

Supplementary Materials for

A platform for automated nanomole-scale reaction screening and micromole-scale synthesis in flow

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Supplementary Text
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Other Supplementary Materials for this manuscript include the following:
(available at www.sciencemag.org/content/359/6374/429/suppl/DC1)

Data File S1

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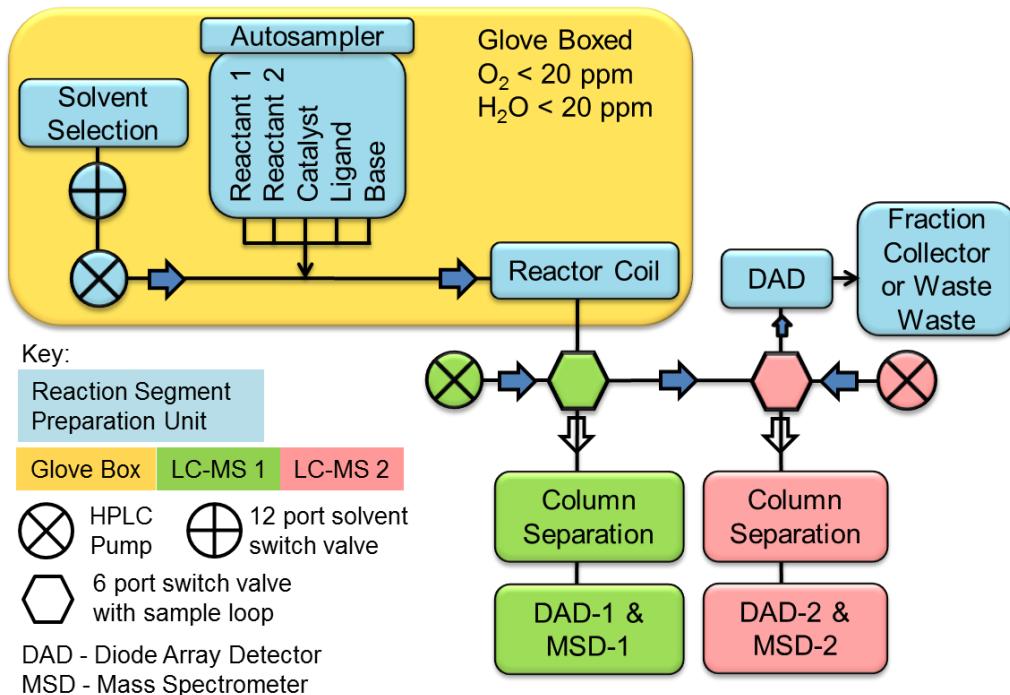
Materials and Methods

Starting materials and other reagents were purchased from commercial suppliers and were used without further purification unless otherwise indicated. All reactions were performed under a positive pressure of nitrogen, argon, or with a drying tube, at ambient temperature (unless otherwise stated), in anhydrous solvents, unless otherwise indicated. Analytical thin-layer chromatography was performed on glass-backed Silica Gel 60_F 254 plates (Analtech (0.25 mm)) and eluted with the appropriate solvent ratios (v/v). The reactions were assayed by high-performance liquid chromatography/mass spectrometry (LC-MS) or thin-layer chromatography (TLC) and terminated as judged by the consumption of starting material. The TLC plates were visualized by UV, phosphomolybdic acid stain, or iodine stain. Microwave assisted reactions were run in a Biotage Initiator. ^1H NMR spectra were recorded on a Bruker instrument operating at 400 MHz unless otherwise indicated. ^1H NMR spectra are obtained as $\text{DMSO}-d_6$ or CDCl_3 solutions as indicated (reported in ppm), using chloroform as the reference standard (7.25 ppm) or $\text{DMSO}-d_6$ (2.50 ppm). Other NMR solvents were used as needed. When peak multiplicities are reported, the following abbreviations are used: s = singlet, d = doublet, t = triplet, m = multiplet, br = broadened, dd = doublet of doublets, dt = doublet of triplets. Coupling constants, when given, are reported in hertz. The mass spectra were obtained using liquid chromatography mass spectrometry (LC-MS) on an Agilent instrument using atmospheric pressure chemical ionization (APCI) or electrospray ionization (ESI). High resolution mass measurements were carried out on an Agilent TOF 6200 series with ESI. All test compounds showed > 95% purity as determined by combustion analysis or by high-performance liquid chromatography (HPLC) unless otherwise stated. HPLC

conditions uses a 0.1% AcOH/NH₄COOH/Water based gradient over 1.4 minutes running from 5-95% MeCN using a Waters Acquity UPLC BEH C18 30 x 2.1 mm column at 80 °C with a flow rate of 2.5ml/min and a detection wavelength of 210-360nm. 1µL injections were made directly and ionization monitored in ES+ positive mode.

Flow technology for HTE screening – System configuration

Fig. S1. Schematic representation of the flow system



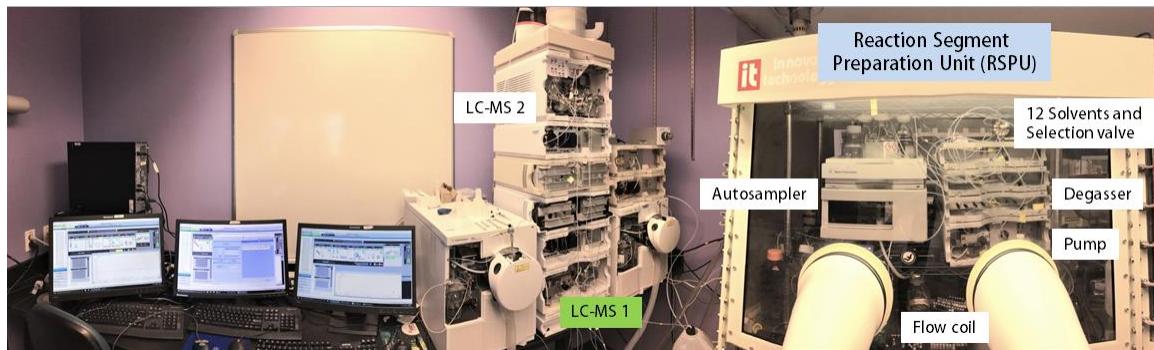
Instrumentation

The instrument used in the study comprised with three key components featuring a reaction segment preparation unit (RSPU), and two LC-MS instruments (LC-MS 1 and LC-MS 2).

The RSPU comprises of an Agilent 1100 Infinity HPLC system (Agilent, Palo Alto, CA, USA) featuring a DAD (G1315), quaternary pump (G1311), two degassers (G1322A), a 12 port valve (G1160), Hip autosampler (G1367), mass directed isolation capabilities and a UIB II (G1390). The autosampler, which was equipped with a 100 μ L syringe, degassers, quaternary pump, and 12 port valve were kept inside the glove box (< 20 ppm O₂, < 20 ppm H₂O) (Inert Innovative Technologies, Boston, MA).

Both LC-MS 1 and LC-MS 2 are identical Agilent 1200 Infinity HPLC systems consisting of a single quadrupole 6140 LC/MSD with an ESI source, a DAD (G1315), binary pump (G4220), column compartment (G1316) Data analysis was performed using Agilent 32-bit ChemStation™ software (Version C.01.07) (37) and iChemExplorer (38) prior to export and visualization with Spotfire (39).

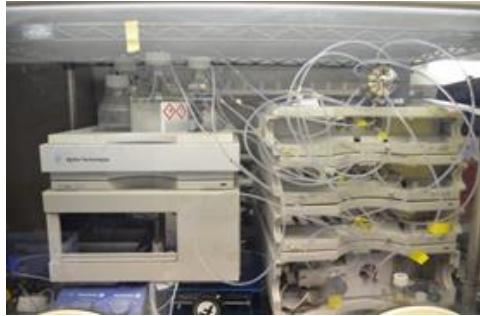
Fig. S2. Photographic representation of the whole system



The photograph shows a panoramic representation of the whole system as described in the above paragraphs. Looking from right to left, the three computers control the two UPLC/MS systems (depicted as LC-MS 1 and LC-MS 2), with the third system

coordinating control of the RSPU for segment preparation, injection, queueing, and overall run control. The two UPLC/MS systems are shown to the right, and are external to the glovebox with the central stack splitting and directing the flow to the waiting LC-MS *etc* as described in the text. Within the glove-box, the central RSPU makes up the prescribed segments (for detail see below) for injection into the flowing solvent stream (driven by the quaternary pump), which flows in a continuous manner through the flow coil.

Fig. S3. Photographic representation of the RSPU/quaternary pump set-up



Situated in the glovebox, the unit on the left features the pumps and the degasser units. One pump passes through the solvent selection valve (shown at the top of the stack, and described in more detail in Fig. S6) prior to mixing with the output from a second pump, allowing binary solvent mixtures to be evaluated in the system. In the Suzuki-Miyaura described within the main text, this enables varying organic solvents to be evaluated in constant mixtures with water, which helps with solubilization of the inorganic bases utilized as well as facilitates the hydrolysis of the boron-based electrophiles utilized. On the left herein is the RSPU (described in more detail in Fig. S4).

Fig. S4. Photographic representation of the RSPU



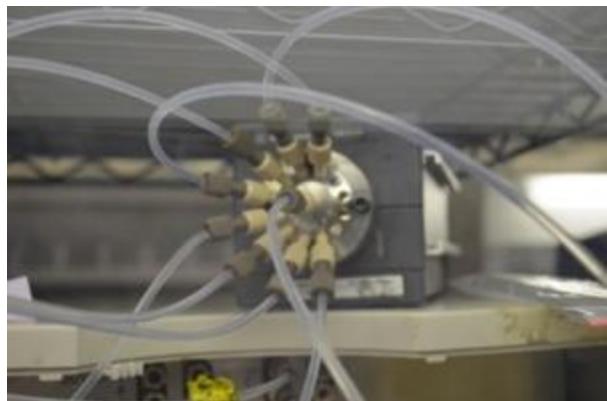
The standard Agilent autosampler set-up is capable of handling a range of configurations in terms of plate set-up. In the current report, we have focused on utilizing 2 x 96 well plates, but have also demonstrated the ability to handle both 24 and 384 well plates within our current system. The Chemstation software controls the preparation of the segments with the autoinjector capable of very accurate dosing between 0.5 – 100 µL. Note that the vials utilize a micro-stir bar thus enabling the stock solutions to be agitated and heated throughout the process and a crimp seal cap to limit evaporation.

Fig. S5. Photographic representation of the flow coil



The schematic on the left hand side shows a cutaway representation (top plate removed for clarity to show the reactor coil) of a similar reaction coil to the one used in the experiments described herein (0.5 mm i.d., 710 µL internal volume) (40). The coil shown is manufactured from copper, whereas the one used in our experiments is made from Hastelloy. These coils were originally designed for use with the Accendo Conjure flow reactor (11), and their utility has previously been described in reports from this laboratory. On the right, the actual experimental set-up is shown with the coil placed on an IKA stirrer/hotplate to enable the reaction to be heated. The input stream to the coil can be seen at the front of the photograph, and the temperature probe for the hotplate is shown contacting the top plate of the reactor coil. Although these Accendo reactor coils were used herein, the versatility of the system does allow a range of flow-based reactors to be used based on a simple plug/play design.

Fig. S6. Photographic representation of the solvent selection valve



As shown in Fig. S3, this is positioned at the top of the quaternary pump/degasser stack. This is capable of allowing a total of 12 inputs (organic solvent selection) with one output. The output from the valve makes up the composition of Pump A in defining the continuum of the reaction solvent in the experiments under investigation (in the current study, 90% of component A is combined with 10% aqueous – component B, though as noted in the main text, the use of component B is not mandatory).

General experimental methods

The general method typically follows the steps summarized in table S1, with the implicit details for each step provided in the following text.

Table S1. General Experimental Method

Step	Description
1	Preparation of stock solutions under an inert atmosphere and then load them to the plate in the autosampler of the Reaction Segment Preparation Unit (RSPU) (Fig. S4).
2	Load sequence tables and methods to RSPU, LC-MS 1 and LC-MS 2 to Agilent ChemStation software.
3	Start the run and RSPU will start creating segments at 45 sec intervals. Meanwhile, LCMS-1 and LCMS-2 will wait for the segments to reach the analysis.
4	Reaction segments were run with a flow rate of 1 mL/min through a Hastelloy coil heated to 100 °C and having a residence time of 1 min at 100 bar.
5	On exiting the reactor, the segment will reach the 6 port switch value of LCMS-1 and the filled 5uL loop is switched into LCMS-1 whilst the remainder will flow past LCMS-2 and eventually to the fraction

	collector or waste (Fig. S8).
6	LCMS-1 will be running the first segment that was loaded to the sample loop with UV/MS and record data in the assigned space as detailed in the sequence table.
7	Meanwhile LC-MS 2 will be waiting for the 2nd segment to reach it and once it does it follows step 5 & 6.
8	Once the first segment analysis has finished LC-MS 1 proceeds to the next line in the sequence table to await the third segment. These iterations continue with LC-MS 1 evaluating the odd-numbered segments, and LC-MS 2 evaluating the even-numbers.
9	Steps 3-8 will be repeated automatically without user supervision until RSPU, LC-MS 1 and LC-MS 2 reach the end of the sequence table.
10	Data was then analyzed in batch mode using Agilent ChemStation and iChemExplorer (<i>I</i>) with visualization and manipulation of the data carried out in Spotfire.

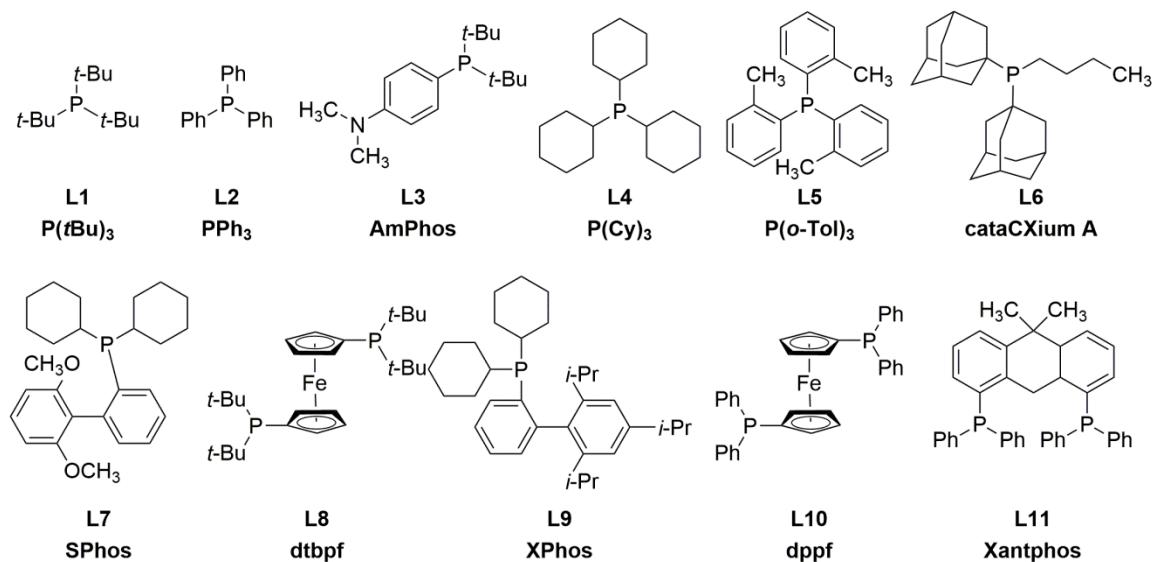
Detailed description of steps in Table S1

Step 1

Stock solutions of each component (reactants, ligands, bases and Pd source) were made up in vials (Thermo Scientific 8 x 30 vials with micro/stirbar – Part no. C4008-1SB. 8 mm seals part no. 201 876) inside the glove box ($\text{H}_2\text{O} < 20 \text{ ppm}$ and $\text{O}_2 < 20 \text{ ppm}$) and placed in the 96 well plate in the following format shown in Fig. S4. The ligands that

were used in the study are shown in Fig. S7. Note : Though we used 96 well plate to load the samples into autosampler in our reported study here, we have also validated the system in experiments with both experimented with 24 and 384 well plates.

Fig. S7 – Ligands used in the reported Suzuki-Miyaura reaction optimization



Step 2-4

With the goal to run 1536 reactions at once, our sequence tables were prepared to fulfill this requirement. The RSPU sequence table (see Fig. S12) had 1537 (one reaction as a blank) lines, with 769 (first reaction as blank for LC-MS 1 whereas the first two reactions are blank for LC-MS 2) lines for both LC-MS 1 and LC-MS 2 (see Fig. S10). It should be noted that we changed the sequence table to 96 and 384 based on the desired number of reactions we wanted to explore. Typically we added ligand (12 variables) to the sequence table and created 8 different methods to accommodate 8 bases we had. A typically used

method and injector program that instructs the autosampler to draw and inject the reaction components are shown in Figs. S11 and S13.

UPLC-MS Analysis

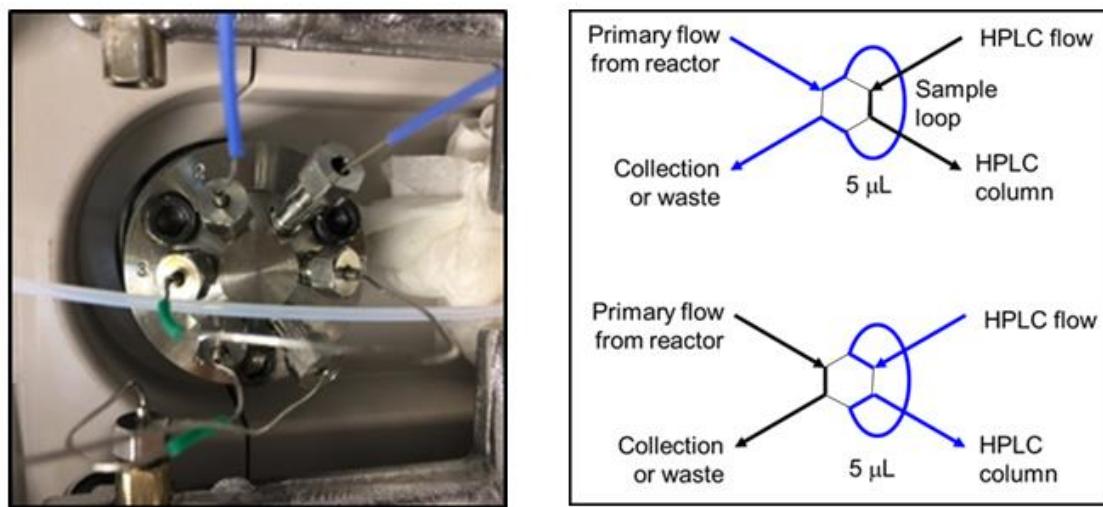
LC-MS analysis uses a 0.1% AcOH/NH₄COOH/Water based gradient over 1.4 minutes running from 5-95% MeCN using a Waters Acquity UPLC BEH C18 30 x 2.1 mm column at 80 °C with a flow rate of 2.5ml/min and a detection wavelength of 210-360nm. 5µL injections were made directly and ionization monitored in ES+ positive mode.

Once the run started RSPU will continue to generate reactions/segments as instructed in the method and in the sequence table while LC-MS 1 and LC-MS 2 will be waiting for analysis.

Steps 5-10

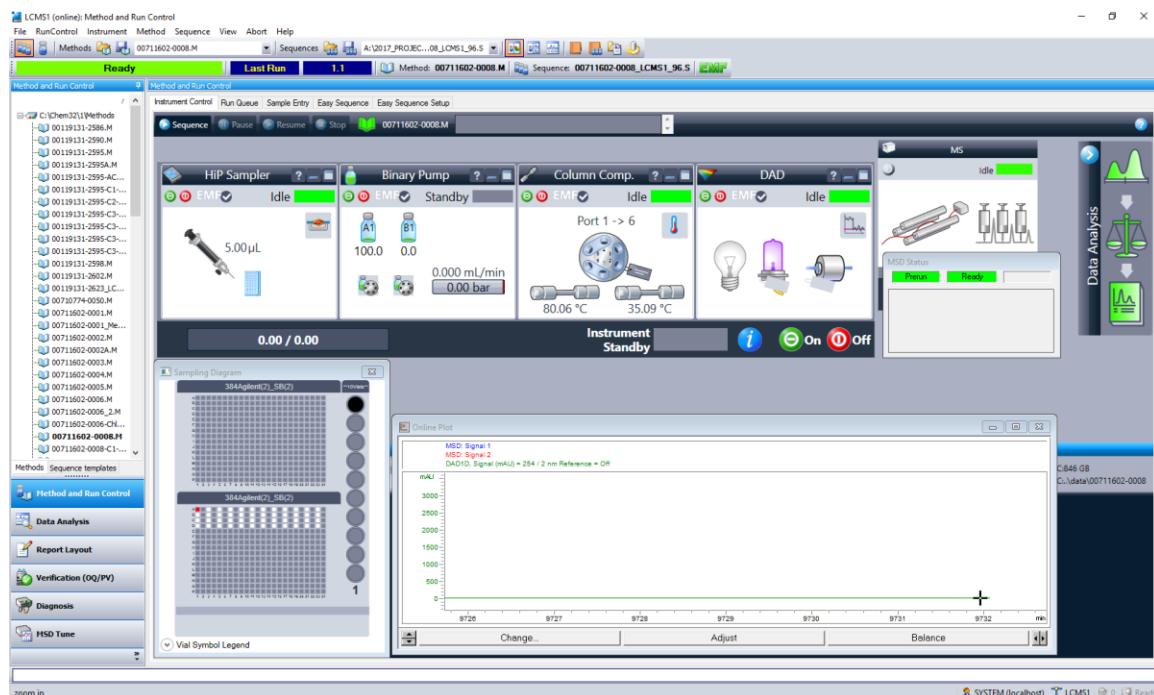
On exiting the reactor, the segment will reach the 6 port switch value of LCMS-1 and the filled 5uL loop is switched into LCMS-1 whilst the remainder will flow past LCMS-2 and eventually to the fraction collector or waste (Fig. S8). Similarly, the second segment will onto LC-MS 2 (as the LC-MS 1 is in analysis mode) This process will continue automatically as directed by individual sequence tables of each instrument until it reaches the end. The data was recorded for each reaction based on the sequence table and further analyzed through batch analysis in Agilent ChemStation before being processed by iChemExplorer, and visualized via Spotfire.

Fig. S8. Six port valve set-up



Photograph and schematic shows the set-up of the six way valve described in the previous paragraph. Note that the flow system sends the signal to trigger valve rotations directing the segments to the appropriate LC-MS system.

Fig. S9. Screenshot of Chemstation utilized by LC-MS 1 and LC-MS 2



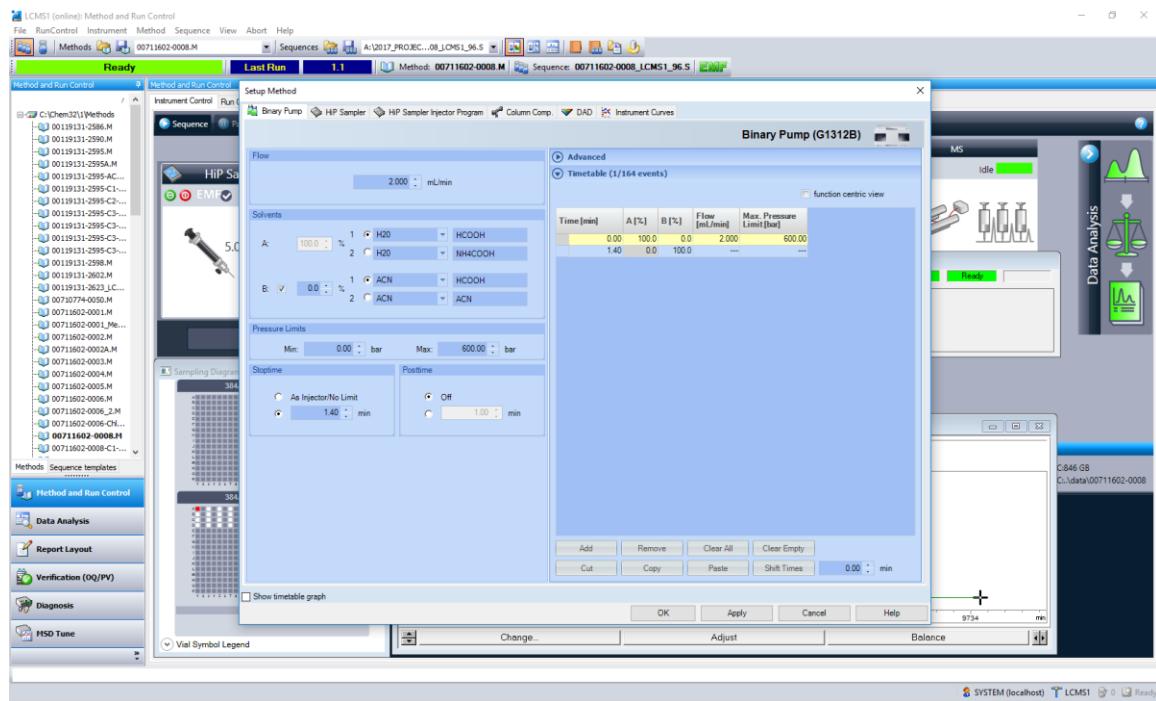
This is a screenshot from the standard Chemstation set-up showing the various components in place within the system.

Fig. S10. Screenshot of Sequence Table for LC-MS 1 and LC-MS 2

Line	Sample Container	Sample	Sample Name	Method Name	Injection Source	Injection Vol...	Inj/Loc	Data File	Target Mass
1	Use Current Configuration	-	10	00711602-0008	As Method	-	1		
2	Use Current Configuration	-	P1-A1	00711602-0008_2min_100C	As Method	-	1		
3	Use Current Configuration	-	P1-A3	00711602-0008_2min_100C	As Method	-	1		
4	Use Current Configuration	-	P1-A5	00711602-0008_2min_100C	As Method	-	1		
5	Use Current Configuration	-	P1-A7	00711602-0008_2min_100C	As Method	-	1		
6	Use Current Configuration	-	P1-A9	00711602-0008_2min_100C	As Method	-	1		
7	Use Current Configuration	-	P1-A11	00711602-0008_2min_100C	As Method	-	1		
8	Use Current Configuration	-	P1-A13	00711602-0008_2min_100C	As Method	-	1		
9	Use Current Configuration	-	P1-A15	00711602-0008_2min_100C	As Method	-	1		
10	Use Current Configuration	-	P1-A17	00711602-0008_2min_100C	As Method	-	1		
11	Use Current Configuration	-	P1-A19	00711602-0008_2min_100C	As Method	-	1		
12	Use Current Configuration	-	P1-A21	00711602-0008_2min_100C	As Method	-	1		
13	Use Current Configuration	-	P1-A23	00711602-0008_2min_100C	As Method	-	1		
14	Use Current Configuration	-	P1-B1	00711602-0008_2min_100C	As Method	-	1		
15	Use Current Configuration	-	P1-B3	00711602-0008_2min_100C	As Method	-	1		
16	Use Current Configuration	-	P1-B5	00711602-0008_2min_100C	As Method	-	1		
17	Use Current Configuration	-	P1-B7	00711602-0008_2min_100C	As Method	-	1		
18	Use Current Configuration	-	P1-B9	00711602-0008_2min_100C	As Method	-	1		
19	Use Current Configuration	-	P1-B11	00711602-0008_2min_100C	As Method	-	1		
20	Use Current Configuration	-	P1-B13	00711602-0008_2min_100C	As Method	-	1		
21	Use Current Configuration	-	P1-B15	00711602-0008_2min_100C	As Method	-	1		
22	Use Current Configuration	-	P1-B17	00711602-0008_2min_100C	As Method	-	1		
23	Use Current Configuration	-	P1-B19	00711602-0008_2min_100C	As Method	-	1		
24	Use Current Configuration	-	P1-B21	00711602-0008_2min_100C	As Method	-	1		
25	Use Current Configuration	-	P1-C23	00711602-0008_2min_100C	As Method	-	1		
26	Use Current Configuration	-	P1-C1	00711602-0008_2min_100C	As Method	-	1		
27	Use Current Configuration	-	P1-C3	00711602-0008_2min_100C	As Method	-	1		
28	Use Current Configuration	-	P1-C5	00711602-0008_2min_100C	As Method	-	1		
29	Use Current Configuration	-	P1-C7	00711602-0008_2min_100C	As Method	-	1		
30	Use Current Configuration	-	P1-C9	00711602-0008_2min_100C	As Method	-	1		
31	Use Current Configuration	-	P1-C11	00711602-0008_2min_100C	As Method	-	1		
32	Use Current Configuration	-	P1-C13	00711602-0008_2min_100C	As Method	-	1		
33	Use Current Configuration	-	P1-C15	00711602-0008_2min_100C	As Method	-	1		
34	Use Current Configuration	-	P1-C17	00711602-0008_2min_100C	As Method	-	1		
35	Use Current Configuration	-	P1-C19	00711602-0008_2min_100C	As Method	-	1		
36	Use Current Configuration	-	P1-C21	00711602-0008_2min_100C	As Method	-	1		
37	Use Current Configuration	-	P1-C23	00711602-0008_2min_100C	As Method	-	1		
38	Use Current Configuration	-	P1-D1	00711602-0008_2min_100C	As Method	-	1		
39	Use Current Configuration	-	P1-D3	00711602-0008_2min_100C	As Method	-	1		
40	Use Current Configuration	-	P1-D5	00711602-0008_2min_100C	As Method	-	1		
41	Use Current Configuration	-	P1-D7	00711602-0008_2min_100C	As Method	-	1		

This shows the sequence table for LC-MS 1 starting with a blank run. Note, the sequence table for LC-MS 2 is slightly different, and will start with two as opposed to one blank in order to stagger the instruments. LC-MS 1 runs the odd segments (A1, A3, A5...etc), whilst LC-MS 2 runs the even segments (A2, A4, A6....).

Fig. S11. Screenshot of Method Setup for LC-MS 1



This screenshot details the LC-MS method used for analysis of the segments. As stated previously, specifically this analysis uses a 0.1% AcOH/NH₄COOH/Water based gradient over 1.4 minutes running from 5-95% MeCN using a Waters Acuity UPLC BEH C18 30 x 2.1mm column at 80 °C with a flow rate of 2.5ml/min and a detection wavelength of 210-360nm. 5µL injections were made directly and ionization monitored in ES+ positive mode.

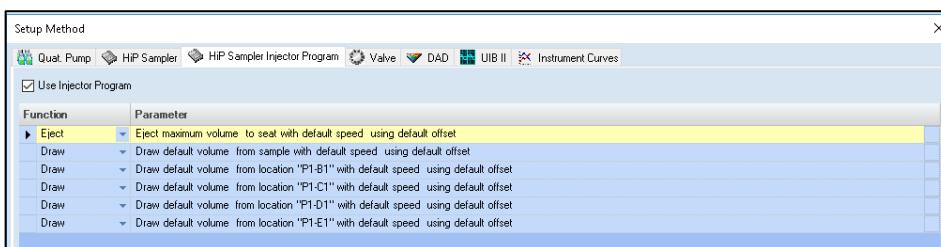
Fig. S12. Screenshot of the Sequence Table for the RSPU

Line	Sample Con.	Sample Location	Sample Name	Method Name	Injection Source	Injection Volume	Inj/Loc	Data File	Target Mass
1	Use Curr.	P1-A1	00711602-0008_P1B1_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
2	Use Curr.	P1-A1	00711602-0008_P1B1_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
3	Use Curr.	P1-A2	00711602-0008_P1B1_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
4	Use Curr.	P1-A3	00711602-0008_P1B1_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
5	Use Curr.	P1-A4	00711602-0008_P1B1_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
6	Use Curr.	P1-A5	00711602-0008_P1B1_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
7	Use Curr.	P1-A6	00711602-0008_P1B1_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
8	Use Curr.	P1-A7	00711602-0008_P1B1_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
9	Use Curr.	P1-A8	00711602-0008_P1B1_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
10	Use Curr.	P1-A9	00711602-0008_P1B1_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
11	Use Curr.	P1-A10	00711602-0008_P1B1_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
12	Use Curr.	P1-A11	00711602-0008_P1B1_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
13	Use Curr.	P1-A12	00711602-0008_P1B1_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
14	Use Curr.	P1-A1	00711602-0008_P1B1_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
15	Use Curr.	P1-A2	00711602-0008_P1B1_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
16	Use Curr.	P1-A3	00711602-0008_P1B1_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
17	Use Curr.	P1-A4	00711602-0008_P1B1_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
18	Use Curr.	P1-A5	00711602-0008_P1B1_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
19	Use Curr.	P1-A6	00711602-0008_P1B1_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
20	Use Curr.	P1-A7	00711602-0008_P1B1_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
21	Use Curr.	P1-A8	00711602-0008_P1B1_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
22	Use Curr.	P1-A9	00711602-0008_P1B1_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
23	Use Curr.	P1-A10	00711602-0008_P1B1_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
24	Use Curr.	P1-A11	00711602-0008_P1B1_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
25	Use Curr.	P1-A12	00711602-0008_P1B1_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
26	Use Curr.	P1-A1	00711602-0008_P1B2_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
27	Use Curr.	P1-A2	00711602-0008_P1B2_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
28	Use Curr.	P1-A3	00711602-0008_P1B2_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
29	Use Curr.	P1-A4	00711602-0008_P1B2_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
30	Use Curr.	P1-A5	00711602-0008_P1B2_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
31	Use Curr.	P1-A6	00711602-0008_P1B2_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
32	Use Curr.	P1-A7	00711602-0008_P1B2_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
33	Use Curr.	P1-A8	00711602-0008_P1B2_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
34	Use Curr.	P1-A9	00711602-0008_P1B2_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
35	Use Curr.	P1-A10	00711602-0008_P1B2_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
36	Use Curr.	P1-A11	00711602-0008_P1B2_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
37	Use Curr.	P1-A12	00711602-0008_P1B2_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
38	Use Curr.	P1-A1	00711602-0008_P1B4_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
39	Use Curr.	P1-A2	00711602-0008_P1B4_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
40	Use Curr.	P1-A3	00711602-0008_P1B4_P1C1_P1D1_P1E1_AON_H	As Method	1	1			
41	Use Curr.	P1-A4	00711602-0008_P1B4_P1C1_P1D1_P1E1_AON_H	As Method	1	1			

This screenshot shows the segment preparation for the RSPU.

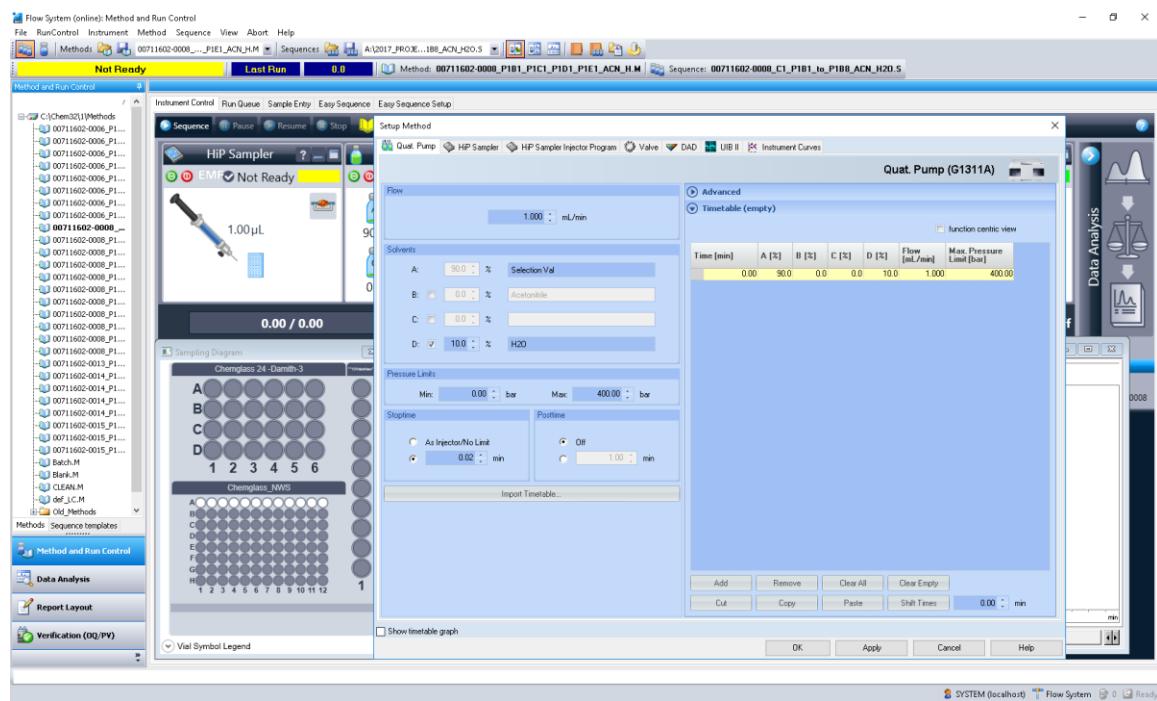
Fig. S13. Screenshot of Method Setup for RSPU showing the Injector Program

Utilized



This screenshot shows the injector program for the RSPU specifying how the components are injected into the system. Herein, the default location represents the ligands (Fig. S7), B1 (base), C1 and D1 (substrates) whilst E1 is Pd(OAc)₂.

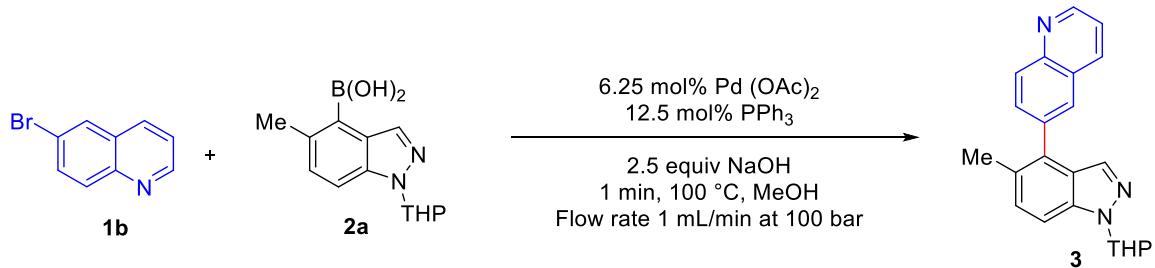
Fig. S14. Screenshot of Flow System Method Set-up



This screenshot shows the method set-up for the flow system allowing variation of the gradient and the residence time through adjustment of the flow rate. Herein, solvent A is the solvent coming from the solvent selection valve (Fig. S6), whereas solvent B is water.

Experimentals

Experiment 1. Validation of Four Component Mixing – Model Suzuki-Miyaura Reaction.

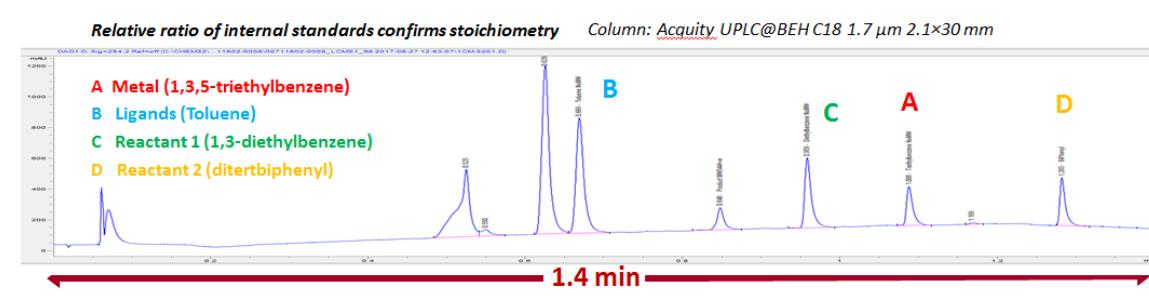


Stock solutions of each of the reaction components were made as follows: 6-bromoquinoline **1b** (0.4 M in 1,3-diethylbenzene), [5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl]boronic acid **2a**, (0.4 M in DMF, with 10 mg of internal standard, 4,4'-di-*tert*-butylbiphenyl added), Pd(OAc)₂ (0.025 M in 1,3,5-triethylbenzene), PPh₃ (**L2**, 0.05 M in toluene, Fig. S7), and NaOH (1M in water). The reaction was prepared by concurrent aspiration of 1 μL of these components according to the general method using the Agilent autosampler and injection into a flow stream of the reaction solvent, MeOH. The reaction segments were run with a flow rate of 1 mL/min through a Hastelloy coil heated to 100 °C leading to a residence time of 1 min at 100 bar. Once the segments passed through the reactor coil, the output was fractionated into a 96-well plate in 40 μL fractions. Each of the fractions was then analyzed *via* an off-line LC-MS utilizing a standard method that enables separation of each of the four aforementioned four internal standards (1,3-diethylbenzene, 4,4'-di-*tert*-butylbiphenyl, 1,3,5-triethylbenzene and toluene) (Fig. S15). The experiment was then repeated under exact conditions with the above mentioned stock solutions with injections of 2 μL, 4 μL, 8 μL

and 16 μL per component. The fractions were collected and analyzed as described previously with the results represented in Fig 2B in the main text, with the normalized data captured in Tables S2.

Note all reactions set-up and run in glove box at H_2O (<20 ppm) and O_2 (<20 ppm) control. In order to run all the reactions under similar conditions the draw speed of the liquid stocks was changed based on the number of microliters being injected. Typically, the draw speed for 1 μL injection/reaction is 60 $\mu\text{l}/\text{min}$ with it being changed to 120 $\mu\text{l}/\text{min}$ for a 2 μL injection/reaction etc.

Fig. S15 – Example of chromatogram obtained from fraction analysis indicating separation of internal standards utilized

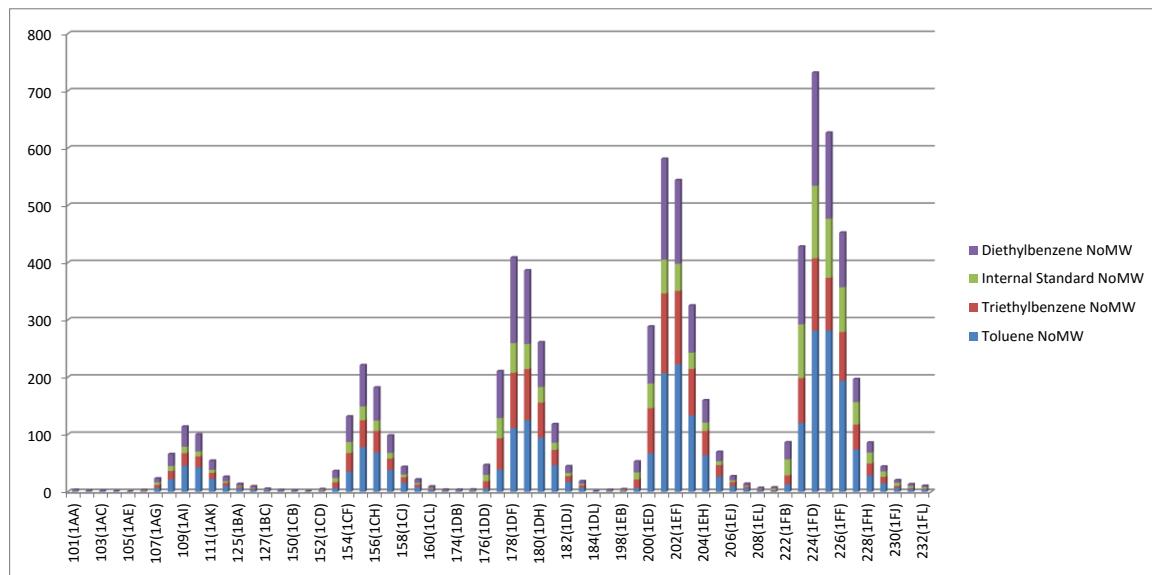


LC-MS analysis used a 0.1% AcOH/NH₄COOH/Water based gradient over 1.4 minutes running from 5-95% MeCN using a Waters Acquity UPLC BEH C18 30 x2.1 mm column at 80 °C with a flow rate of 2.5ml/min and a detection wavelength of 210-360nm. 1 μL injections were made directly and ionization monitored in ES+ positive mode.

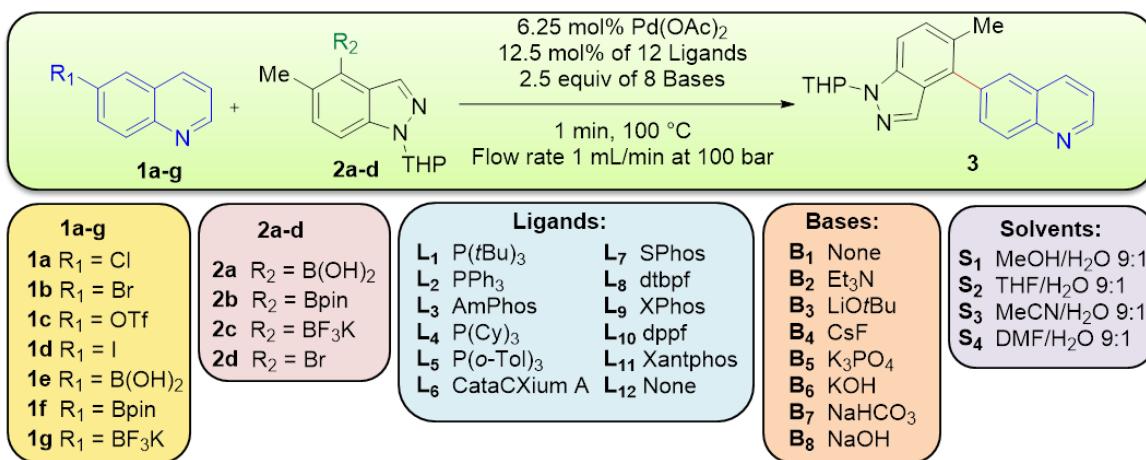
Table S2 – Normalized data for four component mixing experiment

Vial #	Fraction	Toluene	Triethylbenzene	1,4-di-tert -butyl-biphenyl	Diethylbenzene
101(1AA)	1				
102(1AB)	2				
103(1AC)	3				
104(1AD)	4				
105(1AE)	5	1 uL injections			
106(1AF)	6				
107(1AG)	7	24.16497089	22.76144449	34.71122142	18.36236321
108(1AH)	8	29.63769926	23.11078131	25.80554152	21.44597791
109(1AI)	9	37.45064711	21.04278684	19.91912617	21.58743988
110(1AJ)	10	40.80788205	20.67105464	17.60342938	20.91763393
111(1AK)	11	39.02503445	21.05714753	19.12910496	20.78871306
112(1AL)	12	36.69036536	22.0950619	20.52277373	20.691799
125(1BA)	13				
126(1BB)	14				
127(1BC)	15				
149(1CA)	16				
150(1CB)	17				
151(1CC)	18				
152(1CD)	19	2 uL injections			
153(1CE)	20				
154(1CF)	21	24.04973819	25.07526781	28.37179905	22.50319495
155(1CG)	22	32.85634688	22.71301194	21.83791877	22.59272241
156(1CH)	23	35.54731888	22.22846401	19.99554398	22.22867312
157(1CI)	24	36.14606799	21.91732419	20.3250992	21.61150863
158(1CJ)	25	34.29019022	22.41600782	22.40958317	20.88421878
159(1CK)	26				
160(1CL)	27				
173(1DA)	28				
174(1DB)	29				
175(1DC)	30	4 uL injections			
176(1DD)	31				
177(1DE)	32	16.31353334	26.30548653	31.83548506	25.54549506
178(1DF)	33N	25	25	25	25
179(1DG)	34	29.96139059	24.62168021	22.51092317	22.90600602
180(1DH)	35	33.61429405	24.89399013	20.8989936	20.59272222
181(1DI)	36	36.25099498	23.90089108	21.06310005	18.78501389
182(1DJ)	37				
183(1DK)	38				
184(1DL)	39				
197(1EA)	40				
198(1EB)	41	8 uL injections			
199(1EC)	42				
200(1ED)	43	20.71555325	27.92821298	28.49812265	22.85811111
201(1EE)	44	33.18196041	25.56800419	20.27458005	20.97545534
202(1EF)	45	38.38888918	25.37322181	17.48902404	18.74886496
203(1EG)	46	38.2171995	26.68460842	17.55846992	17.53972215
204(1EH)	47	36.97164973	28.1312285	18.11592346	16.78119832
205(1EI)	48				
206(1EJ)	49				
207(1EK)	50				
208(1EL)	51				
221(1FA)	52	16 uL injections			
222(1FB)	53				
223(1FC)	54	23.41542208	17.55426956	39.33266429	19.69764407
224(1FD)	55	33.30224427	17.11987153	32.20424474	17.37363945
225(1FE)	56	39.11216281	14.6850998	30.69021104	15.51252635
226(1FF)	57	36.52936531	18.4566832	31.63727726	13.37667423
227(1FG)	58	30.9921059	21.11185697	35.30979418	12.58624296
228(1FH)	59				
229(1FI)	60				
230(1FJ)	61				
231(1FK)	62				
232(1FL)	63				

Fig. S16 – Barchart data analysis of normalized fractions (see also Fig. 2B)



Experiment 2. Model Suzuki-Miyaura cross-coupling electrophiles 1a-d/2d with 2a-c/1e-g evaluated across a matrix of 11 ligands (plus one blank) x 7 bases (plus one blank) x 4 solvents (5760 reactions).



(I) Suzuki-Miyaura cross-coupling electrophiles **1a-d with **2a-c** evaluated across a matrix of **11** ligands (plus one blank) x **7** bases (plus one blank) x **4** solvents (**4608** reactions.**

Stock solutions of each of the reaction components were made as follows: **1a-1c** (0.4 M in 1,3-diethylbenzene), **2a-2c** (with added internal standard, 4,4'-di-*tert*-butylbiphenyl 0.4 M in DMF), Pd(OAc)₂ (0.025 M in 1,3,5-triethylbenzene), ligands **L1-L11** (0.05 M in toluene, Fig. S7, plus a toluene blank), and bases (**B1-B8**, namely a water blank; Et₃N 1M in THF; LiOtBu 1M in hexane; CsF, K₃PO₄, KOH NaHCO₃, NaOH 1M in water).

Matrix of reactions:

1536 Reactions:

1a-1d, **2a**, Pd(OAc)₂, ligand (**L1-L11**, and blank toluene), base (**B1-B8**, and H₂O as blank) against 4 solvents (MeOH, THF, MeCN, DMF; 9:1 with solvent: H₂O)

The reactions were prepared by concurrent aspiration of 1 µL of these components as described in the general method using an Agilent autosampler and injection into a flow stream of the reaction solvent (MeOH, THF, MeCN, DMF; 9:1 with solvent: H₂O). Using a particular reaction solvent, the reaction segments were run with a flow rate of 1 mL/min through a Hastelloy coil heated to 100 °C and having a residence time of 1 min at 100 bar. The total run time for 1536 reactions was about 24 hours and it took *ca.* 2 hours for analysis of the data. Similarly the rest of the 1536 data sets with **2b** and **2c** were carried out. (It should be noted that after continuous 1536 data set obtained for **2a** with

electrophiles **1a-1d**, the remainder of the data was acquired in either sets of 96 or 384 reactions that were queued into a sequence to facilitate real time processing and analysis of the data).

(II) Suzuki-Miyaura cross-coupling electrophiles **1e-1g with **2d** evaluated across a matrix of 11 ligands (plus one blank) x 7 bases (plus one blank) x 4 solvents (1152 reactions.**

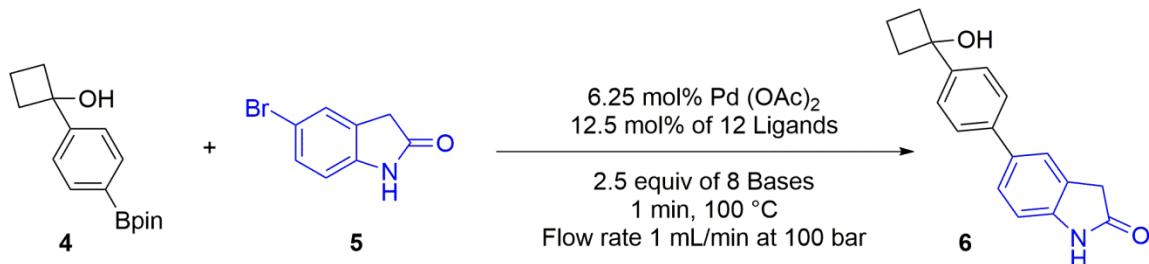
Stock solutions of each of the reaction components were made as follows: **1e**, **1g** (0.4 M in H₂O), **1f** (with added internal standard, 4,4'-di-*tert*-butylbiphenyl 0.4 M in DMF) **2d** (0.4 M in 1,3-diethylbenzene), Pd(OAc)₂ (0.025 M in 1,3,5-triethylbenzene), ligands **L1-L11** (0.05 M in toluene, Fig. S7, with a toluene blank), and bases (**B1-B8**, namely a water blank; Et₃N 1M in THF; LiOtBu 1M in hexane; CsF, K₃PO₄, KOH NaHCO₃, NaOH 1M in water). The reactions were prepared by concurrent aspiration of 1 μL of these components as described in the general method using Agilent autosampler and injection into a flow stream of the reaction solvent (MeOH, THF, MeCN, DMF; 9:1 with solvent: H₂O). Using particular reaction solvent, the reaction segments were run with a flow rate of 1 mL/min through a Hastelloy coil heated to 100 °C and having a residence time of 1 min at 100 bar.

Detailed results can be found in the attached Adobe PDF of MS Excel Results Spreadsheet with representative data shown in Table S3. *Yield is based on LC/MS %.*
Area UV data only.

Table S3. Representative Data for the first 100 reactions (full data in data file S1)

	A	F	J	K	S	Y	AY	BC	BN	BR	BS	CC	CG	DG	EG	EH
	Reactant_1_No	Reactant_1_Short_Hand	Reactant_1_nt_1_q	Reactant_1_mmol	Reactant_2_Name	Reactant_t_2_eq	Catalyst_1_Short_Hand	Catalyst_1_eq	Catalyst_2_Short_Hand	Catalyst_2_e_q	Catalyst_2_mmol	Reagent_1_Short_Hand	Reagent_1_nt_1_q	Solvent_1_Short_Hand	Product_Yield_PCT_Area_UV	Product_Yield_Mass_Ion_Count
1																
2	1	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	PtBu3	0.1250	0.00005	NaOH	2.5	MeCN	4.8	6262.1
3	2	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	PtPh3	0.1250	0.00005	NaOH	2.5	MeCN	4.1	13245.6
4	3	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	AmPhos	0.1250	0.00005	NaOH	1.5	MeCN	2.6	3009.2
5	4	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	PtCy3	0.1250	0.00005	NaOH	2.5	MeCN	4.4	30860.7
6	5	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	Pt-OtBu3	0.1250	0.00005	NaOH	2.5	MeCN	1.9	2486.3
7	6	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	CatCXum A	0.1250	0.00005	NaOH	2.5	MeCN	3.3	9592.5
8	7	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	SPhos	0.1250	0.00005	NaOH	2.5	MeCN	8.3	10343.1
9	8	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	dppf	0.1250	0.00005	NaOH	2.5	MeCN	7.5	951.4
10	9	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	XPhos	0.1250	0.00005	NaOH	2.5	MeCN	9.7	27256.2
11	10	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	dppf	0.1250	0.00005	NaOH	2.5	MeCN	14.3	7746.5
12	11	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	Xanthos	0.1250	0.00005	NaOH	2.5	MeCN	2.1	8918.7
13	12	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	None			NaOH	2.5	MeCN	17.1	81111.3
14	13	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	PtBu3	0.1250	0.00005	NaHC03	2.5	MeCN	3.2	4185.9
15	14	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	PtPh3	0.1250	0.00005	NaHC03	2.5	MeCN	4.8	12755.6
16	15	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	AmPhos	0.1250	0.00005	NaHC03	2.5	MeCN	2.5	2850.5
17	16	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	PtCy3	0.1250	0.00005	NaHC03	2.5	MeCN	5.3	35597.2
18	17	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	Pt-OtBu3	0.1250	0.00005	NaHC03	1.5	MeCN	2.0	2606.6
19	18	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	CatCXum A	0.1250	0.00005	NaHC03	1.5	MeCN	3.3	11110.4
20	19	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	SPhos	0.1250	0.00005	NaHC03	2.5	MeCN	69.2	80639.8
21	20	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	dtbf	0.1250	0.00005	NaHC03	2.5	MeCN	5.1	6992.3
22	21	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	XPhos	0.1250	0.00005	NaHC03	2.5	MeCN	83.2	93978.7
23	22	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	ddpf	0.1250	0.00005	NaHC03	2.5	MeCN	1.5	7745.9
24	23	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	Xanthos	0.1250	0.00005	NaHC03	1.5	MeCN	1.8	511.7
25	24	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	None			NaHC03	1.5	MeCN	11.0	49532.0
26	25	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	PtBu3	0.1250	0.00005	CsF	1.5	MeCN	1.8	3386.8
27	26	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	PtPh3	0.1250	0.00005	CsF	2.5	MeCN	4.4	14015.8
28	27	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	AmPhos	0.1250	0.00005	CsF	2.5	MeCN	2.7	40016.1
29	28	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	PtCy3	0.1250	0.00005	CsF	2.5	MeCN	6.5	37162.7
30	29	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	Pt-OtBu3	0.1250	0.00005	CsF	2.5	MeCN	2.1	2770.5
31	30	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	CatCXum A	0.1250	0.00005	CsF	2.5	MeCN	3.3	9690.6
32	31	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	SPhos	0.1250	0.00005	CsF	1.5	MeCN	68.4	77144.4
33	32	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	dtbf	0.1250	0.00005	CsF	2.5	MeCN	5.8	6066.0
34	33	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	XPhos	0.1250	0.00005	CsF	2.5	MeCN	73.0	83146.1
35	34	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	ddpf	0.1250	0.00005	CsF	2.5	MeCN	13.2	4335.3
36	35	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	Xanthos	0.1250	0.00005	CsF	2.5	MeCN	2.1	517.9
37	36	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	None			CsF	2.5	MeCN	10.2	40248.3
38	37	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	PtBu3	0.1250	0.00005	K3PO4	1.5	MeCN	3.0	4320.0
39	38	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	PtPh3	0.1250	0.00005	K3PO4	1.5	MeCN	4.7	11853.5
40	39	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	AmPhos	0.1250	0.00005	K3PO4	2.5	MeCN	2.6	3671.1
41	40	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	PtCy3	0.1250	0.00005	K3PO4	2.5	MeCN	5.8	36076.5
42	41	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	Pt-OtBu3	0.1250	0.00005	K3PO4	2.5	MeCN	1.9	2827.8
43	42	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	CatCXum A	0.1250	0.00005	K3PO4	2.5	MeCN	3.7	10833.3
44	43	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	SPhos	0.1250	0.00005	K3PO4	2.5	MeCN	5.3	63071.2
45	44	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	dtbf	0.1250	0.00005	K3PO4	2.5	MeCN	5.8	5469.2
46	45	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	XPhos	0.1250	0.00005	K3PO4	2.5	MeCN	6.07	63192.9
47	46	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	ddpf	0.1250	0.00005	K3PO4	2.5	MeCN	14.4	3651.0
48	47	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	Xanthos	0.1250	0.00005	K3PO4	2.5	MeCN	2.3	700.2
49	48	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	None			K3PO4	2.5	MeCN	10.0	39301.8
50	49	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	PtBu3	0.1250	0.00005	KOH	2.5	MeCN	5.6	9067.9
51	50	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	PtPh3	0.1250	0.00005	KOH	2.5	MeCN	4.8	11866.1
52	51	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	AmPhos	0.1250	0.00005	KOH	2.5	MeCN	2.5	44.2
53	52	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	PtCy3	0.1250	0.00005	KOH	2.5	MeCN	6.5	3719.5
54	53	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	Pt-OtBu3	0.1250	0.00005	KOH	2.5	MeCN	2.1	3719.1
55	54	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	CatCXum A	0.1250	0.00005	KOH	2.5	MeCN	3.2	8883.8
56	55	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	SPhos	0.1250	0.00005	KOH	2.5	MeCN	7.84	90780.4
57	56	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	XPhos	0.1250	0.00005	KOH	2.5	MeCN	9.22	111091.5
58	57	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	ddpf	0.1250	0.00005	KOH	2.5	MeCN	14.2	7878.9
59	58	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	Xanthos	0.1250	0.00005	KOH	2.5	MeCN	2.3	1067.1
60	59	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	None			KOH	1.5	MeCN	18.2	67813.5
61	60	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	PtBu3	0.1250	0.00005	LiOBu	2.5	MeCN	5.6	9159.9
62	61	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	PtPh3	0.1250	0.00005	LiOBu	2.5	MeCN	5.8	91517.8
63	62	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	AmPhos	0.1250	0.00005	LiOBu	2.5	MeCN	9.8	9542.3
64	63	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	PtCy3	0.1250	0.00005	LiOBu	2.5	MeCN	9.28	102595.9
65	64	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	Pt-OtBu3	0.1250	0.00005	LiOBu	2.5	MeCN	15.4	6378.4
66	65	1a-6-Cl-Q	1.0	0.0004	2a, Boronic Acid	1.00	Pd(OAc)2	0.0625	CatCXum A							

Experiment 3. Model Suzuki-Miyaura cross-coupling of boronate 4 with electrophile 5 evaluated across a matrix of 11 ligands (plus one blank) x 7 bases (plus one blank) x 6 solvents (576 reactions).



Ligands:	Bases:	Solvents:
L1. P(<i>t</i> Bu) ₃	B ₁ None	S1. MeOH
L2. PPh ₃	B ₂ Et ₃ N	S2. MeOH/H ₂ O 9:1
L3. AmPhos	B ₃ LiOtBu	S3. DMF/H ₂ O 9:1
L4. P(Cy) ₃	B ₄ CsF	S4. DMF
L5. P(o-Tol) ₃	B ₅ K ₃ PO ₄	S5. THF/H ₂ O 9:1
L6. CataCXium A	B ₆ KOH	S6. TFE/H ₂ O 9:1
L7. SPhos	B ₇ NaHCO ₃	
L8. dtbpf	B ₈ NaOH	
L9. XPhos		
L10. dppf		
L11. Xantphos		
L12. None		

Stock solutions of each of the reaction components were made as follows: **4** (with added internal standard, 1,3-diethylbenzene 0.4 M in DMF), **5** (with added internal standard, 4,4'-di-*tert*-butylbiphenyl 0.4 M in DMF), Pd(OAc)₂ (0.025 M in 1,3,5-triethylbenzene), ligands **L1-L12** (0.05 M in toluene, Fig. S7, plus a toluene blank), and bases (**B1-B8**, namely a water blank; Et₃N 1M in THF; LiOtBu 1M in hexane; CsF, K₃PO₄, KOH NaHCO₃, NaOH 1M in water).

Matrix of reactions:

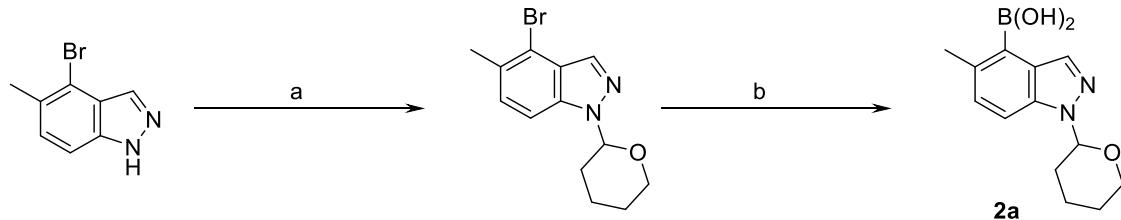
576 Reactions:

4, 5, Pd(OAc)₂, ligand (**L1-L11**, and blank toluene), base (**B1-B8**, and H₂O as blank) against 6 solvents (MeOH, MeOH/H₂O, DMF, DMF/H₂O, THF/H₂O, TFE/H₂O. All mixtures with water were in a ratio of 9:1)

The reactions were prepared by concurrent aspiration of 1 µL of these components as described in the general method using an Agilent autosampler and injection into a flow stream of the reaction solvent (MeOH, MeOH/H₂O, DMF, DMF/H₂O, THF/H₂O, TFE/H₂O. All mixtures with water were in a ratio of 9:1). Using a particular reaction solvent, the reaction segments were run with a flow rate of 1 mL/min through a Hastelloy coil heated to 100 °C and having a residence time of 1 min at 100 bar. The total run time for 576 reactions was about 8 hours and it took *ca.* 2 hours for analysis of the data. The processed data is represented in Fig. 5B in the main text.

Batch Chemistry Experiments

Experiment 4. Synthesis of [5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1*H*-indazol-4-yl]boronic acid, 2a



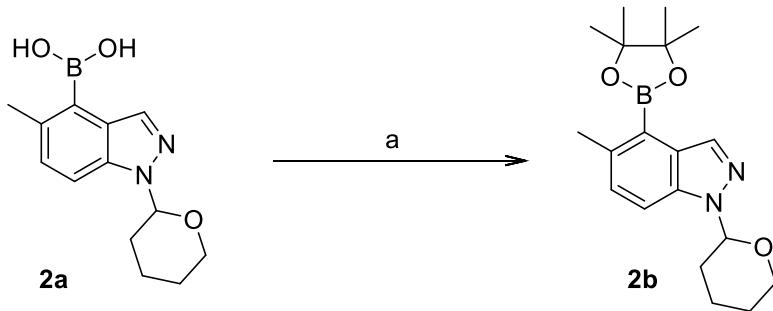
Reagents and conditions: (a) 3 eq. 3,4-dihydro-2*H*-pyran, 0.1 eq. PPTS, CH₂Cl₂, 35 °C, 20 h, 85%; (b) 2 eq. triisopropyl borate, 2 eq. *n*-BuLi (2.5 M in hexanes), THF, -70 °C, 4 h, 76%.

4-Bromo-5-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole ; To a stirred solution of 4-bromo-5-methyl-1*H*-indazole (800.0 g, 3.79 mol) in CH₂Cl₂ (12.0 L) was added 3,4-dihydro-2*H*-pyran (956.51 g, 11.37 mol) followed by PPTS (95.25 g, 0.379 mol) at room temperature. After the addition was completed, the reaction mixture was stirred at 35 °C for 20 hours. TLC (petroleum ether : EtOAc = 4 : 1) showed the starting material had been completely consumed. The mixture was diluted with H₂O (10 L) and CH₂Cl₂ (15 L). The aqueous layer was separated and extracted with CH₂Cl₂ (8.0 L). The combined organic layers were washed with brine (10 L), dried over Na₂SO₄, filtered and concentrated to afford the crude product, which was triturated with petroleum ether (5.0 L). The mixture was filtered, and the filter cake was washed with petroleum ether (1.0 L) to afford 4-bromo-5-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (950 g, 85%) as a colorless solid. ¹H NMR (400 MHz, CDCl₃) δ 7.98 (d, *J* = 6.8 Hz, 1 H), 7.44 (d, *J* = 8.8 Hz, 1 H), 7.98 (d, *J* = 9.2 Hz, 1 H), 5.67 (dd, *J* = 6.8, 2.8 Hz, 1 H), 4.02 – 3.98 (m, 1 H),

3.76 – 3.72 (m, 1 H), 2.55 – 2.49 (m, 1 H), 2.53 (s, 3 H), 2.19 – 2.04 (m, 2 H), 1.78 – 1.66 (m, 2 H); ^{11}B NMR (128 MHz, DMSO- d_6) 32.45.

[5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1*H*-indazol-4-yl]boronic acid (2a**);** To a stirred solution of 4-bromo-5-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (210.0 g, 711.44 mmol) and triisopropyl borate (267.61 g, 1.42 mol) in THF (2.0 L) cooled to - 70 °C was added in a dropwise manner *n*-BuLi (526.5 mL, 2.5 M in hexanes, 1.32 mol) over a period of 3 hours whilst maintaining the solution temperature between - 70 °C and - 65 °C. After the addition was completed, the reaction mixture was stirred at - 70 °C for 1 hour. TLC (petroleum ether : EtOAc = 4 : 1) indicated that the starting material had been completely consumed. The reaction mixture was quenched through the addition of saturated aqueous NH₄Cl solution (2.0 L), and diluted with MTBE (2.0 L). The aqueous layer was separated, and extracted with MTBE (1.0 L), and the combined organic layers washed with brine (1.5 L), dried over Na₂SO₄, filtered and concentrated *in vacuo* at 25 °C. The residue obtained was dissolved in MTBE (300 mL), and petroleum ether (1.2 L) was added in a dropwise manner to the solution at room temperature. During the addition, a white solid precipitated, which was filtered, washed with petroleum ether (800 mL) to afford [5-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-4-yl]boronic acid **2a** (280 g, 76%) as a colorless solid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.30 (S, 2 H), 7.90 (s, 1 H), 7.65 (d, *J* = 8.8 Hz, 1 H), 7.20 (d, *J* = 8.4 Hz, 1 H), 5.78 (dd, *J* = 7.2, 2.8 Hz, 1 H), 3.90 – 3.76 (m, 1 H), 3.74 – 3.72 (m, 1 H), 2.46 (s, 3 H), 2.43 – 2.40 (m, 1 H), 1.96 – 1.94 (m, 1 H), 1.93 – 1.91 (m, 1 H), 1.60 – 1.58 (m, 1 H), 1.57 – 1.56 (m, 1 H).

Experiment 5. Synthesis of 5-methyl-1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole, 2b

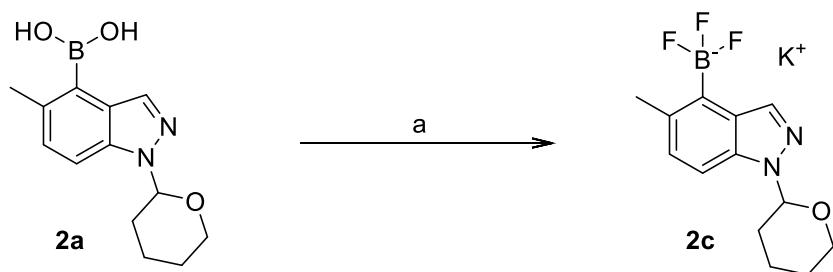


Reagents and conditions: (a) 1.5 eq. 2,3-dimethylbutane-2,3-diol, 3 eq. MgSO₄, THF, 50 °C for 20 h then 70 °C for 3 h, 72%.

5-methyl-1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (2b) ; To a suspension of [5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl]boronic acid **2a** (127 g, 0.48 mol) in THF (1.5 L) was added 2,3-dimethylbutane-2,3-diol (86.55 g, 0.73 mol) and MgSO₄ (176.34 g, 1.46 mol) at 20 °C. After the addition, the resulting mixture was stirred at 50 °C for 20 hours. TLC (petroleum ether : EtOAc = 4 : 1) showed that some of the boronic acid still remained. The mixture was heated to 70 °C for 3 hours. TLC (petroleum ether : EtOAc = 4 : 1) showed that the starting material had been consumed. The mixture was diluted with CH₂Cl₂ (1.5 L), washed with H₂O (800 mL), dried over Na₂SO₄, filtered, concentrated to give a crude residue, which was purified by column chromatography on silica gel (gradient of petroleum ether : EtOAc from = 50 : 1 to 20 : 1) to give 5-methyl-1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole **2b** (120 g, 72%) as a colorless solid. LC-MS (ESI) *m/z* 343.1 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 8.40 (s, 1 H), 7.83 (d, *J* = 8.8 Hz, 1 H), 7.51 (d, *J* = 9.2 Hz, 1 H), 5.72

(dd, $J = 6.4, 2.8$ Hz, 1 H), 4.03 – 4.02 (m, 1 H), 4.00 – 3.98 (m, 1 H), 2.67 (s, 3 H), 2.59 – 2.58 (m, 1 H), 2.17 – 2.08 (m, 2 H), 1.78 – 1.76 (m, 3 H), 1.42 (s, 12 H).

Experiment 6. Synthesis of potassium trifluoro[5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl] trifluoroborate, 2c

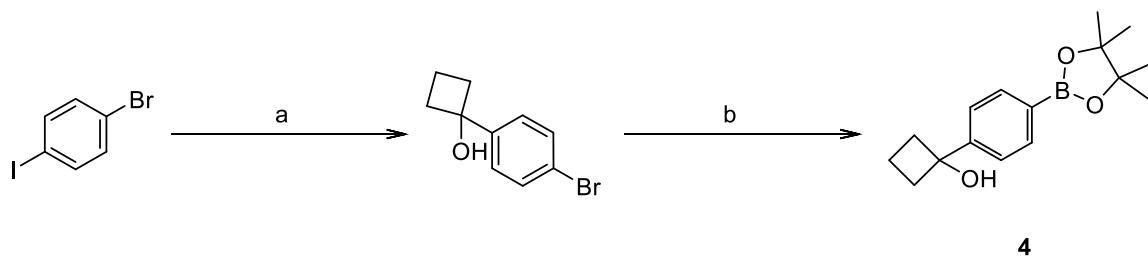


Reagents and conditions: (a) 3 eq. KHF₂, MeOH, H₂O, 0 °C to room temperature, 24 h, 88%.

Potassium trifluoro[5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl] trifluoroborate, (2c) ; To a mixture of [5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl]boronic acid **2a** (6.00 g, 23.1 mmol) in MeOH (6.74 mL) was added KHF₂ (5.41 g, 67 mmol) in a single portion at 0 °C, followed by the dropwise addition of water (15.4 mL) at 0 °C. The ice-bath was removed, and the reaction allowed to warm to room temperature whilst stirring for 24 hours. The reaction mixture was evaporated to dryness, and both the ¹¹B and ¹⁹F NMR checked to confirm reaction completion. The residue was placed under high vacuum 1 hour. Acetone (10 mL) was added, and the solid filtered. The filtrate was then concentrated to afford potassium trifluoro[5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl] trifluoroborate **2c** (6.50 g, 88%) as a colorless solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.17 (s, 1 H), 7.32 (d, $J = 8.4$ Hz, 1 H), 7.08 (d, $J = 8.3$

Hz, 1 H), 5.76 (dd, $J = 9.7, 2.4$ Hz, 1 H), 3.99 – 3.94 (m, 1 H), 3.82 – 3.78 (m, 1 H), 2.61 (s, 3 H), 2.15 – 2.11 (m, 1 H), 2.02 – 1.97 (m, 1 H), 1.87 – 1.77 (m, 1 H), 1.70 – 1.65 (m, 2 H); ^{11}B NMR (128 MHz, DMSO- d_6) 3.52; ^{19}F NMR (376 MHz, DMSO- d_6) 132.90.

Experiment 7. Synthesis of 1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]cyclobutanol, 4



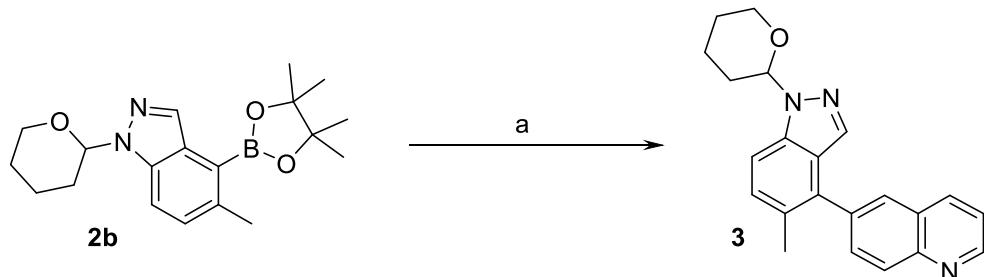
Reagents and conditions: (a) 1.1 eq. *n*-BuLi (2.5 M in hexanes) then 1.1 eq. cyclobutanone , THF, -78 °C, 1 h, 79%;; (b) 4 % Pd(dppf)Cl₂, 1.2 eq. B₂PiN₂, 3 eq. KOAc, 1,4-dioxane, 90 °C, 18 h, 76%.

1-(4-Bromophenyl)cyclobutanol ; To a solution of 4-bromoiodobenzene (103 g, 0.364 mol) in THF (1 L) was added *n*-BuLi (160 mL, 2.5 M in hexanes, 0.40 mol) in a dropwise manner at -78 °C under an inert atmosphere of N₂. The reaction mixture was then allowed to stir at this temperature for 30 minutes. Cyclobutanone (25.5 g, 0.364 mol) was then added in a dropwise manner to the reaction, which was then allowed to stir for 30 minutes. TLC (petroleum ether : EtOAc = 20 : 1) showed that the starting materials had been consumed. The reaction was quenched with a solution of saturated aqueous NH₄Cl solution (200 mL) and extracted with EtOAc (3 x 500 mL). The combined organic layers were washed with brine (500 mL), dried over Na₂SO₄, filtered and concentrated to

give a crude residue, which was purified by column chromatography on silica gel (gradient of petroleum ether : EtOAc from 50 : 1 to 5 : 1) to afford 1-(4-bromophenyl)cyclobutanol (65 g, 79%) as a colorless oil ; ^1H NMR (400 MHz, CDCl_3) δ 7.49 (d, $J = 8.8$ Hz, 1 H), 7.38 (d, $J = 8.4$ Hz, 1 H), 2.53 – 2.49 (m, 2 H), 2.38 – 2.35 (m, 2 H), 2.05 (s, 2 H), 1.71 – 1.66 (m, 1 H).

1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]cyclobutanol (4); A mixture of 1-(4-bromophenyl)cyclobutanol (62 g, 0.27 mol), B_2pin_2 (83.8 g, 0.33 mol), KOAc (79.4 g, 0.81 mol) and $\text{Pd}(\text{dpf})\text{Cl}_2$ (7.9 g, 0.011 mol) in 1,4-dioxane (600 mL) was stirred at 90 °C for 18 hours under an inert atmosphere of N_2 . After cooling, the reaction was filtered, and the filtrate concentrated *in vacuo* to give a crude residue, which was purified by column chromatography on silica gel (gradient of petroleum ether : EtOAc from 15 : 1 to 5 : 1) to give 1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]cyclobutanol **4** (57 g, 76%) as an off-white solid; ^1H NMR (400 MHz, CDCl_3) δ 7.83 (d, $J = 8.0$ Hz, 1 H), 7.51 (d, $J = 8.4$ Hz, 1 H), 2.57 – 2.53 (m, 2 H), 2.39 – 2.36 (m, 2 H), 2.06 – 2.02 (m, 2 H), 1.73 – 1.69 (m, 1 H), 1.37 (s, 12 H).

Experiment 8. Batch synthesis scale-up of 6-[5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1*H*-indazol-4-yl]quinolone, 3



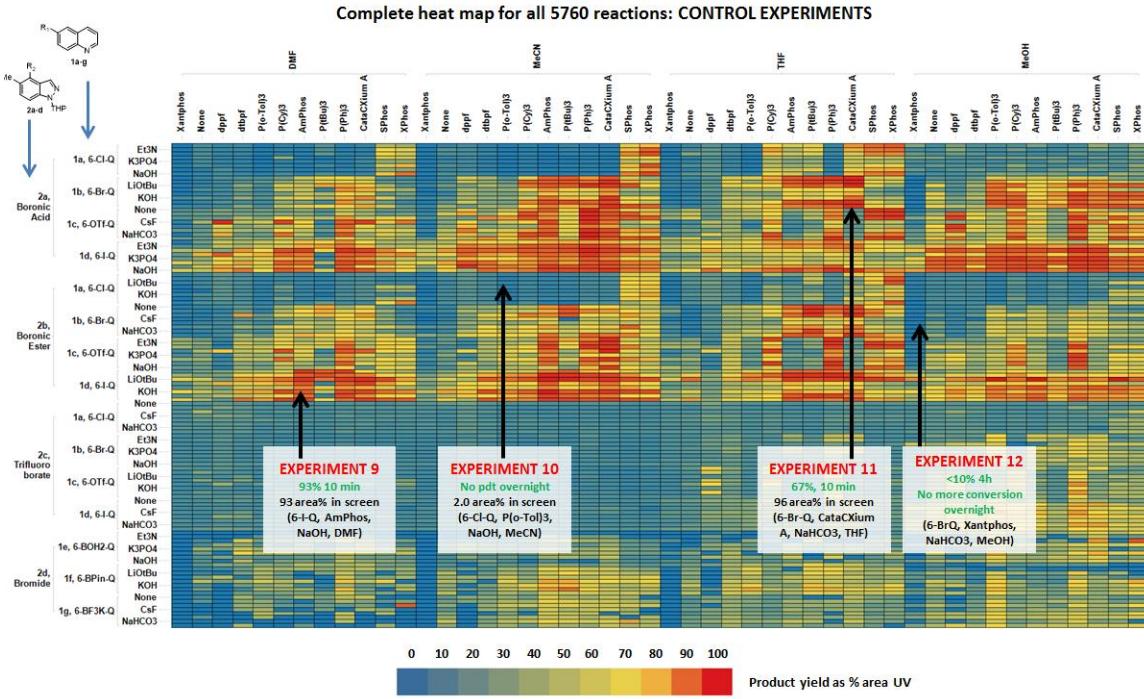
Reagents and conditions: (a) 1eq. Bromoquinoline (**1b**), 6.25 mol% Pd(OAc)₂, 12.5 mol% PPh₃, 2.5 eq. NaOH, MeOH/H₂O, 100 °C, 10 minutes, 79%.

6-[5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1*H*-indazol-4-yl]quinolone (3) ; A vial was charged with Pd(OAc)₂ (5.93 mg, 0.026 mmol) and PPh₃ (13.9 mg, 0.053 mmol) and evacuated and backfilled with N₂. The mixture was then treated with MeOH (4.23 mL), and water (0.423 mL). The mixture was warmed slightly (~ 50 °C for 2 min) to bring all the solids into solution and then sparged with N₂ continuously for a total of 5 minutes. A separate vial was charged with 6-bromoquinoline **1b** (88 mg, 0.42 mmol) and 5-methyl-1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole **2b** (145 mg, 0.42 mmol). This vial was also sealed and evacuated and backfilled with N₂. The catalyst mixture was rapidly transferred to the Suzuki coupling partners *via* syringe along with the 6 N aqueous NaOH (0.176 mL). The reaction vessel was sealed then submerged in the oil bath, which had been preheated to 100 °C, and stirred for 10 minutes. The vial was removed and allowed to cool slightly. Analysis by LC-MS showed the major peak had a mass corresponding to the desired product. The solvent was evaporated *in vacuo*, and the residue subjected to chromatography on silica gel

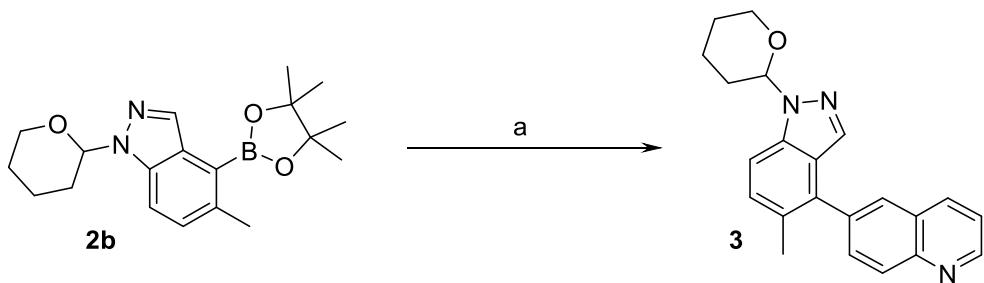
(EtOAc/heptanes 10 to 80%) to afford 6-[5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1*H*-indazol-4-yl]quinolone **3** (115 mg, 79%) as an off-white solid. LC-MS (ESI) *m/z* 343.3 [M+H]⁺; ¹H NMR (400 MHz, CD₃OD) δ 8.91 (d, *J* = 4.4 Hz, 1 H), 8.43 (d, *J* = 8.3 Hz, 1 H), 8.17 (d, *J* = 8.7 Hz, 1 H), 7.97 (s, 1 H), 7.84 – 7.77 (m, 1 H), 7.66 – 7.58 (m, 3 H), 7.43 (d, *J* = 8.7 Hz, 1 H), 5.84 – 5.79 (m, 1 H), 4.03 (d, *J* = 11.5 Hz, 1 H), 3.83 (td, *J* = 11.0, 3.0 Hz, 1 H), 2.56 – 2.44 (m, 1 H), 2.35 (s, 3 H), 2.16 – 2.07 (m, 1 H), 2.06 – 1.97 (m, 1 H), 1.89 – 1.61 (m, 3 H); ¹³C NMR (100 MHz, CD₃OD) 151.91, 148.37, 140.26, 139.20, 138.91, 134.36, 133.95, 133.50, 131.69, 130.26, 130.14, 129.17, 129.63, 126.78, 123.40, 111.16, 86.90, 69.08, 31.04, 26.70, 24.13, 19.76.

Experiments 9 – 12 – Batch syntheses for “positive” and “negative control purposes for the synthesis of 6-[5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1*H*-indazol-4-yl]quinolone,
3

Several permutations in batch were selected to be run according to the heatmap shown below, and gave good correlation with the flow results. Two positive controls gave isolated yields of 67% (experiment 11) and 93% (experiment 9). Two negative controls showed <10% conversion (experiment 12) after an overnight run and no trace of desired product (experiment 10) in the other overnight by LCMS.



Experiment 9. Batch synthesis scale-up of 6-[5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1*H*-indazol-4-yl]quinolone, 3 (positive control)

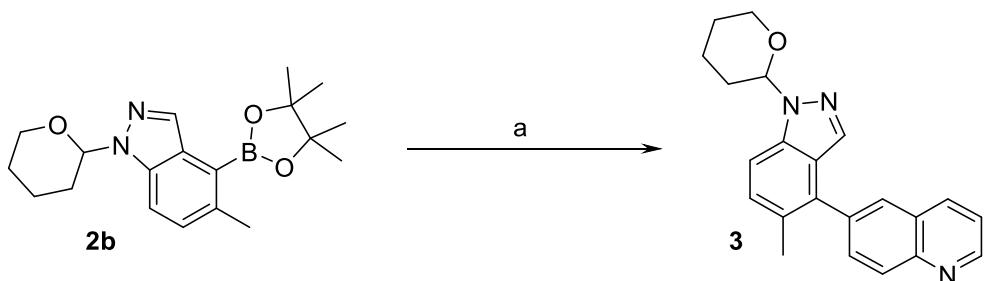


Reagents and conditions: (a) 1eq. Iodoquinoline (**1d**), 6.25 mol% Pd(OAc)₂, 12.5 mol% Amphos, 2.5 eq. NaOH, DMF/H₂O, 100 °C, 10 minutes, 93%.

6-[5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1*H*-indazol-4-yl]quinolone (3) ; A vial was evacuated and backfilled with N₂. The vial was then charged with Pd(OAc)₂ (3.98 mg, 0.017 mmol), Amphos (25.1 mg, 0.035 mmol), 6-iodoquinoline **1d** (72 mg, 0.28 mmol) and 5-methyl-1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-

yl)-1*H*-indazole **2b** (97 mg, 0.28 mmol). The mixture was then treated with DMF (2.5 mL), and water (0.3 mL). The mixture was then sparged with N₂ continuously for a total of 5 minutes before being treated with 6 N aqueous NaOH (0.118 mL). The reaction vessel was sealed then submerged in the oil bath, which had been preheated to 100 °C, and stirred for 10 minutes. The vial was removed and allowed to cool slightly. Analysis by LC-MS showed the major peak had a mass corresponding to the desired product. The solvent was evaporated *in vacuo*, and the residue subjected to chromatography on silica gel (EtOAc/heptanes 10 to 80%) to afford 6-[5-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-4-yl]quinolone **3** (91 mg, 93%) as an off-white solid.

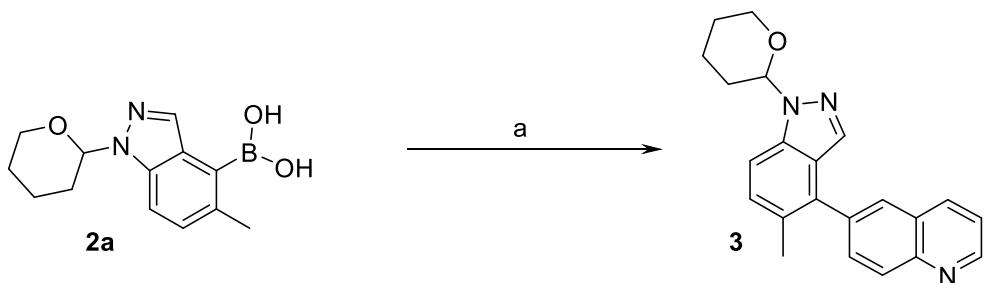
Experiment 10. Batch synthesis scale-up of 6-[5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1*H*-indazol-4-yl]quinolone, 3 (negative control)



Reagents and conditions: (a) 1 eq. Chloroquinoline (**1a**), 6.25 mol% Pd(OAc)₂, 12.5 mol% P(*o*-Tol)₃, 2.5 eq. NaOH, MeCN/H₂O, 100 °C, 18 h, no reaction.

6-[5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1*H*-indazol-4-yl]quinolone (3) ; A vial was charged with Pd(OAc)₂ (1.60 mg, 0.007 mmol), P(*o*-Tol)₃ (4.34 mg, 0.014 mmol) 6-chloroquinoline **1a** (19 mg, 0.11 mmol), 5-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole **2b** (39 mg, 0.11 mmol), and evacuated and backfilled with N₂. The mixture was then treated with MeCN (1.0 mL), and water (0.1 mL), and sparged with N₂ for 5 minutes prior to the addition of 6 N aqueous NaOH (0.048 mL). The reaction vessel was sealed then submerged in the oil bath, which had been preheated to 100 °C, and stirred for 18 hours. Analysis by LC-MS showed no conversion to desired product.

Experiment 11. Batch synthesis scale-up of 6-[5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1*H*-indazol-4-yl]quinolone, 3 (positive control)

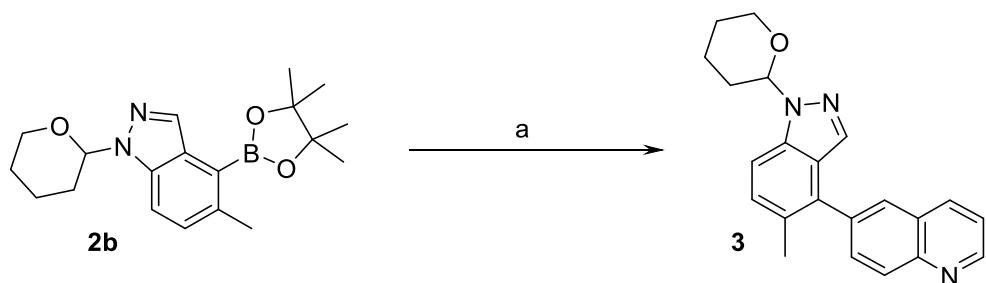


Reagents and conditions: (a) 1eq. Bromoquinoline (**1b**), 6.25 mol% Pd(OAc)₂, 12.5 mol% cataCXium A, 2.5 eq. NaHCO₃, THF/H₂O, 100 °C, 10 minutes, 67%.

6-[5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1*H*-indazol-4-yl]quinolone (3) ; A vial was charged with Pd(OAc)₂ (3.57 mg, 0.016 mmol), catAXium A (11.4 mg, 0.032 mmol) 6-bromoquinoline **1b** (53 mg, 0.25 mmol), NaHCO₃ (53.5 mg, 0.64 mmol) and [5-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-4-yl]boronic acid **2a** (66 mg, 0.26 mmol) and evacuated and backfilled with N₂. The mixture was then treated with MeOH (2.25 mL), and water (0.25 mL). The vial was sparged with N₂ for 5 minutes. The reaction vessel was sealed then submerged in the oil bath, which had been preheated to 100 °C and stirred for 10 minutes. The vial was removed and allowed to cool slightly. Analysis by LC-MS showed the major peak had a mass corresponding to the desired product. The solvent was evaporated *in vacuo*, and the residue subjected to chromatography on silica gel (EtOAc/heptanes 10 to 80%) to afford 6-[5-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-

indazol-4-yl]quinolone **3** (59 mg, 67%) as an off-white solid.

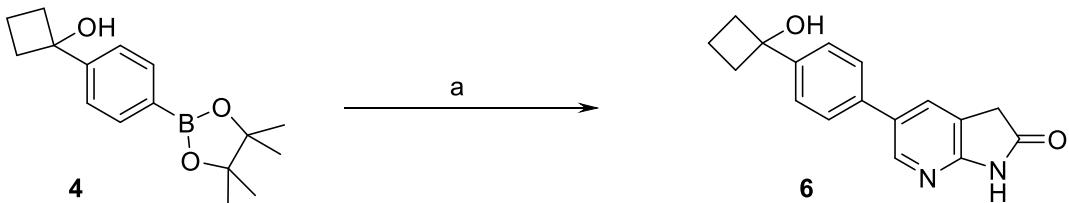
Experiment 12. Batch synthesis scale-up of 6-[5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1*H*-indazol-4-yl]quinolone, **3 (negative control)**



Reagents and conditions: (a) 1eq. Bromoquinoline (**1b**), 6.25 mol% Pd(OAc)₂, 12.5 mol% Xantphos, 2.5 eq. NaHCO₃, MeOH/H₂O, 100 °C, 18 h, <10% conversion.

6-[5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1*H*-indazol-4-yl]quinolone (3) ; A vial was charged with Pd(OAc)₂ (2.36 mg, 0.011 mmol), Xantphos (12.2 mg, 0.021 mmol) 6-bromoquinoline **1b** (35 mg, 0.17 mmol), 5-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole **2b** (58 mg, 0.17 mmol), and NaHCO₃ (35.3 mg, 0.42 mmol) and evacuated and backfilled with N₂. The mixture was then treated with MeOH (1.5 mL) and water (0.17 mL) and the solution sparged with N₂ continuously for a total of 5 minutes. The reaction vessel was sealed then submerged in the oil bath, which had been preheated to 100 °C, and stirred for 18 hour. Analysis by LC-MS showed <10% conversion to desired product.

Experiment 13. Batch synthesis scale-up of 5-[4-(1-hydroxycyclobutyl)phenyl]-1,3-dihydro-2H-pyrrolo[2,3-*b*]pyridin-2-one 6

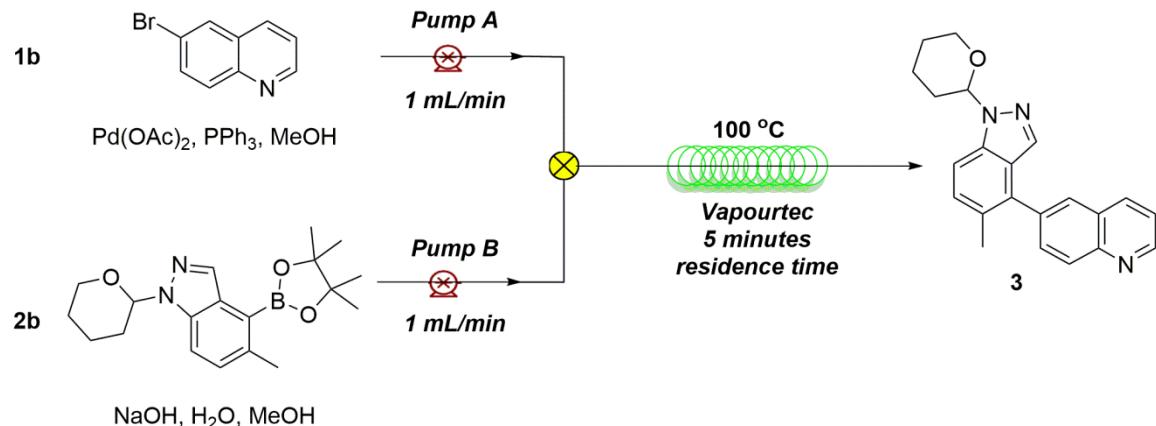


Reagents and conditions: (a) 1 eq. 5-bromo-1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one **5**, 6.25 mol% Pd(OAc)₂, 12.5 mol% PPh₃, 2.5 eq. NaOH, MeOH/H₂O, 100 °C, 90 minutes, 79%.

5-[4-(1-hydroxycyclobutyl)phenyl]-1,3-dihydro-2H-pyrrolo[2,3-*b*]pyridin-2-one ; A vial was charged with 1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]cyclobutanol **4** (154 mg, 0.562 mmol), 5-bromo-1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one **5** (120 mg, 0.562 mmol), Pd(OAc)₂ (7.88 mg, 0.035 mmol) and CataCXium A (12.6 mg, 0.035 mmol) and evacuated and backfilled with N₂. The mixture was then treated with THF (5.00 mL), water (0.6 mL) and Et₃N (0.373 mL), and sparged with N₂ continuously for a total of 5 minutes. The reaction vessel was sealed then submerged in the oil bath, which had been preheated to 100 °C, and stirred for 90 minutes. The vial was removed and allowed to cool to room temperature. The solvent was evaporated *in vacuo*, and the residue subjected to chromatography on silica gel (acetone/CH₂Cl₂ 10 to 80%) to afford 5-[4-(1-hydroxycyclobutyl)phenyl]-1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one **6** (128 mg, 89%) as a colorless solid. LC-MS (ESI) *m/z* 281.2 [M+H]⁺ ; ¹H NMR (400 MHz,

DMSO-*d*₆) δ 11.07 (s, 1 H), 8.38 (s, 1 H), 7.85 (s, 1 H), 7.62 – 7.51 (m, 4 H), 5.51 (s, 2 H), 3.61 (s, 1 H), 2.48 – 2.42 (m, 2 H), 2.38 – 2.28 (m, 2 H), 2.01 – 1.90 (m, 1 H), 1.73 – 1.68 (m, 1 H); ¹³C NMR (100 MHz, DMSO-*d*₆) 176.2, 159.8, 145.1, 143.2, 134.8, 129.9, 129.7, 125.2, 125.1, 119.5, 74.6, 39.8, 37.2, 13.3.

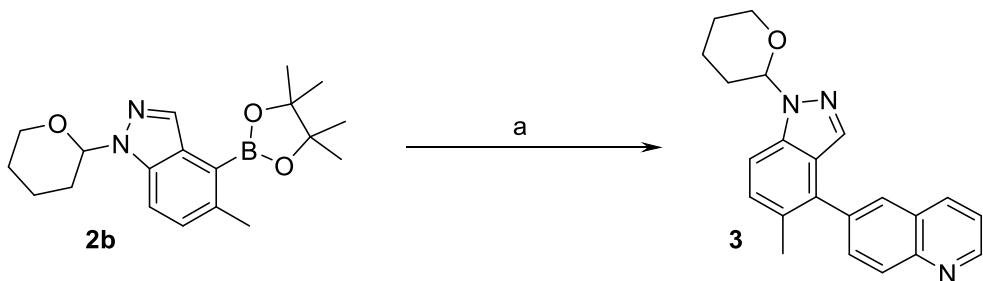
Experiment 14. Flow Vapourtec synthesis scale-up of 6-[5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1*H*-indazol-4-yl]quinolone, 3



Two stock solutions were prepared as follows. Solution **A** comprised of 6-bromoquinoline **1b** (180 mg, 0.86 mmol), Pd(OAc)₂ (12 mg, 0.052 mmol), PPh₃ **L2** (30 mg, 0.052 mmol) in methanol (10 mL) while Solution **B** contained 5-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole **2b** (290 mg, 0.04 mmol) in methanol (8 mL) to which was added a solution of NaOH (87 mg, 2.2 mmol) in water (2 mL). The two solutions were mixed using a Vapourtec R series reactor each at a flow rate of 1 mL/min, and passed through a 10 mL PTFE reactor heated to 100 °C for a residence time of 5 minutes. The product stream was collected,

evaporated *in vacuo*, and extracted into EtOAc (2 x 10 mL). The organics were dried over Na₂SO₄, and chromatographed over silica gel eluting with a isocratic gradient of 35 % EtOAc in heptanes to afford 6-[5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1*H*-indazol-4-yl]quinolone **3** (115 mg, 42%) as a colorless solid. The NMR spectra were identical to those obtained previously for this compound.

Experiment 15. Scale-up and scale out of 6-[5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1*H*-indazol-4-yl]quinolone, **3 in the current flow platform**

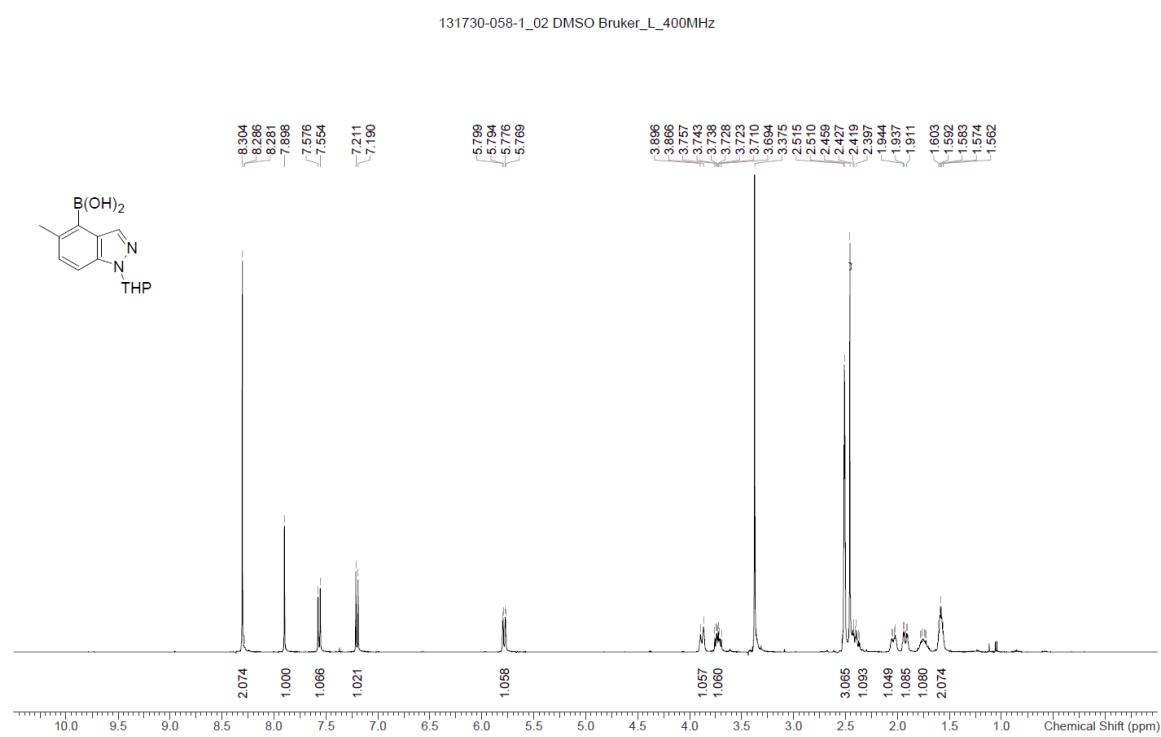
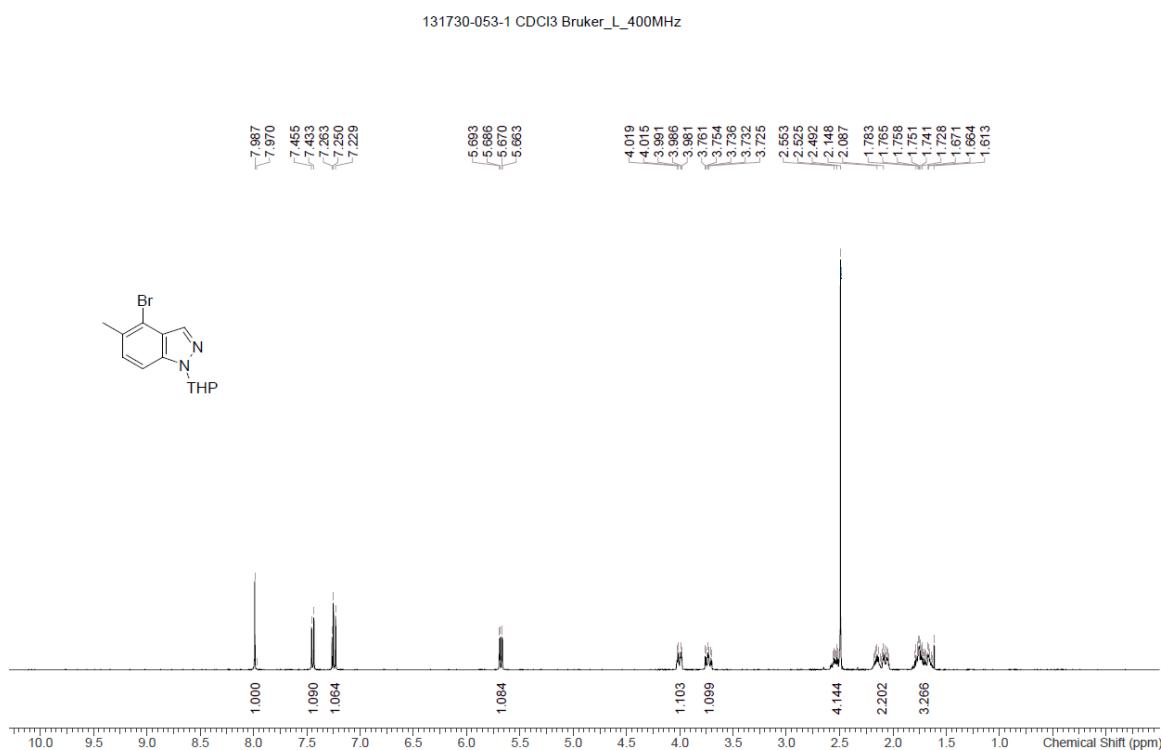


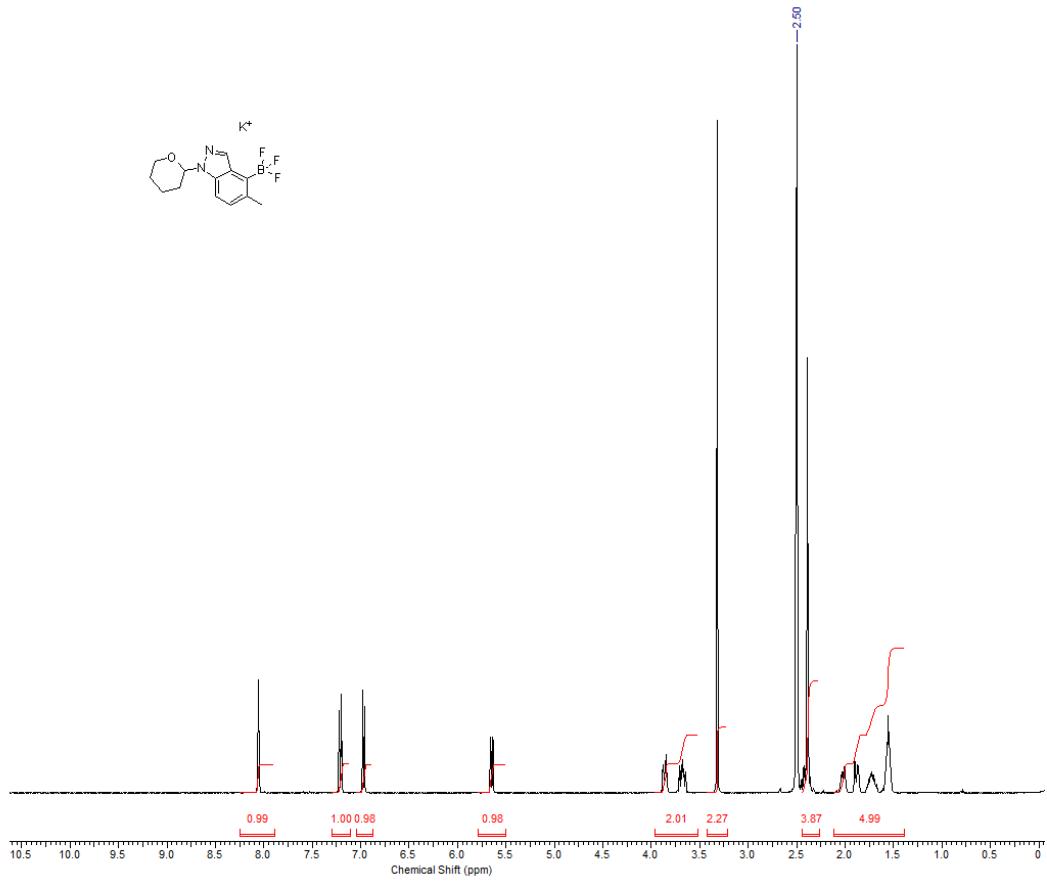
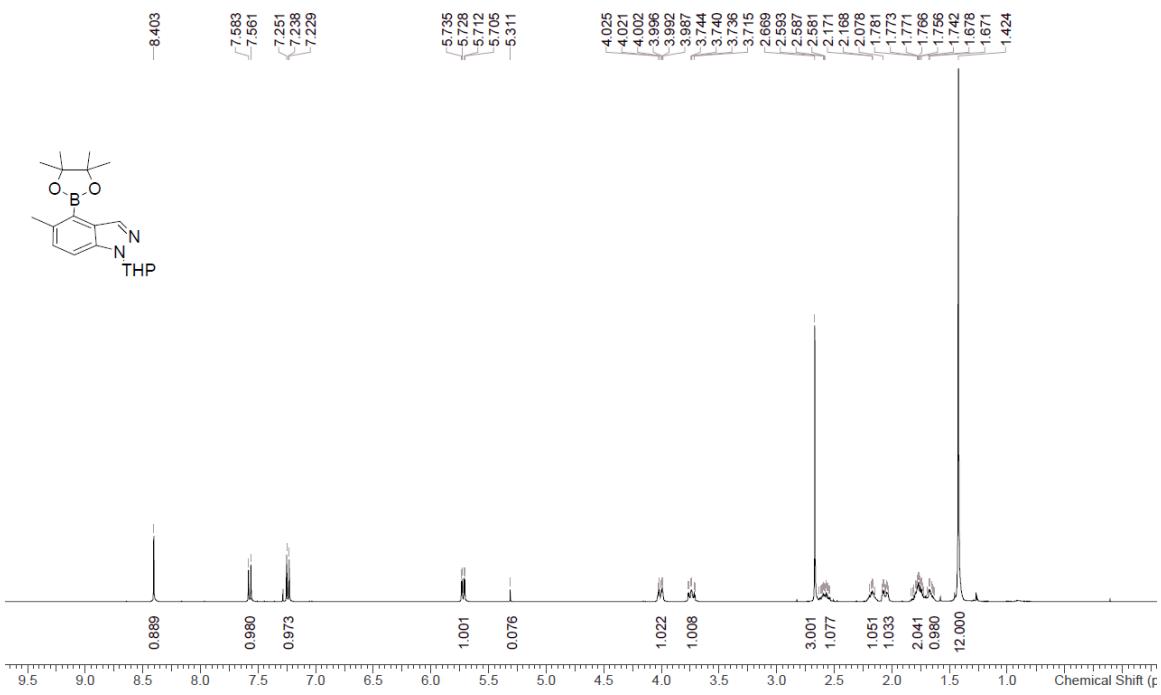
Reagents and conditions: (a) 1eq. Bromoquinoline (**1b**), 6.25 mol% Pd(OAc)₂, 12.5 mol% PPh₃, 2.5 eq. NaOH, MeOH/H₂O, 100 °C, 75 minutes, 59%, 3.2 μmol per reaction segment and 100 segments collected (total 0.32 mmol), Flow rate 1 mL/min at 100 bar

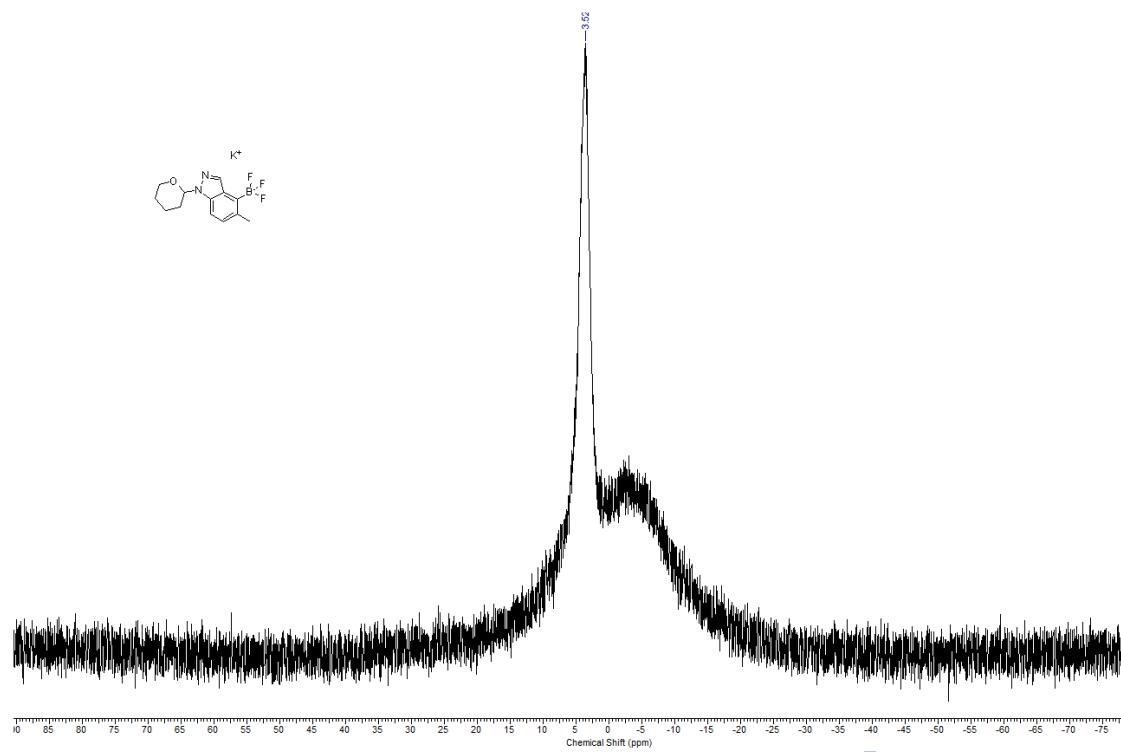
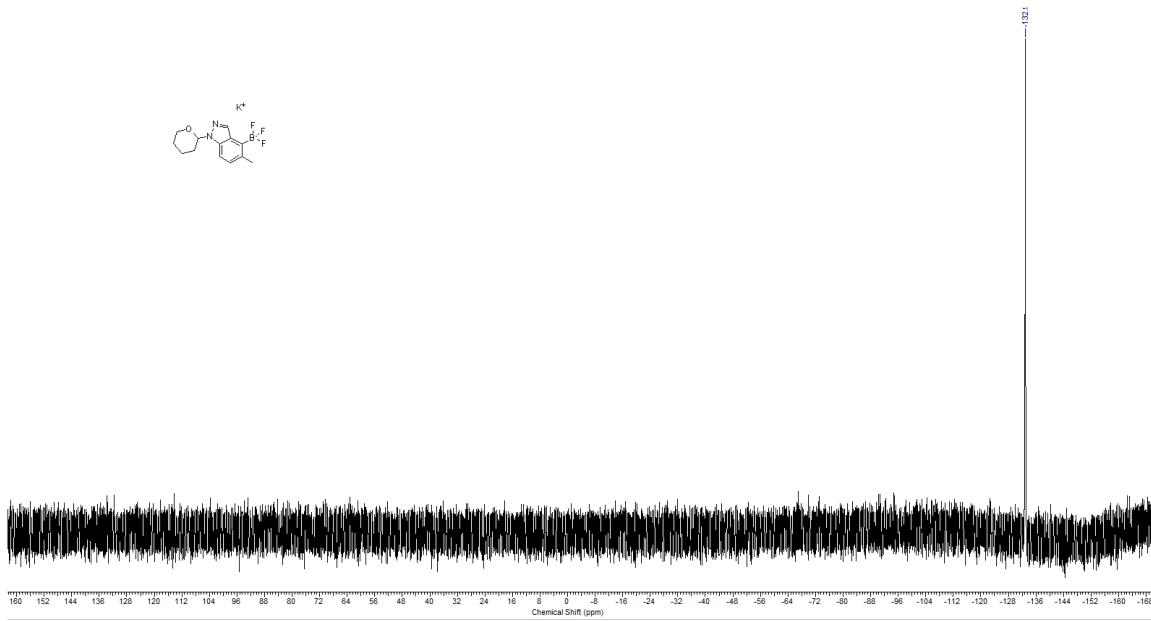
Stock solutions of each of the reaction components were made as follows: **1b** (0.4 M in 1,3-diethylbenzene), **2b** (0.4 M in DMF), Pd(OAc)₂ (0.025 M in 1,3,5-triethylbenzene), PPh₃ **L2** (0.05 M in toluene) and NaOH 1M in water). The reactions were prepared by concurrent aspiration of 8 μL of these components (scale of 112 mg, 3.2 μmol per reaction segment) as described in the general method using Agilent autosampler and

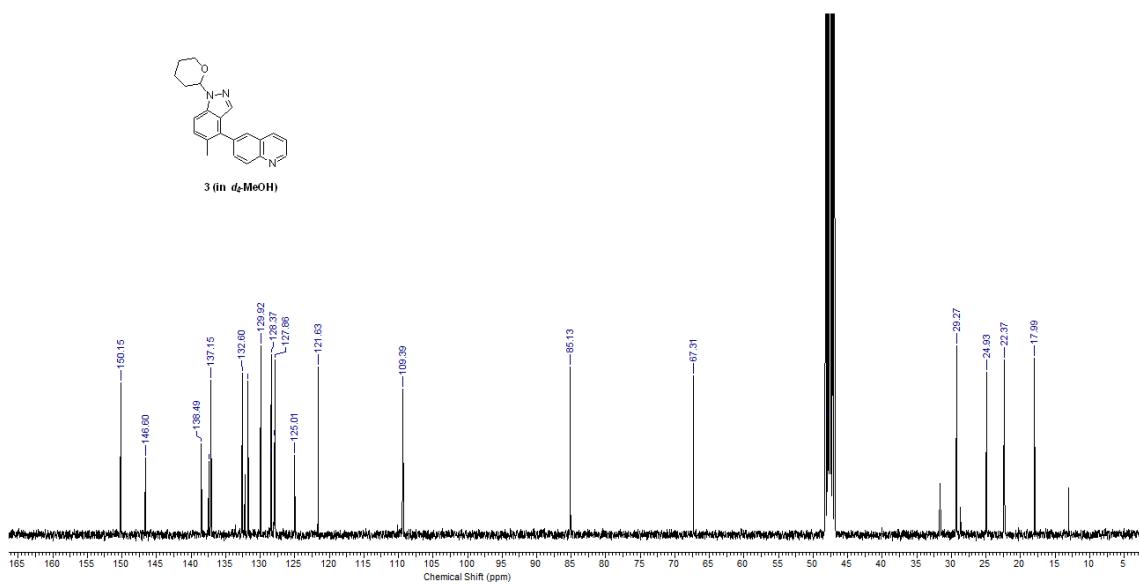
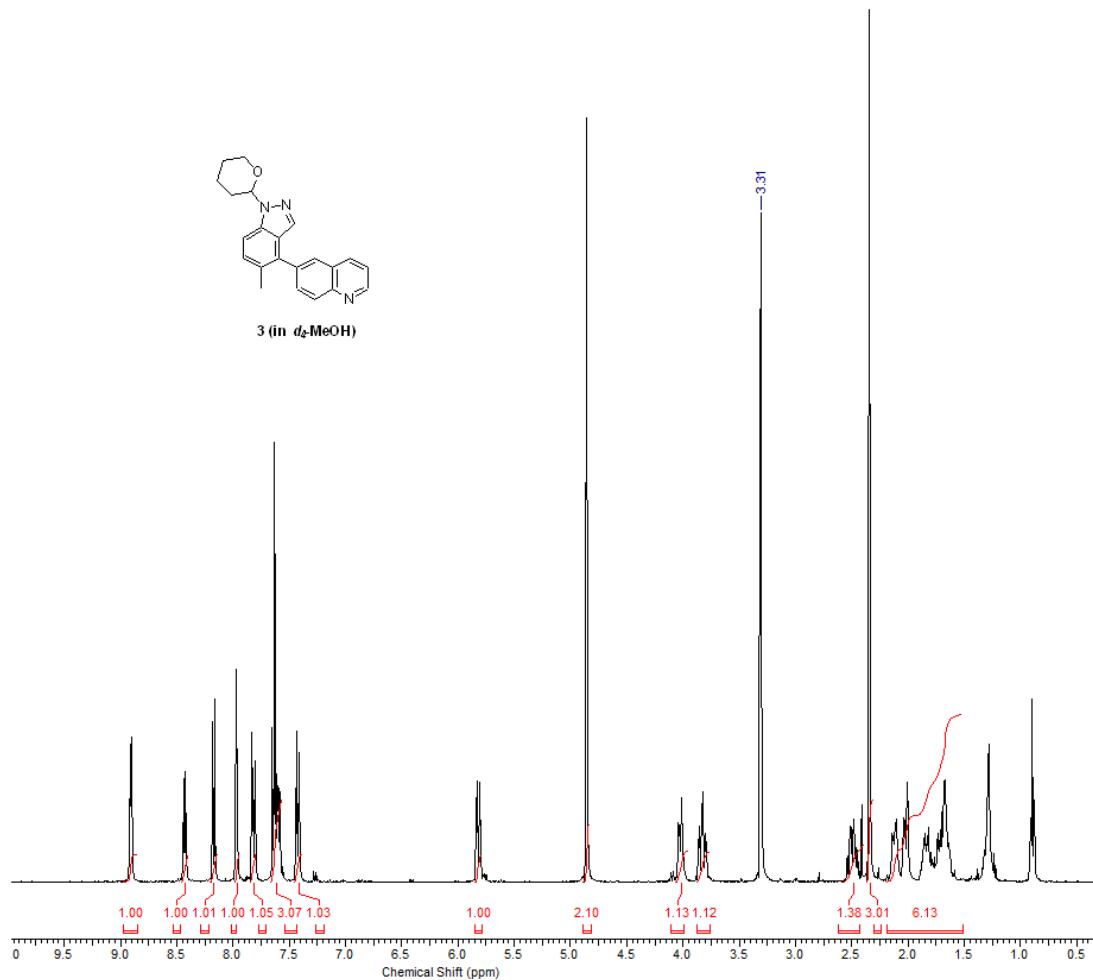
injection into a flow stream of MeOH/ H₂O (9:1). The reaction segments were run with a flow rate of 1 mL/min through a Hastelloy coil heated to 100 °C and having a residence time of 1 min at 100 bar. The instrument was programmed to inject 100 of the same reaction segments *via* the sequence table. The reaction segments that were exiting the Hastelloy coil were collected, evaporated *in vacuo*, and extracted into EtOAc (2 x 10 mL). The organics were dried over Na₂SO₄, and chromatographed over silica gel eluting with a isocratic gradient of 35 % EtOAc in heptanes to afford 6-[5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1*H*-indazol-4-yl]quinolone **3** (65 mg, 59%) as a colorless solid. The NMR spectra are identical to those obtained previously for this compound.

Appendix S1. Characterization data for 2a, 2b, 2c, and 3

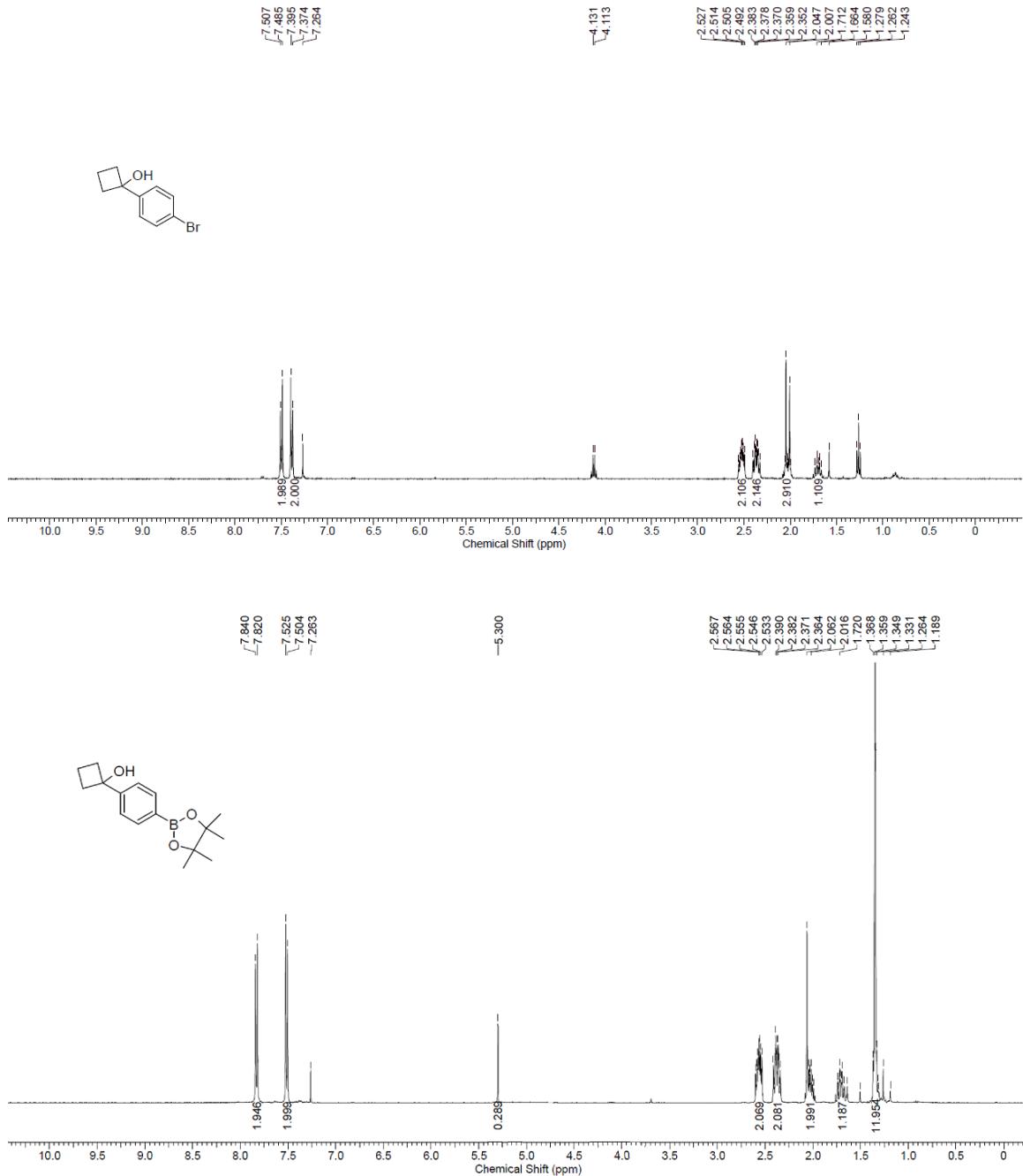


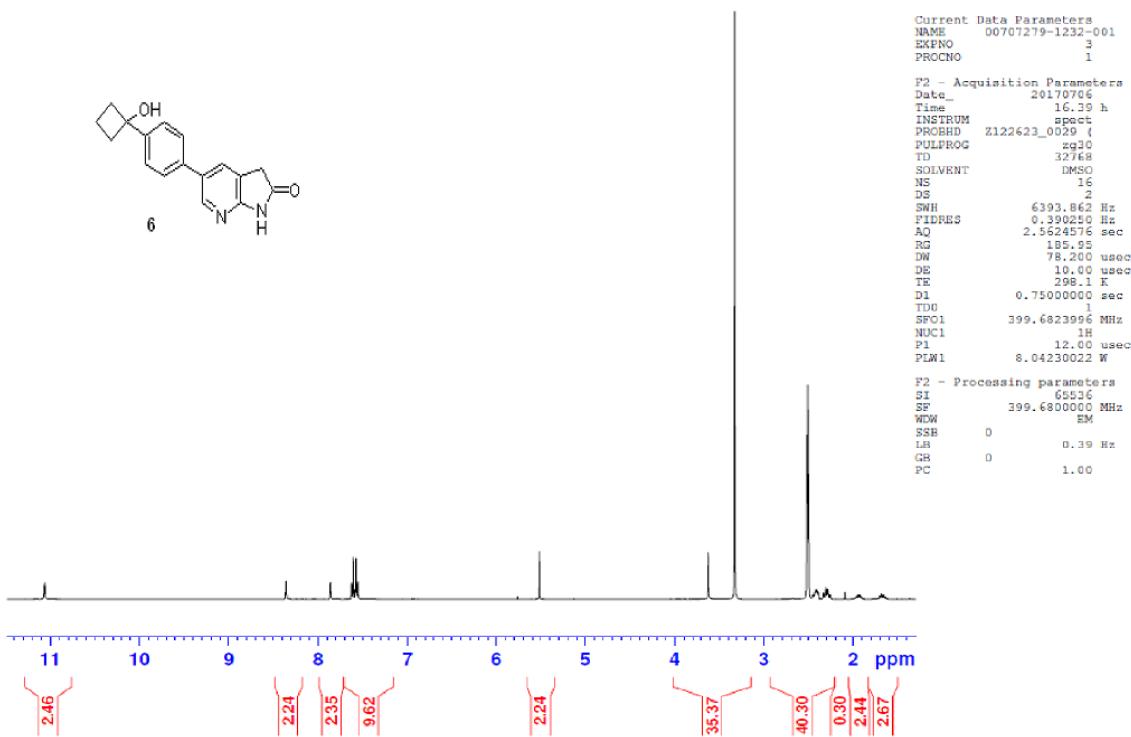






Appendix S2. Characterization data for 4 and 6





Appendix S3. Additional visualizations

Fig. S17 : Expanded visualization of Fig. 3 – Complete heatmap of 5760 reactions of 1a-d with 2a-c, and the reaction of 2d with 1e-g

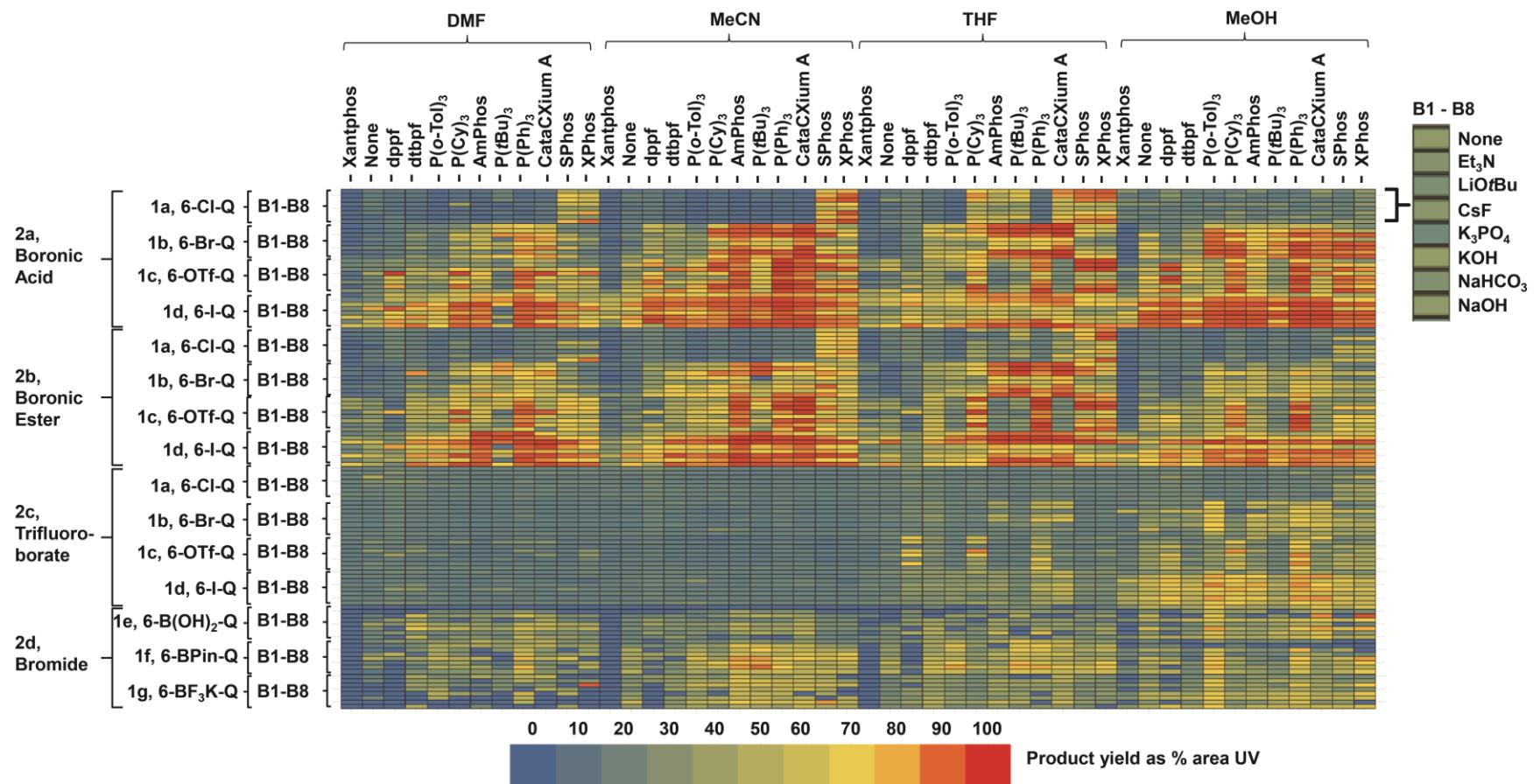


Fig. S18 : Expanded visualization of Fig. 4B – Heatmap of quinoline electrophiles 1a-d with 2a evaluated across a matrix of 11 ligands (plus one blank) x 7 bases (plus one blank) x 4 solvents.

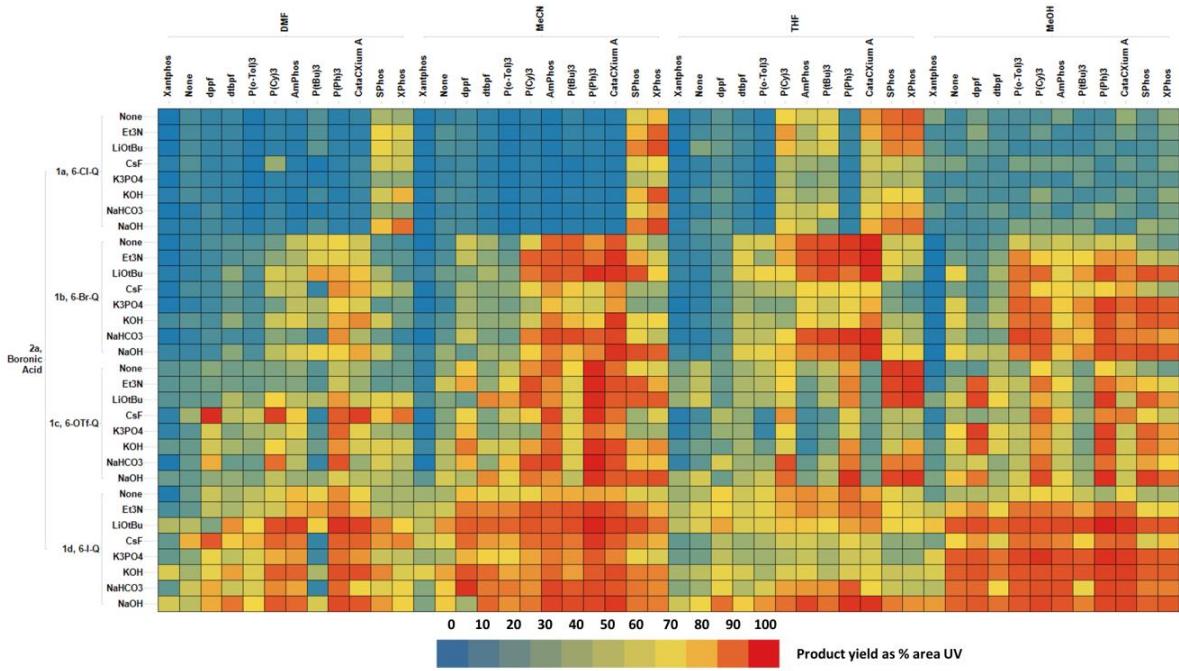


Fig. S19 : Expanded visualization of Fig. 4B – Heatmap of quinoline electrophiles 1a-d with 2b evaluated across a matrix of 11 ligands (plus one blank) x 7 bases (plus one blank) x 4 solvents.

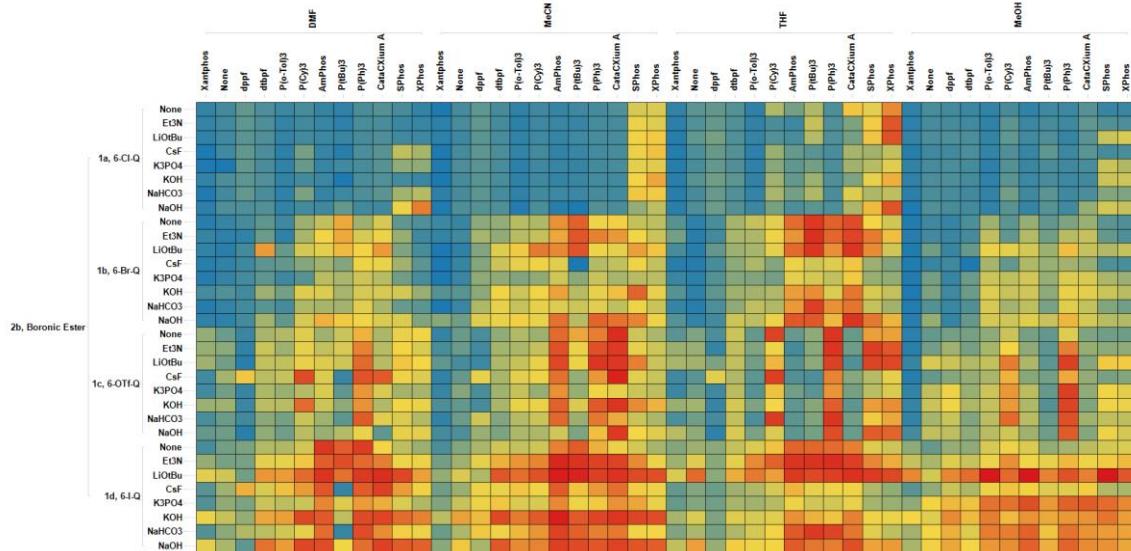


Fig. S20 : Expanded visualization of Fig. 4B – Heatmap of quinoline electrophiles 1a-d with 2c evaluated across a matrix of 11 ligands (plus one blank) x 7 bases (plus one blank) x 4 solvents.

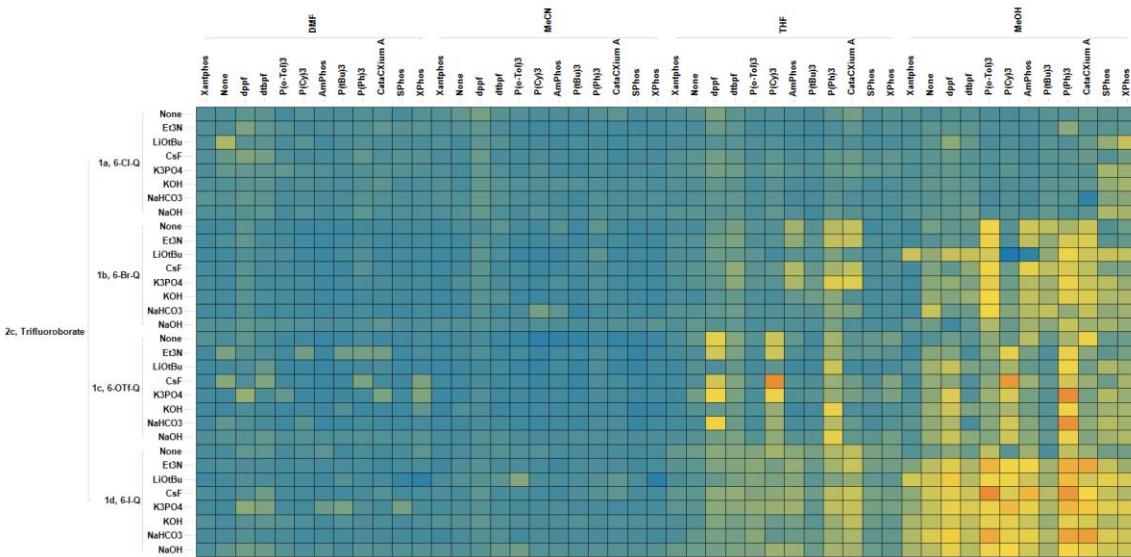


Fig. S21 : Heatmap of 2d with 1e-g evaluated across a matrix of 11 ligands (plus one blank) x 7 bases (plus one blank) x 4 solvents.

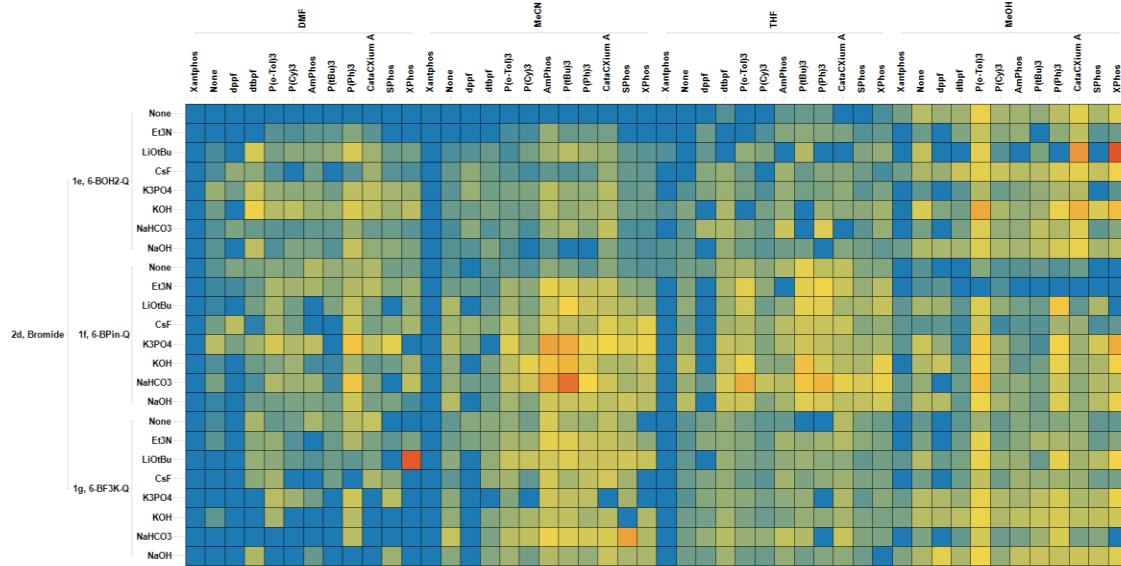


Fig. S22 : Box-plot comparison of quinoline electrophiles 1a-d with boronic acid and derivatives 2a-c.

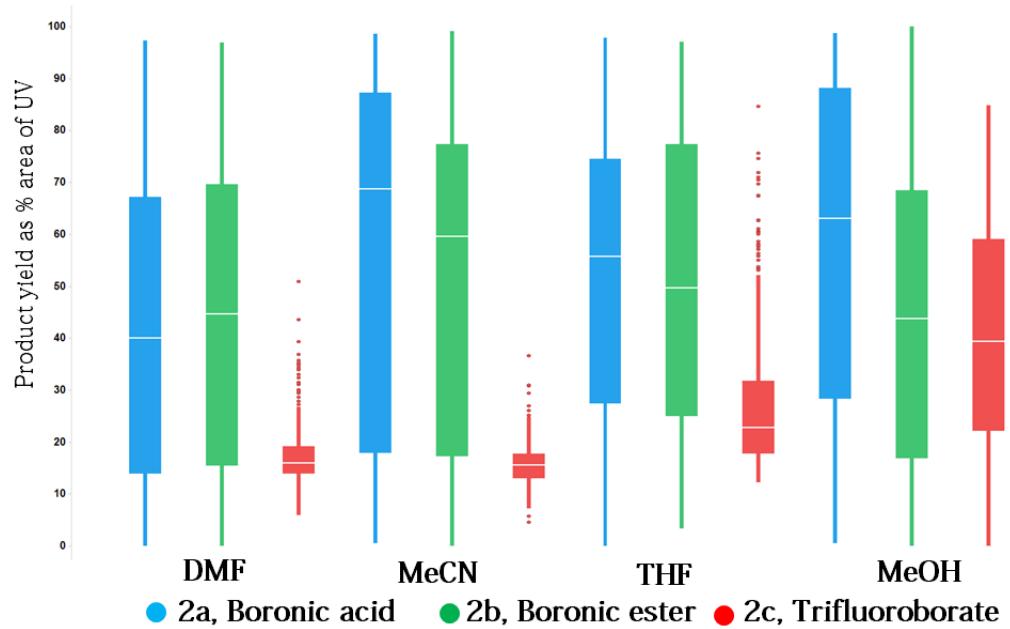


Fig. S23 : Box plot comparison of boron-based derivatives 2a-c in the reaction with quinoline-based electrophiles 1a-d.

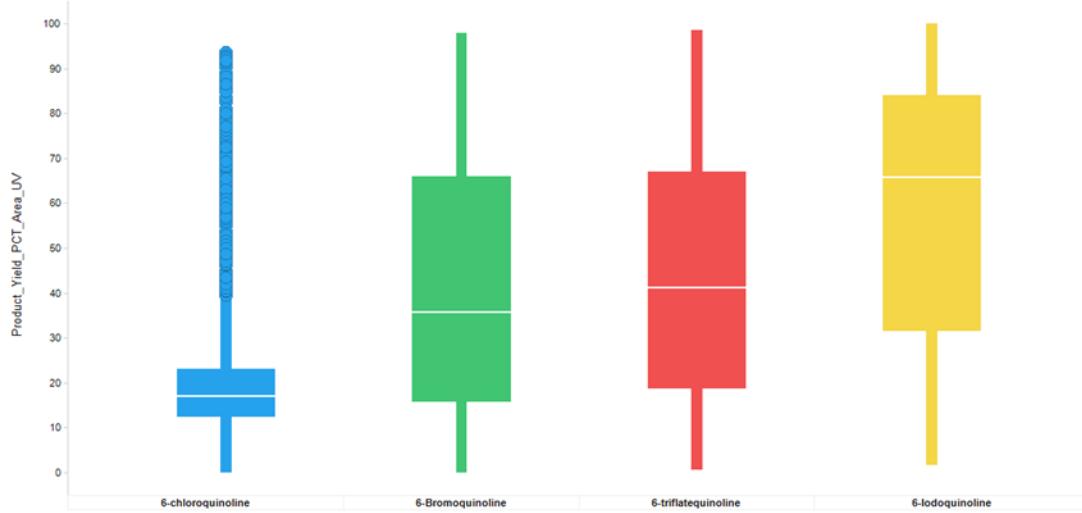
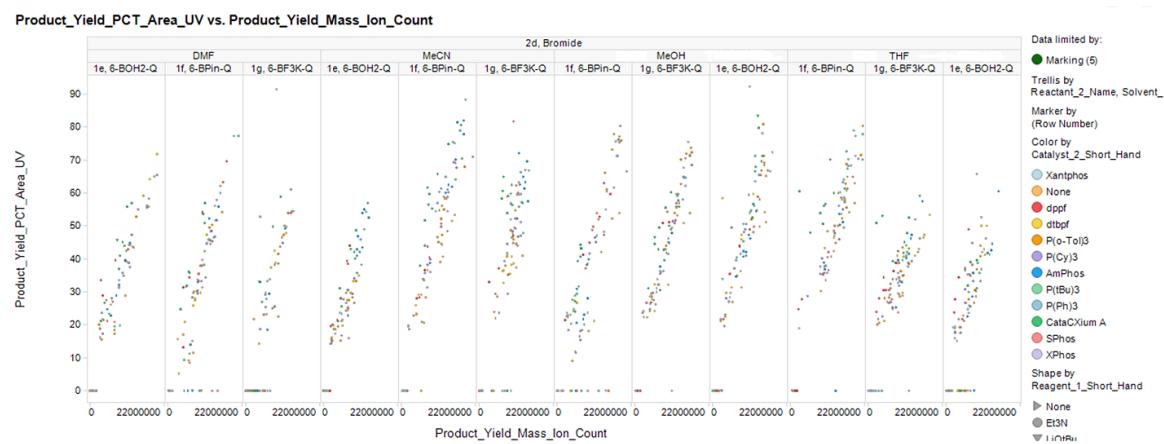


Fig. S24 : Spotfire comparison of UV vs mass ion count for the reaction of bromide 2d with 1e-g



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24. Although water was incorporated into the Suzuki-Miyaura reaction described herein, further experimentation has demonstrated that the system performs equally well for nonaqueous reaction screens.
25. For an example of a typical reaction screen from our laboratories, see (35).

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29. With regard to the modest yields obtained with the Vaportec system, no optimization work was undertaken in terms of combination and stoichiometry of the reagents or residence time in the reactor. In addition, using a two-pump setup necessitated making up mixed solutions of several reaction components before mixing. The major observed by-product in these experiments was homocoupling of the quinoline, **1b**.
30. A potential question arises as to whether the solvent used to make up the stock solution can influence the reaction. However, as demonstrated by Jouyban *et al.* (36), the impact of a mixed solvent in terms of a dielectric constant is a weighted average of the mixed components. As such, the effect of injecting a different solvent into a 9/1 organic/aqueous mixture that is diluted out 1:100 will largely be negated so long as it is inert to the chemistry being screened. The validity of this argument is borne out by the fact that the scaled batch experiments work in a similar manner to the flow experiments even without the solvents used to make up the stock solutions. However, although no effect of the small amount of stock solvent present in the reaction system has been observed thus far, we cannot preclude its potential involvement in all transformation screening.
31. The monomer **5** was used in 13 in-house library campaigns all involving Pd-mediated couplings (9 were Suzuki–Miyaura couplings whereas the remainder were Buchwald–Hartwig reactions). In none of the examples evaluated did **5** lead to any of the desired product in the library matrix.
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33. These results reinforce the efficiency of the mixing within the system, including the aqueous component. In this experiment, two systems are evaluated in which “pure” organic solvents (DMF, MeOH) have been utilized, with no reactions performing well. This is to be expected as the experiment uses the BPin derivative, which to react requires hydrolysis to the B(OH)₂ derivative (22). If sufficient mixing did not occur with the aqueous-based systems then poor reactivity would be expected for all reactions.
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