Supplementary Information

Going-with-the-flow: Nickel-catalysed Suzuki-Miyaura cross-couplings in continuous flow and translation into APIs Savolitinib and Baxdrostat

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Contents

1. General considerations

For experiments that were run at the University of Leeds, HPLC data were obtained on an Agilent 1100 series HPLC instrument with a DAD, calibrated against an internal standard using a known standard of product and the data was processed with Chemstation software.

For experiments that were run at AstraZeneca, HPLC-MS/MS data were obtained on a Shimadzu uHPLC/MS/MS instrument (MCETW_GR6401_UHQDA) and calibrated using a known standard of product.

Three Suzuki-Miyaura cross coupling (SMCC) reactions were studied in this work. A 'model' reaction (a) for the fundamental batch and flow investigations, and two API reactions (Savolitinib (b) and a Baxdrostat intermediate (c)) for further flow experiments (Figure S1).

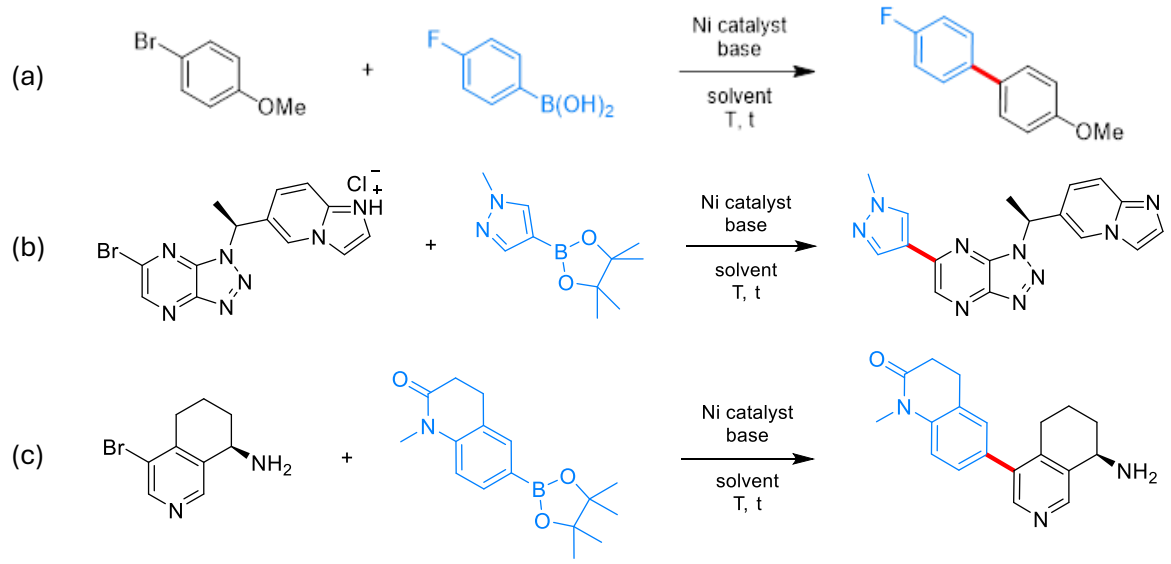


Figure S1. *Reaction schemes for the Ni-catalysed SMCC reactions studied in this work. A 'model' SMCC reaction of 4-bromoanisole with 4-fluorophenylboronic acid to form 4-fluoro-'4-mexthoxybiphenyl (a). A pharmaceutically relevant SMCC, synthesising Savolitinib API (b). A pharmaceutically relevant SMCC, synthesising Baxdrostat API intermediate (c). Further detailed schemes are provided for each SMCC reaction in the relevant sections of this document.*

1.1 Analytical data for 4-fluoro-4'-methoxy-1,1'-biphenyl

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 -7.46 (m, 8.7 Hz, 4 H), 7.10 (t, J = 8.7 Hz, 2 H), 6.97 (d, J = 8.7 Hz, 2 H), 3.85 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 163.27, 159.06, 136.92, 132.49, 128.17, 127.99, 115.49, 114.20, 55.31. $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -116.62 ppm.

1.2 Analytical data for Savolitinib

Previously reported.[1]

1.3 Analytical data for Baxdrostat intermediate

^{1}H NMR (500MHz, DMSO-d_6): δ 8.62 (s, 1H), 8.14 (s, 1H), 7.25-7.22 (m, 2H), 7.16 (d, J = 8.1 Hz, 1H), 3.96-3.93 (m, 1H), 3.29 (s, 3H), 2.93-2.90 (m, 2H), 2.65-2.52 (m, 4H), 1.99 (br. s, 2H), 1.94-1.76 (m, 2H), 1.65-1.55 (m, 2H). ^{13}C{1H} NMR (125 MHz, DMSO-d_6) δ 169.3, 149.2, 146.6, 142.7, 139.7, 135.3, 131.5, 128.3, 128.0, 126.0, 114.7, 47.0, 32.4, 31.1, 29.0, 27.2, 24.5, 18.6.

2. Standard batch catalytic protocol

2.1 General considerations

All batch reactions were carried out at University of Leeds. Where stated, reactions were carried out under an inert atmosphere of dry nitrogen using a Schlenk line. Anhydrous solvents were dried by passing over activated alumina to remove water, copper catalyst to remove oxygen, 3 Å molecular sieves to remove any remaining water via the Dow-Grubbs solvent system and degassed by purging with argon. All chemicals were purchased from Merck, Alfa Aesar or Fluorochem. 4-Fluorophenylboronic acid was purified from chloroform prior to use. All other chemicals were used without further purification.

2.2 Experimental protocol

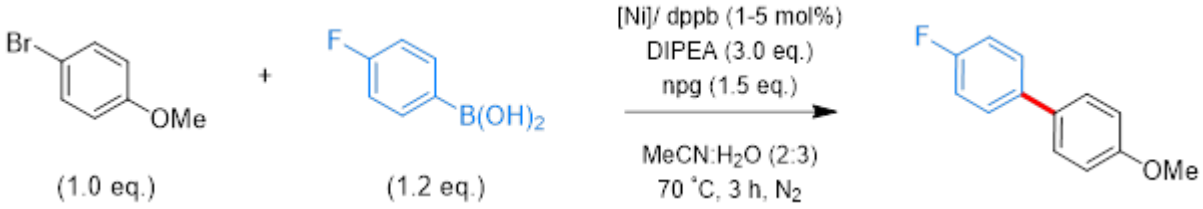


Figure S2. *'Model' Ni-catalysed SMCC reaction of 4-bromoanisole with 4-fluorophenylboronic acid to form 4-fluoro-'4-mexthoxybiphenyl. [Ni] = $Ni(PPh_3)_2$(o-tolyl)Cl; dppb = 1,4-bis(diphenylphosphino)butane; DIPEA = N,N-diisopropylethylamine; npg = neopentyl glycol.*

An oven-dried reaction vial (Vial 1) equipped with a silicone sceptre and magnetic follower was charged with Ni catalyst and dppb (1:1, 0.01 – 0.05 eq.), then evacuated and backfilled with nitrogen. Dry, degassed acetonitrile (1.2 mL, 40% solvent volume) was added via syringe and the vial was heated to 40 °C with stirring. A second oven-dried vial (Vial 2) equipped with a silicone sceptre and magnetic follower was charged with 4-bromoanisole (1.0 eq.), 4-fluorophenylboronic acid (1.2 eq.) and neopentyl glycol (1.5 eq.), then evacuated and backfilled with nitrogen. After 30 mins of stirring, the contents of Vial 1 were transferred into Vial 2 via syringe, and degassed water (1.8 mL, 60% solvent volume) and 1-fluoro-3,5-dimethoxybenzene (0.5 eq., HPLC standard) were added. The resulting mixture was allowed to stir for 5 mins to thermally equilibrate at 70 °C. DIPEA (3.0 eq.) was then added via syringe to Vial 2 to commence the reaction (t_0).

Reaction samples (10 µL) were taken at relevant intervals via syringe and quenched by rapid dissolution in acetonitrile (1 mL). An aliquot of each quenched reaction sample (0.5 mL) was transferred to a HPLC vial for analysis.

2.3 Analytical protocol

Reaction samples were injected onto an InfinityLab Poroshell C18 HPLC column (4.6 x 100 mm length, 4 µm particle size). HPLC mobile phases were A H_2O (18.2 MΩ), B MeCN, both buffered with 0.1% TFA. Details of the HPLC gradient used are as follows: 10% to 90% B 3.5 mins, 90% to 10% B 0.5 min, 10% B 1 min, flow rate 1.75 mL min^{-1}, column temperature 30 °C.

Analyte peak areas were translated to analyte concentrations to determine product yield using the following analytical workflow. Firstly, HPLC peak areas were normalised against the internal standard (IS) (using the 1-fluoro-3,5-dimethoxybenzene) to produce HPLC area ratios *(*Equation S1).

$$HPLC\ area\ ratio\ (analyte) = \frac{HPLC\ peak\ area\ (analyte)}{HPLC\ peak\ area\ (internal\ standard\ (IS))} \quad \textit{Equation S2}$$

HPLC area ratios were then converted to concentrations using analyte response factors (Equation S2).

$$[Analyte] = \frac{HPLC\ area\ ratio\ (analyte)}{Response\ factor\ (analyte)} \quad \textit{Equation S3}$$

The response factor for each analyte was determined by analysing the correlation between HPLC area ratios and known concentrations across a series of calibration standards (0.01 – 0.14 M). Fitting a linear trendline to the data indicated the response factor of each analyte, as the constant of the linear equation (y = **m**x) (Figure S3). The linear relationships derived from these plots had R^2 values > 0.99, ensuring minimal error in converting analyte peak areas to concentrations.

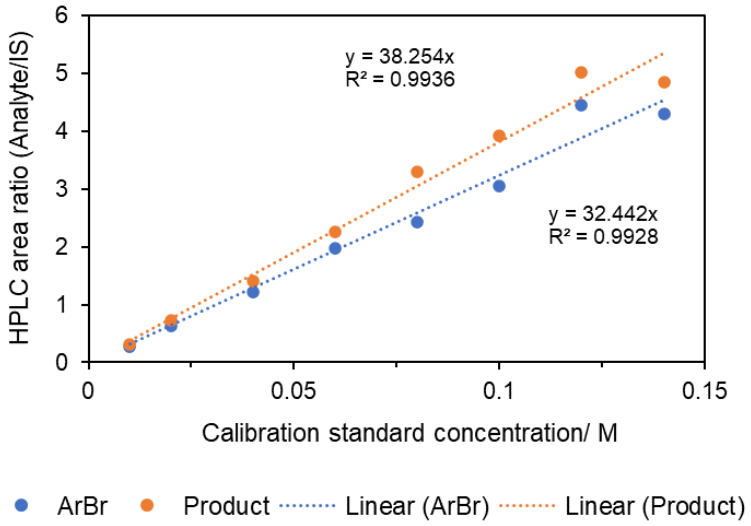


Figure S3. *HPLC calibration of 4-bromoanisole (starting material) and 4-fluoro-4'-methoxybiphenyl (SMCC product) for the quantitative analysis of the model Ni-catalysed SMCC reaction (**Figure S2**). Excellent R^2 values (>0.99) were obtained for both calibrations. Response factors (linear equation constant 'm' (y = mx) were determined for both analytes.*

Reaction yields could then be calculated(Equation S3).

$$Yield = \frac{[Analyte]}{Inital\ [Starting\ material]}$$ *Equation S4*

2.3 Results

A parallel screen of five catalyst loadings (1, 1.5, 2, 2.5, and 5 mol%) was conducted using the same stock solution to ensure consistency across reactions. All reactions were run in accordance with the standard batch catalytic protocol, at a reaction concentration (ArBr) of 0.18 M.

Table S1. *Concentration of starting 4-bromoanisole [ArBr] and SMCC product [ArAr], and yields obtained in batch reactions investigating various Ni-catalyst loadings (1.0, 1.5, 2.0, 2.5 and 5.0 mol%).*

Time (min)	Cat loading 1.0 mol%			Cat loading 1.5 mol%			Cat loading 2.0 mol%			Cat loading 2.5 mol%			Cat loading 5.0 mol%		
	[ArBr] (M)	[ArAr] (M)	Yield (%)	[ArBr] (M)	[ArAr] (M)	Yield (%)	[ArBr] (M)	[ArAr] (M)	Yield (%)	[ArBr] (M)	[ArAr] (M)	Yield (%)	[ArBr] (M)	[ArAr] (M)	Yield (%)
0	0.167	0.000	0.0	0.167	0.000	0.0	0.167	0.000	0.0	0.167	0.000	0.0	0.167	0.000	0.0
0.5	0.163	0.002	1.1%	0.157	0.006	3.4	0.157	0.005	3.0	0.161	0.005	3.1	0.161	0.002	1.3
1	0.153	0.002	1.5	0.142	0.006	3.3	0.151	0.007	4.0	0.161	0.010	6.0	0.148	0.011	6.5
2.5	0.131	0.004	2.2	0.128	0.006	3.4	0.106	0.007	4.3	0.123	0.013	8.1	0.147	0.043	26.0
5	0.130	0.005	3.1	0.120	0.021	12.8	0.097	0.026	15.4	0.102	0.019	11.6	0.060	0.047	28.1
7.5	0.112	0.006	3.9	0.101	0.020	12.1	0.081	0.035	20.9	0.101	0.072	43.4	0.026	0.060	36.2
10	0.109	0.016	9.4	0.087	0.027	16.0	0.068	0.083	49.8	0.073	0.080	48.0	0.008	0.087	52.4
15	0.101	0.023	13.9	0.083	0.041	24.8	0.050	0.088	52.9	0.040	0.094	56.4	0.004	0.118	70.7
20	0.098	0.030	17.8	0.071	0.048	28.5	0.038	0.101	60.7	0.042	0.107	64.4	0.002	0.146	87.9
30	0.096	0.032	19.3	0.054	0.059	35.2	0.024	0.110	66.0	0.034	0.124	74.5	0.000	0.154	92.3
45	0.097	0.040	23.9	0.041	0.063	38.0	0.014	0.117	70.0	0.016	0.147	88.3	0.000	0.159	95.4
60	0.096	0.037	22.4	0.039	0.083	49.8	0.012	0.123	73.7	0.001	0.155	93.2	0.000	0.159	95.6
90	0.095	0.037	22.5	0.040	0.096	57.8	0.008	0.123	73.8	0.004	0.161	96.9	0.000	0.165	99.0
120	0.092	0.034	20.2	0.037	0.089	53.4	0.006	0.119	71.2	0.000	0.162	97.0	0.000	0.166	99.6
180	0.109	0.044	26.6	0.041	0.097	58.5	0.008	0.126	75.4	0.001	0.162	97.4	0.000	0.166	99.9

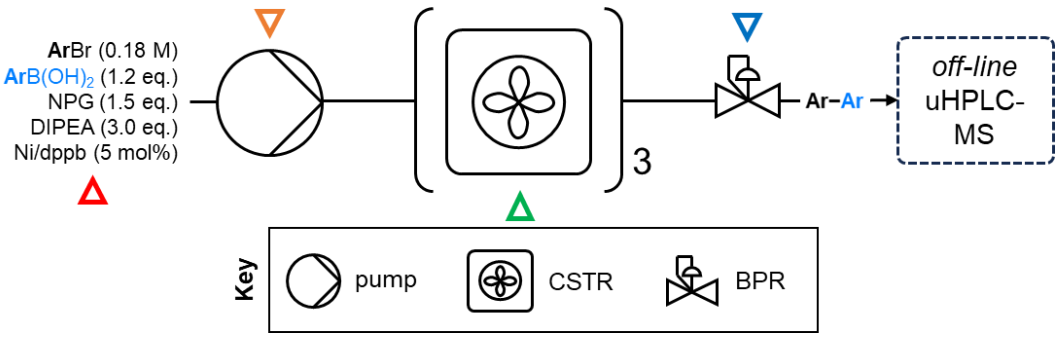
3. Standard flow catalytic protocol

3.1 General considerations

All flow reactions discussed in this work were carried out at AstraZeneca (Chemical Development, Pharmaceutical Technology & Development, Operations, AstraZeneca, Macclesfield, UK). Where stated, reactions were carried out under an inert atmosphere of dry nitrogen using a Schlenk line. Reaction solvents (acetonitrile and water) were degassed by purging with nitrogen. All chemicals were purchased from Merck, Alfa Aesar or Fluorochem and used without further purification.

3.2 Flow reactor set up

A SyrDos syringe pump, a fReactor continuous stirred tank reactor (CSTR) unit (5 mL total volume) and back pressure regulator (BPR) were connected in series using PFA tubing (1/16”) (Figure S4). The fReactor unit consisted of three 1.6 mL reactors held in an aluminium heating block, enabling reactor temperature control. The reactor outlet was sampled at specified time intervals (equivalent to ½ reactor residence time). Samples (~0.05 mL) were quenched by rapid dissolution (2 mL), then analysed by offline HPLC-MS. The offset between the set temperature of the temperature probe and heat transfer to the reaction solution *via* the heating block and CSTR casing was accounted for in setting temperature values.[2] A nitrogen line was connected to the reservoir vessel to provide a headspace of inert gas over the reaction stock solution for the duration of a reaction, minimising oxygen exposure.



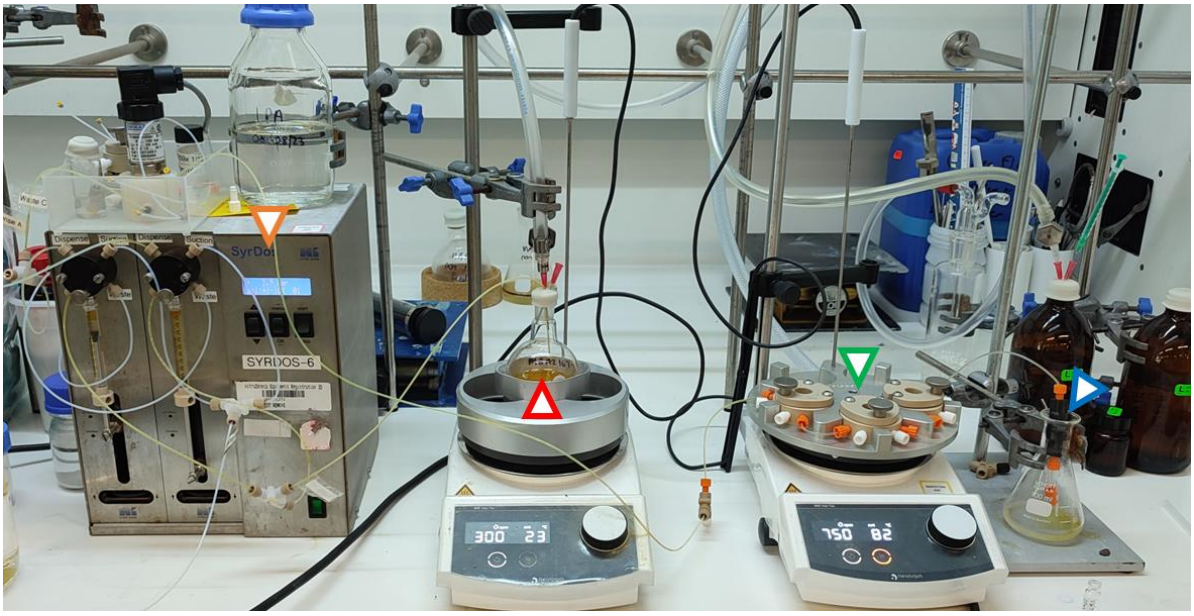


Figure S4. *Schematic of the flow setup used for the development of a continuous Ni-catalysed SMCC reaction (top). Image of the flow reactor setup used for the development of a continuous Ni-catalysed SMCC reaction (bottom). Correspondence between the two is shown by coloured icons.*

Throughout this work, configurable parameters of the setup were varied as per the requirements of each experiment. These parameters were: flow rate, temperature, stock solution concentration and catalyst ([Ni]/dppb) concentration (catalyst loading). BPR cartridges were selected per experiment depending on the temperature of the reactor.

3.3 Experimental protocol

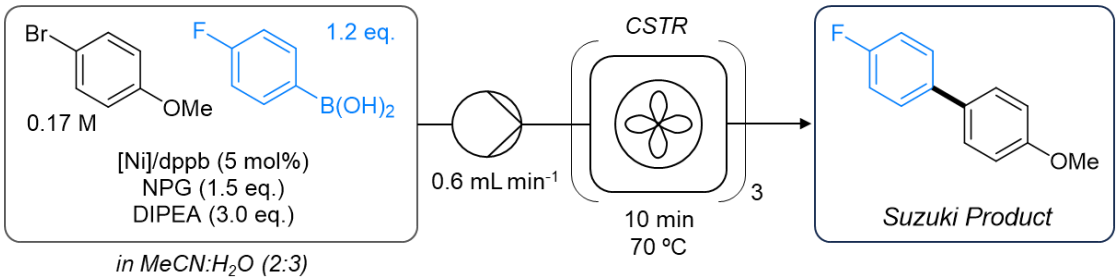


Figure S5. *Flow reaction scheme of the 'model' SMCC reaction of 4-bromoanisole with 4-fluorophenylboronic acid to form 4-fluoro-'4-mexthoxybiphenyl. [Ni] = $Ni(PPh_3)_2$(o-tolyl)Cl; dppb = 1,4-bis(diphenylphosphino)butane; DIPEA = N,N-diisopropylethylamine; npg = neopentyl glycol. m-Terphenyl (0.1 eq.) was used as an internal standard.*

An oven dried round bottom flask (rbf) was charged with solid reagents and purged with N_2 for 0.5 h. The feed reservoir remained under N_2 for the duration of the experiment. Degassed solvents were added to the rbf by syringe, followed by ArBr, then base. The rbf feed reservoir was stirred for the duration of the reaction. The flow reactor was filled with reaction solvent (MeCN:H_2O (2:3)) and the CSTR heated to the desired reaction temperature. The SyrDos pump was connected to the feed stock and switched on (t_0). A sample of the feed stock solution (0.05 mL) was removed for initial analysis at t_0. The reaction feed stock was pumped through the CSTR cascade at a specified flow rate in relation to the desired reaction residence time. Samples from the output feed were taken at intervals t = (0.5 x residence time). The reaction was stopped at t = (5 x residence time) and a second sample was taken of the feed stock (0.05 mL aliquot) to assess the final extent of reaction in the feed reservoir (t_{fin}).

3.4 Results

Initial experiments tested the feasibility of this work, translating the model SMCC reaction previously studied in batch, into flow, as per the reaction conditions in Figure S5. A promising product yield of 74% was obtained at steady state (Figure S6). Steady state was assumed to be 3 x reactor residence time (here 30 min, where residence time was set to 10 min). Reasonably consistent reactant / product concentrations and product yields after this time validated this assumption (Figure S6).

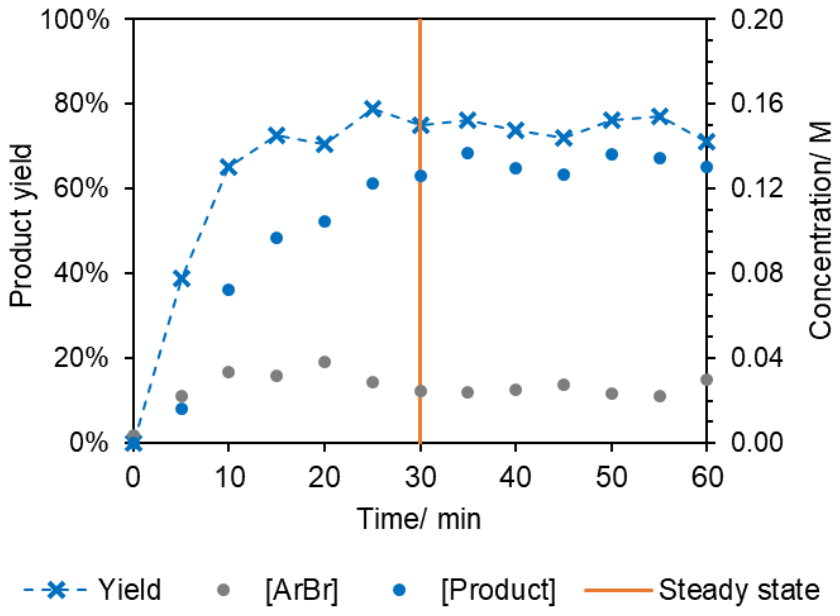


Figure S6. *Reaction yields and concentrations of starting 4-bromoanisole [ArBr] and SMCC product [Product] with time for a continuous Ni-catalysed SMCC reaction. Expected steady state indicated by solid orange line (30 min).*

Pre-flow product formation was assessed, given the one reservoir, one pump configuration of the reactor, to determine if this set up was feasible i.e. there was no significant reaction progress in the reservoir. Samples from the feed reservoir were taken pre- and post-reaction. Minimal conversion of starting material to product (<10% total reaction conversion) was observed in the reservoir (Figure S7). This value was deemed to be acceptable.

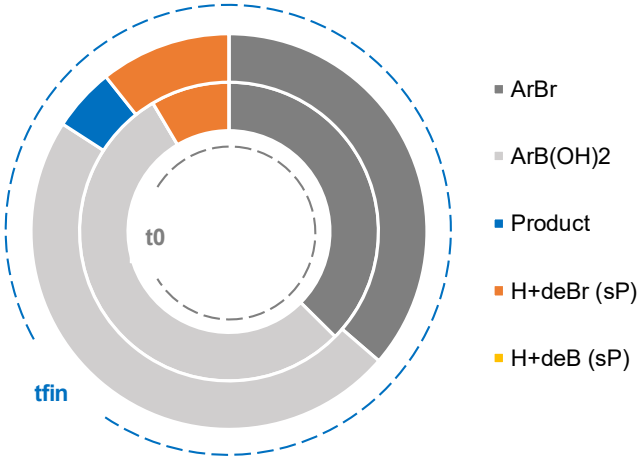


Figure S7. *Analysis of the reaction feed reservoir pre- (t0) and post- (tfin) reaction. Minimal (<10% final yield) conversion to product (blue) is observed in the reservoir at the end of the experiment, although formation of the proto-debrominated (H^+deBr) side product (sP) is observed in both pre- and post- reservoir samples.*

4. Design of Experiment (DoE)

4.1 Experimental protocol

The standard flow catalytic protocol was used for all DoE reactions. Flow rate, temperature, stock solution (ArBr) concentration and catalyst loading were varied by the following ranges (Table S2):

Table S2. *Experimental ranges of flow and reaction variables used during the DoE (and preliminary OVAT) experiments.*

Variable	*Range*
Flow rate (mL min^{-1}) (residence time (min))	0.4 – 1.2 (15 – 5)
Temperature (ºC)	30 – 80
Stock solution (ArBr) concentration (M)	0.13 – 0.23
Catalyst loading (mol%)	1 – 5

4.2 OVAT experiments

Factor ranges for the DoE study were informed by preliminary 'one-variable-at-a-time'(OVAT) experiments. Reaction residence time and concentration were increased (to 15 min and 0.2 M, respectively) and temperature and catalyst loading were decreased (to 30 ºC and 1 mol%, respectively), compared to the 'benchmark' flow reaction conditions (Figure S5). Significant variation in product yields were observed, indicating positive correlations across all variables (Figure S8).

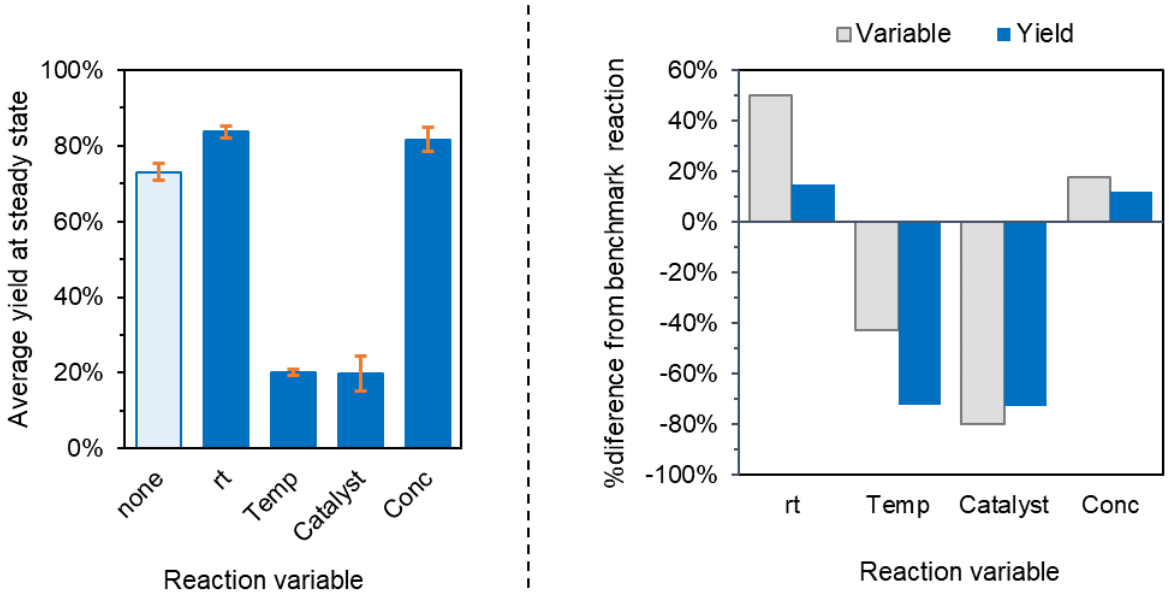


Figure S8. *Results from the pre-DoE variable screen. Average yields at steady state across the variation of different reaction variables (residence time (rt), reactor temperature (Temp), Ni catalyst loading (Catalyst) and reaction concentration (Conc)), alongside average yield obtained using 'standard' reaction conditions (none). Error bars are displayed for each result. Both increases and decreases in reaction yield were observed under the alternative reaction conditions (left). A comparison of % differences (compared to the benchmark flow reaction) between new variable values and resultant yields, across OVAT screening experiments. Positive correlations were seen in all experiments. (right)*

4.3 DoE study

A screening DoE study was run to efficiently probe optimal reaction conditions to improve product yield whilst investigating the feasibility of more sustainable reaction conditions e.g. lower catalyst loading. MODDE Pro software was used to analyse the results of the DoE study using multiple linear regression (MLR) to model the reaction design space. Study design, raw data, and model diagnostic outputs from MODDE are included below.

4.3.1 Study design

Table S3. *DoE study factors, abbreviations (used in MODDE), units and ranges ('Settings')*

Name	Abbreviation	Units	Type	Settings
Residence time	Res	min	Quantitative	5 to 15
Temperature	Temp	C	Quantitative	30 to 80
Catalyst loading	Cat	mol%	Quantitative	1 to 5
Concentration	Conc	M	Quantitative	0.13 to 0.23

***Table S4**. DoE study response - SMCC product yield*

Name	Abbreviation	Units	Condition	Objective	Min	Target	Max	Predicted min	Predicted max	Response range
Yield	Y	%	Observed	Predicted				--	--	

***Table S5.** DoE study design summary*

Design Summary

Objective	Screening
Process model	Interaction
Mixture model	--
Design	**Full Fac (2 levels)**
Runs in design	16
Center points	3
Replicated runs	0
Replicates	0
N = actual runs	19
Maximum runs	12000
Constraints	No

4.3.2 Raw data

***Table S6**. DoE study worksheet, showing each experiment's ID, run order, factor settings and resultant response used in the subsequent analysis.*

Worksheet

Exp No	Exp Name	Run Order	Incl/Excl	Residence time	Temperature	Catalyst loading	Concentration	Yield
17	N17	1	Incl	5	30	1	0.23	6.01318
8	N8	2	Incl	5	80	1	0.13	51.8144
4	N4	3	Incl	5	80	5	0.13	70.2521
11	N11	4	Incl	5	80	1	0.23	62.1989
1	N1	5	Incl	10	55	3	0.18	54.9743
19	N19	6	Incl	15	30	5	0.23	38.6326
7	N7	7	Incl	15	30	1	0.13	11.0236
16	N16	8	Incl	15	80	1	0.23	76.9304
12	N12	9	Incl	15	80	5	0.23	99.5094
6	N6	10	Incl	5	30	5	0.23	10.711
3	N3	11	Incl	10	55	3	0.18	37.5252
13	N13	12	Incl	10	55	3	0.18	42.1423
9	N9	13	Incl	15	30	5	0.13	10.0098
5	N5	14	Incl	15	80	1	0.13	61.8069
2	N2	15	Incl	15	80	5	0.13	94.8134
14	N14	16	Incl	5	80	5	0.23	92.387
18	N18	17	Incl	15	30	1	0.23	16.7183
15	N15	18	Incl	5	30	1	0.13	17.1913
10	N10	19	Incl	5	30	5	0.13	6.51063

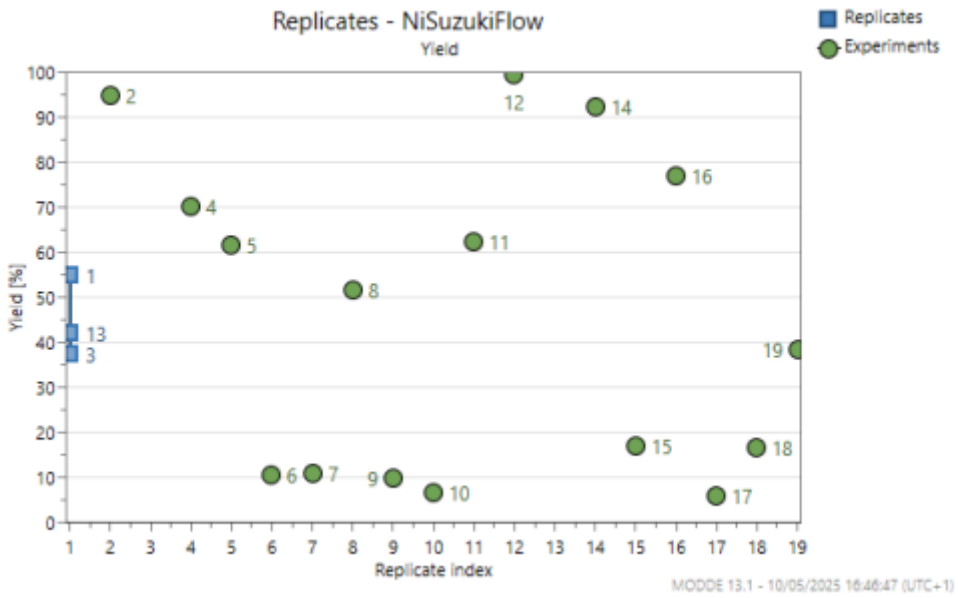


Figure S9. *DoE study replicates plot showing the variability in responses for replicate experiments alongside the distribution of all DoE experiments, indicating good experimental reproducibility.*

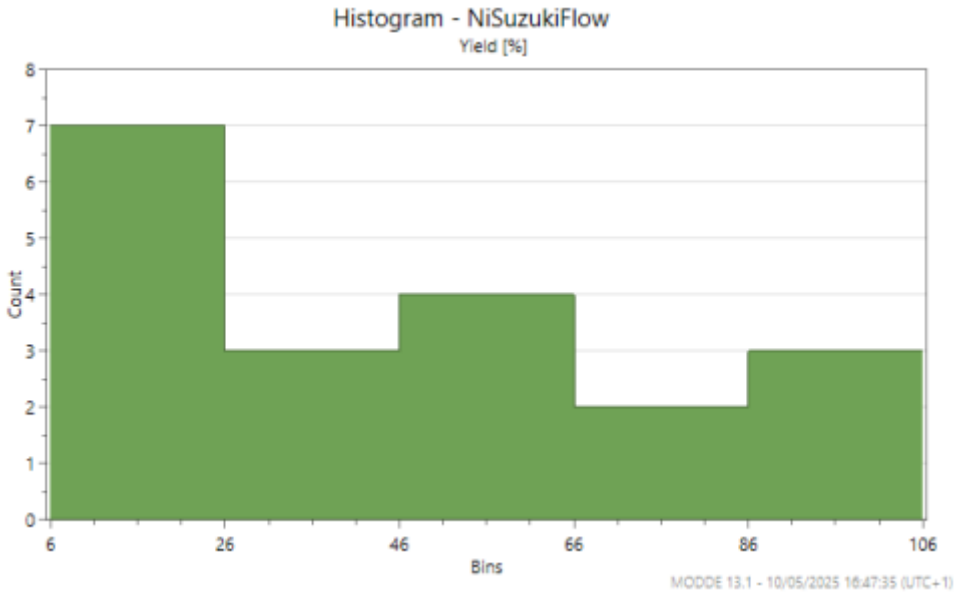


Figure S10. *DoE study histogram.*

4.3.3 Model diagnostics

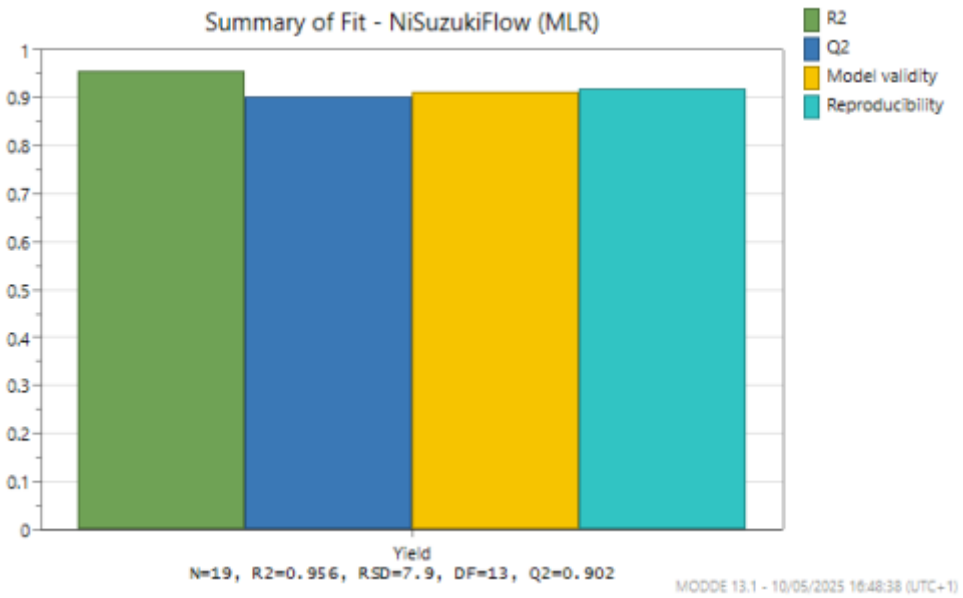


Figure S11. *Summary of fit graph for the MLR model fitted for yield, generated in MODDE Pro. High values across all parameters indicate an excellent model.*

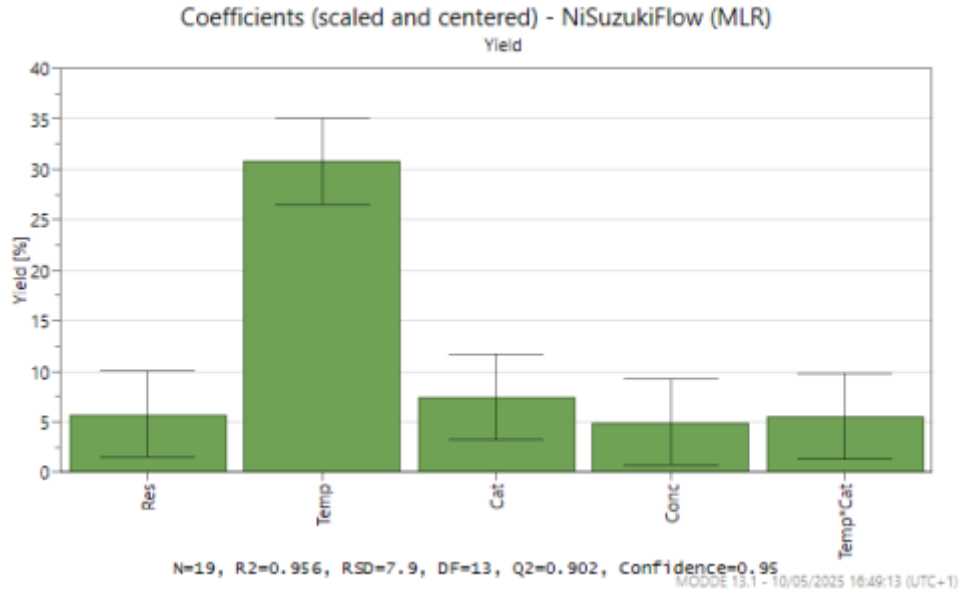


Figure S12. *Coefficients plot representing significant factors in the DoE model, indicating the average effect of each response on increasing the factor from the centre point of the design space to its designated upper limit.*

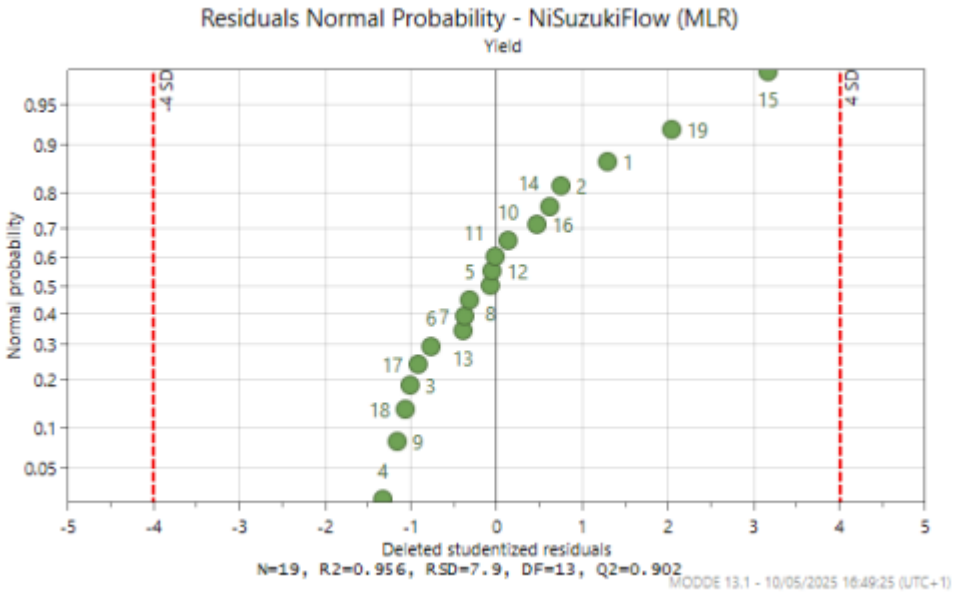


Figure S13. *The Normal Probability Plot of residuals displays the residuals on a double Log scale, allowing for the detection of outliers and assessment of the normality of the residuals.*

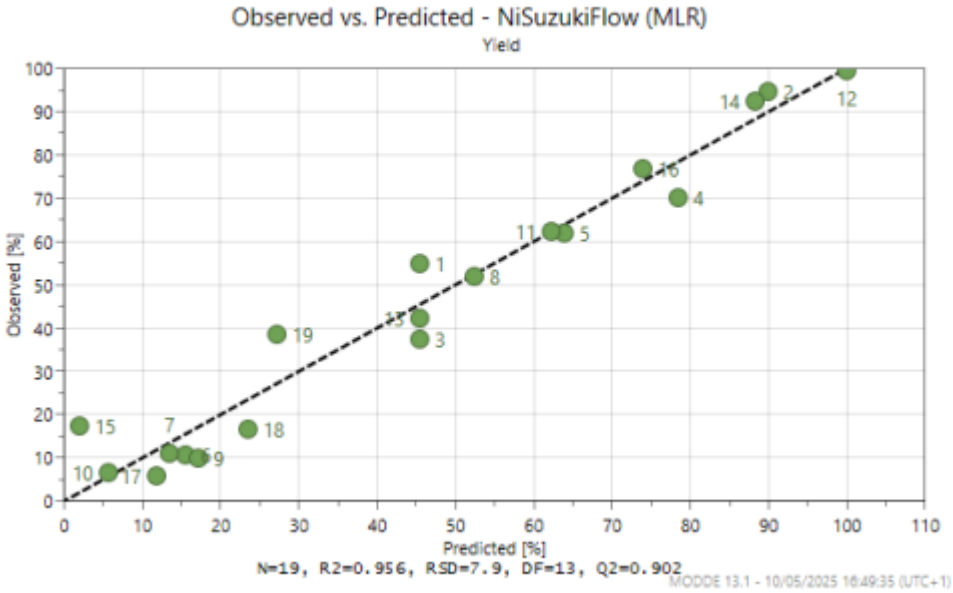


Figure S14. *Observed vs. predicted analysis, plotting observed experimental responses against the predicted model response for each experiment, illustrating the model's accuracy and wellness of fit. The clustered distribution of the data points along the 1:1 line indicated indicates good performance in both*

5. Temperature ramp investigation

The effect of increasing temperature on the reaction outcome was explored further, by ramping the reactor temperature over the course of a flow reaction to investigate a higher temperature range: 70 – 120 °C. Moderately yielding reaction conditions were selected to provide a balance between product and impurity formation, with the effect on both being investigated in this experiment. The formation of protodebrominated and protodeboronated side products is typically promoted by elevated temperatures,[3] and so this was hypothesised to be the likely cause of impurity formation.

The standard flow catalytic protocol was used. Residence time (10 min), stock solution (ArBr) concentration (0.18 M) and catalyst loading (3 mol%) were fixed, and reaction temperature varied by intervals of 10 °C, ranging from 70 to 120 °C. These reaction conditions were predicted to give a product yield of 75% (and an impurity HPLC area% of 19%) at the maximum DoE temperature (80 °C). A nonlinear relationship between product yield and temperature and a positive correlation between impurity formation and temperature were observed (**Figure S15**).

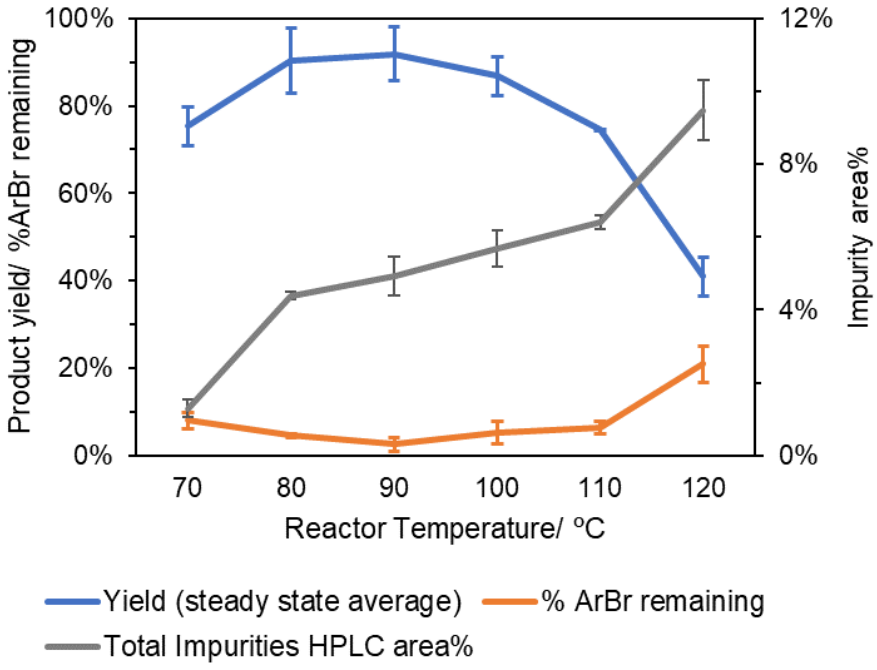


Figure S15. *Comparison of product yield, total impurity area% and remaining starting material (ArBr) across increasing reactor temperature. Flow reaction conditions were: residence time (10 min), catalyst loading (3 mol%) and reactor concentration (0.18 M). Error bars are standard deviation.*

Increasing temperature was beneficial up to 90 °C, an increase in yield was seen up to 92%. However, from 100 - 120 °C, product yield fell sharply to 41%.

6. Translation to pharmaceutically relevant syntheses

The learnings from the development of the model SMCC rection in flow were applied to two pharmaceutical SMCC reactions: Savolitinib API and the Baxdrostat API intermediate (**Figure S1**). The standard flow catalytic protocol was followed, with flow and reaction conditions set as shown in Figure S16.

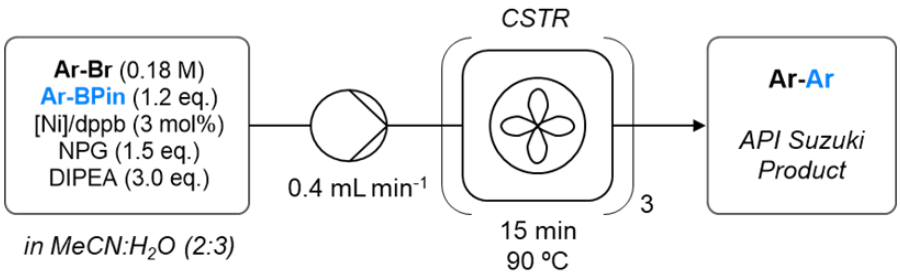


***Figure S16**. Flow reaction scheme for the pharmaceutically relevant SMCC reactions in flow. [Ni] = $Ni(PPh_3)_2$(o-tolyl)Cl; dppb = 1,4-bis(diphenylphosphino)butane; DIPEA = N,N-diisopropylethylamine; npg = neopentyl glycol. m-Terphenyl (0.1 eq.) was used as an internal standard.*

Analyte area% and reaction conversion were used to assess the reaction outcomes, with reaction conversion being calculated as shown in Equation S4.

$$Reaction\ conversion = \frac{HPLC\ area\%\ (Product)}{(HPLC\ area\%\ (ArBr) + HPLC\ area\%\ (Product))} \quad \text{Equation S5}$$

6.1 Savolitinib synthesis in flow

Moderate reaction conversions and low impurity formation was observed for the synthesis of Savolitnib in flow (Figure S17).

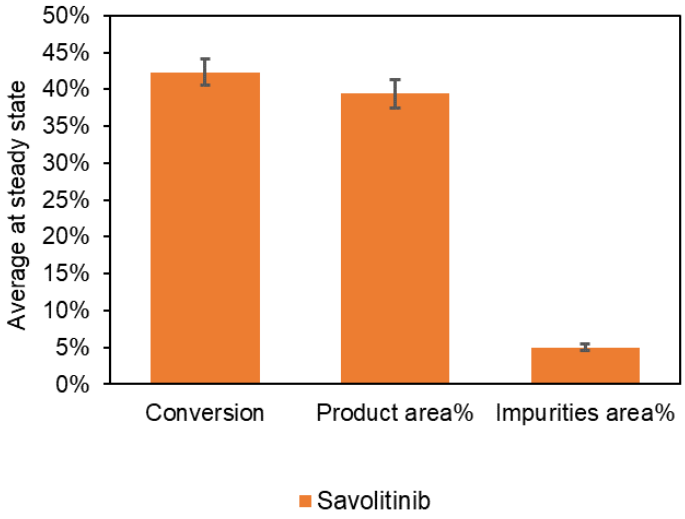


Figure S17. *Comparison of reaction metrics for the Ni-catalysed SMCC reaction to synthesise Savolitnib API in flow. Average values at steady state for conversion, product and total impurity area% are shown. Error bars indicate standard deviation*

6.2 Baxdrostat intermediate synthesis in flow

Moderate reaction conversions and low impurity formation was observed for the synthesis of the Baxdrostat intermediate in flow (Figure S18).

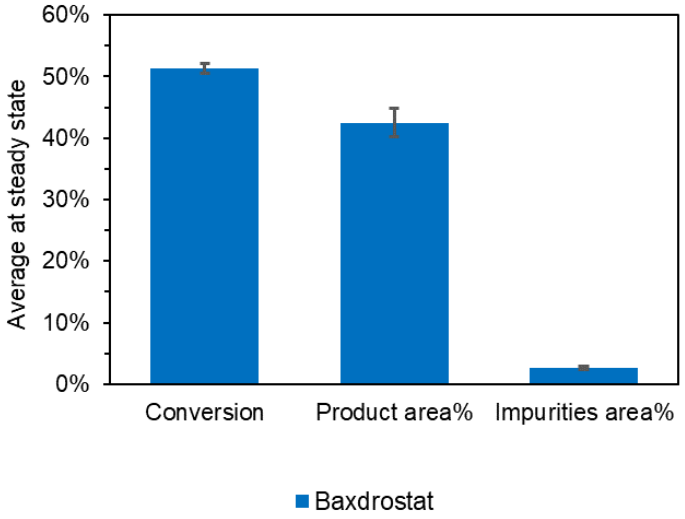


Figure S18. *Comparison of reaction metrics for the Ni-catalysed SMCC reaction to synthesise Baxdrostat API intermediate in flow. Average values at steady state for conversion, product and total impurity area% are shown. Error bars indicate standard deviation*

7. References

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(2) Kapur, N. fReactor: Intuitive tools for flow chemistry: Temperature within the fReactor-Classic downloaded fromhttps://freactor.com/getrunning_fReactorClassic.html 2019.

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