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Latest Highlights in Liquid-Phase Reactions for Organic Synthesis in Microreactors

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ABSTRACT: The attention for microreactors for organic synthesis reactions, in both academia and industry, has considerably increased over the past few years, as indicated by the progressively growing number of publications. A review of articles on liquid-phase organic syntheses in microreactors in 2011−2012 is presented in this contribution. The main topics discussed in this review are noncatalytic and homogeneously catalyzed reactions, multistep syntheses, heterogeneously catalyzed reactions, microwave-assisted reactions, and photocatalytic reactions. A number of important publications from the period 2008−2010 are also mentioned to complete the overview. The goal of the present review is to illustrate the important topics of the publications during the past few years on organic synthesis in microreactors.

INTRODUCTION

The attention for microreactors for organic synthesis, in both academia and industry, has significantly increased over the past decade, as indicated by the progressively growing number of publications. Besides a significant number of articles, a few books have already been published on microreaction technology in general[1−3] and in particular for its application in organic synthesis.[4,5] The recently published book of C. Wiles and P. Watts[4] published in 2011 thoroughly describes the fundamentals of microreaction technology, including design of microflow devices, applications of microreactors in synthesis of various types of organic molecules in gas- and liquid-phase, as well as industrial applications of microreactor technology.

Microreactor technology is currently one of the most innovative and rapidly developing fields in chemical engineering; synthesis; and chemical, pharmaceutical, analytical and biochemical process technology.[6] The key advantage of the microreactors in organic synthesis is the possibility to achieve a high degree of control of the reaction parameters such as temperature, pressure, residence time, etc.[7,8]

Most chemical reactions involve combining two or more reagents, and for this reason *fast mixing* to achieve homogeneity in the solution is very important and can be more effectively obtained in a microreactor in comparison to a macroreactor.[9] Microreactors enable reproducible mixing of reactants and thus precise control of stoichiometry.[10] Due to the high surface-to-volume ratio of microreactors, *heat transfer* occurs rapidly, enabling fast cooling or heating and thus precise temperature control.[9,11] Hence, highly exothermic reactions can be conducted in a controlled way by taking advantage of efficient heat transfer in a microreactor,[12] sometimes even eliminating the need for external cooling and thus decreasing the overall process energy demands.[13] Precise *residence time control* can be achieved easily by varying the length of the microchannels or the flow rates that are very important for control of the reactions involving unstable, short-lived reactive intermediates.[9,14] Moreover, during the *multistep syntheses* in flow reactors, reagents can be added continuously with a higher degree of control. The continuous processing allows efficient reaction optimization: small aliquots of product can be collected as they are produced and analyzed in order to decide how to change reaction conditions and parameters without interruption of the process.[15] Due to the improved reaction profiles, microreactors are very suitable for accurate *kinetic studies*.[16] The relatively small reaction volume means *greater safety* through smaller amounts of reagents, particularly for highly hazardous compounds.[10] One more important benefit of microreactor technology is its distinctive *scalability* via scale-out or numbering-up concepts.[12,17,18] It is also noteworthy that the continuous microreactor technology is perfect for reaction screening, since it allows testing of reaction parameters in a fast and efficient way.[19] From an environmental point of view, flow microreactors are considered as a sustainable alternative in chemical research and industry as the levels of hazardous waste are reduced.[20]

A review of articles on liquid-phase reactions for organic synthesis in microreactors during 2011−2012 is given in this contribution. The review consists of the following five main sections: noncatalytic and homogeneously catalyzed reactions, multistep syntheses, heterogeneously catalyzed reactions, microwave-assisted reactions, and photocatalytic reactions. A number of important publications from the period 2008−2010 are also discussed to complete the overview. The review is focused on the liquid-phase organic syntheses, and thus, bioprocesses and gas- and gas−liquid-phase reactions are not included in this review. The aim of the present article is to provide an overview of the main topics of the publications during the past few years on organic synthesis in microreactors.

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1. NONCATALYTIC AND HOMOGENEOUSLY CATALYZED LIQUID-PHASE REACTIONS IN MICROREACTORS

1.1. Rearrangement Reactions. The Claisen rearrangement is a fundamental organic reaction for the production of a large variety of important intermediates and fine chemical products.[21,22] This rearrangement (Figure 1) is a powerful

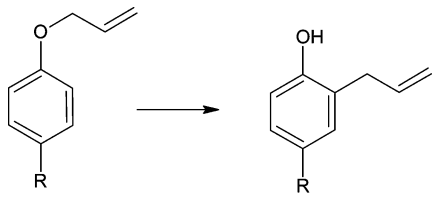

Figure 1. Claisen rearrangement of allyl para-substituted phenyl ethers. Adapted from ref 23.

reaction for carbon−carbon bond formation. The Claisen rearrangement of allyl *p*-substituted phenyl ethers usually requires high temperatures (e.g., 200 °C) and long reaction times under conventional conditions. Long exposure times of the reaction mixtures at high temperatures with poor temperature control is problematic and may cause the formation of many undesired compounds and therefore low yields of the desired products. The efficient microreactor syntheses of several allyl phenols with high purities without any solvent and workup were done via Claisen rearrangement of allyl para-substituted phenyl ethers.[23] After optimization of the temperature and residence time, the highest yield of 2-allyl-4-chlorophenol (82%) was achieved at 220 °C in 24 min, while the conventional Claisen rearrangement reaction gave only 14% yield. High reaction efficiency is suggested to benefit mainly from the improved heat exchange in the microreactor. Additionally a number of other para-substituted substrates were studied in optimized conditions; the products were obtained in high yields (69−97%).

A highly efficient noncatalytic Claisen rearrangement using a microreaction system in subcritical water (sub-H_2O) was reported by Sato et al.[21] It was assumed that sub-H_2O itself could work as a Lewis acid (catalyst for Claisen rearrangement) but also that the dielectric constant could be controlled in the sub-H_2O region by the adjustment of the reaction pressure and temperature. The sub-H_2O microreaction system can provide a continuous operation with instantaneous heating. Thus, highly selective aromatic and aliphatic Claisen rearrangement was performed in the absence of catalyst using a sub-H_2O microreaction system. The products were obtained with an excellent selectivity (>90%) at a temperature of 265 °C, pressure of 50 bar, and a residence time of 149−284 s. It was mentioned that the approach induced by a sub-H_2O microreaction system is environmentally benign, and therefore can attract particular attention for 'green' organic synthesis.

The Claisen rearrangement reaction was performed under high-pressure and high-temperature water (HPHT-H_2O) conditions in a microreactor by the same authors.[22] The optimal reaction conditions were found for Claisen rearrangement of allyl aryl ether. The residence time was optimized by varying the flow rates of the substrate and HPHT-H_2O. At a residence time of 149 s (HPHT-H_2O flow rate of 6.96 g·min^{-1} and substrate flow rate of 0.25 g·min^{-1}), the yield of the desired product *o*-allylphenol of 96% was achieved. The Claisen rearrangement of *o*-methyl and *p*-methyl allyl aryl ether was carried out at lower temperature (210 °C) and shorter residence time (13.4 s). Compared to the conventional batchwise method, HPHT-H_2O microreaction results in similar yield and selectivity of the desired products within a shorter reaction time and at a lower temperature.

Another example of a Claisen rearrangement was reported by Wang and co-workers.[24] The thermal Claisen rearrangement of *O*-allyl-substituted isotetronic acids in xylene was successfully performed in microreactors at 150 °C. Different fused silica microcapillaries (I.D. 250, 320, and 530 μm) were used. The efficiency of the microreactor was tested at different temperatures (110−150 °C) and residence times (10−50 min). The yield was improved significantly with the increase of the temperature: ∼10, 30, and 80% at 110, 130, and 150 °C, respectively, at 30 min residence time. The optimal conditions were found to be as follows: a temperature of 150 °C and a residence time of 40 min, resulting in a maximum yield of 89%. The analogous rearrangement reaction performed in a sealed tube resulted in only 86% yield of the desired product at 170 °C and 22 h reaction time. The experiments with the number of substituted substrates confirmed the superior performance of the microreactor (Figure 2, Table 1). Whereas yields from the

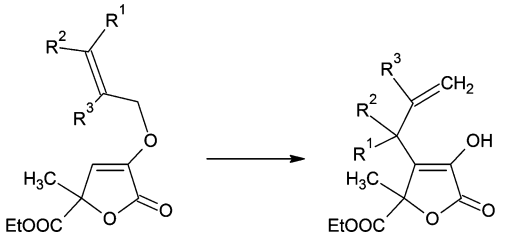

Figure 2. Synthesis of β-allyl-substituted isotetronic acids via Claisen rearrangement in a microreactor and sealed tube. Adapted from ref 24.

Table 1. Results of synthesis of β-allyl substituted isotetronic acids in microreactor and sealed tube; adapted from ref 24.

			microfluidic system			sealed tube		
R1	R2	R3	time, min	*T*, °C	yield, %	time, h	*T*, °C	yield, %
H	H	H	40	150	89	22	170	86
H	H	CH_3	40	150	87	24	170	85
H	CH_3	H	40	150	85	25	170	82
H	Ph	H	40	150	75	25	180	70

microreactor were not significantly better than those obtained from a sealed tube, the reaction time and thus energy requirements were substantially less. Furthermore, a microreactor system will be far more amenable to scale-up than a sealed tube.

The sulfuric acid-catalyzed Beckmann rearrangement of cyclohexanone oxime (dissolved in cyclooctane) to ε-caprolactam (Figure 3) was performed in a microreactor by Schouten et al.[11] The microreactor consists of a low-temperature mixing zone (65 °C) followed by a high-temperature reaction zone (100−127 °C). Under these temperature conditions and residence time of 10 s a selectivity of 99% was achieved. In the case where both stages (mixing and reaction) were performed at a single temperature and under all other process conditions, a similar complete conversion of

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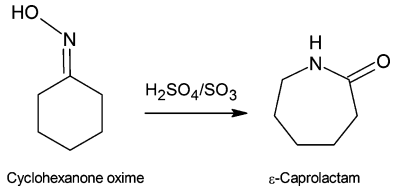

Figure 3. Beckmann rearrangement of cyclohexanone oxime to ε-caprolactam. Adapted from ref 11.

cyclohexanone oxime could also be reached, but the selectivity to ε-caprolactam was limited to a value of just 95%. Thus, suppressing the reaction during mixing (by using lower temperature in the mixing zone) was found to be a key tool to increase the selectivity to ε-caprolactam.

A multistep microreactor synthesis of the aminonaphthalene derivate as a key intermediate in the synthesis of the duocarmycin-based prodrug for a selective treatment of cancer is described by Tietze et al.[25] The conditions for the synthesis in the batch mode were adjusted for application in a microreactor, and the results of both methods were compared. The final step in the synthesis of aminonaphthalene was a Curtius rearrangement of the corresponding carboxylic acid with the Shioiri–Yamada reagent in the presence of *tert*-butanol. According to the proposed mechanism the intermediate azide obtained from carboxylic acid would lead to the isocyanate which further reacts with *tert*-butanol to give the final product (Figure 4). It was expected that the gas (N_2)

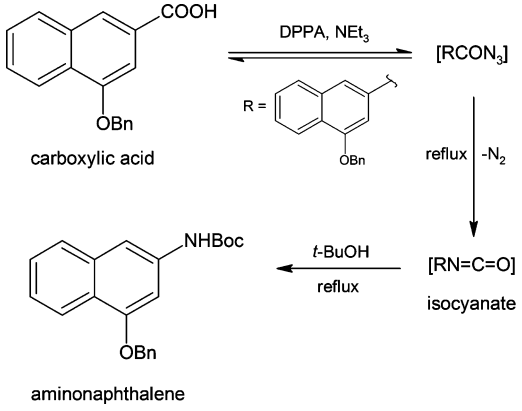

Figure 4. Curtius rearrangement for the synthesis of aminonaphthalene. Adapted from ref 25.

formation would have a negative effect on the steady state in the microreactor. Thus, the isocyanate was synthesized in the batch mode. After the gas evolution had finished, the resulting solution was introduced into the microreactor together with *tert*-butanol. Under these conditions the obtained yield of 52% of aminonaphthalene was much lower than those in the batch mode (83%) which is presumed to be a result of the instability of the isocyanate. However, it was noted that the formation of a suspension was observed in the batch mode while a homogeneous solution was collected at the outlet of the microreactor, and this can be explained by the finer size of the particles.

1.2. Condensation Reactions. The Paal–Knorr cyclocondensation of 1,4-diketones with amines (Figure 5) and other nitrogen derivatives is a well-established and valuable procedure for the preparation of heterocycles. This process is industrially relevant, since it directly yields relatively complex

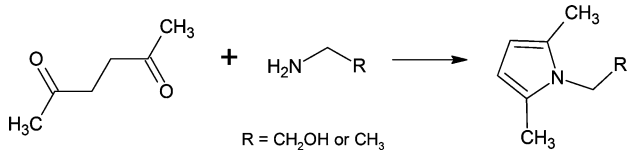

Figure 5. Paal–Knorr cyclocondensation of 1,4-diketones with amines. Adapted from ref 19.

pyrroles from amines and diketones. A challenge of this reaction is the exothermic behavior, especially when performed at high concentrations. Due to the improved control of the reaction conditions in a microreactor, the synthesis of the pyrrole (>90%) in high yields using microflow chemistry was successfully performed.[19]

Full parametric optimization was performed, aiming at optimal conditions for the continuous-flow equipment and focusing on maximal reduction of the reaction time while maintaining 100% conversion. Experimentally as well as by mathematical modeling, the optimal settings were found at a reaction time of 100 s, a temperature of 20 °C, and an amine/diketone ratios of 5 and 10 for ethanolamine and ethylamine substrates, respectively. In both cases, the reaction model showed a broad and therefore robust area at which high yields were obtained. Further, the reaction was scaled up and validated at a microreactor system consisting of four microstructured flow reactors which were placed in parallel and integrated into a single multilayered reactor module with a total internal volume of 9.6 mL. A full-scale reaction run was performed with ethanolamine as the amine substrate. With a total feed of 5.4 mL·min^{-1} and a run time of 60 min, 100% conversion was achieved, giving a total isolated yield of 55.8 g of pyrrole.[19]

An automated microreactor system combined with continuous online IR analysis was developed to maximize the production rate of a Paal–Knorr reaction of 2,5-hexanedione and ethanolamine.[26] The use of continuous, online analysis allowed several measurements of reactor effluent concentrations within a short time, ensuring that each experiment had reached steady state. As a result of the optimization of the reaction conditions, a conversion of 76.4% was achieved at an optimum temperature of 212 °C and a 6 min residence time.

Direct oxidative amidation of aromatic aldehydes with amines in a microreactor flow system using aqueous hydrogen peroxide (30 wt %) as a cheap and clean oxidant without the use of other reagents has been reported.[27] The presented method incorporates aldehydes and amines in one single operation under mild conditions, while avoiding any bases or catalytic materials, thus providing an economical and clean route for amide synthesis. The yields for these reactions were found to be closely comparable with those reported for the reaction in batch; however, the reaction in microreactor was much faster than the one in batch (reaction time 15–40 min and 1–6 h, respectively). The reaction temperature used in the flow process (70–110 °C) was slightly higher than the one in batch (70–75 °C). Moreover, a higher excess of amines (4–10 equiv) was used in flow than that in batch (1.3 equiv). However, the excess amines can be readily separated from the reaction. The use of a continuous-flow microreactor as an investigation tool enables the precise control and rapid scanning of reaction parameters and hence efficient optimization of the reaction conditions.

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A safe, green, and functional-group-tolerant flow reaction of the direct amide bond formation mediated by Grignard reagents (the Bodroux reaction) has been described.[20] The procedure was applied to a wide variety of primary and secondary amines and anilines, as well as to aromatic and aliphatic esters. The flow approach leads to improved yields and selectivities in the reaction, which has a sustainable purification procedure and simple scale-up. This reaction represents an efficient and green alternative to the use of alkylaluminium and metal-catalyzed procedures.

The reaction conditions were optimized for the reaction of 2,4-difluoroaniline with ethyl benzoate (Figure 6). A higher

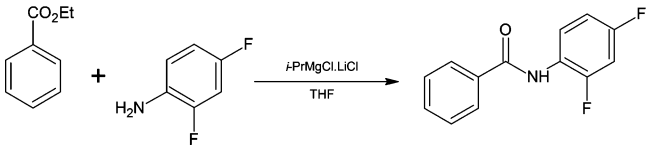

Figure 6. Reaction of ethyl benzoate with 2,4-difluoroaniline. Adapted from ref 20.

yield was obtained in the flow procedure in comparison to the batch one, despite the lower excess of amine and the much shorter reaction time. Yields were further improved by the optimization of the reaction temperature, time, and number of equivalents of aniline and alkylmagnesium chloride. With the use of the optimized flow procedure, up to 1.2 $g \cdot h^{-1}$ of amide was produced. Further, an alkyl and an aryl ester were selected in conjunction with alkyl, aryl and primary and secondary amines. All compounds were isolated in good to excellent yields (up to 93%). Then the reaction was also performed with a wider range of amines and esters including heterocyclic systems and other functional groups. High yields of the products (up to 95%) and high chemoselectivity of the reaction were observed.[20]

The formation of biaryl substructures is a key step in the synthesis of many biologically active compounds. Decarboxylative cross-couplings were found to be an advantageous alternative to metal-catalyzed cross-couplings and C−H-activation reactions. The flow technology is attractive for decarboxylative cross-couplings, as they require high temperatures that are difficult to control in larger batch reactors. The reaction between 2-nitrobenzoic acid and 4-tolyl triflate, with addition of KOtBu and Cu- and Pd-catalysts was chosen as a model reaction to be tested in flow mode.[28] The initial solution was passed through a stainless steel coil on a heated Vapourtec R2+/R4 reactor. The influence of the temperature, Pd-catalyst type, residence time, and ligand on the yield of the desired product was investigated. Under optimized conditions (5 mol % $CuNO_3(phen)(PPh_3)_2$, 2 mol % $Pd(OAc)_2$, KOtBu, 170 °C, 1 h) 75% conversion based on the aryl triflate was achieved. In contrast to a batch reaction, the desired biaryl was formed with almost 100% selectivity in flow, and side products were observed only in trace amounts. After optimization, coupling of various carboxylic acids and aryl triflates was studied. Thiazole, 2-nitrosubstituted benzoic acids, 2-benzofuran, and 2-thiophene substrates were coupled in good yields (up to 82%). In comparison to yields of batch reactions, comparable yields were obtained in a shorter reaction time in flow mode.[28]

The pyrazole substructure is known to be a component in many pharmaceutically active ingredients (APIs). One of the most attractive synthetic methods to obtain pyrazole is the Knorr cyclocondensation of hydrazines with 1,3-dicarbonyl compounds. The synthesis can be easily performed; however, the presence of diazonium and hydrazine causes potential safety limitations for a scale-up procedure (Figure 7a). As a result, the development of a continuous-flow process to address the safety concerns in scale-up was reported.[29] In the design of a continuous-flow process for the synthesis of the desired product, the hazardous intermediates were avoided (Figure 7b). Methyl ether-protected aniline used as the starting material was combined with $BF_3 \cdot THF$ in THF as one feed stream, while *tert*-butyl nitrite in THF was introduced as a separate stream. The diazonium fluoroborate salt (light and fluffy solid) was well suspended in THF. The resulting mixture was directly added to a receiving flask containing $SnCl_2$ and ketoenamine in ethanol. After an extractive workup, the pyrazole was isolated by chromatography, and after methyl ether deprotection using $PhBCl_2$, the desired product was isolated in 35−40% overall yield. In a second step, a continuous extraction was included in the process to allow the separation of the water-soluble

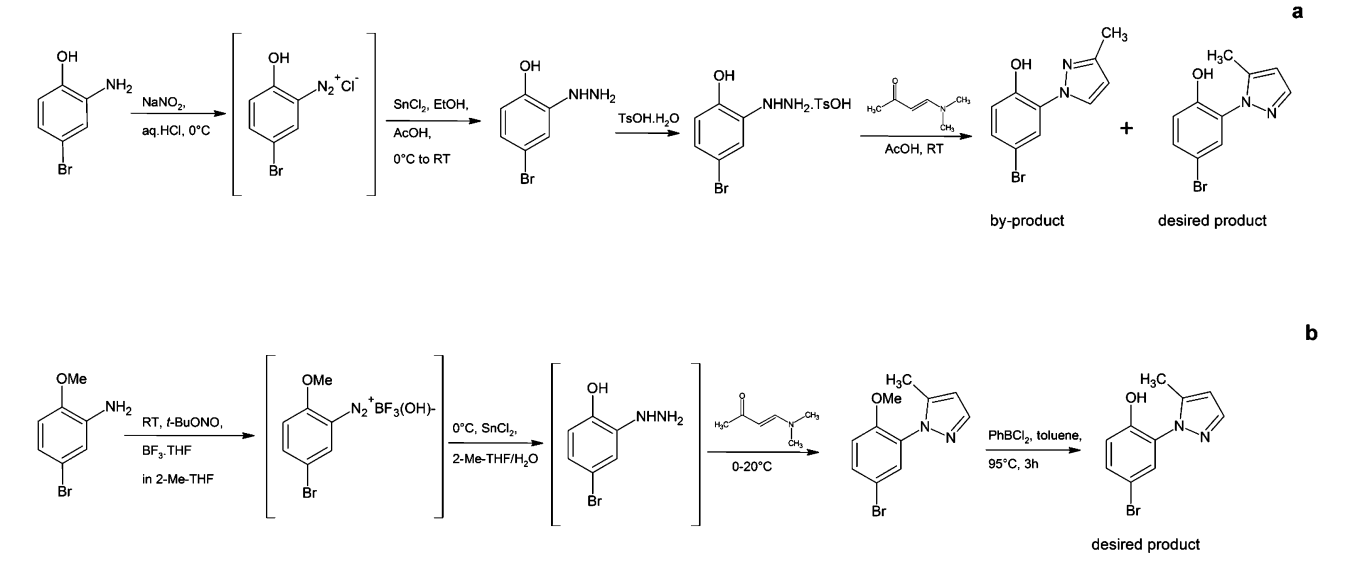

Figure 7. (a) Original synthesis of *N*-aryl pyrazole; (b) new synthesis of *N*-aryl pyrazole. Adapted from ref 29.

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diazonium salt from the organic-soluble impurities. The organic layer was continuously removed as a waste stream, while the aqueous phase was directed into a reaction vessel containing $SnCl_2$. The overall yield of the desired product was increased to 51−55%. Thus, the robustness of the process on any scale smaller than 1 kg of methyl ether-protected aniline was demonstrated. Further investigation of the scale-up processing as well as improvement of the product isolation is currently in progress.[29]

Formation of the highly reactive unstable Pd-tri*tert*-butylphosphine catalyst precursor by using a flow microreactor with subsequent use in a catalytic Suzuki-Miyaura coupling reaction was reported by the group of Yoshida.[30] A catalyst was prepared using a flow microreactor system at room temperature according to the following procedure: solutions of $[Pd(OAc)_2]$ and tBu_3P in THF were mixed in a T-shaped micromixer and then passed through a microtube reactor (I.D. 500 μm, residence time 0.65 s). After a steady state was reached, the resulting solution was transferred into a vessel filled with *p*-bromotoluene, phenylboronic acid, and potassium hydroxide in THF/H_2O for 10 s. Then the mixture was stirred at 24 °C. Three conventional synthetic methods were also studied to compare. The reaction was found to be complete within 5 min in the case of the flash method, while in all conventional methods much longer time was required. Using the optimized conditions for the catalyst formation, the Suzuki−Miyaura coupling reactions of several aryl halides with arylboronic acids was performed. The reactions were exceptionally fast even at room temperature (RT), and the corresponding coupling products were obtained within 5 min in almost 100% yield.[30]

Another example of Suzuki−Miyaura coupling reactions of heteroaryl halides and (hetero)arylboronic acids in continuous-flow conditions was reported.[31] The reaction conditions (solvent, Pd-catalyst loading, type of base) were first optimized in the batch reactor and then transferred to a 400 μL packed-bed flow reactor (stainless steel spheres, 60−125 μm packing). A wide range of heterobiaryl components was obtained in good to excellent yields (82−99%) by employing low catalyst loadings (0.05−1.5 mol % Pd). It was reported that the efficiency of a biphasic reaction in a batch reactor is highly dependent on the effectiveness of the mixing process. To scale up such a process in batch, these reaction conditions require advanced mixing devices. However, with the proposed microfluidic system, it is possible to scale up the reaction just by extending the operating time of the flow reactor. Noteworthy is the use of a packed-bed layer in the flow reactor, which improves the contact between the immiscible phases.

A one-pot procedure for the synthesis of dihydrobenzosiloles from styrenes via the Ni-catalyzed β-hydrosilylation, followed by the Ir-catalyzed dehydrogenative cyclization in a microreactor was recently described.[32] First, the screening of the various Ni-catalysts for hydrosilylation was carried out . It was observed that $NiCl_2{\cdot}(PPh_3)_2$ and $NiBr_2{\cdot}(PPh_3)_2$ gave the desired product in good yield and high regioselectivity. Further, it was found that the second step—intramolecular dehydrogenative cyclization—can be performed in a one-pot manner after completion of the hydrosilylation step to produce dihydrobenzosilole in 86% overall yield. Then, other styrenes (possessing MeO, Me, F, Cl, and CO_2Me groups in ortho, meta, and para positions) were tested. All the reactions resulted in the corresponding dihydrobenzosiloles with good yields (49−86%). Hydrosilylation of α-substituted styrenes was found not to be successful in the presence of a Ni-catalyst; however, the desired hydrosilylated products were synthesized in high yields by employing a Lewis acid catalyst, $B(C_6F_5)_3$. After the following dehydrocyclization step, 3-methylbenzosilole and 3-phenyldehydrobenzosilole were obtained in 79 and 76% yields, respectively. Finally, the mechanism for the dehydrocyclization was proposed.[32]

A novel copper-catalyzed oxidative coupling of 2-carbonyl-substituted phenols and β-ketoesters with ethers was reported by Kumar et al.[33] (Figure 8). Optimal conditions were found

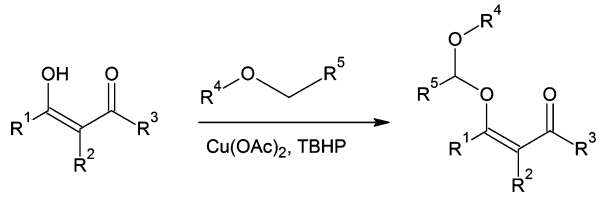

Figure 8. Copper-catalyzed oxidative cross-dehydrogenative-coupling of β-ketoesters or carbonyl-substituted phenols with ethers. Adapted from ref 33.

for the batch process to be as follows: 1 mol % of $Cu(OAc)_2$ catalyst, residence time of 20−30 min, and a temperature of 100 °C. Under these conditions 81% isolated yield of the desired acetal was achieved. Transformations with related compounds (such as cyclic ethers, unsymmetrical ethers, β-keto-esters) were performed with further minor adjustments of the reaction parameters. To make these potentially hazardous syntheses scalable, the authors translated the reaction conditions to a continuous-flow mode using a Uniqsis FlowSyn reactor equipped with a 20 mL internal volume stainless steel coil (I.D. 1.0 mm). A first solution, containing Cu-catalyst and 2-hydroxyacetophenone substrate in 1,4-dioxane, and the second mixture of TBHP in decane were passed through a glass static mixer and were subsequently heated in the coil reactor. Within the 20 min residence time results similar to those obtained in a batch reactor were achieved.

The synthesis of bioactive compounds via efficient reactions of two monophosphate components—GlcNAc monophosphate (**1**) and uridine monophosphate phosphoromorpholidate (**2a**) or phosphoro-*p*-anisidate (**2b**)—in a split-and-recombination (SAR) microreactor has been demonstrated.[34] SAR mechanism of micromixers or microreactors exponentially enlarges the material interface between fluids, and thus they can be effectively used for biochemical, polymer, or viscous fluids mixing. An SAR-microreactor fabricated from poly(dimethylsiloxane) in a three-dimensional (3D) configuration was used for biochemical synthesis. The reactor possesses 125 periodic units (width of each unit was 50−300 μm, height was 50−100 μm, and length was 600 μm) with a total volume of 1.5 μL. The 85% conversion and 68% yield of saccharide-nucleoside diphosphate was achieved in 10 s residence time using an SAR-microreactor in the reaction between **1** and **2a**, while the coupling reaction in a conventional batch reactor resulted in only 80% conversion in 2 days. The effect of residence time on the efficiency of diphosphate formation was studied by modification of the flow rate. The conversion remained almost unchanged, but the yield of diphosphate was slightly improved (from 68 to 74%) with the increase of residence time from 10 to 30 s. In the case of the coupling reaction of **1** and **2b**, the yield of the desired product increased

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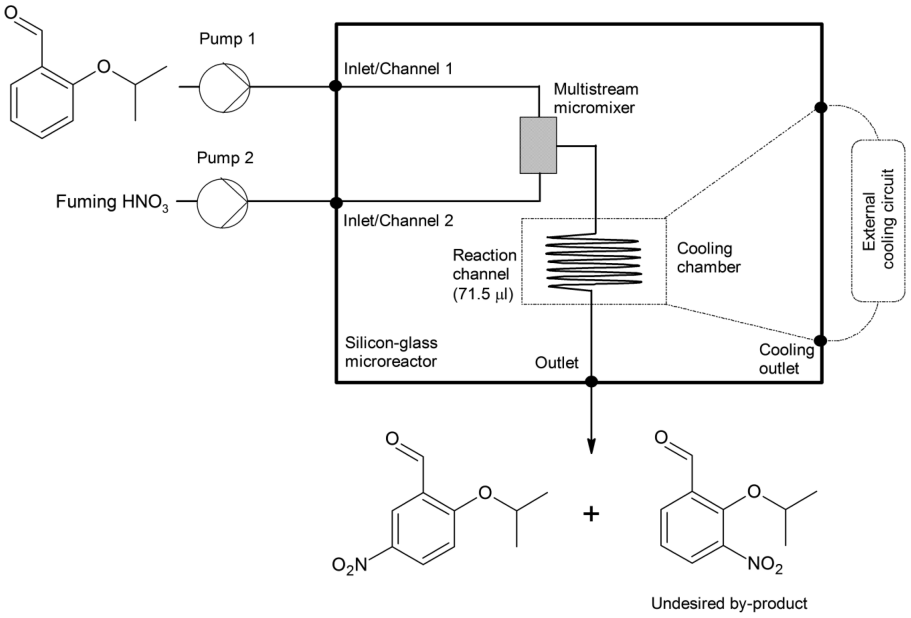

Figure 9. Setup for nitration of 2-isopropoxybenzaldehyde in continuous flow. Adapted from ref 39.

from 4 to 94% with the extension of the reaction time from 1 to 90 s.

1.3. Electrophilic Substitution Reactions. *1.3.1. Nitration.* The nitro derivatives of aromatic compounds are applied in a variety of fields such as synthesis of dyes, pesticides, pharmaceutical drugs, and nonlinear optical materials.[35−37] Nitrobenzaldehyde is used as a raw material for the preparation of benzodiazepines and other cardiovascular drugs. Specifically, the ortho isomer has explicit applications and is usually desired in good yield and high purity.[35] Nitration is the most common synthesis method for producing the nitro derivatives of aromatic compounds.[36] However, in most of the conventional methods of direct nitration of benzaldehyde, the thermodynamically more favorable meta isomer is the main product obtained (usual molar ratio of the products is ortho/meta = 1:4). This ratio can be modified by changing the ratio of the nitrating mixture with respect to benzaldehyde or by varying the internal composition of the nitrating mixture (HNO_3/H_2SO_4).[35]

In the typical batch reaction of direct nitration of benzaldehyde, the mixing of the nitrating mixture and the substrate is done very slowly by adding either the substrate to the nitrating agent or vice versa. The reaction is usually carried out at a temperature of −5 to 15 °C for 2−6 h. Nitration of aromatic compounds is not only fast but is often accompanied by a strong exotherm during addition of the nitrating mixture.[36−38] Performing such exothermic and hazardous reactions in a continuous-flow mode is advantageous because the heat produced in a small reaction volume can be more rapidly dissipated so that exothermic runaway can be avoided and the reactive mixture can be quenched quickly.[36]

Direct nitration of benzaldehyde in a continuous microreactor system has been reported by Kulkarni et al.[35] The effect of molar ratio, temperature, and type of micromixer was studied. The mixing of two phases was found to be a critical point, especially at higher temperatures. The choice of a micromixer (T-mixer or caterpillar micromixer) had a significant effect on the performance.

The nitration of various compounds (intermediates in drugs syntheses)—methyl-2-amino-4-bromo-benzoate, 1-benzosuberone, and 8-bromo-1*H*-quinolin-2-one—in microflow mode was demonstrated by The Novartis Preparation Laboratories.[38] These three nitration reactions were scaled up at high production rates using commercially available equipment (Vapourtec R2C/R4/R1C setup). As an alternative to a traditional nitrating mixture (HNO_3 + H_2SO_4), mixtures of acetic acid or acetic anhydride with fuming nitric acid were used. In all three examples yields comparable to that of the batch reactions were achieved; however, during the nitration of methyl-2-amino-4-bromo-benzoate, no byproduct formation was observed under flow conditions. Nitration in continuous flow was found to be a safe alternative to running dangerous exothermic reactions in batch and to show significant time reduction, especially during the screening of the reaction parameters to find the optimal reaction conditions.

The use of continuous-flow processing for selective, efficient, and reproducible synthesis of 2-isopropoxy-5-nitrobenzaldehyde (building block in the preparation of a ligand of nitrosubstituted Hoveyda−Grubbs metathesis catalyst) by nitration of 2-isopropoxybenzaldehyde was reported by Olszewski and co-workers.[39] Nitration was done with red fuming HNO_3 in a microflow setup including a silicon-glass microreactor (Figure 9), with a productivity of 13 g·h^{-1}. After fast screening of the reaction conditions, the reaction temperature of 10 °C and the residence time of 76 s were found to be optimal, and an excellent 87% selectivity (65% yield) of the desired para isomer was reached. Thus, the flow reaction showed considerable time savings in the optimization of the reaction conditions, high reproducibility, and better yield along with improved selectivity of the nitration process compared to those of the batch experiment.

The development of a simple and practical flow reactor for nitration to produce 100−1000 kg of nitroaromatics was reported recently.[36] Nitropyridine (nitration product) was chosen for the optimization as large quantities were required as a starting material for the synthesis of an API in clinical development. The nitropyridine can be prepared in a

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conventional batch process by treating *N*-(5-bromo-4-methyl-pyridin-2-yl)acetamide with a nitrating mixture (HNO_3 + H_2SO_4) at 25−33 °C in 52−55% yield. Because of the high exothermicity (156 kJ·mol^{-1}), this reaction is foreseen to be potentially hazardous for large-scale batch production. Thus, the synthesis of nitropyridine was realized in a simple continuous-flow reactor consisting of four main units: the feed vessels, the mixer, the residence loop, and a collecting vessel. All of the units were connected using stainless steel tubing and ports. First, the demonstration run was performed on kilogram scale; then a 4 h trial was conducted, charging 10 kg of *N*-(5-bromo-4-methyl-pyridin-2-yl)acetamide that resulted in 59% isolated yield of the desired product. The reactants were charged accurately by applying a modest nitrogen pressure on the feed tanks. Workup consisted of simply quenching into water followed by pH adjustment, filtration, and recrystallization.

1.3.2. Acylation. Development of selective monoacylation of symmetrical diamines without any catalyst or special reagent is highly important, since the products (monoacylated diamines) are key intermediates for the synthesis of numerous biologically active products. The existing synthesis methods suffer from several limitations such as using acylating agents having acidic protons in basic medium, aggressive and expensive reagents, challenging separation/purification of products, long reaction times, preparation of special acylating agents, exothermicity, etc. The enhanced mixing and heat transfer of microreactors allow them to become practical tools in such reactions to control reaction kinetics. A systematic study with a model reaction of 1,3-diaminopropane with benzoic acid *N*-hydroxysuccinimide ester was performed in a continuous capillary microreactor, droplet microreactor, and flask reactor, for comparison. Both droplet and capillary microreactors showed significantly better results in monoacylation selectivity than the batch reactor under identical conditions. The better performance of a microreactor can be explained by high mixing efficiency and heat-dissipation capacity. It was also found that the product composition depends largely on the reaction times as well as the manner of mixing. Finally after optimization, the capillary microreactor with external ultrasonic agitation was chosen for further experiments. Various aromatic, heteroaromatic, and aliphatic acid chlorides gave excellent yields (87−93%) of monoacyl piperazine in the microreactor under ultrasonic irradiation. Highly selective monoacylation of homopiperazine was also achieved with similar success (yield 89−94%), and no diacylation product was isolated in any experiment.[40]

Friedel−Crafts acylation was used as one of the steps in a nine-step synthesis of the aminonaphthalene in a microreactor.[25] The acid (**3**, Figure 10) was used for the Friedel−Crafts acylation. For this transformation the conventionally used reagents Ac_2O and KOAc or NaOAc were not suitable because of the poor solubility of the salts in organic solvents that can cause clogging of the microreactor. Since the transformation is base accelerated (in the absence of a base the desired product was not formed), NEt_3 was employed and proved to be more suitable than KOAc, giving a yield of 86−96% in the batch reactor. For the reaction in the microreactor, the reagents were premixed at room temperature and then pumped into the preheated microreactor (130 °C) by one inlet to give the desired product (**4**, Figure 10) with 100% yield.

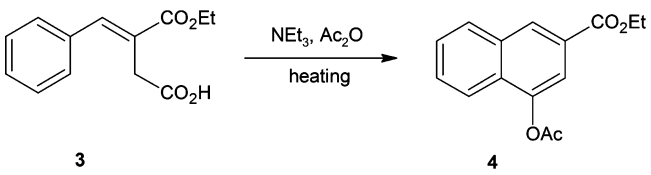

Figure 10. Friedel−Crafts acylation. Adapted from ref 25.

Safe and efficient synthesis of 1,3,4-oxadiazoles via *N*-acylation of 5-substituted tetrazoles using continuous-flow processing in a high-temperature and high-pressure regime was has been reported.[41] 1,3,4-Oxadiazole derivatives are widely applied as intermediates of pharmaceutically and biologically active compounds (such as anti-inflammatory, antimicrobial, anticonvulsant, and antiviral drugs). In addition, other existing synthetic methods of 1,3,4-oxadiazoles consist of *N*-acylation of the tetrazole nucleus, followed by extrusion of nitrogen and formation of a 1,5-dipole with subsequent cyclization (Figure 11). The little attention shown to this synthetic route is related

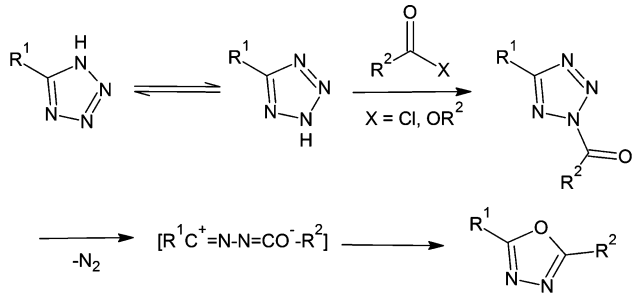

Figure 11. Mechanism of the Huisgen 1,3,4-oxadiazole synthesis. Adapted from ref 41.

to the thermal instability of the tetrazole nucleus as well as the involvement of hazardous azide precursors. Initially, the authors performed two model transformations of 5-phenyl-1*H*-tetrazole with acetic anhydride and benzoyl chloride in a batch reactor using microwave heating. Solvent, temperature, molar ratio of the reagents, and residence time were modified. The best yield (93%) of the desired 1,3,4-oxadiazole was achieved in a batch reactor with microwave heating by applying 2 equiv of acetic anhydride at 5 min reaction time and 220 °C (14 bar). In the case of benzoyl chloride, the isolated yield of 2,5-diphenyl-1,3,4-oxadiazole of 90% was attained at 200 °C (10 bar) within 8 min in batch mode. The method was extended to 12 5-aryl-1*H*-tetrazoles as starting materials, in combination with a number of electrophiles (acetic, propionic, and pivalic anhydrides and benzoyl and propionyl chloride). The expected 2,5-disubstituted-1,3,4-oxadiazoles were obtained in 61−99% yields using microwave batch processing. Finally, the reaction conditions were translated from the microwave batch to high-temperature and high-pressure flow conditions. These experiments were performed in a FlowSyn microreactor setup (Uniqsis Ltd.) and resulted in the desired products with high yields and excellent purities, comparable to those of the batch process. The reaction conditions were transferred from batch to flow mode with the only minor change being the addition of triethylamine to the reaction mixture to neutralize HCl, which corrodes the stainless steel of the reactor. Using the flow method with enhanced safety, a throughput of approximately 85 g/day of 2-(1,1-diphenylethyl)-5-methyl-1,3,4-oxadiazole can be realized.[41]

1.3.3. Halogenation: Fluorination, Chlorination, and Iodination. Fluorination reactions are gaining increasing

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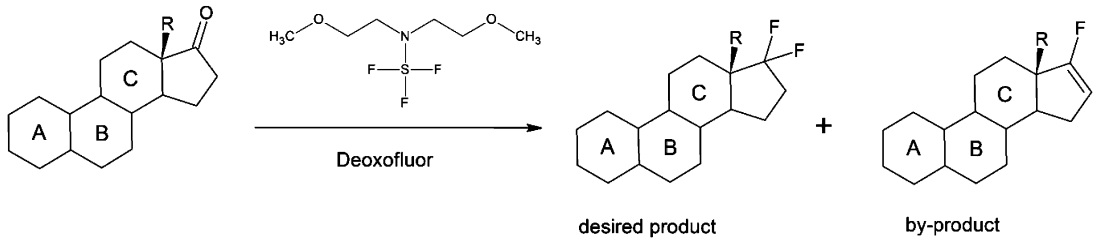

Figure 12. Fluorination of steroids with Deoxofluor. Rings A, B, and C represent the rest of the steroid molecule that remains unchanged in the reaction. Adapted from ref 42.

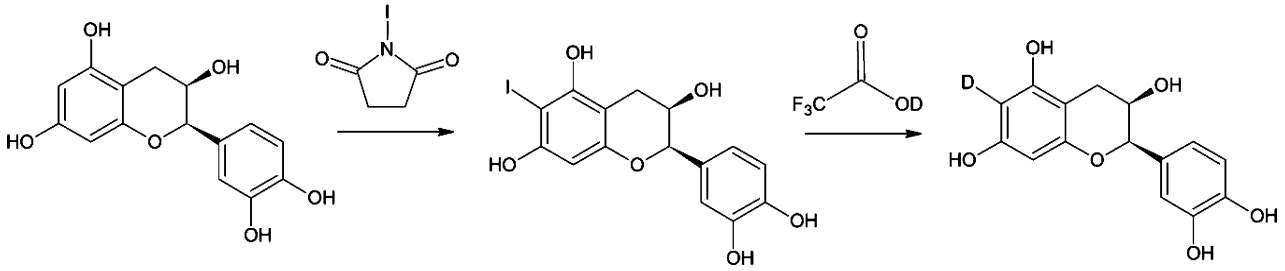

Figure 13. Two-step synthesis: conversion of (−)-epicatechin to 6-iodoepicatechin and conversion of 6-iodoepicatechin to deuterium-labeled epicatechin in position 6. Adapted from ref 45.

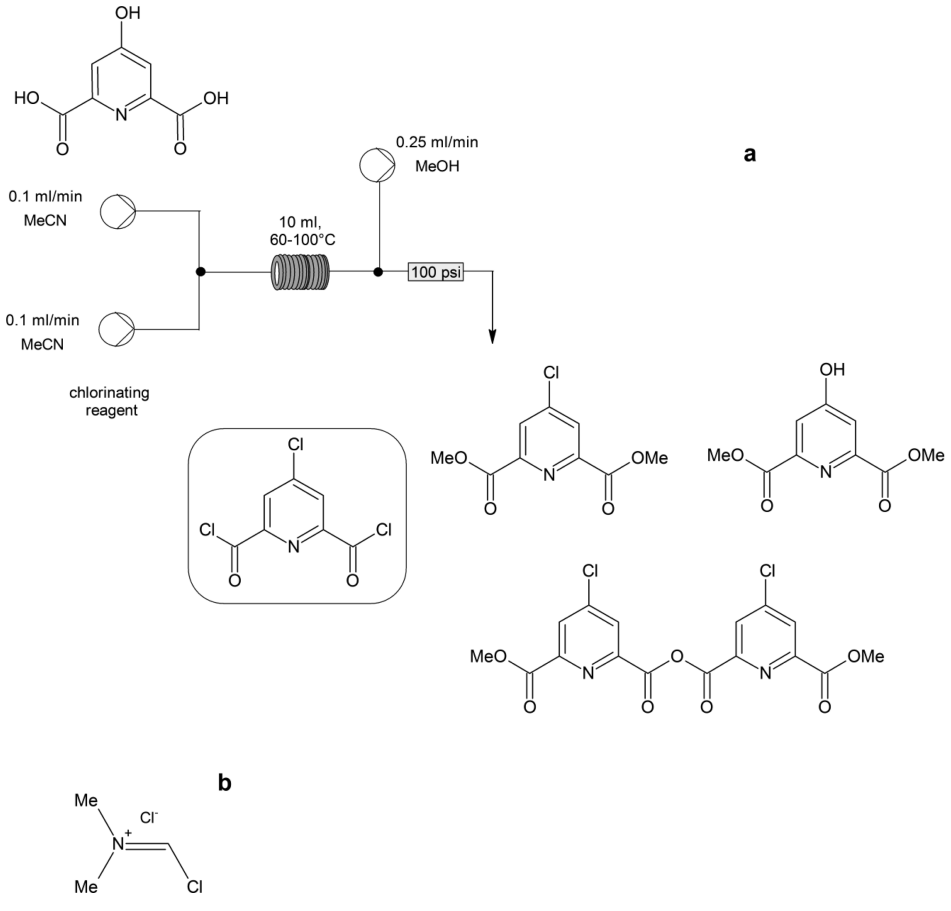

Figure 14. Chlorination of chelidamic acid in flow (a), structure of Vilsmeier reagent (b). Adapted from ref 46.

interest in medicinal chemistry. A model-based approach of fluorination of steroids to produce the corresponding geminal difluoride (Figure 12) in continuous mode was demonstrated by Negi et al.[42] A model based on batch reactor data was implemented to find optimal conditions for the continuous process. Although time-consuming, this approach is believed to give a better understanding of the reaction, resulting in a better process design and scale-up. Deoxofluor (bis(methoxyethyl)-aminosulfur trifluoride) was used as a fluorinating agent to substitute commonly used DAST (diethylaminosulfur trifluoride) due to temperature instability of the latter. The effects of solvent quantity, Deoxofluor equivalent, temperature, and

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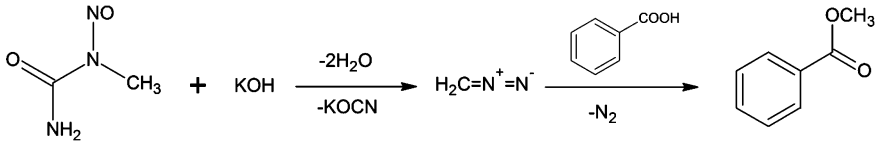

Figure 15. Methylation of benzoic acid with diazomethane produced in situ by basic decomposition of *N*-methyl-*N*-nitrosourea with KOH. Adapted from ref 47.

residence time were investigated through computer simulations. This narrowed range of experiments was performed to find the optimal conditions. A safe continuous process for a deoxofluorination reaction has been developed and optimized. A residence time of 30 min and a temperature of 120 °C were found to be the optimum. In this case 3 mol equiv of Deoxofluor was selected to achieve a minimum of 75% conversion. Higher equivalents led to higher conversions but also to higher operating costs.

As was already mentioned above, DAST, a commonly used fluorinating agent, is unstable at temperatures above 90 °C. It reacts violently with water, is volatile, and is reported to be explosive when overheated.[42,43] Flow-based microreactor technology offers many advantages, one of which is an ability to handle hazardous fluorinating reagents safely.[43,44] To perform the fluorination of alcohols and carbonyl compounds to their corresponding fluoro derivatives in a convenient and safe way the R2+/R4 combination flow reactor commercially available from Vapourtec was chosen by Ley and co-workers.[43] Typically, the fluorination reaction was performed at 60−90 °C with a residence time of 30 min and CH_2Cl_2 as a solvent. Initially, different alcohols were converted into their corresponding monofluorides. The desired products were isolated in good to excellent yields and purities (>95%) after evaporation of the solvent. Then the benzylic and aliphatic alcohols were converted into their corresponding fluoride species, which was found to be very chemoselective. Furthermore, the fluorination of allylic alcohols such as geraniol gave the quaternary fluoride with very high selectivity. Later, the conversion of a small collection of carbonyl compounds into their corresponding difluorides was carried out. The residence time was extended to 45 min in some cases to achieve complete conversion. In each case, the products were isolated in excellent yields and purities.[43]

Iodination of (−)-epicatechin to 6-iodoepicatechin and then its conversion to deuterium-labeled epicatechin in position 6 (Figure 13) in a simple T-shaped microreactor has been demonstrated.[45] Both the iodination reaction between epicatechin and *N*-iodosuccinimide and the deuteration reaction between the crude 6-iodoepicatechin and trifluoroacetic acid-d were performed in acetone at 30 °C at 10 $\mu L \cdot min^{-1}$ flow rate. Proton NMR was used to monitor the reaction and the purity, and stability was analyzed by LC/MS. Due to the high conversion in the first step, there is no need for further purification of the intermediate product; thus, principally the two-step synthesis could be performed in a single microreactor. The stability tests of the final deuterium-labeled compound showed that it was stable in water for up to 2 h.

Chlorination of 4-oxo-1,4-dihydropyridine-2,6-dicarboxylic acid into 4-chloropyridine-2,6-dicarbonyl dichloride (Figure 14a) in flow meso-reactor (3 mm I.D.) was reported as one of the steps in synthesis of *C*2-symmetric chiral PyBox ligands.[46] The chlorination was performed by using stoichiometric amounts of various chlorinating reagents in order to minimize workup. Reaction with oxalyl chloride in acetonitrile resulted in incomplete formation of the chlorinated product. After quenching the output stream with excess methanol, the 4-hydroxy and the 4-chloro dimethyl esters together with the symmetrical 4-chloro anhydride were isolated. In the case of thionyl chloride, an excess of the reagent was required in order to achieve good conversions. Then, the commercially available Vilsmeier reagent (Figure 14b) dissolved in acetonitrile/DMF (9:1) mixture was used. The reaction performed at a temperature of 75 °C and a residence time of 57 min resulted in full chlorination of the substrate. The desired acid chloride could be isolated by collecting the final reaction mixture in anhydrous diethyl ether to precipitate the triethylammonium salts, which could then be filtered off. This procedure allowed the isolation of the pure trichlorinated product with acceptable workup (evaporation of the solvent).

1.3.4. Esterification. Diazomethane is a highly reactive and selective reagent for the synthesis of pharmaceuticals and fine chemicals. However, the large-scale production becomes challenging because of the toxicity and explosive characteristics of diazomethane. An optimized continuous generation of diazomethane through the base-induced decomposition of *N*-methyl-*N*-nitrosourea was reported by Rossi et al.[47] (Figure 15).

The continuous process conditions were first optimized using benzoic acid as a model compound for esterification in a small-volume LowFlow Corning reactor and then was scaled-up into a GEN1 reactor of larger size. Under the optimized conditions, a constant yield of 75% of methyl benzoate was achieved at room temperature and a residence time of 19 s in a small-volume LowFlow reactor. A scale-up was carried out on a larger GEN1-type fluidic module where a nearly quantitative yield of methyl benzoate was obtained. The optimized conditions (reagents ratio, residence time) for the LowFlow and GEN1 systems differ probably due to a different glass microstructure of the channels which can affect the mass transfer rate. This work has shown the effectiveness of flow reactors to handle the preparation of hazardous diazomethane.[47]

Esterification of *p*-substituted benzoic acids by iodomethane using an organic superbase, 1,8-bis-(tetramethylguanidino)-naphthalene in DMF was chosen as a model reaction for a detailed kinetic study in a continuous-flow reactor, and its comparison to the one obtained in batch mode.[48] The rate constants were determined for the reaction with a different alkylating agent and solvent. Reaction constants were found to decrease in the following order: *tert*-butylbromoacetate > iodomethane > benzyl bromide > iodoethane >2-iodopropane, and DMF > acetonitrile. It was found that the reaction follows second-order kinetics which is preserved up to complete conversion in the continuous-flow microreactor. Moreover, the effect of temperature (4−70 °C) and also alkylation kinetics of a series of *p*-substituted benzoic acids was studied. The flow

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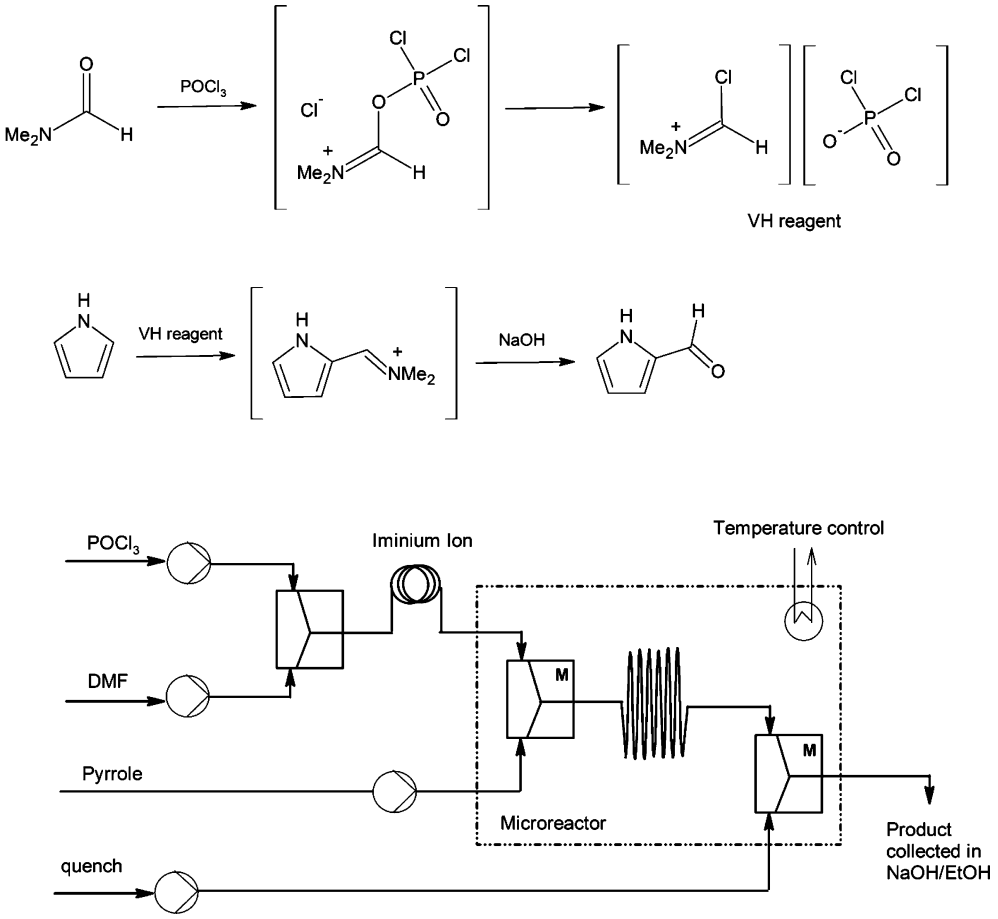

Figure 16. Vilsmeier–Haack formylation of pyrrole (top) and schematic drawing of the microreactor setup (bottom). Adapted from ref 51.

setup enabled authors to measure the reaction rates consuming less than 0.5 mmol of substrate per condition.

A catalyst-free condensation of acid chlorides and alcohols to obtain the different esters was developed in continuous mode.[49] At the first step, the reactions between benzoyl chloride and different alcohols (methanol, ethanol, *iso*-propanol) were performed. The reaction temperature, the residence time and the stoichiometric ratio of both reagents were optimized. A temperature above the atmospheric boiling point of the alcohols was found to be preferable. Full conversion of benzoyl chloride with methanol into methyl benzoate was obtained with a residence time of 300 s, a reaction temperature of 80 °C and 1.3 equiv. of MeOH. After the workup, pure methyl benzoate was obtained with a yield of 90% after evaporation of the excess MeOH. In case of condensation of benzoyl chloride and ethanol, full conversion was achieved at 110 °C with 1.3 equiv. of EtOH. For the condensation of benzoyl chloride and *i*PrOH, the optimized conditions were found to be as follows: a reaction temperature of 120 °C, a residence time of 300 s and 1.3 equiv of *i*PrOH. To extend the scope of the reaction, the continuous-flow procedure was evaluated for solid acid chlorides and alcohols in solution, resulting in 98% conversion in the case of *p*-cresol and benzoyl chloride. Next, the condensation of a solid acid chloride (4-BrC_6H_4COCl) with a solid *p*-cresol, both dissolved in acetonitrile, was performed. The reactions were carried out at a temperature of 140 °C, a residence time of 400 s, and a concentration of the reagents in acetonitrile of 1.5 M, which led to 79% conversion. Finally, the upscaled condensation of benzoyl chloride and methanol resulted in a productivity of 2.2 g·min^{-1} of ester with an isolated yield of 98%. It is noteworthy that the recuperation of formed HCl could be done by purging the reaction mixture with dry nitrogen gas and subsequently trapping the HCl vapour in water. Thus, the developed continuous-flow procedure was shown to be a green alternative for the existing methods of esterification of acid chlorides.[49]

1.3.5. Other Reactions. A direct ligand-free arylation of various aryl bromides using ultrasonic irradiation in a flow capillary microreactor is presented by Zhang et al.[50] First, optimization of the reaction parameters was done in a batch reactor using the reactions of 2-iodo- and 2-bromo-benzyl phenyl ether with different bases (K_2CO_3, Cs_2CO_3, KOAc, NaOAc, etc.), 5 mol % $Pd(OAc)_2$ as a catalyst, and tetrabutylammonium bromide as an additive for the prevention of palladium-black generation. The optimal combination of the substrate, base, and solvent was found and employed for the reaction in the microreactor. The microreactor clogged in a reaction less than 2 h that used 2-iodobenzyl phenyl ether, resulting in a very low conversion and selectivity towards the desired product. The problem of clogging was solved using ultrasonic treatment, which enables the rapid dispersion of solids, and thus blockage of the microchannels is avoided. As a result >98% conversion (89.3% isolated yield) was achieved in 6 h at 90 °C. The microreactor showed a higher efficiency in comparison with that of the batch reactor, where 90% conversion was achieved in 24 h at 100 °C. A number of functionalized coupling products possessing various substituents (nitro, aldehyde, ketone, ester, phenyl, etc.) was

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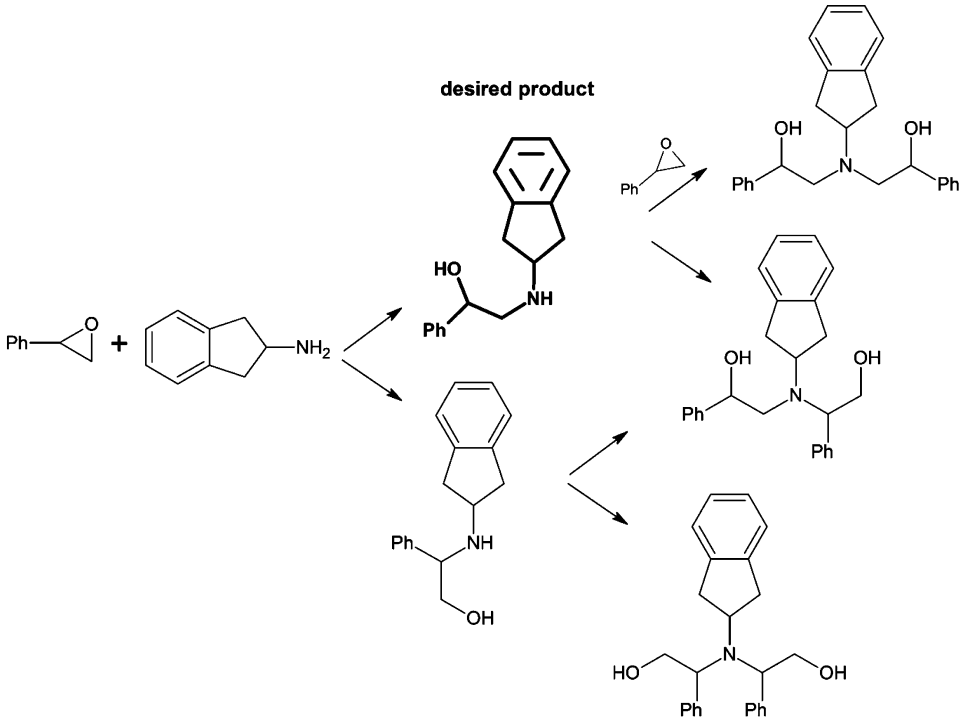

Figure 17. Aminolysis of styrene oxide with 2-aminoindan, including bisalkylation reactions. Adapted from ref 16.

synthesized with excellent yields (up to 97%) under mild conditions without using complex ligands and expensive additives.[50]

The Vilsmeier−Haack formylation of aromatic compounds is an important step in the synthesis of intermediates of fine chemicals and pharmaceutical products. Since this process requires the use of hazardous chemicals to produce the highly reactive intermediates, the use of microreactor technology where the reaction takes place on a microliter scale was found to be a good alternative. The Vilsmeier−Haack formylation of aromatic compounds in a flow microreactor was reported by van den Broek et al.[51] The formylation of pyrrole was chosen as a model reaction (Figure 16). 2-Formylpyrrole was first synthesized in a batch reactor in a three-step procedure. The continuous-flow experiments were performed using Future Chemistry's Flowstart B-200 setup. The Vilsmeier−Haack reagent (chloroiminium ion) was synthesized in 90 s reaction time. For the second step of the reaction the following conditions were optimized: the reaction time (10−300 s), temperature (0−60 °C), and molar ratio of $POCl_3$/pyrrole substrate (1:4). Full conversion was achieved in 180 s at 60 °C and a molar ratio of 1.5 with the production rate of 6.0 $g{\cdot}h^{-1}$. On the basis of the optimal conditions obtained with pyrrole, a screening of the number of different substrates was performed. The products of amine-substituted arenes were synthesized in 180 s with good yields (53−81%), while the di- and triformylation reactions of triphenylamine were found to be less effective.

As already mentioned, the use of microflow reactors allows the safe handling of hazardous and highly reactive compounds such as the Vilsmeier reagent, which is widely used for the formylation of activated arene compounds. The formation of β-chloroacroleins in continuous mode starting from acetophenone derivatives and in situ generated Vilsmeier reagent was described by Pellegatti et al.[52] The Vilsmeier reagent was prepared from DMF and phosphorus oxychloride in the first microreactor. After addition of acetophenone in DMF via the T-mixer, the chloroiminium salt is formed, which was then hydrolyzed to the corresponding β-chloroacrolein by addition of the reaction mixture to a flask containing aqueous NaOAc solution. The reaction conditions—temperature and the residence time—were chosen depending on the stability and reactivity of the corresponding chloroiminium ion (40−80 °C, 10−80 min). Various substituted acetophenones were efficiently converted to the corresponding β-chloroacroleins or 3-formylchromones with up to 98% yield. This approach was found to be less efficient in case of acetylated heterocycles probably due to the low stability of the corresponding iminium salts. The direct use of the generated β-chloroacroleins was demonstrated for the synthesis of a β-chloroacrylonitrile and of 1,4-disubstituted, 1,5-diaryl, and 1,4,5-triarylsubstituted pyrazoles. Moreover the authors mentioned that that this technique should be readily adaptable for large-scale applications.

1.4. Nucleophilic Substitution Reactions. The synthesis of β-amino alcohols is important for the pharmaceutical industry and as such has been studied by a number of academic research groups. A number of active pharmaceutical ingredients, are formed through β-amino alcohol precursors, which are often difficult to synthesize and are therefore inevitably expensive. The β-amino alcohol functional group can be assembled by a number of synthetic pathways, such as, for example, the ring-opening of epoxides with amine nucleophiles. Although the epoxide aminolysis can be performed without a catalyst, it generally proceeds slowly at solvent reflux temperatures. Elevating the reaction temperature is typically limited by the stability of the reagents and/or the product, and the use of solvents with higher boiling points can affect the reaction rate. In previous work[18] the authors demonstrated highly efficient aminolyzes of epoxides using a continuous-flow silicon microreactor. Excellent yields and conversions with terminal

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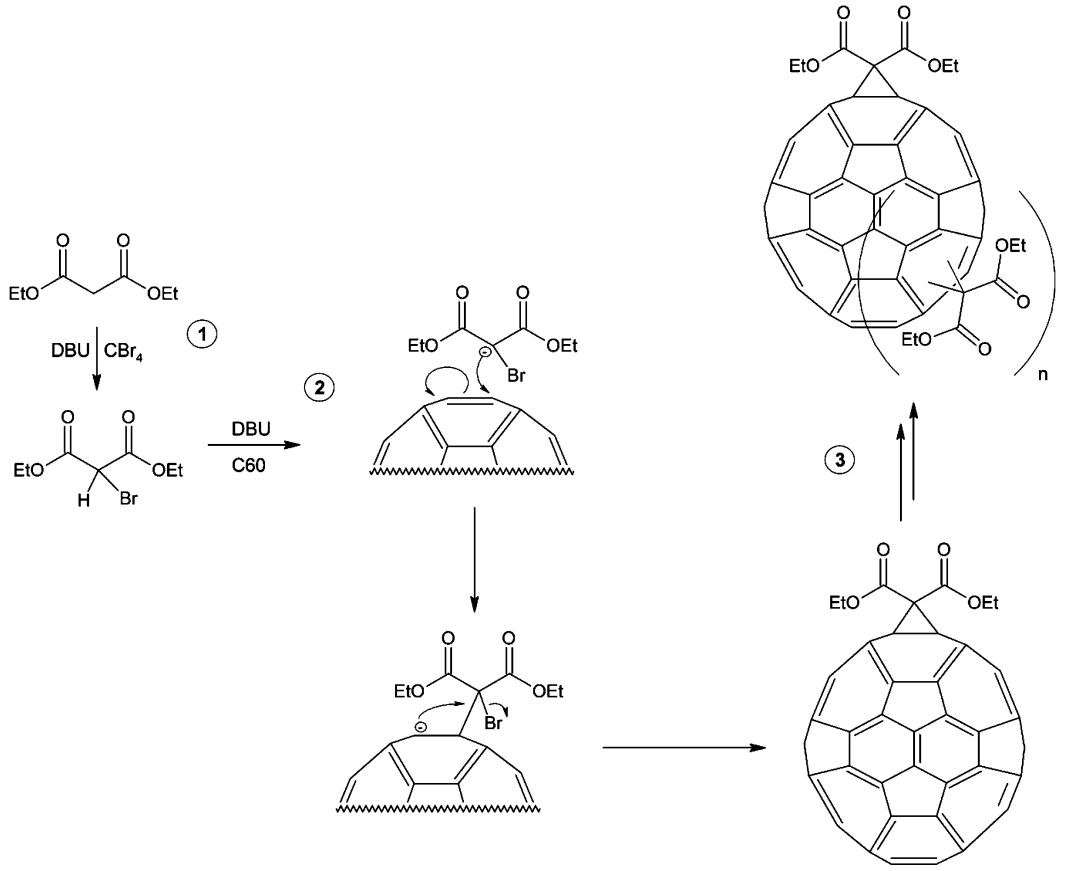

Figure 18. Formation of diethyl bromomalonate and intermolecular nucleophilic attack of the bromomalonate anion to the fullerene cage and intramolecular ring-closure. Adapted from ref 55.

epoxides were obtained at residence times under 5 min in ethanol under high temperature (180−240 °C) and pressure.

To enable the determination of the optimal set of conditions for performing epoxide aminolysis, a systematic kinetic evaluation of the reaction was carried out.[16] The aminolysis of styrene oxide with 2-aminoindan (Figure 17) was performed with ethanol as the solvent, using very low concentrations of reagents to allow the measurement of initial reaction rates. The overall reaction model showed that the reaction should be performed at the highest possible temperatures with a large excess of the amine reagent to obtain optimal yields. Synthesis of 9 g of desired product was achieved in 30 min, with 100% conversion and 78% HPLC-yield, which is in good agreement with the prediction of the kinetic model. Thus, it was shown, that a robust high-pressure, high-temperature microreactor with very rapid thermal control enabled a highly efficient reaction and kinetics evaluation.

The direct transformation of 1,3-dichloropropyl pivaloate into 3-chloro-2-hydroxypropyl pivaloate was reported.[53] The results of both batch and flow capillary systems were compared. The continuous microreactor is referred to a capillary tube submerged in a heated thermostat bath. It was found that the performance of the reaction in continuous-flow mode at high pressure and high temperature (180−200 °C) reduced considerably the reaction time (0.5−10 min) compared to the batch system (48 h), giving similar yields. However, the flow process gives an inferior purity profile. This may be tolerated in case of easy separation or when the byproduct is of commercial value as well as the desired product.

Catalyst-free transesterification of soybean oil in supercritical ethanol to produce fatty acid ethyl esters (FAEE) in a continuous microtube reactor was reported by da Silva et al.[54] First, the esterification was performed at 300 °C, a pressure of 200 bar and an oil to ethanol molar ratio of 1:20 resulting in 40 wt % of FAEE. As a next step, the reaction was conducted in series. Ethanol was added to the reaction mixture obtained in the first step and then passed through the reactor at the same temperature and pressure conditions. The content of FAEE was found to increase compared to the first reaction step (40 wt %) to approximately 77 wt %. The recycle reactor was employed using different recycle ratios (20 and 40 wt %, on the basis of oil to ethanol feed stream) at 300 °C, a residence time of 25 min, and a pressure of 200 bar. The contents of FAEE of around 67 and 80 wt % were obtained for recycle ratios of 20 and 40 wt %, respectively. These results confirm that reaction conversions may be improved by using the reactor with a recycle configuration.

The optimization of the continuous-flow cyclopropanation reaction of diethyl malonate with C60-fullerene (Figure 18) via kinetic analysis was demonstrated by Maggini et al.[55] In order to compare, the reaction was also performed in batch mode. A Y-shaped glass microreactor (150.332.2 chip type, Micronit Microfluidics BV) or a commercial slit interdigital micromixer was used to mix the solution streams which then reacted in a fused silica capillary. First, it was found that the reaction is quite fast, reaching a plateau after about 120 s. Further, the kinetics of the reaction were studied by varying the residence time from 1 to 120 s. The values of the reaction rate constants were found to be 3.13×10^2, 2.10×10^4, and 5.23×10^3 $L^2 \cdot mol^{-2} \cdot s^{-1}$ for

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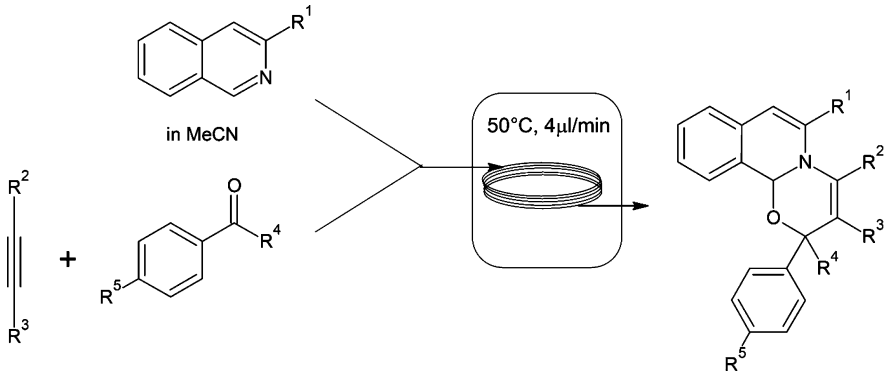

Figure 19. Three-component 1,4-dipolar cycloaddition in a flow microreactor. Adapted from ref 58.

the first, second and third reaction (Figure 18), respectively. Thus the formation of the diethyl bromomalonate intermediate (reaction 1) was found to be the rate-determining step. The influence of the reaction conditions on the selectivity to the desired product was determined taking into account reactions 2 and 3 and using commercial diethyl bromomalonate (to exclude the reaction 1). It was observed that selectivity and conversion does not depend on the reagents ratio (1:1, 1:1.5 or 1:2). It was also found that high (95%) selectivity values can be achieved at low (32%) conversion with high reproducibility of the reaction composition.

1.5. Cycloaddition and Cyclization Reactions. The hetero Diels–Alder reactions of nitroso dienophiles leading to polyfunctional 3,6-dihydro-1,2-oxazine building blocks received considerable attention over the past decade.[56] Two classes of nitroso compounds (aryl- and acylnitroso dienophiles) were primarily used. These cycloaddition reactions are exothermic and stoichiometry sensitive, hence in order to avoid side-reactions accurate thermal and stoichiometric control is required, which can be realized in a microreactor. The cycloadditions of various dienes with nitrosodienophiles were successfully conducted under microflow conditions, demonstrating the first example of a continuous lab-scale production of 1,2-oxazines with a production rate of 0.2–1 $g \cdot h^{-1}$.[56] The CPC College System from Cytos (47 mL total volume) and the X-Cube from ThalesNano (6 mL total volume) were used. A temperature from 0 to 95 °C, a pressure from 1 to 100 bar, flow rates from 0.2 to 1 $mL \cdot min^{-1}$, and different solvents (acetone, methanol, THF, acetonitrile, and DMF) were studied. Using equimolar solutions of reagents, similar or higher yields (up to 96%) to the corresponding batch reactions were obtained, without metal catalysts or specific additives. Moreover, a continuous process offers the efficient heat exchange, the easy control of the reaction stoichiometry and shorter residence times.

The [3 + 2] cycloaddition of an unstabilized azomethine ylide with an electron-deficient alkene is considered to be an important reaction for the synthesis of intermediates of valuable pharmaceuticals. A popular way to synthesize the required azomethine ylide is the acid or fluoride source promoted reaction of the silylated aminal ether in the presence of an alkene which traps the ylide to form the pyrrolidine. Because of its exothermicity, this reaction is conducted in continuous mode and offers advantages over conventional batch reactions in terms of safety and mixing efficiency. The reaction between silylated aminal ether and ethyl acrylate in anhydrous toluene with 10 mol % TFA was used to optimize the reaction conditions in a Vapourtec R2+/R41 flow reactor.[10] The residence time was varied from 5 to 60 min; and a temperature range between 20 and 100 °C with an operating pressure of 7–9 bar was studied. The reaction proceeded at room temperature with a lower yield of product under a shorter residence time. The yields were found to be good at 70–100 °C, with a slight trend to better yields with longer residence times. Even with a residence time as short as 10 min at 70 °C, the yield was satisfactory (89%), although with only 5 min residence time at 100 °C, it was significantly lower (54%). Thus, the feasibility of a potentially hazardous cycloaddition reaction under continuous flow was proven.

Another application of microreactors for an exothermic cycloaddition was described by Abele et al.[57] Diels–Alder reactions of α-acetoxyacrylonitrile or acrylonitrile as dienophile and (cyclohexa-1,5-dien-1-yloxy)trimethylsilane as diene were performed in a stainless steel microreactor. The best compromise for α-acetoxyacrylonitrile between short residence times and low temperatures was found at 10 min and 250 °C; however, this led to the formation of several byproducts and polymerization. The reaction of a diene with acrylonitrile has been transferred into a continuous process at 215 °C with a residence time of ∼1 min by using a large excess of this dienophile. The crude yield was comparable to the one obtained in the batch reaction.

A three-component 1,4-dipolar cycloaddition reaction of isoquinolines, acetylenedicarboxylates and 2,2,2-trifluoro-1-phenylethanone (Figure 19) was developed in a continuous-flow microreactor.[58] Under the optimized conditions (temperature of 50 °C and residence time of 60 min), a series of 2-(trifluoromethyl)-2*H*-[1,3]oxazino[2,3-*a*]isoquinoline derivatives was synthesized with high yields (up to 83%). The process was also applied to similar reactions using aromatic aldehydes as the carbonyl component. The excellent mixing of reagents associated with the flow technique suppressed the formation of the byproduct and ensured the high selectivity and efficiency of the process.

Many routes to synthesize 2,4,5-trisubstituted imidazoles—important intermediates in the synthesis of pharmaceuticals—have been developed and recently improved, including the use of catalysts. Preparation of those catalysts requires expensive reagents and harsh reaction conditions, and microwave-assisted processing, which is difficult to scale up. A new general method for the synthesis of 2,4,5-trisubstituted imidazoles was developed by using a continuous-flow microreactor system under pressure.[17] Aryl-, alkyl-, and heteroaryl-substituted imidazoles were obtained in high yields within few minutes under superheating conditions. Through performing reactions in continuous microflow systems under pressure, a rapid and

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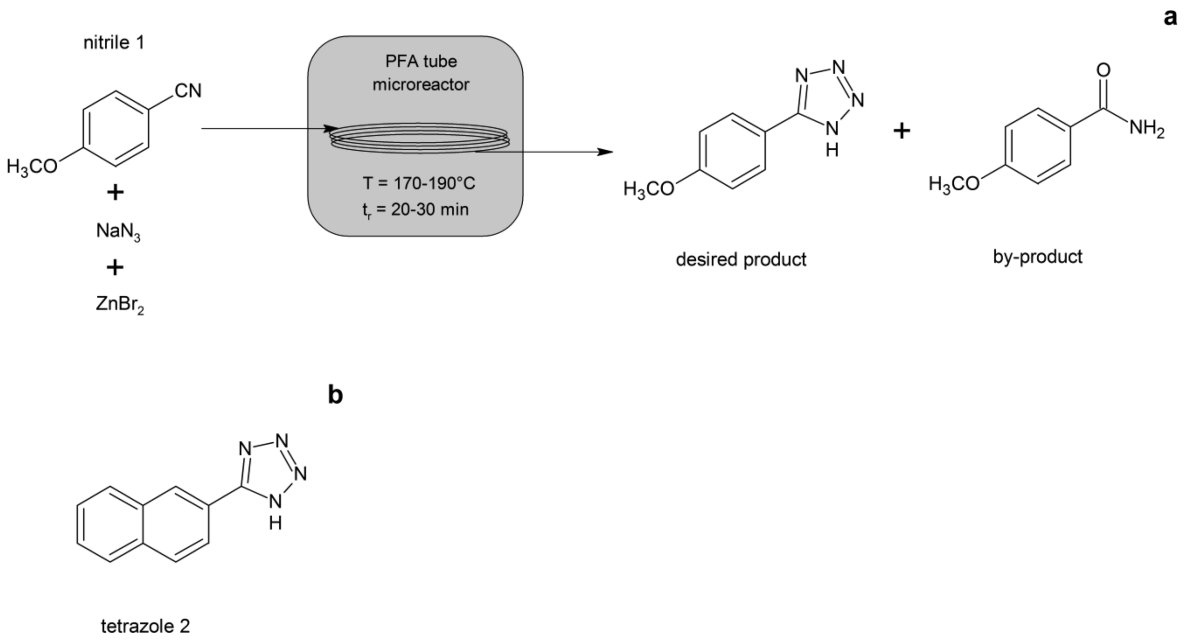

Figure 20. Continuous-flow synthesis of tetrazoles in microreactor (a), structure of **tetrazole 2** (b). Adapted from ref 60.

evenly superheated (above the boiling point of solvents) environment was achieved. The influence of ammonium acetate, temperature (120−180 °C) and residence time on the yield of the products was investigated. Using the optimized conditions (180 °C, 2 min), reactions with various substrates (*o*-, *m*-, *p*-substituted aromatic aldehydes, aromatic heterocyclic aldehydes, aliphatic aldehydes with short carbon chains and small carbocyclic rings) were performed with good to excellent yields (80−95%). The authors showed, that in addition to the efficiency and simplicity, this process provides a rapid, green, and easy to scale up procedure for the synthesis of 2,4,5-trisubstituted imidazoles.

An efficient method to synthesize tetrasubstituted imidazoles via a one-pot modified Debus-Radziszewski flow reaction for their subsequent transformation into the corresponding imidazolium ionic liquids is reported.[59] Continuous-flow synthesis of *N*-hexyl-imidazoles was performed in *n*-pentanol at a temperature of 120 °C and a concentration of 0.5 M of NH_4OAc. The optimal residence time was found to be 48 min, to give the best yields of extracted product of 36%. The synthesis of the *N*-ethyl-imidazole derivatives was not feasible due to the formation of ethylamine gas bubbles in the microreactor channels. The imidazole core, obtained in the microreactor, is then easily methylated with iodomethane to obtain imidazolium iodides, followed by metathesis reactions which give dicyanamide and bis(trifluoromethylsulfonyl)imide ionic liquids in almost quantitative yields.

Safe and efficient syntheses of tetrazole products from nitriles performed in a flow microreactor were described by Palde et al.[60] Tetrazoles are known to be an important class of heterocycles which are used in different areas of the chemical industry. The known methods of tetrazole synthesis are not suited for large-scale synthesis since explosive reagents, toxic metal-containing compounds, or an excess of azide is required. One of the advantages of microreactors is the small amount of hazardous compounds used during the reaction, thus minimizing the safety risks. Initially, the authors tested the reaction between **nitrile 1** (Figure 20a), NaN_3, and $ZnBr_2$ in a microreactor made of perfluoroalkoxyalkane tubing. Under the optimized conditions 81% yield of the desired product and less than 1% of byproduct were achieved. Different nitriles were tested in the optimal reaction conditions, resulting in excellent yields (up to 98%). Finally, synthesis of **tetrazole 2** (Figure 20b) was successfully scaled up using an Uniqsis FlowSyn continuous-flow reactor (volume of heated zone 6.9 mL). The reaction was running continuously for 2.5 h to yield 9.7 g of **tetrazole 2** (96% yield) which corresponds to a production rate of 116 g·day^{-1}.[60]

The exothermic cycloaddition reaction between isoamylene and *α*-methylstyrene which yields the Iindane compounds 1,1,2,3,3,-pentamethylindane and 3-ethyl-1,1,3-trimethylindane (intermediates in the synthesis of musk fragrances) was performed in a microreactor[61] (Figure 21). The influence of

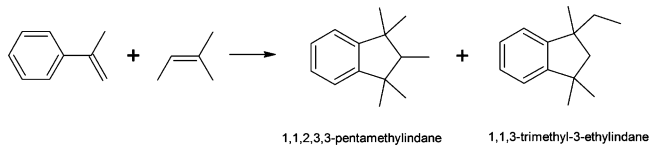

Figure 21. Cycloaddition reaction between isoamylene and *α*-methylstyrene. Adapted from ref 61.

the catalyst concentration (sulfuric acid, 65−90 wt %), reaction temperature, residence time, and the molar ratio of the reagents on the product yield and average reaction rate was studied. For this mass transfer limited cycloaddition reaction, which involves two immiscible phases (an aqueous catalyst and organic reactants), the microreactor was found to be much more efficient than a semibatch reactor even at very high stirrer speeds. At optimized reaction conditions, the yield obtained in the microreactor (62%) was higher than the one in the semibatch reactor (41%). It is also noteworthy that, because of a better mass transfer efficiency, the highest yield in the microreactor was obtained immediately after the achievement of steady state (total run time of few seconds), while in the semibatch reactor the whole experimental run took ∼4 h. Because of this large difference in residence time between the

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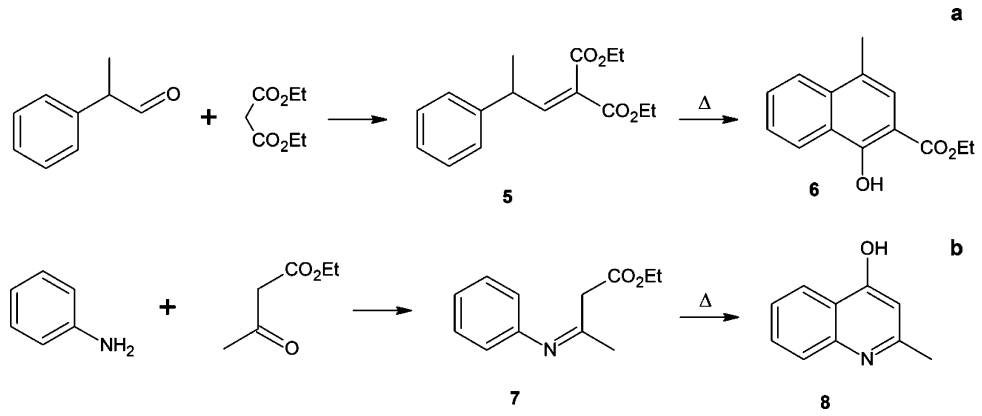

Figure 22. Thermal cyclization route to (a) ethyl-1-hydroxy-4-methylnaphthalene-2-carboxylate **2**; (b) 2-methyl-4-hydroxy-quinolines **4**. Adapted from ref 62.

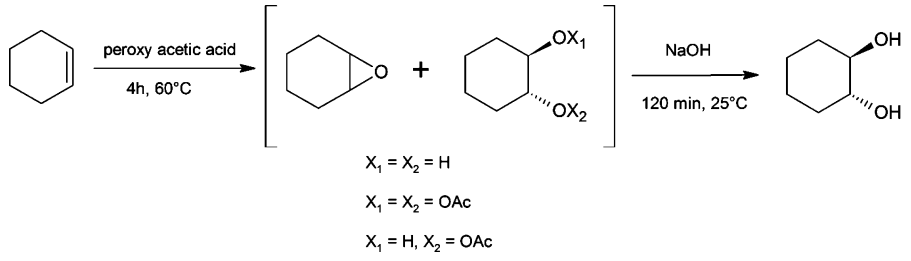

Figure 23. Epoxidation of cyclohexene in batch mode. Adapted from ref 64.

two reactors, an optimum catalyst concentration was found to be 70 wt % in the semibatch reactor rather than the 90 wt % in the microreactor.

Thermal ring-closing reactions (Gould–Jacobs and Conrad–Limpach types) performed in a continuous-flow microreactor were reported by Lengyel et al.[62] Various thermal cyclizations of alkylidene *β*-diesters using a low-boiling point solvent (THF) at HPHT conditions (300–360 °C and 100–160 bar) and short residence times (0.5–5 min) were realized in a 'loop' X-Cube Flash microreactor. Using this procedure, various heterocylic ketones and hydroxyquinolines were synthesized in moderate to high yields and high purity. In comparison, most of these reactions reported previously in the literature were performed under batch conditions using high-boiling solvents, often at higher temperatures and sometimes under MW heating. On the basis of these results, benzannulation reactions were performed via a thermal cyclization approach to typical Knoevenagel adducts derived from the condensation of aralkyl aldehydes and malonic esters. Thermal cyclization of the 2-phenylpropionaldehyde malonic ester adduct **5** led to the corresponding ethyl-1-hydroxy-4-methylnaphthalene-2-carboxylate **6** in 67% yield (Figure 22a). Cyclization of the Schiff's base **7**, derived from aniline and a *β*-ketoester, resulted in 4-hydroxy-2-methylquinoline **8** in excellent yield (92%) (Figure 22b). Here the important advantage of the continuous-flow processing is the use of a solvent with a low boiling point which is recyclable and easy to handle during the workup.

Cyclization of propargylamides in flow conditions was described.[63] This reaction is one of the steps in the synthesis of 2-aminoadamantane-2-carboxylic acid, which has been shown to possess novel transport inhibitory properties. After optimization of the reaction conditions by modifying bases, concentrations, temperatures, and reaction times, the efficient flow cyclization of a benzoyl propargylamide derivative (~90% yield) occurred at 100 °C with reaction time of 2 h. It was observed that at higher temperatures large quantities of undesired byproduct were formed. It is noteworthy that the adapted conditions for the flow procedure allowed the reaction at elevated temperature without byproduct formation. Thus, the desired product was obtained at 120 °C, with a residence time of 24 min (1:16 molar ratio of amide to KOH). The corresponding acetyl derivative was less reactive, requiring a prolonged residence time (48 min) to achieve complete conversion to the desired product. In both cases an overall high yield (~90%) of the cyclized products was obtained.

1.6. Electrophilic and Nucleophilic Addition Reactions. The Prilezhaev dihydroxylation is a transformation which is often used in organic synthesis for the epoxidation of olefins and subsequent hydrolysis into the corresponding *trans*-diol. Initially in this reaction, a peroxy acid was formed in situ by mixing the carboxylic acid with hydrogen peroxide and sulfuric acid. Because of the thermal instability and explosive character of the peroxides, the batch process is difficult to scale up and to use in industrial applications. To simplify the oxidation, several alternative oxidizing agents such as *m*-chloroperoxybenzoic acid were used. In a microreactor the reaction can be performed with enhanced safety since only milliliters of the substances are used; thus, only small amounts of peroxy acid are present during the process. The oxidation of olefins in flow by using the commercially available peroxy acetic acid was recently demonstrated.[64] The dihydroxylation of cyclohexene using peroxy acetic acid was chosen as a model reaction (Figure 23). The batch synthesis was performed for comparison. Reaction parameters such as temperature (25–60 °C), reaction time (60–300 s), and molar ratio of the reagents were modified to increase the yield. The optimal reaction conditions led to full conversion of cyclohexene in a reaction time of 300 s, at a temperature of 60 °C, and a molar ratio of

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1.2. In spite of the yield (82%) similar to that of the conventional batch procedure, performing dihydroxylation in flow enables better control, improved safety, and shorter reaction time.[64]

The Koch–Haaf reaction—the formylation of alcohols or olefins in the presence of a strong acid—is one of the organic syntheses for the preparation of carboxylic acids. Since the reaction is highly exothermic, the precise temperature control, sufficient cooling, and slow addition of reagents should be ensured. The authors[65] performed the Koch–Haaf reaction (carbonylation of 1-adamantanol) in a microflow reactor at room temperature without any cooling equipment. An acid-tolerant system (combination of a Hastelloy-made micromixer and a PTFE tube as a residence time unit) was used for this study. The desired product (1-adamantanecarboxylic acid) was obtained in 89% isolated yield after a 1.5 min residence time. The batch reaction gave 1-adamantanecarboxylic acid in 92% yield; however, the slow addition of a solution of 1-adamantanol and external cooling were necessary. The reactions of 2-adamantanol and 2-methyl-2-adamantanol were also performed in flow mode, giving 10–20% higher yields than the ones obtained in batch reactor.[65]

An efficient procedure for the Hemetsberger–Knittel synthesis of indoles via thermolysis of azidoacrylates using continuous-flow reactors is reported by O'Brien et al.[66] The method was then applied to the preparation of related heterocycles and finally pharmaceutical intermediates. A commercially available Vapourtec R series flow reactor was used. The indole syntheses were performed at 220 °C and a 6 s residence time, using toluene as a solvent (Figure 24a). Indoles were prepared with yields up to 85%. The synthesis of pyrrole (Figure 24b) was successfully performed at 180 °C with 97% yield in 12 s. Synthesis of azidoacrylates bearing heteroaryl groups was conducted under the same reaction conditions as were used for the synthesis of indoles. Some of the products were formed in excellent yields (99%, Figure 24c); only the reaction of the 4-substituted pyridine failed due to decomposition of the starting material. Finally, the precursor of the pharmaceutical intermediate (a D-amino acid oxidase (DAAO) inhibitor) was prepared in 12 s at 180 °C with quantitative yield and excellent purity (Figure 24d).

A two-phase phase transfer catalyzed Wittig reaction (Figure 25) performed in a fluorinated ethylene propylene microtube reactor (250 μm I.D.) was described by Šinkovec et al.[6] An important advantage of microstructured reactors is that stable two-phase slug-flow regimes with a high degree of control over the slug size distribution can be achieved. After the slug-flow stability test, the flow rates of 50–200 μL·min^{-1} and an aqueous-to-organic (AO) phase volumetric ratio of 0.5:6 were found to give a stable flow. The comparison between flow and batch reactors was done by performing the Wittig reaction of *p*- and *o*-methoxybenzaldehydes. It was found that, due to the higher surface-to-volume ratio of the organic phase and a more efficient mass transport, the overall reaction rate for both aldehydes was higher in the microreactor than in the batch reactor: 90% conversion of *p*-methoxybenzaldehyde was achieved in 500 and 900 s in the flow and batch reactors, respectively. Different flow rates (50–200 μL·min^{-1}), AO ratios (0.5–6), and concentrations of aqueous sodium hydroxide solution (0.1–1M) were tested. The overall reaction rate was found to increase with the increase of AO. The negligible influence of the flow rate on the reaction rate was explained by the fact that internal circulation within the slug was not affected

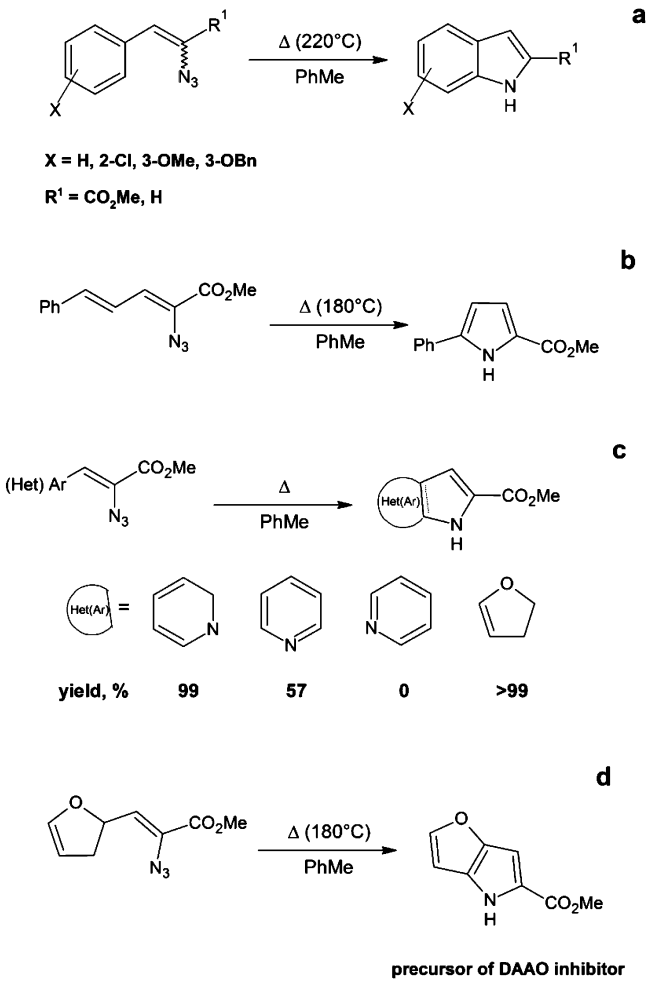

Figure 24. Synthesis of indoles. Adapted from ref 66.

by the increase of flow rate. A higher concentration of sodium hydroxide solution resulted in a higher overall reaction rate in both reactors; however, lower maximal conversion of *p*-methoxybenzaldehyde at a higher concentration of sodium hydroxide solution was observed, probably due to the decomposition of the phosphonium salt in a concentrated hydroxide medium. Moreover, the conversion was found to be lower in flow than in the batch reactor, due to the high concentration of OH^- ions at the interfacial area which cause the faster decomposition of the phosphonium salt in the microreactor. Finally, it was concluded that in a two-phase system the specific interfacial area is crucial for the desired interactions between the two phases. A microreactor process with a stable flow pattern, and thus a known and precisely controlled specific interfacial area, provides a great advantage over the standard batch method.

The formation of benzyl azide from benzylamine using imidazole-1-sulfonyl azide hydrochloride as diazotransfer reagent was performed in a microreactor at small and large scale by the group of Rutjes.[67] Two different glass microreactors with an internal volume of 92 and 7.0 μL were used for long and short reaction time, respectively. Initially, the optimization of the synthesis of benzyl azide was performed using zinc chloride as catalyst and methanol/dichloromethane (3:10) as a solvent. The influence of the residence time, reaction temperature and the stoichiometric ratio of imidazole-1-sulfonyl azide hydrochloride with respect to benzylamine on

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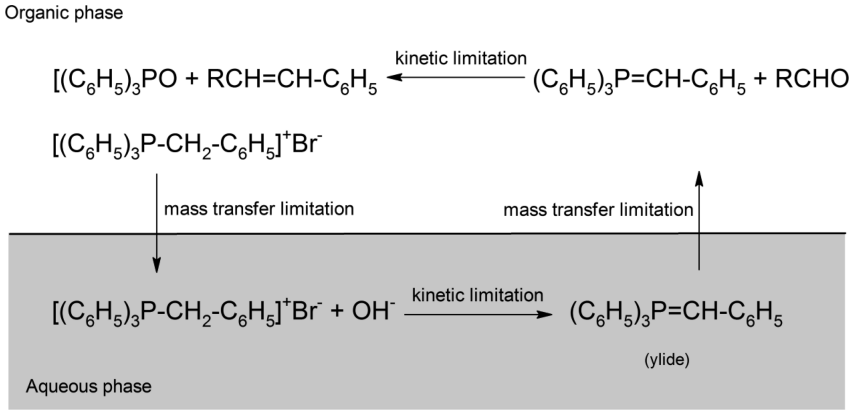

Figure 25. Wittig reaction of benzyltriphenylphosphonium salt and benzaldehyde. Adapted from ref 6.

the yield of benzyl azide was investigated by a mathematical model as well as experimentally. The theoretical set of optimal reaction conditions was found to be as follows: residence time of 535 s, a stoichiometric ratio of 4.6 and a temperature of 1.8 °C. It is noteworthy that for sixty optimization experiments, only 400 mg of benzylamine and 1 g of imidazole-1-sulfonyl azide hydrochloride was employed. Taking into account these results the authors carried out a scale-up experiment using a Uniqsis FlowSyn reactor at RT and 600 s residence time. The desired benzyl azide (GC yield of 97%) was produced with a production rate of ~1 $g \cdot h^{-1}$. Thus, the reaction was successfully scaled up by a factor of 200 using a single-flow microreactor.[67]

1.7. Oxidation and Reduction Reactions. DIBALH reduction of nitriles to aldehydes is known to be an important transformation in organic chemistry. Since this reduction suffers from the instability of the intermediates, it can be successfully performed in flow microreactors which allow a much better control of reactions where unstable intermediates are formed.[68] In the referenced work the Sigma-Aldrich Starter Kit microreactor connected to a syringe pump was used. After optimal reaction conditions (0 °C, 1.5 equiv of reducing agent, and residence time of 20 s) were found for the reduction of benzonitrile to benzaldehyde, the reduction of other aromatic nitriles was performed using slightly modified reaction conditions. Excellent yields of the desired products (up to 99%) were achieved. Finally, aliphatic nitrile (Figure 26) was selected because its reduction product (aldehyde) is applied in medicinal chemistry. This compound was obtained in excellent yield (84–93%) at 50 °C.

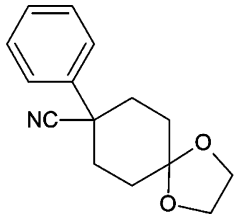

Figure 26. Aliphatic nitrile. Adapted from ref 68.

A large variety of enantioselective reactions for the synthesis of pharmaceutical intermediates using metal-complex catalysts is realized nowadays mainly in batch mode. However, it is known that the enantioselectivities are often affected by the reaction temperature, which can be precisely controlled in flow microreactors. The enantioselective borohydride reduction of various substrates catalyzed by optically active cobalt complexes in a stainless steel microreactor was reported by Hayashi et al.[69] The reaction of 6-methoxy-1-tetralone was carried out at 0 °C, and the residence time was varied in the range of 0.2–12 min. Even after optimization of the residence time, the enantioselectivity was still not improved in comparison to that of the batch system. The addition of methanol to the initial solution and optimization of the reaction temperature was found to efficiently accelerate the continuous-flow reaction and to improve the chemical yield as well as the enantioselectivity so that the desired product was obtained in 91% yield with 90% ee in 12 min residence time. The reduction of a few other substrates showed excellent yields and improved enantioselectivity in comparison to those of the batch process. A long operating time for the large-scale synthesis was also investigated. Finally, reduction of 3.1 g of 6-methoxy-1-tetralone to 3.0 g of the corresponding alcohol with 96% yield and 92% ee was demonstrated.

The organocatalytic asymmetric transfer hydrogenation of benzoxazines, quinolines, quinoxalines, and 3*H*-indoles in continuous-flow microreactors with inline FTIR analysis was recently presented.[70] Optimization of the reaction conditions was performed for transfer hydrogenation of benzoxazine in the presence of Hantzsch dihydropyridine as hydrogen source and a catalytic amount of a chiral Brønsted acid. The temperature was modified in the range between 5 and 60 °C, giving the optimal temperature of 60 °C. A rise in product yield from 50 to 98% was observed with an increase of the residence time from 20 to 60 min. Next, the scope of the Brønsted acid-catalyzed reduction of 3-aryl-substituted benzoxazines and quinolines was studied (Figure 27). In general, 3-aryl-benzoxazines were isolated in good yields (81–98%) and with excellent enantioselectivities (97–99%). The performance of the quinoline hydrogenation was found to be affected by the residence time and the amount of catalyst. The best yield (96%) and enantioselectivity (94%) was achieved in 60 min using 0.5 mol % of the catalyst. The batch reaction performed under the same conditions resulted in the same enantioselectivity but with a significantly lower yield (67%). Additionally, the optimized conditions were found for the reduction of quinoxalines and 3*H*-indoles resulting in the desired products with good to high yields and excellent enantioselectivities.

Syntheses of performic and peracetic acids from the corresponding carboxylic acids and hydrogen peroxide using sulfuric acid as a catalyst were performed in a microstructured reactor.[71] A microstructured reactor consisted of a Slit

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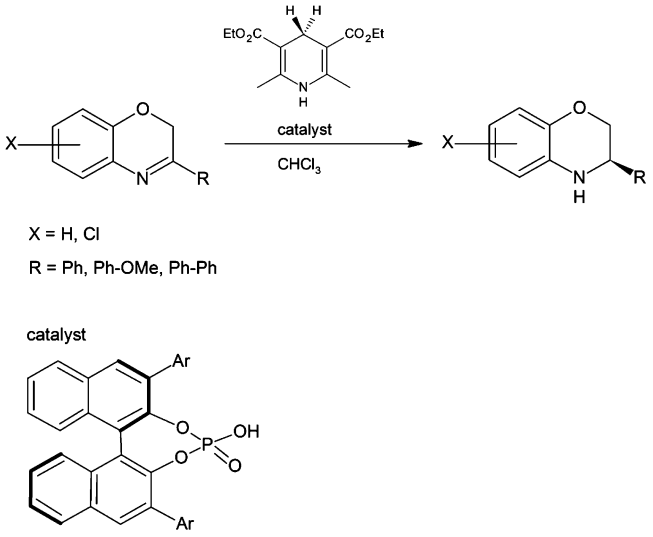

Figure 27. Brønsted acid-catalyzed reduction of benzoxazines. Adapted from ref 70.

Interdigital Micromixer with parallel sinusoidal channels (IMM) and PTFE tubing (I.D. 1.0 or 1.6 mm). The optimization of the reaction conditions (temperature and catalyst concentration) was done independently for peracetic and performic acids. Similar behavior was observed in both cases; however, performic acid was found to be more reactive with hydrogen peroxide than acetic acid. For peracetic acid the equilibrium was reached in 30 min at 50 °C and in 10 min at 70 °C, whereas for performic acid it was reached in 7 min at 30 °C and in 4 min at 40 °C. The concentration of sulfuric acid was more crucial for the formation of peracetic acid than for that of performic acid. In the latter case, the formation of the product was already observed without the catalyst, and increasing the catalyst concentration over 6 wt % had a minor effect on the reaction rate.

The kinetic study of the multiphase cyclohexanecarboxylic acid−oleum reaction (exothermal reaction, important step in the ε-caprolactam synthesis) in a microreactor was reported by Wang et al.[72] The main parts of the microreactor setup were a microsieve dispersion device (micromixer), which produces microdroplets, a reaction pipe (I.D. 1 mm) and temperature sensors. Three different solvents (hexane, heptane, and octane) were used, and the final temperature of each system did not exceed the boiling point of the solvent. It was measured that the temperature rose near the beginning of the reaction pipe but stabilized towards the end of the pipe, indicating the completion of the reaction. It was observed that full conversion could be reached in less than 1 s and the reaction rate increased with the increase of the flow rate. The average diameter of droplets was determined by the online CCD camera and found to be 60 μm and not affected by flow velocity. By means of a mathematical model it was found that the transport of cyclohexanecarboxylic acid from the oil phase to the sulfuric acid phase is the rate-determining step of the reaction. Due to perfect mixing and temperature control, the excellent selectivity of >97% was obtained in a microreactor near 90 °C, much higher than the selectivity achieved in a common batch reactor.

An efficient oxidation of alcohols, aldehydes, and nitroalkanes using permanganate as the oxidant within a continuous-flow reactor is reported by Sedelmeier et al.[73] The problem of continuous-flow reactors—inability to cope with reactions that lead to precipitates and thus to reactor clogging—was solved by ultrasonic treatment to disperse the manganese dioxide formed during the reaction. The screening of the solvents showed that oxidation reactions proceed more efficiently in water-miscible solvents such as methanol and ethanol, while hexane and dichloromethane which formed biphasic systems gave noticeably slower reactions. The amine bases such as Hünig's base, triethylamine, and 1,1,3,3-tetramethyl guanidine were found to be as efficient as inorganic bases such as KOH and K_2CO_3. After the optimization of the reaction conditions, it was observed that even substoichiometric quantities of the permanganate oxidant gave excellent conversions within short residence times of 5−8 min. The oxidation of both benzylic and aliphatic nitroalkanes proceeded smoothly. As a next step, the nitro derivative 1,2-dimethoxy-4-(nitromethyl)benzene was generated on a multigram scale (90% yield, 177 g) using the flow sequence shown in Figure 28. Furthermore, the methyl 4-nitrobutanoate was successfully oxidized into the corresponding aldehyde in 87% yield. In order to further expand the synthetic potential of the process, conditions for the direct conversion of nitroalkanes into the corresponding acids were determined. Optimal conversions were achieved by combining a solution of a primary nitroalkane and KOH in methanol as stream 1 with a

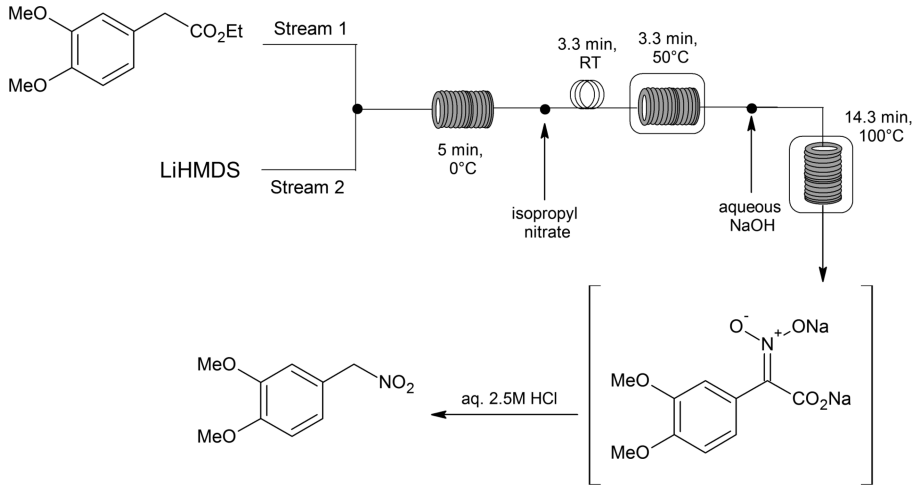

Figure 28. Reactor setup for the synthesis of 1,2-dimethoxy-4-(nitromethyl)benzene. Adapted from ref 73.

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buffered solution of $KMnO_4$ and Na_2HPO_4 in water as stream 2. In summary, an efficient process for the $KMnO_4$-mediated oxidation of alcohols, aldehydes, and nitroalkanes under flow conditions was developed. Additionally, the authors showed that MnO_2 slurries can be handled within a flow reactor by application of ultrasonication.

1.8. Polymerization. The properties of microreactors such as efficient heat transfer, mixing of the reagents, and lower residence time of the products at the elevated temperatures are advantageous for performing polymerizations.[74,75]

The use of a highly sterically hindered amine for the controlled nitroxide-mediated polymerization of styrene and butyl acrylate with alkoxyamine as an initiator in a flow microreactor was demonstrated.[74] The residence time and temperature were varied to study their effect on the conversion, number-average molecular mass, and polydispersity index (PDI) of the resulting polymer. After separate optimization of the reaction conditions for polymerization of styrene and butyl acrylate, the synthesis of a block copolymer of those two compounds was performed using two microflow reactors. Butyl acrylate was initially polymerized at 120 °C for 2 h, and the second polystyrene block was added by subsequent polymerization of styrene at 140 °C for 2 h. Under these conditions, a high conversion (76%) and small PDI (1.26) of poly(butyl acrylate)-*block*-poly(styrene) was achieved. Polymerization of methyl methacrylate with different initiators was also studied.

Highly oxygen-sensitive radical polymerizations with the reversible addition−fragmentation chain transfer (RAFT) approach using a laboratory-scale capillary flow reactor system was recently reported.[75] The limitations of the capillary microreactor geometry due to blockage, which can occur in case of highly viscous fluids, were also investigated. The flow experiments were performed in a commercially available tubular flow reactor (Vapourtec R2/R4 reactor heater) with two different coils: a perfluoroalkoxy polymer coil and a stainless steel coil (I.D. 1 mm, total volume 10 mL). Also the reaction was conducted in a batch microwave reactor for comparison. The reaction temperature was varied between 70 and 100 °C, and reaction times were chosen in the range of 30−120 min. A number of different monomers, initiators, and RAFT agents were used to achieve both high conversion and a relatively low viscous product solution. Since the RAFT polymerization is known to be very sensitive to traces of oxygen, the starting mixture was degassed, and subsequently its exposure to air during the reaction was carefully precluded. While the batch and the steel flow reactors perform almost identically, the perfluoroalkoxy polymer flow reactor showed no polymerization in the RAFT process. The reason is suggested to be the oxygen permeability of the polymer tubing. A series of different RAFT polymerizations were conducted in the stainless steel flow and batch reactors, using the following monomers: *N*-isopropylacrylamide, *N*,*N*-dimethyl acrylamide, *n*-butyl acrylate, and vinyl acetate and different initiators (ethyl acetate, acetonitrile, and 1,4-dioxane). Generally, conversions in flow were lower by less than 5%. Polymers with narrow molecular-weight distribution (PDI = 1.1−1.3) were obtained in both reactors; however, the PDI of polymers obtained in the flow reactor was generally higher by 0.02−0.08. These results show that RAFT polymerization is generally suitable for flow processing in stainless steel capillary microreactors.

Living anionic polymerization of alkyl methacrylates initiated by 1,1-diphenylhexyllithium performed in a flow microreactor system was described by the group of Yoshida.[76] First, the anionic polymerization of methyl methacrylate (MMA) by 1,1-diphenylhexyllithium was done in a conventional batch reactor at various temperatures (from −78 to 0 °C). Wide molecular-weight distribution (M_w/M_n = 1.32) of the polymers was observed even at −78 °C due to the insufficient temperature control in a glass reaction flask. Next, the anionic polymerization of MMA was carried out in a flow microreactor system at various temperatures (from −78 to +24 °C), with the inner diameters of the micromixer of 250−1000 μm, the flow rates of the initial solutions of 0.25−6 mL·min^{-1}, and the residence times of 0.7−23.6 s being used. The polymers were obtained in quantitative yield within a residence time of 11.8 s at 24, 0, −28, and −48 °C, with a narrow molecular-weight distribution (M_w/M_n down to 1.15). Efficient heat transfer and short residence time of the microreactor is supposed to be responsible for preventing decomposition of the reactive polymer chain end. Polymerization reactions of other alkyl methacrylates (*n*-butyl methacrylate and *tert*-butyl methacrylate) were also investigated using the microreactor system. The polymers with a narrow molecular-weight distribution were prepared even at temperatures higher than 0 °C.

Livingness of the reactive carbanionic polymer chain was confirmed by the following experiments. Solutions of alkyl methacrylate and 1,1-diphenylhexyllithium were introduced via the micromixer to the microreactor where polymerization occurred. Then, a solution of the same monomer was introduced to the second micromixer, which was connected to the second microtube reactor where the sequential polymerization took place, resulting in the increase of the number-average molecular weight (M_n) of the product. The authors specified that the sequential polymerization can be efficiently performed without significant decomposition of the living polymer end. On the basis of these results the authors verified this methodology for the synthesis of structurally defined block copolymers composed of two different monomers. The principle of the experiment was as follows: after polymerization of an alkyl methacrylate in the first microreactor, a solution of a different alkyl methacrylate was introduced to the second micromixer. A polymer of higher M_n with narrow molecular-weight distribution (M_w/M_n down to 1.13) was successfully synthesized.[76]

The controllable suspension polymerization of butyl acrylate (BA) performed in a coaxial capillary microreactor was demonstrated by Liu et al.[77] The main advantages of this method are that the reaction heat removal can be enhanced by accurate control of heat transfer, drop flow in the capillary can provide an identical reaction time in each droplet, and the reactor clogging is prevented via efficient separation of the droplets by an immiscible, continuous inert fluid. A coaxial capillary microreactor was manufactured on a 40 × 20 × 3 mm^3 PMMA plate. Two quartz capillaries with I.D.'s of 0.53 and 0.19 mm were inserted for introducing the continuous (SDS, PVA, water, Na_2SO_4) and dispersed (BA and AIBN) phases, respectively. All the experiments in the microreactor were performed in the droplet-flow regime (flow rate of the monomer 5−50 μL·min^{-1}). The polymerization was also carried out in batch mode for comparison. The synthesis in the microreactor was found to be more efficient than the one in a batch reactor in terms of reaction time and poly(butyl acrylate) properties. The conversion of ∼70% was achieved in 3.11 and 15 min in flow and batch mode, respectively. The PDI of the polymer obtained in the microreactor was much lower than that in batch (1.89 and 7.83, respectively), while M_n was

significantly larger (138.083 and 20.291, respectively). Moreover, the results obtained in a microreactor were found to be well reproducible. It was observed that in the batch reactor the size of the droplet was widely distributed and droplet agglomeration occurred. The size of the droplet was found to affect heat transfer efficiency, and small droplets were responsible for obtaining a narrower molecular weight distribution. This assumption was confirmed by CFD calculations of the temperature profile within a single droplet. Further optimization showed that the reaction time, temperature, and AIBN-to-BA ratio had relatively weak effects on the PDI, while M_n could be adjusted by changing the AIBN concentration and the reaction temperature.[77]

2. MULTISTEP SYNTHESES

Although microreactor technology in organic synthesis has been mostly applied to single-step reactions, recent research results on multistep reactions performed in flow were reported.[15,78,79]

Consecutive multistep organic synthesis in microflow is advantageous due to a better control over reaction parameters and fast optimization. Moreover, multistep reactions in flow enable an improved and more controlled addition of reagents without delays.[15] Automated microreactor-based continuous-flow systems have the potential to accelerate the production of small-molecule libraries which is of great importance for high-throughput chemical synthesis.[79]

Yoshida has reported several multistep organic syntheses in extreme conditions (low temperature) using organometallic compounds.[13,14,80−84] A microflow system was reported to allow the generation and transformation of *o*-, *m*-, and *p*-nitro-substituted aryllithium compounds in a controlled manner.[80] The microflow system consisted of two T-shaped micromixers (M1 and M2) and two microtube reactors (R1 and R2) (Figure 29). The synthesis was performed at various temperatures

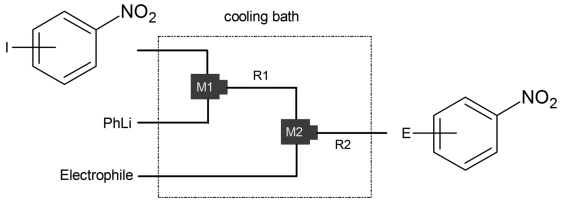

Figure 29. Microflow system for the I−Li exchange reaction followed by the reaction of the lithiated species with electrophiles. Adapted from ref 80.

(from −80 to 0 °C) and residence times (0.01−3.2s). The products were formed in high yields (up to 92%). Moreover, it was shown that the microflow method is very effective for the selective use of either the kinetically or the thermodynamically preferred organolithium reagent, whereby the desired reactivity can be selected by precisely controlling the residence time.

Another example[81] showed that homocoupling of two aryl halides can be successfully performed in microflow mode in under a minute. The integration of the halogen−lithium exchange reaction with the $FeCl_3$-promoted homocoupling was studied (Figure 30). Integrated flow microreactor systems consisted of three micromixers and three microtube reactors. A solution of *p*-bromoanisole in THF and a solution of *n*-butyllithium in hexane were introduced to mixer 1 by syringe pumps. The resulting mixture was passed through reactor 1 and was then mixed with a solution of $FeCl_3$ in mixer 2. After passing through reactor 2, where the coupling reaction occurred, the reaction mixture was mixed with methanol via mixer 3 to quench the reaction in the reactor 3. The yield (up to 76%) was found to depend on both temperature and residence time. The productivity of the present system was shown to be acceptable for large-scale laboratory synthesis (6.2 $g \cdot h^{-1}$). It is worth noting that the integrated reactions were complete within the overall residence time of 14.7 s, even at low temperatures such as −48 °C. Thus, it was suggested that the reaction could also be applied to less stable aryllithium compounds.

It was demonstrated[82] that the Murahashi coupling can be much faster than the competing reaction with alkyl halides if an appropriate catalyst is used, and that the space integration of Br−Li exchange and Murahashi coupling using an integrated flow microreactor system enables the cross-coupling of two different aryl bromides (Ar^1Br and Ar^2Br). It was found that the use of a palladium catalyst bearing a carbene ligand led to faster cross-coupling relative to the occurrence of the side reactions, and the yield of desired product **9** increased significantly at the expense of the undesired byproducts **10** and **11** (Figure 31).

A further example of a Br−Li exchange reaction performed in a flow microreactor at higher temperatures (−78 °C) than usually used in batch (−100 °C) was described in ref 84. The lithiation of *o*-dibromobenzene was chosen as a model reaction, as this molecule can easily form benzyne with concomittent loss of selectivity upon lithiation. Initially, the conditions of the Br−Li exchange reaction were optimized using the microsystem involving two T-shaped micromixers and two microreactors. The reactions were carried out with various residence times and temperatures. The yield was found to be very low at temperatures higher than −60 °C. At lower temperatures the yield increased because of slower benzyne formation, but further decrease of the temperature resulted in the decrease of the yield, since the Br−Li exchange reaction was incomplete . Using the optimized conditions, the sequential introduction of two groups on the benzene ring was successfully achieved with various electrophiles using the microsystem consisting of four micromixers and four microtube reactors. The reaction temperature for the first and second microtube reactors was −78 °C, whereas that for the third and fourth reactors was 0 °C, because the second aryllithium intermediate is much more stable than *o*-bromophenyllithium.

Asymmetric carbolithiation is an attractive reaction in organic synthesis, because carbon−carbon bond formation leads to the formation of chiral organolithium intermediates, which can be used for further transformations. However, organolithium intermediates are configurationally very unstable. A method for asymmetric synthesis based on suppressing the epimerization of a configurationally unstable chiral organolithium

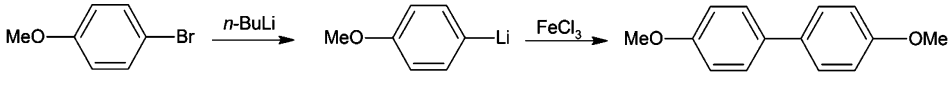

Figure 30. Halogen−lithium exchange of *p*-bromoanisole followed by oxidative homocoupling with $FeCl_3$. Adapted from ref 81.

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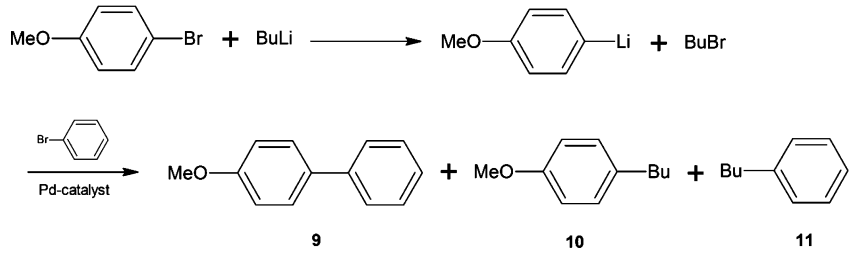

Figure 31. Br−Li exchange and Murahashi coupling. Adapted from ref 82.

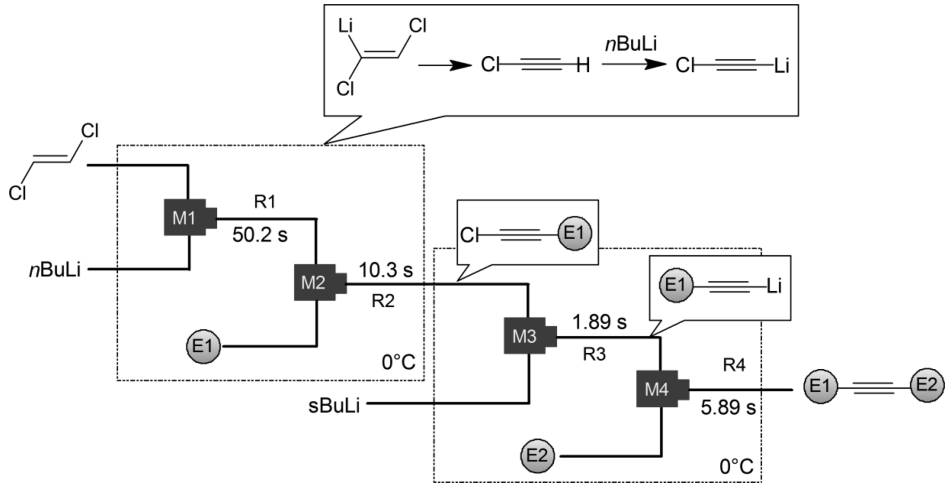

Figure 32. Integrated flow microreactor system for the synthesis of asymmetric disubstituted alkynes. Adapted from ref 85.

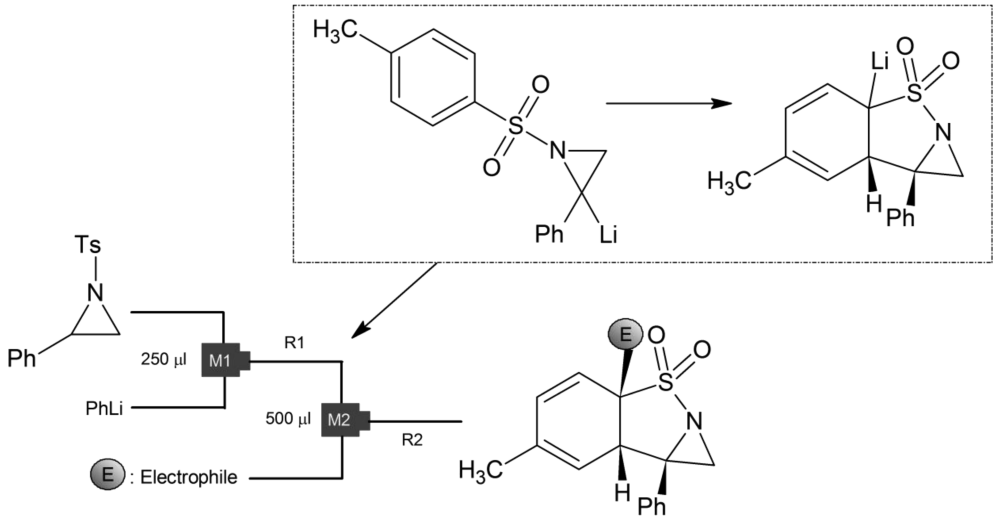

Figure 33. Flow microreactor system for the deprotonation of 2-phenyl-*N*-tosylaziridine with PhLi followed by reaction with electrophile. Adapted from ref 13.

intermediate based on precise control of the residence time in a flow microreactor system was described.[83] Enantioenriched allenes were synthesized with up to 90% yields from the asymmetric carbolithiation of conjugate enynes.

Sequential reactions (synthesis of asymmetric disubstituted alkynes via different routes) were performed in an integrated flow microreactor system that consists of four micromixers (M1, M2, M3, and M4) and four microtube reactors (R1, R2, R3, and R4), as shown in Figure 32.[85]

Synthesis of disubstituted pyridines in a microreactor system was reported.[14] It was shown that generation of pyridyllithium species followed by reactions with electrophiles can be effectively performed using a flow microreactor at much higher temperatures than those required for batch reactors. Both the Br/Li exchange reaction of 2,3-dibromopyridine with butyllithium and the reaction with iodomethane were optimized. The reaction was carried out in both a flow microreactor and batch macroreactor. High yields of 2-bromo-3-methylpyridine were obtained even at 0 °C in a flow microreactor (in a batch reactor the product was not observed at temperatures above −28 °C) by choosing an optimal residence time, demonstrating that the use of the flow microreactor enabled the reaction to

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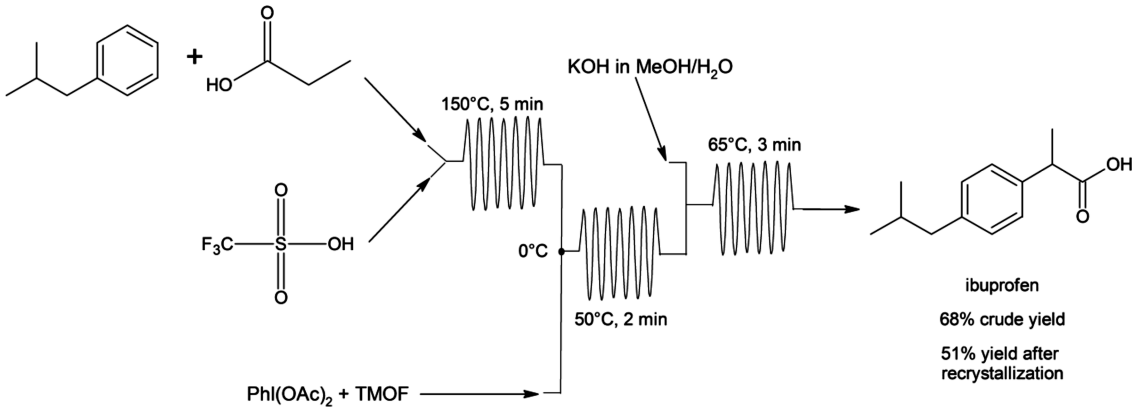

Figure 34. The three-step, continuous-flow synthesis of ibuprofen. Adapted from ref 78.

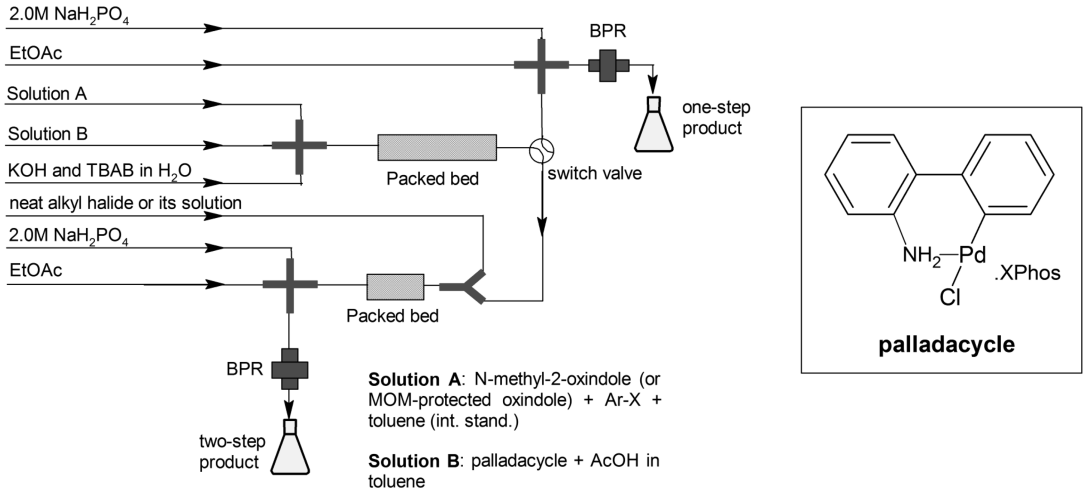

Figure 35. Flow setup for the α-arylation/alkylation sequence (left) and the structure of palladacycle (right). Adapted from ref 86.

proceed without cryogenic conditions. In the next step, the introduction of two electrophiles using dibromopyridines as starting materials was examined. The reaction of 2,3-(or 2,5- or 2,6-)dibromopyridine was examined using a flow microreactor system composed of four T-shaped micromixers and four microtube reactors. the sequential introductions of two electrophiles were achieved with various combinations of electrophiles, to obtain disubstituted pyridines with yields up to 75%.

An efficient synthesis of tricyclic sulfonamides in a flow microreactor was developed and described.[13] The method is based on the deprotonation of *N*-tosylaziridines with subsequent intramolecular nucleophilic addition of the resulting aziridinyllithium intermediate on the aromatic ring (attached to a nitrogen atom) followed by the introduction of various electrophiles (Figure 33). The reactions were performed without using cryogenic conditions, whereas batch syntheses require much lower temperatures such as −78 °C.

A three-step, continuous-flow synthesis of ibuprofen (a high-volume, nonsteroidal anti-inflammatory drug) in a flow microreactor was reported by McQuade et al. (Figure 34). This procedure eliminates the need for purification and isolation of intermediates The developed synthesis generates approximately 9 mg·min^{-1} crude ibuprofen. Potential scale-up of this method would also have an advantage from the precise temperature control (from 150 to 50 °C in sequential steps) and the excellent control of exotherms (caused by transitioning from pH 1 to 14).[78]

The palladium-catalyzed α-arylation/alkylation of various substrates—an important reaction for the synthesis of natural products and APIs—was successfully performed in continuous mode using a microflow setup (Figure 35). All of the previous conditions reported for this process required high catalyst loadings and/or long reaction times. Moreover, these conditions unavoidably result in heterogeneous mixtures. With optimized conditions, the scope and limitations of the two-step flow system using various oxindoles, aryl halides, and alkylating reagents was explored. Generally, for the α-arylation reaction, both aryl chlorides and bromides were excellent coupling partners. With only 1 mol % of palladacycle (Figure 35) as the precatalyst, several halides could be coupled with *N*-alkyl oxindoles at 100 °C in excellent yields (up to 95%) in less than 4 min.[86]

Continuous in situ generation of phosgene and further formation of acid chloride in a microflow system was demonstrated by Fuse et al.[87] Phosgene is known to be a very useful gas in organic synthesis, although it is highly toxic. In situ preparation of phosgene from less toxic solid triphosgene is relatively safe. The acid chloride formation/amidation sequence was chosen to demonstrate continuous in situ generation and reaction of phosgene. The acid chloride was subsequently coupled with an amine in high yield without severe epimerization (Figure 36), giving the amides with higher

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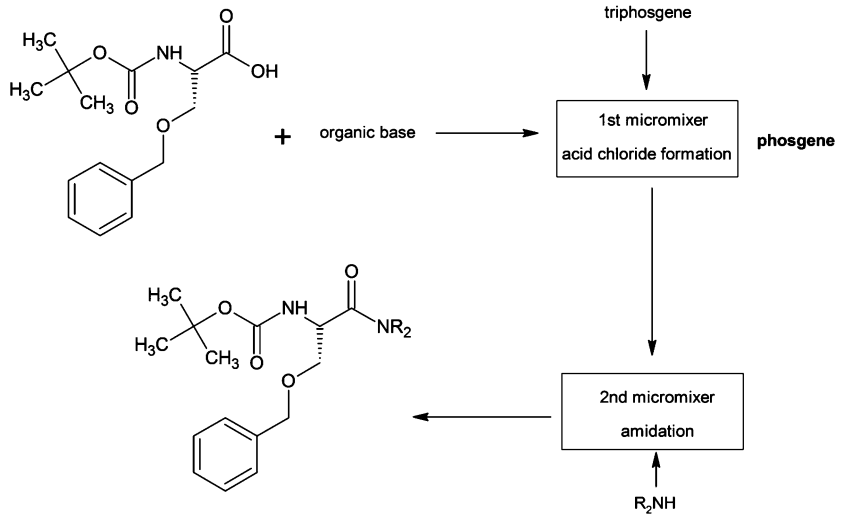

Figure 36. Continuous-flow synthesis of amide from carboxylic acid via in situ generated acid chloride. Adapted from ref 87.

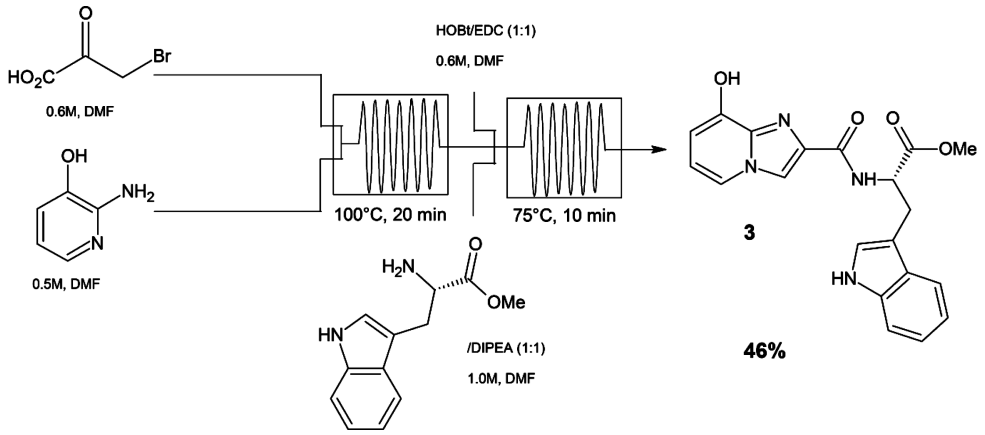

Figure 37. Continuous-flow synthesis of Mur ligase inhibitor. Adapted from ref 79.

yields in flow (up to 98%) in comparison with batch (up to 83%) mode.

The first continuous-flow synthesis of imidazo[1,2-*a*]-pyridine-2-carboxylic acids directly from 2-aminopyridines and bromopyruvic acid was reported by Herath et al.[79] The process was applied to the multistep synthesis of imidazo[1,2-*a*]pyridine-2-carboxamides (Figure 37), using a multistep continuous-flow system without isolation of intermediates. The Mur ligase inhibitor (potential antibacterial active compound) was reported to be synthesized in a flow process with 46% yield, that is much higher than the overall yield of the batch two-step synthesis (16%).

A simple continuous-flow system has been developed for the continuous DIBALH reduction of esters.[88] Benefits of the microflow process (precise temperature control, high reproducibility, etc.) allow the challenges of a batch process such as unwanted overreduction, low reproducibility, difficult temperature control, and lack of scalability to be overcome. The continuous system consisted of three precooling loops (P1, P2, and P3), two reactors (R1 and R2), each constructed from standard PFA tubing and two T-shaped mixers (M1 and M2) (Figure 38).The reaction parameters have been successfully optimized and applied to yield a selective and reproducible synthesis of aldehydes from esters. It was shown that, even at

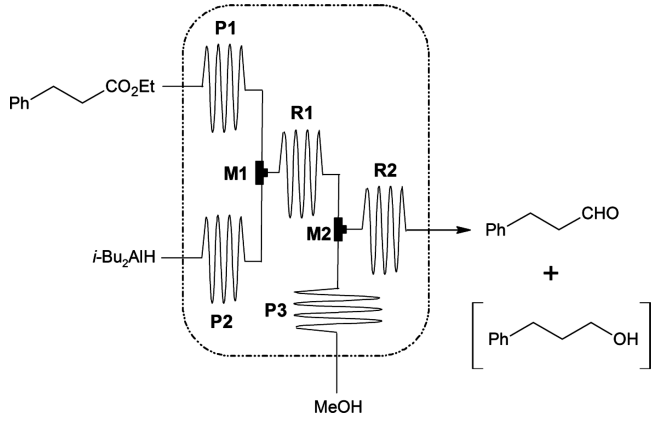

Figure 38. Continuous DIBALH reduction of ethyl hydrocinnamate using a continuous-flow system at −78 °C. Adapted from ref 88.

very short residence times (<50 ms), essentially full conversion and complete selectivity were achieved.

Investigation of multistep microflow syntheses consisting of a combination of a ruthenium-catalyzed ring-closing metathesis followed by a Heck coupling reaction was reported by Ahmed-Omer et al.[15] The transformations of a number of substrates were described. For example, metathesis of *N*,*N*-diallyl-2-iodoaniline was performed with excellent yield (98%) followed

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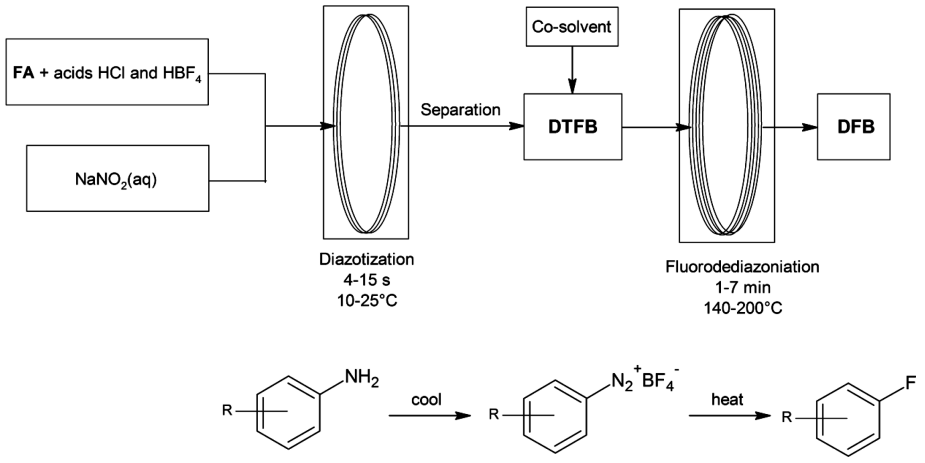

Figure 39. Synthesis of *o*-difluorobenzene. Adapted from ref 89.

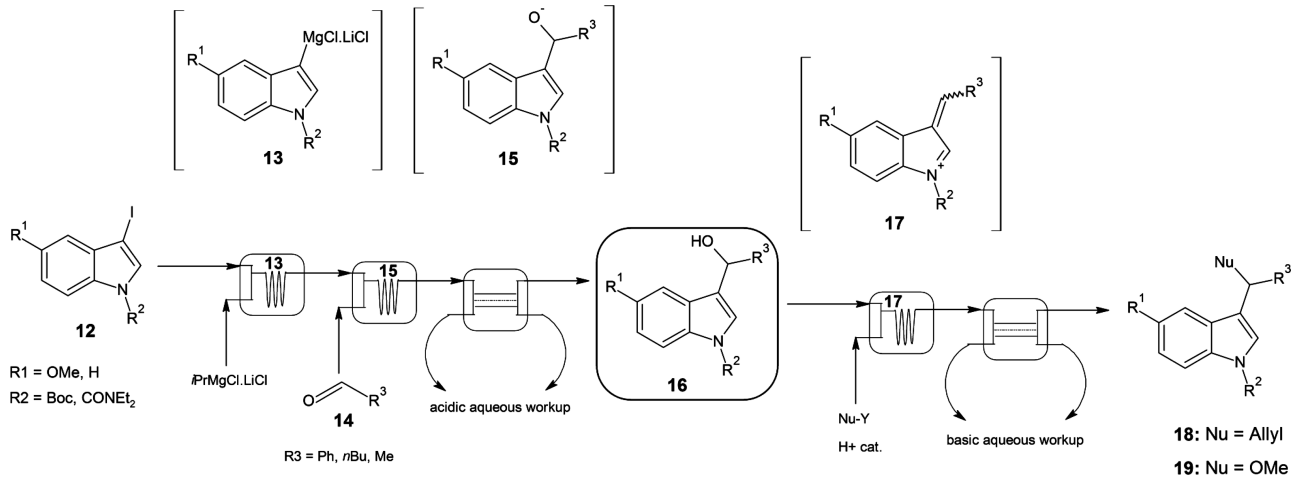

Figure 40. Multistep continuous-flow synthesis of 3-hydroxymethylindoles and their nucleophilic substitution reaction. Adapted from ref 90.

by a Heck reaction using methyl acrylate (yield 38−64%). Another synthesis was carried out using the metathesis precursor *N*,*N*′-diallylaniline and a Grubbs II catalyst, resulting in the intermediate 1-phenyl-2,5-dihydro-1*H*-pyrrole in 96% yield after optimization. The resulting compound was then reacted with iodobenzene to give the final product in 53−60% yield. Generally it was shown that ring-closing metathesis was successfully performed; however, the Heck reactions were not so efficient in multistep procedures in comparison with single-step coupling.

The multikilogram-scale process for the Balz−Schiemann synthesis of *o*-difluorobenzene (DFB) including the generation of diazonium tetrafluoroborate (DTFB) from *o*-fluoroaniline using two continuous-flow reactors was described[89] (Figure 39). The continuous-flow diazotization setup consists of two peristaltic pumps, T-joint connected to a reacting tube (Hastelloy, 6 mm I.D.) immersed in a thermostat-controlled oil bath. After the optimization of the mole ratio of acids, the residence time, and the temperature, 80% isolated yield of dry DTFB was achieved in 10 s. The continuous fluorodediazoniation resulted in a maximum DFB yield of 97%. The authors noted that the process is readily adapted for the preparation of similar compounds and can be easily scaled-up by increasing the reactor size or operating several reactors in parallel.

An automated flow synthesis and reactions of 3-hydroxymethylindoles in microreactors were described[90] (Figure 40). In the first step, the optimal metalation conditions for the starting 3-iodoindoles was determined. A solution of indole **12** in THF was treated with *i*PrMgCl·LiCl at 0 °C at different residence times in the first microreactor. The resulting flow was mixed with a solution of deuterated methanol in a second reactor. The conversion of 72% to the deuterated product was achieved in 1 min residence time and improved to >95% by increasing the residence time to 10 min. Further extension of the reaction time had no influence on the conversion. Next, the reaction of indole Grignard reagent **13** with aldehydes was performed at 0 °C and a residence time of 7 min. The outlet flow was consequently sent to a continuous extraction module into which an aqueous solution of NH_4Cl was added. Reactions of all combinations of four iodoindoles and three aldehydes were successfully carried out, resulting in products **16** with good isolated yields (40−66%). Further, complete allylation of substrates **16** was achieved within 8 min at 30 °C in the presence of 20 mol % of *p*-TSA in acetonitrile. To obtain the final products **18**, the reaction flow was mixed with an aqueous Na_2CO_3 solution with following extraction with 1,2-dichloroethane to obtain products **18** with 43−71% yield. The reactivity of indoles **16** was further tested in *p*-TSA-catalyzed generation of methoxy ether derivatives **19**. The reaction was performed at 30 °C for 20 min to give the products **19** in excellent yields (90−98%).[90]

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The two-step synthesis of imidazole-based carbohydrate derivatives in a split-and-recombine microreactor (SAR-microreactor) which combined mixing mechanisms of both diffusion and chaotic advection was demonstrated by Chen et al.[91] The microreactor (total volume 0.165 μL) was shaped as a 3D SAR-microstructure with the following dimensions of each of the 20 periodic units: width 50−300 μm, height 50−100 μm, length 600 μm (Figure 41). A solution of aldose (D-glucose, D-maltose,

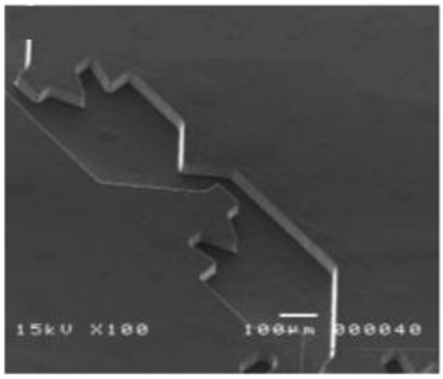

Figure 41. Geometric design of a periodic unit of SAR-microreactor (SEM image). Adapted from ref 91.

or D-maltotriose) and a solution of 2,3-naphthalenediamine in AcOH were introduced into the first microreactor to obtain an intermediate Schiff base; then the product passed into the second microreactor where it was oxidized by the solution of iodine in AcOH. The final reaction mixture was quenched by sodium thiosulfate. The reactions were conducted at RT with 0.1−10 s residence time. The products were obtained with ∼90% yields within 10 s reaction time. This was much more efficient compared to the batch process which resulted in 70% yield in 6 h. Thereafter, the authors compared the reaction yields in microreactors of T- and SAR-types using the same conditions. The T-microreactor showed significantly worse results than the SAR +microreactor. For example, the reaction of D-glucose for 1 s resulted in 70% yield in the SAR-microreactor and only in 30% yield in the T-microreactor. This was explained by the residence time being too short to achieve sufficient diffusion along its length for the efficient mixing, thus confirming the importance of the SAR-microreactor design.[91]

It is well-known that Grignard reagents are extremely important for C−C bond-formation reactions. Although a large number of Grignard reagents are commercially available, sometimes the synthesis of more functionalized reagents is necessary. The synthesis of arylmagnesium reagents and their subsequent coupling with carbonyl compounds under continuous-flow conditions with inline IR-monitoring was demonstrated by Ley et al.[92] Solutions of *i*PrMgCl·LiCl in THF and *m*-iodotoluene in THF were mixed in the T-piece, and then the mixture was delivered to the first 10-mL tubular coil reactor at RT (Figure 42). The third stream containing the carbonyl compound in THF was mixed with the main stream via the second T-piece. IR inline monitoring was found to be an efficient tool to control the formation of organomagnesium reagent. Further reaction of the Grignard reagent with ketones and aldehydes was carried out in the second microreactor at RT. All desired products of the reaction of the Grignard reagent with ketones and aldehydes were isolated in 65−95% yield in a 45 min residence time. It is noteworthy that the reactions of the Grignard reagents with carbonyl compounds in a microreactor were mostly more efficient in comparison to those in batch processes. The experiments with less reactive electron-rich aromatic bromides were performed using the same setup, only the volumes of the first and second microreactor were 20 and 5 mL, respectively. Only *p*-tolualdehyde was used as an electrophile. The exchange reactions of 3,4-dichlorobromobenzene and 2-chlorobromobenzene were very efficient, giving yields comparable to that of aryl iodides (80−88%). Moreover, the procedure was adapted to 3-bromopyridine, resulting in pyridin-3-yl(*p*-tolyl)methanol in 81% yield.

3. HETEROGENEOUSLY CATALYZED LIQUID-PHASE REACTIONS IN MICROREACTORS

Heterogeneously catalyzed syntheses of fine chemicals using continuous-flow microreactors offer several key advantages in comparison to reactions carried out in batch reactors.[93,94]

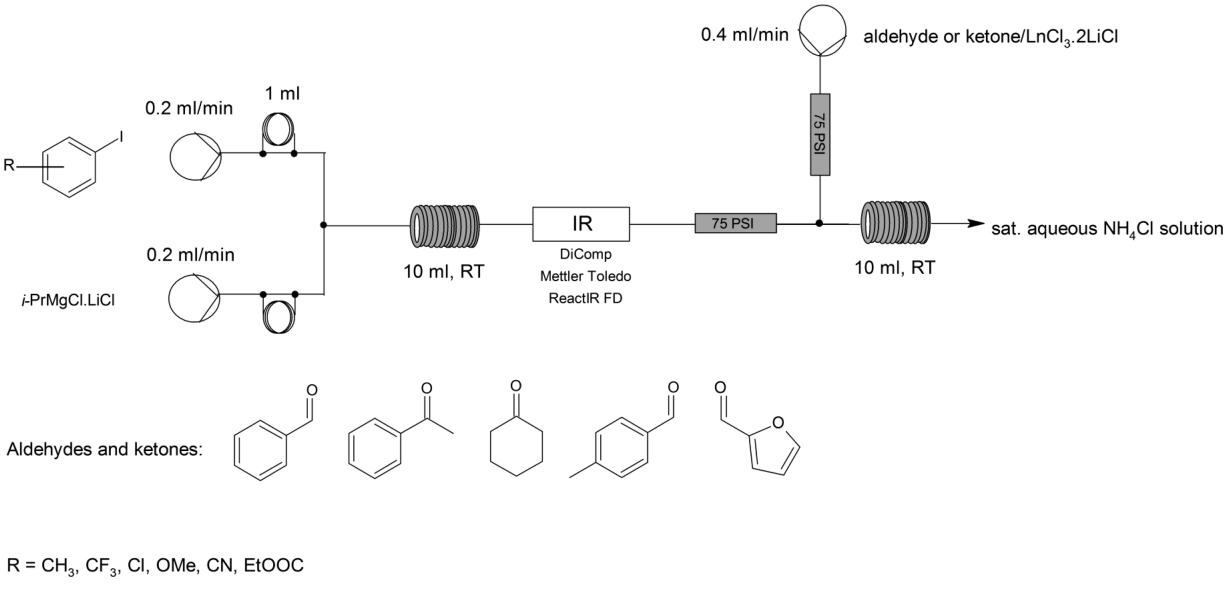

Figure 42. Schematic of flow setup for the LiCl-mediated I/Mg exchange reaction. Adapted from ref 92.

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Various methods of introduction of heterogeneous catalyst into the microreactor were reported. They include packing the channels with catalysts, coating the channels walls, using catalytically active monoliths, etc.

3.1. Microreactors with Catalytic Coating. The performance of a zeolite capillary reactor in the Knoevenagel condensation reaction between benzaldehyde and ethyl cyanoacetate to ethyl-2-cyano-3 phenyl acrylate was described.[94] The zeolite film was deposited on the walls of the quartz capillary (I.D. 0.5 mm) by a hydrothermal flow synthesis method after channel surface modification and seeding. The catalyst-coating thickness, solvent, components ratio, and residence time were optimized. High (near 100%) and stable reaction conversion was achieved using ionic liquids which could be recovered and reused further.

Aromatic diisocyanates which are used for the synthesis of aromatic polyurethanes are usually obtained by the reaction of aromatic diamines with phosgene, which is a highly toxic compound. One of the alternatives to phosgene is dimethyl carbonate that by reaction with aromatic amines will give aromatic *O*-methyl carbamates and then aromatic diisocyanates. However, an active and selective catalyst is necessary for this process. In the publication by García et al.[95] a catalytic study of nanoparticulated CeO_2 and Au/CeO_2 for selective carbamoylation of aniline by dimethyl carbonate using a microreactor was reported (Figure 43). The reactor consists of a stainless steel

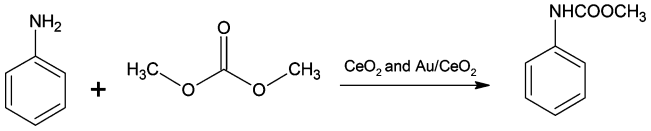

Figure 43. Carbamoylation of aniline by dimethyl carbonate. Adapted from ref 95.

plate (5 × 10 cm^2) having parallels channels (width 10 μm). The catalyst was coated on the reaction plate with an excellent adherence. Au/CeO_2 catalyst exhibits better results than CeO_2, giving a 35% average conversion without decay in the catalytic activity and 100% selectivity to the desired *N*-phenyl-*O*-methylcarbamate.

A microreactor setup containing a gold-coated microcapillary for oxidation of benzyl alcohol in the presence of H_2O_2 was described in ref 96. Gold nanoparticles with different diameters were synthesized according to three different procedures. After the activation of the walls of fused silica capillaries (I.D. 200 μm), the functionalization with linkers (APTES or MPTES) was carried out, and then gold nanoparticles were anchored. The microcapillaries were tested in a selective oxidation of benzyl alcohol by hydrogen peroxide at 80 °C. The microreactors doped with small (2−3 nm) gold particles showed high yields of benzoic acid (>90%). The catalyst with larger particle size (15 nm) showed lower activity. Stability tests showed that the activity of the gold particles anchored with APTES linker significantly decreased with an increase in the time on-stream from 30 to 120 min. The microreactors based on MPTES linker were found to be more stable, giving >90% yield of benzoic acid even after 2 h on-stream due to the stronger bonding of the linker to the gold nanoparticles. The batch reaction was conducted in the glass reactor with gold nanoparticles for comparison and resulted in no conversion of benzyl alcohol. This difference with the microreactor is explained by the presence of a SiO_2 support which can significantly reduce H_2O_2-competitive dismutation reactions.

3.2. Packed-Bed Microreactors. *3.2.1. Functionalized Supports.* Important benefits of heterogeneous organocatalysis combined with microreactor technology such as the absence of metal leaching, the enhanced resistance of supports to mechanical degradation, and potential long-term usage are mentioned by Bortolini et al.[97] The authors tested the catalytic activity of silica-supported 5-(pyrrolidin-2-yl)tetrazole catalyst in the continuous-flow aldol reaction of cyclohexanone with *p*-nitrobenzaldehyde. A stainless steel column (50 mm length, 2.1 mm I.D.) was filled with tetrazole-functionalized silica. An initial continuous-flow experiment was performed by using a 3-fold excess of cyclohexanone. After optimization, the applicability of the method was shortly investigated by performing the reactions between cyclohexanone with various aromatic aldehydes. The corresponding mixtures of aldol adducts were produced at 50 °C with high conversion efficiency (≥95%) and reasonable enantioselectivity. It is noteworthy that, during the whole optimization procedure (around 80 h), no deactivation of the packing silica was detected. A loss of catalytic activity was observed only after 120 h, and full deactivation occurred after 7 days on-stream.

The efficiency and stability of silica-supported proline and proline-like organocatalysts in slow aldol condensation of cyclohexanone with *p*-nitrobenzaldehyde and the fast α-amination of isovaleraldehyde with dibenzyl azodicarboxylate is reported by the same group.[98] Preparation of proline-functionalized silicas by a covalent immobilization strategy was done under batch conditions. Activity and stability of covalently and noncovalently anchored **organocatalysts 1** and **2** (Figure 44) were first tested in an aldol condensation reaction in a

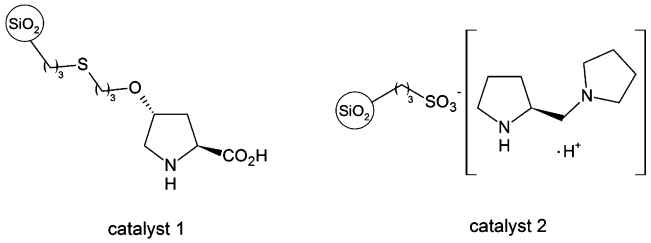

Figure 44. Covalently proline-functionalized silica (**1**) and noncovalently supported chiral amine catalyst (**2**). Adapted from ref 98.

batch reactor at RT for 24 h with 10 mol % of catalyst. **Catalyst 1** was found to be active in toluene as a solvent giving 67% yield and 78% ee_{anti} stereoselectivity of the product, which is comparable with the results reported before for the homogeneous proline catalyst. The catalyst also showed high stability by giving the same yield and stereoselectivity after recycling. **Catalyst 2** was also stable and showed a higher activity (>95% yield), but a lower stereoselectivity (55% ee_{anti}). Continuous-flow experiments were carried out in two reactors (R1 and R2) prepared by filling stainless steel columns (I.D. 2.1 mm) with **catalysts 1** and **2**, respectively. After optimization of the reaction conditions (flow rate, aldehyde concentration, and temperature) in R1, the ee_{anti} stereoselectivity of 78% and conversion of 82% was achieved. Moreover, no deactivation of the catalyst for 24 h was observed. In contrast, **catalyst 2** of R2 deactivated under flow conditions within 2 h. Next, the fast α-amination of isovaleraldehyde with dibenzyl azodicarboxylate reaction was tested in R1. Complete conversion was achieved at

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25 °C with a productivity of the flow process of 10.8 $mmol_{product}·h^{-1}·mol_{catalyst}^{-1}$ which is approximately 3 times higher than in the batch process.

The synthesis of performic acid in a packed-bed microstructured reactor was described by Ebrahimi et al.[99] The cation-exchange resins (Dowex 50Wx8 and Dowex 50Wx2) having sulfonic acid as a functional group were used as catalysts. Initially, the activity and stability of the cation-exchange resin catalysts as well as of sulfuric acid in the reaction between formic acid and H_2O_2 were tested in a batch reactor. The activity of Dowex 50Wx8 was found to be close to that of sulfuric acid and higher than that of Dowex 50Wx2. A slight decrease of the activity of the Dowex 50Wx8 was observed after its reuse for five times, while the activity of Dowex 50Wx2 remained unchanged after three runs. However, the Dowex 50Wx2 catalyst particles were completely deformed after three experiments. The increase of the temperature and catalyst loading led to an increase of the activity of both catalysts. Then the performic acid was synthesized continuously in a microreactor (I.D. 1.6 mm) packed with Dowex 50Wx8 catalyst. The experiment with the homogeneous catalyst (sulfuric acid) was performed for comparison. As well as in the batch reactor, the increase of the temperature and catalyst loading in the microreactor resulted in an enhanced activity. No effect of the catalyst particle size was observed, indicating the absence of internal diffusion limitations. In spite of the better activity of sulfuric acid, the heterogeneous cation-exchange resin catalyst is more advantageous because of the easy separation of the catalyst from the reaction mixture and the absence of corrosion.

3.2.2. Supported Metal Catalysts. Pd-catalyzed Sonogashira coupling—the most practical method for synthesizing aryl- and vinyl-acetylenes—was tested in a flow reactor.[100] The authors underlined several advantages of continuous-flow technology for this process, e.g. that the reaction parameters can be modified in wider ranges (up to 350 °C and 200 bar), reaction rates are increased due to enhanced heat/mass transfer, and high reproducibility and faster screening of reaction parameters can be achieved. Immobilized catalysts in a fixed-bed flow CatCart (catalyst cartridges) system were tested in a number of coupling reactions (Figure 45). The main advantage of a CatCart system is that the filtration of the catalyst from the reaction mixture is omitted because the catalyst is retained in the CatCart filter. Three commercially available polymer-bound catalysts and 10% Pd/C were tested. As can be seen from Figure 45, high conversions and selectivities towards the desired products were achieved, and the choice of the best catalyst strongly depends on the starting compounds. A Pd/C catalyst showed no activity in the coupling reaction with 4-bromo-anisole and a low conversion to the more reactive 4-iodo-anisole (53%). Noteworthy is that the complete screening (24-reaction matrix) required only 8 h. This study demonstrated that catalyst screening using flow devices can be performed in a fast and efficient way.

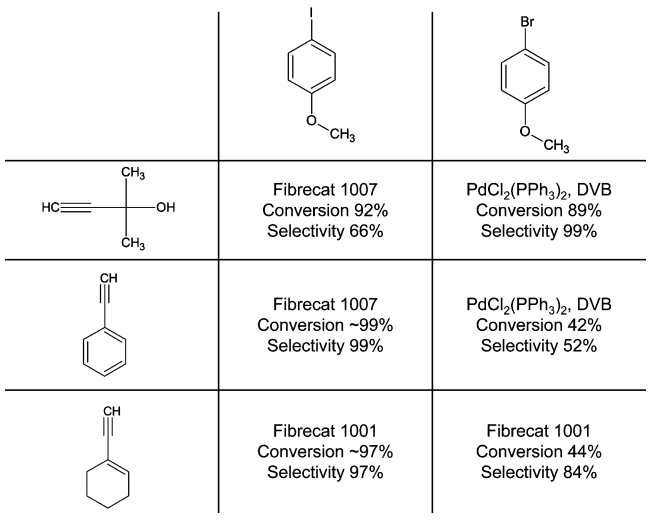

Figure 45. Summary of the best-performing catalysts for different coupling reactions. Adapted from ref 100.

The possibility of employing suspension catalysis in microchannel liquid–liquid slug flow for catalytic transfer hydrogenation of *m*-nitrotoluene to *m*-toluidine was investigated by Ufer et al.[101] The reaction of a 11 M aqueous potassium formate solution and nitrotoluene dissolved in toluene was performed in a PTFE microcapillary (I.D. 1.6 mm) at 70 °C with a Pd/C catalyst. The flow results were compared to those of conversion in a batch reactor. It was observed that the conversion in the batch reactor was higher than in the microcapillary at longer residence time due to the higher energy input giving near perfect mixing and the very high interfacial surface areas. However, at high flow rates, despite the much lower energy input, the intensified internal circulation in the capillary slug flow resulted in conversion similar to that of the batch reactor. The conversion was further improved with the increase of the catalyst loading.

3.3. Monolith Microreactors. Macroporous monoliths are characterized by a higher surface-to-volume ratio and a very efficient mixing of fluids or reactants and can be used as a multichannel microreactor. The preparation and evaluation of the performance of the novel type of Al-MonoSil monolith catalyst in a Diels–Alder cycloaddition between crotonaldehyde and cyclopentadiene was reported.[93] Al-MonoSil monoliths with an I.D. of 6 mm and different lengths placed in the flow setup showed the constant conversion of 80% after initial stabilization. It was reported that an Al-MonoSil monolith can be successfully used as a continuous-flow reactor for the Diels–Alder reaction with controlled productivities giving 13 kg of adduct per week and per liter of monolith.

3.4. Membrane Microreactors. A microreactor system based on a carbon nanofiber membrane for hydrogenation and electroreduction reactions was described by Watkins et al.[102] The carbon membrane microreactor was represented by a glass tube (I.D. 3.5 mm) in which a carbon membrane disc was placed. Initially, the voltammetry experiments on an electroreduction reaction of benzaldehyde derivatives were performed under triple-phase boundary conditions (Figure 46a). Two products (benzhydrol and meso-pinacol) were observed at 100% conversion of the starting material. The ratio of the compounds could be modified by changing the benzaldehyde concentration. The reduction of various aromatic aldehydes was conducted at different reduction potentials, resulting in negligible (*p*-methoxybenzaldehyde) to full (*p*-trifluoromethyl-benzaldehyde) conversions depending on the functional group of the aldehyde. Further, electroreductions of two *p*-trifluoromethyl-benzalimines (Figure 46b) were carried out. The amine was formed with 100% selectivity from benzylimine; however, only 50% conversion was achieved in 4 h. In the case of the reduction of the isopropylimine derivative, complete conversion was observed within 4 h with formation of two

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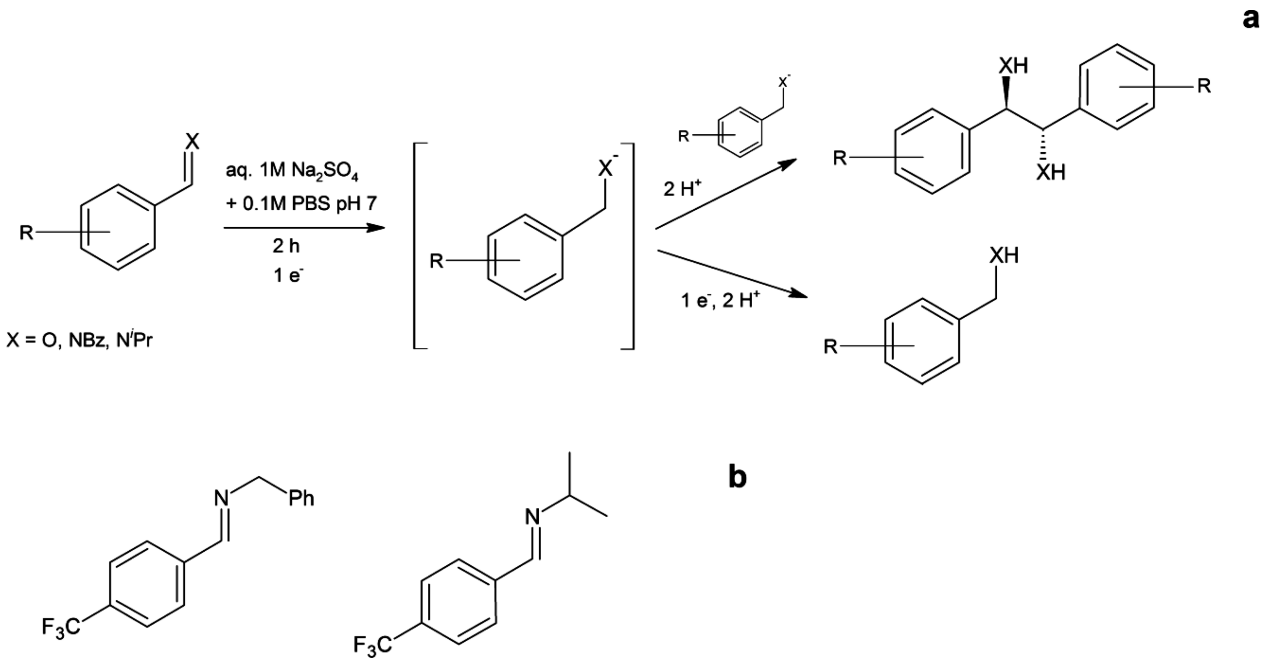

Figure 46. (a) Reduction of substituted benzaldehydes in a liquid−liquid carbon membrane microreactor; (b) *p*-trifluoromethyl-benzalimines. Adapted from ref 102.

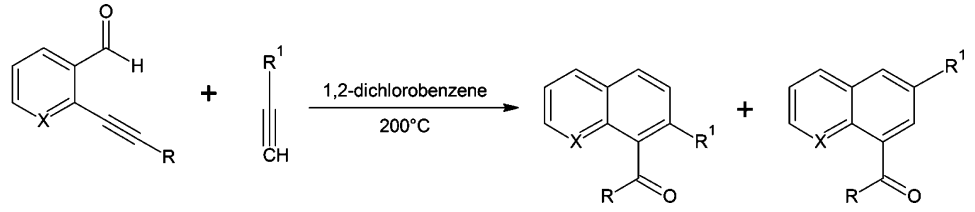

Figure 47. Benzannulation reactions in metal-coated microcapillaries. Adapted from ref 103.

products in a 1:1 ratio. It was also found that the pH of the aqueous phase is less important than the mobility of protons through the organic phase.

4. MICROWAVE-ASSISTED REACTIONS

Microwave-assisted organic synthesis has a significant impact on organic and medicinal chemistry by considerably shortening reaction times, producing cleaner product mixtures, and making high-energy transformations routine. Within the past few years, microwave technology has also been applied to reactions performed in a flow regime.[103,104]

Although it was demonstrated that microwave chemistry has the advantage of reducing reaction times and even improving product yields when reactions are run on a small scale, scale-up of these methodologies can be challenging.[104,105]

Microwave-assisted continuous-flow benzannulations of aryl-, alkyl-, and silylalkynes with alkynylbenzaldehydes with yields up to 80% were reported[103] (Figure 47). The reactions were conducted in glass capillaries internally lined with thin metal films of gold, copper, silver, and gold-on-silver. The reactions showed wide functional group tolerance and good to excellent regioselectivity in the cycloaddition. The authors are further evaluating new materials to replace the glass tube with the plan of making the process more sustainable.

The review of 2008 presents the scale-up possibilities for a variety of transition metal-catalyzed C−C bond-forming reactions applying microwave heating and microtechnology.[105]

5. PHOTOCATALYTIC REACTIONS

Two detailed reviews on photochemical reactions in microflow were published in 2011 and 2012 by M. Oelgemöller et al.[106,107]

The thorough review of 2011[107] is devoted to the recent advances in microflow photochemical technologies. The paper includes the comparison of the features of the batch and microflow photoreactors as well as a broad range of examples of photochemical reactions such as photoadditions, photoreductions, photodecarboxylations, etc. It was highlighted that microflow photochemistry efficiently combines the advantages of microscale and flow conditions. Microchemical processes result in the reduction of irradiation times, enhanced selectivity, and increased light efficiency, thus demonstrating the superiority of microflow photochemistry over conventional techniques.

Another review of M. Oelgemöller[106] emphasizes selected examples of photochemical transformations in microflow reactors such as photoaddition, photorearrangement, photoisomerization reactions as well as gas−liquid photoreactions. A few examples of heterogeneous photocatalytic reactions in microreactors with immobilized photocatalysts are also included. It was noted that the photoreactions in flow result not only in higher yields, improved selectivity, and enhanced energy efficiencies but also in reduction of solvent volumes, and in waste minimization. An example of industrial-scale flow photochemical process is also described (synthesis of anticancer

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drug precursor 10-hydroxycamptothecin with production rate of 2 kg/day). Some additional examples, which were not mentioned in the reviews of Oelgemöller[106,107] are described below.

Photocatalytic transformations are gaining considerable attention as an interesting synthetic methodology in terms of 'green' processing and due to their potential for developing new chemical reactions. One of the limitations for the performance of such reactions in large batch reactors is the difficult scale-up procedure due to the requirements for special equipment and limited light penetration through the reaction media. Besides precise mass- and heat-transfer control, the important advantage of microreactors for this application is the superior light penetration through the samples in the narrow reaction channels (according to Beer–Lambert law)[108,109] and removal of photoproducts from the irradiated area.[106]

Diastereodifferentiating [2 + 2] photocycloaddition of chiral cyclohexenone with cyclopentene performed in a microflow reactor equipped with UV–LED lamps (365 nm) for photoreaction was described by Terao et al.[109] The results obtained in a microreactor were compared with those of a quartz cuvette cell (batch reactor). First, the photoreaction of chiral cyclohexenone after irradiation for 10 min at 25 °C was studied. At a low concentration (47 mM) the conversion and the diastereoselectivity were almost equal in both reactors; however, the significant decrease of conversion in the batch reactor was observed when using higher concentrations of the reagents. In the microreactor, the conversion decreased only slightly with the increase of the concentration. This high efficiency of the microreactor can be explained by its superior light penetration potential. The authors noted that the diastereoselectivity of this reaction was not enhanced using a microreactor. An improvement of the diastereoselectivity was achieved using additives (naphthalene and 1-nitronaphthalene). The positive effect of 1-nitronaphthalene on the diastereoselectivity in the microreactor was explained by the combination of the strong $\pi-\pi$ interaction between the substrate and the additive and the superior light penetration capability of the microreactor.

The continuous photochemical synthesis of terebic acid from maleic acid (Figure 48) performed in two different micro-

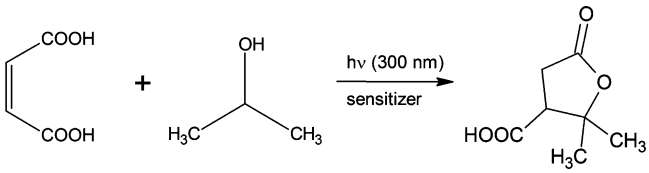

Figure 48. Photochemical synthesis of terebic acid. Adapted from ref 110.

reactor setups was reported.[110] The reaction was initially studied in a batch Rayonet reactor (RPR-200) equipped with 16 × 8 W UVB lamps using benzophenone, 4-carboxybenzophenone, and acetone sensitizers. Without sensitizer, no reaction occurred, and the full conversion of maleic acid and the highest yield of terebic acid (81%) were achieved after 1 h using acetone. Then the reaction was conducted in a smaller Rayonet reactor (RMR-600) equipped with 8 × 4 W UVB lamps at different irradiation times (5–180 min). The reaction performed at an irradiation time of 180 min resulted in an 84% yield of the desired product. On the basis of these results, the synthesis of terebic acid was next studied under microflow conditions in two microreactors with different configurations. The first microreactor was fabricated from Foturan glass and consisted of a top cooling channel and a bottom reaction channel (volume 1.68 mL). The irradiation was done by a UV panel consisting of five UVB-lamps (5 × 8 W). The conversion of maleic acid increased almost linearly with the reaction time (10–60 min) and reached 100% within 1 h, giving terebic acid in 79% yield. The second flow microreactor was represented by a UV-transparent fluorinated ethylene propylene copolymer capillary (I.D. 0.8 mm) irradiated using a single UVB (1 × 8 W) lamp. The conversion of 99% was obtained at 15 min residence time, and the product was isolated in 83% yield at 30 min residence time. The fact that the lowest light power of 8 W was used for the microcapillary reactor makes this result even more important. Moreover, the calculated energy efficiency was ~17 times higher in the case of the capillary microreactor compared to those of the other reactors.[110]

A successful development of a flow process for the enhancement of the productivity of (enantioselective) photocatalytic reactions was reported.[108] Since the productivity in batch reactors is limited by the light penetration through the reaction media, continuous microflow methods are considered to be an alternative approach. The aza-Henry transformations of different substrates under microflow conditions using both $[Ru(bpy)_3]Cl_2$ and $[Ir(ppy)_2(dtbbpy)]PF_6$ as catalysts were chosen as model reactions. The generation of the corresponding aza-Henry product with an approximately 20–30-fold acceleration without formation of any side products was observed. The temperature, catalyst amount, and residence times were optimized so that the desired products were achieved in good yields (up to 86%) and in shorter time in flow (45 min) than in the batch mode (18 h). The authors reported that enantioselective, synergistic photocatalytic reactions can be easily scaled up from a microreactor to a tubular reactor with productivities of 0.037 and 1.92 mmol·h^{-1}, respectively.

The development and use of a simple continuous-flow photoreactor to perform $Ru(bpy)_3^{2+}$-catalyzed visible light-mediated reactions is reported.[111] A 4.7 mL photoreactor, constructed of fluorinated ethylene polymer tubing placed between two cold white LED lamps (emission in the 400–500 nm range) was used. The known reduction of methyl-4-azidobenzoate to the corresponding amine was tested first as a model reaction. Full conversion was achieved at 1 min residence time in the presence of 5 mol % catalyst or in 2 min with 1 mol % catalyst. The Hantzsch ester was then excluded from the reaction mixture, and with increasing the residence time to 20 min, the amine was prepared in 89% yield. The comparative batch reaction resulted in 70% yield of amine in 4 h reaction time. Then the authors tested a few other important photocatalytic reactions. For example, it was found that combination of 1% $Ru(bpy)_3^{2+}$, iPr$_2$NEt, and HCO_2H was sufficient to achieve the reduction of the C–Cl bond within 30 min residence time without using the Hantzsch ester. The reductive opening of a chalcone-α,β-epoxide was successfully performed using 0.5 mol % of $Ru(bpy)_3^{2+}$ in 10 min residence time, resulting in the alcohol in 84% yield. Thus, Ru-catalyzed visible light-mediated reactions were simplified by excluding the expensive activator (Hantzsch ester) and by lowering catalyst loadings.

Optical transparent and solvent-resistant microreactors fabricated with an inorganic polymer, allylhydridopolycarbosilane (AHPCS), for the photocatalytic degradation of 4-

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Table 2. Most important advantages of microflow processing for different types of liquid-phase organic synthesis reactions

reaction type	main advantages of microreactor flow technology				
	precise temperature control, improved heat-transfer	enhanced safety	improved mixing	environmental aspects	superior light penetration depth
rearrangement reactions	+			+[a]	
condensation reactions	+	+		+[b]	
electrophilic substitution reactions: nitration		+	+		
acylation		+	+		
halogenation		+			
esterification		+	+		
nucleophilic substitution reactions	+				
cycloaddition and cyclization reactions	+	+			
electro- and nucleophilic addition reactions	+	+			
oxidation and reduction reactions	+				
polymerization	+		+		
heterogeneously catalyzed reactions				+[c]	
photocatalytic reactions					+

[a]Use of 'green' solvents. [b]No use of extra reagents, sustainable purification. [c]No need to separate the catalyst from the reaction mixture in case of the catalytic coatings, monoliths, or packed-bed reactors.

chlorophenol with TiO_2 catalysts was described by Yoon et al.[112] The catalytic performance of the AHPCS-microreactor fabricated by UV-imprinting was compared with the commercial glass microreactor (ICC-DY10, IMT, Japan) with identical dimensions as well as with a simple batch reactor. Two different TiO_2 photocatalysts were used: Degussa P25 TiO_2 nanoparticles (20−200 nm) as a slurry for the batch process and glass microbeads coated by TiO_2 via a sol−gel method for the AHPCS-microreactor. The empty AHPCS-microreactor showed a 95% conversion at various flow rates (5−20 $\mu L \cdot min^{-1}$) which was comparable with the results of the glass microreactor. Then, the AHPCS-microreactor was filled with TiO_2-coated glass beads to study the sterilization effect of the photocatalytic microreactor. A significant decrease of the numbers of live *Escherichia coli* cells was observed. It was shown that an inorganic polymer-based microreactor with high optical transparency and excellent stability is a practical tool for different photochemical reactions.

The photochemical degradation of potentially health hazardous polybrominated diphenyl ethers (PBDE) in different solvents was performed in a continuous photomicroreactor.[113] The degradation of decabromodiphenyl ether (deca-BDE) dissolved in hexane was used as a model reaction. The reaction was performed at RT and various residence times, using a 100 W Hg-lamp for irradiation. A high degree of debromination of deca-BDE (~80%) was achieved within 96 s. The resulting mixture of lower brominated PBDEs was found to be similar to that obtained in a batch reactor with a TiO_2 catalyst in 240 min. After increase of the residence time to 192 s, the degradation reached 90%, and tetra- and tri-BDEs appeared in the mixture. With further extension of the residence time to 3.6 min the amount of lower brominated PBDEs further increased. Thus, the photomicroreactor showed a higher efficiency in comparison to that of the batch reactor due to the high surface-to-volume ratio and the accurate control of the reaction parameters.

CONCLUSIONS

Microflow technology demonstrates many advantages over conventional techniques and typically results in the reduction of reaction times, enhanced selectivity and product yield, improved safety and sustainability, and more opportunities for the scale-up of the process.

It is noteworthy that various types of organic liquid-phase reactions benefit more from certain characteristics of microflow reactors. As a conclusion, we summarize the most important advantages of the microreactors according to the reaction type in Table 2.

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Notes

The authors declare no competing financial interest.

ABBREVIATIONS

AIBN	2,2-azobis(isobutyro)nitrile
APTES	(3-aminopropyl)triethoxysilane
CFD	computational fluid dynamics
DAST	diethylaminosulfur trifluoride
Deoxofluor	bis(methoxyethyl)-aminosulfurtrifluoride
DIBALH	diisobutylaluminum hydride
DMF	*N,N′*-dimethylformamide
DPPA	diphenylphosphoryl azide
FTIR spectroscopy	Fourier transform infrared spectroscopy
GlcNAc	*N*-acetyl-D-glucosamine
I.D.	internal diameter
IR spectroscopy	infrared spectroscopy
LED	light-emitting diode
MPTES	(3-mercaptopropyl)triethoxysilane
PFA	perfluoroalkoxy alkane
PMMA	poly(methyl methacrylate)
PTFE	polytetrafluoroethylene
p-TSA	*p*-toluene sulfonic acid
PVA	poly(vinyl alcohol)
RT	room temperature
SDS	sodium dodecyl sulfate
TBHP	*tert*-butyl hydroperoxide
TFA	trifluoroacetic acid

THF	tetrahydrofuran
UV	ultraviolet

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