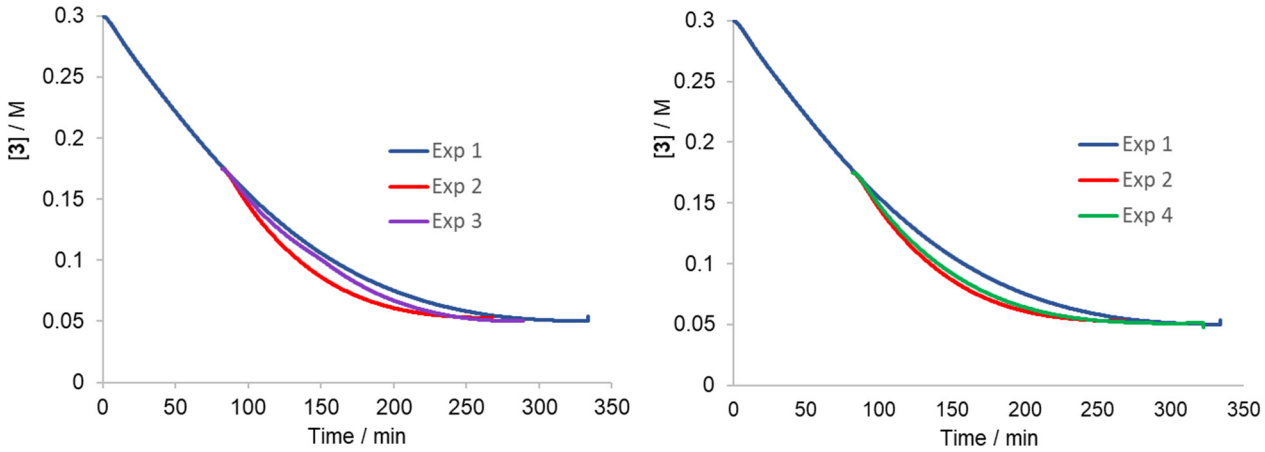


Figure S5. 'Same excess' experiments in the presence of hydroquinone (experiment 3, Table 1) or product **3** (experiment 4, Table 1).

3 Job plot

A Job plot, also known as the method of continuous variation, is commonly used in analytical, biological and supramolecular chemistry to determine the stoichiometry of (reversible) binding.[5,6] Experimentally, this involves changes in a physical property (in this case, ^{19}F chemical shift) as the molar ratio of the binding partners is changed.

For this study, p-(trifluoromethyl)benzenesulfonic acid (*p*-CF_3-$C_6H_4SO_3H$) was used as a fluorinated surrogate of TsOH. This enabled the use of ^{19}F NMR as a means of determining

the position of the equilibrium. A series of solutions in acetone-d_6 were prepared with differing [$Pd(OAc)_2$] : *p*-CF_3-$C_6H_4SO_3H$ molar ratios, keeping the total concentration ([$Pd(OAc)_2$] + [*p*-CF_3-$C_6H_4SO_3H$]) constant (Table S1). The ^{19}F NMR spectra of the samples was then recorded. The unbound p-CF_3-$C_6H_4SO_3H$ gave rise to a singlet resonance at δF -62.64 ppm (referenced to α,α,α-trifluorotoluene). In the presence of $Pd(OAc)_2$, ligand exchange occurs to generate a mixture of species. The ensuing equilibrium was found to be in fast exchange with respect to the NMR time scale. As such, the signals of all the species in equilibrium appear as a time-averaged signal and the change in chemical shift (Δδ) is proportional to the molar ratio of the component species. Figure S6 shows the resultant Job plot. Plotting the data in this way shows the molar ratio of the components in the dominate species as a maximum.

Procedure: Stock solutions of $Pd(OAc)_2$ and 4-(trifluoromethyl)-benzenesulfonic acid were prepared as described below in Table S1. α,α,α-Trifluorotoluene ($PhCF_3$) was used as an internal standard and all stock solutions were prepared in volumetric flasks:

(i) Stock solution A

$PhCF_3$ (1.6 mmol, 196.45 μL) was dissolved in acetone and the volume adjusted to 2 mL providing a 0.8 M stock solution.

(ii) Stock solution B

$Pd(OAc)_2$ (0.04 mmol, 9.0 mg) and stock solution A (50 μL) were dissolved in acetone and the volume adjusted to 2 mL such that the final concentration of both $Pd(OAc)_2$ and $PhCF_3$ was 0.02 M.

(iii) Stock solution C

p-CF_3-$C_6H_4SO_3H$ (0.04 mmol, 9.0 mg) and stock solution A (50 μL) were dissolved in acetone and the volume adjusted to 2 mL such that the final concentration of both *p*-CF_3-$C_6H_4SO_3H$ and trifluorotoluene was 0.02 M.

The three stock solutions were used to prepare samples 1-7 (**Table S1**) and their ^{19}F NMR spectra recorded. As a non-deuterated solvent (acetone) was used, a sealed capillary tube insert containing D_2O was used to provide the deuterium lock. Chemical shifts are referenced to $PhCF_3$ (δ_F = -62.32 ppm) (**Figure S2**). The Job plot was constructed from the change in chemical shift ($\Delta\delta_F$).

Table S1 Volumetric mixtures of stock solutions constituting NMR samples.

	$Pd(OAc)_2$		*p*-CF_3-$C_6H_4SO_3H$	
Sample	Vol. Stock B / µL	Mole fraction[a]	Vol. stock C / µL	Mole fraction
1	500	1.00	0	0.00
2	425	0.85	75	0.15
3	350	0.70	150	0.30
4	250	0.50	250	0.50
5	150	0.30	350	0.70
6	75	0.15	425	0.85
7	0	0.00	500	1.00

[a] $[Pd(OAc)_2]$ or [*p*-CF_3-$C_6H_4SO_3H$] / ($[Pd(OAc)_2]$ + [*p*-CF_3-$C_6H_4SO_3H$])

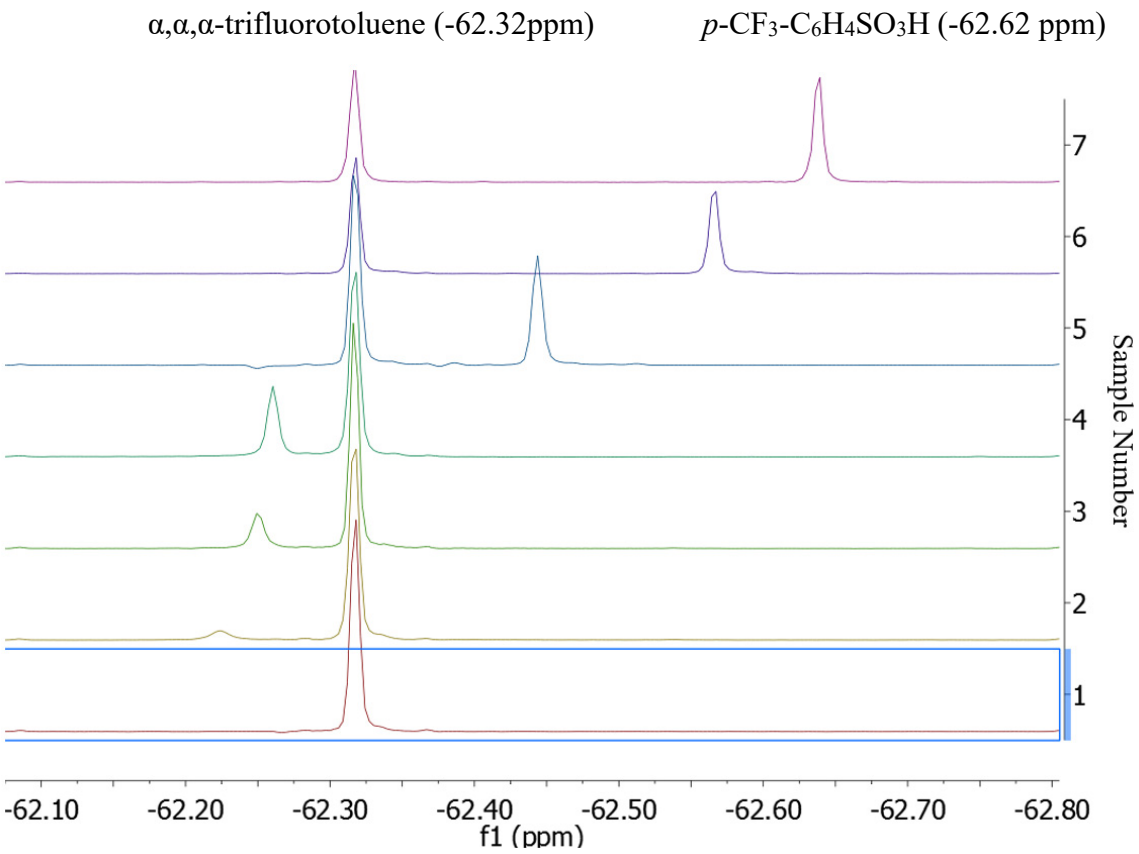


Figure S6. ^{19}F NMR spectra of samples 1-7 (Table S1), $\delta^{19}F$ is referenced to $PhCF_3$.

4 Kinetic Modelling

In the context of this work, a kinetic model is a series of differential equations that describe changes in concentrations over time. Using the appropriate software, these equations can be solved allowing for concentrations and reaction rates to be calculated, thus simulating the reaction profiles. Such models are typically used in process chemistry and chemical engineering to predict the consequences of changing reaction components. However, provided the model is based on a proposed mechanism, kinetic modelling can also be used as a mechanistic tool. In similar manner to the steady-state rate equation, a model that accurately reproduces the experimental data provides further evidence that the proposed mechanism accurately represents the observed kinetics.

Using the equations presented in Scheme 8, a set of differential equations were written for each experiment (16 sets of equations), and the initial conditions for each experiment were defined independently. The same rate constants (k_1, k_{-1}, k_2, k_3, k_4 and k_{-4}) were used across all sets of differential equation. By using an ODE solver, the values of 6 rate constants can be derived from the 16 datasets (a total of 144 differential equations).

Table S2. Reaction conditions for the 16 independent reactions used in the kinetic modelling.

Expt #	[**1**]/M	[**2**]/M	[BQ]/M	[Pd]/M	[TsOH]/M	[**3**]/M	[HQ]/M	comment
1	0.3	0.25	0.25	0.0125	0.125	0	0	'standard'
2	0.5	0.25	0.25	0.0125	0.125	0	0	'different
3	0.75	0.25	0.25	0.0125	0.125	0	0	excess' of **1**
4	0.75	0.56	0.75	0.0375	0.75	0	0	'different
5	0.75	0.375	0.75	0.0375	0.75	0	0	excess' of **2**
6	0.3	0.25	0.25	0.00625	0.125	0	0	Different
7	0.3	0.25	0.25	0.0075	0.125	0	0	[Pd]
8	0.3	0.25	0.25	0.01	0.125	0	0	
9	0.3	0.25	0.375	0.0125	0.125	0	0	'different
10	0.3	0.25	0.45	0.0125	0.125	0	0	excess' of BQ
11	0.3	0.25	0.5	0.0125	0.125	0	0	
12	0.3	0.25	0.625	0.0125	0.125	0	0	
13	0.175	0.125	0.125	0.0125	0.125	0	0	
14	0.175	0.125	0.125	0.0125	0.125	0	0.125	

15	0.175	0.125	0.125	0.0125	0.125	0.125	0	'same
16	0.175	0.125	0.125	0.0125	0.125	0.125	0.125	excess' experiments

Reactions were all performed in acetic acid at 30 °C. All experiments were conducted using calorimetry except entries 4 and 5, which were performed by HPLC analysis of reaction aliquots.

Fitting of kinetic model to experimental data was performed using Berkerly Madonna ODE solver, yielded rate constants listed in Scheme 8. The goodness-of-fit was assessed by a visual comparison of simulated data against experimental data. These are presented in the following figures:

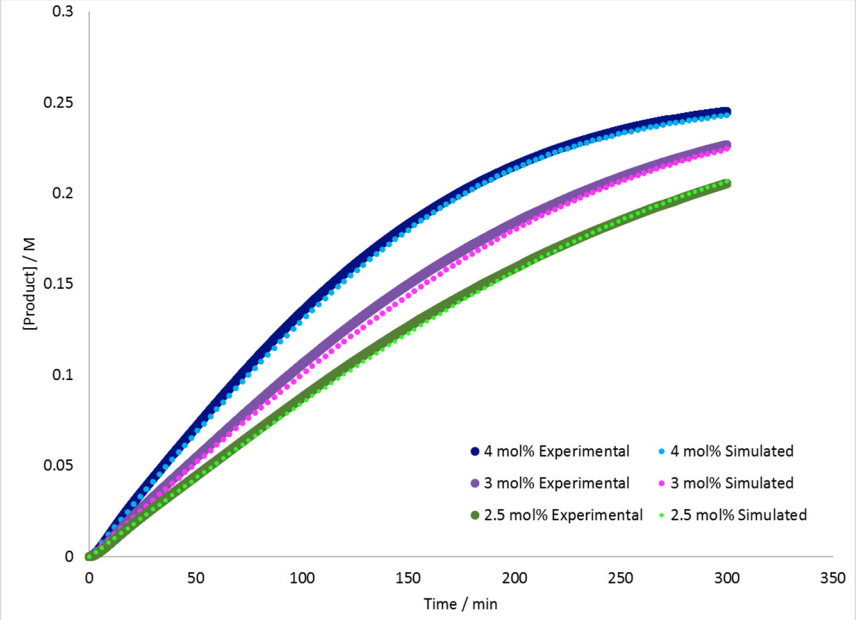


Figure S7. Experimental and simulated data for different catalyst loadings (2.5-4 mol%). Initial concentrations: 4'-methylacetanilide = 0.3 M, butyl acrylate **2** = 0.25 M, BQ = 0.25 M, TsOH = 0.125 M.

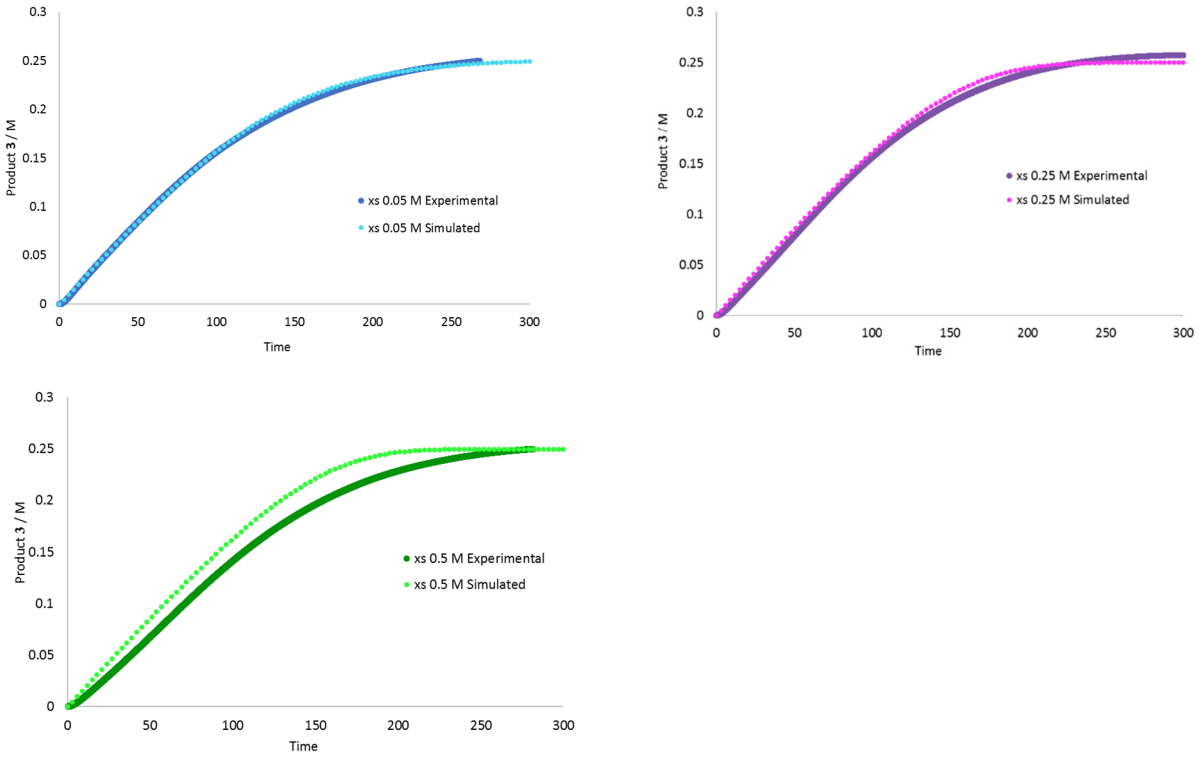


Figure S8. Experimental and simulated data for 'different excess' of 4-methylacetanilide **1** = 0.75 M (0.5 M excess), 0.5 M (0.25 M excess) or 0.3 M (0.05 M excess), butyl acrylate 2 = 0.25 M, BQ = 0.25 M, $Pd(OAc)_2$ = 0.0125 M, TsOH = 0.125 M. Note: An over-estimation of the rate was observed in the presence of a large excess of [**1**] (0.75 M; 3 equivalents with respect to the alkene). This may be close to/exceed the solubility limit of 4'-methylacetanilide in the reaction mixture.

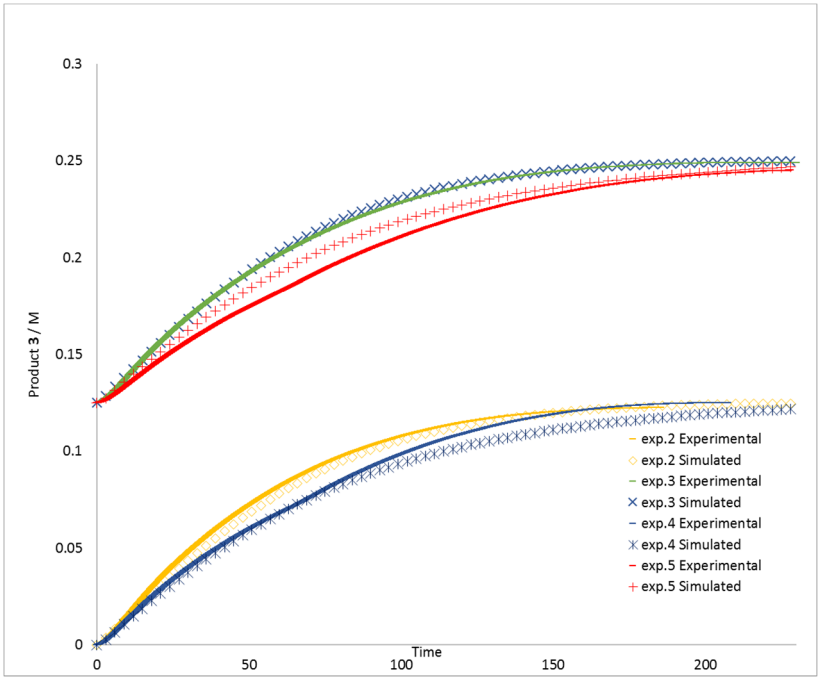


Figure S9. Experimental and simulated data for 'same excess' experiments. See Table 1 for reaction conditions.

5 References

1. M. D. K. Boele, G. P. F. van Strijdonck, A. H. M. de Vries, P. C. J. Kamer, J. G. de Vries and P. W. N. M. van Leeuwen, *J. Am. Chem. Soc.* 2002, **124**, 1586-1587.
2. K. J. Laidler, *Chemical Kinetics*, Harper & Row, New York, 3rd ed., 1987
3. D. G. Blackmond, *J. Am. Chem. Soc.* 2015, **137**, 10852-10866.
4. D. G. Blackmond, *Angew. Chem. Int. Edit.*, 2005, **44**, 4302-4320.
5. P. Job, *Ann. Chim*. 1928, **9**, 113.
6. J. S. Renny, L. L. Tomasevich, E. H. Tallmadge and D. B. Collum, *Angew. Chem. Int. Ed.* 2013, **52**, 11998-12013.