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INVITED REVIEW PAPER

Recent advances for serial processes of hazardous chemicals in fully integrated microfluidic systems

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Abstract−The development and enlargement of toxic and hazardous chemicals are severely limited by health and safety concerns. We summarize studies on fully integrated micro-chemical systems and total processes to reduce accidental exposure to various regents that are toxic, explosive, or carcinogenic, which significantly improved the safety of work involving risky compounds. This review covers the leak-free continuous-flow processes of hazardous chemicals in fully integrated microfluidic systems, specially denoted as micro-total envelope systems (μ-TESs), that are conducting a serial process of the generation of hazardous reagents, in-situ purification and separation, subsequent reaction, and product isolation with improved efficiencies. These attempts suggest safe and efficient tools and processes of useful but hazardous chemicals for researchers and manufacturing workers in the field of pharmaceutic discovery, natural products, biology as well as materials synthesis.

Keywords: Toxic Chemicals, Total Process System, Micro-total Envelopment System, Separator, Extraction Unit, Tube in Tube System, Dual Channel Microreactor, Silicon Nanowire Reactor, Diaze Compound, Azide, Carbon Monoxide, Ozone, Chloro Methyl Methyl Ether

INTRODUCTION

For centuries, solution-phase synthesis has been conducted using the conventional batch mode in stationary reactors with stirring or shaking. However, miniaturized flow reactors, called microreactors, designed for performing chemical reactions in continuous flow, have received increasing interest in both academia and industry. Continuous-flow microfluidic devices as an efficient synthetic tool offer many advantages over conventional reactors [1]. A high surface-to-volume ratio and excellent properties of heat and mass transfer in the confined microspace of the microchannel are typically intrinsic characteristics of microreactors [2-4]. The high surface-to-volume ratio enables rapid mixing by facilitating better transport of reacting species in short diffusion distances. This enhancement accelerates reaction rates by shifting the diffusion-controlled reaction to the kinetically controlled reaction regime and reduces the reaction time. In addition, the excellent heat transfer rates allow for precise temperature control, and the uniform reaction conditions improve the product profile and yields with superior selectivity.

The microreactor technology (MRT) of the chemist's round-bottomed flask of the 21st century is evolving into highly advanced techniques for chemical processes for the production of specialty chemicals. MRT has proved itself to be an ideal tool for new chemistry and process development due to its fast and easy screening parameters as well. Furthermore, the multi-layering of continuous-flow reactors readily enables the scale-up synthesis from gram to kilogram amounts in a single day. The MRT has demonstrated vast improvements in energy efficiency and reaction speed as well as yield, productivity, safety and reliability by much finer control of process parameters.

Alternatively, the small reaction volume of less than a milliliter in the microreactor facilitates the safe and easy handling of hazardous or unstable materials and highly exothermic reactions, because only a small amount required at a given time attenuates the risk of an accident even when various carcinogenic, explosive, toxic, or noxious reagents are exposed. The instant and on-site production of the wanted chemicals reduces the necessity to store extremely high amounts of potentially hazardous, unstable, or inflammable intermediates. With the development of MRT, the performance and safety envelope of chemistry can be further improved, and the conventional definitions of "hazardous" or "harsh" reaction conditions can also be altered [5]. It is very useful to summarize the reported works on attempts via integrated micro-flow system and process to decrease the accidental exposure of various explosive, toxic or noxious regents. Many research groups have already written reviews about continuous-flow reactions, including gaseous, explosive, hazardous, and toxic chemicals [6-19]. However, the reactions of toxic and explosive reagents in a microreactor only partially addressed the associated safety concerns.

We focus here on the concept of fully integrated microfluidic systems and the process applications that conduct a serial process of the generation of hazardous reagents, in-situ purification and separation, subsequent reaction, and product isolation, as illustrated in Scheme 1. To emphasize these efforts, all unique systems devised

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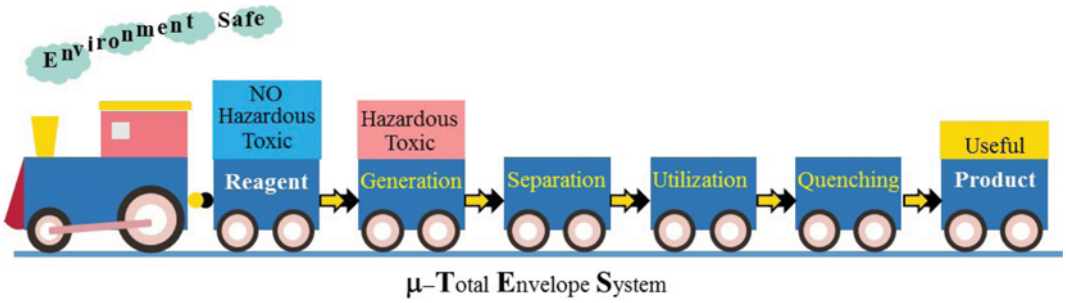

Scheme 1. Conceptual scheme of micro-total envelope system (μ-TES) from the generation of toxic chemicals to the work-up step in a completely enveloped and continuous-flow manner.

Scheme 2. Overall scope covered in this review: micro-total envelope system (μ-TES) as a platform composed of various functional components (left), and hazardous chemical processes utilizing μ-TES (right).

for specifically performing the automated total process from the in-situ generation of hazardous chemicals to the work-up step in a completely enveloped and continuous-flow manner are newly categorized with new terminology as micro-total envelope systems (μ-TESs). Initially, the μ-TES platform enables the synthesis of the hazardous and toxic reagent in a microreactor component by using the non-hazardous and toxic compound as a starting reagent. The generated hazardous and toxic reagent is separated and purified from the reaction mixture, the subsequent reaction of the obtained toxic reagent synthesizes the desired product, and the sequential decomposition of the unreacted toxic reactant is conducted by quenching to isolate the final desired product [20]. In the various and crucial organic compounds involving hazardous, noxious, or explosive chemistry, diazo compounds (diazomethane and ethyl diazoacetate), ozone, carbon monoxide, hydrazoic acid, chloromethyl methyl ether, and halogen azide compounds have been employed for utilizing the microreactors in drug discovery, natural products, ion-exchange membranes, materials synthesis and biology area. This review covers the recently developed leak-free total processes of these chemicals in the integrated microfluidic systems reported from 2006, excluding the cases of harmful reagent use as starting compounds. In particular, it focuses on how various types of micro-total envelope systems can contribute to improve the safety as well as the efficiency in chemical processes.

DIAZO COMPOUNDS

Diazo compounds have versatile chemistry and are widely used in organic synthesis. In this class, diazomethane and ethyl diazoacetate (EDA), as the most useful diazo-reagents, are both carbene precursors that can be used as methylating agents. They are useful to produce cyclopropanes, epoxides or heterocycles that contain the nitrogen, sulfur, and oxygen functional group. Diazo compounds are also utilized in carbon chain extensions and ring expansion reactions. However, the industrial processes involving large-scale batch-wise handling are generally avoided due to their potentially explosive and toxic nature. The advent of continuous-flow MRT has significantly improved the processing performance of potentially explosive, toxic, and hazardous chemical reactions regarding safety. Hence, μ-TES and the automated total process could be a final solution for a leak-free approach for hazardous diazo compounds.

DIAZOMETHANE

Classically, diazomethane has been separated from the aqueous saline phase by distillation and/or gaseous extraction, which are inappropriate for handling a toxic gas with a high possibility of detonation or leakage. The flow-based system could offer many advantages over the batch process, including reduced processing time, precise time control, and enhanced selectivity. Many research groups have studied the synthesis and utilization of diazomethane in flow reactors. However, they mostly either performed the synthesis of diazomethane as a final product or used diazomethane as a starting reagent, which could not avoid potential external exposure. We only focused on the in-situ generation, separation, and utilization of diazomethane in various μ-TESs.

Recently, a serial process of in-situ generation, separation, and reactions of pure anhydrous diazomethane was developed by introducing a separation method of pure anhydrous diazomethane diffused through a thin polydimethylsiloxane (PDMS) membrane dividing two compartments in the resistant polymer-coated channel (Fig. 1) [21]. The solution in the bottom channel was designed to flow in parallel with the gas in the upper channel; both channels were in direct contact through a thin gas-permeable PDMS membrane (thickness: 45 μm) along the flow path. To prevent the leaking of as-synthesized diazomethane in the channel, the inner wall surface of the channel was coated by non-gas-permeable poly

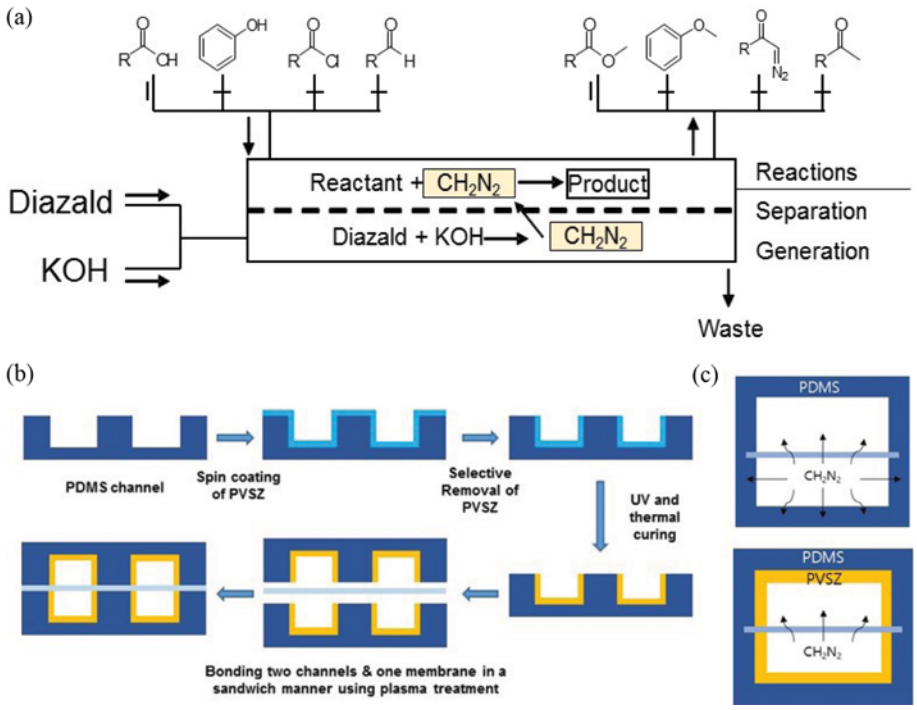

Fig. 1. (a) Serial process of in-situ diazomethane synthesis, followed by separation and subsequent reaction in a dual-channel microreactor. (b) Procedure of dual-channel fabrication. (c) Random diffusion and guided diffusion of as-synthesized diazomethane in a dual channel with/without PVSZ coating. *Angew. Chem. Int. Ed.*, 50, 5952 (2011).

(vinylsilazane) (PVSZ, KION VL-20, Clarient) (Fig. 1(b)). The PVSZ-coated PDMS dual-channel microreactor was 75 cm long and 60 μL in volume.

The gaseous diazomethane thus generated by the liquid-phase reaction in the bottom channel was in-situ separated to move into the upper channel by diffusing through the membrane. Additionally, the separated diazomethane was continuously consumed by alternative organic reactions to yield various products separately, such as not only the methylation of benzoic acid and phenol, but also the conversion of aldehydes to methyl ketones. In particular, the produced diazomethane could be utilized for the Arndt-Eistert reaction, which is extremely sensitive to moisture. The solvent-resistant dual-channel microreactor chip as a new conceptual device was capable of generating on demand, separating, and reacting such toxic reagents without any accumulation, leakage, or detonation. A major drawback of this microreactor chip was that only 63% of the total generated diazomethane could be separated, resulting in a low throughput (0.58-2.88 mmol of product per day).

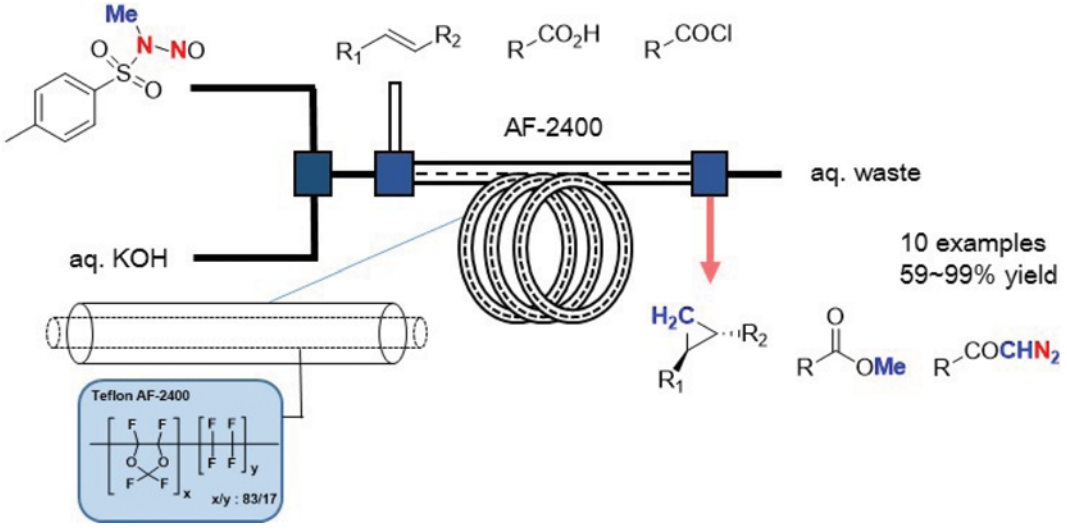

Fig. 2. Continuous synthesis and utilization of diazomethane in a tube-in-tube AF-2400 reactor. AF-2400 membrane with 100 μm thickness and PTFE outer tubing system were used for the reactions. *Org. Lett.*, 15, 5590 (2013).

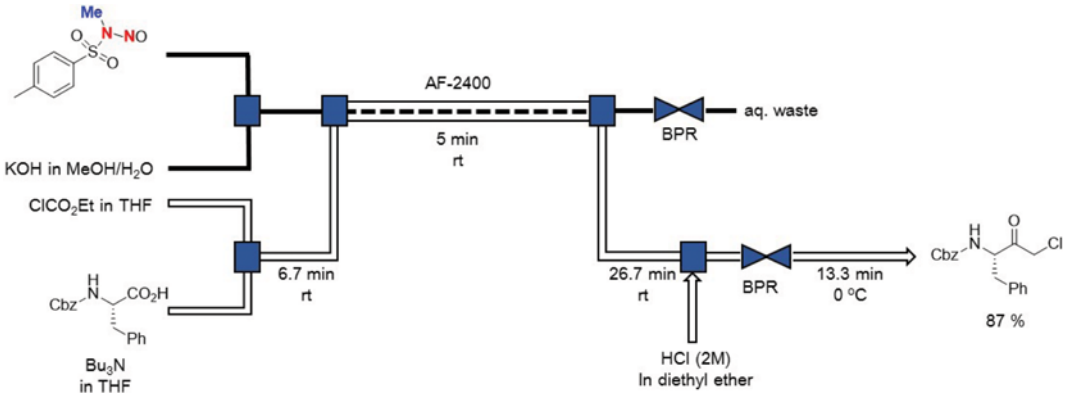

Fig. 3. Scheme of generation of an anhydrous and ethereal solution of diazomethane and formation of α-diazo ketone in a continuous-flow tube-in-tube system. AF-2400 membrane with 100 μm thickness (0.8 mm i. d., 1 mm o.d., 4 m length) and PTFE outer (1.59 mm i.d., 3.2 mm o.d., 4 m length) tubing system. *J. Org. Chem.*, 79, 1555 (2014).

Approximately one-third of the generated diazomethane was flowing in the solvent stream and appeared as hazardous byproduct. Furthermore, the durability and productivity of the microfluidic device (~1 mmol/day) were also far below the satisfactory levels. Therefore, developing a robust microfluidic set-up for the toxic, explosive, and hazardous reagents process (CH_2N_2, $N_2CHCOOEt$, organic azides, etc.) without compromising on safety and waste hazard concerns was demanded.

To enhance the productivity of diazomethane, Kappe et al. developed a similar system and used an AF-2400 based tube-in-tube reactor [22] that was developed by Ley et al. in 2010 (Fig. 2) [23]. Teflon AF-2400 is composed of tetrafluoroethylene with perfluorodimethyldioxolane additive as a crystallization inhibitor. The chemical resistance and mechanical strength of AF-2400 is similar to that of poly(tetrafluoroethylene) (PTFE), but it has high porosity and an amorphous structure. Accordingly, the AF-2400 tube (0.8 mm i.d., 1 mm o.d., 4 m length) served as a robust, hydrophobic membrane that selectively permeated gaseous components but not liquids. The inner AF2400 membrane tube was surrounded within an impermeable outer PTFE tube (1.59 mm i.d., 3.2 mm o.d., 4 m length]; it was possible to increase the output to 35 mmol/day. They showed the in-situ generation and direct separation/utilization of diazomethane via methylation, the synthesis of cyclopropane, and the Arndt-Eistert reaction with 11 examples with 59-99% yields.

Kappe et al. also reported an additional approach to generate anhydrous ethereal diazomethane for the synthesis of α-diazo ketone in the continuous-flow approach in 2014 [24]. From N-protected amino acids, eight α-halo ketones were synthesized with a three-step synthetic route through the utilization of ethereal diazomethane (Fig. 3). One of the products, enantiopure α-chloro ketone, a key intermediate for atazanavir (HIV protease inhibitor), could be synthesized in an 87% isolated yield with improved productivity (1.84 g, 1.25 mmol/hr). Furthermore, the continuous-flow system demonstrated that it was suitable for hazardous gas reactions without any intervention during several hours of operation time.

After the successful synthesis of α-diazo ketone in a one-flow and tube-in-tube system, it was further used to synthesize β-amino acids via the Arndt-Eistert homologation from their corresponding α-amino acids [25]. The synthesis of β-amino acids was a four-step process: In the first step, diazomethane was in-situ generated and directly extracted from the aqueous solution using a gas-permeable membrane, AF-2400. In the second step, anhydrous CH_2N_2 was reacted with the activated amino acid by acylation. To remove the excess diazomethane, AF-2400 tubing was

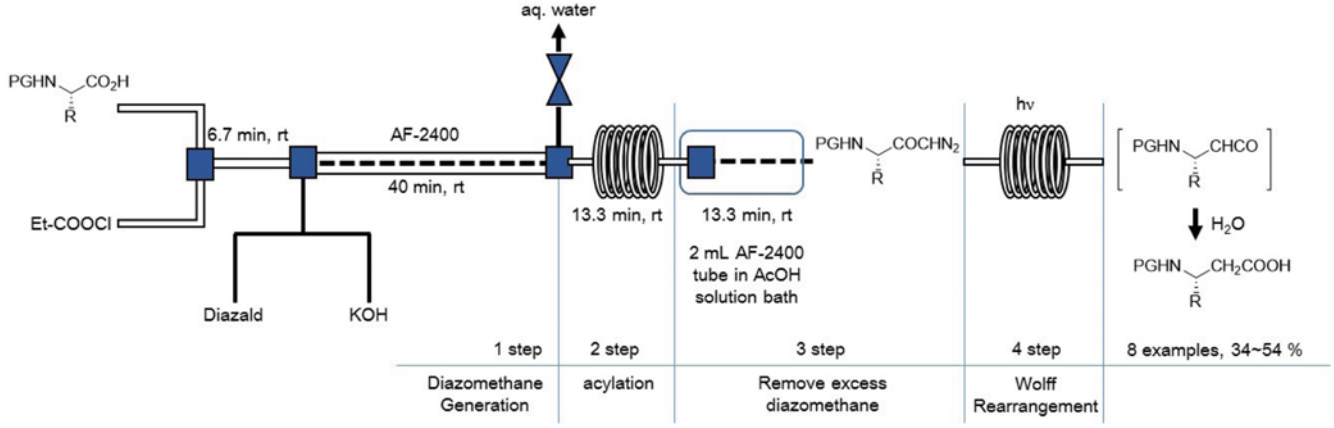

Fig. 4. Flow set-up of continuous four-step Arndt-Eistert homologation of α-amino acids for eight kinds of β-amino acid products by photo-Wolff rearrangement. *RSC Advances*, 4, 37419 (2014).

attached and submerged in the acetic acid alcoholic solution bath in the third step. Finally, β-amino acids was achieved by photo-Wolff rearrangement in reasonable overall yields in the fourth step (Fig. 4). Eight β-amino acids were synthesized with 34-54% yields.

For industrial purposes, flow microreactors have also been tried to synthesize diazomethane. Maggini et al. achieved much higher methylation productivity using diazomethane (19 mol/day at 53 mL/min of total flow rate) [26]. A commercially available glass flow reactor system (Corning Advanced-Flow *Low Flow*) was used to verify the high productivity by optimizing the condition, and scale-up synthesis was achieved by numbering the glass flow reactors, designated as "*GEN1*-type modules." N-methyl-N-nitrosourea (MNU) in a water/acetic acid slurry was selected as a relatively safe starting material for generating diazomethane. Note that N-methyl-N-nitroso-p-toluenesulfonamide (MNTS, Diazald) and N-methyl-N′-nitro-N-nitroso guanidine (MNNG) were not used due to their shock-sensitive reactivity, high toxicity, and cost.

ETHYL DIAZOACETATE

Ethyl diazoacetate (EDA) is also an important compound for the C2 synthon (a synthetic building block with two carbons) among the most common diazo compounds [27,28]. In the μ-TES shown in Fig. 5, the toxic and explosive EDA [29,30] was synthesized by the diazotization of glycine ethyl ester hydrochloride in aqueous plugs followed by the in-situ efficient separation of the 99% EDA in the principle of extraction from the aqueous to the organic toluene plug with better solubility for the EDA. Next, the continuous separation of alternating aqueous and organic plugs was achieved with a microfluidic separator equipped with a hydrophobic PTFE membrane with a pore size of 0.45 μm that was preferentially wetted by the extracted EDA-containing toluene droplet and passed through the membrane holes. The non-wetting aqueous phase did not penetrate the membrane and was separated as waste.

The in-situ-generated and separated EDA was reacted with aldehydes via a 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)-catalyzed coupling reaction to yield 10 kinds of diazo compounds, and 2-keto esters were also obtained through the reaction between EDA and hydrocinnamaldehyde catalyzed by $BF_3{\cdot}OEt_2$ in an on demand manner.

OZONE

Oxidation with ozone (ozonolysis) has been desirable in organic synthesis for decades [31]. Ozone (O_3) is used to generate oxygen-containing chemical compounds such as alcohol, ketones, aldehydes or acids as environmentally clean and efficient method through the oxidative cleavage of the C-C double bond [32-34]. The direct ozonolysis of alkenes using ozone gas is considered an atom-efficient and environmentally benign process compared with the method using toxic osmium tetraoxide (OsO_4). However, direct ozonolysis always involves potentially dangerous intermediate products, such as ozonides and their peroxide forms [35]. Explosive oxygen/ozone in the gas phase and ozonides in the liquid phase could be generated as side products in ozonolysis reactions. Furthermore, ozonolysis is a highly exothermic reaction, and temperature control is critical during operation time [36]. Additionally, a mass transfer problem could occur by the low solubility property of ozone in most solvents even under a low temperature. Thus, the development of the continuous-flow method in integrated microreactors with a high surface-area-to-volume ratio can enhance both reaction performance as well as the safety profile of the process. Here, the in-situ-generated ozone gas from oxygen gas was utilized for direct ozonolysis in the specially devised μ-TES (Fig. 6(a)). Note that ozone could be generally synthesized by either high voltage or a UV light source (Fig. 6(b)).

In 2006, Jensen and co-workers first attempted direct ozonolysis in a silicon-Pyrex multichannel microreactor with a pressure drop zone and reaction zone. The ozone was produced by an electric discharge in a commercial ozonizer (OT-5, OzonetechnologyAB) cooled by a recirculating water cooler [37]. Ozone/oxygen gas mixtures were generated from 95% O_2 gas balanced with 5% N_2. The concentration of ozone in oxygen was monitored in the concentration range of 5.6-7.4% prior to the microreaction by cali-

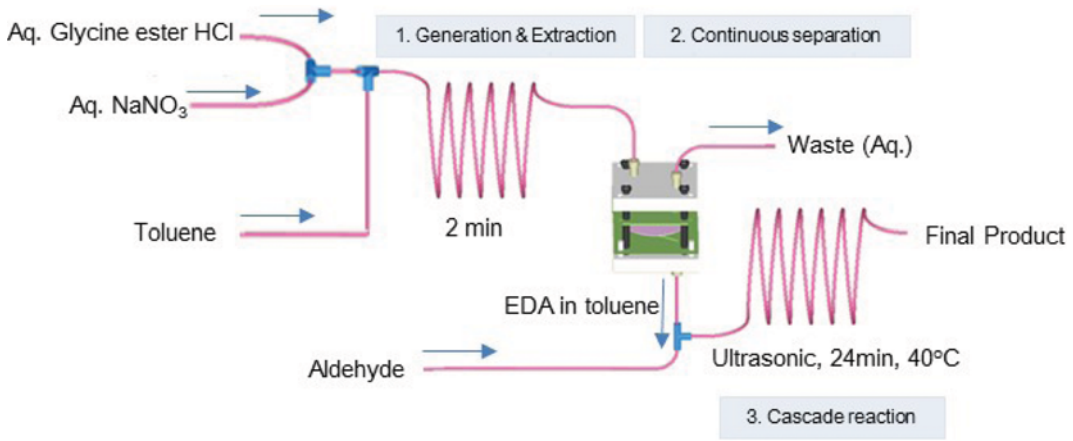

Fig. 5. Integrated microfluidic system composed of PFA capillary (800-μm i.d., 120-cm length, 600-μL volume) for generation and separation of ethyl diazoacetate (EDA) and reacted with aldehydes in acid and base-catalyzed reaction. Estimated productivity of 105 mmol/day at 75 μL/min for starting substances. *Green Chem.*, 16, 116 (2014).

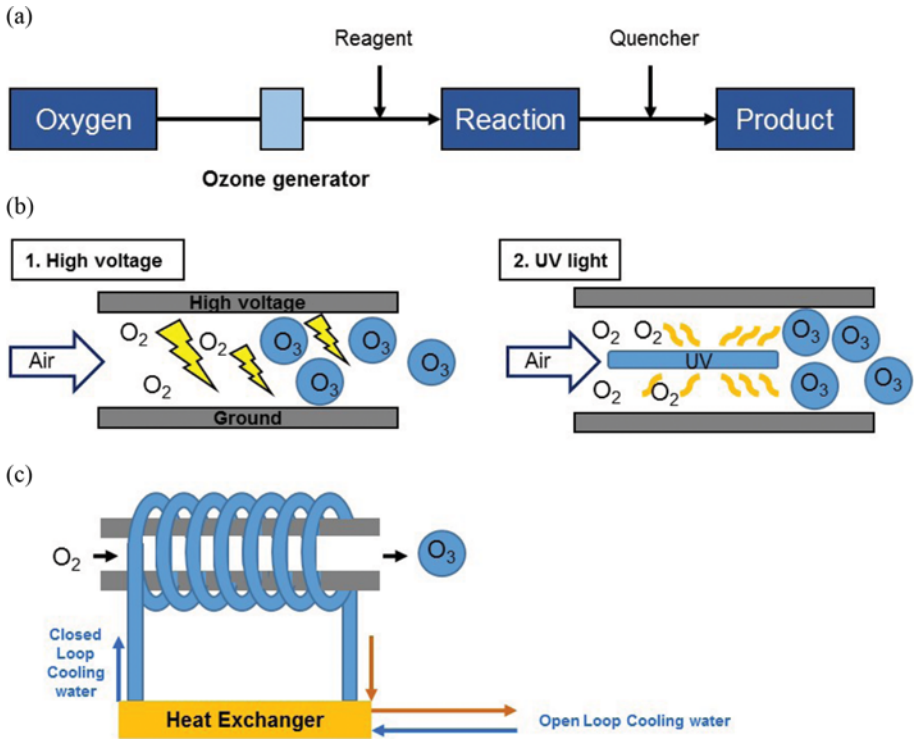

Fig. 6. (a) Schematic diagram of ozonolysis process in a μ-TES. (b) Two methods of ozone generation under high voltage and UV light. (c) During ozone generation, a cooling unit is necessary for dissipating the heat.

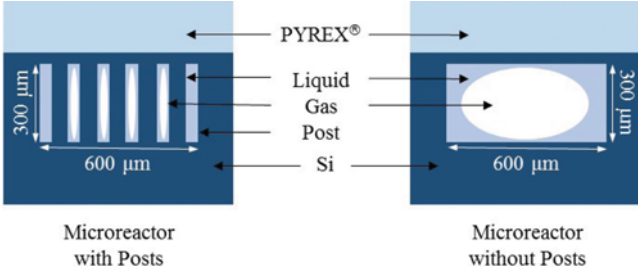

Fig. 7. Cross-section of the microreactors for gas-liquid binary phase reaction: with posts and without posts in the microchannel. *Ind. Eng. Chem. Res.*, 45, 8036 (2006).

brated UV absorption at 254 nm. The reaction channel had 16 individual microchannels embedded with post microstructures (Fig. 7).

The oxidation of triethyl phosphite, octylamine, and 1-decene as model reactions demonstrated that the fabricated microposts enhanced the overall mass transfer coefficient analogous to packing in conventional systems. The posts had the additional benefit of producing a larger heat transfer area from the removal of the reaction energy. The ozonolysis of an amine and an olefin relevant to the production of fine chemical intermediates produced complete conversion and high selectivity (almost 100%) even at a short reaction time of 0.67 sec. Thus, the uniform contact between gas and liquid substances in the microstructured multichannel microreactors revealed the potential for safely performing highly reactive ozone reactions.

Jahnisch et al. reported an industrially crucial ozonolysis-reduction sequential reaction for the synthesis of a vitamin D precursor [38]. A continuous-flow and integrated system in a microreactor with a miniaturized FTIR was employed for in-situ monitoring of the ozonolysis and sequential steps (Fig. 8). In the first step, the FTIR installed near the outlet analyzed the generation of the aldehyde and peroxide. Then, the processed liquid reactant separated by a gas separator could be mixed with $NaBH_4$ in DMF for reduction. The cleavage of double bonds in the substrate was carried out in a solvent mixture of methanol and dichloromethane with ozone at temperatures below −10 °C. Further, the reduction to the corresponding alcohol was then reacted by adding solid sodium borohydride. This procedure gave a high yield on a laboratory scale. In the ozonolysis step, the substrate was prepared as 0.2 mmol/mL in $MeOH/CH_2Cl_2$ and conducted at −10 °C to −17 °C with a flow rate of 1.2 mmol/min. In the reduction step, $NaBH_4$ dissolved in DMF solution as 3.5 mmol/mL was injected at a flow rate of 3.6 mmol/min under 10 °C to 15 °C. Under the optimized condition, these two-step sequential reactions were conducted in the five-channeled continuous microstructured reactor, and an extrapolated substrate throughput of about 1.22 kg/day (e.g., desired product (alcohol): 0.76 Kg/day isolated yield) was feasible.

Gavriilidis and coworkers reported the ozonolysis of various organic substrates to give carbonyl compounds, carboxyl acids, and nicotinic acids in a lab-scale capillary flow system [39,40]. The ozonolysis of alkyl and aryl alkenes gave the corresponding aldehydes and ketones at −10 °C within 1 hr of residence time in a continuous-flow system. In addition, the ozonolysis of aryl-substituted furans could be conducted to produce the corresponding carboxyl acids at room temperature in the flow system.

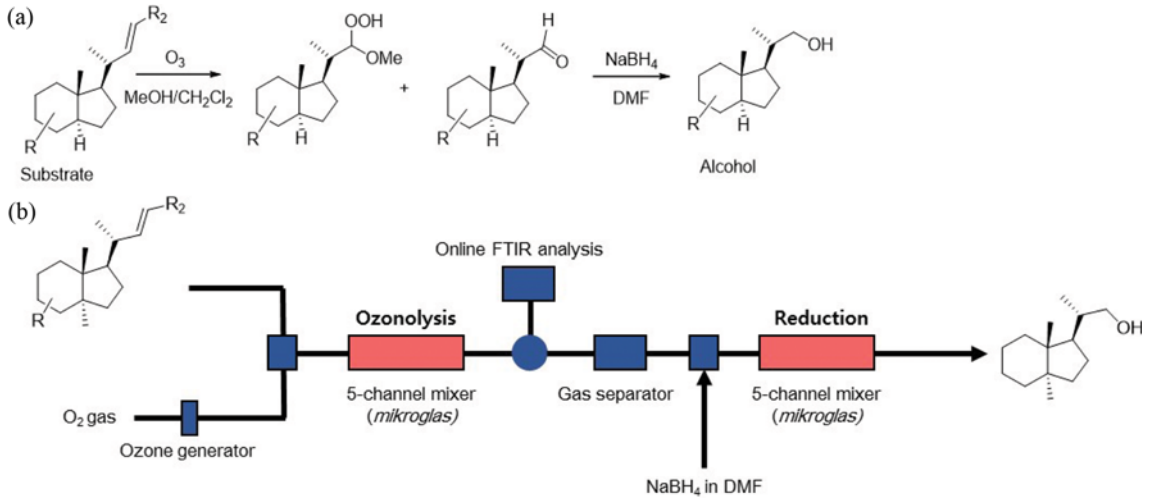

Fig. 8. (a) Ozonolysis-reduction sequential reaction for vitamin D precursor synthesis in (b) a five-channel microreactor (*mikroglas*) by conducting at −10 °C and reduction at 10-15 °C, which was analyzed by online FTIR. *Org. Process. Res. Dev.*, 13, 952 (2009).

In a commercially available continuous-flow device, various ozonolysis laboratory-scale applications were performed by Kappe et al. [41]. Ozonolysis at atmospheric pressure was conducted by the flow ozonolysis reactor (O-Cube) from −25 °C to room temperature at 0.2 to 2.0 mL/min of flow rates, attaining a high productivity of 10 g/day. The oxygen gas was pumped in to the commercial ozone generator and generated ozone flowed into the pre-cooled substrate feed. The ozonolysis then occurred in a Teflon pre-cooling loop. After the reaction mixture passed into the cooled reaction coil, a quenching reagent was supplied to stop the reaction by two further syringe pumps. In the process, the exothermic ozonolysis and quenching reactions were safely conducted in the flow system with excellent temperature control and without unstable ozonide intermediates.

Ley et al. demonstrated a tube-in-chamber microreactor including a semipermeable Teflon AF-2400 membrane for direct ozonolysis (Fig. 9) [23].

Teflon AF-2400 with high chemical resistance of PTFE was sustained at reactive gas and organic solvents, while ozone permeable poly(dimethylsiloxane) (PDMS) rubber could not be used for these

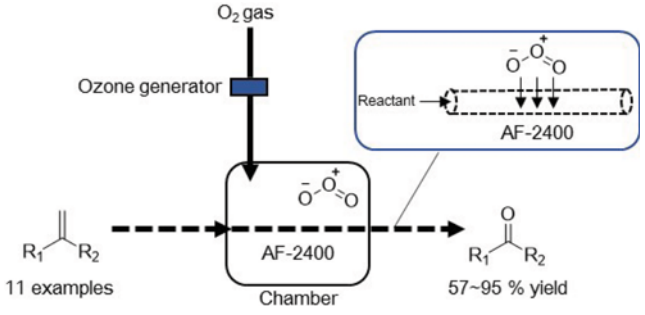

Fig. 9. Safe ozonolysis process in a tube-in-chamber flow reactor. Generated ozone was stored in the closed chamber and consumed by injected reactant through AF2400 tubing (AF-2400) for 1 hr of retention time (0.6-mm i.d., 0.8-mm o.d., 90-cm length). *Org. Lett.*, 12, 1596 (2010).

reactions due to its low chemical stability with significant swelling in a range of common organic solvents. Initially, the reaction was evaluated by controlling device variables (e.g., solvent/reactant concentration, reaction time, tube length, and membrane permeability) using dyes that are known to be bleached by ozone as a reaction readout. The ozonolysis for a series of alkenes was achieved in good yields (57-95%) by using a 90-cm length of AF-2400 tubing with a connected syringe pump set up to deliver 1-hr residence time in the apparatus. Note that hazardous peroxide species were formed and quenched with triphenylphosphine. Here, to enhance safety, the approach of incorporating the final quenching step in the flow would be suggested by either mixing the ozonide stream with a stream of quench reagent or passing the ozonide stream through a cartridge packed with solid-supported quench reagent. This feature would allow for combination of the ozonolysis with other chemical transformations as part of a multistep flow sequence.

Ley et al. developed a sequential flow reaction for the synthesis of 2-aminoadamantane-2-carboxylic acid [42]. Flow reactor technology was utilized for the preparation and scale-up synthesis of a five-step reaction (Fig. 10(a)). In step 4, oxidative cleavage of the exocyclic alkene was conducted with ozonolysis. The substrate (0.2 M solution in DCM)-combined stream into the gas flow passed through a coil reactor (2.5 mm i.d. 20 mL) within 5 min. The endothermic process was probably responsible for the "spraying phenomena" (latent heat of evaporation) that occurred when the liquid phase reactant entered the fast-moving gas flow. For the next step, developing a safe and clean system was necessary to prevent a side reaction. Flowing argon throughout the collected solution in a vented chamber could eliminate the excess ozone. The solution that eliminated ozone was then injected into a polymer-supported thiourea-packed bed column reactor. Thiourea induced the reductive cleavage of the ozonide (Fig. 10(b)). The output stream was periodically tested for residual ozone and the presence of unreacted ozonide by an ozone test kit. Under optimized conditions, 6.6 g/hr of product could be obtained in a continuous-flow manner. By equating, over 200 g/day could be achieved when the continuous manner was

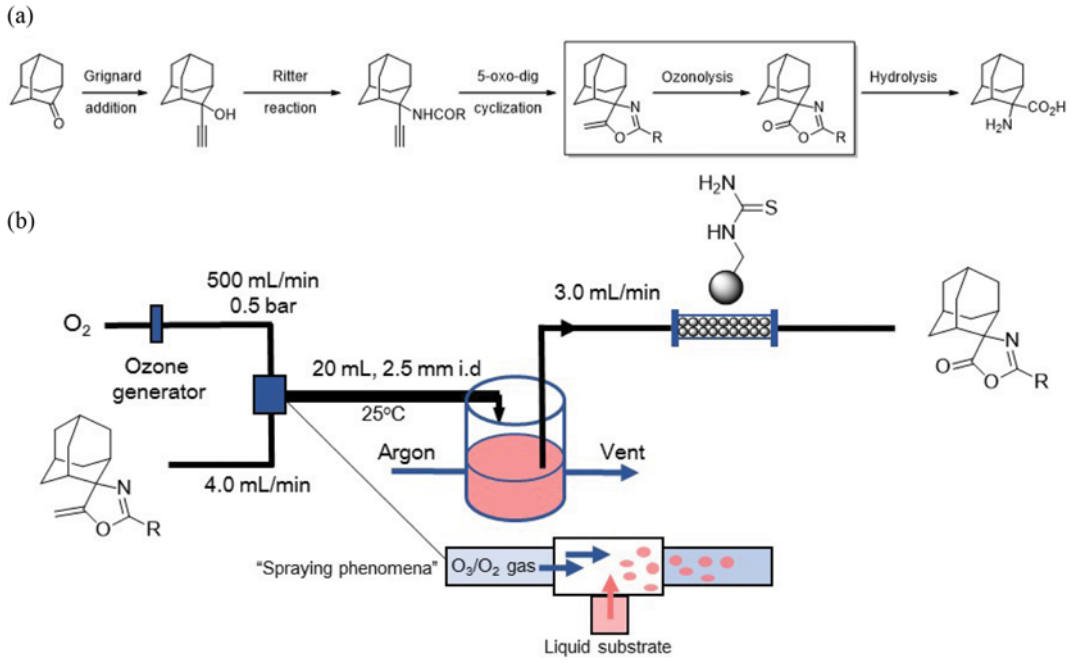

Fig. 10. Proposed synthesis of 2-aminoadamantane-2-carboxylic acid using a PTFE tubing system for ozonolysis. Remaining ozone could be eliminated in the polymer-supported thiourea-packed bed column reactor. Productivity of 6.6 g/hr, equating to over 200 g/day when processing in a continuous fashion. *Org. Process. Res. Dev.*, 16, 798 (2012).

applied.

Similarly, Riva et al. demonstrated a flow-based reaction for the synthesis of coumarin-8-carbaldehydes [43]. In the total chemical process, a series of four steps (allylation, Claisen rearrangement, isomerization, and ozonolysis) is sequentially performed to deliver the desired product. They conducted ozonolysis for the oxidative cleavage of double bonds (Fig. 11). The united flow stream is introduced to the reaction tube (2.5-mm i.d.) in a residence time of approximately 75 sec. The output stream is collected into a nitrogen purge chamber, and the excess ozone is eliminated by passing nitrogen through the vessel. The solution is handled in the same manner as in Ley's work to induce the reductive cleavage of the ozonide. The corresponding product of aldehydes can be produced in 92% isolated yield.

CARBON MONOXIDE

Over many decades in synthesis chemistry, carbonyl groups have

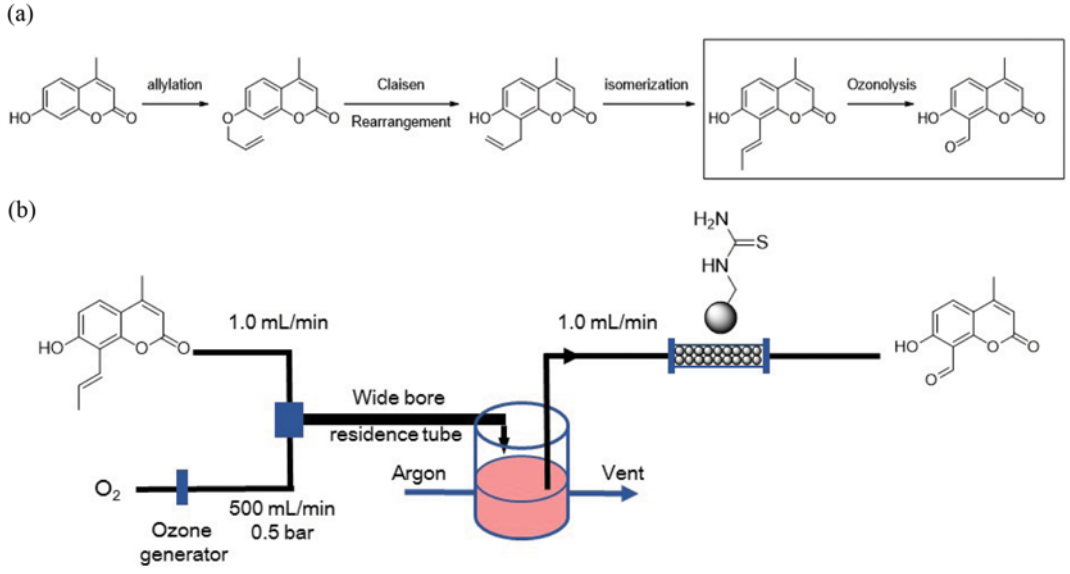

Fig. 11. A reaction scheme for the synthesis of coumarin-8-carbaldehydes in a PFA polymer tubular reactor (2.5-mm i.d., 6.5-mL volume) to produce 37 g of product for 4.5 hr at ~75 sec of residence time. *Chem. Eur. J.*, 18, 9901 (2012).

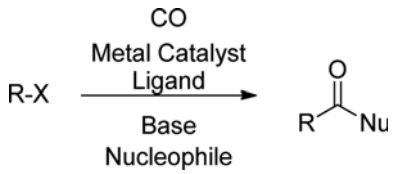

Fig. 12. General scheme for transition-metal-catalyzed reactions of aryl and vinyl halides with carbon monoxide with suitable nucleophiles.

played an important role in a wide range of significant bond-forming processes. To synthesize the carbonyl groups, it is one of the most well-known methods that aryl or vinyl halides are reacted with carbon monoxide (CO) and nucleophile in the presence of transition metal catalyst (Fig. 10). Indeed, the CO gas is often utilized in a number of industrial processes, such as the Fischer-Tropsch process [44] and alcohol generation [45]. However, because of strong binding affinity between CO and 'haem iron', CO disturbs oxygen transport, which damages human health at concentrations below 50 ppm [46]. In recent years, carbonylation in a flow microreactor has been used to increase green credentials [47-58] compared to traditional carbonylation reactions using a flask reactor or an autoclave. However, containing, delivering, and utilizing CO gas in stoichiometric amounts remains a safety issue.

CARBON MONOXIDE GENERATION FROM FORMIC ACID

Ryu et al. generated CO gas by mixing concentrated sulfuric acid with formic acid in situ (Morgan reaction) instead of directly inserting CO gas to the inner gas-permeable tube (Fig. 13) [59]. Their "tube-in-tube" reactor was mainly composed of two Swagelok T-pieces, a Hastelloy mixer (150 μm width, MiChS β 150), and stainless steel outer tube (3.17 mm o.d., 2.0-mm i.d.), and an inner Teflon AF-2400 tube (1 mm o.d., 0.8 mm i.d., 53 cm length). Heck aminocarbonylation was conducted in a flow system by decomposition of formic acid in sulfuric acid as a safe way to provide CO with water. The generated CO reacted with the mixture and the dioxane solution (flow rate 0.5 mL/hr) in the AF-2400 reactor at 80 °C. The mixture of products was collected at the outlet for 600

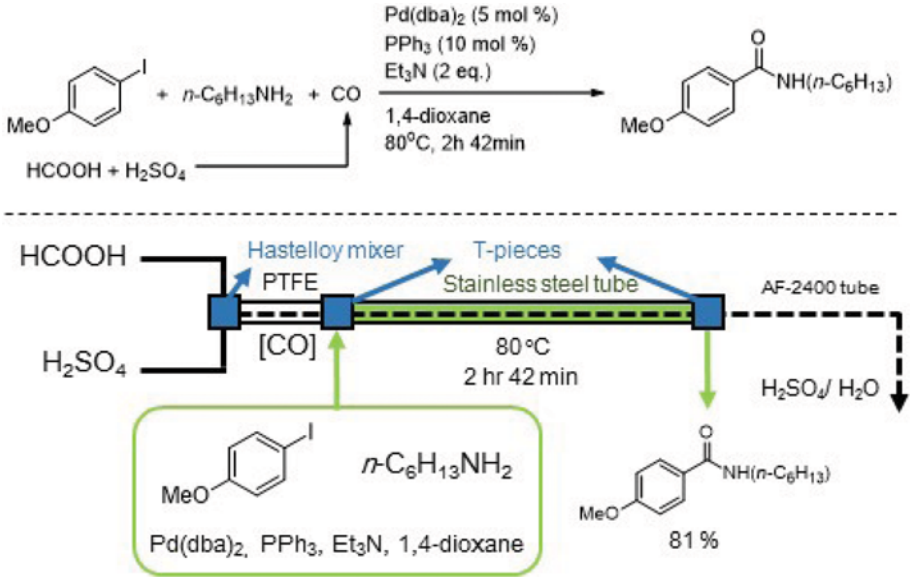

Fig. 13. Generation of CO gas with sulfuric acid/formic acid and subsequent supply of CO to the inner tube for carbonylation. *Org. Lett.*, 15, 2794 (2013).

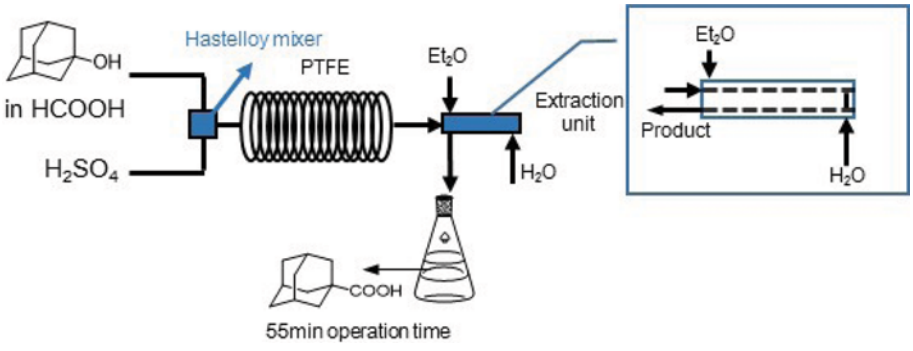

Fig. 14. Koch-Haaf reaction of adamantanols in a continuous-flow reactor composed of a Hastelloy mixer (150-μm i.d.) and extraction unit (1-mm i.d.) with PTFE tubing (1-mm i.d., 3-m length) to obtain 7.1 g of product with 88% yield. *Beilstein J. Org. Chem.*, 7, 1288 (2011).

min. They showed that the use of CO bombes for carbonylation could be avoided, and this enhanced the safety of handling the facile reactor. However, a productivity issue remained with a sluggish total flow rate (513.6 μL/hr) and long residence time (2 hr 42 min).

In addition, Ryu et al. reported a similar work on a Koch-Haaf reaction of adamantanols: the carbonylation of alcohols [60]. They also used a mixture of concentrated sulfuric acid and formic acid in a Hastelloy-made micromixer. The acid mixture generated CO in situ, and the carbocation formed after the elimination of the hydroxyl group and produced a multi-gram scale of 1-adamantanecarboxylic acid (Fig. 14). Unlike in the batch system, the reaction (1.5 min retention time) at room temperature without any cooling system was feasible for producing 7.1 g of final product with 88% yield within 1 hr operation time.

AZIDES

Azides are anions with the formula N_3^- and serve as a conjugate base of hydrazoic acid (HN_3). A linear anion, N_3^-, can be described by several resonance structures, $N^-=N^+=N^-$. Organic azides, RN_3, are potentially explosive by decomposing even with very weak stimulus of external energy impact such as heat, pressure or light. Due to the lower sensitivity of inorganic azides, chemists and engineers have usually used sodium azide as a starting material for the in-situ synthesis of organic azides [61,62]. Additionally, the azido functional group containing molecules tends to decompose vigorously and requires strict safety precautions. Therefore, numerous works utilizing azides in continuous-flow systems have been reported within recent years. The small internal space in the flow-process system relatively reduces the risk in handling azides over the batch reactor. There are many reports on the generation of azide organic compounds [63-65] or organic azides as starting reagents [66-74] in flow systems. Herein, we have focused on the generation of organic azides in the integrated platform of μ-TES to perform a serial process of in-situ generation, separation, and utilization.

Jamison et al. developed a total flow synthesis of rufinamide (well-known anticonvulsant drug for Lennox-Gastaut syndrome or epilepsy) from a difluoro-substituted benzyl bromide, sodium azide, and methyl propiolate (Fig. 15) [75]. The difluorobenzyl azide from the corresponding difluorobenzyl bromide and sodium azide reacted with the expensive and reactive propiolamide from the methyl propiolate and aqueous ammonia in copper tubing at 110 °C with a 100 psi back-pressure regulator (BPR). The rufinamide was produced in 92% yield within 11 min of overall residence time. The copper tube served as a catalyst with improved reactivity and regioselectivity, while the PFA and stainless tubing rendered only

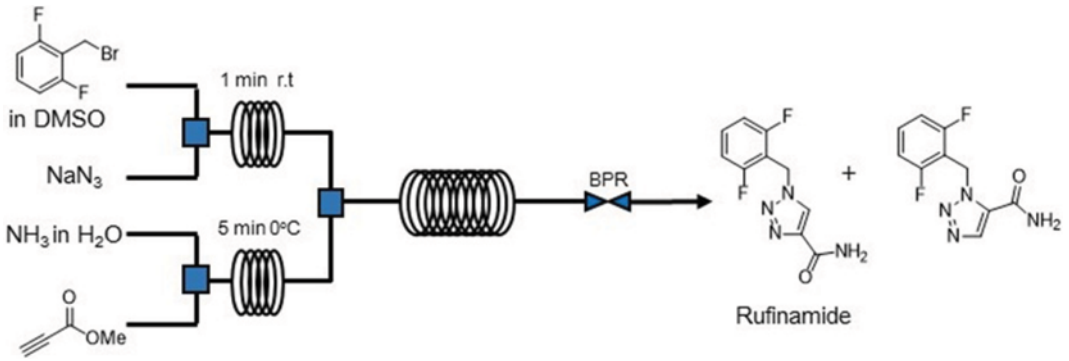

Fig. 15. Total flow synthesis of rufinamide by in-situ azide synthesis in a copper tube reactor (1/16-inch o.d., 0.03-inch i.d.) at 110 °C, 100 psi BPR, and 11 min residence time. *Org. Process Res. Dev.*, 18, 1567 (2014).

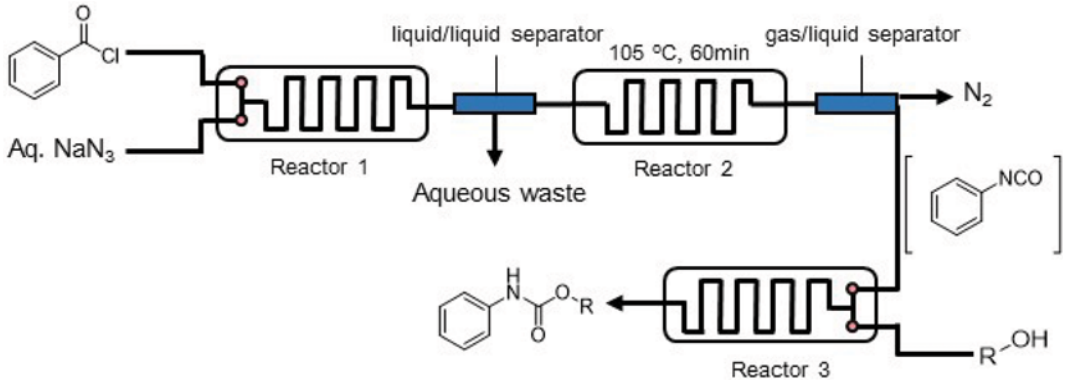

Fig. 16. Curtius rearrangement consisting of three reaction steps with two separation steps in an integrated microfluidic reactor. In reactor 1, acid chloride is converted to organic azide. In the liquid/liquid separator, organic and aqueous flows were separated. In reactor 2, organic azide is converted to isocyanate in the loaded solid acid catalyst. The nitrogen gas is separated by a gas/liquid separator. In reactor 3, the isocyanate reacts with alcohol to generate carbamate. *Angew. Chem. Int. Ed.*, 46, 5704 (2007).

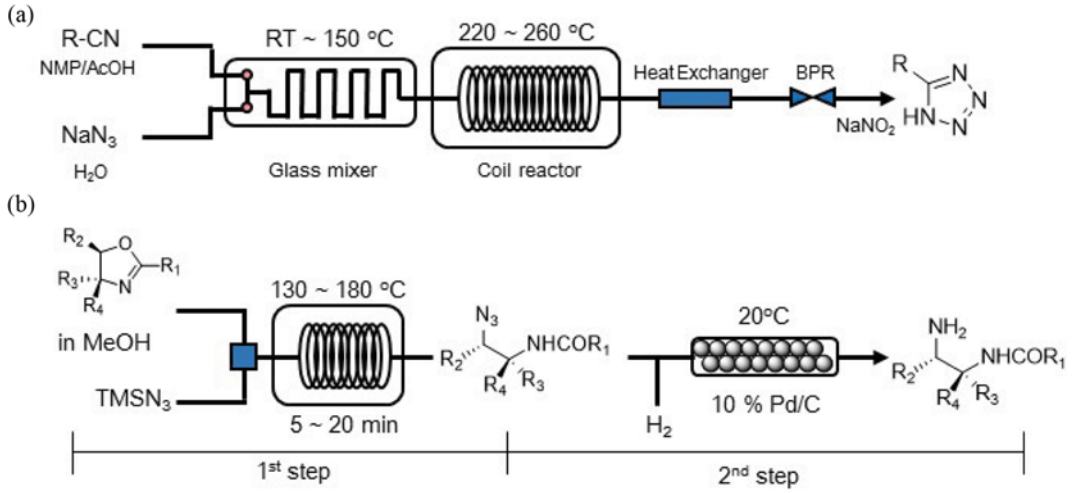

Fig. 17. (a) Synthesis of heterocyclic tetrazole (isolated 18.9 g/day) by in-situ generation and use of hydrazoic acid (HN_3) under high temperature in a microreactor composed of glass mixer block (2.0-mL volume) and coil reactor (1.0 mm-i.d., 10.7-mL volume). *Angew. Chem. Int. Ed.*, 49, 7101 (2010). (b) Production of N-(2-azidoethyl)acylamides by efficient and safe ring opening reaction. *Chem. Eur. J.*, 17, 13146 (2011).

10% and 7% yield, respectively. In addition, BPR pressures of 140 psi, 75 psi, and 40 psi gave yields of 56%, 67%, and 43%, respectively.

Jensen et al. also performed an integrated continuous-flow multistep synthesis of acyl azides via Curtius rearrangement consisting of three reaction steps with separation steps (Fig. 16) [76]. The sodium azide dissolved in aqueous solution was reacted with benzoyl chloride in toluene to generate the organic azide in a silicon-based microreactor. The chemical resistance by the glass and the excellent heat-transfer property from silicon was provided by the use of glass-coated silicon microreactors. Then, the alternating aqueous and organic plugs were continuously separated by the selective wetting of the organic solution on the hydrophobic membrane with a 0.1-1 mm range of pore sizes in a microfluidic separator, which prohibited the aqueous phase penetration. In the second step, the acyl azide was transformed to isocyanate by heating the azide to 105 °C within 60 min or by using a solid acid catalyst-packed bed reactor. The released nitrogen was removed in a second separator part by the flowing and wetting of liquid through the membrane to prevent gas penetration. Finally, the separated isocyanate was reacted with an alcohol to generate carbamate.

Kappe et al. demonstrated the synthesis of 5-substituted 1*H*-tetrazole derivatives by in-situ generation and the use of hydrazoic acid (HN_3) under high temperature conditions in a capillary microreactor (Fig. 17(a)) [77,78]. Tetrazoles are useful heterocyclic groups for various applications, such as organic and transition-metal catalysis, propellants, and explosives, and are commonly used in medicinal chemistry [79-82]. First, thereaction of aqueous sodium azide and acetic acid generates the unstable and explosive HN_3. Then, the produced HN_3 is in-situ reacted with nitriles to form a tetrazole product via cycloaddition under 220-260 °C for ~10 min in a heated coil reactor. Furthermore, the reaction mixture is quenched in a heat exchanger and flows directly into an aqueous $NaNO_2$ reservoir to immediately decompose the unconsumed hydrazoic acid.

Kappe et al. also demonstrated 2-oxazolinones derivatives providing N-(2-azidoethyl)acylamides by an efficient and safe ring opening reaction (Fig. 17(b)) [83]. From solvolysis between trimethylsilyl azide ($TMSN_3$) and MeOH, the HN_3 is generated and utilized to form N-(2-azidoethyl)acylamide at 130-180 °C within 5-20 min in a microreactor. This neuraminic acid analogue is a significant structural moiety of drug compounds, such as neuraminidase inhibitors zanamivir and oseltamivir. The synthesized N-(2-azidoethyl)acylamides are reduced by H_2 over Pd/C in MeOH to the desired N-(2-aminoethyl)acylamides in a continuous-flow ring opening/hydrogenation process.

Wirth et al. generated iodine azide, which they in-situ reacted with aldehyde to synthesize a more stable carbonyl azide [84]. Due to weak I-N bonds, iodine azide is much more hazardous, explosive, and toxic than carbonyl azide. These weak bonds could be homolytically cleaved and reacted with molecules with weak C-H bonds, such as benzyl ethers [85] or aldehydes [86]. They successfully generated iodine azide from tetrabutylammonium azide and iodine monochloride in a microfluidic device. The generated iodine azide was reacted with various benzaldehydes and then heated to form carbonyl azides (Fig. 18).

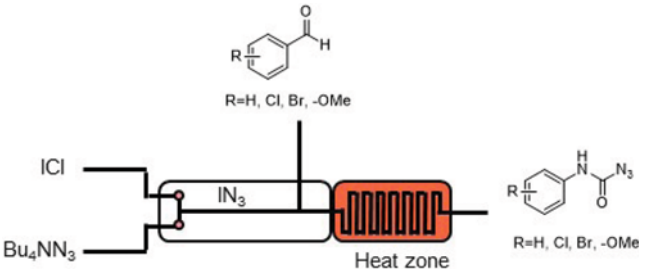

Fig. 18. In-situ generation of IN_3 and utilization for formation of carbonyl azide. After mixing, the aldehyde with the iodine azide reagent passes through a capillary (196-μL volume) at 80 °C (heat zone). *Beilstein J. Org. Chem.*, 5, 30 (2009).

CHLOROMETHYL METHYL ETHER (CMME)

Chloromethyl methyl ether (CMME, CH_3OCH_2Cl), is mostly used as an alkylating agent in industrial solvents and water repellents and as a chloromethylation reagent for ion-exchange resins. CMME is useful for introducing a methoxymethyl (MOM) protecting group, and thus, it is often called MOM-Cl or MOM chloride. However, it has been reported that the carcinogenic and genotoxic problems could occur by moisture-sensitive CMME due to spontaneously interacting with nucleophilic DNA in the absence of enzymes [87]. However, clear-cut solutions have not been reported yet to avoid the direct exposure to the carcinogenic reagent in CMME chemistry [88-90].

Kim et al. recently reported the unique μ-TES platform and the total process with zero exposure of CMME in a series of synthesis, separation, reaction, and work-up [20]. CMME was produced from a reaction between safe reactants (hexanoyl chloride and dimethoxymethane) in a PTFE capillary tube microreactor at 55 °C. A newly developed Si nanowire (SiNW)-embedded microseparator was used for the safe and efficient separation of the produced CMME vapor from the liquid reaction mixture (methyl hexanoate and CMME). The superamphiphobic SiNW microseparator showed a membrane-free separation process at the interface of the stable gas-liquid laminar flow. The separated CMME gas was utilized for functional group protection and polymer chloromethylation. Then, the remaining CMME was quenched to ensure zero exposure to carcinogenic reagents, which completely removed the safety issues. The usefulness of the SiNW microseparator is attributed to its superamphiphobic surface with high liquid-repelling and strong gas-retaining properties. The contact angles of water (164°) on the surface and of the three organic solvents of DMSO (155°), hexadecane (120°), and methyl hexanoate (105.5°) were achieved by a series of cone-shaped SiNW clusters by selective etching, decoration with SiO_2 nanoparticles by a sol-gel process, and final fluorination (Fig. 20). The reliable gas-liquid laminar flow allowed us to separate a volatile CMME gas from the product mixture at two outlets. The SiNW channel was 500 μm in width, 70 μm in height, and 43 cm in length, and it was sealed by bonding with the resistant PVSZ-coated PDMS channel (500-μm width, 15-μm height, and 40-cm length).

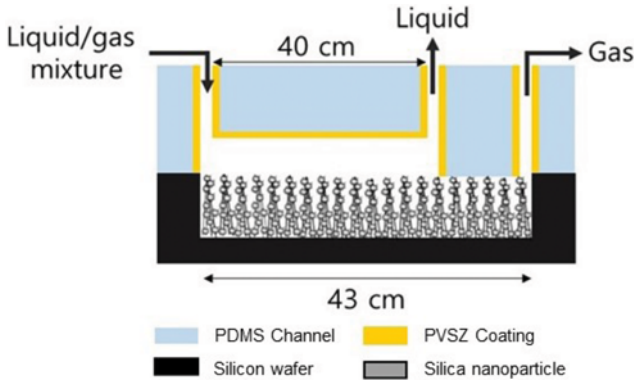

Fig. 20. Unique silicon nanowire microseparator design to separate a volatile CMME gas from liquid mixture at gas-liquid laminar flow.

USEFULNESS IN PHARMACEUTICAL MEDICINE AND BIOMEDICINE

MRT, as an efficient chemical process technology, has been mainly employed for producing versatile types of industrial pharmaceutical compounds at the intermediate scale (i.e., kilograms to a few tons). These continuous-flow microreactions are very attractive in terms of their low cost, superior reliability and safety, better sustainability, and novel pathways that are not otherwise accessible by conventional processes [91,92]. In particular, the combination of MRT with μ-TES and the total process concept enables faster responses to changes in demand, and the relatively small scale of inventories allows not only lower working capital but also reduced storage of potentially hazardous intermediate amount, including

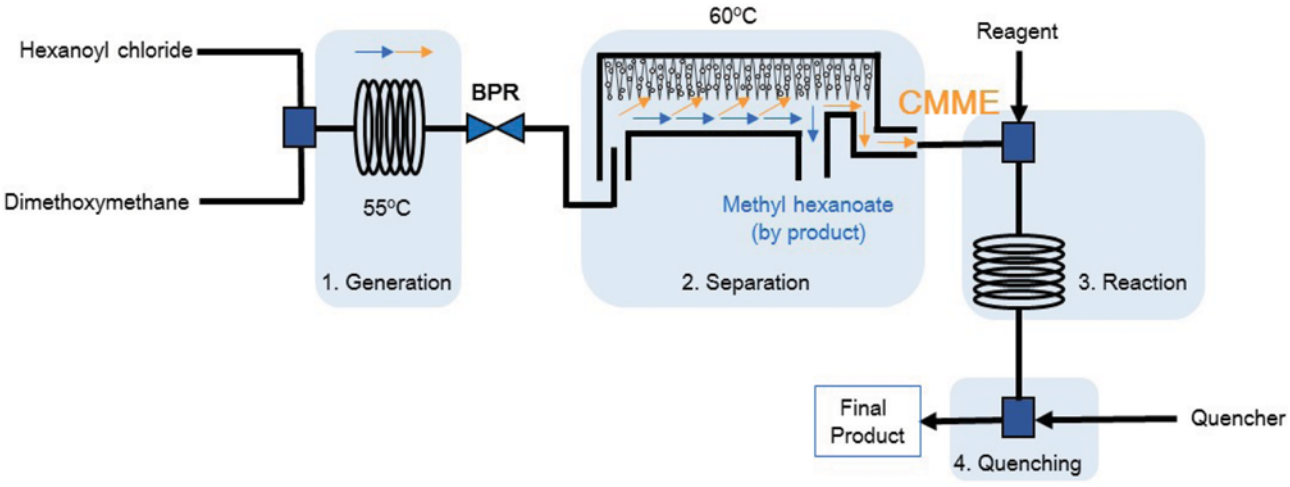

Fig. 19. In-situ generation of chloromethyl methyl ether (CMME), separation in a silicon nanowire separator unit, and utilization reactions, such as functional group protection and polymer chloromethylation. Hexanoyl chloride flow rate at 36 μL/min and dimethoxymethane at 22 μL/min, separation rate of CMME at 17.5 μL/min. *Nat. Commun.*, 7, 10741 (2016).

high-potency active pharmaceutical ingredients (APIs). McQuade et al. developed a continuous-flow synthesis of ibuprofen as a nonsteroidal anti-inflammatory medicine by an efficient three-step process without purification of intermediates and generated ~15 g/day [93]. Potential scale-up would also have merit from exact temperature control (from 150 °C to 50 °C in sequential steps) and efficient control of exotherms (due to pH changing from pH 1 to 14). In addition, other groups have synthesized various kinds of drug molecules, such as atazanavir [94], darunavir [24], rufinamide [95], artemisinin [96], aliskiren [97], and CCR8 ligands [98], in a continuous-flow synthetic manner. Finally, Trout et al. reported the first example of an end-to-end, continuous manufacturing process for a pharmaceutical product. Their plant in one tightly controlled process synthesized a chemical intermediate and serially performed all the subsequent reactions, separations, crystallizations, drying, and formulation to produce finally the tablet type of drug product. The total throughput nominally over 1 kg/day of aliskiren hemifumarate as an anti-hypertensive (blood pressure lowering) medicine corresponded to 2.7×10 tablets/year and extended to 2.4 kg/day by changing control set points in the plant [94]. This innovative chemical plant is entirely enclosed and highly compact in size (2.4×7.3 m^2). Thus, the involved number of unit operations is reduced by 75%, and the process time is reduced by 20 times compared to the batch system. In biomedicine, less time-consumption from prototype to product should promote personalized devices and treatments, enhance the related research and development, and help reduce significantly the cost of clinical trials and overall access to healthcare [99].

CONCLUSION AND FUTURE WORK

In light of the great importance of MRT, the concept of the μ-TES and the automated total process definitely provides new insights into organic polymer and drug syntheses involving hazardous, noxious, or explosive chemistry. This review can contribute to be broadly used in those syntheses where the toxic reagent chemicals generated in situ could be separated by solvent extraction, distillation, and membrane separation principles. In addition, purified hazardous chemicals have been used for the synthesis of target products in a continuous-flow but safe manner. However, a method to better control solids and undissolved reagents is still strongly needed. In the context, the further development of advanced μ-TES platforms by integrating and interconnecting multiple functional units that are devised with new materials and new principles is in continuous demand. Moreover, new total process technologies for various chemical mixtures can be rapidly developed in broader applications across a range of drug, polymer functionalization, and material products.

The future of chemistry and chemical engineering must be owned by a workforce combining knowledge of the literature with new ideas for finding practical synthesis and processing technology augmented by new machinery and tools [100]. In addition to the widely used soft lithography, new fabrication techniques, such as 3D printing, can offer a greater opportunity to develop new systems with higher productivity and functionality [101]. Eventually, the integration of chemical processing and hardware platforms to control superior chemical outcomes will be accelerated to explore molecular nanotechnology, catalyst optimization, complex chemical processes, and drug design. Indeed, advances in the tools of synthesis, such as machine-assisted processes, will be accomplished by collaboration among chemists, engineers, and even robotics and software developers.

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COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

REFERENCES

1. T. Wirth, *Microreactors in Organic Synthesis and Catalysis*, Wiley-VCH (2008).
2. G. M. Whitesides, *Nature*, **442**, 368 (2006).
3. C. G. Frost and L. Mutton, *Green. Chem.*, **12**, 1687 (2010).
4. S. Marre and K. F. Jensen, *Chem. Soc. Rev.*, **39**, 1183 (2010).
5. N. Kockmann and D. M. Roberge, *Chem. Eng. Technol.*, **32**, 1682 (2009).
6. B. Gutmann, D. Cantillo and C. O. Kappe, *Angew. Chem. Int. Ed.*, **54**, 6688 (2015).
7. C. J. Mallia and I. R. Baxendale, *Org. Process. Res. Dev.*, **20**, 327 (2016).
8. R. Porta, M. Benaglia and A. Puglisi, *Org. Process. Res. Dev.*, **20**, 2 (2016).
9. D. Webb and T. F. Jamison, *Chem. Sci.*, **1**, 675 (2010).
10. C. Wiles and P. Watts, *Green. Chem.*, **14**, 38 (2012).
11. B. J. Deadman, S. G. Collins and A. R. Maguire, *Chem. Eur. J.*, **21**, 2298 (2015).
12. S. T. R. Müller and T. Wirth, *ChemSusChem*, **8**, 245 (2015).
13. H. Amii, A. Nagaki and J.-i. Yoshida, *Beilstein J. Org. Chem.*, **9**, 2793 (2013).
14. M. Brzozowski, M. O'Brien, S. V. Ley and A. Polyzos, *Acc. Chem. Res.*, **48**, 349 (2015).
15. N. Oger, E. Le Grognec and F.-X. Felpin, *Org. Chem. Front.*, **2**, 590 (2015).
16. S. G. Newman and K. F. Jensen, *Green. Chem.*, **15**, 1456 (2013).
17. D. T. McQuade and P. H. Seeberger, *J. Org. Chem.*, **78**, 6384 (2013).
18. H. P. L. Gemoets, Y. Su, M. Shang, V. Hessel, R. Luque and T. Noel, *Chem. Soc. Rev.*, **45**, 83 (2016).
19. P. J. Cossar, L. Hizartzidis, M. I. Simone, A. McCluskey and C. P. Gordon, *Org. Biomol. Chem.*, **13**, 7119 (2015).
20. A. K. Singh, D.-H. Ko, N. K. Vishwakarma, S. Jang, K.-I. Min and D.-P. Kim, *Nat. Commun.*, **7** (2016).
21. R. A. Maurya, C. P. Park, J. H. Lee and D.-P. Kim, *Angew. Chem. Int. Ed.*, **50**, 5952 (2011).
22. F. Mastronardi, B. Gutmann and C. O. Kappe, *Org. Lett.*, **15**, 5590 (2013).
23. M. O'Brien, I. R. Baxendale and S. V. Ley, *Org. Lett.*, **12**, 1596 (2010).
24. V. D. Pinho, B. Gutmann, L. S. M. Miranda, R. O. M. A. de Souza

and C. O. Kappe, *J. Org. Chem.*, **79**, 1555 (2014).
25. V. D. Pinho, B. Gutmann and C. O. Kappe, *RSC Adv.*, **4**, 37419 (2014).
26. E. Rossi, P. Woehl and M. Maggini, *Org. Process. Res. Dev.*, **16**, 1146 (2012).
27. G. Maas, *Angew. Chem. Int. Ed.*, **48**, 8186 (2009).
28. R. A. Maurya, K.-I. Min and D.-P. Kim, *Green Chem.*, **16**, 116 (2014).
29. H. E. Bartrum, D. C. Blakemore, C. J. Moody and C. J. Hayes, *J. Org. Chem.*, **75**, 8674 (2010).
30. L. J. Martin, A. L. Marzinzik, S. V. Ley and I. R. Baxendale, *Org. Lett.*, **13**, 320 (2011).
31. P. S. Bailey, *Chem. Rev.*, **58**, 925 (1958).
32. P. S. Bailey, *Ozonolysis in Organic Chemistry*, Academic Press (1978).
33. W. H. Bunnelle, *Chem. Rev.*, **91**, 335 (1991).
34. T. I. Zvereva, V. G. Kasradze, O. B. Kazakova and O. S. Kukovinets, *Russ. J. Org. Chem.*, **46**, 1431 (2010).
35. L. B. P. G. Urben, *Bretherick's Handbook of Reactive Chemical Hazards*, 7th Ed., Oxford (1990).
36. S. Caron, R. W. Dugger, S. G. Ruggeri, J. A. Ragan and D. H. B. Ripin, *Chem. Rev.*, **106**, 2943 (2006).
37. Y. Wada, M. A. Schmidt and K. F. Jensen, *Ind. Eng. Chem. Res.*, **45**, 8036 (2006).
38. S. Hübner, U. Bentrup, U. Budde, K. Lovis, T. Dietrich, A. Freitag, L. Küpper and K. Jähnisch, *Org. Process. Res. Dev.*, **13**, 952 (2009).
39. M. D. Roydhouse, A. Ghaini, A. Constantinou, A. Cantu-Perez, W. B. Motherwell and A. Gavriilidis, *Org. Process. Res. Dev.*, **15**, 989 (2011).
40. M. D. Roydhouse, W. B. Motherwell, A. Constantinou, A. Gavriilidis, R. Wheeler, K. Down and I. Campbell, *RSC Adv.*, **3**, 5076 (2013).
41. M. Irfan, T. N. Glasnov and C. O. Kappe, *Org. Lett.*, **13**, 984 (2011).
42. C. Battilocchio, I. R. Baxendale, M. Biava, M. O. Kitching and S. V. Ley, *Org. Process. Res. Dev.*, **16**, 798 (2012).
43. J. Zak, D. Ron, E. Riva, H. P. Harding, B. C. S. Cross and I. R. Baxendale, *Chem. Eur. J.*, **18**, 9901 (2012).
44. F. Fischer and H. Tropsch, *Brennstoff-chem.*, 97 (1926).
45. H. Adkins and G. Krsek, *J. Am. Chem. Soc.*, **71**, 3051 (1949).
46. N. I. Sax and R. J. Lewis, *Dangerous properties of industrial materials*, 7th Ed., Van Nostrand Reinhold (1989).
47. P. W. Miller, N. J. Long, A. J. de Mello, R. Vilar, J. Passchier and A. Gee, *Chem. Commun.*, 546 (2006).
48. M. T. Rahman, T. Fukuyama, N. Kamata, M. Sato and I. Ryu, *Chem. Commun.*, 2236 (2006).
49. E. R. Murphy, J. R. Martinelli, N. Zaborenko, S. L. Buchwald and K. F. Jensen, *Angew. Chem. Int. Ed.*, **46**, 1734 (2007).
50. P. W. Miller, N. J. Long, A. J. de Mello, R. Vilar, H. Audrain, D. Bender, J. Passchier and A. Gee, *Angew. Chem. Int. Ed.*, **46**, 2875 (2007).
51. P. W. Miller, L. E. Jennings, A. J. de Mello, A. D. Gee, N. J. Long and R. Vilar, *Adv. Synth. Catal.*, **351**, 3260 (2009).
52. T. Fukuyama, M. T. Rahman, N. Kamata and I. Ryu, *Beilstein J. Org. Chem.*, **5**, 34 (2009).
53. X. Gong, P. W. Miller, A. D. Gee, N. J. Long, A. J. de Mello and R. Vilar, *Chem. Eur. J.*, **18**, 2768 (2012).
54. C. Csajági, B. Borcsek, K. Niesz, I. Kovács, Z. Székelyhidi, Z. Bajkó, L. Ürge and F. Darvas, *Org. Lett.*, **10**, 1589 (2008).
55. P. Koos, U. Gross, A. Polyzos, M. O'Brien, I. Baxendale and S. V. Ley, *Org. Biomol. Chem.*, **9**, 6903 (2011).
56. M. A. Mercadante and N. E. Leadbeater, *Org. Biomol. Chem.*, **9**, 6575 (2011).
57. C. B. Kelly, C. Lee, M. A. Mercadante and N. E. Leadbeater, *Org. Process. Res. Dev.*, **15**, 717 (2011).
58. M. A. Mercadante and N. E. Leadbeater, *Green. Process. Synth.*, **1**, 499 (2012).
59. C. Brancour, T. Fukuyama, Y. Mukai, T. Skrydstrup and I. Ryu, *Org. Lett.*, **15**, 2794 (2013).
60. T. Fukuyama, Y. Mukai and I. Ryu, *Beilstein J. Org. Chem.*, **7**, 1288 (2011).
61. M. Cartwright and J. Wilkinson, *Propellants Explos. Pyrotech.*, **35**, 326 (2010).
62. S. Bräse, C. Gil, K. Knepper and V. Zimmermann, *Angew. Chem. Int. Ed.*, **44**, 5188 (2005).
63. M. E. Kopach, M. M. Murray, T. M. Braden, M. E. Kobierski and O. L. Williams, *Org. Process. Res. Dev.*, **13**, 152 (2009).
64. M. Weber, G. Yilmaz and G. Wille, *Chim. Oggi.*, **29**, 8 (2011).
65. M. M. E. Delville, P. J. Nieuwland, P. Janssen, K. Koch, J. C. M. van Hest and F. P. J. T. Rutjes, *Chem. Eng. J.*, **167**, 556 (2011).
66. C. D. Smith, I. R. Baxendale, S. Lanners, J. J. Hayward, S. C. Smith and S. V. Ley, *Org. Biomol. Chem.*, **5**, 1559 (2007).
67. I. R. Baxendale, S. V. Ley, A. C. Mansfield and C. D. Smith, *Angew. Chem. Int. Ed.*, **48**, 4017 (2009).
68. C. O. Kappe and E. Van der Eycken, *Chem. Soc. Rev.*, **39**, 1280 (2010).
69. S. Ceylan, T. Klande, C. Vogt, C. Friese and A. Kirschning, *Synlett.*, **2010**, 2009 (2010).
70. A. C. Varas, T. Noël, Q. Wang and V. Hessel, *ChemSusChem*, **5**, 1703 (2012).
71. M. Fuchs, W. Goessler, C. Pilger and C. O. Kappe, *Adv. Synth. Catal.*, **352**, 323 (2010).
72. A. R. Bogdan and K. James, *Chem. Eur. J.*, **16**, 14506 (2010).
73. A. R. Bogdan and K. James, *Org. Lett.*, **13**, 4060 (2011).
74. A. R. Bogdan and N. W. Sach, *Adv. Synth. Catal.*, **351**, 849 (2009).
75. P. Zhang, M. G. Russell and T. F. Jamison, *Org. Process. Res. Dev.*, **18**, 1567 (2014).
76. H. R. Sahoo, J. G. Kralj and K. F. Jensen, *Angew. Chem. Int. Ed.*, **46**, 5704 (2007).
77. B. Gutmann, J.-P. Roduit, D. Roberge and C. O. Kappe, *Angew. Chem. Int. Ed.*, **49**, 7101 (2010).
78. B. Gutmann, D. Obermayer, J. P. Roduit, D. M. Roberge and C. O. Kappe, *J. Flow. Chem.*, **2**, 8 (2012).
79. L. A. Flippin, *Tetrahedron Lett.*, **32**, 6857 (1991).
80. M. B. Talawar, A. P. Agrawal, M. Anniyappan, D. S. Wani, M. K. Bansode and G. M. Gore, *J. Hazard. Mater.*, **137**, 1074 (2006).
81. H. Singh, A. S. Chawla, V. K. Kapoor, D. Paul and R. K. Malhotra, *Prog. Med. Chem.*, **17**, 151 (1980).
82. R. J. Herr, *Bioorganic & Medicinal Chemistry*, **10**, 3379 (2002).
83. B. Gutmann, J.-P. Roduit, D. Roberge and C. O. Kappe, *Chem. Eur. J.*, **17**, 13146 (2011).
84. J. C. Brandt and T. Wirth, *Beilstein J. Org. Chem.*, **5**, 30 (2009).
85. C. Viuf and M. Bols, *Angew. Chem. Int. Ed.*, **40**, 623 (2001).
86. C. M. Pedersen, L. G. Marinescu and M. Bols, *Org. Biomol. Chem.*, **3**, 816 (2005).

87. R. J. Linderman, M. Jaber and B. D. Griedel, *J. Org. Chem.*, **59**, 6499 (1994).
88. M. A. Berliner and K. Belecki, *J. Org. Chem.*, **70**, 9618 (2005).
89. D. M. Barnes, J. Barkalow and D. J. Plata, *Org. Lett.*, **11**, 273 (2009).
90. A. Jasti, S. Prakash and V. K. Shahi, *J. Membr. Sci.*, **428**, 470 (2013).
91. A. Mitic and K. V. Gernaey, *Chem. Eng. Technol.*, **38**, 1699 (2015).
92. L. Hosta-Rigau, M. J. York-Duran, T. S. Kang and B. Städler, *Adv. Funct. Mater.*, **25**, 3860 (2015).
93. A. R. Bogdan, S. L. Poe, D. C. Kubis, S. J. Broadwater and D. T. McQuade, *Angew. Chem.*, **121**, 8699 (2009).
94. S. Mascia, P. L. Heider, H. Zhang, R. Lakerveld, B. Benyahia, P. I. Barton, R. D. Braatz, C. L. Cooney, J. M. B. Evans, T. F. Jamison, K. F. Jensen, A. S. Myerson and B. L. Trout, *Angew. Chem. Int. Ed.*, **52**, 12359 (2013).
95. P. Zhang, M. G. Russell and T. F. Jamison, *Org. Process. Res. Dev.*, **18**, 1567 (2014).
96. K. Gilmore, D. Kopetzki, J. W. Lee, Z. Horvath, D. T. McQuade, A. Seidel-Morgenstern and P. H. Seeberger, *Chem. Commun.*, **50**, 12652 (2014).
97. P. L. Heider, S. C. Born, S. Basak, B. Benyahia, R. Lakerveld, H. Zhang, R. Hogan, L. Buchbinder, A. Wolfe, S. Mascia, J. M. B. Evans, T. F. Jamison and K. F. Jensen, *Org. Process. Res. Dev.*, **18**, 402 (2014).
98. T. P. Petersen, S. Mirsharghi, P. C. Rummel, S. Thiele, M. M. Rosenkilde, A. Ritzén and T. Ulven, *Chem. Eur. J.*, **19**, 9343 (2013).
99. M. D. Symes, P. J. Kitson, J. Yan, C. J. Richmond, G. J. T. Cooper, R. W. Bowman, T. Vilbrandt and L. Cronin, *Nat. Chem.*, **4**, 349 (2012).
100. D. E. Fitzpatrick, C. Battilocchio and S. V. Ley, *ACS Cent. Sci.*, **2**(3), 131 (2016).
101. A. K. Au, W. Huynh, L. F. Horowitz and A. Folch, *Angew. Chem. Int. Ed.*, **55**, 3862 (2016).

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