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Going-with-the-flow: nickel-catalysed Suzuki–Miyaura cross-couplings in continuous flow and translation into APIs savolitinib and baxdrostat

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Nickel-catalysed cross-coupling reactions offer a versatile and more sustainable approach to forming carbon–carbon bonds, expanding the scope of accessible structures and enabling new synthetic strategies. The use of flow chemistry in catalysis can offer several advantages over traditional batch conditions, including faster rates, better heat and mass transfer and ease of scaling up. In this work we report the translation of a benchmark nickel-catalysed Suzuki–Miyaura cross-coupling reaction into continuous flow. Using a Design of Experiment approach, high yield of cross-coupled product has been achieved at 1 mol% catalyst loadings which was not attainable in batch under analogous conditions. Optimised conditions were transferred directly to two APIs, savolitinib and a baxdrostat intermediate, with good conversion established without any further screening of conditions.

Introduction

Carbon–carbon cross-coupling reactions are among the most powerful tools in organic chemistry.[1] They allow for the efficient and selective formation of carbon–carbon bonds, enabling the synthesis of complex molecules with high precision. These reactions are widely used in pharmaceuticals, agrochemicals, materials science, and fine chemical industries. Suzuki–Miyaura cross-coupling (SMCC) is one of the most widely used carbon–carbon bond-forming reactions in applied synthetic chemistry.[2–5] It typically involves the precious palladium-catalysed coupling of an aryl or vinyl halide with an organoboron compound in the presence of a base. However, nickel catalysts are emerging as promising alternatives to palladium due to their cost-effectiveness and unique reactivity.[6–11] Nickel can activate more challenging substrates such as unreactive alkyl halides and heteroaryl halides which are important in industrial target structures. Due to its ability to undergo single-electron transfer (accessing oxidation states Ni^0, Ni^I. Ni^{II} and Ni^{III}), nickel also performs well in radical-type mechanisms.

Translating batch reactions into continuous flow can deliver substantial improvements in process efficiency and sustainability.[12–15] Unlike batch reactions, where reactants are combined into a single vessel with an intrinsic start and end to each 'batch', flow reactions are conducted in continuous streams, with simultaneous input of reagents and removal of products. This enables enhanced process control and significantly improved heat and mass transfer, resulting in improved reaction yields, productivity and safety in comparison to batch operations. The use of continuous flow in SMCC reactions has largely been focused on palladium catalysed processes, delivering improvements in reaction performance.[16–21] However, the application of nickel catalysts in continuous SMCC reactions remains unexplored, with no published examples to our knowledge. In addition to the advantages of continuous flow chemistry outlined above, the translation of Ni-catalysed processes into flow could offer further merit, specific to these catalytic systems. For example, prevention of catalyst deactivation through enhanced process control could deliver productivity enhancements unachievable in batch, which also lends itself to the reduction of side reactions and improved reaction robustness. Furthermore, considering industrial process and scale up, reduced handling requirements and exposure to material in flow could alleviate concerns surrounding the toxicity of nickel, improving process safety.

Goals of study:

- Development of Ni-catalysed SMCC reactions in flow.
- Design of Experiment study to determine the individual and combined effects of different factors.
- Determination of conditions under which reactions run successfully at relatively low catalyst loadings.

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• Translation of the flow conditions to industrially relevant API examples.

Results and discussion

Batch experiments with translation into flow

Guo *et al.* developed conditions for Ni-catalysed SMCC reactions using $Ni(PPh_3)_2$(*o*-tolyl)Cl as a pre-catalyst, which was successful in coupling a wide range of pharmaceutically relevant substrates (Fig. 1).[22] These conditions (reported by Bristol Myers Squibb Company) are one of the most process-friendly, and robust for API-like compounds, for Ni-catalysed SMCCs currently in the literature. The reactions incorporate an additional 1,4-bis(diphenylphosphino)butane (dppb) ligand, neopentyl glycol as an additive, and an optimised biphasic solvent system of 2 : 3 2-MeTHF : H_2O at 50–70 °C. Glycol type compounds are known to enhance SMCC reactions. Aqueous biphasic reaction mixtures are regularly used in palladium-catalysed SMCC reactions.[24] However, the use of a monophasic solvent system would be more amenable to continuous flow chemistry. Therefore, modified reaction conditions using MeCN : H_2O (2 : 3) were initially developed in batch.†

The cross-coupling of 4-bromoanisole with 4-fluorophenylboronic acid was examined under batch using similar conditions to Guo *et al.*, with a solvent switch from 2-MeTHF to MeCN (Fig. 2(a)). Five Ni pre-catalyst loadings ranging from 1–5 mol% were chosen, with regular samples being taken to generate time course profiles (Fig. 2(b)). Activity was high when using 5 mol% and 2.5 mol% pre-catalyst loading, with ~50% yield achieved in 10 minutes and >99% after 120 minutes. Whilst initial activity was relatively high in the first 10 minutes at 2.0 mol% pre-catalyst loading, this dropped off with a maximum yield of 70%. Yield was lower for 1.5 mol% catalyst loading and only reached a maximum of ~20% at 1 mol% catalyst loading. Catalyst deactivation in these batch SMCC reactions is clearly problematic at low pre-catalyst loadings, presenting a challenge for scale-up processes. Variation in the electronic effects of the substrates is known to impact reaction performance in SMCC reactions.[25] Electron withdrawing groups on the organohalide species tend to promote oxidative addition, whilst electron donating groups on the organoboron species generally facilitate transmetalation. The latter trend is particularly relevant in Ni-catalysed SMCC reactions, where transmetalation is often observed to be the rate limiting step.[26] Therefore, a second reaction was examined at 5 mol% pre-catalyst loading using an organoboron reagent with an electron donating group (Fig. 2(c)). As expected, initial rates were higher for this second reaction, with comparable overall product yields being achieved for both SMCC reactions (>99% yield after 2 h). The success of these reactions using organoboron reagents, with contrasting electronic effects, indicates that MeCN is a suitable replacement for 2-MeTHF. Hence, these conditions were adopted for flow.

A SyrDos syringe pump, a fReactor[27] continuous stirred tank reactor (CSTR) unit (3 × 2 mL) and back pressure regulator (BPR) were connected in series using PFA tubing (1/16″) (Fig. 2(d)). The fReactor unit consisted of three 2 mL reactors held in an aluminium heating block, enabling full reactor temperature control. 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 given reaction, minimising exposure to trace air. Reaction (a) was used as a benchmark for development in flow. Initially, reaction temperature (70 °C) and reagent concentration (0.17 M) were kept in line with the batch protocol, with solvent and reagent equivalents also remaining the same. The residence time was set to 10 minutes based on a ~50% yield (product) at this time-point in batch. Samples were collected every 5 minutes and quenched for off-line uHPLC analysis. At steady state, the initial flow conditions resulted in a product yield of 74% (Fig. 2e). Achieving a greater yield than in the batch experiment after 10 minutes reaction time was very encouraging and highlights the advantages of running these reactions using continuous flow technologies.

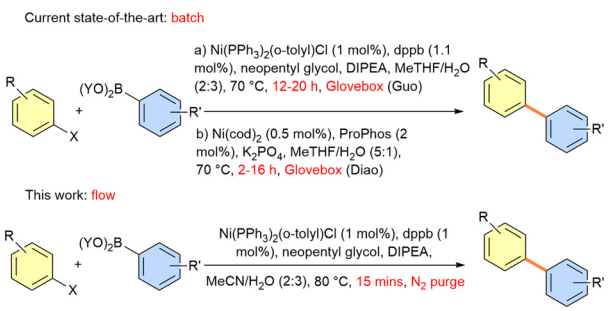

Fig. 1 Current state-of-the-art in Ni-catalysed SMCC reactions in batch,[22,23] and work developed here in flow.

† Scott Rice, AstraZeneca, Unpublished results.

Design of Experiment

To further develop and enhance the Ni-catalysed SMCC reaction in flow, a Design of Experiment (DoE) approach was used to determine the individual and combined effects of different factors. The overall aim was to efficiently probe optimal reaction conditions to improve product yield whilst investigating the feasibility of more sustainable reaction conditions, *e.g.* lower pre-catalyst loading. Four factors were selected for the DoE study; residence time, temperature, catalyst loading and reaction concentration. To confirm the suitability of these factors and establish high and low bounds for the design space, a series of one variable at a time (OVAT) experiments were conducted (see Section S4.2). From this, residence time (5–15 minutes), temperature (30–80 °C), catalyst loading (1–5 mol%) and reagent concentration (0.13–0.23 M) ranges were selected for the DoE study.

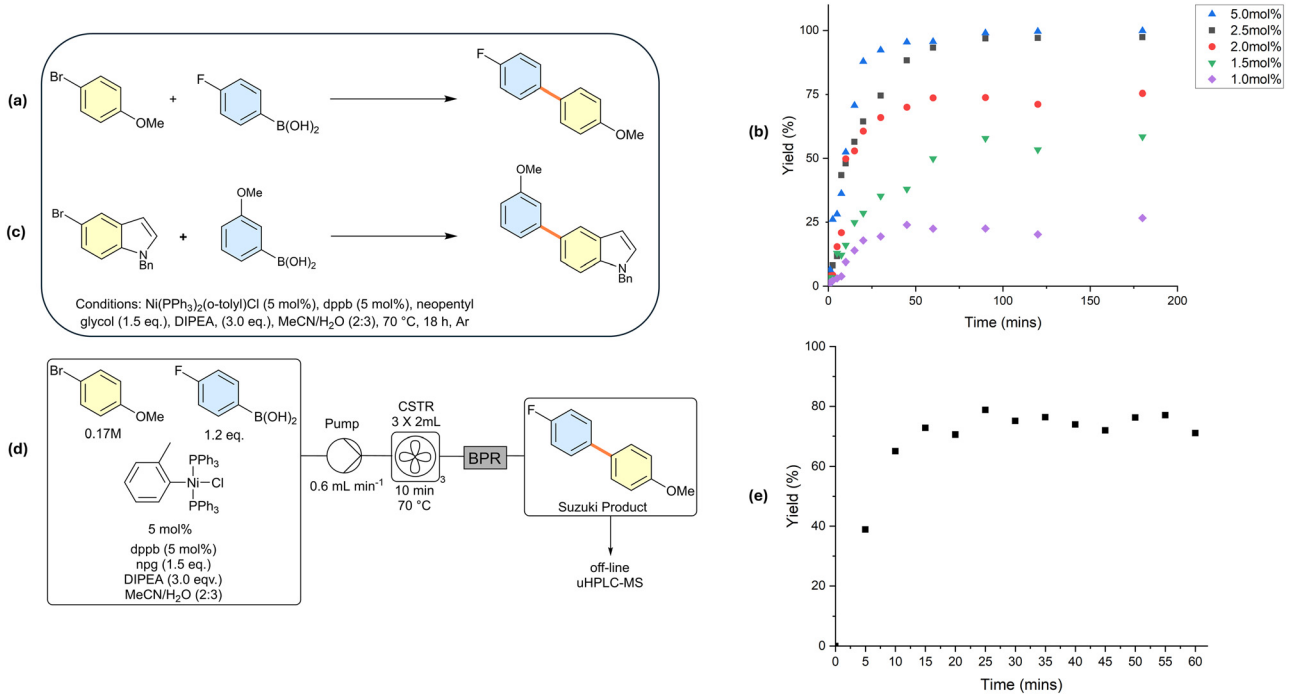

Fig. 2 (a) Ni-catalysed SMCC reaction of 4-bromoanisole and 4-fluorophenylboronic acid in batch. (b) Plot of the yields of product *versus* reaction time for different catalyst loadings in the SMCC reaction of 4-bromoanisole and 4-fluorophenylboronic acid in batch. (c) Ni-catalysed SMCC reaction of 1-benzyl-5-bromo-1*H*-indole and 3-methoxyphenylboronic acid in batch. (d) Ni-catalysed SMCC reaction of 4-bromoanisole and 4-fluorophenylboronic acid in continuous flow. (e) Plot of the yields of product *versus* sampling time (residence time = 10 minutes) for the SMCC reaction of 4-bromoanisole and 4-fluorophenylboronic acid in flow.

16 experiments were performed (*i.e.* four factors at two levels each) in addition to three technical replicates of the centre point. All 19 reactions proceeded with a degree of success, with product yields ranging from 1–99% (Fig. 3(a)). MODDE Pro software was used to analyse the results of the DoE study using multiple linear regression. Values >0.9 were obtained for all 'summary of fit' parameters, indicating that the model will predict, to a high degree of confidence, the yield in the continuous flow Ni-catalysed SMCC reaction. The model's accuracy was analysed by comparing observed product yields to predicted yields for each experiment. All data points were clustered closely along the 45° line indicating a well-fitted model, as corroborated by the DoE summary of fit (Fig. 3(b)).

All four factors had a positive effect on the reaction. The reactor temperature was the most significant with an average positive effect of 31%, 25% greater than any other coefficient in the model (Fig. 3(c)). Additionally, a significant interaction was observed between temperature and pre-catalyst loading. As temperature increased, the lines representing high and low levels of catalyst loading diverged, indicating that the effect of catalyst loading became more pronounced at higher temperatures (Fig. 3(d)). Although significant, the relative effect of this interaction was less than the individual effects of the factors involved.

The design space resulting from this analysis was mapped using a 4D contour plot to indicate regions where product yield can be maximised (Fig. 4). The greatest reactor temperature, residence time, catalyst loading and concentration resulted in the highest product yields, illustrated by the red region in the top right corner of the contour plot. Temperature was evidently the most significant factor, with even moderate yields (>50%) obtained at high temperature (80 °C) when the other factors were minimised. Elevated temperatures may provide improvements in reaction yield due to acceleration of initial rates, even at low pre-catalyst loading, whilst the precise reaction control of a flow reactor minimises potential side reactions that would otherwise also be enhanced. Reducing pre-catalyst loadings to ≤1 mol% would maximise sustainability gains (mainly CO_2 savings) from using Ni-catalysed SMCC reactions in comparison to palladium.

Furthermore, nickel is included as "critical" in the UK 2024 Criticality Assessment,[28] hence decreasing pre-catalyst loading is of significant interest. In this study, by maximising the other three factors, a product yield of 77% was achieved at 1 mol% pre-catalyst loading, a significant increase from the initial 9% yield in the batch reaction and 20% yield in the OVAT flow experiment run at 1 mol% catalyst loading (Table 1).

The notable improvements in yield at 1 mol% pre-catalyst loading when conducted in flow highlights the advantages of continuous flow for these types of reactions. Enhanced heat transfer and precise temperature control allows for operation at higher temperatures without deactivating the Ni catalyst species. A longer residence time ensures that reactants have

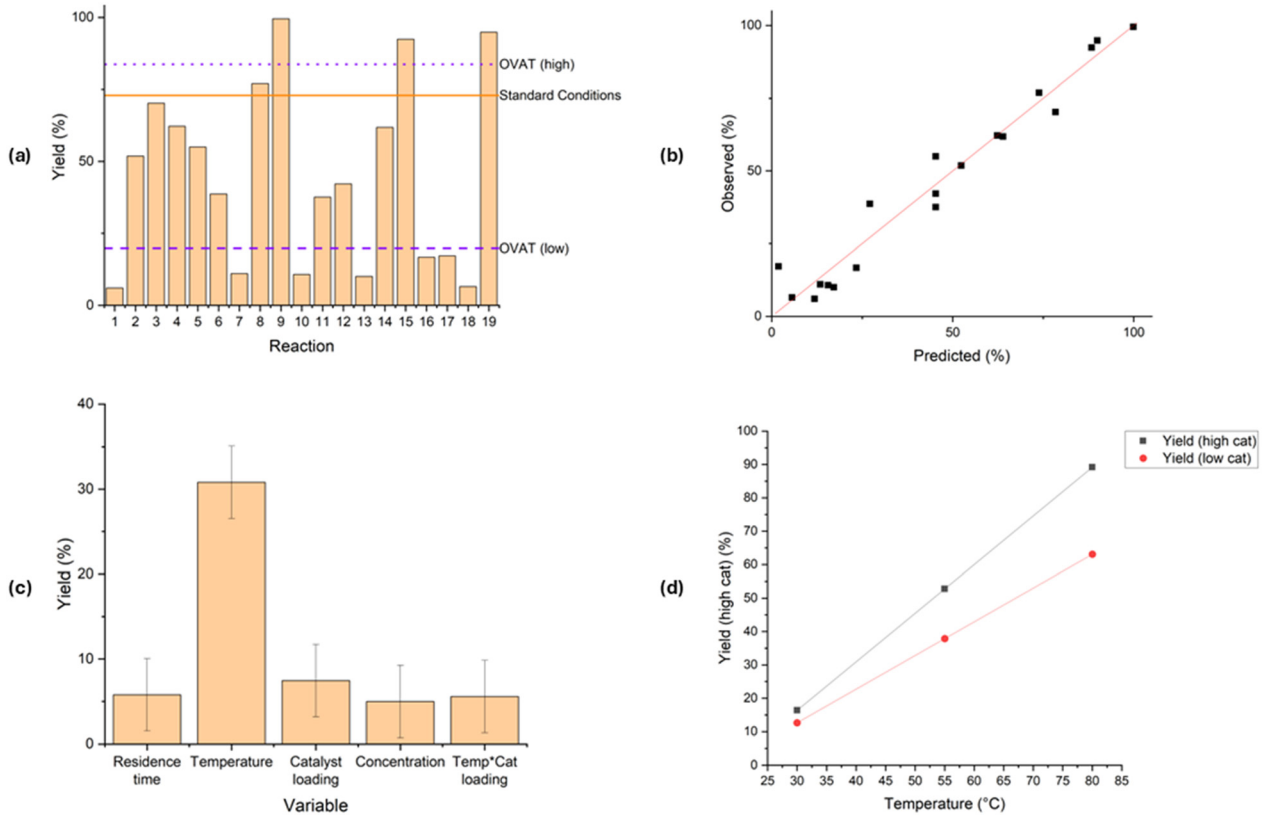

Fig. 3 (a) Plot of reaction yields obtained across DoE experiments for the Ni-catalysed SMCC reaction of 4-bromoanisole and 4-fluorophenylboronic acid in continuous flow. Horizontal lines are added for the highest (increased residence time) and lowest (decreased catalyst loading) yields obtained in the initial OVAT experiments, and for the yield obtained in the initial batch reaction under standard conditions. (b) Observed *versus* predicted yields generated in MODDE Pro, illustrating the model's wellness of fit. (c) DoE coefficient plot representing significant factors in the DoE model. (d) Factor interaction plot for temperature and catalyst loading, illustrating interaction between the two factors.

adequate time to fully react, particularly for low pre-catalyst concentrations, whilst improved mass transfer and the ability to maintain high reactor concentrations ensure consistent delivery of reactants to the pre-catalyst, maximizing its effectiveness. Additionally, operating in flow can minimise catalyst deactivation and side reactions by continuously removing products and inhibitory species from the reactor, maintaining pre-catalyst activity throughout the process. Using a systematic DoE approach, greater than 33% improvement in reaction yield was achieved in comparison to initial OVAT flow studies (Table 1).

Translation to active pharmaceutical ingredients (APIs)

Savolitinib is an API that targets the MET protein which, when mutated or overexpressed, can contribute to cancer progression.[29] Clinical trials are actively evaluating its efficacy for the treatment of various cancer types including non-small cell lung[30] and papillary renal cell carcinoma.[31] The synthesis of Savolitinib involves a late-stage SMCC reaction of a heteroaryl bromide with a heteroaryl pinacolborane (Fig. 5(a)).[32] This step typically involves a palladium catalyst at relatively high catalyst loadings (≥1.0 mol%), with an isolated yield of 76% being achieved at large scale (~100 kg). The ability to replace palladium with nickel in these types of industrially-relevant reactions would significantly reduce costs and ensure long-term sustainability of the process. However, Lewis basic heteroaryl reagents can be challenging for nickel due to their coordinating ability, in addition to pinacol being the least reactive of the common SMCC nucleophiles.[33,34] Boronic esters are often selected in industrial processes to alleviate analytical and manufacturing challenges with boronic acids. They are also thought to be more stable to decomposition through protodeboronation, aiding process efficiency and reproducibility. Baxdrostat is an API that is undergoing clinical trials to assess its efficacy in treating cardiovascular and renal conditions.[35,36] This also involves a late stage SMCC reaction of a heteroaryl with a pinacolborane (Fig. 5(b)). These challenging, applied and timely reactions were examined in the Ni-catalysed SMCC reaction using continuous flow technologies.

Flow reactions for the two API examples were conducted using the same reactor setup as previous flow experiments (Fig. 5(c)). Optimised conditions from a temperature ramp study (see Section S5) following the DoE optimisation were selected as they demonstrated the highest yields at a relatively low catalyst loading (3 mol%) in the model SMCC reaction. As previously discussed, the deployment of lower Ni loadings is of

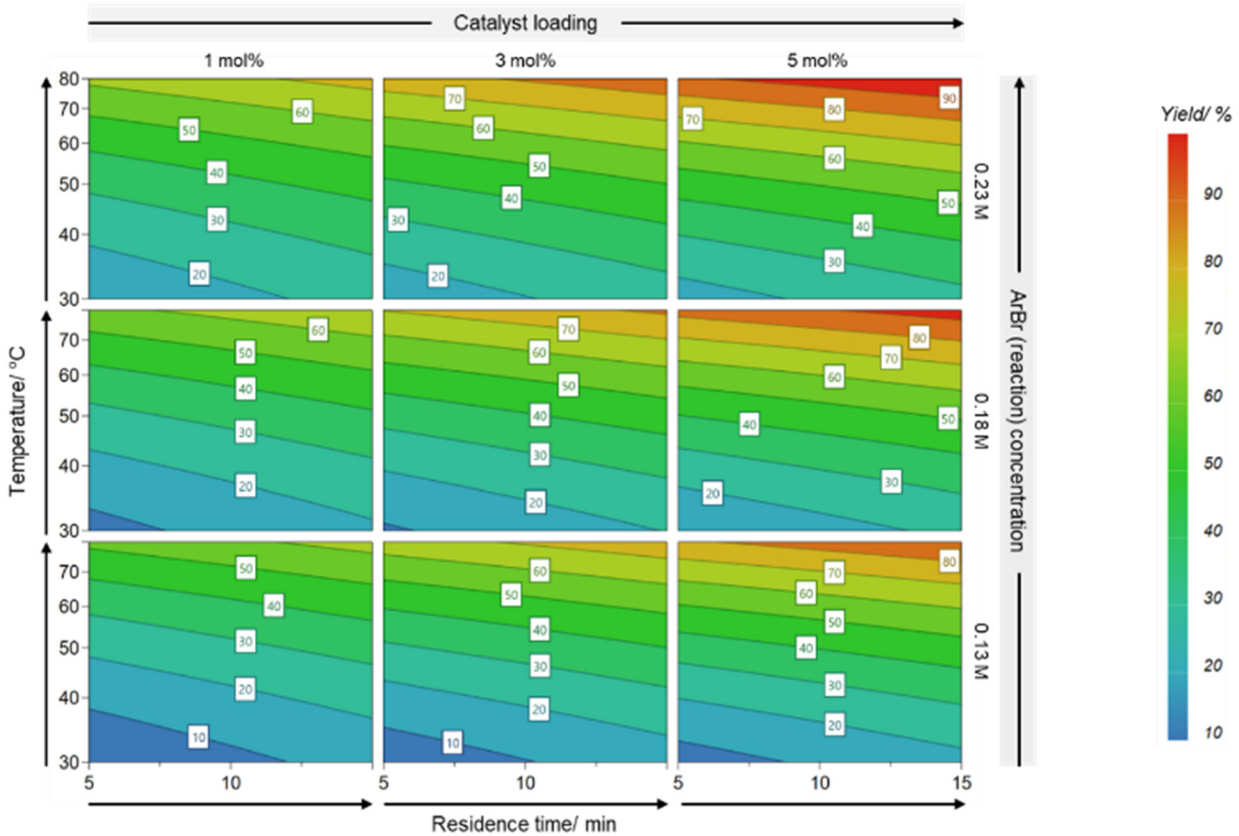

Fig. 4 4D contour plot, generated in MODDE Pro, illustrating the effect of temperature (left axis), residence time (bottom axis), concentration (right axis) and catalyst loading (top axis) on product yield for the Ni-catalysed SMCC reaction of 4-bromoanisole and 4-fluorophenylboronic acid in continuous flow. The value of the response in a given region of the design space (yield) is indicated by colour scale; low (<10%, blue) to high (>90%, red). Yield was shown to be maximised (98.4%) in the top right corner of the design space (all factors high).

Table 1 Comparison of yields obtained in the Ni-catalysed SMCC reaction of 4-bromoanisole and 4-fluorophenylboronic acid through modifying conditions under different reaction approaches

Reaction type	Catalyst loading (mol%)	Temperature (°C)	Residence time (min)	Reagent concentration (M)	Yield (%)
Batch	5	70	10	0.17	52
Batch	1	70	10	0.17	9
Flow (OVAT)	5	70	10	0.17	74
Flow (OVAT)	1	70	10	0.17	20
Flow (DoE)	5	80	15	0.23	>99
Flow (DoE)	1	80	15	0.23	77

significant industrial interest, so it was selected as a priority reaction criteria here. Additionally, due to solubility limits of both organobromide starting materials, 0.18 M was the highest practical reactor concentration. By simply transferring flow conditions developed on a model reaction to the production of APIs, good conversions of 42% and 51% for savolitinib and baxdrostat intermediate respectively were achieved (Fig. 5(d)). Product area percentages were only slightly lower than conversion, particularly in the case of savolitinib, showing the selectivity of this reaction with few by-products. The outcome of these reactions demonstrates the remarkable tolerance of the continuous flow chemistry and conditions to more complex substrates, and in particular the ability to couple continuous flow with the replacement of palladium by nickel in industrially relevant SMCC processes. The reaction conditions were developed on a simple substrate and have shown that they can be translated to complex APIs with no modification.

Conclusions

The use of continuous flow chemistry for the Ni-catalysed SMCC reaction has been demonstrated for the first time. Transferring a model batch reaction into continuous flow has highlighted the advantages of this technology for these types of reactions. A systematic DoE study enabled high yields to be obtained at relatively low catalyst loadings when using

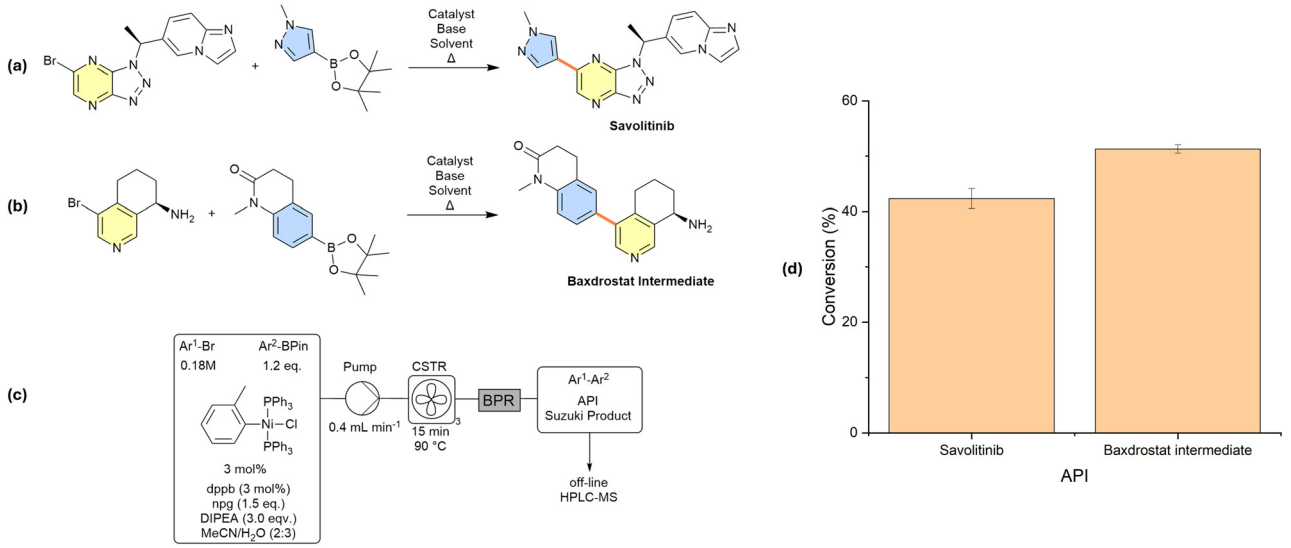

Fig. 5 SMCC reactions in the synthesis of APIs (a) savolitinib and (b) baxdrostat. (c) Ni-catalysed SMCC reactions to produce APIs in continuous flow. (d) Plot of the reaction yields obtained for savolitinib and baxdrostat intermediate.

continuous flow, which were not achievable in batch conditions. Direct translation of the continuous flow conditions to two APIs with promising outcomes has demonstrated the potential for industrial application with the potential to improve the speed, scalability efficiency and sustainability of Ni-catalysed SMCC reactions.

Author contributions

M. Bradbury conducted most of the experimental work, data acquisition and analysis. S. Rice conducted preliminary experimental work leading to the identification of appropriate reaction conditions. Experimental work was performed at AstraZeneca under the supervision of S. Rice, R. Munday and M. Jones, and at the University of Leeds under the supervision of C. Willans, R. Bourne and N. Kapur. All authors have contributed to regular discussion and intellectual contribution to the work. The manuscript was written by C. Willans with input from all authors.

Conflicts of interest

There are no conflicts to declare.

Data availability

Raw data for this article are available through the University of York Research Database at https://doi.org/10.15124/7b2ec6df-bdd3-4176-9a8f-9163ddd3cd1e.

Supplementary information (SI): detailing analytical data, catalytic and analytical protocols (flow and batch), design of experiment and temperature ramp investigations. See DOI: https://doi.org/10.1039/d5cy01194a.

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Notes and references

1 N. Hazari, P. R. Melvin and M. M. Beromi, *Nat. Rev. Chem.*, 2017, **1**, 0025.
2 D. Blakemore, in *Synthetic Methods in Drug Discovery*, Royal Society of Chemistry, 2016, pp. 1–69, DOI: 10.1039/9781782622086-00001.
3 I. Maluenda and O. Navarro, *Molecules*, 2015, **20**, 7528–7557.
4 M. C. D'Alterio, È. Casals-Cruañas, N. V. Tzouras, G. Talarico, S. P. Nolan and A. Poater, *Chem. – Eur. J.*, 2021, **27**, 13481–13493.
5 Y. M. A. Yamada and A. Sen, *Synthesis*, 2024, **56**, 3555–3574.
6 J. Yamaguchi, K. Muto and K. Itami, *Eur. J. Org. Chem.*, 2013, **2013**, 19–30.
7 V. P. Ananikov, *ACS Catal.*, 2015, **5**, 1964–1971.
8 Z. Li and L. Liu, *Chin. J. Catal.*, 2015, **36**, 3–14.
9 J. B. Diccianni and T. Diao, *Trends Chem.*, 2019, **1**, 830–844.
10 B. A. Baviskar, P. V. Ajmire, D. S. Chumbhale, M. S. Khan, V. G. Kuchake, M. Singupuram and P. R. Laddha, *Sustainable Chem. Pharm.*, 2023, **32**, 100953.
11 S. Datta, A. Chandra and S. Bhattacharya, *Inorg. Chim. Acta*, 2024, **572**, 122249.
12 B. Gutmann, D. Cantillo and C. O. Kappe, *Angew. Chem., Int. Ed.*, 2015, **54**, 6688–6728.
13 D. Dallinger and C. O. Kappe, *Curr. Opin. Green Sustainable Chem.*, 2017, **7**, 6–12.
14 M. B. Plutschack, B. Pieber, K. Gilmore and P. H. Seeberger, *Chem. Rev.*, 2017, **117**, 11796–11893.

15 L. Capaldo, Z. Wen and T. Noël, *Chem. Sci.*, 2023, **14**, 4230–4247.
16 T. N. Glasnov and C. O. Kappe, *Adv. Synth. Catal.*, 2010, **352**, 3089–3097.
17 C. Len, S. Bruniaux, F. Delbecq and V. S. Parmar, *Catalysts*, 2017, **7**, 146.
18 J. D. Sieber, F. Buono, A. Brusoe, J.-N. Desrosiers, N. Haddad, J. C. Lorenz, Y. Xu, H. Wu, L. Zhang, Z. S. Han, F. Roschangar, J. J. Song, N. K. Yee and C. H. Senanayake, *J. Org. Chem.*, 2019, **84**, 4926–4931.
19 Z. Jaman, A. Mufti, S. Sah, L. Avramova and D. H. Thompson, *Chem. – Eur. J.*, 2018, **24**, 9546–9554.
20 T. Noël and S. L. Buchwald, *Chem. Soc. Rev.*, 2011, **40**, 5010–5029.
21 A. I. Alfano, S. Barone and M. Brindisi, *Org. Process Res. Dev.*, 2025, **29**, 281–298.
22 X. Guo, H. Dang, S. R. Wisniewski and E. M. Simmons, *Organometallics*, 2022, **41**, 1269–1274.
23 J. Yang, M. C. Neary and T. Diao, *J. Am. Chem. Soc.*, 2024, **146**, 6360–6368.
24 Y. Shi, J. S. Derasp, T. Maschmeyer and J. E. Hein, *Nat. Commun.*, 2024, **15**, 5436.
25 A. K. Cooper, D. K. Leonard, S. Bajo, P. M. Burton and D. J. Nelson, *Chem. Sci.*, 2020, **11**, 1905–1911.
26 P.-A. Payard, L. A. Perego, I. Ciofini and L. Grimaud, *ACS Catal.*, 2018, **8**, 4812–4823.
27 N. Kapur, https://freactor.com/learning.html.
28 UK 2024 Criticality Assessment, 2024.
29 H. Jia, G. Dai, J. Weng, Z. Zhang, Q. Wang, F. Zhou, L. Jiao, Y. Cui, Y. Ren, S. Fan, J. Zhou, W. Qing, Y. Gu, J. Wang, Y. Sai and W. Su, *J. Med. Chem.*, 2014, **57**, 7577–7589.
30 AstraZeneca, AZD9291 in Combination With Ascending Doses of Novel Therapeutics, https://clinicaltrials.gov/study/NCT02143466.
31 AstraZeneca, Savolitinib vs. Sunitinib in MET-driven PRCC, https://clinicaltrials.gov/study/NCT03091192.
32 N. K. Adlington, L. R. Agnew, A. D. Campbell, R. J. Cox, A. Dobson, C. F. Barrat, M. A. Y. Gall, W. Hicks, G. P. Howell, A. Jawor-Baczynska, L. Miller-Potucka, M. Pilling, K. Shepherd, R. Tassone, B. A. Taylor and A. Williams, *J. Org. Chem.*, 2019, **84**, 4735–4747.
33 M. C. Haibach, A. R. Ickes, S. Tcyrulnikov, S. Shekhar, S. Monfette, R. Swiatowiec, B. J. Kotecki, J. Wang, A. L. Wall, R. F. Henry and E. C. Hansen, *Chem. Sci.*, 2022, **13**, 12906–12912.
34 A. J. J. Lennox and G. C. Lloyd-Jones, *Chem. Soc. Rev.*, 2014, **43**, 412–443.
35 M. W. Freeman, Y. D. Halvorsen, W. Marshall, M. Pater, J. Isaacsohn, C. Pearce, B. Murphy, N. Alp, A. Srivastava, D. L. Bhatt and M. J. Brown, *N. Engl. J. Med.*, 2023, **388**, 395–405.
36 M. W. Freeman, M. Bond, B. Murphy, J. Hui and J. Isaacsohn, *Hypertens. Res.*, 2023, **46**, 108–118.