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Review

Functional Group Interconversion Reactions in Continuous Flow Reactors

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Abstract: An overview of the current uptake of continuous flow techniques for various functional group interconversion reactions is presented. Besides highlighting a variety of prominent examples and their main features, this review provides insights in specific reaction classes such as oxidations, reductions, rearrangements as well as different C-H functionalization processes. While this review can only include key examples from the last decade, the reader will find a solid foundation of important transformations along with further references to inform and appreciate the opportunities arising from modern synthesis technologies such as flow synthesis.

Keywords: flow synthesis, functional group interconversion, oxidation, reduction, rearrangement, C-H functionalization.

1. INTRODUCTION

The last 20 years have witnessed an impressive transformation of how synthetic chemists prepare complex molecules with ever increasing efficiency. This has been paralleled by the advent and exploitation of numerous enabling technologies for chemical synthesis including polymer-supported reagents and catalysts, microwave reactors, design of experiments (DoE) and continuous flow chemistry. The latter is one of the most impactful developments in synthetic chemistry, a field in which round bottomed flasks have been the reaction vessels of choice for centuries. Moving from traditional glassware to microchips and small diameter tubing in which solutions of reactants are subjected to all reaction conditions imaginable has thereby provided countless opportunities for streamlining chemical processes. The popularity of continuous flow synthesis over batch processing is the result of key advantages that arise from reactor miniaturization, namely improved heat and mass transfer, that allows for increased control and safety over the chemical reaction [1]. The resulting continuous flow processes can thereby be automated and coupled with inline purification and analysis tools to realize the union of the synthesis of target compounds and concomitant data generation [2]. Individual steps can consequently be linked into telescoped end-to-end syntheses [3] of advanced chemical entities such as natural products [4] or active pharmaceutical ingredients [5]. Scale-up of these processes can be achieved by running the flow reactors for extended periods or operating several reactor units in parallel [6]. Consequently, the salient features of flow processing can be applied to small scale syntheses of compound libraries as well as the manufacture of individual high-value targets thus accounting for the popularity of flow synthesis in academia and chemical industry alike [7]. While these underlying features are well-understood, the development of highly efficient and scalable flow processes is a challenging undertaking which requires the input from synthetic chemists and chemical engineers [8]. In addition, active research in previously dormant and traditionally isolated disciplines, such as photochemistry [9], electrochemistry [10] and biocatalysis [11] have recently garnered exciting developments towards more sustainable chemical synthesis when coupled with continuous flow techniques.

While the efficient chemical synthesis of complex target molecules is of paramount importance towards the discovery of new bioactive compounds, the underlying executing of a plethora of functional group interconversions is pivotal for realizing this goal. In this review we wish to survey the impact of flow processing on achieving superior results when targeting a variety of important functional group interconversion reactions.

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2. DISCUSSION

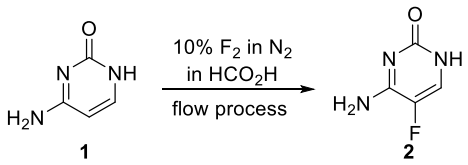
As outlined in the introduction continuous flow processing has been exploited extensively to bring about the introduction and interconversion of multiple functional groups to enable the construction of valuable target compounds. The following sections will thus highlight selected examples that demonstrate recent applications that exploit the salient features of flow chemistry, including safety, efficiency, reproducibility and scalability. We will thereby firstly discuss examples that convert ubiquitous aromatic and olefinic C-H bonds into functionalized building blocks that enable further derivatization. The impact of flow chemistry on the interconversion of hydroxy and amine groups into a variety of complementary functional handles will then showcase a variety of direct transformations that are oftentimes avoided in batch mode due to safety concerns. Subsequent reports will focus on important oxidation and reduction processes, before discussing rearrangement reactions that exploit flow approaches to render new functional groups. Modern flow methods utilizing enzymes, light or electricity will highlight some new approaches geared towards improving the atom economy of the underlying transformations. Lastly, we will touch on industrial considerations for exploiting flow-based functional group interconversion processes.

2.1. Functionalization of C(sp^2)-H Bonds

The functionalization of alkenes and electron-rich aromatic systems by means of different halogenation processes is a very important strategy in synthetic chemistry. The corresponding halogenated products can thereby serve as intermediates for further functionalization or represent the final target. Interestingly, chlorinated and brominated systems are most frequently encountered in natural products, whereas fluorinated and chlorinated systems are prevalent in drugs and agrochemicals.

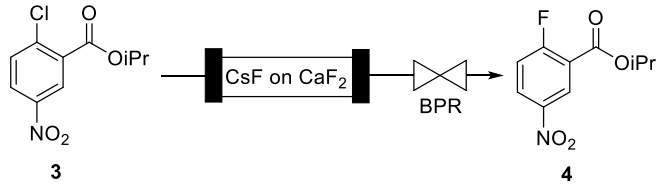
As discussed in a recent review article flow chemistry has been playing an important role in facilitating halogenation reactions [12]. This can be explained by the reactive nature of halogenating reagents that make many of these transformations challenging to perform in batch mode. The miniaturization offered by flow processing thereby provides not only better mass and heat transfer than related batch reactions, but moreover affords a fully contained environment within the flow reactor that is additionally controlled by software to enable automated shut-down in case of unstable conditions.

Continuous fluorination reactions are a special case due to the high reactivity of fluorine gas (used typically as 10% F_2 in N_2), towards glass and metal used in the construction of reactor materials. Bespoke set-ups are pivotal in combination with high safety standards when executing flow reactions with elemental fluorine [13]. In recent applications, Sandford and co-workers demonstrate successful approaches for the synthesis of the antifungal agent flucytosine [14] (**2**, Scheme 1) as well as various carbonyl-based building blocks and aromatic scaffolds [15].



Scheme 1: Continuous fluorination using fluorine gas.

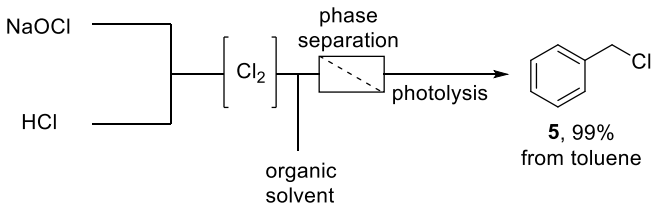
Additionally, the nucleophilic fluorination of electron-deficient aromatic substrates has been reported based on heterogeneous fluoride species (CsF on CaF_2) loaded into a packed bed-reactor cartridge ([16], Scheme 2).



Scheme 2: Nucleophilic fluorination via immobilized fluoride.

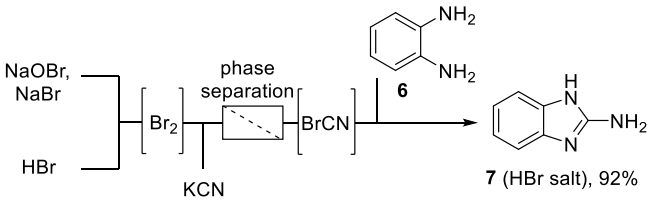
Additionally, flow-based fluorination methods are important for the generation of radiolabeled drugs due to the short lifetime of ^{18}F that necessitates fast and on-site processing due to the rapid decay of this isotope [17].

In contrast to direct fluorination reactions, the introduction of chloride and bromide commonly avoids the use of corrosive chlorine gas or bromine as reagents in small scale applications. For instance, this can be achieved by using readily available reagents such as sodium hypochlorite (Scheme 3) [18], or *N*-bromosuccinimide (NBS) that generate the desired reactive species in situ [19]. In recent years, this trend towards using safer and more convenient precursors for flow halogenation methods lead to the concept of using flow reactors as generators for halogens and other high-energy species as recently reviewed by Kappe [20].



Scheme 3: Example of continuous flow photochlorination reaction based on situ formation of Cl_2 [18].

For example, bromine was generated *in situ* from a mixture of $NaOBr_3$/NaBr and hydrobromic acid, prior to reaction with aqueous KCN to create cyanogen bromide (BrCN). The latter was then subjected to an inline extraction process before reacting with 1,2-diaminobenzenes to render a series of benzimidazole products without isolation of any harmful intermediates [21] (Scheme 4).

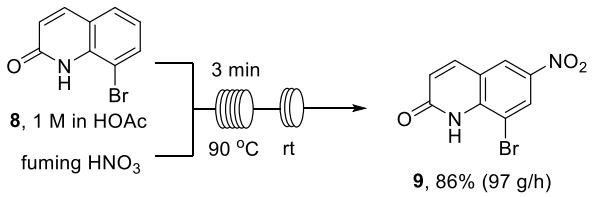


Scheme 4: Preparation and use of BrCN in flow mode.

Analogously, iodinated building blocks can be created through flow-based methods either using molecular iodine [22], interhalogen species such as I-Cl (to generate other iodination species) [23], or by electrochemical procedures that create iodonium species (e.g. I^+) oxidatively [24].

Nitration of aromatic substrates is an important transformation for the introduction of nitro groups, which may serve as amine precursors. As most nitration procedures operate via an electrophilic aromatic substitution mechanism the reactive nitrosonium cation needs to be created *in situ* from concentrated nitric acid. This represents a serious safety concern especially when scaled approaches are targeted in industry. Miniaturization and containment as offered through flow processing thereby mitigate these concerns and provides for excellent reaction control that in many reported cases minimizes the formation of side-products [25].

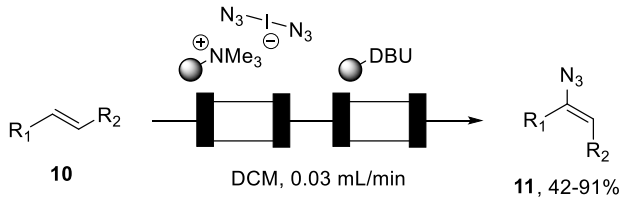
A report from Novartis [26] outlines how the careful study of the energy profile of high-energy nitration reactions is critical to assess the safety profile and determine suitable conditions. The continuous nitration of bromoquinolinone **8** with fuming nitric acid is an example that was not safe to scale in batch, whereas a continuous flow approach produced the desired product **9** safely in high yield (86%) and productivity (97 g/h) as shown in Scheme 5.



Scheme 5: Continuous flow nitration reported by Novartis.

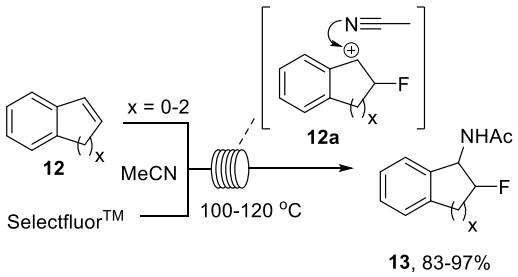
In an analogous study the safe scale-up of nitration reactions to pilot scale was demonstrated exploiting several plate reactors (numbering up) [27].

Besides facilitating the functionalization of aromatic C(sp^2)-H bonds, flow processing has also been exploited for related olefinic moieties including readily available styrenes. Kirschning and co-workers demonstrated the use of an immobilized iodine azide equivalent (I-N_3) that was packed in a flow cartridge reactor [28]. Passing a styrene solution through this packed bed reactor thus rendered the corresponding addition products that could be subjected to a second cartridge filled with an immobilized base to bring about the elimination of HI (Scheme 6). Overall, this flow process renders a variety of useful vinyl azide species (**11**) which are emerging building blocks in organic chemistry [29].



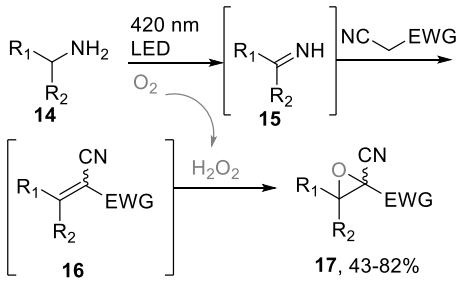
Scheme 6: Flow synthesis of vinyl azides.

An analogous difunctionalization protocol for styrenes was reported by Ley and co-workers who developed a fluoro-Ritter reaction in flow [30]. This combines the use of Selectfluor™ as an electrophilic fluorine source to render a benzylic cation (**12a**) that is intercepted by the acetonitrile solvent. The final products **13** possessing amide and fluoride functionalities are potentially useful compounds in organic synthesis whose conventional preparation would involve multiple steps (Scheme 7).



Scheme 7: Fluoro-Ritter reaction in flow mode.

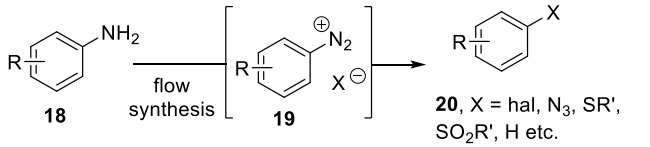
A final strategy frequently utilized for the functionalization of styrenes and other alkenes is based on epoxidation reactions. These formal oxidative transformations have been reported multiple times in flow mode as this presents benefits in view of the choice of reagent (e.g. mCPBA, H_2O_2, O_2 etc.) due to increased safety and mass transfer when performed in a microreactor [31]. An interesting and innovative variant was reported by Seeberger and co-workers [32] who designed an effective flow process that couples not only the formation of the alkene intermediate (**16**) with a telescoped epoxidation step, but moreover utilizes the by-product of the first photochemical step (H_2O_2) as the oxygen source in the epoxidation. Thus, this study represents a neat approach combining photochemical flow processing with atom economic target synthesis (Scheme 8).



Scheme 8: Integrated generation and functionalization of alkenes in flow.

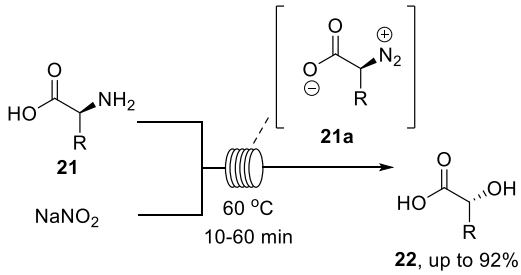
2.2. Direct Functional Group Interconversions of Amines and Alcohols

The interconversion of amines and their derivatives into a wide variety of other functional groups can be achieved via the intermediacy of diazonium salts. Due to their instability and propensity to liberate nitrogen gas diazonium salts are preferably generated and consumed through continuous flow processes [33]. The intermediate diazonium salt (**19**) can thereby be converted in flow mode into halogens [34], azides and related targets [35], thioethers [36], sulfonyl chlorides and sulfonamides [37] or subjected to a proto-dediazotization process [38]. A further important flow-based application of diazonium salts concerns the generation of new C-C bonds via cross-coupling reactions with alkenes [39]. Aryl diazonium salts have also been reported as precursors of benzynes utilizing anthranilic acid substrates [40].



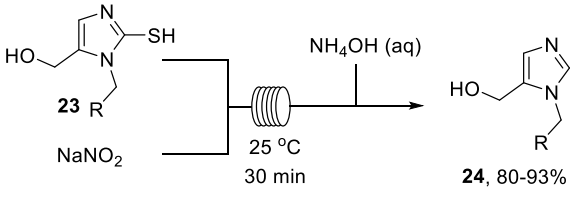
Scheme 9: Overview of diazonium chemistry in flow.

The generation of the diazonium species commonly exploits either $NaNO_2$ or alkyl nitrites (e.g. tBuONO) as diazotization reagents under acidic conditions. While the vast majority of reported cases utilizes aryl amine starting materials, alkyl amines are reported in a few cases such as the conversion of α-amino acids into chiral α-hydroxy acid building blocks (**22**, Scheme 10) [41].



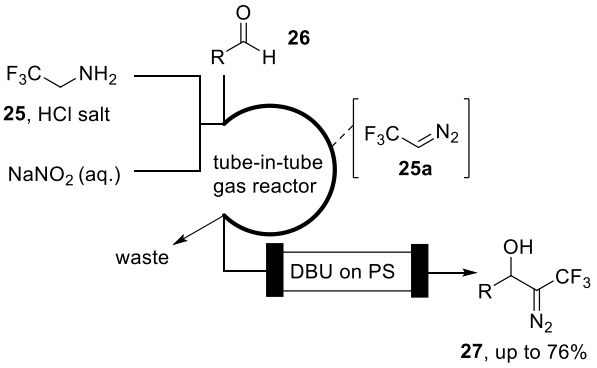
Scheme 10: Flow-based conversion of α-amino acids into chiral α-hydroxy acid building blocks.

An unusual case study reports on the use of diazotization conditions ($NaNO_2$/ aq. HOAC) to bring about the desulfurization of a series of thioimidazoles in flow mode [42]. This process also exploits a quenching protocol of residual nitrite and/or nitrous oxides based on reaction with aqueous ammonia to generate nitrogen gas and water as benign by-products (Scheme 11).



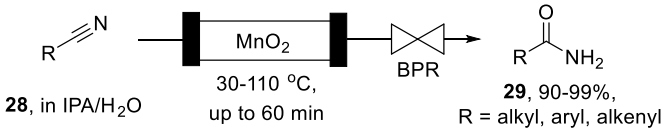
Scheme 11: Desulfurisation of thioimidazoles in flow.

Recent work by Kappe also highlights the utility of primary alkyl amines such as trifluoroethyl amine (**25**) in the generation and use of trifluoromethyl diazomethane **25a** as a versatile building block for the incorporation of CF_3 groups into organic compounds [43]. This work utilizes a tube-in-tube reactor to transfer the gaseous intermediate **25a** across a membrane into a stream of aldehyde substrates to trigger an addition reaction in a subsequent column filled with immobilized base (DBU on polystyrene) as shown in Scheme 12.



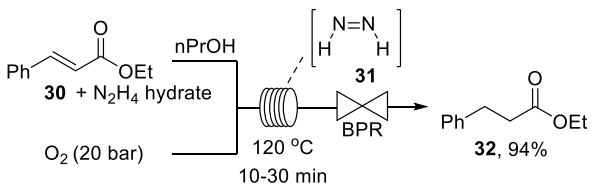
Scheme 12: Formation and use of trifluoromethyl diazomethane in flow.

Primary amides also feature NH_2 groups that can facilitate important functional group interconversion reactions. These include the Hofmann rearrangement (see Section 2.4) and the required amide substrates can be conveniently generated via a flow-based hydration protocol exploiting packed bed reactors filled with MnO_2 (Scheme 13) [44].



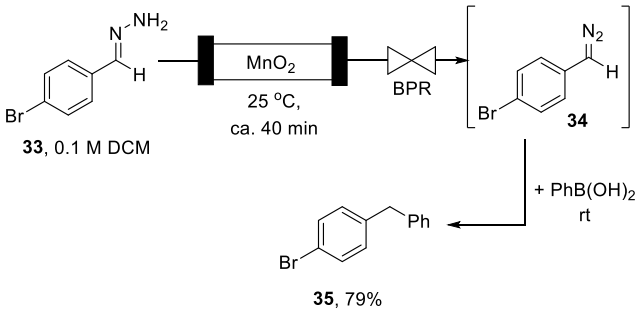
Scheme 13: Heterogeneous hydration of nitriles in flow.

Analogously, hydrazines and hydrazones are useful building blocks whose interconversion into diverse functionalities can be facilitated by continuous flow processing. Kappe and co-workers demonstrated the generation and use of diimide **31** from hydrazine and oxygen in a flow-based reduction protocol for alkenes [45]. Although this clean transfer hydrogenation process is known for over a century, safety concerns would preclude exploitation of this transformation in scaled batch processes. This problem is effectively resolved in flow mode (Scheme 14).



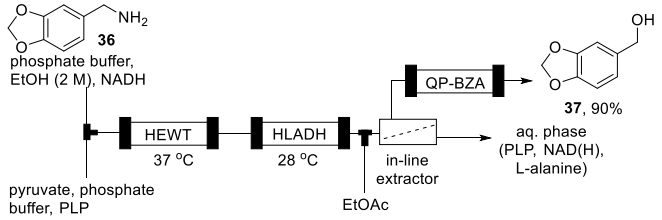
Scheme 14: Generation and use of diimide **31** through flow processing.

Related hydrazones have been reported as simple yet effective substrates in flow-based syntheses of various diazo species utilizing MnO_2 as a heterogeneous reagent in packed bed reactors (Scheme 15). As demonstrated by Ley and co-workers these reactive intermediates (e.g. **34**) can then be converted via cross-coupling reactions with aryl boronic acids to render sp^3-rich building blocks [46] or via Cu-promoted coupling reactions with terminal alkynes to create valuable allenes [47].



Scheme 15: Generation and use of diazo compounds from hydrazones in continuous flow.

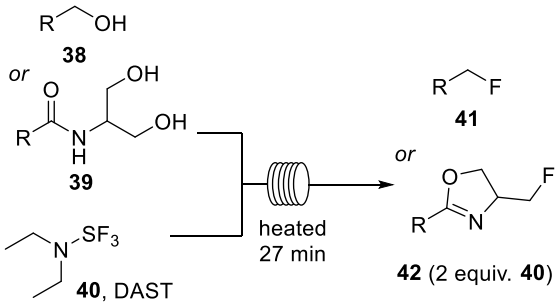
Lastly, flow processing has recently highlighted the applicability of its many beneficial features to biocatalyzed transformations including valuable transamination protocols that convert amines into ketones and aldehydes. Paradisi and co-workers recently demonstrated a powerful flow approach that telescoped such a transamination process with a subsequent reduction step to directly convert amines into alcohols [48]. This flow process utilized immobilized enzymes (HEWT, HLADH) placed into flow cartridges to increase the mass transfer and thus accelerate the reactions. This was effectively applied to a variety of substrates including chiral amines that rendered chiral alcohols in excellent enantiopurity (Scheme 16).



Scheme 16: Continuous transamination reactions.

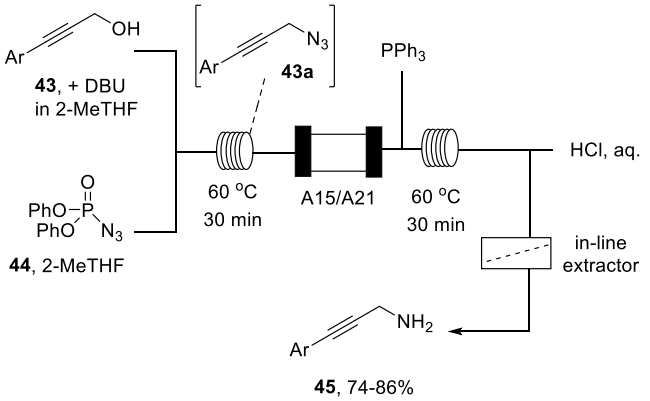
Alcohols are themselves valuable and ubiquitous substrates that are frequently exploited in flow processes. Besides classical oxidative transformations that will be discussed in Section 2.3, a variety of other important functional group interconversions deserve highlighting.

The interconversion of alcohols into fluorides is a frequently reported process as suitable reagents (e.g. DAST, DeoxoFluor etc.) require careful handling which benefits from the contained environment offered by flow reactors. Recent studies by Ley [30, 49] and Seeberger [50] highlight robust reaction protocols that render monofluorinated products from alcohols as well as oxazoline products upon cyclisation of β-hydroxyamides (Scheme 17). Analogously, ketones and aldehydes can be converted via these methods into valuable difluoromethyl groups.



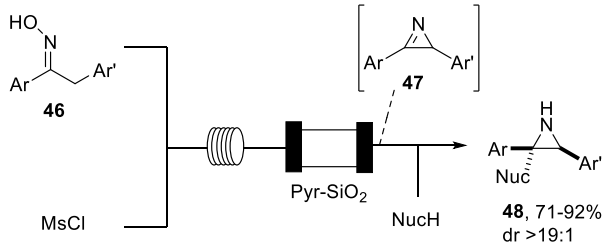
Scheme 17: Deoxofluorination of alcohols using DAST.

In addition, flow processing has been exploited to directly convert propargylic alcohols into azides using DPPA (**44**) as the azide source [51]. Reaction telescoping in combination with in-line extraction furthermore enabled the conversion of the intermediate azides (**43a**) into amines via a Staudinger reaction protocol (Scheme 18).



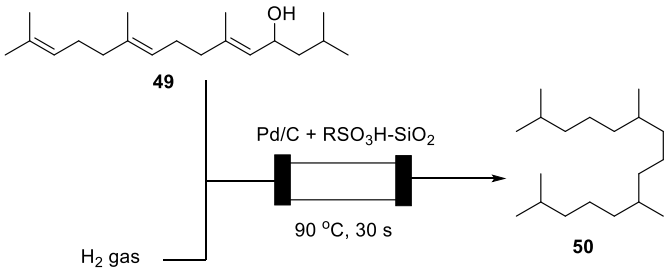
Scheme 18: Flow-based synthesis and derivatization of propargylic azides.

Baxendale and co-workers recently highlighted a flow protocol for the activation of the hydroxyl group of oximes with MsCl to render 2*H*-azirines (**47**) and subsequently aziridines (**48**) via intramolecular cyclization process [52]. The use of an immobilized pyridine base facilitated the generation and purification of the 2*H*-azirine species that reacted readily and in high diastereoselectivity with various nucleophiles towards useful aziridine products (Scheme 19).



Scheme 19: Synthesis of aziridines from oximes in flow.

Lastly, the dehydroxylation of allylic alcohols has been studied under hydrogenation conditions in flow reactors. An immobilized sulfonic acid catalyst combined with Pd/C facilitated this functional group interconversion that included the dehydration and subsequent hydrogenation of various alkene groups rendering the natural product pristane **50** in a highly atom-economical manner [53] as shown in Scheme 20.

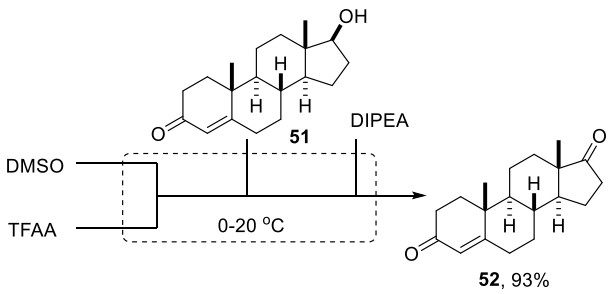


Scheme 20: Flow synthesis of pristane (**50**) from allylic alcohol building block **49**.

2.3. 'Classical' Oxidation and Reduction Processes

Oxidation and reduction reactions are amongst the most frequently employed functional group interconversions in organic chemistry. These transformations are commonly exploited to adjust the oxidation state of numerous functional groups based on oxygen, nitrogen, and sulfur. Although countless variations of these redox reactions have been developed over the last century, chemists with a focus on industrial synthesis often view these reactions more critical due to their modest atom-economy. Consequently, recent efforts have rendered more efficient oxidation and reduction protocols exploiting the key reagents in catalytic quantities. More recently flow chemistry has been utilized to further streamline and intensify these reactions in view of safety (obnoxious reagents), efficiency (high throughput) and wider process windows (higher pressure/temperature). The following section will highlight selected transformations for which valuable flow processes have been developed over the years.

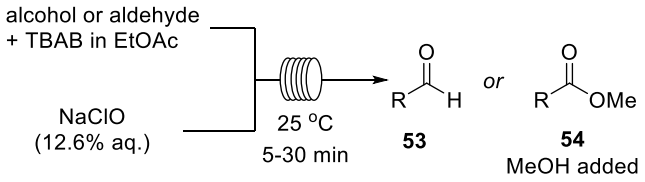
The oxidation of alcohols to aldehydes, ketones and carboxylic acid species is a prime example with many reagents available to the synthetic chemist. Chemoselective procedures that deliberately produce versatile aldehydes from primary alcohols play a special role in the chemist's toolbox. The Swern oxidation is such a transformation that is commonly exploited in batch syntheses. Scalability of this reaction in batch mode is not straightforward due to the low temperature required in view of the reaction's exothermicity and potential of side reactions such as the Pummerer reaction. Furthermore, the generation of malodorous by-products such as dimethyl sulfide make this transformation challenging to scale. A recent flow process has therefore been developed that provides excellent heat transfer in combination with a small footprint and fully contained set-up [54].



Scheme 21: Moffatt-Swern oxidation in flow mode.

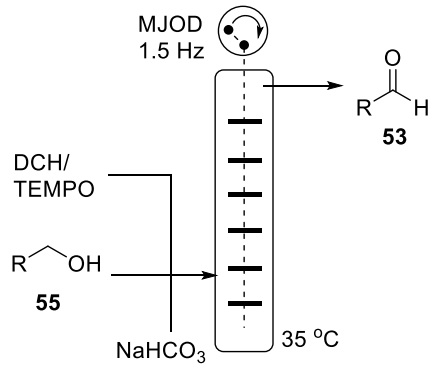
As seen in Scheme 21, this set-up uses a variety of pumps to premix the reagents at a modestly low temperature (compared to -78 °C in batch) before combining the active reagent with different alcohol substrates. This process offers excellent reaction control that translates for the shown testosterone substrate (**51**) into both high yield of product **52** (93%) and throughput (64 g/h).

A second example demonstrating the efficacy of flow processing when performing selective oxidations of alcohols to aldehydes and ketones has been reported by the Jamison group [55]. In this report a simple PFA tube reactor is used at ambient temperature. The substrate and TBAB (phase transfer catalyst) is dissolved in EtOAc and mixed via a T-piece with a stream of bleach (NaClO 12.6%, aq.) of a known stoichiometry. Upon exiting the flow reactor, the reaction mixture is quenched with aq. Na_2SO_3 solution prior to work-up by extraction. The authors demonstrate this valuable process on various substrates that give the desired products in excellent yields. Additionally, increasing the stoichiometry of the bleach oxidant and adding methanol to the reaction mixture allows for creation of methyl ester products from primary alcohol substrates (Scheme 22).



Scheme 22: Use of bleach as oxidant in flow reactions.

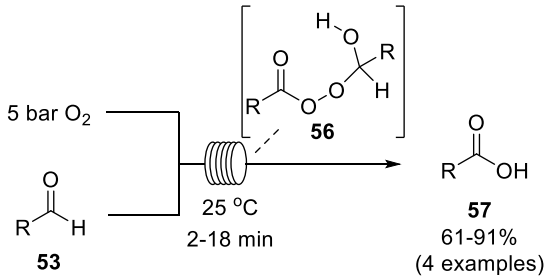
A further interesting study utilizing flow-based oxidation of alcohols to aldehydes is shown in Scheme 23. This process uses catalytic amounts of TEMPO in combination with dichlorohydantoin (DCH) as the stoichiometric oxidant [56]. The flow process is based on a multi-jet oscillating disc (MJOD) reactor to increase mass transfer and render the process more efficient. In addition, the authors demonstrate an interesting extension where substitution of the oxidant DCH with the related diiodohydantoin (DIH) provides a means to convert aldehydes in the presence of ammonia into versatile nitrile products.



Scheme 23: TEMPO-catalysed reactions in a MJOD reactor.

Besides using traditional oxidants (DMSO/TFAA, NaOCl, TEMPO/DCH etc.) that generate a significant amount of chemical waste by-products a variety of flow-based oxidation protocols have been reported utilizing molecular

oxygen in combination with a suitable catalyst to bring about the desired oxidation reaction [57]. Understandably, these oxidation protocols are not only greener but also offer further advantages regarding downstream processing and product isolation. Flow processing thereby offers increased mass transfer and safety at elevated pressure and temperature which is particularly relevant in industrial settings. Amongst the many published reports that describe the effective execution of continuous oxygen-based flow oxidations, methods that use readily available and non-toxic oxidants such as Ru/Al_2O_3 [58] or Cu(I)/TEMPO [59] are noteworthy. Furthermore, catalyst-free variants using oxygen gas as the sole oxidant have been reported in flow mode to bring about the conversion of aldehydes via a Criegee intermediate (**56**) to carboxylic acids [60] as summarized in Scheme 24.

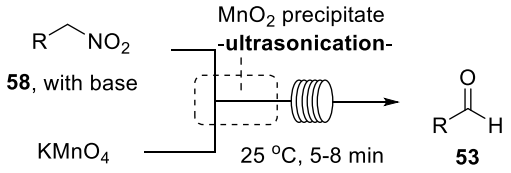


Scheme 24: Aerobic oxidations in flow mode.

In contrast to oxidative functional group transformations of alcohols and carbonyls, analogous variants affecting closely related nitrogen-based systems such as amines and imines are clearly underexplored [61]. This may point to a lack of efficient and chemoselective methods as well as the availability of methods for generating such target compounds by other means including condensation reactions (to give imines or oximes) or reductive processes (to prepare amines from amides or nitriles). However, despite the general scarcity of these transformations a number of cases are reported in the literature that exploit flow processing.

One class of formally oxidative processes that exploit amines towards aldehyde and ketone products can be seen in modern transamination processes that render the target products under mild conditions [48, 62].

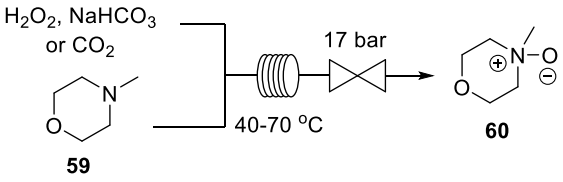
The Nef oxidation of alkyl nitro substrates using $KMnO_4$ as oxidant was reported by Ley and co-workers as an effective means to generate various aldehydes and ketones [63]. This simple approach combined solutions of the substrate with the oxidant in the presence of a base via a T-piece to facilitate this process. To avoid clogging issues through the insoluble MnO_2 that was generated as by-product ultrasonication of the mixing element and reactor coil was found effective. By varying the stoichiometry of the oxidant, it was thereby possible to produce aldehyde (or acid) products from the nitro substrates as shown in Scheme 25.



Scheme 25: Nef oxidation reactions in flow.

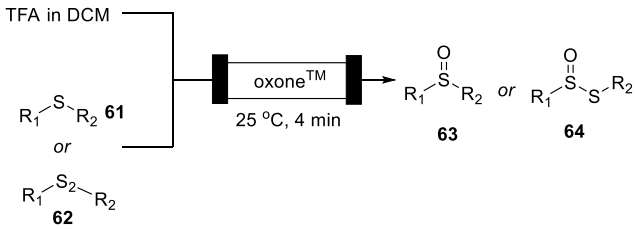
An oxidative route rendering amide and nitrile products has been reported utilizing dihalohydantoins as oxidants to convert alcohols via aldehydes to the target products. In these cases, substituted amines would render amide products [64] whereas ammonia as amine source would give rise to nitrile products [56].

Lastly, the efficient conversion of tertiary amines such as *N*-methyl morpholine into *N*-oxides has been described via a microreactor utilizing H_2O_2 and bicarbonate as reactants [65]. Optimization of this flow process produced the target product in high yield that may find use in Cope elimination reactions (Scheme 26).



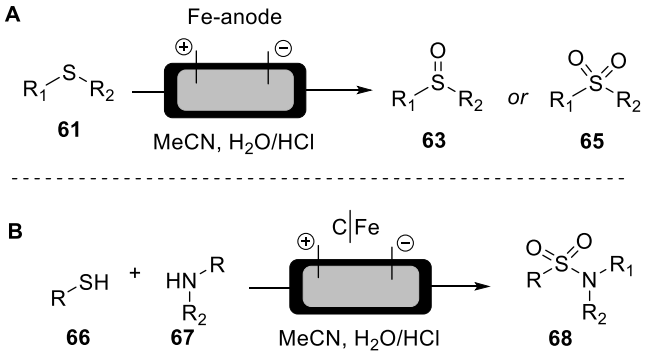
Scheme 26: Oxidation of tertiary amines to *N*-oxides in flow.

Oxidation of sulfur-based functional groups such as thiols and thioethers are also an underreported class of transformations. However, recent years have seen a small number of interesting studies in flow mode such as a recent publication by Wirth and co-workers reporting the use of a packed bed reactor filled with oxone™ (2 $KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) as a suitable reagent to convert a variety of thioethers chemoselectively into the corresponding sulfoxide **63** [66]. The authors furthermore demonstrated that competitive oxidation of related selenoethers is not observed, whilst various disulfides are oxidized into thiosulfinates (**64**, Scheme 27).



Scheme 27: Flow-based oxidation of sulfides and disulfides.

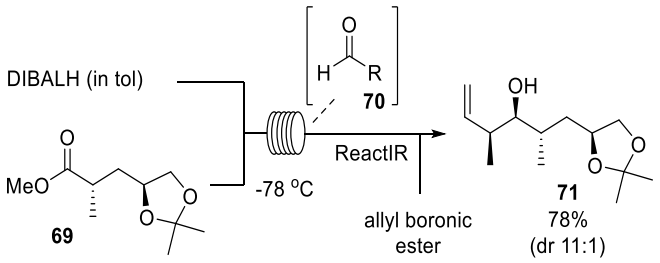
In recent years flow chemistry has enabled significant progress in fields of synthetic chemistry that are traditionally neglected and thus remained niche areas for a long time. Synthetic electrochemistry is amongst those fields that have started to see renewed interest due to several advantages arising from miniaturized flow reactors as highlighted in recent reviews [10, 67]. An interesting application relating to greener methods for functional group interconversions reports the effective transformation of thioethers to sulfoxides (**63**) and sulfones (**65**) respectively [68]. Selectivity is thereby a function of the applied potential. This study also details to oxidative coupling of thiols to disulfides under continuous electrochemical conditions (Scheme 28 A). A related study by the same group highlights a further expansion to generate a variety of sulfonamides (**68**) which are important functionalities in drug discovery programs through flow electrosynthesis (Scheme 28 B) [69].



Scheme 28: Electrosynthesis of sulfoxides and sulfonamides in flow.

In analogy to oxidative transformations, reduction reactions are widely utilized to affect countless functional group interconversion reactions. This next section will highlight a selection of continuous reduction processes applied to the conversion of various functionalities based on oxygen-, nitrogen-, and carbon-based systems.

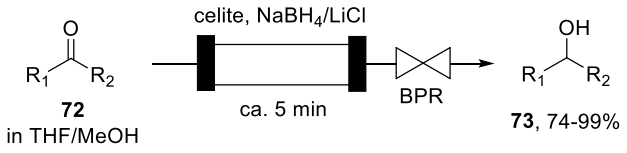
Reductions exploiting soluble hydride-based reagents are amongst the most popular options allowing for easy control of reactivity and stoichiometry. Diisobutylaluminium hydride (DIBALH) is a powerful reducing reagent that is commercially available as solutions in toluene or ethereal solvents. Though careful choice of reaction conditions can provide a means for chemoselective reductions with this reagent, batch-based processes are often not providing for high levels of selectivity. Flow processing however offers better spatiotemporal reaction control and can thus facilitate the selective reduction of esters to aldehydes. This has been demonstrated by the Ley group on the continuous reduction of a chiral ester building block (**69**) to the corresponding aldehyde that was further converted by a telescoped crotylation protocol (Scheme 29) [70].



Scheme 29: DIBALH reduction as part of multistep flow route towards **71**.

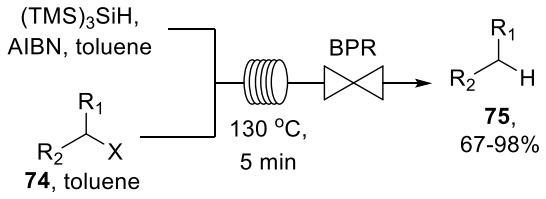
More recently, researchers from Eisai exploited flow-based DIBALH reductions in the scaled synthesis of an advanced aldehyde building block en route to the anti-cancer drug eribulin mesylate [71], and a team based at Gilead highlighted the value of flow processing in the selective monoreduction of a pyridine diester substrate on scale [72]. In addition, DIBALH has been used successfully for the reduction of aryl nitriles to the corresponding aldehyde functionality [73].

In a similar manner, Seeberger and co-workers have reported on the flow-based reduction of various ketones, aldehydes and imines utilizing a mixture of $NaBH_4$, LiCl and celite packed into a flow cartridge reactor [74]. This approach proved effective for the generation of the desired reduction products (**72**) and avoided issues with clogging due to precipitation of inorganic salts in the flow reactor (Scheme 30).



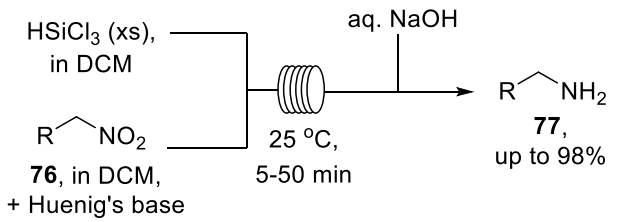
Scheme 30: Use of packed bed reactors for reductions of carbonyls in flow mode.

A further class of useful reduction processes that can benefit from continuous flow processing exploit homogeneous reagents that act as hydride donors. As the following examples will show, flow chemistry can provide for a safer means to handle these oftentimes harmful reagents or intensify the process to achieve faster and more selective reduction reactions. An early example was reported by the Seeberger group demonstrating the use of tris(trimethylsilyl)silane in a number of radical reduction reactions [75]. As shown in Scheme 31, the substrate is mixed with a stream containing AIBN and TTMSS upon entering a heated microreactor (130 °C, 5 min) to facilitate the radical deoxygenation or dehalogenation of a variety of substrates furnishing the desired products in high chemical yields.



Scheme 31: Flow approach for the use of tris(trimethylsilyl)silane (X = halide, xanthate).

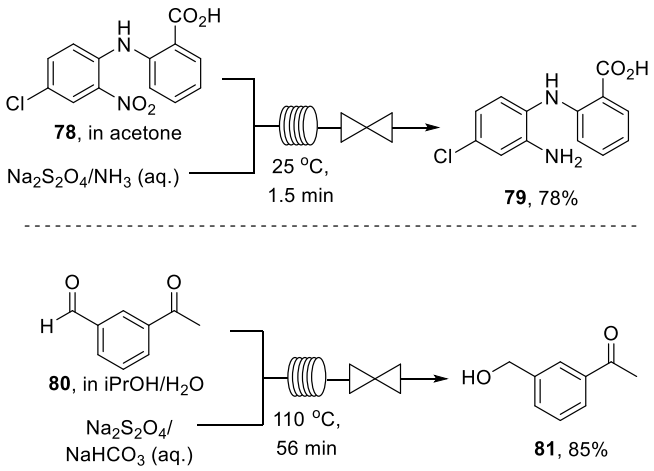
Trichlorosilane is another silicon-based reducing reagent that is difficult to handle due to its propensity to hydrolyze under liberation of corrosive HCl gas. A recent flow approach has thus demonstrated its use toward the metal-free reduction of various aromatic and aliphatic nitro compounds [76] rendering a mild procedure in which labile substituents such as bromides are tolerated (Scheme 32).



Scheme 32: Flow reductions via trichlorosilane.

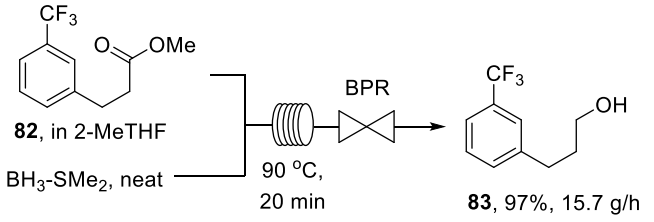
The authors thereby used an excess of Huenig's base in the reaction mixture and quenched the crude product with a stream of aqueous NaOH upon exiting the PTFE reactor.

A flow protocol for the mild and selective reduction of nitro groups to amines [77] as well as carbonyl based substrates to alcohols [78] was recently reported by the Riley group. In these studies, sodium dithionite ($Na_2S_2O_4$) was used as a readily available and non-toxic reducing agent that would enable the preparation of the desired target compounds in good to excellent chemical yields (Scheme 33).



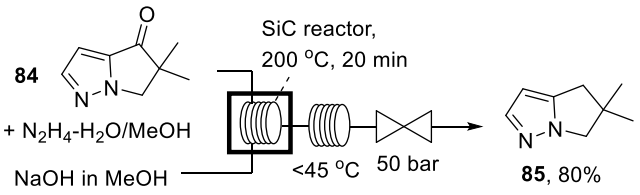
Scheme 33: Reductions of nitro and carbonyl compounds with sodium dithionite in flow mode.

The Kappe group reported recently on a valuable flow protocol to use borane-dimethylsulfide as a neat reagent for the reduction of amides to amines and esters to alcohols [79]. In this protocol the borane reagent is mixed with solution of the substrate dissolved in 2-MeTHF before entering a heated coiled reactor (90 °C, 20 min). This flow approach provides the target products in high yields and throughputs while minimizing contact of the operator to the harmful and malodorous borane reagent (Scheme 34).



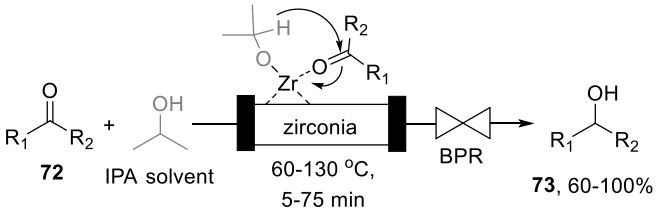
Scheme 34: BH_3-SMe_2 based reductions in flow.

The same laboratory also reported on a collaborative effort highlighting the use of a silicon carbide-based flow reactor to enable Wolff-Kishner reductions of ketones and aldehydes under forcing conditions [80]. The use of hydrazine as the reducing agent in the presence of NaOH at high temperatures (190-200 °C) and pressures (~45 bar) made this reactor material the most suitable option to realize a robust flow process with high chemical throughput (Scheme 35).



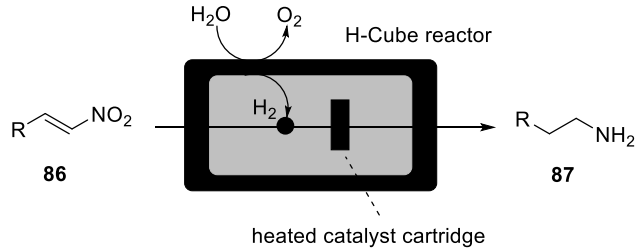
Scheme 35: Wolff-Kishner reduction in silicon carbide flow reactor.

A further class of popular reduction processes involves transfer hydrogenation reactions in which the solvent (e.g. isopropanol) serves as the reducing agent. A report by the Ley group demonstrated this for the Meerwein-Ponndorf-Verley reduction of various ketones and aldehydes exploiting hydrous zirconia as a catalyst [81]. A solution of the carbonyl substrate in isopropanol was thereby pumped through a heated packed-bed reactor filled with hydrous zirconia to render a variety of alcohol products in short times and high yields (Scheme 36).



Scheme 36: Zirconia-mediated Meerwein-Ponndorf-Verley reduction in continuous flow mode.

The use of heterogeneous hydrogenation catalysts is a common feature in flow-based reduction processes using hydrogen gas as reducing agent. Flow processing offers a powerful technology to safely utilize hydrogen gas under forcing conditions (high pressure/temperature). Numerous heterogeneous hydrogenation catalysts are readily available (e.g. Pd/C, Raney-Ni, PtO_2, Ru/C etc.) that can be purchased in pre-packed cartridges for popular flow reactors such as the H-Cube® system [82] that generates hydrogen gas by electrolysis of water *in situ* (Scheme 37).



Scheme 37: Hydrogenations via the H-Cube® reactor.

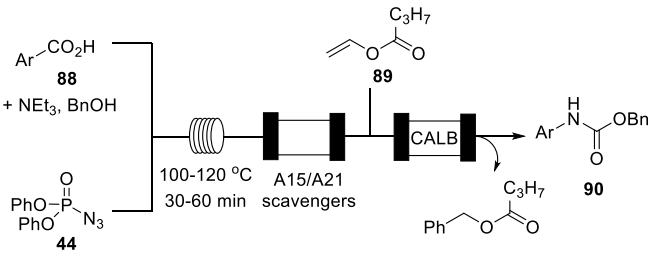
Alternative set-ups exploit external hydrogen gas cylinders such as in the HEL flow reactor [83]. The importance of flow-based hydrogenation reactions manifests in numerous studies reporting on the reduction of nitro groups, alkenes, imines as well as debenzylation reactions. Further examples concern the reductive conversion of feedstock chemicals such as glycerol [84] and the saturation of drug-like

heterocycles in flow mode [85]. Lastly, continuous hydrogenation reactions have also been reported exploiting homogeneous transition metal catalysts that affect the conversion of esters to alcohols under mild conditions [86].

2.4. FGI by Rearrangement Reactions in Flow Mode

The interconversion of oftentimes very different functional groups can be achieved effectively via a variety of rearrangement reactions. As these transformations are frequently based on breaking stable functionalities prior to their reconstitution, these processes typically utilize high-energy species and can be accompanied by the release of energy and gaseous by-products as leaving groups (e.g. N_2 or CO_2) to provide sufficient driving force. For these reasons flow procedures are often considered to be safer alternatives compared to batch processing.

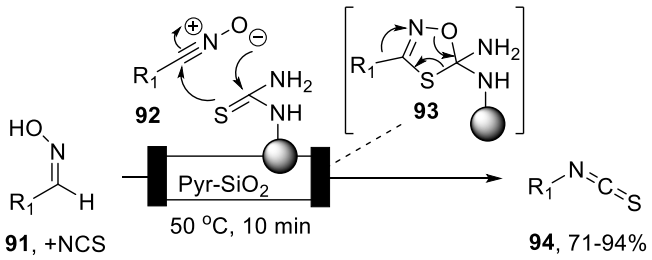
A classic example is the Curtius rearrangement that converts carboxylic acids into amine derivatives (e.g. carbamates, ureas etc.) via acyl azide intermediates. The need to use azide species at high temperatures and the subsequent liberation of nitrogen gas render this powerful reaction difficult to exploit in a safe manner. It is thus not surprising that several flow methods for the Curtius rearrangement have been reported over the last 15 years [87]. The use of diphenylphosphoryl azide (**44**, DPPA) is thereby a common feature to activate carboxylic acids and transform the resulting acyl azide into isocyanate intermediates upon heating. As shown in Scheme 38, in-line purification can be achieved via scavenger resins, and immobilized enzymes (e.g. CALB) have been used to further facilitate downstream purification [88].



Scheme 38: Curtius rearrangement with inline scavenging and tagging in flow mode.

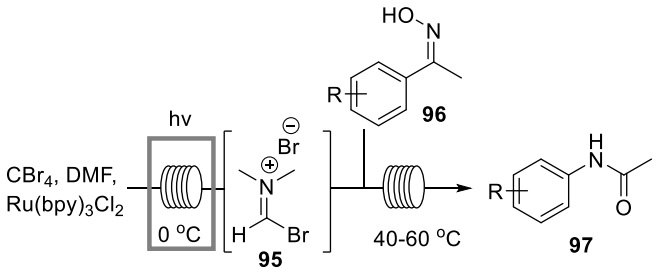
A related process that converts primary amides into isocyanates and subsequent amine derivatives is the Hofmann rearrangement. In this transformation the primary amide is activated by treatment with an oxidant (e.g. NBS or NaOCl) to introduce a leaving group bound to the nitrogen atom. The rearrangement is initiated thermally and proceeds in analogy to the Curtius rearrangement. Recent flow procedures exploit the safety provided through miniaturization to produce the desired target compounds [89].

A lesser-known variant of the Curtius and Hofmann rearrangements produces isothiocyanates from chlorooxime substrates and thiocarbonyl-based reagents. The popular use of isothiocyanates in preparing thioureas makes this a useful transformation. A recent flow application [90] demonstrates a small-scale process in which chlorooximes were generated *in situ* and passed through a cartridge containing an immobilized thiourea species as the sulfur source and an immobilized base (Pyr-SiO_2). As shown in Scheme 39 this leads to the generation of a nitrile oxide intermediate (**92**) that undergoes a dipolar cycloaddition-cycloreversion sequence. The use of the immobilized reagents assures that all spent reagents and by-products are retained in the flow cartridge facilitating the purification process.



Scheme 39: Generation of isothiocyanates through cycloaddition cascades.

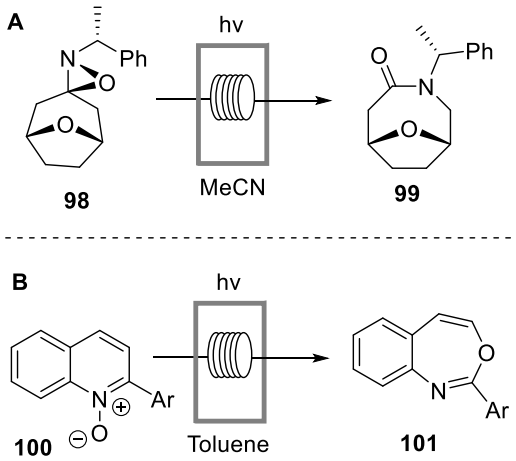
The Beckman rearrangement is a further example of a useful transformation that converts ketones via oximes into ubiquitous amide products. A recent flow protocol by Chen and co-workers [91] demonstrated a photochemical variant in which DMF is firstly converted into the Vilsmeier-Haack reagent (**95**) utilizing CBr_4 and $Ru(bpy)_3Cl_2$ as a photocatalyst. Subsequent activation of preformed oxime substrates and thermal rearrangement renders the amide targets (**97**) in good yields (Scheme 40).



Scheme 40: Light-driven Beckman rearrangement.

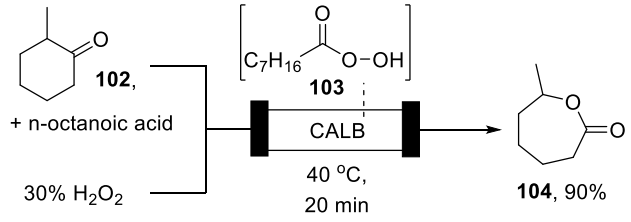
A related photochemical flow protocol was reported by Cochran and Waal [92] who demonstrated the generation of strained oxaziridines (**98**) and their light-driven conversion to a set of drug-like lactones (**99**) (Scheme 41-A).

Smith and co-workers also exploited a photochemical process that initially couples *in situ* generated aromatic *N*-oxides with aryl diazonium salts prior to a rearrangement delivering a series of benzo[1,3]oxazepines via a ring expansion process (Scheme 41-B) [93].



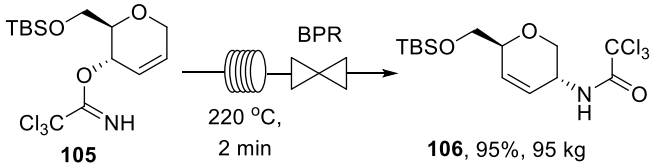
Scheme 41: Photochemical ring expansion reactions.

A related process to the Beckman rearrangement is the Baeyer-Villiger oxidation of ketones to esters. This transformation exploits the use of peracids that trigger a rearrangement step. As the generation and use of peracids is not deemed safe when scaled to larger quantities, a recent flow protocol demonstrates the *in situ* formation of peracids from H_2O_2 exploiting CALB as an immobilized biocatalyst [94]. The resulting continuous process provided the target structures under mild and safe conditions as shown in Scheme 42.



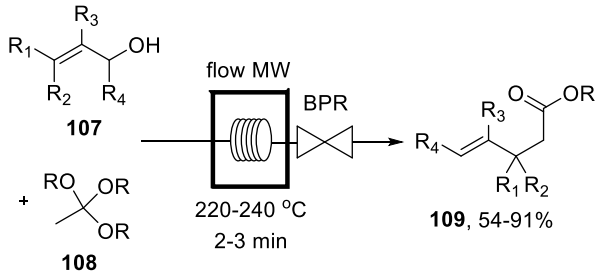
Scheme 42: CALB-assisted Baeyer-Villiger oxidation.

Sigmatropic rearrangements comprise a further and very diverse class of valuable rearrangement reactions that bring about the interconversion of various functional groups. An example where flow processing allows for more consistent yields as a result of shorter residence times and therefore minimized degradation was recently reported for an Overman rearrangement [95]. This [3,3]-sigmatropic rearrangement converted a chrial heterocyclic acetimidate substrate (**105**) into the corresponding allylic trichloroacetamide product **106**. The use of a BPR allowed superheating of the toluene solvent to 220 °C which shortened the residence time to only 2 minutes thus facilitating the scale-up of the flow process (95 kg in 84 h) as shown in Scheme 43.



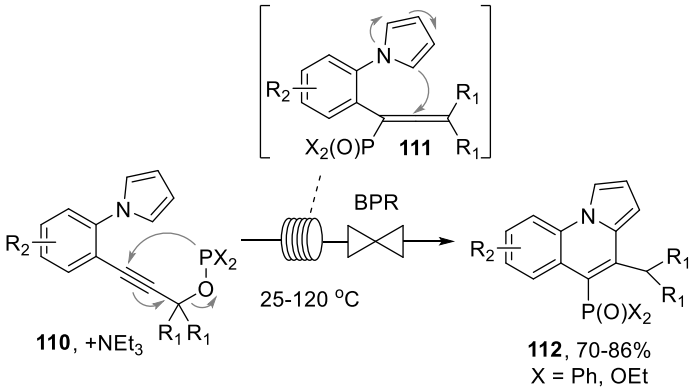
Scheme 43: Scaled Overman rearrangement in flow mode.

A number of more common Claisen [96] and Johnson-Claisen [97] rearrangements have been reported in flow mode. Application of high temperatures again translates into short residence times providing simple and scalable access into a series of cyclic and aliphatic rearrangement products possessing new alkene, ketone and ester functionalities (Scheme 44).



Scheme 44: Johnson Claisen rearrangements in flow microwave reactors.

[2,3]-Sigmatropic rearrangements also facilitate the transformation of heteroatom-based substrates. A recent flow application demonstrated this on a series of propargylic phosphonates **110** being converted via a Wittig rearrangement into phosphate and phosphine oxide products upon heating [98]. The resulting allene species (**111**) were intercepted by an adjacent pyrrole ring rendering a series of pyrrolo[1,2-a]quinolines (**112**) in high yields (Scheme 45).



Scheme 45: Flow-based Wittig rearrangement reactions.

A related study exploited a photochemical Doyle-Kirmse rearrangement between allylic thioethers and diazo species [99]. This simple process enabled the formal insertion of a phenylacetate moiety into the S-C bond of the allylic thioether moiety through a [2,3]-sigmatropic rearrangement step.

As can be seen from the above examples flow processing is oftentimes found superior to batch mode procedures when effective heating or application of photochemical reaction conditions are needed. These features that are derived from the small dimensions of flow devices therefore facilitate these rearrangement reactions and thus the interconversion of many functional groups. Similar studies have reported on the beneficial use of continuous processing in related rearrangements including a photo-Favorskii rearrangement to

generate the drug ibuprofen [100], the Michaelis-Arbuzov rearrangement to generate phosphonates from phosphites [101], the photochemical di-π-methane rearrangement [102], the Pummerer rearrangement [103], the Newman-Kwart rearrangement [104], the Smiles rearrangement [105] or the Kornblum-DeLaMare rearrangement [106].

CONCLUSION

In surveying the chemical literature for recent applications of flow chemistry in important functional group interconversion processes this review has clearly confirmed the value of this technology in expanding the chemist's toolbox. Though only selected classes of transformations were discussed, it is without doubt that flow processing provides key advantages regarding reaction control, safety, scalability, process windows and efficiency. Continuous flow approaches have been developed in many cases for classical reactions that were cumbersome to use in batch mode. Consequently, numerous creative and highly effective procedures exploiting flow processing are now available and, in many cases, offer a safer and more step economic route into versatile building blocks. This observation resonates with industrial campaigns where flow processing has often allowed turning a promising small-scale method into a robust flow process. Amongst the transformations surveyed, flow approaches are particularly attractive when high reaction control is vital and only miniaturized flow set-ups provide the necessary heat and mass transfer. In the case of rearrangement reactions that are usually unimolecular processes, flow processing allows to rapidly reach high temperatures to trigger the desired transformation in a short period of time before degradation can become a problem. Furthermore, the use and release of gases as reagents or by-products can be accommodated via flow processing with ease by using back-pressure regulators. Consequently, many reactions liberating nitrogen gas such as diazotization reactions or Curtius rearrangements benefit from flow processing. The use of oxygen or hydrogen gas in redox processes is a further example where flow processing is safer and more efficient. Although many oxidation and reduction processes have been reported using standard stoichiometric reagents, the use of cheap and readily available gaseous reagents (e.g. oxygen, hydrogen) in combination with suitable catalysts is far more sustainable and therefore highly relevant in industrial applications of flow chemistry. The trend to explore and exploit modern biocatalyzed transformations furthermore shows a desire to realize greener functional group interconversions as seen in valuable transamination or lipase-mediated reactions. In addition, many modern applications show the potential to develop light-driven reactions in flow reactors to effectively bring about a desirable reaction in the absence of high temperatures. Continuous photochemical processes thereby highlight how both classical and modern photocatalysis can contribute to clean and efficient transformations. The same developments are now visible for continuous electrochemical processes where smart reactor dimensioning allows for excellent reaction control with many potential target transformations. Based on these findings it can be concluded that functional group interconversions not only benefit from continuous flow processing, but moreover will remain highly relevant whenever green procedures can be realized through modern flow technology.

CONFLICT OF INTEREST

The authors declare that no conflict of interest exists regarding this publication.

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