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Generation and Use of Reactive Intermediates Exploiting Flow Technology

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Abstract: Continuous flow technology has matured into a valuable and widely exploited technology across academic and industrial laboratories. The safe and on-demand generation of reactive intermediates using miniaturized flow set-ups is of particular value to realize safer and more streamlined synthesis routes yielding important chemical building blocks. This focused review provides an update on recent studies highlighting the use of photochemistry, metalation reactions and electrochemistry to generate a variety of reactive intermediates showcasing successful implementations of flow processing as well as areas offering further opportunities.

Keywords: Electrochemistry · Flow chemistry · Photochemistry · Reactive intermediates · Sustainability

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1. Introduction

Recent decades have witnessed significant changes in how chemists produce molecules of interest which is largely driven by more stringent safety and sustainability requirements. Continuous flow technology has thereby emerged as one of the most powerful approaches to overcome limitations associated with classical synthetic transformations in academic as well as industrial settings.[1–4] Flow chemistry in its simplest form exploits the continuous processing of solutions of substrates and reagents based on bespoke mixing elements and reactors to trigger the desired transformation in miniaturised set-ups imparting high levels of selectivity and reaction control.[5–7] Key features such as improved heat and mass transfer result from these small footprint set-ups that harness the benefits of high surface area to volume ratios as well as superb micromixing *via* T-piece mixers or advanced static mixing elements. Recent years have seen the development and commercialization of various flow reactor types to facilitate a large variety of chemical reactions at different scales. The scalability of continuous flow reactors is of paramount importance for process intensification where productivities of kilogram quantities per hour can be achieved, meeting commercial scale requirements in industry.[8–13] These advantages have resulted in safe and readily scalable flow processes particularly for numerous transformations that are challenging to scale-up due to reaction exotherms and side-product formation. One specific area of synthetic chemistry that has benefited significantly concerns the safe generation and use of reactive intermediates.[14–19] The containment provided by tubular or plate-type flow reactors combined with their small volumes provides high levels of control allowing chemists to generate short-lived and often hazardous entities *in situ* which allows for more streamlined routes towards desirable fine chemical products in a scalable manner. This has enabled chemists to exploit a plethora of classical reactive intermediates whilst investigating synthetic routes exploiting new reactivities that may not be feasible in analogous batch reactions.[20,21] To provide an update on the latest developments in this rapidly evolving field this short review will highlight selected case studies from recent publications exploiting photochemistry, cryogenic reactions as well as electrochemistry for the on-demand preparation of various reactive intermediates.

2. Photoflow Chemistry

Over the last 25 years the prevalence of photochemistry exploiting continuous flow reactor technology has increased steadily.[22] The Bouguer-Beer-Lambert law describes the inverse relationship between path length and light transmittance. The short path length of flow reactor tubing has allowed chemists to circumvent this limitation when performing photochemical reactions,

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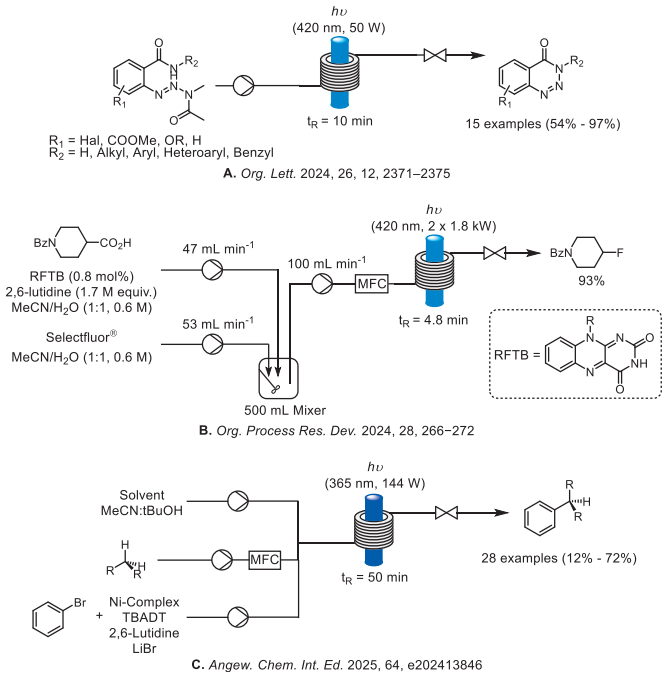
even when scaling up.[23] Shown below (Scheme 1) are three highlights from the last three years where continuous flow chemistry was used to scale photochemical reactions effectively.



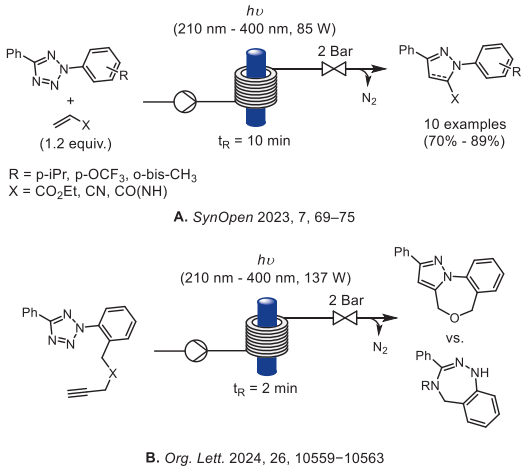
Scheme 1. Highlights of photochemical reactions.

In 2024, the Baumann group developed a mild and scalable method to generate benzotriazin-4(3*H*)-ones, which are medicinally important scaffolds, from amide bearing triazenes (Scheme 1 **A**). The methodology provides an atom economical method which relies on direct absorption (420 nm LEDs) by the triazene substrates. Optimization, scope, and scale-up were demonstrated using a commercial Vapourtec E-Series reactor allowing them to generate 15 triazenes (54–94%) with a productivity of 0.338 g h^{-1} at 4.18 mmol scale. This method improves the safety profile of this reaction, minimizing operator exposure to hazardous chemistry.[24]

A decarboxylative fluorination reaction of an aliphatic acid was quickly taken from screening through to multi-kilo scale with the assistance of high-throughput experimentation (HTE) and design of experiment (DoE) (Scheme 1 **B**). In the interest of moving away from transition metal photoredox catalysts, a flavin-based photocatalyst was identified as a sustainable and inexpensive alternative which absorbs readily in the visible region (380–495 nm). A two-input feed system allowed for separation of incompatible Selectfluor® and 2,6-lutidine which were then combined in a mixing vessel prior to being pumped into the photoreactor. The process was scaled up to 1.5 kg input of substrate over 4.5 hours with no issues, giving a theoretical productivity of 6.56 kg/day.[25] The Noël group showed the power of combining photoredox chemistry and gaseous reagents in flow to form new carbon-carbon bonds (Scheme 1 **C**). Using inexpensive and readily available C1–C4 gases and a pressurised continuous flow reactor they were able to generate 28 alkylated (hetero)aromatic products at 0.3 mmol scale in good yields (12–72%). The process was run at 1 mmol scale to generate the desired product in 55% yield at a productivity of 0.94 mmol h^{-1}. Combining tetrabutylammonium decatungstate (TBADT) as a hydrogen atom transfer (HAT) catalyst with nickel-catalysed cross coupling methodology allows for this process to be conducted at room temperature. Coupling photoredox HAT with metal-catalysis and continuous flow therefore allows for highly flammable and inert gaseous reagents to be used in a safe, scalable, and mild manner.[26]

2.1 *Direct Absorption of Light*

The most straightforward mode of reactivity is initiated by direct absorption of light by the reagents.[27] Sufficient overlap of the reagent's absorption wavelength and the light source emission wavelength is preferential.[28] The following section will show recent examples where continuous photoflow chemistry was used exploiting this reactivity. In 2022 the Baumann group studied the photolysis of tetrazole-based building blocks to generate nitrile imine dipole intermediates for subsequent 'photo-click' reactions (Scheme 2).[29,30]



Scheme 2. 'Photo-click' reactions in continuous flow mode.

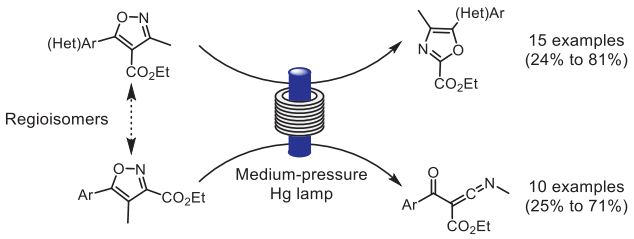
This procedure was developed in continuous flow mode and allows for high atom economy with nitrogen gas as the only by-product. A small library of pyrazoles and pyrazolines was generated using different dipolarophiles and tetrazoles exploiting a medium-pressure Hg-lamp with a Vapourtec E-Series flow module (Scheme 2 **A**). Scale-up was demonstrated for a 2 h run giving a productivity of 1.6 g h^{-1}.[29] An intramolecular version of this reaction was developed subsequently where propargylic/allylic ethers were reacted under similar conditions to afford useful tricyclic pyrazoles and pyrazolines in good yields (Scheme 2 **B**). When secondary propargylic/allylic amines were used novel benzotriazepines were obtained *via* an unprecedented mode of reactivity.[30]

The Kappe group targeted generating 1,2-difluorobenzene, which is a valuable starting material found in many APIs using continuous flow chemistry. Retrosynthetic analysis indicated that starting from 2-fluoroaniline would deliver the corresponding diazonium salt using HF/pyridine and $NaNO_2$, which could then be photochemically decomposed to the desired product. Chemical compatibility of flow reactor components and highly corrosive reagents must be considered on a case-to-case basis, the authors provided a pragmatic discussion in the supporting information on their process which can be applied to others. Many commercial flow reactor companies offer key components in alternative materials of construction when specific corrosive reagents are employed. For this process they opted for PTFE peristaltic pumps which showed no degradation in contact with HF/pyridine. Initially, a fully continuous process was sought for, but the diazonium formation step was efficient and sufficiently fast in batch. Therefore, directing the diazonium salt into a Vapourtec E-Series reactor and directly irradiating it with a high-power LED afforded the desired product in good yield and productivity under steady

state conditions, while avoiding the isolation of the unstable diazonium salt.[31]

Cyclobutenes are privileged scaffolds with desirable properties for synthetic applications and thus routes towards these species are of keen interest.[32] Typically, the [2+2]-photocycloaddition between alkenes and alkynes is used to directly excite these substrates using a medium-pressure Hg-lamp. In an improved flow process a high-powered UV-A LED (365 nm) was used instead of a Hg-based lamp to generate cyclobutenes under milder and more selective conditions. The reaction was optimized using a Vapourtec E-Series reactor using maleimide and propargyl alcohol as the model system.[33] Similarly, the same light source (365 nm) and reactor set-up yielded a variety of cyclobutene-containing carbocycles when alkyne-bearing chalcones were used as substrates or when mixtures of cyanopyridines and aryl aldehydes were excited in the presence of DIPEA.[34,35]

Oxazoles are valuable heterocyclic scaffolds often found in alkaloids and other bioactive species. Recently, a continuous flow method using a medium-pressure Hg-lamp was reported yielding highly substituted oxazoles *via* a photoisomerization process from related isoxazoles. This atom economical procedure was found to be general and gave access to a range of di- and trisubstituted oxazoles in good yields (24–81%).[36] Interestingly, when a regioisomer of the starting isoxazole reagent was used ketenimines were synthesized and subsequently trapped to afford new heterocyclic products (Scheme 3).[37]



Scheme 3. Oxazole or ketenimine formation dependent on regioisomer in continuous flow.[36,37]

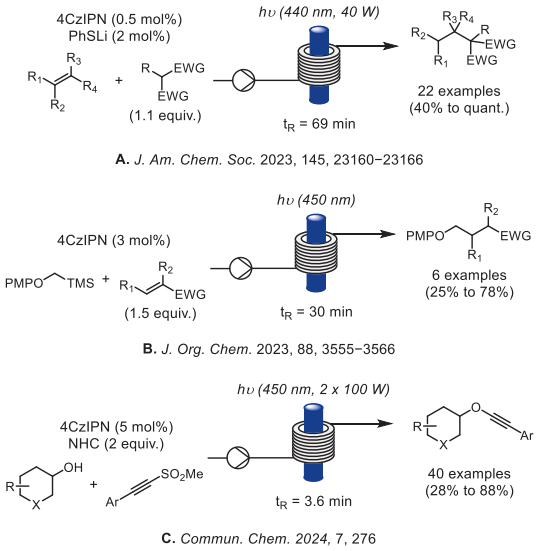
2.2 *Organocatalysed Photochemistry*

In cases where direct absorption of light by the substrate is not sufficient to trigger a photochemical reaction, photocatalysts and photosensitisers can be used.[38] This section will focus on examples where photoflow chemistry was performed in the presence of a photo-organocatalyst.

Linking both photochemical and thermal steps researchers at the University of Nottingham were able to efficiently synthesize bicyclic lactones at scale using telescoped continuous flow reactions. Moving from batch to flow, both steps showed improvements in yields when isopropyl thioxanthone was used as the photosensitizer and the reaction mixture was excited with a custom-made medium-pressure Hg-lamp.[39] Similarly, a team at the University of Bristol telescoped a photochemical and thermal process which used a thioxanthone-based photosensitizer to red-shift the reaction into the visible region, allowing blue LEDs (455 nm) to be used effectively.[40]

A photocatalyst/photosensitizer which has seen increased popularity due to its favourable photophysical properties is 4CzIPN (Scheme 4).

The Kobayashi group used this photocatalyst in combination with lithium thiophenoxide to employ unactivated alkenes as electrophilic partners for the α-alkylation of 1,3-dicarbonyl compounds, which typically requires transition metal catalysts.[41,42] A broad substrate scope was demonstrated in both batch and flow



Scheme 4. Continuous flow processes using 4CzIPN as a photocatalyst.

and on scale using Kessil lamps (440 nm) and a custom-made reactor set-up (Scheme 4 **A**).

Researchers from the Woo group developed a 4CzIPN-photocatalyzed Giese-type reaction of poorly activated Michael acceptors with a silicon-based radical precursor whereby the reactor set-up was a Vapourtec system with a blue LED light source (450 nm). Carrying on from previous work it was postulated that in order to expand the scope to include less activated Michael acceptors, a more reducing photocatalyst would be required for the single-electron reduction of the penultimate anionic radical addition intermediate. The generality of the procedure was explored in batch and subsequently demonstrated in flow which improved scalability while retaining the yields (Scheme 4 **B**).[43]

The Sonogashira coupling of alkyl/aryl halides and (pseudo) halides is the most general method for forging C–C bonds to alkynes but this process typically relies on transition metal catalysis which is not sustainable or cost-effective.[44] A photochemical method for the deoxygenative alkynylation of alcohols aided by *N*-heterocyclic carbenes (NHC) and 4CzIPN was developed by researchers from the Ma group. The procedure proved to be general, uses visible light (450 nm LEDs), and could be scaled in continuous flow. A library of products was generated including examples demonstrating the late-stage functionalization of existing biomolecules (Scheme 4 **C**).[45]

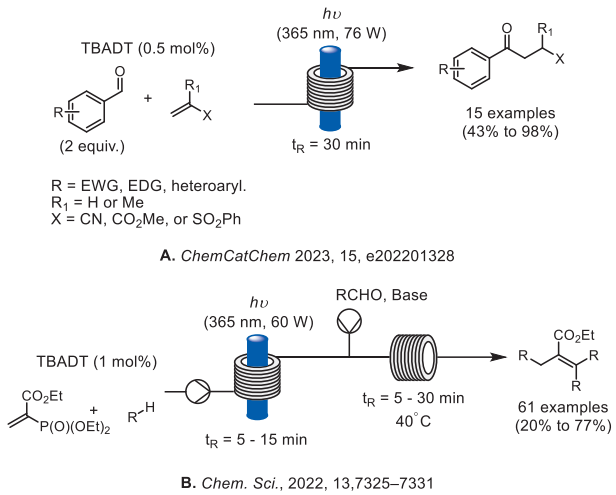
2.3 *Metal-photocatalysed Applications*

Although it is sometimes prudent to avoid the use of metal-based species in chemical processes due to cost and toxicity concerns, they should still be considered until comparable metal-free methods are developed. The next, and final photochemistry section will focus on studies where metallophotocatalysts or photosensitizers were exploited by continuous flow reactor technology.

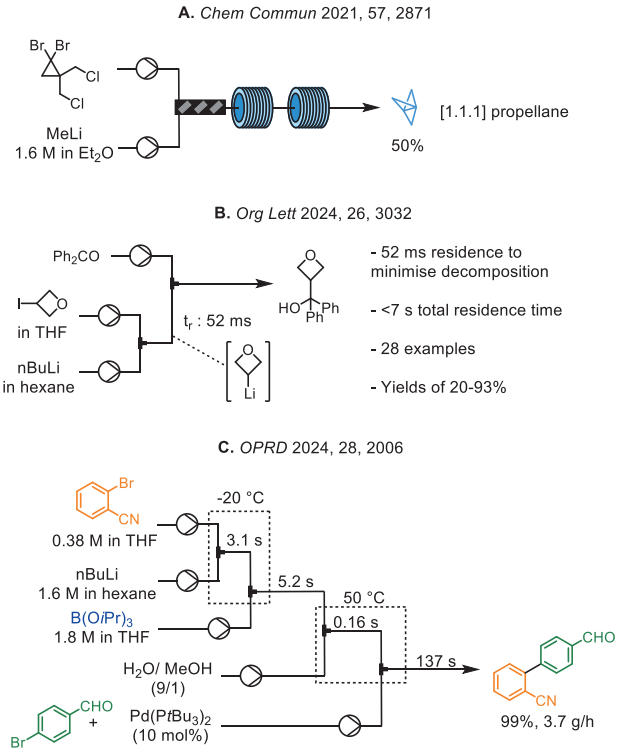
TBADT has proved to be an effective photocatalyst in recent years for C–H functionalization and C–C bond formation *via* HAT processes (Scheme 5).[46]

For instance, the Baumann group showed that using a Vapourtec E-Series reactor in conjunction with a high-intensity 365 nm LED a variety of β-keto nitriles could be accessed at high concentrations (0.5 M) and low TBADT loadings (0.5 mol%) (Scheme 5 **A**).[47]

Recently, the Noël group has developed a powerful telescoped method which combines TBADT-mediated HAT photocatalysis with a Horner-Wadsworth-Emmons reaction to generate versatile



Scheme 5. TBADT-mediated photoflow processes.



Scheme 6. Selected highlights of continuous flow lithiation reactions.

reaction products for further derivatization (Scheme 5 **B**). The process is general, fast, and scalable.[48] They demonstrated the process up to 4 mmol scale with a yield of 60%, corresponding to a productivity of 18 mmol h^{-1}, where significant yield drops were observed in batches above 1 mmol. While the large molecular weight of TBADT could pose challenges for its application at commercial scales, the Noël group has demonstrated effective procedures employing membrane-based nanofiltration to recycle this and other expensive photocatalysts. This combination of flow chemistry and nanofiltration not only ensures the viability of TBADT at commercial scale but also enhances the sustainability of the process by enabling catalyst reuse.[49]

A novel, photocatalytic methodology for synthesising fentanyl was developed by the Oliveira group. They used a ruthenium-based photocatalyst for both telescoped reductive aminations which was excited with blue LEDs (450 nm, 120 W). With custom-made batch and flow photochemical reactors they were able to intensify the process and increase the previous 16% yield to 47% yield.[50] Finally, the Cambeiro group effectively scaled up an iridium photosensitized Giese-type addition for the hydroaminoalkylation of aryl-substituted alkenes. The methodology was readily scaled in continuous flow mode using a Vapourtec E-Series flow system equipped with blue LEDs.[51]

3. Reactive Intermediates (Organometallics)

Lithiation reactions are highly versatile synthetic methods used for the metalation of organic compounds, enabling many subsequent transformations. However, these reactions are often avoided in both academia and especially within industry due to their highly exothermic nature and potential to 'runaway'. Sufficient mixing and cooling are required to maintain the reaction safety and minimize side product formation. For this reason, the continuous flow process has become a staple for scaling and optimizing lithiation reactions.

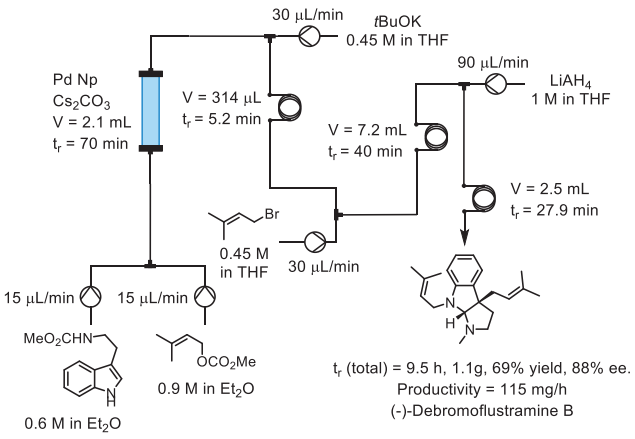
The Baumann group has applied these advantages to the synthesis of [1.1.1]propellane and bicyclo[1.1.1]pentanes. In batch, conditions to synthesize [1.1.1]propellane use MeLi or PhLi as a lithium species and temperatures of –78 °C. The published procedures are additionally not suited to lab scale reactions (1–10 mmol) due to the volatility of [1.1.1]propellane and suffer from inconsistent yields. As such the reaction was translated to a continuous flow reaction set-up. Utilizing a static mixer, MeLi and the tetrahalide substrate could be sufficiently mixed, taking advantage of superior mass transfer in flow mode. The reactor was cooled to –15 °C, 60 °C higher than batch, without the worry of 'runaway' exothermic reactions thanks to better heat transfer and miniaturization. This work also demonstrated how the [1.1.1]propellane could be further derivatized, notably achieving a 1.6 g h^{-1} productivity of BCP-I_2 (Scheme 6 **A**).[52]

More recently, the Luisi group developed a methodology to rapidly prepare 3-oxetanylithium *in situ* which can subsequently react with suitable electrophiles within a total residence time of 7 seconds. The generated lithiated species exists for a short time of 52 milliseconds before quenching through mixing with a suitable electrophile, minimizing both the presence of the lithiated species and additionally preventing undesirable ring opening of the oxetanylithium. Achieving such a reaction in batch, while possible, would be highly dangerous due to the need for immediate addition of lithiation species and electrophile. Through the *in situ* generation of oxetanylithium, the hazards can be greatly reduced. The group applied this methodology to 28 examples across a range of electrophiles, even demonstrating its use in late-stage functionalization with improved yields compared to batch. The group showed the scalability of this methodology with a run time of 6 minutes, giving a theoretical productivity of 1.3 g h^{-1} (Scheme 6 **B**).[53]

To further exemplify the use of flow in enabling high throughput lithiation reactions, the work by the Nagaki group demonstrated a high productivity generation of borylated aromatics for use in Suzuki couplings. Again, utilizing the superior mass and heat transfer offered by flow, the group was able to achieve a lithium halogen exchange reaction at a temperature of –20 °C with a residence time of 0.31 seconds. A subsequent telescoped addition of triisopropyl borate and a residence time of 0.52 seconds gave the aromatic boronic acid with a throughput up to 197 g h^{-1} (93% yield). To further demonstrate the utility of this methodology the group telescoped the boronic acid synthesis with a continuous flow Suzuki coupling. This successfully generated precursors for valsartan and diflunisal with total residence times of 143 seconds (3.7 g h^{-1}, 99%) and 91 seconds (6.5 g h^{-1} 91%), respectively (Scheme 6 **C**).[54]

As the Nagaki group's work displays, the use of metal catalysts has greatly benefited from continuous flow processing. The catalyst can be homogenous which benefits from heat and mass transfer advantages in flow. Alternatively, using packed-bed reactors solid metal or solid supported metal catalysts can be loaded

into a suitable column and the reaction mixture can be continuously passed over this. This immobilization can in turn allow for recycling the metal catalyst and reduces the need for metal removal during purification following a reaction (Scheme 7).



Scheme 7. Application of packed bed catalyst reactor.

As shown by the Chen group, palladium nanoparticles can be used in a packed-bed reactor for the synthesis of (–)-debromoflustramine B. Palladium nanoparticles were investigated in both batch and continuous flow mode, where the group found that the main reason for reduced catalytic activity was due to the need for aqueous NH_4Cl during work-up. Using the nanoparticles in a packed-bed flow reactor the reagent solution could be carried through the telescoped procedure without the need for such an aqueous work-up allowing for the catalyst to maintain its activity and be easily recovered from the packed-bed reactor. Overall, the group successfully synthesized the target (–)-debromoflustramine B in a 69% (86% *e.e.*) yield over a four-step telescoped flow process requiring only one chromatographic separation. It is worth noting that reported batch procedures range from 3–7 steps and often require multiple chromatographic purifications.[55]

Similarly, using a resin-bound ruthenium catalyst, the Kobayashi group utilized a packed-bed reactor for the C–H amidation of phenylpyridine derivatives. The group was able to demonstrate applications with a wide range of substrates (19 examples, 27–96%). The longevity of the catalyst species was tested during a 200 h continuous process, giving an average yield of 82% (3.29 g) with no detected catalyst leaching and turnovers exceeding 290. It was found that batch reactions gave rise to significant catalyst leaching of up to 7.5%, demonstrating the potential of flow to prolong catalytic activity for metal catalysts.[56]

4. Electrochemistry in Flow Mode

As with photochemistry, the use of electrochemistry has risen in popularity since the turn of the last century. With the chemical industry becoming more conscientious of its environmental impact, the desire to explore and develop more sustainable alternatives has led to a resurgence of electrochemistry in organic synthesis.[57] Conventional redox reactions rely on stoichiometric amounts of redox reagents, while electro-organic synthesis proceeds through electron transfer between organic molecules and electrodes. Additionally, redox reagents are often based on costly metals that are potentially hazardous and generate large amounts of waste. The comparable cost of electrical power is insignificant and provides a more economically efficient process.[58] Many of the benefits of flow also apply to electrochemistry, helping to overcome some of its limitations. The greater mass transfer of flow benefits the heterogenous nature or electrochemical reactions that occur near the electrode surface. Additionally, the miniaturization of electrochemical reactors provides a narrow interelectrode distance, which means the need for an electrolyte is reduced or even completely removed.[59] Flow reactors are also more suited to reaction scale-up and offer greater reproducibility and robustness during scale-up.[60] For these reasons continuous flow processing has become an attractive option for taking electrochemical reactions to pilot scale and beyond.[61] The focus of this section will be on recent publications showcasing how innovative continuous electrochemical methods were developed.

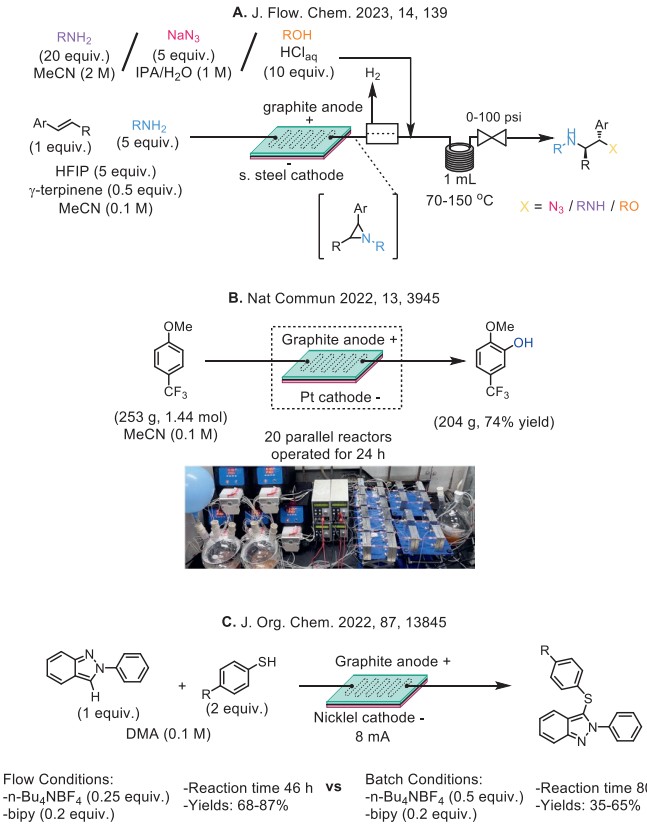
In 2023, the Ošeka group, while investigating the use of electrochemical flow reactors for the synthesis of aziridines from alkenes and primary amines, found that the excess amine reacted with the formed product over time to give vicinal diamines *via* aziridine ring opening. Through telescoping the electrochemical reaction with a thermal reactor, the group could selectively form these new products in short residence times of 5 minutes. This methodology was applied to the synthesis of both symmetrical and non-symmetrical vicinal diamines, amino ethers, amino alcohols, and amino azides, thus demonstrating broad reaction scope (Scheme 8 **A**). The synthesis of vicinal amino azides benefited from such a flow set-up as the hazards can be reduced allowing for safer access to these useful compounds.[62]

The electrochemical hydroxylation of arenes by trifluoroacetic acid provides access to aryl oxygen compounds under mild conditions. Use of such a method in a continuous flow cell was reported by the Ošeka group in 2022. However, the scope of this method was limited to electron-rich arenes.[63] Later that same year the Xu group published a methodology which could broaden the reaction scope to electron-neutral and -deficient arenes. The broad scope of this methodology demonstrated high selectivity, potential application in late-stage functionalization, and scalability. Usiing 20 reactors in parallel, it allowed the production of 1 mol (204 g day^{-1}) of phenolic product (Scheme 8 **B**).[64]

The Sharma group developed an electrochemical synthesis for the novel regioselective sulfenylation of 2*H*-indazoles. This was achieved with good yields (50–83%) across a range of examples (24 substrates) without the need for metal catalysts or oxidants. This work also compared several examples where either a batch electrocell or an electroflow microreactor were used, showing that flow allowed for lower concentration of supporting electrolyte (0.5 equiv. batch *vs* 0.25 equiv. flow), higher reaction yields (22% in batch to 33% in flow), and shorter overall reaction times (80 h batch *vs.* 46 h flow) on gram scale reactions (Scheme 8 **C**).[65]

Work from the Xu group used a homemade continuous flow electrochemical method to achieve an aza-Wacker-type cyclization to afford saturated *N*-heterocycles in a single-pass method. The reaction did not require metal catalysts, electrolyte, or additives. A wide substrate scope was demonstrated for di-, tri-, and tetrasubstituted alkenes with 46 examples and yields up 95%. Additionally, the group demonstrated numbering-up of flow reactions using four reactors in parallel giving a throughput of 0.67 g h^{-1}.[66]

N-Nitrosamines are compounds known for their hazardous nature; however, their application as nitric oxide donors makes them versatile synthetic species. As such the Wirth group aimed to develop a continuous flow electrochemical method for *N*-nitrosamine synthesis. Building on known batch electrosynthesis methods the group utilized the commercially available Vapourtec electrochemical reactor to successfully synthesize 27 examples using sodium nitrate as the nitrosating agent with yields up to 99%. In comparison to previous literature the reaction could be completed in the absence of strong acids or redox reagents. The group also incorporated in-line purification strategies demonstrating the ability to minimize contact of hazardous materials with operators.[67]

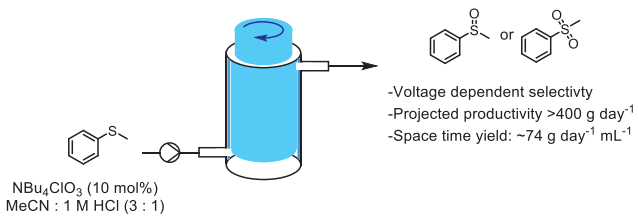


Scheme 8. Highlights of flow electrochemical reactions.

As aldehydes and ketones are important pharmaceutical building blocks, the oxidation of alcohols under benign conditions is of great interest. The Lei group developed an electrochemical flow method for this transformation. In comparison to previous batch publications, this approach achieved significantly higher yields and selectivities. Using a homemade reactor cell, scale-up was demonstrated up to 100 mmol, yielding the desired product in 99% yield in 20 hours.[68]

In 2022 the Oliveria group successfully developed an electrochemical method for α-sulfenylation of ketones without the need of added oxidants or metal catalysts. Work began using a batch electrochemical cell where they successfully optimized the reaction and applied it to a range of thiols and ketones. However, to further the study this methodology was applied under continuous flow conditions using the commercially available Syrris Asia Flux microflow electro-cell. Following a brief re-optimization of the reaction conditions, the group was successful in translating the batch reaction to the flow set-up with a yield of 83% and throughput of 0.36 g day^{-1} in a 225 µL reactor.[69]

So far within this section, the publications shown have used variations of parallel plate reactors for their continuous flow electrochemical reactions. These reactor types are amongst the most common due to their commercial availability and simplicity in both set-up and modularity. One main drawback of parallel plate reactors is that the requirement for good mass transfer is often achieved by high flow rates, resulting in short residence times. This can require flow reactions to be recirculated in order to achieve good conversion. An alternative reactor which aims to address this issue is the Taylor Vortex reactor. This set-up utilizes a rotating electrode within a cylindrical electrode (Scheme 9). The rotating electrode generates Taylor vortices perpendicular to the reaction flow rate. This allows for superior mass transfer within the solution without the need for high flow rates. This improvement makes these reactors more suitable for telescoping. A recent example of this from the George group showed that methoxylation of *N*-formylpyrrolidine (a standard electrochemical reaction for comparisons) could be completed on a multi-mole per day scale. Additionally, a selective oxidation of thioanisole (>97% for either sulfoxide or sulfone products) could reach production of over 400 g per day.[70] While only parallel plate and rotating electrode reactors have been mentioned in this review it should be noted that a variety of reactor designs have been developed.[71]



Scheme 9. Use of a rotating electrode reactor for thioanisole oxidation.

5. Conclusions

The number of publications citing continuous flow chemistry continues to grow steadily as this tool becomes more widely available. It is hoped that this review will bolster the idea that flow chemistry can help when reactive intermediates are involved. For photochemistry the advantages brought about by the short path lengths are undeniable when translating batch reactions to flow. Equally, when scaling up a photochemical process is required, flow should be a consideration. Traditionally, the small scale of photochemical reactions has hindered their use as a tool for large scale manufacturing, but with the application of flow reactors, chemists can choose excited state pathways which may possess improved step economy relative to the ground state alternatives, leading to improved sustainability and lower manufacturing costs. Organometallic chemistry involving lithiations and similar reactions that are mixing sensitive can also be enhanced in continuous flow, improving their safety and efficiency, especially on larger scales. Finally, although in its relative infancy, the flow electrochemistry literature referenced here shows that electrochemistry can be intensified and scaled by exploiting continuous processing with lower reliance on stoichiometric redox reagents with large potential waste generation. Although flow is not applicable to every reaction, it is a powerful enabling technology that can serve the needs of process chemists. By lowering manufacturing costs, improving productivity, and increasing the safety profile of reactions, the production of pharmaceuticals, agrochemicals, and fine chemicals will continue to become more efficient and the cost to the end user will fall. Moreover, flow technology has positively impacted on chemical sustainability, showcasing another clear advantage for academic research and industrial applications alike which will be a key driver for innovative solutions focusing on methodology development, process intensification and the integration of new reactor designs going forward.

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Abbreviations

4CzIPN	1,2,3,5-Tetrakis(carbazol-9-yl)-4,6-dicyanobenzene
API	Active pharmaceutical ingredient
BCP	Bicyclo[1.1.1]pentane
DIPEA	N,N-diisopropylethylamine
DoE	Design-of-Experiment
EDG	Electron donating group
EWG	Electron withdrawing group
HAT	Hydrogen atom transfer
HFIP	Hexafluoroisopropanol
Hg-lamp	Mercury vapour lamp
HTE	High-throughput experimentation
LED	Light-emitting diode
NHC	N-heterocyclic carbene
PMPO	Paramethoxyphenyl ether
PTFE	Polytetrafluoroethylene
RFTB	Riboflavin tetrabutyrate
TBADT	Tetrabutylammonium decatungstate
TMS	Trimethylsilyl
t_R	Residence time

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