A Paradigm Shift: From Batch Processing to Flow Chemistry

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Abstract

Customisable flow chemistry reactors are becoming more affordable and accessible to wider research community. Coupled with rapidly advancing machine learning (ML) optimisation algorithms, time consuming research activities like catalyst discovery, reaction screening and optimisation can now be achievable quicker in flow, placing us in an interesting crossroad: should we start thinking about flow integration earlier in the research phase? In this perspective, parallels and differences between batch and flow heterogeneous catalytic reaction optimisations will be discussed with practical examples. Challenges in flow and batch processing are compared, combined with fresh perspectives of how reaction conditions can be adjusted more flexibly in multi-pass flow setting. Finally, recent progress of integrating computational techniques into flow process optimisation of contemporary “chemical looping” and paired reactions for more sustainable chemical productions will also be discussed.

Introduction

Catalysis plays a pivotal role in the production of virtually all products that we use every day: fuel, plastic and many of its derivatives, fertilisers, and pharmaceutical products[1–3]. Traditionally, catalytic reactions were performed as batch processes. Many early civilisations had already implemented various forms of enzymatic catalysis[4] in large barrels to produce wine, soap, or vinegar. However, the systematic study of catalysis did not start until Faraday reported his experiments with ("perfectly clean") electrified metals that cause reaction of gaseous species[5], including nitrous oxide and hydrogen. This paper piqued the interest of many[6], not only because it is the earliest description of heterogeneous catalysis, but also because Faraday had correctly identified the necessary adsorption process: "The gases are so far condensed as to be brought within the action of their mutual affinities at the existing temperature."[5]

Flow chemistry has been an integral part of bulk chemical industry since the demonstration of flow ammonia production in the 1900s[7,8] followed by the success of Carbide and Carbon Chemicals Corporation in developing flow process for gasoline separation from raw natural gas[9]. Today, flow chemistry is typically the favourable option for a factory with very large (approx. >5000 ton/year) output[10,11], as the high capital expenditure in building large flow reactors can be justified by the high production volume and profit margin.

The benefit of flow chemistry is a little bit less clear for fine chemicals and pharmaceutical synthesis industry that often produces much lower output. Rapidly changing patent landscape and "seasonal" product lines means very high-volume production is unlikely to be favourable. Generally, batch processing is the standard approach for fine chemical and active pharmaceutical ingredients (API) synthesis, but individual decision on the mode of operation can be decided based on cost analysis and complexity of the desired product[12,13].

Effort is constantly being made to explore applications of flow to fine chemical synthesis, as evidenced by the increasing research output towards microreactor technologies for organic synthesis[14]. A recent study showed that flow microreactor technology can outperform batch methods in terms of economic feasibility and environmental impact for a range of pharmaceutical synthesis processes, offering a

reduction in capital costs upwards of 50% and an average E-factor[15] reduction of 87% (lower number is better) for the seven processes studied[16]. Flow chemistry is also gaining popularity for early phase development that involves hazardous chemical transformations[13]. Although more work must be done to evaluate the broader applicability of flow to fine chemical synthesis, this indicates that flow catalysis may yet have a part to play in the fine chemical production methods of the future.

When researching novel synthetic reactions in a laboratory setting, batch processing provides a familiar and established framework to observe the kinetic behaviour. Batch setups are intuitive for discovering new catalytic materials, as it is straightforward to load and screen multiple material candidates to determine the effect of different catalytic properties. Recently, a more modern approach that combines automated synthesis and machine learning (ML) algorithms has resulted in faster and much more efficient catalyst discovery[17–19]. Looking towards the future, as adoption of flow processes increases in fine synthesis, discovery of new chemistry in the academic laboratory will need to adapt and aim to close the gap between initial research results in batch and the eventual implementation in flow setting as early as possible.

Beyond literature review coverage, this perspective opts for a slightly unorthodox approach. We included some of our own experimental data that compares established catalytic reaction in a more controlled fashion (performed by the same researcher, using the same reagents, catalyst, and following the same analytical apparatus and procedures). When writing this perspective, we discover that obtaining relevant experimental comparison between batch and flow setup of simple reactions in the literature is more difficult than expected, possibly due to publication bias[20], where only positive and novel results are published, compounded with problems of variability, reproducibility, and replicability[21,22]. This way, a more equitable comparison of batch and flow setting can be provided, while allowing us to deliver a fresh viewpoint in reaction optimisation[20–22]. Finally, we will also discuss how ML and computational approaches can be integrated for optimising multi-staged flow reactions, including for contemporary “chemical looping” synthetic pathways that are more sustainable for the future[1,23,24].

Challenges in Batch and Flow Processing

Batch process has been a valuable method for reaction discovery. However, it suffers from inherent limitations, which includes prolonged reaction times, unfavourable catalyst utilisations, and excessive reaction downtime. Furthermore, scaling up of a batch process by means of constructing larger reactors with similar geometry[25], sometimes leads to diminished returns. Larger batch reactors typically have poorer energy transfer coefficient and compromised product yield as well as selectivity, leading to poorer life cycle impact assessment in all categories when compared to flow processes[26].

In recent years, flow chemistry has emerged as a promising alternative to traditional batch processing, offering several advantages that address these limitations. Flow systems facilitate continuous operation and allow for real-time monitoring of reactions, enabling precise control over reaction conditions and leading to enhanced kinetic profiles[27,28]. This continuous mode of operation not only reduces reaction times but also streamlines the scalability of processes, improving the overall efficiency and safety of the catalytic development process[29,30].

Historically, the construction of flow processes can be expensive, requiring costly capital expenditure for process control systems. Thus, industries usually reserve flow processes for very high volume or high-value chemical production that has no other safe or viable alternative processing methods[12]. Optimisation in flow is different from batch; due to the continuously running process, a sufficiently robust catalyst is the bare minimum requirement, so flow reactors are usually not suitable as a catalyst discovery platform. Nonetheless, control over retention time and more efficient energy transfer (heat or other energy sources like photons or electrons) allows for more a selective product distribution. Often combinations of experiments and computational methods are required for understanding and optimising flow reactions[31,32].

In recent years, the cost of setting up flow reactions for lab scale catalysis has gone down significantly. This is mainly due to the decreasing cost of precise control systems and electronics. Furthermore, increase in the availability of optimisation algorithms has accelerated the implementation of flow reactions for lab scale reactions, leading to an increase in research on flow reactions in tandem with optimisation algorithms[33,34].

One example we wish to highlight is the use of titanosilicate (TS) based catalysts. TS is an important subset of zeolites – the crystalline aluminosilicates structured frameworks with discrete micropores. The pore sizes often coincide with the size of important product molecules, making them ideal candidates for shape-selective catalysts with exceptional catalytic and absorption capabilities[35]. Discovered over 40 years ago, TS-1 is a well-established and extensively studied catalyst in selective (partial) oxidation reactions. This class of reactions is crucial for processes such as the conversion of methane to formaldehyde, methanol, or syngas[36]. TS-1 plays a pivotal role in the annual production of over one million tonnes of propylene oxide[37]. This proficient catalyst can be synthesised as nanosized crystals (Figure 1(a)) and readily supports various co-catalysts like phosphotungstic acid while keeping the structure intact[38] (Figure 1(b)).

Although the activity of TS-1 has been identified to originate from the Ti^{IV} sites which replace a small fraction of the Si^{IV} within the zeolite framework[39,40] (Figure *1*(b)), decades of research have discovered more intricate details[39,41] on the inner workings of TS-1. Previously, DFT calculations showed that the formation of Ti(η^2-OOH), Ti(η^1-OOH), and Ti(η^1-O_2H_2) are energetically favourable[40], and these complexes prefer to exist in hydrated form.

More recently, a $\mu^2\eta^2$-peroxo species sandwiched in a di-nuclear Ti site has been identified through ^{17}O NMR and DFT calculations (Figure *1* (b)). A bis-hydroperoxo species (TS1-$(OOH)_2$) can then be formed facilely with additional H_2O_2, acting as the active epoxidation sites (Figure *1* (c)). This observation is interesting because it explains both the origin of TS-1 activity, and that the TS-1 can still be active even at low Ti substitution — as the tetraethylorthotitanate precursor is already forming dinuclear or trinuclear species[42] during synthesis.

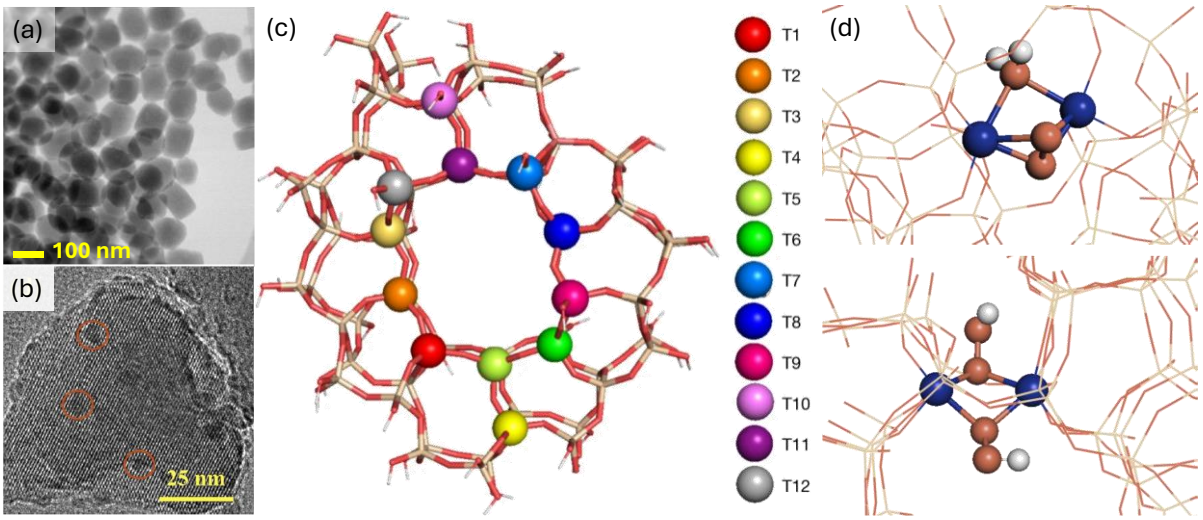

Figure 1: High resolution TEM micrographs of (a) nanosized TS-1 with 0.5% Ti substitution and (b) TiO_2 and phosphotungstic acid supported on TS-1. (c) Representation of TS-1, which is used industrially in the epoxidation of propylene with H_2O_2. In TS-1, a small fraction of Si atoms in the 12 crystallographically inequivalent T sites (coloured spheres) of the MFI framework are isomorphically replaced by Ti atoms; additional framework atoms are shown in red (O) and beige (Si). (d) Dinuclear site proposed, based on ^{17}O NMR and periodic DFT calculations (blue spheres, Ti; red spheres, O; white spheres, H).: (a), (c) and (d) reproduced with permission from Gordon et al.[41] (b) reproduced with permission from Bi et al.[38]

One of the biggest challenges of partial oxidation reaction arises from attempting to maintain selectivity while improving the conversion of substrate into products. Numerous attempts have been made to search for new catalysts which improve activity while maintaining the suppression of byproducts. However, not nearly as much attention is given to the mode of operation, which can have a substantial effect on the reaction outcome.

Case Studies on Batch and Flow Processing for Allyl Alcohol and Furfural Oxidation

To showcase the advantages of flow catalysis, we first examine two reactions using TS-1 catalyst (Si/Ti ratio = 7.2 as determined via XRF), that highlight distinct challenges of selective oxidation reactions with heterogeneous catalysis. Although there are many catalytic materials applicable to these chemical transformations, we focused on TS-1 due to its established usage, as the aim of this work was to evaluate the relative benefits of batch versus flow processing. Our first case is the allyl alcohol (AA) epoxidation in aqueous solution. AA epoxidation using TS-1 as a heterogeneous catalyst and hydrogen peroxide (H_2O_2) as an oxidant is a promising route for the sustainable production of glycidol, an important chemical intermediate. Research in this field, while showing a high conversion and selectivity, has largely been

constrained to batch processes using organic solvents due to significant side reactions towards glycerol in aqueous solution[43].

Therefore, we sought to investigate the potential for flow chemistry to overcome these limitations in batch. Comparison and optimisation studies were conducted to find the reaction parameters corresponding to an optimal reaction mass yield. The mass yield was chosen to align with industry, where production targets are set according to the mass amount required. Batch reactions were conducted as a baseline using temperature homogenised 20 mL headspace vials as reaction vessels. For the flow reaction, an in-house developed automatable flow reactor system was used for sample collection[31]. TS-1 catalyst was pelletised as broken into a uniformly sized distribution of granules before being loaded into a flow cell. Further details on the experimental setup can be found in the supporting information.

We found that increased temperature greatly improved the conversion of AA in batch reactor, from 9% to 68% after 1 hour, with an increase in temperature from 40 to 80 °C, respectively (Table S1). However, conversion increases were marred by a corresponding decrease in selectivity, as the ring-opening solvolysis reaction that yields unwanted glycerol occurred with increasing potency. This is largely in line with literature[44], that it represents a significant disadvantage of the batch process, where it is difficult to operate in a kinetically favourable condition while maintaining selectivity to the desired main product. Similar trends were observed for the other variables, where an increase in reaction time, peroxide amount and catalyst loading increased the conversion of AA, however also reduced the selectivity to glycidol.

Figures of merit comparison between batch and flow with similar active reactor volume demonstrate how flow setup enables vast opportunities for AA epoxidation reaction yield improvement (Figure 2a). We found that flow afforded higher reaction temperature, which improved the reaction kinetics while maintaining selectivity through residence time tuning. The favourable catalyst to substrate ratio enabled a high conversion in a brief period, with 14% conversion achieved in just 15 s.

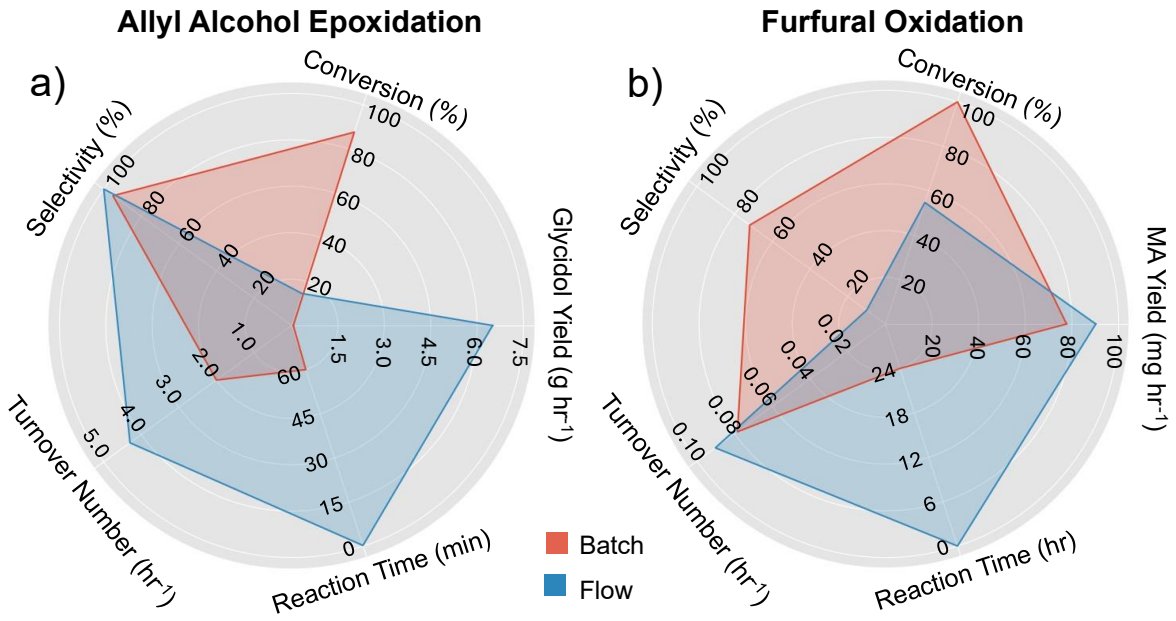

Figure 2: Figures of merit comparison between Batch and Flow Catalytic Results, with bars representing the conversion, product yield, reaction time, turnover number and (a) selectivity to glycidol for Allyl Alcohol Epoxidation and (b) selectivity to 5-HFO+MA for Furfural Oxidation.

In contrast to standard batch-based catalytic studies[45], which prioritise achieving high conversion to maximise product yield, our flow-based approach underscores the distinct advantages of focusing on selectivity for yield improvement. The low single pass conversion in flow systems can be readily compensated by recycling reactants, making high conversion less critical for achieving high mass yields. This flexibility allows the system to operate at low to moderate conversion levels while maximising selectivity. As a result, this mode of operation can help to ensure that nearly all converted reactants contribute directly to the desired product and reduce the burden of downstream purification. A lower conversion was achieved in the flow process, yet the mass yield in both systems was higher, due to high selectivity and reactant throughput. This method underlines the effectiveness of yield-centric evaluation in flow catalysis, suggesting criteria for catalytic efficiency evaluation in research.

Although a greater mass of catalyst was used in the flow test for AA epoxidation, we found that the turnover number was over twice that of the batch process (4.3 hr^{-1} in flow compared to 2.0 hr^{-1} in batch). This suggests that the catalyst is more efficiently used for glycidol synthesis in flow. This efficiency likely arises from the continuous supply of reactants to the catalyst surface and the prompt removal of products, which prevents accumulation and potential deactivation effects that are more common in batch systems. By maintaining optimal reactant availability and minimising product

build-up, the flow system enhances catalytic turnover, effectively leveraging the catalyst mass for higher productivity in glycidol synthesis.

Our second case is furfural oxidation, which is a sustainable route for technologically important C_4 dicarboxylic acids and lactones production. Compared to AA epoxidation, furfural oxidation is much more complex, with multiple competing reaction pathways and many chemical intermediates[46–48]. A proposed reaction pathway of furfural partial oxidation is shown in Figure 3, listing major products detected in our experiments and possible side reactions reported in the literature. The selectivity of the products can change depending on the catalyst and conditions used. For example, the use of metallic catalysts and readily available molecular oxygen (or air) oxidants often led to furoic acid[49]. Brønsted acid-type catalysts (like Amberlyst™) tend to favour succinic acid products[50], while Lewis acid type catalysts like TS-1 can be an effective catalyst to mediate the furfural oxidation to the more valuable maleic acid (MA)[51]. Due to the nascency of the field, however, literature is limited to batch optimisation.

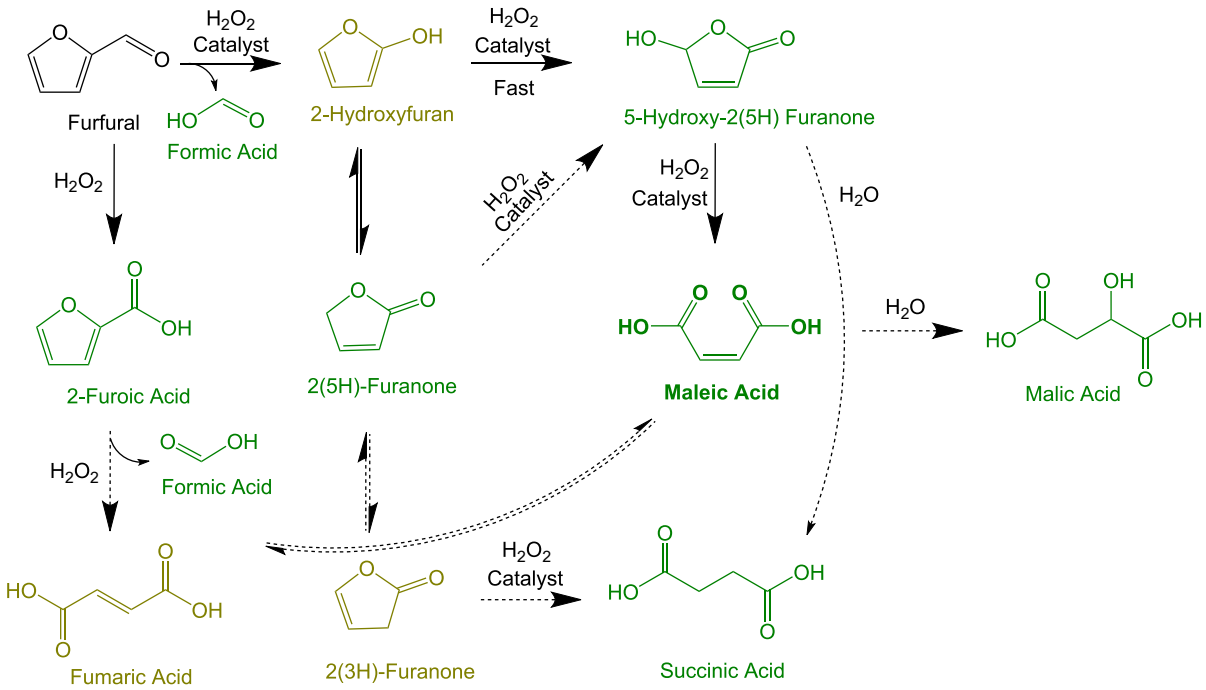

Figure 3: Proposed reaction pathway showing major intermediates of furfural oxidation using TS-1 catalyst, interpreted from the literature[47,52,53] and observed catalytic results. Green colour represents molecules that were observed in our experiments, while gold colour represents inferred presence of intermediate molecules based on detected products in the proximity reaction steps. Solid arrows represent reactions with higher probability or faster reaction rate based on the quantity of detected molecules, while dashed arrows represent reactions with slower or lower probability. Two-sided arrows represent tautomerisation.

Our initial attempts to translate furfural oxidation reaction to flow resulted in a moderate increase of MA yield from 77.7 to 90.2 mg hr^{-1} (Figure 2b). Furfural oxidation to MA, being a multistep reaction, presents a more challenging catalytic task than AA

epoxidation. We note that 55% conversion of furfural was achieved in 57 s, however, the selectivity to MA was 10%. This was mainly due to an incomplete conversion from the major intermediate, 5-Hydroxy-2(5H)-furanone (5-HFO), as the combined selectivity to 5-HFO and MA was 94%. Although the exact reaction mechanism for the transformation of furfural into MA is disputed, it is widely accepted that the terminal step involves the oxidation of 5-HFO into MA. We found that the conversion from furfural into 5-HFO was fast and selective, however, the subsequent transformation into MA proved to be slower, meaning that a single pass reaction struggled to push the reaction to MA.

With respect to the initial optimisation results, we posit that the transformation of furfural into MA can be viewed as a series of reactions with the rate determining step being the oxidation of 5-HFO, the final intermediate. Thus, it may be better to treat this reaction as a two-step process: furfural oxidation into 5-HFO, then 5-HFO oxidation into MA. It is clear that the kinetics for these two steps are not the same, thus providing opportunities to optimise the reaction segments separately. To the best of our knowledge, an approach that addresses this staged reaction approach has yet to be documented in the literature.

So, to investigate this further, we introduced an idea to conduct a dynamic multi-pass flow reaction, altering the reaction flow condition to suit kinetic requirements. A baseline measurement was done using a “vanilla” multi-pass by continuously recycling the reaction medium through the reactor at the same conditions. As can be seen in Figure 4, the conversion from furfural into 5-HFO occurs mainly during the first 12 reactor passes, corresponding to a reaction time of approximately 12 minutes. At this point, the conversion of furfural is 89%, meaning that 5-HFO exists as the highest concentration constituent in the reaction medium. Although there is only one step remaining in the reaction to synthesise MA, the MA yield increased from 7% to 13% from 12 to 40 reactor passes, a moderate increase as compared to the 5-HFO yield of 61% achieved after 12 reactor passes.

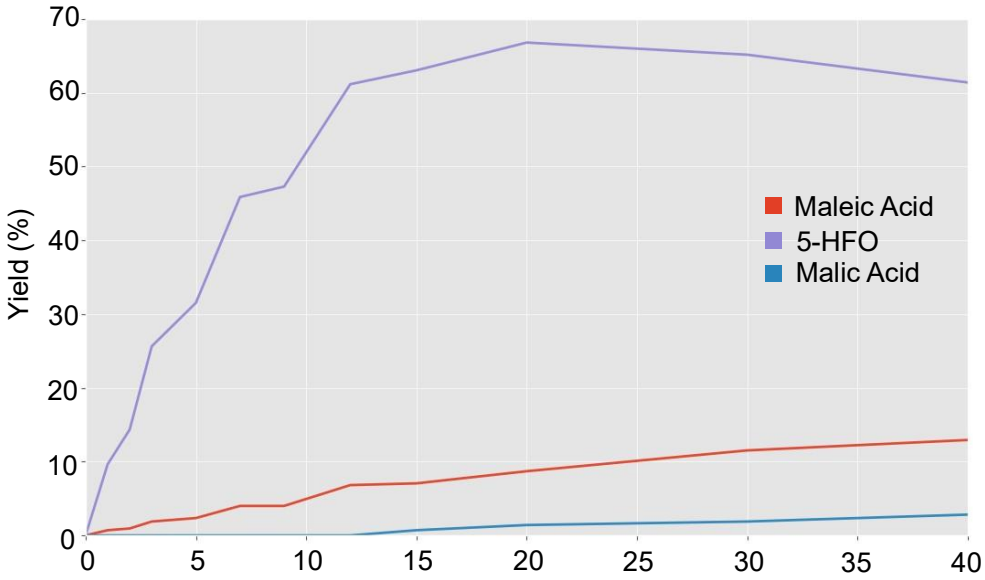

Figure *4*: Yield distribution of multipass flow reaction for furfural oxidation, showing the major products of maleic acid, 5-hydroxy 2(5H)-furanone (5-HFO), and malic acid.

Promisingly, the other quantified byproducts totalled to less than 10% after 40 reactor passes, meaning that the reaction is likely to be selectively proceeding via the MA pathway. To try and overcome the kinetic barrier from 5-HFO to MA, we tried to increase the temperature of the reaction from 60 to 80 °C after 15 reactor passes. Interestingly, the yield of MA in the increased temperature test after 40 reactor passes was less than the reaction conducted at 60 °C (Figure 5), favouring instead to form malic acid (MAOH) through hydrolysis of MA (Figure 3).

This leads to an interesting dilemma; lower temperatures minimise the hydrolysis of MA however a kinetic barrier is encountered for 5-HFO oxidation into MA, whereas increased temperature helps to overcome the kinetic barrier but leads to hydrolysis of MA into MAOH. As a comparison, the baseline batch process (Supporting Information) allows for milder oxidation that leads to a relatively high yield (62%) of MA. However, 24 hours of reaction time was needed to achieve this.

Although we were unsuccessful in pushing the reaction selectivity towards MA due to MAOH formation, this result is not optimised. The second temperature (80 °C) adopted after 12 reactor passes was arbitrarily chosen based on an intuition that higher temperature is required to push 5-HFO conversion into MA. It is our belief that a combination of conditions exists which will convert furfural into 5-HFO, then subsequently efficiently convert 5-HFO into MA. This is a benefit of flow processes, where multiple reactors can be integrated in-line seamlessly.

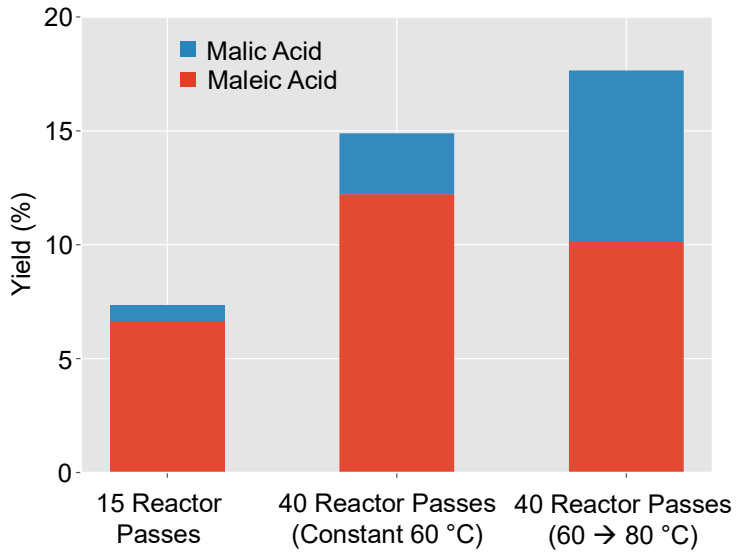

Figure 5: Comparison between 15 multipass reaction at 60 °C, 40 multipass reaction at 60 °C, and multipass reaction with temperature increased to 80 °C after 15 reactor passes, showing diverging yields of maleic acid and malic acid.

The Role of Machine Learning and Computational Integration in Reaction Optimisation

The two flow optimisation case studies presented in above highlight the potential upsides that we may expect when studying selective oxidation reactions with heterogeneous catalysis in flow. With AA epoxidation, we learnt how a flow process enables precise control over reaction conditions to manage reaction kinetics, affording higher yield and turnover of desired product over a batch process.

Today, we are seeing more prevalent integration of process automation and machine learning (ML) optimisation, where the process condition can be optimised autonomously without prior chemistry or engineering knowledge[31]. We believe the real implementation of large-scale flow processes requires a more comprehensive pairing of flow process, ML, and in-depth computational fluid dynamics (CFD) modelling studies. CFD simulations provide detailed insight into fluid dynamics, mass transfer phenomena, and reaction kinetics, enabling efficient reactor design and scale-up. Targeted integration of CFD can explain the rationale behind ML-suggested optimum parameters and find scale-up pathways by considering real factors like reaction mechanisms, kinetics, and geometry of the reactors[32]. For instance, Saleem et al. demonstrated through CFD that spiral and serpentine channel reactors improved

productivity by approximately 23% compared to traditional flat parallel-plate reactors, due to better mixing and mass transfer[32].

ML algorithms, meanwhile, facilitate rapid and efficient exploration of complex, multi-dimensional reaction parameter spaces, reducing experimental time and resource usage. Similarly, ML methods can rapidly pinpoint optimal reaction conditions by simultaneously optimising multiple parameters. For example, Gupta et al. demonstrated this by optimising reaction parameters for electrochemical trifluoromethylation, using an automated ML-driven setup to achieve a 270% yield improvement in just two iterations[31].

We believe ML will also be instrumental in finding optimum conditions for stepped reactions. In the case of furfural oxidation, we have shown that a more effective solution may be obtained by treating the reaction as an interconnected multi-stage process. With ML integration, targeted optimisation of each segment can then be crafted, leading to opportunities for improved overall efficiency and yield. To the best of our knowledge, there is no example that demonstrates ML-aided multi-staged flow reaction optimisation. One of the closest examples that we found in the literature was published by Clayton et al., where the concept of combined flow reaction and workup optimisation is presented (Figure *6*)[54]. This demonstration represents a breakthrough, where a subsequent reaction workup process (simulated by cascades of continuous stirred reaction) is considered when optimising the upstream chemical reaction process to achieve most efficient overall (isolated) yield. Such process is usually not considered in the “typical” optimisation literature when doing the survey for this perspective.

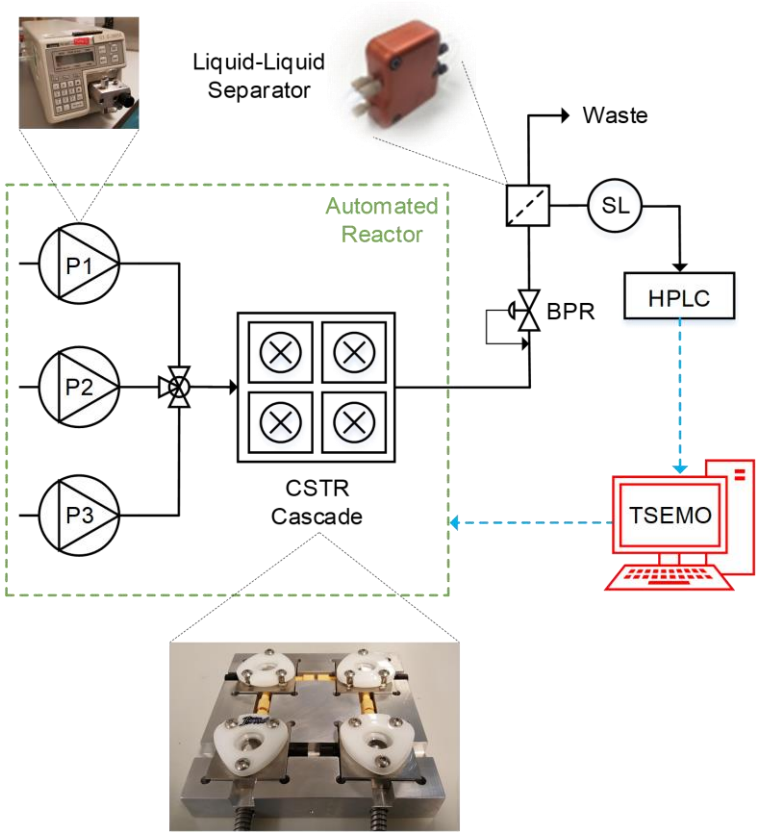

Figure 6: illustration of “multi-stepped” process optimisation, consisting of a single reaction followed by reaction workup in a series of continuous stirred reactor cascade and “TSEMO” algorithm. Reproduced from Clayton et al[54], SI (CC BY 4.0).

Future Directions

It is also conceivable to apply such multi-staged flow-optimisation concept to reactions with diverse products or parallel reactions. One of the prime targets is catalytic CO_2 conversion, an important “chemical-looping” process for CO_2 upcycling that can be performed using thermal[55], electrochemical[56], or photochemical[57] energy. Intensive and systematic research on electrocatalytic CO_2 conversion has been going for longer than five decades[58,59]. However, focusing the selectivity of CO_2 conversion towards longer carbon chained products is still quite challenging, due to the diverse reaction pathway with 14 products containing 1-2 carbon atoms[24]. *CO is thought to be the most important intermediate[60], which means CO_2 conversion can be viewed (roughly) as a two major step process of CO_2 to CO and CO to multi carbon products (C_{2+})[61], which can be the ideal test bed for the multi-stepped (or multi-objective) ML-aided flow optimisation.

Fortuitously, CO_2 conversion reaction research has embraced flow reaction scheme early, with newer studies today targeting the aspects[62,63] of the reactor and reaction

engineering. Studies into the technoeconomic side has also shown promise for CO_2 conversion to be scaled up with the support of renewable energy inputs[64,65]. However, we have yet to see the integration of multi-segment reaction optimisation being applied here. The closest effort that we found from the literature is the segmented deposition of different catalysts on gas diffusion electrode (GDE) to be applied for flow catalysis[66].

The idea is the CO_2 feed can be rapidly converted into CO in early in the flow reactor using Ag catalyst and longer carbon chained products are to be formed downstream using a separate Cu-based catalyst (Figure 7(a)). From the catalyst point of view, the work is not too novel, as Ag is known to be one of the best CO_2 conversion catalysts to CO and tandem Cu-Ag has been reported before in enhancing CO_2 conversion selectivity[67,68]. However, the clever use of segmented electrode composition in this work opens a new dimension for optimisation, which we think will be a prime field for our proposed multi-segment reaction optimisation. The advent of newly developed direct plasma synthesis and writing techniques[69] can also be integrated with ML optimisation for potentially exciting discovery.

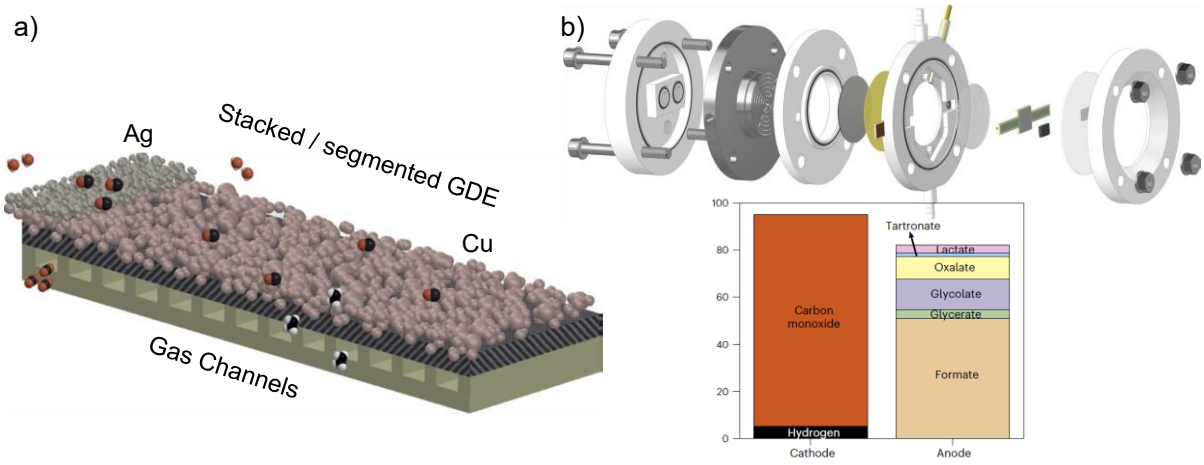

Figure 7: (a) segmented catalyst concentration on gas diffusion electrode (GDE) in flow setup, effectively splitting the CO_2 conversion to two segments: CO_2 to CO and CO to C_{2+} products. Reproduced with permission from Zhang et al[66]. (b) Tandem/paired electrocatalytic CO_2 to CO and photocatalytic of glycerol oxidation. Reproduced with permission from Balog et al[70].

Paired or tandem reaction is another “trendy” pathway that the researchers have taken. Realising the high thermodynamic requirements of the “counter” reactions (usually water oxidation for CO_2 reduction), researchers have sought to use paired reaction pathway to simultaneously reduce the nett reaction energy requirement and to generate more useful product.

Partial oxidation of organic molecules (including furfural[71] or glycerol, Figure 7(b))[70] is one of the most common schemes adopted in the literature. However, we note that in many cases, the anodic reaction is being treated only as a secondary reaction, with no optimisation considered to this side of the reaction. Less useful products were usually obtained, as no suitable catalyst (like TS-1) is involved in this reaction. For example, in the case of furfural oxidation counter reaction, 2-furoic acid is produced instead of MA. It is clear that the overall CO_2 conversion reaction will benefit the proposed multi-staged (or multi compartment for tandem scheme) flow reaction optimisation like what we have discussed in the furfural partial oxidation example.

We believe the application of a more holistic optimisation that considers the entire reaction segments (or tandem), combined with continuous innovations in materials synthesis and catalyst development will go a long way towards realising our sustainable future.

Supplementary information:

Details of the batch and flow reactions and analytical methods are available in the supplementary information, alongside selected batch reaction data.

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References:

1. Friend, C. M. & Xu, B. Heterogeneous Catalysis: A Central Science for a Sustainable Future. *Acc. Chem. Res.* **50**, 517–521 (2017).
2. Schlögl, R. Heterogeneous Catalysis. *Angew. Chem. Int. Ed.* **54**, 3465–3520 (2015).

3. Fechete, I., Wang, Y. & Védrine, J. C. The past, present and future of heterogeneous catalysis. *Catal. Today* **189**, 2–27 (2012).
4. *Handbook of Food Enzymology*. (CRC Press, 2002). doi:10.1201/9780203910450.
5. V. Experimental researches in electricity.—Sixth series. *Philos. Trans. R. Soc. Lond.* **124**, 55–76 (1834).
6. Bayliss, W. M. Faraday's Views on Catalysis. *Nature* **94**, 253–254 (1914).
7. Haber, F. *Thermodynamik Technischer Gasreaktionen: Sieben Vorlesungen*. (R. Oldenburg, 1905).
8. Bosch, C. & Ludwigshafen-On-The-Rhine, O. PROCESS OF PRODUCING AMMONIA. 8 (1911).
9. Stone, D. Birth of the Petrochemical Industry. *ACS* https://www.acs.org/education/whatischemistry/landmarks/petrochemical-industry-birthplace.html (2021).
10. Goršek, A. & Glavič, P. Design of Batch Versus Continuous Processes. *Chem. Eng. Res. Des.* **75**, 709–717 (1997).
11. Douglas, J. M. Conceptual design of chemical processes. in 99–115 (McGraw-Hill, New York, 1988).
12. Holtze, C. & Boehling, R. Batch or flow chemistry? – a current industrial opinion on process selection. *Curr. Opin. Chem. Eng.* **36**, 100798 (2022).
13. Johnson, M. D. *et al.* The History of Flow Chemistry at Eli Lilly and Company. *CHIMIA* **77**, 319 (2023).
14. Gutmann, B., Cantillo, D. & Kappe, C. O. Continuous-Flow Technology—A Tool for the Safe Manufacturing of Active Pharmaceutical Ingredients. *Angew. Chem. Int. Ed.* **54**, 6688–6728 (2015).

15. Sheldon, R. A. The E factor at 30: a passion for pollution prevention. *Green Chem.* **25**, 1704–1728 (2023).

16. Ince, M. C., Benyahia, B. & Vilé, G. Sustainability and Techno-Economic Assessment of Batch and Flow Chemistry in Seven Industrial Pharmaceutical Processes. *ACS Sustain. Chem. Eng.* **13**, 2864–2874 (2025).

17. Shevlin, M. Practical High-Throughput Experimentation for Chemists. *ACS Med. Chem. Lett.* **8**, 601–607 (2017).

18. Lim, C. Y. J. *et al.* Machine learning-assisted optimization of multi-metal hydroxide electrocatalysts for overall water splitting. *Mater. Horiz.* **10**, 5022–5031 (2023).

19. Mou, L., Han, T., Smith, P. E. S., Sharman, E. & Jiang, J. Machine Learning Descriptors for Data-Driven Catalysis Study. *Adv. Sci.* **10**, 2301020 (2023).

20. Brown, A. W., Mehta, T. S. & Allison, D. B. *Publication Bias in Science*. vol. 1 (Oxford University Press, 2017).

21. Ciriminna, R., Angellotti, G., Petri, G. L. & Pagliaro, M. Reproducibility in chemistry research. *Heliyon* **10**, e33658 (2024).

22. Smith, G. & Dickinson, E. J. F. Error, reproducibility and uncertainty in experiments for electrochemical energy technologies. *Nat. Commun.* **13**, 6832 (2022).

23. Abi Ghaida, F. *et al.* Heterogeneous catalytic and chemical looping routes to N_2 activation: general discussion. *Faraday Discuss.* **243**, 198–230 (2023).

24. Handoko, A. D., Wei, F., Jenndy, Yeo, B. S. & Seh, Z. W. Understanding heterogeneous electrocatalytic carbon dioxide reduction through operando techniques. *Nat. Catal.* **1**, 922–934 (2018).

25. Monsalve-Bravo, G. M., Moscoso-Vasquez, H. M. & Alvarez, H. Scaleup of Batch Reactors Using Phenomenological-Based Models. *Ind. Eng. Chem. Res.* **53**, 9439–9453 (2014).

26. Osorio-Tejada, J., Ferlin, F., Vaccaro, L. & Hessel, V. Life cycle assessment of multistep benzoxazole synthesis: from batch to waste-minimised continuous flow systems. *Green Chem.* **24**, 325–337 (2022).

27. Lucarelli, C. & Vaccari, A. Examples of heterogeneous catalytic processes for fine chemistry. *Green Chem* **13**, 1941–1949 (2011).

28. Plutschack, M. B., Pieber, B., Gilmore, K. & Seeberger, P. H. The Hitchhiker's Guide to Flow Chemistry. *Chem. Rev.* **117**, 11796–11893 (2017).

29. Baxendale, I. R. The integration of flow reactors into synthetic organic chemistry. *J. Chem. Technol. Biotechnol.* **88**, 519–552 (2013).

30. Movsisyan, M. *et al.* Taming hazardous chemistry by continuous flow technology. *Chem. Soc. Rev.* **45**, 4892–4928 (2016).

31. Gupta, N. K. *et al.* Towards a greener electrosynthesis: pairing machine learning and 3D printing for rapid optimisation of anodic trifluoromethylation. *RSC Sustain.* **2**, 536–545 (2024).

32. Saleem, A., Mathpati, C., Gupta, N. K., Handoko, A. D. & Karimi, I. A. Experimentally Validated 3D-CFD Analysis of Continuous-Flow Reactor Configurations for the Electrochemical Trifluoromethylation of Caffeine. *Ind. Eng. Chem. Res.* **63**, 19017–19029 (2024).

33. Bai, Y. *et al.* Closed-Loop Multi-Objective Optimization for Cu–Sb–S Photo-Electrocatalytic Materials' Discovery. *Adv. Mater.* **36**, 2304269 (2024).

34. Filipa De Almeida, A. & Rodrigues, T. Machine Learning for the Optimization of Chemical Reaction Conditions. in *Enabling Tools and Techniques for Organic*

Synthesis (ed. Newman, S. G.) 393–421 (Wiley, 2023). doi:10.1002/9781119855668.ch10.

35. Roth, W. J., Nachtigall, P., Morris, R. E. & Čejka, J. Two-Dimensional Zeolites: Current Status and Perspectives. *Chem. Rev.* **114**, 4807–4837 (2014).

36. Pitchai, R. & Klier, K. Partial Oxidation of Methane. *Catal. Rev.* **28**, 13–88 (1986).

37. Lin, M., Xia, C., Zhu, B., Li, H. & Shu, X. Green and efficient epoxidation of propylene with hydrogen peroxide (HPPO process) catalyzed by hollow TS-1 zeolite: A 1.0kt/a pilot-scale study. *Chem. Eng. J.* **295**, 370–375 (2016).

38. Bi, M. *et al.* Titanium dioxide-modified nanosized TS-1 zeolite-supported phosphotungstic acid as a catalyst for deep catalytic oxidative desulfurization of fuel oil. *New J. Chem.* **47**, 12027–12036 (2023).

39. Sankar, G. *et al.* The Three-Dimensional Structure of the Titanium-Centered Active Site during Steady-State Catalytic Epoxidation of Alkenes. *J. Phys. Chem. B* **105**, 9028–9030 (2001).

40. Barker, C. M. *et al.* On the structure and coordination of the oxygen-donating species in Ti↑MCM-41/TBHP oxidation catalysts: a density functional theory and EXAFS study. *Phys. Chem. Chem. Phys.* **4**, 1228–1240 (2002).

41. Gordon, C. P. *et al.* Efficient epoxidation over dinuclear sites in titanium silicalite-1. *Nature* **586**, 708–713 (2020).

42. Caughlan, C. N., Smith, H. S., Katz, W., Hodgson, Wm. & Crowe, R. W. Organic Compounds of Titanium. II. Association of Organic Titanates in Benzene Solution. *J. Am. Chem. Soc.* **73**, 5652–5654 (1951).

43. Harvey, L., Kennedy, E., Dlugogorski, B. Z. & Stockenhuber, M. Influence of impurities on the epoxidation of allyl alcohol to glycidol with hydrogen peroxide over titanium silicate TS-1. *Appl. Catal. Gen.* **489**, 241–246 (2015).

44. Wu, P. A novel titanosilicate with MWW structure III. Highly efficient and selective production of glycidol through epoxidation of allyl alcohol with H2O2. *J. Catal.* **214**, 317–326 (2003).

45. Hutchings, G. J. & Lee, D. F. Control of product selectivity for the epoxidation of allyl alcohol by variation of the acidity of the catalyst TS-1. *J. Chem. Soc. Chem. Commun.* 1095 (1994) doi:10.1039/c39940001095.

46. Rodenas, Y. *et al.* Improving the production of maleic acid from biomass: TS-1 catalysed aqueous phase oxidation of furfural in the presence of γ-valerolactone. *Green Chem.* **20**, 2845–2856 (2018).

47. Shcherban, N. D. *et al.* Furfural Oxidation with Hydrogen Peroxide Over ZSM-5 Based Micro-Mesoporous Aluminosilicates. *Catal. Lett.* **152**, 2920–2932 (2022).

48. Murzin, D. Yu. *et al.* Heterogeneous Catalytic Oxidation of Furfural with Hydrogen Peroxide over Sulfated Zirconia. *Ind. Eng. Chem. Res.* **59**, 13516–13527 (2020).

49. Wu, X. *et al.* Elucidating the role of active oxygen species and hydroxyl groups in the furfural base-free oxidation to furoic acid over δ-MnO2. *Fuel* **359**, 130404 (2024).

50. Choudhary, H., Nishimura, S. & Ebitani, K. Metal-free oxidative synthesis of succinic acid from biomass-derived furan compounds using a solid acid catalyst with hydrogen peroxide. *Appl. Catal. Gen.* **458**, 55–62 (2013).

51. Lou, Y., Marinkovic, S., Estrine, B., Qiang, W. & Enderlin, G. Oxidation of Furfural and Furan Derivatives to Maleic Acid in the Presence of a Simple Catalyst

System Based on Acetic Acid and TS-1 and Hydrogen Peroxide. *ACS Omega* **5**, 2561–2568 (2020).

52. Palai, Y. N., Fukuoka, A. & Shrotri, A. Reaction Pathways for Synthesis of Four Carbon Chemicals from Sugars and Sugar Derived Platform Chemicals. *ChemCatChem* **15**, e202300766 (2023).

53. Fox, M. A., Dulay, M. T. & Krosley, K. Comparison of Oxidative and Excited State Cyclizations of N-Benzyldiphenylamines to N-Benzylcarbazoles. *J. Am. Chem. Soc.* **116**, 10992–10999 (1994).

54. Clayton, A. D. *et al.* Automated self-optimisation of multi-step reaction and separation processes using machine learning. *Chem. Eng. J.* **384**, 123340 (2020).

55. Wang, Q. *et al.* Recent Progress in Thermal Conversion of CO_2 via Single-Atom Site Catalysis. *Small Struct.* **3**, 2200059 (2022).

56. Handoko, A. D. *et al.* Mechanistic Insights into the Selective Electroreduction of Carbon Dioxide to Ethylene on Cu_2 O-Derived Copper Catalysts. *J. Phys. Chem. C* **120**, 20058–20067 (2016).

57. Handoko, A. D., Li, K. & Tang, J. Recent progress in artificial photosynthesis: CO2 photoreduction to valuable chemicals in a heterogeneous system. *Curr. Opin. Chem. Eng.* **2**, 200–206 (2013).

58. Inoue, T., Fujishima, A., Konishi, S. & Honda, K. Photoelectrocatalytic reduction of carbon dioxide in aqueous suspensions of semiconductor powders. *Nature* **277**, 637–638 (1979).

59. Russell, P. G., Kovac, N., Srinivasan, S. & Steinberg, M. The Electrochemical Reduction of Carbon Dioxide, Formic Acid, and Formaldehyde. *J. Electrochem. Soc.* **124**, 1329–1338 (1977).

60. Huang, Y., Handoko, A. D., Hirunsit, P. & Yeo, B. S. Electrochemical Reduction of CO_2 Using Copper Single-Crystal Surfaces: Effects of CO* Coverage on the Selective Formation of Ethylene. *ACS Catal.* **7**, 1749–1756 (2017).

61. Ding, X., Zhang, J. & Li, Y. CO electroreduction: What can we learn from its parent reaction, CO2 electroreduction? *eScience* **3**, 100137 (2023).

62. Larrazábal, G. O. *et al.* Analysis of Mass Flows and Membrane Cross-over in CO_2 Reduction at High Current Densities in an MEA-Type Electrolyzer. *ACS Appl. Mater. Interfaces* **11**, 41281–41288 (2019).

63. Gutiérrez-Sánchez, O., De Mot, B., Bulut, M., Pant, D. & Breugelmans, T. Engineering Aspects for the Design of a Bicarbonate Zero-Gap Flow Electrolyzer for the Conversion of CO_2 to Formate. *ACS Appl. Mater. Interfaces* **14**, 30760–30771 (2022).

64. Handoko, A. D., Khoo, H. H., Halim, I. & Murugappan, K. Feasibility of CO_2 Capture and Utilization: From the LCA Perspective. in *Life Cycle Assessment* 39–53 (WORLD SCIENTIFIC, 2022). doi:10.1142/9789811245800_0003.

65. Spurgeon, J. M. & Kumar, B. A comparative technoeconomic analysis of pathways for commercial electrochemical CO_2 reduction to liquid products. *Energy Environ. Sci.* **11**, 1536–1551 (2018).

66. Zhang, T. *et al.* Highly selective and productive reduction of carbon dioxide to multicarbon products via in situ CO management using segmented tandem electrodes. *Nat. Catal.* **5**, 202–211 (2022).

67. Buckley, A. K. *et al.* Approaching 100% Selectivity at Low Potential on Ag for Electrochemical CO_2 Reduction to CO Using a Surface Additive. *ACS Catal.* **11**, 9034–9042 (2021).

68. Chen, C. *et al.* Cu-Ag Tandem Catalysts for High-Rate CO2 Electrolysis toward Multicarbons. *Joule* **4**, 1688–1699 (2020).

69. Agrotis, S., Emre Sener, M., Hagger, O. S. J., Handoko, A. D. & Caruana, D. J. One-Step synthesis of nanosized Cu-Ag films using atmospheric pressure plasma jet. *Appl. Mater. Today* **39**, 102286 (2024).

70. Balog, Á. *et al.* Paired photoelectrochemical conversion of CO2/H2O and glycerol at high rate. *Nat. Catal.* **7**, 522–535 (2024).

71. Liu, X. *et al.* A paired alkaline electrolyzer for furfural oxidation and hydrogen evolution over noble metal-free NiFe/Ni and Co/MXene catalysts. *Green Chem.* **26**, 11351–11363 (2024).